pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Vandetanib (Caprelsa) for Medullary Thyroid Cancer

March 30, 2017

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding vandetanib for medullary thyroid cancer. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance Report is based on: a systematic review of the literature regarding vandetanib for medullary thyroid cancer conducted by the Endocrine Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on vandetanib for medullary thyroid cancer, a summary of submitted Provincial Advisory Group Input on vandetanib for medullary thyroid cancer, and a summary of submitted Registered Clinician Input on vandetanib for medullary thyroid cancer, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

As per the Health Canada Product Monograph, vandetanib monotherapy is indicated for the treatment of symptomatic or progressive medullary thyroid cancer (MTC) in adult patients with unresectable locally advanced or metastatic disease. "Vandetanib use should be carefully considered based on a risk: benefit assessment in patients with indolent, asymptomatic or slowly progressive disease because of the significant treatment-related risks".[1] The indication does not preclude use in patients with symptomatic and progressive disease, as confirmed by the submitter.

The Submitter, Sanofi Genzyme, has requested funding for the treatment of symptomatic and/or progressive MTC in adult patients with unresectable locally advanced or metastatic disease.

Of note, the Health Canada Product Monograph for vandetanib includes the following serious warnings and precautions:

- should only be prescribed by a qualified physician who has completed the certification with the Vandetanib Restricted Distribution Program and who is experienced in the use of antineoplastic therapy and in the treatment of MTC;
- vandetanib can prolong the QT interval using the Fridericia correction formula (QTcF);
- heart failure (fatal);
- hypertension (Grade 4) or hypertensive crisis.

Vandetanib is an oral tablet available in 100 mg and 300 mg tablets. The recommended dose of vandetanib is 300 mg taken once daily.

The objective of the systemic review is to evaluate the effect of vandetanib, as monotherapy, on patient outcomes compared to standard therapies, placebo, or best supportive care in the treatment of patients with unresectable, locally advanced or metastatic, hereditary or sporadic MTC.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one phase 3, double-blind, randomized, placebo-controlled trial that investigated the safety and efficacy of vandetanib in the treatment of patients with unresectable locally advanced or metastatic MTC (ZETA; N = 331). Of note, the enrolment was not limited to patients with symptomatic or progressive disease; according to the EMA report, in a post-hoc analysis, nearly all patients (95 %, n= 313) had either progressive disease or symptoms at baseline (12 patients without progression and without symptoms and 6 patients with unknown progressive status and without symptoms). The reimbursement criteria refer to "the treatment of symptomatic and/or progressive Medullary Thyroid Cancer (MTC) in adult patients with unresectable locally advanced or metastatic disease", which refer to these three groups of patients: (1) symptomatic MTC only, (2) progressive MTC only, and (3) symptomatic and progressive MTC. Eligible patients were randomized (2:1) to receive double-blind treatment with vandetanib 300 mg once daily or matching placebo. Patients were to continue receiving blinded treatment until they met the criteria for disease progression or other withdrawal criteria. Patients who demonstrated disease progression (investigator-determined) were discontinued from the blinded study treatments and were given the option of initiating open-label treatment with vandetanib or entering the follow-up period for evaluating survival status.

Progression-free survival (PFS) confirmed by independent central review (ICR) was the primary endpoint. The protocol specified that 90 progression events would be required to detect a doubling of PFS in all patients at a two-sided level of significance of 0.05 with 80% power.[2] Secondary endpoints included overall survival, objective response rate, disease control rate, time to worsening of pain, calcitonin response, carcinoembryonic antigen response.

A greater proportion of patients in the placebo group (71.0%) discontinued the double-blind study treatment compared with the vandetanib group (51.9%). At the time of the data cut-off, the proportion of patients remaining on double-blinded treatment was 48.1% and 28.0% in the vandetanib and placebo groups, respectively. Cross-over to open-label treatment with vandetanib was more common in the placebo group compared with the vandetanib group (58.0% versus 19.0% to open label treatment). Dose reductions and interruptions were permitted during the trial as a result of adverse events and occurred more frequently in the vandetanib group compared with the placebo group (35.1% versus 3.0% and 47.2% versus 15.2%, respectively).

Overall, the data for PFS from the ZETA trial appear to be internally valid and were considered by the CGP to be generalizable to the treatment of MTC in the Canadian setting. Although the ZETA trial did not limit enrollment to patients with symptomatic or progressive disease, post hoc subgroup analyses conducted by the manufacturer and the FDA demonstrated results which were similar to those conducted using the full analysis set (FAS) dataset. Due to extensive cross-over to open-label treatment with vandetanib, the result for OS are uninterpretable and likely biased against vandetanib. Health-related quality of life data were captured using the FACT-G instrument; however, conclusions regarding the impact of vandetanib on FACT-G could not be made due to the exploratory nature of the endpoint and the absence of any statistical evaluations.

Efficacy

Overall survival was a secondary endpoint and was defined as the time from randomization to death from any cause. Data for overall survival were immature at the time of the initial data cut-off (i.e., July 2009). At the time of the initial analysis, 14.5% of the trial participants had died (14% and 16% of patients in the vandetanib and placebo groups, respectively). The submitter

reported a hazard ratio of 0.89 (99.98% CI, 0.28 to 2.85; *P* = 0.7115) in accordance with the pre-planned initial analysis of overall survival. At the time of the final analysis, 50.2% and 52.0% of the patients randomized to the vandetanib and placebo groups had died, respectively. There was no statistically significant difference between vandetanib and placebo in the final analysis for OS (HR 0.99; 95.02% CI, 0.72 to 1.38, *P* = 0.9750). No cross-over data were available for the final OS analysis. Of note, pCODR requested from the submitter subgroup analyses related to the following populations as defined by the EMA: progressive, symptomatic, symptomatic or progressive, and symptomatic and progressive. However, the submitter was not able to provide subgroup data related to progressive, symptomatic, symptomatic or progressive patients. Subgroup data for the post hoc symptomatic and progressive patients were reported by the submitter and are presented later in this report.

At the time of the data cut-off, 124 patients (37.5%) had ICR-confirmed disease progression (51.0% in the placebo group and 31.6% in the vandetanib group). Treatment with vandetanib was associated with a statistically significant prolongation of PFS (HR = 0.46; 95% CI, 0.31 to 0.69). The median PFS was 19.3 months in the placebo group and was not reached in the vandetanib group, but was estimated to be 30.5 months using a Weibull model. It is unclear if the use of a Weibull model was pre-planned. Sensitivity analyses were supportive primary analysis. Post-hoc subgroup analyses were conducted to investigate the efficacy of vandetanib in patients whose MTC is symptomatic and progressive and the results were similar to the primary analysis of PFS (see Section 6.3.2 for differences in the subgroup analyses conducted by the manufacturer and by the FDA in terms of clinical criteria of the subgroup and statistical approaches).

Vandetanib-treated patients demonstrated statistically significant improvements in objective response rate (OR 5.48 [95% CI, 2.99 to 10.79]); disease control rate (OR 2.64 [95% CI, 1.48 to 4.69]); time to worsening of pain (HR 0.61 [95% CI, 0.43 to 0.87]); calcitonin response (69.3% versus 3.0%; OR 72.9 [95% CI, 26.2 to 303.2]) and CEA response (51.5% versus 2.0%; OR 52.0 [95% CI, 16.0 to 320.3]). Quality of life was evaluated as an exploratory endpoint using the patient-reported FACT-G scale. No statistical analyses were performed; however, the Submitter reported that there was no difference between vandetanib and placebo for changes from baseline in FACT-G total score or subscales.

Table 1: Key Efficacy Outcomes from the ZETA trial

Outcome	Parameter	Treatment	
		Vandetanib 300 mg	Placebo
PFS (final analysis, Sept. 2015 data cut-off)	n/N (%)	73/231 (32%)	51/100 (51%)
	Median PFS (months)	NA (30.5 predicted)	19.3
	HR (95% CI)	0.46 (0.31 to 0.69)	
	P value	0.0001	
Overall survival (interim analysis July 2009 data cut-off)	n/N (%)	32/231 (13.9%)	16/100 (16%)
	Median OS	NA	NA
	HR (99.98% CI)	0.89 (0.28 to 2.85)	
	HR (95% CI)[a]	0.89 (0.48 to 1.65)	
	P value	0.7115	
Overall survival (final analysis Sept. 2015 data cut-off)	n/N (%)	116/231 (50.2%)	52/100 (52.0%)
	HR (95.02% CI)	0.99 (0.72 to 1.38)	
	P value	0.9750	
ORR	n/N (%)	104/231 (45.0%)	13/100 (13.0%)
	OR (95% CI)	5.48 (2.99 to 10.79)	
	P value	<0.0001	
DCR	n/N (%)	200/231 (86.6%)	71/100 (71.0%)

Outcome	Parameter	Treatment	
		Vandetanib 300 mg	Placebo
	OR (95% CI)	2.64 (1.48 to 4.69)	
	P value	0.0010	
CTN Response	n/N (%)	160/231 (69.3%)	3/100 (3.0%)
	OR (95% CI)	72.86 (26.22 to 303.2)	
	P value	<0.0001	
CEA Response	n/N (%)	119/231 (51.5%)	2/100 (2.0%)
	OR (95% CI)	52.03 (15.95 to 320.3)	
	P value	<0.0001	
TWP	n/N (%)	114/231 (49%)	57/100 (57%)
	Median TWP (months)	7.85 months	3.25 months
	HR (95% CI)	0.61 (0.43 to 0.87)	
	P value	0.0062	

Abbreviations: CEA = carcinoembryonic antigen; CI = confidence interval; CTN = calcitonin; DCR = disease control rate; n = number of patients with event; N = number of patients included in the analysis; NA = not applicable (median was not reached); OR = odds ratio; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; TWP = time to worsening of pain
Source: Data from Clinical Study Report Synopsis,[2] Wells et al (2012),[3] and correspondence from the submitter.
[a] The use of a 95% CI is not reflective of the pre-planned interim analysis for overall survival.

Harms

The safety analysis set included 330 patients (231 in the vandetanib group and 99 in the placebo group). The CGP identified the following adverse events of special interest: correct QT interval (QTc) prolongation, diarrhea, and hypertension. Compared with placebo, a greater proportion of vandetanib-treated patients experienced at least one adverse event (99.6% versus 90.9%), adverse event of CTCAE grade 3 or higher (55.4% versus 24.2%), serious adverse event (30.7% versus 13.1%), or an adverse event which led to discontinuation from the study (12.1% versus 3.0%). The proportion of patients who died as a result of adverse events was similar between the vandetanib and placebo groups (2.2% versus 2.0%, respectively). The most frequent adverse events that occurred at a greater frequency with vandetanib than with placebo were diarrhea (56.3% versus 26.3%), rash (45.0% versus 11.1%), nausea (33.3% versus 16.2%), hypertension (31.6% versus 5.1%), and headache (25.5% versus 9.1%).[2] QT Prolongation was reported in a greater proportion of vandetanib-treated patients (14.3% versus 1.0%).[2] Within the vandetanib group, skin disorders (2.5%) and asthenia (1.7%) were the most common events which led to discontinuation.

Table 2: Summary of Adverse Events

Adverse Events	Patients with AEs, n (%)	
	Vandetanib (N = 231)	Placebo (N = 99)
Any AEs	230 (99.6)	90 (90.9)
AEs of CTCAE grade ≥3	128 (55.4)	24 (24.2)
SAEs	71 (30.7)	13 (13.1)
WDAEs	28 (12.1)	3 (3.0)
Diarrhea	131 (56.7)	27 (27.3)
CTCAE Grade ≥3	25 (10.8)	2 (2.0)
Hypertension	76 (32.9)	5 (5.1)
CTCAE Grade ≥3	20 (8.7)	0
QTc-related AEs	36 (15.6)	4 (4.0)
CTCAE Grade ≥3	20 (8.7)	3 (3.0)

Abbreviations: AE = adverse events; CTCAE = Common Terminology Criteria for Adverse Events; n = number of patients with event; Pt-Y = patient-years; SAEs = serious adverse events; WDAEs = withdrawals due to adverse events
Source: Clinical Study Report Synopsis,[2] Common Technical Document section 2.7.4

Limitations

Vandetanib and placebo were administered in a double-blind manner using matching active and placebo tablets. However, blinding of the study may have been compromised by the increased frequency of adverse events in the vandetanib group compared with placebo group, particularly skin and subcutaneous tissue disorders (90.0% versus 30.3%) and QTc prolongation (14.3% versus 1.0%). Biomarkers levels and AEs are known common effects of tyrosine kinase inhibitors (TKIs). While the primary endpoint, PFS, and some secondary endpoints (i.e., ORR, DCR, and DOR) were confirmed by ICR, other endpoints such as quality of life could be biased by potential unblinding.

Patients in both treatment groups could initiate open-label treatment with vandetanib if they demonstrated disease progression based on the interpretation of the study investigators. Since the primary endpoint (PFS) and some of the secondary endpoints (i.e., ORR, DCR, and DOR) were evaluated by the study's ICR as opposed to the study investigators, 51 patients received open-label treatment prior to demonstrating ICR-confirmed disease progression. Providing the active treatment to those who were randomized to receive placebo could bias the efficacy results against vandetanib for the analyses conducted using the FAS. Data for overall survival were immature at the initial data cut-off (i.e., July 31, 2009). Since the study protocol permitted patients with documented disease progression to receive open-label treatment with vandetanib, the overall survival endpoint could be biased against vandetanib, as those in the placebo group received active treatment.

The primary endpoint (PFS) was supported by using numerous sensitivity and subgroup analyses, which demonstrated results that were consistent with the primary analysis. There was no adjustment for multiplicity in the analyses of the secondary endpoints; therefore, there is an inflated risk of type I error with the statistical evaluation of those endpoints.

The impact of vandetanib on the health-related quality of life for patients with advanced MTC could not be comprehensive evaluated in the ZETA trial, as the FACT-G assessments were limited to an exploratory endpoint with no statistical testing.

The submitter's requested listing criteria for vandetanib is for the treatment of symptomatic and/ or progressive MTC in adult patients with unresectable locally advanced or metastatic disease. The ZETA trial enrolled patients with unresectable locally advanced or metastatic disease MTC; however, the enrolment was not limited to patients with symptomatic or progressive disease. Subgroup analyses for patients with symptomatic and/ or progressive disease were not pre-specified in the analysis plan, and there were differences between the clinical criteria used by the manufacturer and those used by the FDA. There were no baseline characteristics reported for the subgroup analyses and randomization was not stratified according the specific criteria used to defined progressive and/or symptomatic disease; therefore, it is unclear if the treatment groups were well balanced. The primary analysis and the pre-specfied subgroup analyses for PFS were based on progression events as determined by the ICR, regardless of whether or not the patient had received treatment with open-label vandetanib;[4] however, the post-hoc progressive and symptomatic subgroup analyses by Kreissl et al (2014) excluded patients who received treatment with open-label vandetanib.[5] In response to a request from CADTH, the submitter stated that this approach was used because the benefit of vandetanib in patients randomized to placebo may have affected the results for PFS in the ITT analysis, noting the lower hazard ratio that was observed when data from the open-label phase were excluded (HR = 0.27; 95% CI, 0.18 to 0.41).

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

From a patient's perspective, it was reported that ongoing symptoms of thyroid cancer can impact their day-to-day life. Respondents noted that symptoms include feeling tired and listless, and this can affect their emotional well-being and ability to work. Respondents reported using the following therapies to treat thyroid cancer: levothyroxine, sorafenib or other tyrosine kinase inhibitors, vandetanib, radioactive iodine treatment, surgery, chemotherapy and external beam radiation. Respondents who do not have experience with the drug under review expect that it will manage their disease progression and have fewer side effects, such as weight loss, fatigue, and pain, among others than other available treatments. Respondents who have experience with vandetanib indicated that it helped to slow their disease progression. Respondents stated that their side effects were better managed, including vomiting, weight loss, diarrhea and skin rash than with previous treatments. Respondents also reported that the skin rash experienced from other treatments had been reduced, but reported a transient case of acne. Respondents found that vandetanib was easy to use.

Provincial Advisory Group (PAG) Input

Input was obtained from the provinces (Ministries of Health and/or cancer agencies) and federal drug plans participating in pCODR. PAG identified the following as factors that could impact the implementation of vandetanib:

Clinical factors:

- Fills a gap in therapy
- Serious cardiovascular adverse events

Economic factors:

- Controlled distribution program limits prescribing and dispensing to registered physicians and pharmacists
- Additional healthcare resources required to regularly monitor for cardiotoxicities

Registered Clinician Input

Vandetanib would fill a gap in therapy for the very small number of patients with medullary thyroid cancer. Key benefits identified are the increase in progression free survival, high objective response rate and high disease control rate. The harms identified are the side effects associated with vandetanib, which are manageable, and the contraindications for patients with prolonged QT interval or on other medications that prolongs QT interval.

Summary of Supplemental Questions

The following supplemental question was identified as relevant to the pCODR review of vandetanib for MTC: Is PFS an appropriate surrogate for OS in patients with MTC? CADTH did not identify any studies that investigated a correlation between PFS and OS in patients with MTC. Therefore, there is an absence of published evidence evaluating the validity of PFS as a surrogate endpoint for OS in patients with MTC.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 3 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1 (regarding internal validity).

Table 3: Assessment of generalizability of evidence for vandetanib

Domain	Factor	Evidence	Generalizability Question(s)	CGP Assessment of Generalizability
Population	Performance status	Patients with a WHO PS between 0 and 2 were eligible for enrollment in the ZETA trial. 64.0% and 32.0% of the study population had a WHO PS of 0 or 1 at the time of enrolment. Only 4% of patients had a WHO PS of 2 and no patients had a WHO PS of 3 or 4.	Are the results of the trial applicable to patients with a WHO PS of 3 of higher?	The trial results are applicable to WHO PS 2 or less, as per trial criteria. However, the CGP recognize that disease symptoms may result in patients with poor performance status that may be improved with therapy. It is difficult to extrapolate the risk of toxicity in patients with a PS of 3 or greater.
	Absence of pre-specified subgroup analyses for patients with symptomatic and/ or progressive MTC	The post-hoc definitions for symptomatic and progressive MTC differed between the submitter and the FDA. There does not appear to be standardized clinical criteria for these parameters in Canada.	Are the results of the post-hoc subgroup analyses applicable to the Canadian setting?	Yes. The results of the post hoc analyses should also be applicable to the Canadian setting.
	Exclusion of patients with brain metastases	Patients with brain metastases were excluded from the ZETA trial.	Are the trial results generalizable to patients with brain metastases?	Brain metastases are rare for MTC. Prior studies with vandetanib and CNS metastases (RADVAN and the phase I)[6,7] have not demonstrated a safety signal of concern. It would be reasonable therefore to allow patients with CNS metastases to be treated with vandetanib if the situation arises.

Domain	Factor	Evidence	Generalizability Question(s)	CGP Assessment of Generalizability
	Exclusion of patients with certain cardiovascular conditions	Patients were excluded if they had uncontrolled hypertension, symptomatic arrhythmia, symptomatic or AF, ventricular tachycardia, congenital long QT syndrome, left bundle branch block, or a QTc that was unmeasurable or ≥ 480 ms.	Are the trial results generalizable to patients with these cardiovascular conditions?	No, this patient population would be excluded because of the risk benefit of the drug.
	Baseline and demographic characteristics	Only a minority of the patients in the ZETA trial were enrolled at Canadian sites (n = 12; 3.6%).	Are the baseline and demographic characteristics in the trial similar to the Canadian setting?	Yes
Intervention	Protocol for dose interruption of vandetanib treatment	The study protocol specified that dose interruption was required for all grade 3 to 4 toxicities until the event has resolved to baseline or CTCAE grade 1, with the exception of CTCAE grade 3 hypertension.	Is this reflective of how this drug would be used in Canadian clinical practice?	Yes
	Dosage adjustment and interruption	Of the patients who were randomized to receive 300 mg vandetanib, 35.1% had the dosage reduced to 200 mg once daily, 13.9% had the dosage reduced to 100 mg once daily, and one patient (0.4%) received a dosage of 200 mg every other day. Dose interruptions were reported for 47% of the vandetanib group (median duration of 19).	Are the proportions of patients requiring dosage adjustment and/or interruption reflective of how this drug would be used in Canadian clinical practice?	Based on the known toxicities associated with vandetinib it would be used very carefully in Canadian clinical practice. It is likely that some patients would be initiated at a lower starting dose. In this case, the subsequent frequency of dose interruptions and dose reductions is likely to be lower (100 mg or 200 mg, depending on individual patient basis).

Domain	Factor	Evidence	Generalizability Question(s)	CGP Assessment of Generalizability
Outcomes	Confounding effects of crossover from placebo to open-label vandetanib treatment on overall survival	A large proportion of patients randomized to placebo switched to receive treatment with open-label vandetanib.	What is the generalizability of the overall survival analysis results in view of the confounding effects of crossing over to open-label active treatment?	As explained in the systematic review the overall survival endpoint is likely to be biased against vandetanib.
	Modified RECIST criteria	The ZETA trial used modified RECIST criteria, including a calcification correction and retrospective re-examination of hypodense or hypointense hepatic lesions.	Does the use of modified RECIST criteria limit the generalizability of the results to the Canadian setting?	No, the use of modified RECIST criteria was necessary due to the specific manifestations of MTC.
	Progression-survival as a surrogate for overall survival	The primary endpoint of the ZETA trial was progression-free survival assessed by independent central review.	Is progression-free survival an appropriate surrogate outcome of overall survival in MTC?	It is the opinion of the CGP that progression-free survival as reported in the ZETA trial is a very likely surrogate outcome for overall survival in MTC. CADTH did not identify any evidence to evaluate the validity of PFS as a surrogate endpoint for OS in patients with MTC (see Section 7).
Setting	Contact with health professionals and monitoring	Patients in the ZETA trial had extensive contact with health professionals (e.g., six clinical visits within the first two months of treatment and then follow-up every 12 weeks).	Given that patients in routine Canadian practice are likely to have less contact with health care professionals, what is the generalizability of the ZETA study with respect to the following: • the safety of vandetanib; • the frequency and timing of dosage adjustment and/or interruption.	Visits every 2 weeks in the first 2 – 3 months are necessary due to the manifestation of the majority of the adverse events during that period. This is currently standard also with other TKIs and also in Canadian practice.

Abbreviations: AF = atrial fibrillation; CTCAE = Common Terminology Criteria for Adverse Events; MTC = medullary thyroid cancer; WHO PS = World Health Organization Performance Status

1.2.4 Interpretation

The Clinical Guidance Panel concluded that there ***is*** a net clinical benefit to vandetanib in the treatment of progressive and/ or symptomatic MTC in adult patients with unresectable locally advanced or metastatic disease based on the randomized controlled ZETA trial that demonstrated a clinically and statistically significant benefit in progression-free survival for vandetanib compared with placebo with adverse event profiles were as expected. Symptomatic and/ or progressive disease refers to the following three groups of patients: (1) symptomatic MTC only, (2) progressive MTC only, and (3) symptomatic and progressive MTC. These conclusions do not pertain to patients with indolent, asymptomatic or slowly progressive disease.

Burden of Illness and Need

According to American and European data medullary thyroid carcinoma (MTC) accounts for less than 5% of thyroid cancers.[3] For progressive MTC there is currently no reliably effective treatment option in Canada. The current approach to MTC in recently updated guidelines of the American and European Thyroid Associations recommend vandetanib or cabozantinib as single agent first line therapy for patients with advanced progressive MTC.[8,9] Vandetanib would provide an effective treatment option for the very small number of patients with symptomatic and/ or progressive medullary thyroid cancer. Time and logistical coordination are required given that healthcare providers are to register in the controlled distribution program and that patients may be limited to certain centres to access treatment.

Effectiveness

The ZETA trial results provide the evidence base for this recommendation. This was a phase 3, double-blind, randomized, placebo-controlled trial that randomized patients with unresectable locally advanced or metastatic MTC (N = 331) to receive treatment with vandetanib or placebo; nearly all (95%, n=313) of the patients enrolled in the ZETA trial had MTC that was either progressive or symptomatic at baseline; 12 (3.6%) were without progression or symptoms; and 6 (1.8%) were without symptoms but with unknown progression status.[10] Dose reductions, dose interruptions, and crossover to open-label vandetanib were permitted.

The study population of ZETA trial was generally reflective of the broader population of patients with unresectable locally advanced or metastatic MTC. Results of the ZETA trial are applicable for the situation of patients with vandetanib in Canada. Its primary endpoint was progression-free survival. The ZETA trial reported a clinically meaningful and statistically significant benefit in progression-free survival for vandetanib compared with placebo. Median PFS was not reached in the vandetanib arm, and was 19.3 months in the placebo arm (HR = 0.46; 95% CI, 0.31 to 0.69; P < 0.001). The overall survival endpoint is likely to be biased against vandetanib, given a high rate of optional crossover to active drug at progression in the placebo arm. Quality of life data were limited (exploratory). Therefore there was no formal statistical analysis and no difference between vandetanib and placebo for changes from baseline in FACT-G total score or subscales. It is the opinion of the CGP that the increase in progression-free survival may likely result in a benefit in overall survival and symptomatology may be improved by vandetanib. A literature review was conducted and did not identify any evidence to evaluate the validity of PFS as a surrogate endpoint for OS in patients with MTC.

Safety

Two weekly visits during the first two to three months are necessary due to the manifestation of the majority of the adverse events during that period. This is currently standard also with other TKIs. Most of the adverse events are also known for other TKIs with a similar profile of action. In addition patients need to be screened for a QTc > 480 ms. Patients with QT prolongation and cardiovascular conditions (uncontrolled hypertension, symptomatic arrhythmia, symptomatic or AF, ventricular tachycardia, congenital long QT syndrome, left bundle branch block, or a QTc that was unmeasurable or ≥ 480 ms) should be excluded. The adverse events are manageable and require frequent monitoring upfront (i.e. for diarrhea). Control diarrhea and monitor electrolytes upfront to void complications are recommended. Educating patients on possible complications is key.

1.3 Conclusions

The current approach to medullary thyroid carcinoma (MTC) is described in recently updated guidelines of the American and European Thyroid Associations.[8,9] For progressive MTC there is currently no treatment option in Canada. American and European guidelines recommend vandetanib or cabozantinib as single agent first line therapy for patients with advanced progressive MTC. The manufacturer's requested listing criteria for vandetanib is for the treatment of symptomatic and/ or progressive MTC in adult patients with unresectable locally advanced or metastatic disease.

The Clinical Guidance Panel concluded that there ***is*** a net clinical benefit to vandetanib in the treatment of progressive and/ or symptomatic MTC in adult patients with unresectable locally advanced and/ or metastatic disease based on the randomized controlled ZETA trial that demonstrated a clinically meaningful and statistically significant benefit in progression free survival for vandetanib compared with placebo. Also, an increase of overall survival is most likely although this could not be demonstrated during the study due to the often slow progression of the disease and the high crossover to active therapy in the placebo arm of the trial. Adverse events are manageable, and frequent monitoring is recommended. This treatment is not recommended for patients with contraindications as described above. The CGP would like to reiterate that their conclusions of net clinical benefit are for the progressive and/ or symptomatic MTC in adult patients with unresectable locally advanced or metastatic disease and do not include patients with indolent, asymptomatic or slowly progressive disease because of the significant treatment-related risks.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Endocrine Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

The current approach to medullary thyroid carcinoma (MTC) is described in recently updated guidelines of the American and European Thyroid Associations.[8,9] MTC accounts for less than 5% of thyroid cancers.[3] MTC may occur as part of the Multiple Endocrine Neoplasia (MEN) Type 2A or 2B or as sporadic MTC. Virtually all patients with MEN have RET germline mutations. In sporadic MTC somatic RET mutations are found in approximately 50% and somatic HRAS, KRAS, or rarely NRAS mutations are found in another 18 – 80 % of patients.

Early total thyroidectomy and dissection of cervical lymph node compartments, and prophylactic thyroidectomy in carriers of the RET germline mutation for MEN patients is the most important initial and potentially curative therapy of MTC. Although evidence is limited, postoperative EBRT to neck and mediastinum should be considered for patients with high risk for local recurrence. Patients whose MTC is limited to the thyroid gland have a 10-year survival approaching 100%; however, the 10-year survival rate is 75% and 40% for those with regional and distant metastatic spread, respectively.[11]

2.2 Accepted Clinical Practice

For patients with regionally recurrent metastatic disease, (repeated) surgical resection is the first option considered. For oligometastatic disease, surgical metastatectomy, vertebroplasty, thermoablation, cement injection or EBRT should be considered. Treatment with denosumab or bisphosphonates should be considered for prophylaxis and management of symptomatic skeletal metastases.

Patients with advanced disease and paraneoplastic diarrhea should be treated with antimotility agents, somatostatin analogs, surgery or chemoembolization.

Treatment with radiolabeled molecules or pre-targeted immunotherapy may be considered in selected patients, ideally in trial settings. Cytotoxic chemotherapy has been used as systemic therapy for advanced MTC with unclear evidence of benefit. Regimens have typically been dacarbazine-based. In current practice cytotoxic chemotherapy is typically considered as a “last resort” for patients with rapidly progressive disease or who are ineligible or progress on TKI treatment.[11] The VEGFR TKIs vandetanib and cabozantanib have been compared to placebo in randomized trials in advanced MTC. Both trials reported improved progression-free survival and objective response in a significant minority of patients.

2.3 Evidence-Based Considerations for a Funding Population

In the absence of specific data, it is estimated that advanced MTC requiring systemic therapy occurs in fewer than 100 individuals per year in Canada. Vandetanib should only be considered in MTC patients with symptomatic and/ or radiologically progressive unresectable locally advanced or metastatic disease. There are no standardized definitions for progressive or symptomatic MTC that are used in Canadian clinical practice. It is the opinion of the CGP that vandetanib should not be administered to patients with increasing calcitonin levels but no documented metastatic disease or to patients with stable low volume metastatic disease as determined by imaging and calcitonin or CEA doubling times greater than two years.

2.4 Other Patient Populations in Whom the Drug May Be Used

VEGFR TKIs are used to treat many cancer types. It is unlikely that vandetanib would be a choice due to its toxicity profile and lack of data in other cancer types.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Thyroid Cancer Canada (TCC) provided input on vandetanib (Caprelsa) for the treatment of symptomatic and/ or progressive medullary thyroid cancer in adult patients with unresectable locally advanced or metastatic disease, and their input is summarized below.

TCC gathered information through a national online survey posted on the Thyroid Cancer Canada website between February 29, 2016 and April 22, 2016, as well as issued a national online survey to identify patients with medullary thyroid cancer between August 12, 2016 and August 26, 2016. This survey link was also given to physicians to provide to their patients.

TCC received responses from 11 respondents to the August survey, with three responses from patients who have experience with vandetanib. TCC indicated that no demographic information was collected. TCC reported that it received responses from a total of six caregivers.

In addition to the surveys, TCC conducted one-to-one responses from telephone interviews with six respondents who have experience with vandetanib between August 13, 2016 and August 25, 2016.

From a patient's perspective, it was reported that ongoing symptoms of thyroid cancer can impact their day-to-day life. Respondents noted that symptoms include feeling tired and listless, and this can affect their emotional well-being and ability to work. Respondents reported using the following therapies to treat thyroid cancer: levothyroxine, sorafenib or other tyrosine kinase inhibitors, vandetanib, radioactive iodine treatment, surgery, chemotherapy and external beam radiation. Respondents who do not have experience with the drug under review expect that it will manage their disease progression and have fewer side effects, such as weight loss, fatigue, and pain, among others than other available treatments. Respondents who have experience with vandetanib indicated that it helped to slow their disease progression. Respondents stated that their side effects were better managed, including vomiting, weight loss, diarrhea and skin rash than with previous treatments. Respondents also reported that the skin rash experienced from other treatments had been reduced, but reported a transient case of acne. Respondents found that vandetanib was easy to use.

Please see below for a summary of specific input received from the patient advocacy group. Quotes are reproduced as they appeared in the survey and interview questions, with no modifications made for spelling, punctuation or grammar. The statistical data that were reported have also been reproduced as is according to the submission, without modification.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Medullary Thyroid Cancer

Thyroid Cancer Canada (TCC) reported that 11 respondents completed the questions about their experience with thyroid cancer. More specifically, these respondents stated the following:

- Of the aspects of thyroid cancer that were most important to control:
    - 100% of respondents said progression of disease (n=11);
    - 64% of respondents said fatigue (n=7);
    - 45% of respondents said weight gain (n=5);
    - 9% of respondents said difficulty swallowing (n=1).

- Of the ongoing symptoms that affect day-to-day life:
    - 73% of respondents said they are tired and listless (n=8);

- 64% of respondents said they are affected emotionally (n=7);
- 36% of respondents said they are limited from working (n=4);
- 27% of respondents said they have limits on participating in leisure activities (n=3); and
- 27% of respondents said their diet and eating habits are affected (n=3).

TCC noted that nine (9) patients described the limitations they experience:

- unable to be physically active (78%, 7 patients)
- unable to work (56%, 5 patients)
- unable to participate in family or leisure activities (44%, 4 patients)

One respondent interviewed over the telephone noted that living with advanced thyroid cancer is very difficult as she felt having thyroid cancer wasn't taken as seriously as other cancers. She was told when she was diagnosed at stage 4c by health care providers that at least this was "*the good type of cancer to have*".

3.1.2 Patients' Experiences with Current Therapy for Medullary Thyroid Cancer

TCC noted that eleven (11) respondents provided responses about the different therapies they have used since their diagnosis to treat thyroid cancer:

Answer Choices	Responses	
Sorafenib or other Tyrokinase inhibitor (TKI)	**27.27%**	3
Nexavar	**27.27%**	3
Caprelsa	**0.00%**	0
Radioactive Iodine Treatment	**90.91%**	10
Surgery	**100.00%**	11
Chemotherapy	**18.18%**	2
External Beam Radiation	**45.45%**	5
Total Respondents: 11		

Of note, Nexavar is the brand name of sorafenib.

Respondents also reported on the therapies they currently use to treat thyroid cancer:

- lenvatinib (n=4)
- levothyroxine (n=3)
- surveillance (n=1)

Of note, TCC indicated that five (5) respondents skipped this question.

Eleven respondents described the following adverse events experienced with any therapies used:

Answer Choices	Responses	
High blood pressure	**36.36%**	4
Diarrhea	**36.36%**	4
Elevation of proteins in the urine	**0.00%**	0
Feel like throwing up	**27.27%**	3
Head pain	**9.09%**	1
Intense abdominal pain	**0.00%**	0
Joint pain	**18.18%**	2
Loss of appetite	**36.36%**	4
Low energy	**100.00%**	11
Muscle pain	**36.36%**	4
Painful, red or swollen mouth	**9.09%**	1
Throwing up	**27.27%**	3
Tingling, pain, redness and edema of hands and feet	**18.18%**	2
Voice disorder	**36.36%**	4
Weight loss	**45.45%**	5
Total Respondents: 11		

Two respondents who were interviewed by telephone stated that radioactive iodine was a temporary fix and failed, and resulted in requiring them to be treated with systemic therapy.

One respondent noted that her experience with sorafenib was a very difficult journey, but her experience followed the predictable pathway of slowing the progression of the disease for the first 6-7 months, followed by a waning period up to 18 months, and then there was growth and disease progression. The respondent also reported that the gastrointestinal (GI) symptoms from previous treatments were the most difficult to manage.

One respondent reported that following surgery to remove her thyroid, she reported that it resulted in a permanent menopause state with no relief from the symptoms, and this impacted her quality of life. She described experiencing the following symptoms: night sweats, cold spells, headaches, and disrupted sleep as being constant.

When asked to describe how well their current therapy was seen to be controlling their thyroid cancer, nine (9) respondents reported the following:

	Excellent	Very Good	Good	Just OK	Least effective	Total
Disease progression	44.44% 4	22.22% 2	33.33% 3	0.00% 0	0.00% 0	9
Weight gain	12.50% 1	12.50% 1	12.50% 1	25.00% 2	37.50% 3	8
Fatigue	0.00% 0	22.22% 2	22.22% 2	44.44% 4	11.11% 1	9
Dry mouth	12.50% 1	25.00% 2	37.50% 3	25.00% 2	0.00% 0	8
Difficulty swallowing	0.00% 0	14.29% 1	57.14% 4	14.29% 1	14.29% 1	7
Emotional distress	14.29% 1	14.29% 1	28.57% 2	28.57% 2	14.29% 1	7

Three respondents identified financial challenges when accessing therapies to treat thyroid cancer.

3.1.3 Impact of Medullary Thyroid Cancer and Current Therapy on Caregivers

TCC reported that it received a total of six caregiver respondents.

Five (5) respondents identified the following caregiver issues:

- access to specialty physicians (40%, n=2)
- demands on personal time (40%, n=2)
- managing work and caregiving (40%, n=2)
- access to appropriate therapies (20%, n=1)

Six (6) respondents said current treatments affect caregivers in the following ways:

- frequent physician visits (83%, n=5)
- frequent and ongoing assessment for effectiveness (83%, n=5)
- therapies are expensive and affect income (17%, n=1)

Six (6) respondents identified the following challenges for caregivers in dealing with the adverse effects related to the current therapy a loved one is taking:

- fear of recurrence or disease progression (100%, n=6)
- fatigue (50%,n=3)
- managing diet due to painful or swollen mouth, or dry mouth/throat (17%, n=1)

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Vandetanib

When asked about the unmet needs with current therapies they have tried, TCC indicated that six respondents reported the following:

Answer Choices	Responses	
Disease not being managed/controlled	**16.67%**	1
Weight issues	**50.00%**	3
Fatigue greater than can be managed	**33.33%**	2
Issues with appetite	**16.67%**	1
Pain	**0.00%**	0
Other (please specify)	**33.33%**	2
Total Respondents: 6		

Of note, Thyroid Cancer Canada indicated that for the two (2) respondents who responded '*other*', the unmet need was managing bowel issues and diarrhea.

Two respondents commented that they had painful skin rashes while on other kinase inhibitors.

Thyroid Cancer Canada reported that three respondents who completed the online survey have experience with vandetanib.

Respondents indicated the positive effects of vandetanib include:

- Reduction in the progression of thyroid disease (67%)
- Reduced the effects of thyroid cancer (33%)
- Improved overall wellness (33%)
- Decreased the side effects from other treatments (67%)

Respondents indicated the negative effects of vandetanib include:

- Has not affected the progression of thyroid cancer (33%)
- Increased fatigue (33%)

Respondents reported the following symptoms that vandetanib managed better than current therapy included:

- Skin rash (67%)
- Less fatigue (33%)

Weight loss, swallowing difficulties, dry mouth were not noted as either better or worse for respondents taking vandetanib.

In terms of adverse effects with using vandetanib, respondents indicated the following:

- Skin rash (67%)
- Decreased appetite (33%)
- Diarrhea (100%)

TCC conducted interviews with six respondents who have experience with vandetanib. All six respondents expressed that their treatment have extended their lives. These respondents also commented that their physician had confirmed there was a reduction in the progression of their disease. Three respondents indicated that in addition to slowing disease progression, their side effects have been managed better, including vomiting, weight loss, diarrhea and skin rash that they had on previous treatments.

Respondents also reported that the skin rash experienced from other treatments had been reduced, but reported a transient case of acne. Respondents noted that while they experienced diarrhea, but it was milder than the previous treatments.

All six respondents found that vandetanib was easy to use. One respondent noted that she had multiple surgeries, radiation and chemo treatments in the "past 8 years" and since she has started with vandetanib two years ago, it has given her and her family (she has two young children) "*hope for an extended life*".

3.3 Additional Information

None provided.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from the provinces (Ministries of Health and/or cancer agencies) and federal drug plans participating in pCODR. PAG identified the following as factors that could impact the implementation of vandetanib:

Clinical factors:

- Fills a gap in therapy
- Serious cardiovascular adverse events

Economic factors:

- Controlled distribution program limits prescribing and dispensing to registered physicians and pharmacists
- Additional healthcare resources required to regularly monitor for cardiotoxicities

Please see below for more details.

4.1 Factors Related to Comparators

PAG noted that best supportive care or palliative chemotherapy with doxorubicin in some provinces is available. Although vandetanib has been available in Canada for a number of years, PAG noted that vandetanib is not currently a publicly funded treatment option but vandetanib is available to patients with third party drug coverage.

4.2 Factors Related to Patient Population

PAG indicated that vandetanib fills a gap in therapy for the very small number of patients with symptomatic or progressive medullary thyroid cancer.

PAG identified that vandetanib could potentially be used in patients with indolent, asymptomatic or slowly progressive disease. However, given the potential serious toxicities associated vandetanib, PAG noted that use of vandetanib would be limited to patients with symptomatic or progressive disease.

4.3 Factors Related to Dosing

PAG noted that the drug's continuous once daily dosing schedule, the flat dose of 300 mg and one tablet per dose would be enablers to implementation.

PAG noted there are two tablet strengths available to accommodate for dose reductions. There are some concerns with drug wastage if dose reductions require change in tablet strength prior to the previously dispensed strength being all used, However, drug wastage may be limited due to the restricted distribution program.

4.4 Factors Related to Implementation Costs

Vandetanib has black box warnings for QT interval prolongation, heart failure, grade 4 hypertension and hypertensive crisis. PAG noted that additional health care resources are required for regular ECG monitoring and consultations with cardiologists to monitor for serious cardiac toxicities.

4.5 Factors Related to Health System

PAG noted that vandetanib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home and chemotherapy chair time is not required. PAG identified the oral route of administration as an enabler to implementation.

However, PAG noted that only prescribers and pharmacies certified with the restricted distribution program are able to prescribe and dispense vandetanib. PAG has concerns on the significant time and logistical coordination required for the healthcare providers to register in the controlled distribution program and patients may be limited to certain centres to access treatment.

4.6 Factors Related to Manufacturer

PAG indicated that the non-linear pricing of the 100mg and 300mg tablets is a barrier to implementation.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One registered clinician provided input on vandetanib for medullary thyroid cancer and the input is summarized below.

Vandetanib would fill a gap in therapy for the very small number of patients with medullary thyroid cancer. Key benefits identified are the increase in progression free survival, high objective response rate and high disease control rate. The harms identified are the side effects associated with vandetanib, which are manageable, and the contraindications for patients with prolonged QT interval or on other medications that prolongs QT interval.

Please see below for a summary of specific input received from the registered clinician.

5.1 Current Treatment(s) for this Type of Cancer

There is no standard medical treatment available for medullary thyroid cancer in Alberta.

5.2 Eligible Patient Population

The clinician providing input estimated that there would be one to six patients in Alberta with thyroid cancer.

5.3 Identify Key Benefits and Harms with New Drug Under Review

The clinician providing input identified that the benefits of vandetanib include the increase in progression free survival, an objective response rate of 45% and a disease control rate of 87%. These are significant clinical benefits for patients with metastatic or otherwise untreatable locally progressive disease.

The clinician providing input identified that the harms would be the side effects associated with vandetanib (diarrhea, rash, nausea hypertension, headache and prolongation of the QT interval), which can be managed with dose reductions or other pharmacotherapy.

The clinician providing input noted that the only patients who should not receive this drug are ones with prolonged QT interval or who are taking another medication that would also prolong QT interval.

5.4 Advantages of New Drug Under Review Over Current Treatments

The clinician providing input indicated that vandetanib is superior as there is no other available proven therapy. Vandetanib fulfills an unmet need of an effective therapy for metastatic or locally progressive medullary thyroid cancer.

5.5 Sequencing and Priority of Treatments with New Drug Under Review

The clinician providing input indicated that vandetanib is first line therapy as there is no other available agent.

5.6 Companion Diagnostic Testing

No companion diagnostic test is required for the use of vandetanib.

However, the clinician providing input noted metastatic or progressive disease is confirmed by CT, PET/CT or ultrasound scans and the only additional testing needed is EKG to assess QT interval.

5.7 Additional Information

None.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of vandetanib, as monotherapy, on patient outcomes compared to standard therapies, placebo, or best supportive care in the treatment of patients with unresectable, locally advanced or metastatic hereditary or sporadic medullary thyroid cancer (MTC).

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 4: Selection Criteria for the Systematic Review

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators[a,b]	Outcomes
Published and unpublished RCTs	Adults with unresectable, locally advanced or metastatic hereditary or sporadic MTC **Subgroups** • Locally advanced vs. metastatic • Progressive vs. indolent • Symptomatic vs. asymptomatic • WHO PS (≤1 vs. ≥2) • RET mutation (positive versus negative or unknown) • Calcitonin doubling time	Vandetanib monotherapy	• Placebo • Cabozantinib[c]	• **Overall Survival** • **Progression-free survival** • Objective response rate • Quality of life • Disease control rate • Duration of response • Calcitonin • CEA • Time to worsening of pain • Dose adjustments • Adverse events • Serious adverse events • WDAEs • Adverse events of special interest: ▪ QT prolongation ▪ Diarrhea ▪ Hypertension
Abbreviations: CEA = carcinoembryonic antigen; MTC = medullary thyroid cancer; RCT = randomized controlled trial; WHO PS = World Health Organization Performance Status; WDAEs = withdrawals due to adverse events				

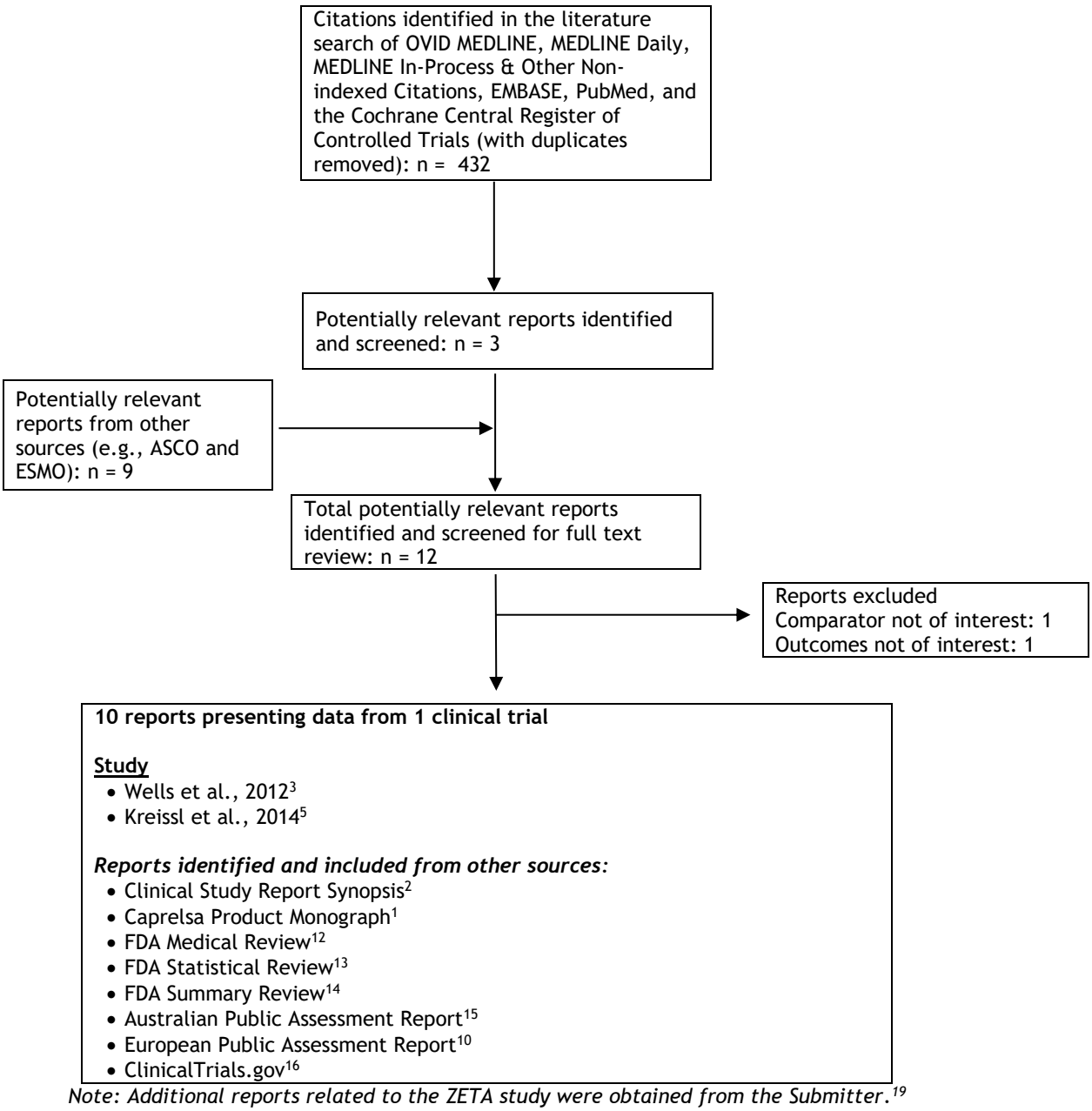
[a] All treatments in combination with supportive care.
[b] Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions).
[c] Identified as agent of interest although not currently available in Canada.

6.3 Results

6.3.1 Literature Search Results

Of the 12 potentially relevant reports identified, one study (ZETA) reported in 10 citations was included in the pCODR systematic review.[1-3,5,10,12-16] Two studies were excluded because they lacked a comparator of interest[17] or an outcome of interest.[18] Additional reports related to the ZETA study were obtained from the Submitter.[19]

Figure 1: QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional reports related to the ZETA study were obtained from the Submitter.[19]

6.3.2 Summary of Included Studies

The pCODR systematic review included one phase 3, double-blind, randomized, placebo-controlled trial that investigated the safety and efficacy of vandetanib in the treatment of patients with unresectable locally advanced or metastatic MTC (ZETA; N = 331).

Table 5: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Outcomes
ZETA **Other identifiers:** • D4200C00058 • NCT00410761 **Characteristics:** Phase 3, double-blind, placebo-controlled RCT **Sample size:** Randomized: 331 Treated: 330 **Locations:** 63 sites in 23 countries (North America [including Canada], Europe, Asia, Australia) **Start date:** 11/2006 **Data cut-off:** 07/2009 **Sponsor:** Astra-Zeneca	**Key Inclusion Criteria:** • Adults (≥ 18 years) • Unresectable, locally advanced or metastatic hereditary or sporadic MTC • ≥1 measurable lesion • WHO PS 0 to 2 • Life expectancy ≥12 weeks **Key Exclusion Criteria:** • Brain metastases[a] • Spinal cord compression[a] • Any of the following within 4 weeks of randomization: major surgery; radiation therapy[b]; chemotherapy • Medications that affect QTc or induce CYP3A4[c] • Any of the following CV conditions: uncontrolled hypertension; arrhythmia (symptomatic or requiring treatment); AF (symptomatic or uncontrolled); ventricular tachycardia (asymptomatic, sustained); congenital long QT syndrome; LBBB; QTc unmeasurable or ≥480 ms • Any of the following within 12 weeks of randomization: significant cardiac event; superior vena cava syndrome; NYHA heart disease ≥2 • Any of the following laboratory measurements: bilirubin >1.5 x ULRR; CrCl <30 mL/min; potassium <4.0 mmol/L; ALT, AST, ALP >2.5 or >5.0[d] × ULRR; magnesium or calcium above CTCAE grade 1 limit	• Vandetanib 300 mg QD (100 mg QD or 200 mg QD reduced dose) • Placebo	**Primary:** • Progression-free survival **Secondary:** • Overall survival • Objective response rate • Disease control rate • Duration of response • Calcitonin • CEA • Time to worsening of pain • FACT-G

Abbreviations: AF = atrial fibrillation; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; CEA = carcinoembryonic antigen; CrCl = creatinine clearance; CTCAE = Common Terminology Criteria for Adverse Events; CV = cardiovascular; FACT-G = Functional Assessment of Cancer Therapy − General; LBBB = left bundle branch block; MTC = medullary thyroid cancer; NYHA = New York Heart Association; QD = once daily; RCT = randomized controlled trial; ULRR = upper limit of reference range; WHO PS = World Health Organization Performance Status

[a] Permitted if treated ≥4 weeks before the first dose and stable without steroid treatment for ≥10 days.
[b] Palliative radiation was permitted.
[c] Somatostatin and somatostatin analogs were permitted.
[d] If judged by the investigator to be related to liver metastases

Table 6: Select Quality Characteristics of Included Studies of Vandetanib in Patients with MTC

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
ZETA	Vandetanib versus matching placebo	PFS	232 (based on 90 progression events)	331	IVRS	Yes	DB	Yes	Yes	No[a]	Yes
Abbreviations: DB = double-blind; ITT = intention to treat; IVRS = interactive voice response service; PFS = progression-free survival											

[a] The protocol for the ZETA trial was amended following the primary analysis of PFS to allow all study investigators to unblind patients who were still receiving the blinded, randomized study treatments. Following unblinding, all patients would be eligible to initiate therapy with open-label vandetanib.[2]

6.3.2.1 Detailed Trial Characteristics

a) Trials

The pCODR systematic review included one phase 3, double-blind, randomized, placebo-controlled trial that investigated the safety and efficacy of vandetanib in the treatment of patients with unresectable locally advanced or metastatic MTC (ZETA; N = 331). Eligible patients were randomized (2:1) to receive treatment with vandetanib 300 mg once daily or matching placebo. Patients were to continue receiving blinded treatment until they met the criteria for disease progression or other withdrawal criteria. Patients who demonstrated disease progression (investigator-determined) were discontinued from the blinded study treatments and were given the option of initiating open-label treatment with vandetanib or entering the follow-up period for evaluating survival status.

Adult men and women with unresectable, locally advanced or metastatic hereditary or sporadic MTC were eligible to be enrolled in ZETA if they had at least one measurable lesion, a WHO performance status between 0 and 2, and life expectancy of at least 12 weeks. As shown in Table 5, patients were to be excluded if they had cardiovascular conditions, such as uncontrolled hypertension, symptomatic arrhythmia, symptomatic or uncontrolled atrial fibrillation, ventricular tachycardia, congenital long QT syndrome, left bundle branch block, or a QTc that was unmeasurable or ≥480 ms.

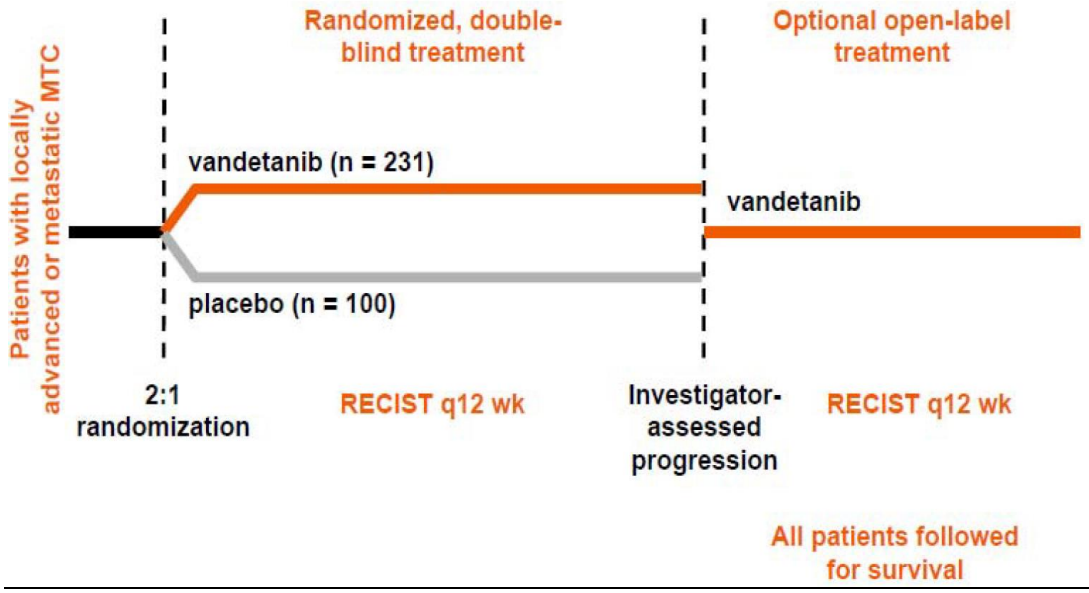
Patients with a range of abnormal laboratory measurements were also excluded, including serum bilirubin greater than 1.5 x the upper limit of the reference range (ULRR); creatinine clearance less than 30 mL/min; serum potassium less than 4.0 mmol/L, and serum magnesium or calcium that exceeded the CTCAE grade 1 limit. Patients were also excluded if they demonstrated elevated liver enzymes (i.e., alanine aminotransferase, alkaline phosphatase, or aspartate aminotransferase) that were 2.5 times greater than the ULRR or greater than 5.0 times the ULRR if the investigator judged the elevation to be related to liver metastases.

Progression-free survival (PFS) was the primary endpoint. The protocol specified that 90 progression events would be required to detect a doubling of PFS in all patients at a two-sided level of significance of 0.05 with 80% power.[2] Disease progression was evaluated using RECIST 1.0 criteria[20] with the following modifications:[4,12]

- Study investigators were to retrospectively evaluate whether or not a hypodense or hypointense lesion observed in the liver within the first two follow-up assessments was present at baseline. If so, these lesions were not be used as evidence of disease progression.
- Growth in calcified portions of metastases did not represent disease progression.

The trial was conducted at 63 sites in 23 countries (Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, France, Germany, Hungary, India, Italy, Korea, Netherlands, Poland, Portugal, Romania, Russia, Serbia, Spain, Sweden, Switzerland, and the United States). There were twelve patients enrolled at Canadian sites.[13]

Figure 2: Schematic of the ZETA study



Abbreviations: MTC = medullary thyroid cancer; q12w = every 12 weeks
Source: Reproduced from Caprelsa Product Monograph[1]

b) Populations

Baseline demographic and disease characteristics for ZETA are summarized in Table 7. There were more males than females enrolled in the study (57.4% versus 42.6%), the mean age of the study participants was 51.5 years, and nearly all patients were white (95.2%). Nearly all patients had stage IVc disease at baseline (94.6%) and M1 metastases (94.9%). The FDA reported that there were no imbalances in the distribution of the metastatic sites, with the liver (65.9%), lymph nodes (61.3%), and respiratory system (56.2%) as the most common locations.[13] The majority of patients had undergone thyroidectomy (90.3%) and lymphadenectomy (75.8%) at the time of enrolment. As shown in Table 7, patients had undergone a range of systemic therapies, with radiation (51.3%) and cytotoxic (20.5%) being the most commonly reported.

For patients whose RET mutation status was identified, the majority were positive for the mutation (56.5%). The RET mutation status for a large proportion of the study population was reported as unknown (41.1%). This failure of the assay to characterize the RET mutation status of so many patients triggered a protocol amendment, where PFS in patients who were positive for the RET mutation was removed as a co-primary endpoint of the ZETA trial.[13]

The baseline characteristics were well balanced with the exception of the proportion of patients with a WHO performance status of 0 (67% and 58% in the vandetanib and placebo groups, respectively), the proportion of patients with hereditary MTC (12.1% and 5.0% in the vandetanib and placebo groups, respectively), and the mean age of participants was lower in the vandetanib group compared with the placebo group (50.7 versus 53.4 years, respectively). Compared with placebo, the vandetanib group was composed of a greater proportion of those between 18 and 39 years of age (21.6% versus 10.0%) and a lower proportion of those between the ages of 40 and 65 years (57.1% versus 70.0%). Reviewers for the EMA noted that the difference between the vandetanib and placebo groups in the proportion of patients who were under 40 years of age was statistically significant.[10] As noted in section 6.3.2.2, sensitivity analyses were conducted to investigate the potential impact of these imbalances on the efficacy results of the study and the results were consistent with the primary analysis.

The EMA reported that, based on a post-hoc assessment by the manufacturer, nearly all (95%, n=313) of the patients enrolled in the ZETA trial had MTC that was either progressive or symptomatic at baseline; 12 (3.6%) were without progression or symptoms; and 6 (1.8%) were without symptoms but with unknown progression status.[10] Symptomatic and progressive disease were defined in a post-hoc manner using the following baseline criteria:[5]

- Symptomatic disease — at least one of the following: a pain score of at least four, opioid use of at least 10 mg per day, diarrhea, flushing, fatigue, pain, nausea, dysphagia, dysphonia, respiratory symptoms, or weight loss.
- Progressive disease — documented disease progression within the 12 months prior to enrolment in the ZETA trial.

Table 7: Baseline and demographic characteristics

Characteristics		Vandetanib (N = 231)	Placebo (N = 99)	Total (N = 330)
Age (years)	Mean (SD)	50.7 (14.1)	53.4 (12.0)	51.5 (13.6)
	≥18 to <40	50 (21.6)	10 (10.0)	60 (18.1)
	≥40 to <65	132 (57.1)	70 (70.0)	202 (61.0)
	≥65 to <75	42 (18.2)	17 (17.0)	59 (17.8)
	≥75	7 (3.0)	3 (3.0)	10 (3.0)
Gender, n (%)	Male	134 (58.0)	56 (56.0)	190 (57.4)
	Female	97 (42.0)	44 (44.0)	141 (42.6)
Race, n (%)	Asian	8 (3.5)	1 (1.0)	9 (2.7)
	Black	1 (0.4)	1 (1.0)	2 (0.6)
	White	218 (94.4)	97 (97.0)	315 (95.2)
	Other	4 (1.7)	1 (1.0)	5 (1.5)
WHO Performance Status, n (%)	0	154 (67.0)	58 (58.0)	212 (64.0)
	1	67 (29.0)	38 (38.0)	105 (32.0)
	2	10 (4.0)	4 (4.0)	14 (4.0)
MTC [b]	Symptomatic and progressive	126 (55)	60 (60)	186 (56)
	Symptomatic only	NA	NA	NA
	Progressive only	NA	NA	NA
	Neither symptomatic, nor progressive disease	NA	NA	NA
	Other	NA	NA	NA
Primary tumour, n (%)	5 (2.2)	1 (1.0)	6 (1.8)	6 (1.8)
	T2	3 (1.3)	0 (0.0)	3 (0.9)

Characteristics		Vandetanib (N = 231)	Placebo (N = 99)	Total (N = 330)
	T3	2 (0.8)	5 (5.0)	7 (2.1)
	T4a	8 (3.5)	5 (5.0)	13 (3.9)
	T4b	6 (2.6)	1 (1.0)	7 (2.1)
	Tx	207 (89.6)	88 (88.0)	295 (89.1)
Lymph nodes, n (%)	N0	29 (12.5)	13 (13.0)	42 (12.7)
	N1a	26 (11.3)	10 (10.0)	36 (10.9)
	N1b	132 (57.1)	59 (59.0)	191 (57.7)
	N2	4 (1.7)	3 (3.0)	7 (2.1)
	N3	0 (0.0)	1 (1.0)	1 (0.3)
	Nx	40 (17.3)	14 (14.0)	54 (16.3)
Metastasis, n (%)	M0	14 (6.1)	3 (3.0)	17 (5.1)
	M1	216 (93.5)	97 (97.0)	314 (94.9)
	MX	1 (0.4)	0 (0.0)	1 (0.3)
Stage, n (%)	Stage III	1 (0.4)	2 (2.0)	3 (0.9)
	Stage Iva	8 (3.5)	0 (0.0)	8 (2.4)
	Stage IVb	6 (2.6)	1 (1.0)	7 (2.1)
	Stage IVc	216 (93.5)	97 (97.0)	313 (94.6)
Prior therapy, n (%)	Thyroidectomy	207 (89.6)	92 (92.0)	299 (90.3)
	Lymphadenectomy	171 (74.0)	80 (80.0)	251 (75.8)
Prior systemic therapy, n (%)	Cytotoxic	50 (21.6)	18 (18.0)	68 (20.5)
	Targeted	22 (9.5)	11 (11)	33 (10.0)
	Radioimmune	10 (4.3)	7 (7.0)	17 (5.1)
	Radioisotope	25 (11.0)	9 (9.0)	34 (10.3)
	Prior radiation	117 (51.0)	53 (53.0)	170 (51.3)
Diagnosis to enrollment (years)	Median (SE)	6.0 (0.4)	6.0 (0.7)	6.0 (0.4)
Time from last progression (months)	Median (SE)	2.43 (0.92)	1.96 (1.18)	2.14 (0.73)
	<6 months, n (%)	157 (69)	72 (73)	229 (70)
	>6 months, n (%)	70 (31)	26 (27)	96 (30)
Sum of lesions (cm)	Median (SE)	12.1 (0.61)	11.1 (1.0)	11.4 (0.53)
CTN (ng/L)	Median (SE)	9620 (5361)	11696 (8358)	10242 (4509)
	Mean (SD)	29011 (80958)	35154 (82739)	30858 (81419)
CEA µg/L	Median (SE)	137 (248)	194 (85)	153 (176)
	Mean (SD)	860 (3749)	523 (842)	759 (3171)
Genetic composition, n (%)	RET positive	137 (59.3)	50 (50.0)	187 (56.5)
	RET negative	2 (0.9)	6 (6.0)	8 (2.4)
	RET unknown	92 (39.8)	44 (44.0)	136 (41.1)
	Hereditary MTC	28 (12.1)	5 (5.0)	33 (10.0) [a]
Associated endocrinopathy, n (%)	MEN 2a	14 (6.0)	3 (3.0)	17 (5.1)
	MEN 2b	7 (3.0)	0 (0.0)	7 (2.1)
	Familial MTC	4 (1.7)	1 (1.0)	5 (1.5)
	Family history of MTC	12 (5.2)	4 (4.0)	16 (4.8)

Abbreviations: CEA = carcinoembryonic antigen; CTN = calcitonin; MEN = multiple endocrine neoplasia; MTC = medullary thyroid cancer; N = number of patients included in the analysis; RET = RET mutation; SD = standard deviation; SE = standard error

Source: FDA Medical Review,[12] European Public Assessment Report,[10] Wells et al., 2012.[3]

[a] The reported value from the published source has been corrected due to an error in reporting.

[b] Submitter was not able to provide the sample sizes.

c) Interventions

During the blinded phase of the study, patients were randomized to either vandetanib 300 mg once per day or matching placebo. Patients were to continue receiving blinded treatment until they met the criteria for disease progression or other withdrawal criteria. Patients who demonstrated disease progression (investigator-determined) were discontinued from the blinded study treatments and were given the option of initiating open-label treatment with vandetanib or entering the follow-up period for evaluating survival status.

Dose reductions and interruptions were permitted during the trial as a result of adverse events. The study protocol specified that dose interruption was required for all grade 3 to 4 toxicities until the event has resolved to baseline or CTCAE grade 1. CTCAE grade 3 hypertension was the exception as patients were permitted to continue on the study treatment provided their blood pressure was controlled following an increase in the patient's anti-hypertensive medication.

As shown in Table 8, both dose reductions and interruptions occurred more frequently in the vandetanib group compared with the placebo group. Of the patients who were randomized to receive 300 mg vandetanib (n = 231), 35.1% had the dosage reduced to 200 mg once per day, 13.9% had the dosage reduced to 100 mg once per day, and one patient (0.4%) received a dosage of 200 mg every other day. Dose interruptions were reported for 47% of patients in the vandetanib group and 15% of patients in the placebo group. The median duration of interruption was 19 days (range: 1 to 101 days) in the vandetanib group and nine days (range: 2 to 30 days) in the placebo group.

Patients could be switched to open-label vandetanib based on disease progression as determined by the study investigators (as opposed to the central independent readers). This created situations where patients in both the vandetanib (10%) and placebo groups (28%) received open-label vandetanib prior to progression being documented by independent central review (ICR).[3]

Table 8: Dose Adjustments and Interruptions

Reduction or Interruption	Events	Vandetanib (N = 231)	Placebo (N = 99)
Dose reduction 200 mg QD	Total	81 (35.1)	3 (3.0)
	AE < grade 3	19 (8.2)	1 (1.0)
	AE ≥ grade 3	19 (8.2)	0 (0.0)
	Diarrhoea < grade 3	5 (2.2)	0 (0.0)
	Diarrhoea ≥ grade 3	5 (2.2)	1 (1.0)
	QTc Prolongation	16 (6.9)	0 (0.0)
	Rash < grade 3	9 (3.9)	0 (0.0)
	Rash ≥ grade 3	6 (2.6)	0 (0.0)
	Other	9 (3.9)	1 (1.0)
Dose reduction 200 mg EOD	Total	1 (0.4)	0 (0.0)
	AE ≥ grade 3	1 (0.4)	0 (0.0)
Dose reduction 100 mg QD	Total	32 (13.9)	0 (0.0)
	AE < grade 3	9 (3.9)	0 (0.0)
	AE ≥ grade 3	6 (2.6)	0 (0.0)
	Diarrhoea < grade 3	1 (0.4)	0 (0.0)
	Diarrhoea ≥ grade 3	4 (1.7)	0 (0.0)
	QTc Prolongation	8 (3.5)	0 (0.0)
	Rash < grade 3	3 (1.3)	0 (0.0)
	Rash ≥ grade 3	2 (0.9)	0 (0.0)
	Other	2 (0.9)	0 (0.0)

Reduction or Interruption	Events	Vandetanib (N = 231)	Placebo (N = 99)
Dose interruptions	Total	109 (47.2)	15 (15.2)
	AE < grade 3	33 (14.3)	7 (7.1)
	AE ≥ grade 3	46 (19.9)	4 (4.0)
	Diarrhoea <grade 3	7 (3.0)	2 (2.0)
	Diarrhoea ≥ grade 3	10 (4.3)	1 (1.0)
	Non-compliance	2 (0.9)	0 (0.0)
	QTc Prolongation	19 (8.2)	0 (0.0)
	Rash < grade 3	3 (1.3)	0 (0.0)
	Rash ≥ grade 3	12 (5.2)	0 (0.0)
	Other	9 (3.9)	4 (4.0)
	Duration (median days [range])	19 (1 to 101)	9 (2 to 30)

Abbreviations: AE = adverse event; EOD = every other day; QD = once daily

Source: Data Reproduced from European Public Assessment Report[10]

d) Outcomes

Primary endpoint

Progression-free survival was the primary endpoint of the ZETA trial. Progression events were based on objective assessment by central independent readers and the analysis was planned for when at least 90 progression events had been observed in the full analysis data set. Given the delay between the evaluation by the study investigators and the central independent readers, the submitter reported that 124 progression events had actually occurred at the time of the data-cut (14 deaths and 110 patients with objective progression by the ICR).[2] The primary analysis was performed using an unadjusted log-rank test and included all available PFS events confirmed by the ICR, including those which occurred after the initiation of open-label treatment with vandetanib (as applicable).

The ZETA study was initially designed to have two co-primary endpoints: 1) PFS in the full study population; 2) PFS in the subpopulation of patients who had RET mutation(s).[13] However, due to the failure of the assay to establish the mutation status in 41% of the enrolled patients, the analysis of patients with a RET mutation was removed as a co-primary endpoint in protocol amendment 5 (implemented in May 2009).[13]

Secondary endpoints

Overall survival was a secondary endpoint and was defined as the time from randomization to death from any cause. There were two planned analyses of overall survival in the ZETA trial: an initial analysis at the time when the other efficacy variables were analyses (i.e., July 2009) and a final analysis when ≥50% of the patients had died (i.e., September 2015). The submitter reported that the significance level for the initial analysis was 0.02% and presented the corresponding 99.98% confidence intervals (CIs). The planned significance level for the secondary analysis of overall survival was 4.98% with corresponding 95.02% CIs.[4]

Objective response rate (ORR) was defined as the proportion of patients who were classified with an ICR-confirmed best objective response (BOR) of complete response (CR) or partial response (PR). The BOR was established using one the following three scenarios (as applicable):

- For patients with ICR-confirmed progression during randomized treatment, the BOR would be determined using RECIST using data up to the point of progression.
- For patients who initiated open-label treatment with vandetanib, but without ICR-confirmed progression during randomized treatment, the BOR would be determined using

any available RECIST scans up to the point of progression (regardless of whether the scan occurred during double-blind or open-label treatment).
- For patients without ICR-confirmed progression, the BOR was determined using data up to the patient's last evaluable RECIST evaluation.[4]

Disease control rate (DCR) was defined as the proportion of patients who were classified as having an ICR-confirmed BOR of CR or PR, or stable disease (SD) for at least 24 weeks. The submitter noted that all centrally reviewed RECIST evaluations were considered in the DCR calculation (regardless of whether or not the patient was receiving double-blind or open-label treatment). The analysis of DCR was performed using logistic regression with treatment as the covariate.[4]

Pain was evaluated using patient-reported opioid use and responses to the Brief Pain Inventory (BPI) questionnaire. The submitter defined worsening of pain as change from baseline of ≥2 on the BPI worst pain scale (range: 0 [no pain] to 10 [worst pain]) or an increase from baseline in opioid use of ≥ 10 mg per day of morphine equivalent.[3] The BPI was administered at baseline and then every week thereafter. Time to worsening of pain was calculated as the interval from randomization to the date the patient demonstrates worsening of pain (with no evidence of improvement within 14 days).[3]

Calcitonin and CEA were measured at baseline, weeks 4, 8, and 12, and then after 12 weeks. Changes in calcitonin and CEA were analyzed according the participant's best response, which were defined as follows:[3]
- Complete response (normalization of serum levels)
- Partial response (50% decrease from baseline maintained over ≥4 weeks)
- Stable disease (between a 50% increase and 50% decrease from baseline levels maintained for at least 4 weeks)
- Progressive disease (50% increase from baseline maintained for ≥4 weeks).

Health-related quality of life was assessed using the patient-reported Functional Assessment of Cancer Therapy - General (FACT-G) questionnaire. Patients were asked to complete the FACT-G questionnaire at baseline and every 12 weeks until discontinuation of the randomized study treatment. At each assessment, the manufacturer calculated the total FACT-G score, as well as scores for the following subscales: physical well-being, social well-being, emotional well-being, and functional well-being.[4] FACT-G was an exploratory endpoint and no statistical analyses were performed.

e) Patient Disposition

Patient disposition for the ZETA trial is summarized in Table 9. A total of 437 patients were enrolled and 331 were randomized 2:1 to receive vandetanib (n = 231) or placebo (n = 100). All but one of the randomized patients received at least one dose of the study treatments. A greater proportion of patients in the placebo group (71.0%) discontinued the double-blind study treatment compared with the vandetanib group (51.9%). The FDA reported that disease progression was the most commonly reported reason for discontinuation of double-blind treatment in both the vandetanib (30.7%) and placebo groups (55.0%).[12] Discontinuations due to adverse events were more commonly reported in the vandetanib group compared with the placebo group (10% versus 3%).[21] At the time of the data cut-off, the proportion of patients remaining on double-blind treatment was 48.1% and 28.0% in the vandetanib and placebo groups, respectively. Cross-over to open-label treatment with vandetanib was more common in placebo group (58.0%) compared with the vandetanib group (19.0%). Deaths were reported for 13.9% of patients in the vandetanib group (21 during double-blind treatment and 11 during open-label treatment) and 16.0% of patients in the placebo group (7 during double-blind treatment and 8 during open-label treatment).

Table 9: Summary of Patient Disposition

Disposition, n (%)	Vandetanib (N = 231)	Placebo (N = 99)
Enrolled	437	
Randomized	231	100
Treated	231 (100.0)	99 (99.0)
Continuing treatment	111 (48.1)	28 (28.0)
Discontinued DB treatment	120 (51.9)	71 (71.0)
No OL treatment received	76 (32.9)	13 (13.0)
Continuing follow-up for OS	37 (16.0)	2 (2.0)
Withdrawn from study	39 (16.9)	11 (11.0)
Died	21 (9.1)	7 (7.0)
Lost to follow-up	0 (0.0)	0 (0.0)
Safety reasons	1 (0.4)	0 (0.0)
Voluntary discontinuation	15 (6.5)	3 (3.0)
Noncompliance	2 (0.9)	1 (1.0)
Received OL vandetanib treatment	44 (19.0)	58 (58.0)
Continuing OL treatment	17 (7.4)	42 (42.0)
Discontinued OL treatment	27 (11.7)	16 (16.0)
Continuing follow-up for OS	10 (4.3)	6 (6.0)
Withdrawn from study	17 (7.4)	10 (10.0)
Died	11 (4.8)	8 (8.0)
Lost to follow-up	1 (0.4)	0 (0.0)
Safety reasons	1 (0.4)	0 (0.0)
Voluntary discontinuation	3 (1.3)	1 (1.0)
Noncompliance	0 (0.0)	1 (1.0)
Other	1 (0.4)	0 (0.0)

Abbreviations: DB = double-blind; OL = open-label; OS = overall survival

Sources: FDA Medical Review[12] and Wells et al., 2012[3]

f) Limitations/Sources of Bias

Internal validity

Randomization was conducted using appropriate methods with adequate measures to conceal treatment allocation (i.e., interactive voice response system [IVRS]). Patients enrolled in ZETA were to be randomized in a 2:1 ratio to receive active or placebo treatment. As shown in the sample size for the groups (i.e., 231 and 100 patients in the vandetanib and placebo groups, respectively) the ratio was greater than 2:1 (approximately 2.3:1). The submitter indicated that this occurred because randomization was stratified according to site in blocks of three and some sites did not fill all three blocks.

As noted in section 6.3.2.1(b), there were imbalances between the vandetanib and placebo groups with respect to the proportion of patients with a WHO performance status of 0, the proportion of patients with hereditary MTC, and the age distribution of patients at baseline. Regulatory agencies noted that these three characteristics may be correlated with one another (i.e., hereditary disease often has a younger age of onset and a younger patient population may demonstrate a better performance status compared with an older population). The primary efficacy analysis was unadjusted for co-variates; however, sensitivity analyses were conducted by the FDA to adjust for differences in performance status and hereditary MTC; the results were similar to the primary analysis of PFS.[12]

Vandetanib and placebo were administered in a double-blind manner using matching active and placebo tablets. However, patients in both treatment groups could initiate open-label treatment with vandetanib if they demonstrated disease progression based on the interpretation of the study investigators. Since the primary endpoint (PFS) and some of the secondary endpoints (i.e., ORR, DCR, and DOR) were evaluated by the study's ICR as opposed to the study investigators, 51 patients (23 with vandetanib and 28 with placebo) received open-label treatment prior to demonstrating ICR-confirmed disease progression. Providing the active treatment to those who were randomized to receive placebo could bias the efficacy results against vandetanib for the analyses conducted using the FAS.

Treatment with vandetanib was associated with an increase in adverse events compared with placebo, particularly skin and subcutaneous tissue disorders (90.0% versus 30.3%) and QTc prolongation (14.3% versus 1.0%). It is possible that some patients and investigators could have surmised that the allocated treatment was vandetanib, given that these events were known to be associated with the drug (based on data from earlier clinical studies). As noted by the FDA statistical reviewers,[13] the potential unblinding of trial participants as a result of the adverse profile limits the ability to interpret the patient-reported endpoints that were evaluated in ZETA. FDA reviewers noted that investigators may have had access to the results for carcinoembryonic antigen and calcitonin, which may have further compromised blinding. In response to an inquiry from CADTH, the manufacturer has stated that the study investigators did not have access to those laboratory measurements during the study.

Reviewers for the FDA indicated that PFS was considered to be an appropriate primary endpoint, noting that it would be challenging to conduct a trial with overall survival as the primary endpoint for MTC patients.[12] The primary efficacy endpoint (i.e., PFS) was evaluated by an ICR.[3] As noted in FDA guidance documentation for the evaluation of clinical trial endpoints for oncology drugs, the use of an ICR is an accepted strategy to reduce potential bias in the interpretation of the radiographic data.[22] RECIST scans were scheduled every 12 weeks for patients enrolled in the ZETA trial. The submitter reported that the time period between scans was similar for both the vandetanib and placebo treatment groups. In addition, a sensitivity analysis was performed using a grouped survival model that assumed progression occurred at the time of scheduled follow-up as opposed to the actual time the observation was recorded. The CGP indicated that timing of RECIST scans were reflective of routine clinical practice for patients with progressive MTC.

There was no adjustment for multiplicity in the analyses of the secondary endpoints; therefore, there is an inflated risk of type I error (i.e., a false positive) with the statistical evaluation of those endpoints. Data for overall survival were immature at the initial data cut-off (i.e., July 31, 2009). The analysis plan for the evaluation of overall survival indicated that the initial assessment at the July 31, 2009 data cut-off would have a significance level of 0.02% (with corresponding 99.98% confidence intervals) and the subsequent analysis would have a significance level of 4.98% (with corresponding 95.02% CIs). Therefore, the hazard ratio and 95% confidence interval reported in the publication by Wells et al (2012) is not reflective of the pre-planned analysis of overall survival.[3]

Since the study protocol permitted patients with documented disease progression to receive open-label treatment with vandetanib, the overall survival endpoint could be biased against vandetanib, as a majority of those in the placebo group (58.0%) received active treatment. The proportion of patients who were receiving open-label treatment with vandetanib at the time of the final analysis of overall survival was not reported. The protocol for the ZETA trial was amended following the primary analysis of PFS to allow all study investigators to unblind patients who were still receiving the blinded, randomized study treatments. Following unblinding, all patients would be eligible to initiate therapy with open-label vandetanib.[2]

The impact of vandetanib on the health-related quality of life for patients with advanced MTC could not be comprehensive evaluated in the ZETA trial, as the FACT-G assessments were limited to an exploratory endpoint with no statistical testing performed. Due to the low rate of compliance (77%), Health Canada stated that no conclusions could be made from the ZETA trial regarding an association between PFS and quality of life.[23]

The submitter's requested reimbursement criteria for vandetanib is for the treatment of symptomatic and/ or progressive MTC in adult patients with unresectable locally advanced or metastatic disease. The ZETA trial enrolled patients with unresectable locally advanced or metastatic disease MTC; however, the enrolment was not limited to patients with symptomatic or progressive disease. Subgroup analyses for patients with symptomatic or progressive disease were not pre-specified in the analysis plan, and there were differences between the clinical criteria used by the manufacturer and those used by the FDA. Baseline characteristics were not reported for the subgroup analyses and randomization was not stratified according the specific criteria used to defined progressive and/or symptomatic disease; therefore, it is unclear if the treatment groups were well balanced.

The primary limitation with the subgroup analyses is that they were conducted in a post hoc manner (i.e., they were not among the subgroup analyses which were pre-specfied in the manufacturer's statistical analysis plan). Although the criteria used in the Kreissl et al (2014)[5] analysis to define progressive (i.e., documented progression ≤12 months prior to enrolment) and symptomatic disease (i.e., any of the following at baseline: pain score >4, ≤10 mg/day opioid use, diarrhoea, flushing, fatigue, pain, nausea, dysphagia, dysphonia, respiratory symptoms, or weight loss) were assessed prior to randomization, the definition was created and applied in a post hoc manner. In addition, the exploratory subgroup analyses conducted by the FDA used alternative criteria for differentiating between symptomatic and asymptomatic patients (i.e., asymptomatic patients were required to have all of the following baseline characteristics: average stool frequency <4/day, average pain of 0, and a WHO PS of 0). The FDA's exploratory subgroup analyses based on disease progression applied thresholds for last documented progression of two and six months, which differs from the 12 month threshold used in the Kreissl analysis.

The primary analysis and the pre-specfied subgroup analyses for PFS were based on progression events as determined by the ICR, regardless of whether or not the patient had received treatment with open-label vandetanib.[4] In contrast, the post-hoc progressive and symptomatic subgroup analyses by Kreissl et al (2014) excluded patients who received treatment with open-label vandetanib.[5] In response to a request from CADTH, the submitter stated that this approach was used because the benefit of vandetanib in patients randomized to placebo may have affected the results for PFS in the ITT analysis. As shown in Figure 3, when the PFS analysis for the full study population excluded patients who received treatment with open-label vandetanib, the hazard ratio was more favourable than the primary analysis which included all randomized patients (i.e., 0.27 versus 0.46, respectively). It is possible that the results for the progressive and symptomatic subgroup would also be less favourable with the inclusion of the open-label treatment population; however, this analysis was not conducted and/or reported by the manufacturer. For the analyses that were conducted (i.e., double-blind treatment only), the effect size reported for the progressive and symptomatic subgroup was consistent with the effect size reported for overall population for PFS (HR of 0.32 and 0.27, respectively).

The subgroup analyses were reported for the primary endpoint of ZETA (PFS) and one of the secondary endpoints (ORR). In the absence of a pre-specified analysis plan for the progressive and symptomatic subgroup, it is unclear if additional analyses were conducted, but not reported in the abstract. The progressive and symptomatic subgroup data are limited to a single conference abstract with some additional data provided in the manufacturer's submission.[24] CADTH noted that confidence intervals were not reported in the conference abstract for the subgroup analysis and

that there is inconsistency in the p value reported for the subgroup analysis based on investigator-determined progression in the conference abstract (i.e., P = 0.0226)[5] and in the submitter's clinical summary (i.e., P < 0.0001).[24]

External Validity

The CGP noted that the study population of ZETA trial was generally reflective of the broader population of patients with unresectable locally advanced or metastatic MTC. Similar observations were noted by reviewers for the EMA and the Australian TGA.[10,15] As noted above, the submitter's requested reimbursement criteria for vandetanib is for the treatment of symptomatic and/ or progressive MTC in adult patients with unresectable locally advanced or metastatic disease; however, enrolment in the ZETA trial was not limited to patients with symptomatic or progressive disease. CADTH requested data for this subgroup of patients; however, the Submitter indicated that such data were not available for the ZETA trial. The FDA noted that the absence of criteria specifying the pace of disease progression and the absence of criteria indicating whether or not a patient was considered to be in need of treatment at the time enrollment were limitations of the ZETA trial.[12] The CGP indicated that there are no standardized definitions for progressive and symptomatic MTC that are used in Canadian clinical practice.

The use of placebo as a comparator is appropriate in the Canadian context as there are no alternative treatments approved by Health Canada for use in the treatment of patients with unresectable locally advanced or metastatic disease. An alternative treatment (cabozantinib) has been approved by the FDA for the treatment of progressive, metastatic MTC;[25] however, this product is not approved for use in Canada and is not currently listed as undergoing review by Health Canada.[21]

The protocol for the ZETA study specified that dose interruption was required for the majority of grade 3 to 4 toxicities until the event had resolved to baseline or to CTCAE grade 1, at which point treatment with the study drug was to resume, but at a reduced dosage (i.e., reduced from 300 mg to 200 mg or 200 mg to 100 mg).[19] The CGP indicated that this approach is a reasonable reflection of how this drug would be used in Canadian clinical practice; however, it was noted that some patients in clinical practice could be initiated at a lower dose and have their dosage gradually increased depending on tolerability. The CGP suggested that in routine clinical practice, patients would be initiated at a lower starting dose than in the ZETA trial based on known toxicities. The subsequent frequency of dose interruptions and dose reductions is likely to be lower.

The protocol for the ZETA trial excluded patients if they had uncontrolled hypertension, symptomatic arrhythmia, symptomatic or AF, ventricular tachycardia, congenital long-QT syndrome, or left bundle branch block. The Canadian product monograph contains a warning that the safety of vandetanib has not been established in patients with these conditions. Patients were also excluded from ZETA if they had a QTc that was unmeasurable or ≥ 480 ms, which is close to threshold specified in the product (i.e., treatment should not be initiated in patients whose QTcF interval is ≥ 500 ms). Vandetanib is contraindicated in patents with uncontrolled hypertension, hypokalemia, hypomagnesemia, or hypocalcemia; therefore, the exclusion of patients with these clinical characteristics is reflective of recommendations in product monograph.

The ZETA trial was not designed to evaluate the comparative safety and efficacy of different doses of vandetanib (e.g., 300 mg, 200 mg, or 100 mg once daily). Exploratory analyses of PFS conducted by the FDA suggested that lower doses of vandetanib could be as effective as the 300 mg recommendation and be associated with fewer adverse events.[14] Therefore, the submitter was required to conduct a phase 4 RCT to compare 150 mg and 300 mg doses of vandetanib in patients with advanced MTC.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Overall Survival

Overall survival was a secondary endpoint and was defined as the time from randomization to death from any cause. There were two planned analyses of overall survival in the ZETA trial: an initial analysis at the time when the other efficacy variables were analyzed (i.e., July 2009) and a final analysis when ≥ 50% of the patients had died (i.e., September 2015). The submitter reported that the significance level for the initial analysis was 0.02% and presented the corresponding 99.98% confidence intervals (CIs). The planned significance level for the secondary analysis of overall survival was 4.98% with corresponding 95.02% CIs.[4]

Data for overall survival were immature at the time of the initial data cut-off. At the time of the initial analysis, 14.5% of the trial participants had died (14% and 16% of patients in the vandetanib and placebo, respectively). The median overall survival was not reached for either treatment group. The submitter reported a hazard ratio of 0.89 (99.98% CI, 0.28 to 2.85; *P* = 0.7115) in accordance with the pre-planned initial analysis of overall survival. An additional unplanned analysis was also reported with a 95% CI of 0.48 to 1.65.

In accordance with the pre-planned statistical analysis, the final analysis of overall survival was performed when ≥ 50% of patients had died (September 7, 2015). At the time of the final analysis, 50.2% and 52.0% of the patients randomized to the vandetanib and placebo groups had died, respectively. There was no statistically significant difference between vandetanib and placebo in the final analysis for OS (HR 0.99; 95.02% CI, 0.72 to 1.38, *P* = 0.9750). The median duration of follow-up at the data cut-off was 419 and 421 weeks for patients randomized to vandetanib and placebo, respectively. There were no sensitivity or subgroup analyses reported for the final analysis of overall survival.

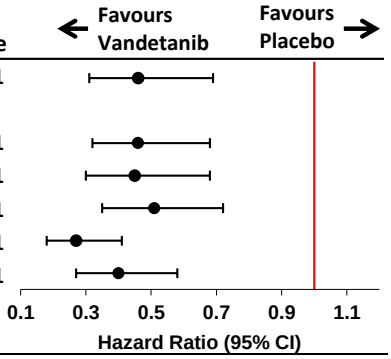
Progression-free Survival

The results for PFS are summarized in Figure 3. At the time of the data cut-off, 124 patients (37.5%) had ICR-confirmed disease progression (31.6% in the vandetanib group and 51.0% in the placebo group). Treatment with vandetanib was associated with a statistically significant prolongation of PFS (HR = 0.46; 95% CI, 0.31 to 0.69; P < 0.001). The median PFS was 19.3 months in the placebo group. The median PFS was not reached in the vandetanib group; however, the submitter used a Weibull model to estimate a median PFS of 30.5 months. It is unclear if the use of a Weibull model was pre-planned. A Kaplan-Meier curve for PFS is shown in Figure 4.

The submitter also conducted the following sensitivity analyses for the PFS evaluation using the log-rank test: per protocol analysis (HR = 0.45; 95% CI, 0.30 to 0.68); the exclusion of events that occurred during open-label treatment (HR = 0.27; 95% CI, 0.18 to 0.41); investigator-determined progression (HR = 0.40; 95% CI, 0.27 to 0.58); and an analysis using the Whitehead method to assess potential impact of a differential frequency of assessments in the two treatment groups (0.51; 95% CI, 0.35 to 0.72). In addition to the above, similar results were obtained using a Cox proportional hazards regression model adjusting for RET mutation status, number of prior therapies, response to prior therapies, hereditary or sporadic MTC status, pre-randomization doubling time in CTN and CEA (HR = 0.46; 95% CI, 0.32 to 0.68).

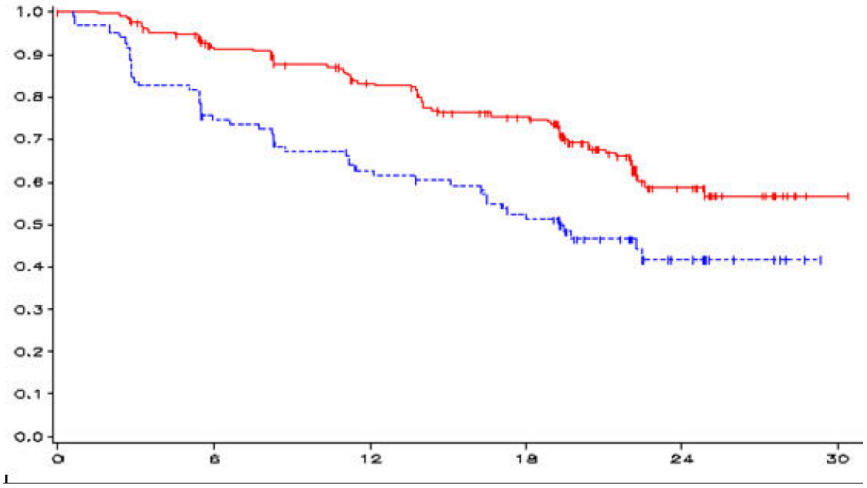
Figure 3: Summary of Progression-free Survival Analyses

Analysis	PFS (n/N) Vandetanib	PFS (n/N) Placebo	HR (95% CI)	P value
Primary analysis	73/231	51/100	0.46 (0.31 to 0.69)	<0.001
Sensitivity analyses				
Cox PH model	73/231	51/100	0.46 (0.32 to 0.68)	<0.001
PP analysis	71/215	48/91	0.45 (0.30 to 0.68)	<0.001
Whitehead's method	73/231	51/100	0.51 (0.35 to 0.72)	<0.001
OL excluded	64/231	59/100	0.27 (0.18 to 0.41)	<0.001
Investigator assessments	101/231	62/100	0.40 (0.27 to 0.58)	<0.001



Abbreviations: CI = confidence interval; HR = hazard ratio; n = number of patients with event; N = number of patients included in the analysis; OL = open-label; PFS = progression-free survival; PH = proportional hazard; PP = per-protocol.
Source: Data from Wells et al, 2012[3]

Figure 4: Kaplan-Meier Curve for Progression-free Survival



months	0	6	12	18	24	30
n-CAPRELSA	231	196	169	140	40	1
n-placebo	100	71	57	45	13	0

Abbreviations: n = number of patients at risk
Source: Reproduced from Caprelsa Product Monograph[1]

The CGP identified the following subgroups of interest for this review: locally advanced MTC versus metastatic MTC; progressive versus indolent disease; symptomatic versus asymptomatic disease; WHO performance status (0 versus ≥1); RET mutation status (positive, negative, or unknown); and calcitonin doubling time. Of these, all of the subgroups with the exception of symptomatic versus asymptomatic disease and progressive versus indolent disease were pre-specified by the submitter.

As shown in Figure 5A, subgroup analyses based on WHO performance status at baseline demonstrated that the results for patients with a performance of 0 or ≥1 were consistent with the overall primary analysis (HR 0.49 [95% CI, 0.27 to 0.90] and 0.46 [95% CI, 0.27 to 0.79], respectively). The results for the subgroup of patients who were classified as being positive for a RET mutation (HR 0.45 [95% CI, 0.26 to 0.78]) or whose RET mutation status was unknown (0.49

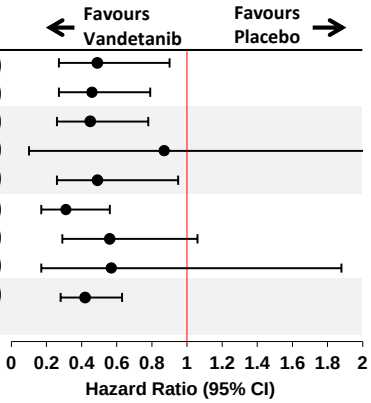
[95% CI, 0.26 to 0.95]) was similar to the overall analysis. The treatment effect for vandetanib appeared to be greater in the subgroup of patients whose calcitonin doubling time at baseline was less than 24 months (HR 0.31 [95% CI, 0.17 to 0.56]) compared with those whose calcitonin doubling time was greater than 24 months (HR 0.56 [95% CI, 0.29 to 1.06]). Due to the limited sample sizes, there was considerable uncertainty in the subgroup analyses for patients whose RET mutation status was negative, those whose calcitonin doubling time was unknown, and those with locally advanced MTC.

The submitter and the FDA conducted a series of post hoc subgroup analyses to investigate the efficacy of vandetanib in patients whose MTC is symptomatic and/or progressive (Figure 5B). The submitter created the following post hoc definition for symptomatic disease based as at least one of the following criteria at baseline: a pain score of at least four, opioid use of at least 10 mg per day, diarrhea, flushing, fatigue, pain, nausea, dysphagia, dysphonia, respiratory symptoms, or weight loss.[5] In contrast, the FDA created the following definition for asymptomatic disease: average baseline stool frequency of less than four per day, baseline average pain of 0, and a baseline WHO PS of 0.[13] The submitter defined patients with progressive MTC as those who had documented disease progression within the 12 months prior to enrolment in the ZETA trial.[5] The FDA did not provide a specific definition for progressive disease but conducted subgroup analyses based on whether or not a patient had documented progression within two or six months prior to enrolment in the trial.[13] The FDA conducted their subgroup analyses using all available ICR-confirmed progression events (i.e., including both double-blind and open-label treatment). The submitter's analyses were conducted using only progression events that occurred during double-blind treatment (one analysis using ICR-confirmed events and one using investigator-determined events). As shown in Figure 5B, the results for all of these post-hoc subgroup analyses were similar to the primary analysis of PFS.

Figure 5: Summary of Progression-free Survival Subgroup Analyses

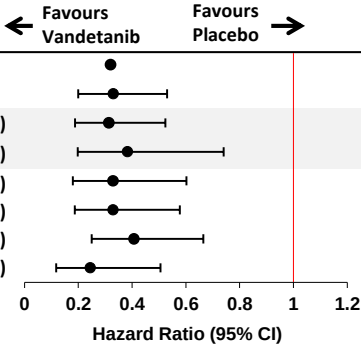
A

Category	Subgroup	Events, n/N (%) Vandetanib	Events, n/N (%) Placebo	HR (95% CI)
WHO PS	≥1	28/77	23/42	0.49 (0.27, 0.90)
	0	45/154	28/58	0.46 (0.27, 0.79)
RET mutation status	Positive	47/137	27/50	0.45 (0.26, 0.78)
	Negative	1/2	5/6	0.87 (0.10, 7.66)
	Unknown	25/92	19/44	0.49 (0.26, 0.95)
CTN doubling time	≤24 months	39/124	27/46	0.31 (0.17, 0.56)
	>24 months	23/83	19/43	0.56 (0.29, 1.06)
	Unknown	11/24	5/11	0.57 (0.17, 1.88)
Disease state	Metastatic	67/ 217	51/97	0.42 (0.28, 0.63)
	Locally advanced	6/14	0/3	NC



B

Source	Population	Analysis	Events, n/N (%) Vandetanib	Events, n/N (%) Placebo	HR (95% CI)[d]
Kreissl 2014	Symptomatic[a] and progression ≤12 months[b]	IRC (DB)	NR	NR	0.32 (CI NR)
		ID (DB)	26/126	41/60	0.33 (0.20, 0.53)
FDA	Symptomatic[c]	IRC (DB, OL)	38/129	25/58	0.314 (0.188, 0.524)
	Asymptomatic[c]	IRC (DB, OL)	21/102	16/42	0.383 (0.198, 0.741)
FDA	Progression <2 months	IRC (DB, OL)	23/110	20/51	0.329 (0.180, 0.602)
	Progression ≥2 months	IRC (DB, OL)	36/118	21/48	0.329 (0.187, 0.578)
	Progression <6 months	IRC (DB, OL)	41/158	27/73	0.407 (0.250, 0.665)
	Progression ≥6 months	IRC (DB, OL)	18/70	14/26	0.245 (0.118, 0.506)



Abbreviations: CI = confidence interval; DB = double-blind; HR = hazard ratio; ID = investigator determined; ICR = independent central review; n = number of patients with event; N = number of patients in the analysis; NR = not reported
Sources: Data for figure 5A from the Clinical Study Report for ZETA.[19] Data for figure 5B from the FDA Statistical Review[13] and Kreissl et al, 2014.[5]
[a] The manufacturer defined symptomatic as at least one of the following at baseline: pain score >4, ≥10 mg/day opioid use, diarrhea, flushing, fatigue, pain, nausea, dysphagia, dysphonia, respiratory symptoms, weight loss.[5]
[b] The manufacturer defined progressive MTC as documented progression ≤12 months prior to enrolment.[5]
[c] The FDA defined asymptomatic patients as follows: average baseline stool frequency of <4/day, baseline average pain of 0, and a baseline WHO PS of 0.[13]
[d] Hazard ratios were calculated using a log-rank test and Cox proportional hazards model for the manufacturer and FDA, respectively.[12]

Objective Response

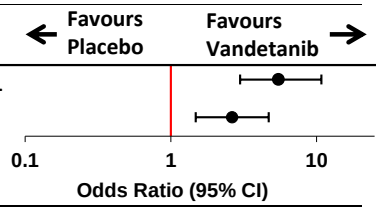
Patients in the vandetanib group were more likely to demonstrate an objective response (i.e., either a complete or partial response) compared with those in the placebo group (45.0% versus 13%). The difference was statistically significant at the time of the data cut-off (OR 5.48 [95% CI, 2.99 to 10.79]; $P < 0.0001$) (Figure 6). No patients demonstrated a complete response.[10] Of the 13 patients who demonstrated a partial response in the placebo group; 12 responses were observed after the patient initiated open-label treatment with vandetanib.[3] A post hoc analysis excluding responses which occurred during open-label treatment was associated with a greater treatment difference between vandetanib (43.7%) and placebo (1.0%) (OR 76.91; 95% CI, 16.68 to 1366).[19]

Disease control rate

Disease control rate (DCR) was defined as the proportion of patients who were classified as having an ICR-confirmed BOR of CR, PR, or SD for at least 24 weeks. A statistically significantly greater proportion of patients in the vandetanib group demonstrated disease control compared with those in the placebo group (86.6% versus 71.0%; OR 2.64 [95% CI, 1.48 to 4.69]; $P = 0.0010$) (Figure 6).[3] An exploratory post hoc analysis excluding patients who received open-label treatment with vandetanib demonstrated results which were similar to the analysis conducted with the full analysis set.[19]

Figure 6: Objective Response and Disease Control Rates

Analysis	Responses (n/N) Vandetanib	Placebo	OR (95% CI)	P value
Objective Response Rate	104/231	13/100	5.48 (2.99 to 10.79)	<0.0001
Disease Control Rate	200/231	71/100	2.64 (1.48 to 4.69)	0.0010

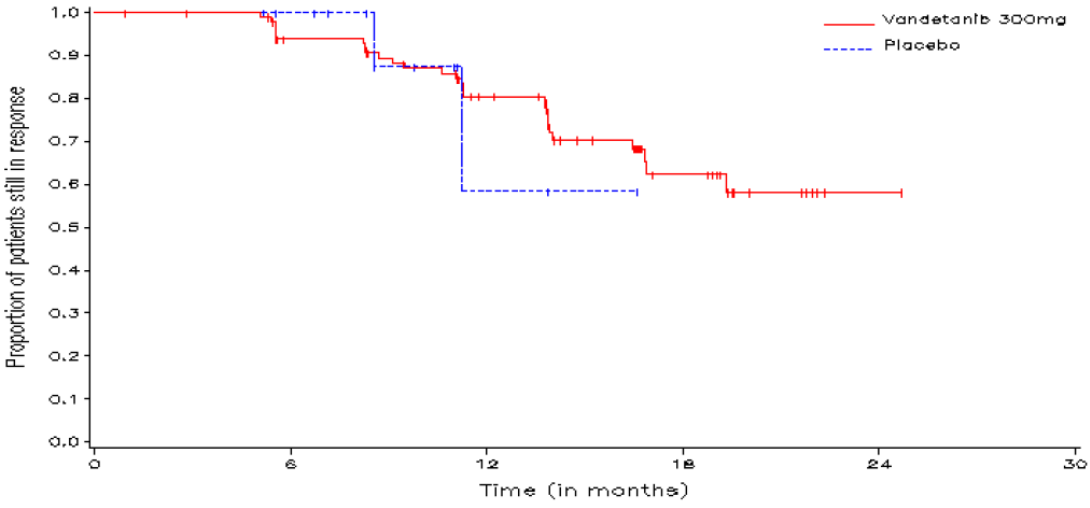


Abbreviations: CI = confidence interval; OR = odds ratio; n = number of patients with event; N = number of patients included in the analysis.
Source: Data from Clinical Study Report Synopsis[2]

Duration of response

Duration of response was calculated from the onset of response to documented tumor progression or death in patients who had a response (45.0% responded for vandetanib versus 13% for placebo, where 12 of 13 responses were after cross over to vandetanib). The median time to response from randomization was 5.8 months for vandetanib and 13.7 months for the placebo group. The median duration of response was not reached at 24 months; however, the submitter used a Weibull model to estimate a median duration of response of 22.2 months for the vandetanib group and 16.3 months in the placebo group.[21]

Figure 7: Kaplan-Meier plot for duration of response



n at months	0	6	12	18	24	30
Vandetanib 300mg	104	87	57	19	1	0
Placebo	13	11	2	0	0	0

Source: Clinical Study Report[4]

Time to Worsening of Pain

The submitter reported that patient compliance with the TWP endpoint (i.e., reporting opioid use and completion of the BPI) was 78.8% in the vandetanib group and 75.0% in the placebo group.[19] Patients in the vandetanib group demonstrated a statistically significant improvement in time to worsening of pain compared with placebo (HR 0.61; 95% CI, 0.43 to 0.87; *P* = 0.0062).[10] The median time to worsening of pain was 7.85 months in the vandetanib group versus 3.25 months in the placebo group.[10] The EMA reported that the results for time to worsening of pain were

supported by a sensitivity analysis conducted using a Cox proportional hazards model (HR 0.64; 95% CI, 0.46 to 0.89).[10,19]

Biomarkers

Compared with placebo, a statistically significantly greater proportion of vandetanib-treated patients demonstrated responses (i.e., complete or partial response) in calcitonin levels (69.3% versus 3.0%; OR 72.9 [95% CI, 26.2 to 303.2]) and CEA levels (51.5% versus 2.0%; OR 52.0 [95% CI, 16.0 to 320.3]) (both $P < 0.0001$).[2] The time to onset of the calcitonin and CEA responses were not reported. Responses for both calcitonin and CEA were composed almost entirely of partial responses; few patients demonstrated a complete response.[19]

Quality of Life

Quality of life was evaluated using the patient-reported FACT-G scale. Higher scores indicate better quality of life. Table 10 summarizes the number of patients with FACT-G data at each time point, the FACT-G total score at each time point, and change from baseline up to week 132 for each treatment group. This was an exploratory endpoint and no formal statistical analyses were performed. The submitter and reviewers for the EMA reported that there was no difference between vandetanib and placebo for changes from baseline in FACT-G scores.[10] The submitter also reported that there did not appear to be differences between vandetanib and placebo in the FACT-G subscales scores over time.[19]

Table 10: Summary of FACT-G Scores

Treatment	Time point	FACT-G Scores [a]		Change from Baseline	
		n	Mean (SD)	n	Mean (SD)
Vandetanib 300 mg	Baseline	218	79.11 (16.716)	—	—
	Week 12	174	77.06 (17.323)	168	−2.01 (11.171)
	Week 24	177	77.22 (17.410)	168	−3.58 (11.678)
	Week 36	154	79.68 (16.808)	147	−2.32 (11.782)
	Week 48	149	78.70 (17.114)	142	−2.25 (12.743)
	Week 60	141	78.84 (17.421)	136	−2.23 (13.316)
	Week 72	117	78.93 (16.871)	112	−2.07 (13.490)
	Week 84	116	79.82 (15.629)	111	−1.74 (12.693)
	Week 96	62	79.51 (15.843)	57	−2.28 (12.089)
	Week 108	31	73.50 (16.477)	28	−3.27 (13.499)
	Week 120	15	72.53 (17.230)	14	−6.09 (15.155)
	Week 132	1	84.67 (NA)	1	11.20 (NA)
Placebo	Baseline	92	77.53 (14.180)	—	—
	Week 12	73	76.97 (16.709)	69	−1.87 (9.107)
	Week 24	63	78.89 (15.478)	62	−0.13 (9.167)
	Week 36	51	80.52 (15.037)	49	−0.65 (9.701)
	Week 48	40	77.82 (15.940)	39	−2.82 (11.314)
	Week 60	38	77.69 (14.194)	37	−4.09 (9.859)
	Week 72	32	77.81 (17.026)	31	−2.80 (12.739)
	Week 84	25	74.67 (14.791)	25	−4.36 (10.567)
	Week 96	14	75.21 (12.085)	14	−3.10 (7.735)
	Week 108	9	69.93 (10.411)	9	−4.80 (11.078)
	Week 120	3	67.22 (19.687)	3	−1.90 (3.804)

Abbreviations: FACT-G = Functional Assessment of Cancer Therapy – General; n = number of patients evaluated; NA = not applicable; SD = standard deviation

Source: Clinical Study Report for ZETA[19]

[a] Possible scores the FACT-G range from 0 to 108 with higher scores indicating better quality of life

Harms Outcomes

The safety analysis set included 330 patients (231 in the vandetanib group and 99 in the placebo group). Compared with placebo, a greater proportion of vandetanib-treated patients experienced at least one adverse event (99.6% versus 90.9%), adverse event of CTCAE Grade 3 or higher (55.4% versus 24.2%), serious adverse event (30.7% versus 13.1%), or an adverse event which led to discontinuation from the study (12.1% versus 3.0%). The proportion of patients who died as a result of adverse events was similar between the vandetanib and placebo groups (2.2% versus 2.0%, respectively).

Table 11: Summary of Adverse Events

Adverse Events	Vandetanib 300 mg		Placebo	
	Events n (%)	Event rate (per 1000 Pt-Y)	Events n (%)	Event rate (per 1000 Pt-Y)
Any AEs	230 (99.6)	21729.8	90 (90.9)	4374.3
AEs of CTCAE grade ≥3	128 (55.4)	663.9	24 (24.2)	270.7
SAEs	71 (30.7)	258.5	13 (13.1)	133.9
SAEs with outcome of death	5 (2.2)	15.1	2 (2.0)	19.6
WDAEs	28 (12.1)	85.6	3 (3.0)	29.5
Abbreviations: AE = adverse events; CTCAE = Common Terminology Criteria for Adverse Events; n = number of patients with event; Pt-Y = patient-years; SAEs = serious adverse events; WDAEs = withdrawals due to adverse events				

Source: Reproduced from Clinical Study Report Synopsis[2]

Adverse Events

Table 12 summarizes the adverse events which occurred in at least 10% of the study participants in either treatment group. The most frequent adverse events that occurred at a greater frequency with vandetanib than with placebo were diarrhea (56.3% versus 26.3%), rash (45.0% versus 11.1%), nausea (33.3% versus 16.2%), hypertension (31.6% versus 5.1%), and headache (25.5% versus 9.1%).[2] QT prolongation was reported in a greater proportion of vandetanib-treated patients (14.3% versus 1.0%).[2]

Table 12: Summary of Adverse Events

Adverse events	Vandetanib 300 mg		Placebo	
	Events n (%)	Events per 1000 Pt-Y	Events n (%)	Events per 1000 Pt-Y
Patients with any AE	230 (99.6)	21729.8	90 (90.9)	4374.3
Skin/subcutaneous disorders	208 (90.0)	4240.7	30 (30.3)	427.6
Rash	104 (45.0)	536.7	11 (11.1)	117.6
Acne	46 (19.9)	178.9	5 (5.1)	51.5
Dry skin	35 (15.2)	121.7	5 (5.1)	52.4
Dermatitis acneiform	35 (15.2)	125.4	2 (2.0)	19.7
Photosensitivity reaction	31 (13.4)	104.0	0 (0.0)	0.0
Pruritus	25 (10.8)	83.9	4 (4.0)	41.5
Gastrointestinal disorders	186 (80.5)	2142.1	56 (56.6)	984.8
Diarrhoea	130 (56.3)	838.5	26 (26.3)	317.7
Nausea	77 (33.3)	326.9	16 (16.2)	175.4
Vomiting	34 (14.7)	116.2	7 (7.1)	70.4
Abdominal pain	33 (14.3)	111.7	5 (5.1)	51.0
Dyspepsia	25 (10.8)	82.9	4 (4.0)	40.7
Infections and infestations	115 (49.8)	563.8	36 (36.4)	447.4
Nasopharyngitis	26 (11.3)	84.8	9 (9.1)	92.8

Adverse events	Vandetanib 300 mg		Placebo	
	Events n (%)	Events per 1000 Pt-Y	Events n (%)	Events per 1000 Pt-Y
General/admin. site disorders	113 (48.9)	554.4	41 (41.4)	604.9
Fatigue	55 (23.8)	206.8	23 (23.2)	291.0
Asthenia	34 (14.7)	114.0	11 (11.1)	115.9
Nervous system disorders	112 (48.5)	546.5	32 (32.3)	427.3
Headache	59 (25.5)	229.6	9 (9.1)	98.5
Musculoskeletal/CT disorders	94 (40.7)	411.3	47 (47.5)	774.8
Back pain	21 (9.1)	68.0	20 (20.2)	228.6
Arthralgia	18 (7.8)	57.7	10 (10.1)	103.4
Pain in extremity	16 (6.9)	50.5	13 (13.1)	139.9
Investigations	92 (39.8)	391.3	16 (16.2)	176.2
ECG QT prolonged	33 (14.3)	113.1	1 (1.0)	9.8
Weight decreased	24 (10.4)	77.1	9 (9.1)	93.6
Vascular disorders	90 (39.0)	406.9	11 (11.1)	117.3
Hypertension	73 (31.6)	300.1	5 (5.1)	50.7
RTM disorders	89 (38.5)	369.8	33 (33.3)	410.4
Cough	25 (10.8)	82.1	10 (10.1)	107.0
Metabolism/nutrition disorders	81 (35.1)	324.5	20 (20.2)	222.0
Decreased appetite	49 (21.2)	170.9	12 (12.1)	125.7
Hypocalcemia	25 (10.8)	82.0	3 (3.0)	30.1
Psychiatric disorders	70 (30.3)	280.4	21 (21.2)	234.6
Insomnia	30 (13.0)	102.4	10 (10.1)	102.8
Abbreviations: AE = adverse event; CT = connective tissue; Pt-Y = patient-year; RTM = respiratory, thoracic and mediastinal				

Source: Reproduced from Clinical Study Report Synopsis[2]

Serious Adverse Events

Table 13 summarizes the serious adverse events that were reported in at least 1% of either treatment group. A greater proportion of patients treated with vandetanib experienced at least one serious adverse event compared with those who received placebo (30.7% versus 13.1%). The most commonly reported serious adverse events in the vandetanib group were pneumonia (2.2%), diarrhea (2.2% each), decreased appetite (1.7%), and hypertensive crisis (1.7%).

Table 13: Summary of Serious Adverse Events Occurring ≥1% of Patients

SOC	Serious adverse events	Vandetanib (N = 231)	Placebo (N = 99)
Infections and infestations	Pneumonia	5 (2.2)	0 (0.0)
	Urinary tract infection	3 (1.3)	0 (0.0)
Gastrointestinal disorders	Diarrhea	5 (2.2)	0 (0.0)
	Abdominal pain	3 (1.3)	0 (0.0)
Metabolism and nutrition disorders	Decreased appetite	4 (1.7)	0 (0.0)
	Hypercalcemia	3 (1.3)	0 (0.0)
Vascular disorders	Hypertensive crisis	4 (1.7)	0 (0.0)
	Hypertension	3 (1.3)	0 (0.0)
Psychiatric disorders	Depression	3 (1.3)	0 (0.0)
Abbreviations: SOC = System, Organ, Class; N = number of patients in the safety analysis			

Source: Product Monograph[1]

Withdrawals due to Adverse Events

Withdrawals due to adverse events are summarized in Table 14. A greater proportion of patients treated with vandetanib withdrew from the ZETA study as a result of one or more adverse events compared with placebo (12.5% versus 3.0%). Within the vandetanib group, skin disorders (2.5%) and asthenia (1.7%) were the most common events which led to discontinuation.

Table 14: Summary of Withdrawals due to Adverse Events

WDAEs, n (%)[a]	Vandetanib (N = 231)	Placebo (N = 99)
Any WDAE	29 (12.5)	3 (3.0)
Skin disorders	6 (2.5)	0
Asthenia	4 (1.7)	0
Fatigue	2 (0.9)	0
Pyrexia	2 (0.9)	0
Diarrhea	2 (0.9)	1 (1.0)
Elevated creatinine	2 (0.9)	0
QTc prolongation	2 (0.9)	0
Hypertension	2 (0.9)	0
General health deterioration	1 (0.4)	0
Dysphagia	1 (0.4)	0
Nausea	1 (0.4)	0
Pancreatitis	1 (0.4)	0
Peritonitis	1 (0.4)	0
Small intestinal perforation	1 (0.4)	0
Vomiting	1 (0.4)	0
Gastrointestinal hemorrhage	0	1 (1.0)
Reduced systolic function	1 (0.4)	0
Cylothorax	1 (0.4)	0
Cough	1 (0.4)	0
Dysphonia	1 (0.4)	0
Dyspnea	1 (0.4)	0
Pneumonitis	1 (0.4)	0
Peripheral ischemia	1 (0.4)	0
Peripheral sensorimotor neuropathy	1 (0.4)	0
Syncope	0	1 (1.0)
Vision blurred	1 (0.4)	0
Arthralgia	1 (0.4)	0
Germ cell cancer	1 (0.4)	0
Left bundle branch block	0	1 (1.0)
Jaw fracture	0	1 (1.0)
Abbreviations: n = number of patients with event; N = number of patients in the analysis; WDAE = withdrawal due to adverse event		

Source: FDA Medical Review[13]

[a] Multiple adverse events could be recording for a single patient.

Adverse Events of Special Interest

The CGP identified the following adverse events of special interest: QTc prolongation, diarrhea, and hypertension. For each of these categories of adverse events, Table 15 summarizes the overall proportion of patients with events, the proportion of events that were classified as being serious adverse events of CTCAE grade 3 or higher, and the proportion of events that led to discontinuation from the study.

Diarrhea was more commonly reported in vandetanib-treated patients compared with placebo-treated patients (56.7% versus 27.3%). In accordance with the protocol for the ZETA study,[13] the submitter reported that patients experiencing diarrhea were treated with standard symptomatic treatment during the ZETA trial. Events that were considered to be CTCAE grade 3 or higher were also more commonly reported in the vandetanib group (10.8%) compared with the placebo group (2.0%). The submitter reported that diarrhea typically occurred within the first six months of treatment and there was a median duration of 267.5 days in the vandetanib group and 49.5 days in the placebo-group. Serious events and events leading to discontinuation occurred in 2.2% and 0.9% of patients in the vandetanib group and 0% and 1.0% of patients in the placebo group (respectively).

Overall hypertensive adverse events were more commonly reported in the vandetanib group compared with the placebo group (32.9% versus 5.1%, respectively). Events of CTCAE grade 3 or higher were reported in 8.7% of patients in the vandetanib group compared with no patients in the placebo group. The submitter reported that these events were primarily managed with anti-hypertensive medication with or without interruption and/or reduction of the vandetanib dosage. Serious events and events leading to discontinuation occurred in 3.0% and 0.9% of patients in the vandetanib group and no patients in the placebo group.

QTc-related adverse events were more commonly reported in the vandetanib group compared with the placebo group (15.6% versus 4.0%, respectively). The majority of QTc-related adverse events were classified as QT prolongation, which occurred in 14.3% of patients in the vandetanib group compared with 1.0% of patients in the placebo group. CTCAE grade ≥ 3 events of QT prolongation (i.e., a corrected QT interval < 500 ms) were reported for 7.8% of the vandetanib group and 1.0% of placebo group.

Table 15: Summary of the Adverse Events of Special Interest

AESI	Severity	Patients with AESI, n (%)	
		Vandetanib (N = 231)	Placebo (N = 99)
Diarrhea	Overall incidence	131 (56.7)	27 (27.3)
	SAE	5 (2.2)	0
	WDAE	2 (0.9)	1 (1.0)
	AE of CTCAE Grade ≥3	25 (10.8)	2 (2.0)
	AE of CTCAE Grade 4	1 (0.4)	0
Hypertension	Overall incidence	76 (32.9)	5 (5.1)
	SAE	7 (3.0)	0
	WDAE	2 (0.9)	0
	AE of CTCAE Grade ≥3	20 (8.7)	0
	AE of CTCAE Grade 4	1 (0.4)	0
QTc-related AEs	Overall incidence	36 (15.6)	4 (4.0)
	SAE	3 (1.3)	0
	WDAE	2 (0.9)	1 (1.0)
	AE of CTCAE Grade ≥3	20 (8.7)	3 (3.0)
	AE of CTCAE Grade 4	1 (0.4)	1 (1.0)
Abbreviations: AE = adverse event; AESI = adverse event of special interest; CTCAE = Common Terminology Criteria for Adverse Events; n = number of patients with events; SAE = serious adverse event; WDAE = withdrawal due to adverse event			

Source: Common Technical Document section 2.7.4[19]

Deaths

The proportion of patients who experienced a fatal SAE in ZETA trial was similar between the vandetanib (2.2%) and placebo groups (2.0%). The submitter reported that one patient in the vandetanib group died as a result of acute cardiac failure, which was considered by the investigator to be related to the study drug.

6.4 Ongoing Trials

There were no ongoing or unreported trials identified that would meet the inclusion criteria for the pCODR systematic review.

7 SUPPLEMENTAL QUESTIONS

The following supplemental question was identified as relevant to the pCODR review of vandetanib for MTC: Is PFS an appropriate surrogate for OS in patients with MTC?

Topics considered in this section are provided as supporting information.

Methods
A literature search was performed. Published literature was identified by searching PubMed as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were progression free survival, medullary thyroid cancer, and validity of outcomes. Retrieval was not limited by publication year, but was limited to the English language. The search was completed on November 17, 2016. One reviewer screened citations for any studies that investigated a correlation between PFS and OS in patients with MTC.

Conclusions
CADTH did not identify any studies that investigated a correlation between PFS and OS in patients with MTC. Therefore, there is an absence of published evidence evaluating the validity of PFS as a surrogate endpoint for OS in patients with MTC. It is the opinion of the CGP that PFS, as reported in the ZETA trial, is a very likely surrogate outcome for overall survival in MTC.

8 COMPARISON WITH OTHER LITERATURE

None identified.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Endocrine Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on vandetanib for medullary thyroid cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Endocrine Clinical Guidance Panel is comprised of three clinicians. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

See section Appendix B for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials July 2016**, **Embase** 1974 to 2016 August 19, **Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches	Results
1	(vandetanib* or Caprelsa* or HSDB 8198 or HSDB8198 or Zactima* or ZD 6474 or ZD6474 or 443913-73-3 or YO460OQ37K or azd 6474 or azd6474).ti,ab,rn,hw,nm,kf.	4447
2	"N-(4-bromo-2-fluorophenyl)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-amine".af.	485
3	"N (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4 quinazolinamine".af.	1
4	or/1-3	4541
5	exp Thyroid Neoplasms/	111944
6	Thyroid Gland/	111043
7	(thyroid* or thyreoid*).ti,ab,kf.	376317
8	or/5-7	408680
9	4 and 8	1067
10	9 use cctr	16
11	9 use ppez	209
12	*vandetanib/	517
13	(vandetanib* or Caprelsa* or HSDB 8198 or HSDB8198 or Zactima* or ZD 6474 or ZD6474 or 443913-73-3 or YO460OQ37K or azd 6474 or azd6474).ti,ab,kw.	1774
14	"N-(4-bromo-2-fluorophenyl)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-amine".af.	485
15	"N (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4 quinazolinamine".af.	1
16	or/12-15	1912
17	exp thyroid tumor/	66769
18	exp thyroid gland/	117524
19	(thyroid* or thyreoid*).ti,ab,kw.	379672
20	or/17-19	406863
21	16 and 20	579
22	21 use oemezd	360
23	10 or 11 or 22	585
24	remove duplicates from 23	392
25	limit 24 to english language	367

2. **Literature search via PubMed**
   A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Add to builder	Query	Items found
#4	Add	Search **(#1 AND #2 AND #3)**	8
#3	Add	Search **Publisher[sb]**	505463
#2	Add	Search **Thyroid Neoplasms[mh] OR Thyroid Gland[mh] OR thyroid*[tiab] OR thyreoid*[tiab]**	180063
#1	Add	Search **vandetanib*[tiab] OR Caprelsa*[tiab] OR HSDB 8198[tiab] OR HSDB8198[tiab] OR Zactima*[tiab] OR ZD 6474[tiab] OR ZD6474[tiab] OR 443913-73-3[rn] OR YO460OQ37K OR azd 6474[tiab] OR azd6474[tiab] OR "n (4 bromo 2 fluorophenyl) 6 methoxy 7 (1 methyl 4 piperidinylmethoxy) 4 quinazolinamine"[tiab] OR "N-(4-bromo-2-fluorophenyl)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazolin-4-amine"[nm]**	705

3. **Cochrane Central Register of Controlled Trials (Central)**
   Searched via Ovid.

4. **Grey Literature search via:**

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Search: Thyroid OR Thyroids | vandetanib OR Caprelsa OR Zactima OR HSDB 8198 OR HSDB8198 OR ZD 6474 OR ZD6474

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: vandetanib, Caprelsa, Zactima

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: vandetanib, Caprelsa, Zactima

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

Retrieved via Embase, except ASCO 2016

European Society for Medical Oncology
http://www.esmo.org
Retrieved via Embase, except ESMO 2014 & ESMO 2016

Search: vandetanib, Caprelsa, Zactima, thyroid cancer
last 5 years

APPENDIX B: DETAILED METHOLODGY OF LITERATURE REVIEW

Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with epub ahead of print, in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (July 2016) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were vandetanib (Caprelsa) and thyroid cancer.

No filters were applied to limit the retrieval by study type. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of January 3, 2017.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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