NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Cabozantinib and vandetanib for treating unresectable locally advanced or metastatic medullary thyroid cancer [ID56]

Committee papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Cabozantinib and vandetanib for treating unresectable locally advanced or metastatic medullary thyroid cancer [ID56]

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- Ipsen Ltd
- SanofiGenzyme

4 Response to consultee and commentator comments on the redacted Assessment Report from School of Health and Related Research

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- Ipsen Ltd
- SanofiGenzyme

6 Professional group, patient group and NHS organisation submissions from:
- Butterfly Thyroid Cancer Trust (BTCT)
- Association for multiple endocrine neoplasia disorders (AMEND)
- Royal College of Physicians
- NHS England

7 Expert personal statements from:
- Gareth Bowen, patient expert, nominated by Butterfly Thyroid Cancer Trust
- Dr Mary Lei, clinical expert, nominated by Sanofi Genzyme to follow

Any information supplied to NICE which has been marked as confidential has been redacted. All personal information has also been redacted.

Pre-meeting briefing

Cabozantinib and vandetanib for treating unresectable locally advanced or metastatic medullary thyroid cancer

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the companies, the consultees and their nominated clinical experts and patient experts and
- the Assessment Group (AG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

1

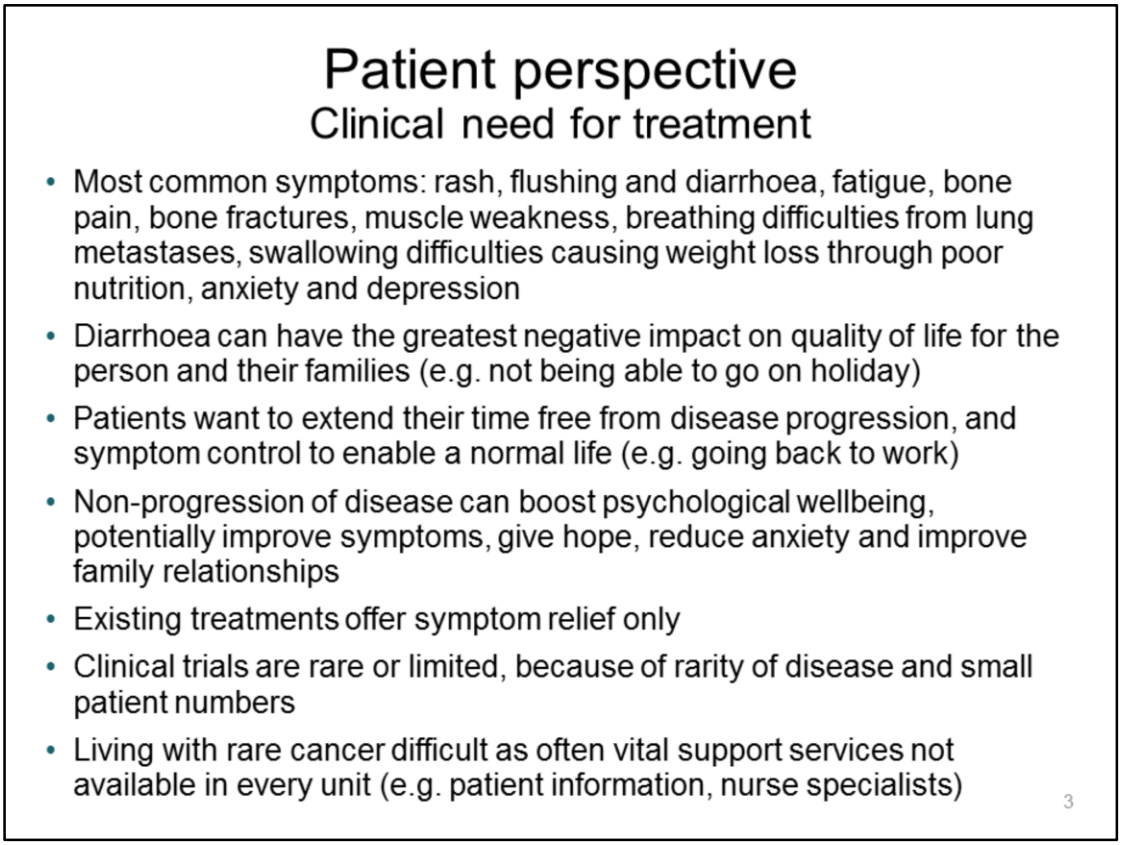
Medullary thyroid cancer (MTC)

- Medullary is one of four types of thyroid cancer
- Thyroid cancer accounts for <1% cancer cases in UK
- MTC accounts for ~3% of adult thyroid cancer cases
- A rare cancer occurring in parafollicular cells (C-cells)
- Can be sporadic (~75%), or
- Genetically determined: familial, Multiple Endocrine Neoplasia (MEN) 2 or MEN3 (~25%)
- ~90 cases diagnosed in England in 2014
- Patients typically present with a lump in the neck
- ~50% patients with sporadic MTC present with stage III or IV disease
- Distant metastases present in 7-23% newly diagnosed cases
- 10-year survival for stage III disease (advanced) ~71%
- 10-year survival for stage IV disease (advanced and metastatic) ~21%

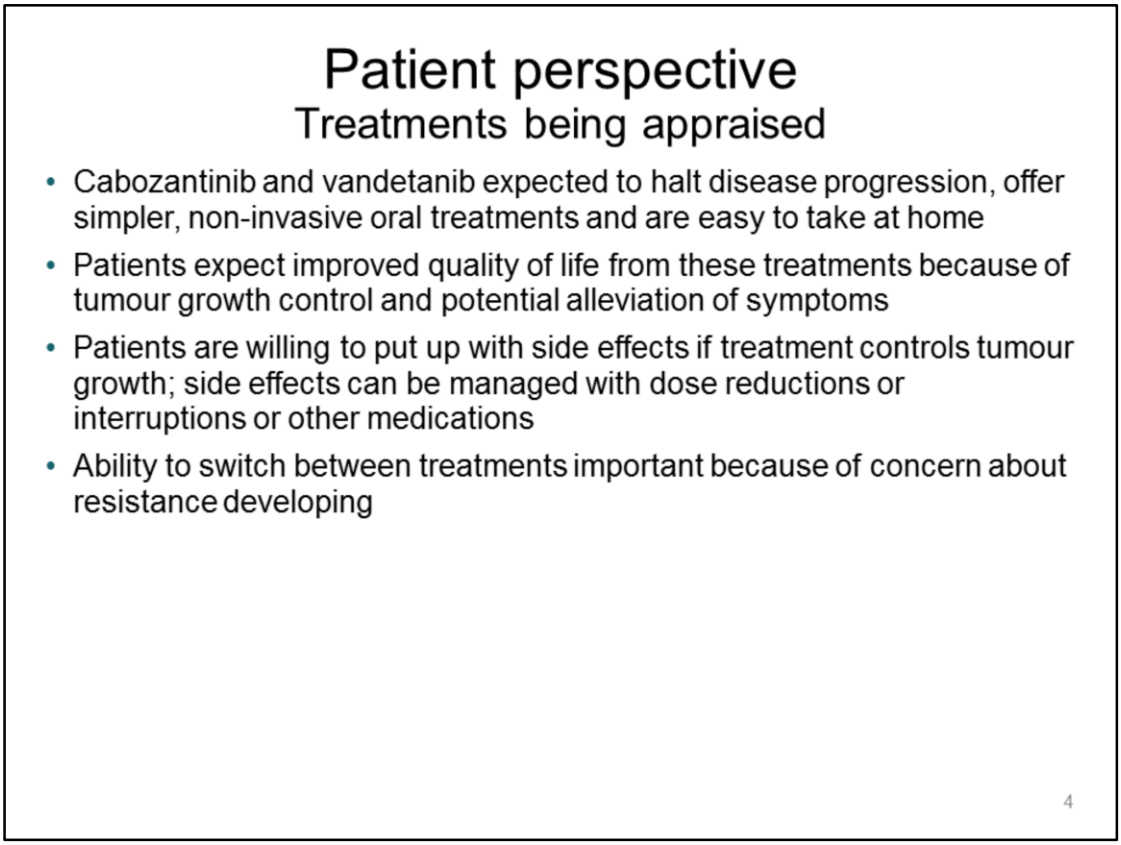
2

Source: NICE scope; AG report: pages 10-11; Ipsen submission: pages 5, 28-29; Sanofi submission: pages 33-34;
Cancer Research UK thyroid cancer statistics; Association for Multiple Endocrine Neoplasia Disorders website

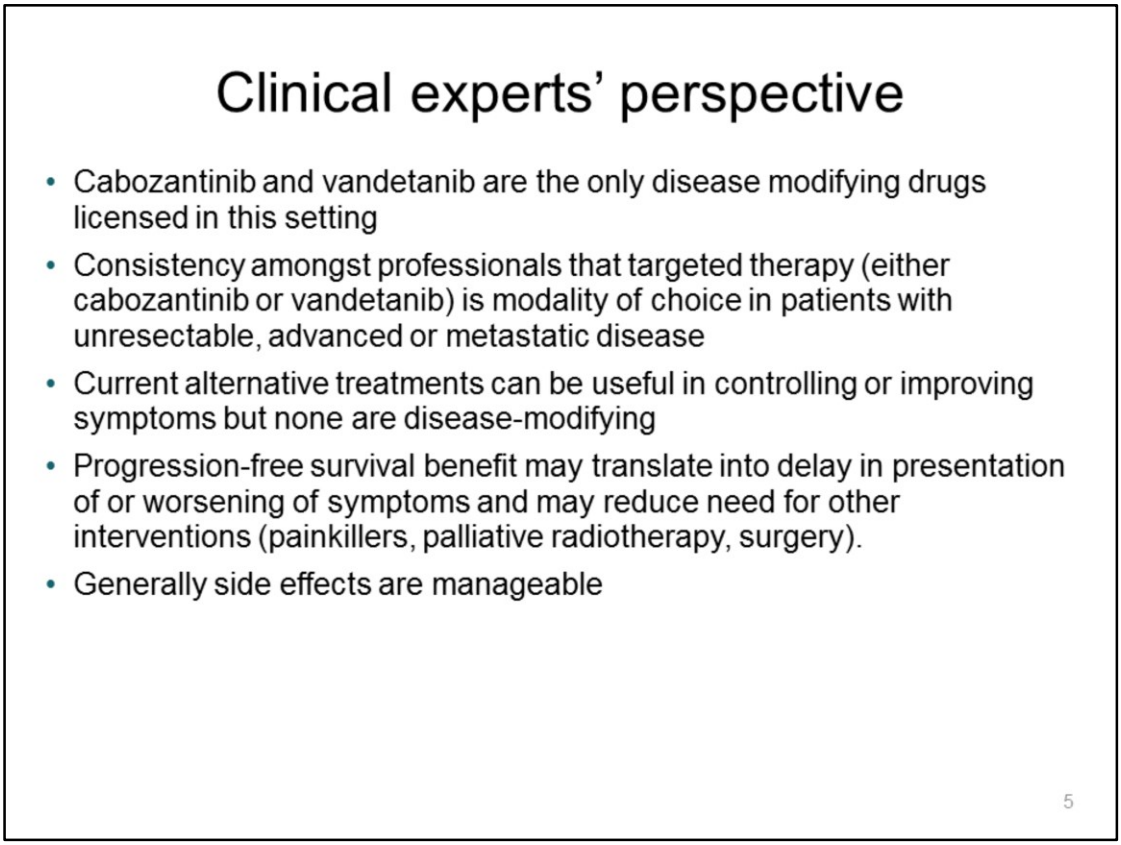
Note: MTC can occur as part of an inherited disorder called Multiple Endocrine Neoplasia (MEN). MEN types 2 and 3 were formerly known as MEN2a and MEN2b



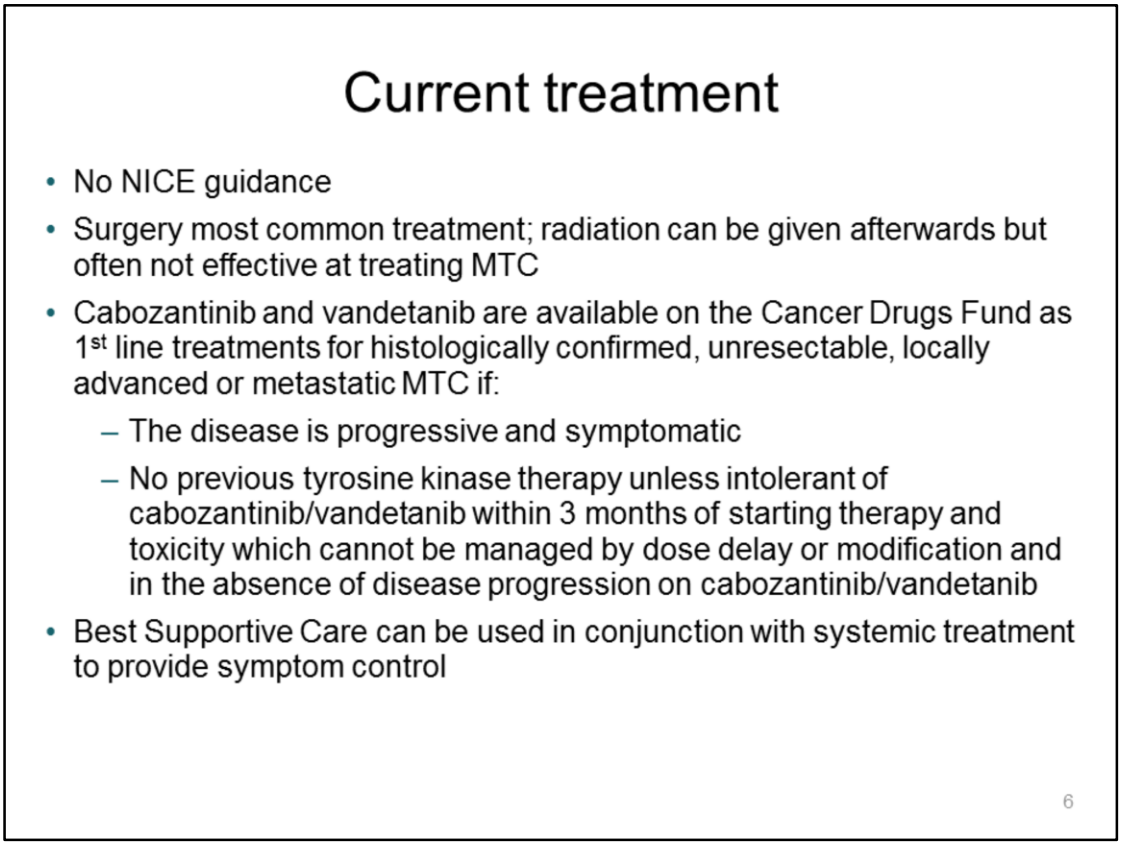
Source: AMEND submission, Butterfly submission



Source: AMEND submission, Butterfly submission



Source: NCRI-ACP-RCP-RCR submission

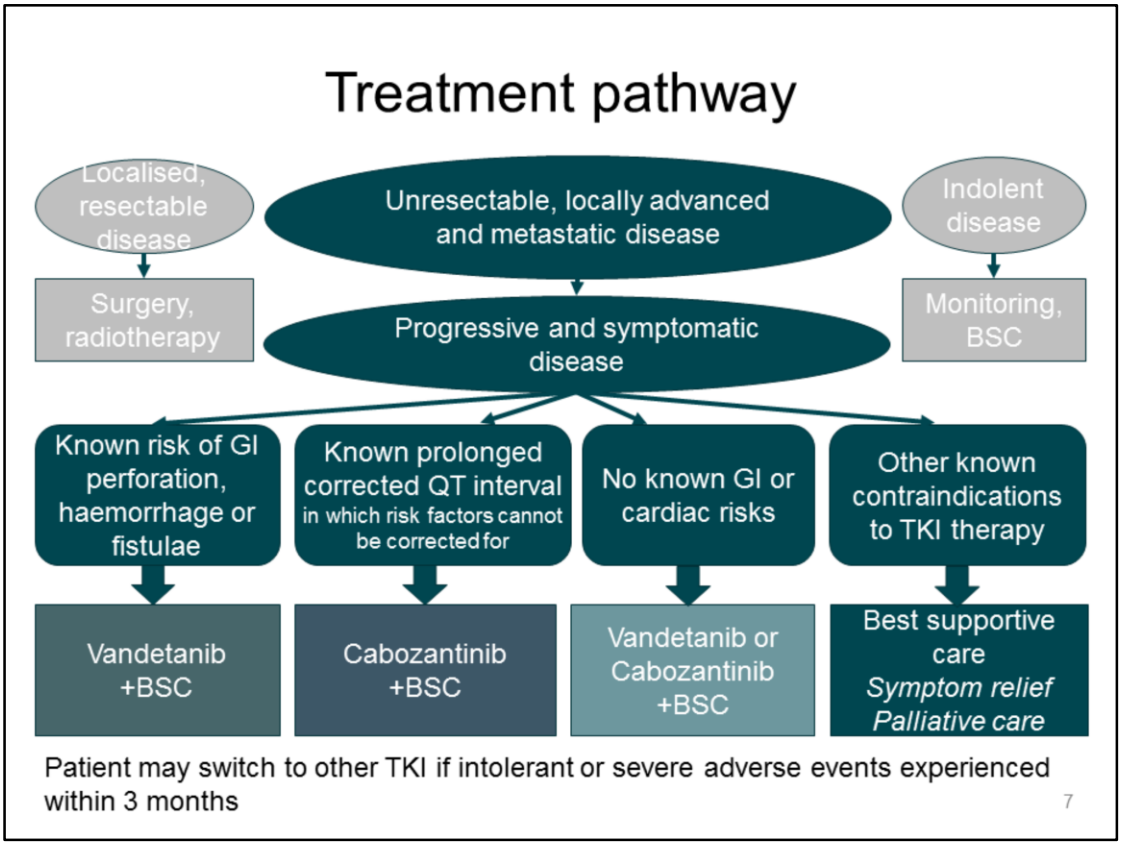


In 2016, 25 new patients accessed vandetanib through the CDF; 7 new patients accessed cabozantinib *Source: AG report: page 13*

Vandetanib has been available on the CDF since 2012; cabozantinib since 2014 *Source: Sanofi submission: pages 8, 29, 60*

Cabozantinib funded in Wales (approved in January 2015) but not Scotland *Source: Ipsen submission: page 26*
Vandetanib not funded in Wales or Scotland *Source: Sanofi submission: Table 8, page 28*

Cabozantinib and vandetanib are recommended by British Thyroid Association, European Thyroid Association and American Thyroid Association guidelines *Source: Ipsen submission: pages 30-31; Sanofi submission: page 37*



Source: AG report: Adapted from Figure 1, page 15

Interventions

Marketing authorisations and mechanism of action

	Cabozantinib (Cometriq)	Vandetanib (Caprelsa)
Company	Ipsen	SanofiGenzyme
Mechanism of action	Inhibits multiple receptor tyrosine kinases (RET, VEGFR2 and MET)	Inhibits growth factor receptors and RET tyrosine kinases (RET, VEGFR2 and EGFR)
Marketing authorisation	Treatment of adults with **progressive**, unresectable locally advanced or metastatic MTC	Treatment of **aggressive and symptomatic** MTC in patients with unresectable locally advanced or metastatic disease
	For patients in whom RET mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision.	
Administration	Oral, capsule	Oral, tablet

EGFR, epidermal growth factor receptor; MET, mesenchymal-epithelial transition; RET, Rearranged during Transfection; VEGFR, vascular endothelial growth factor receptor

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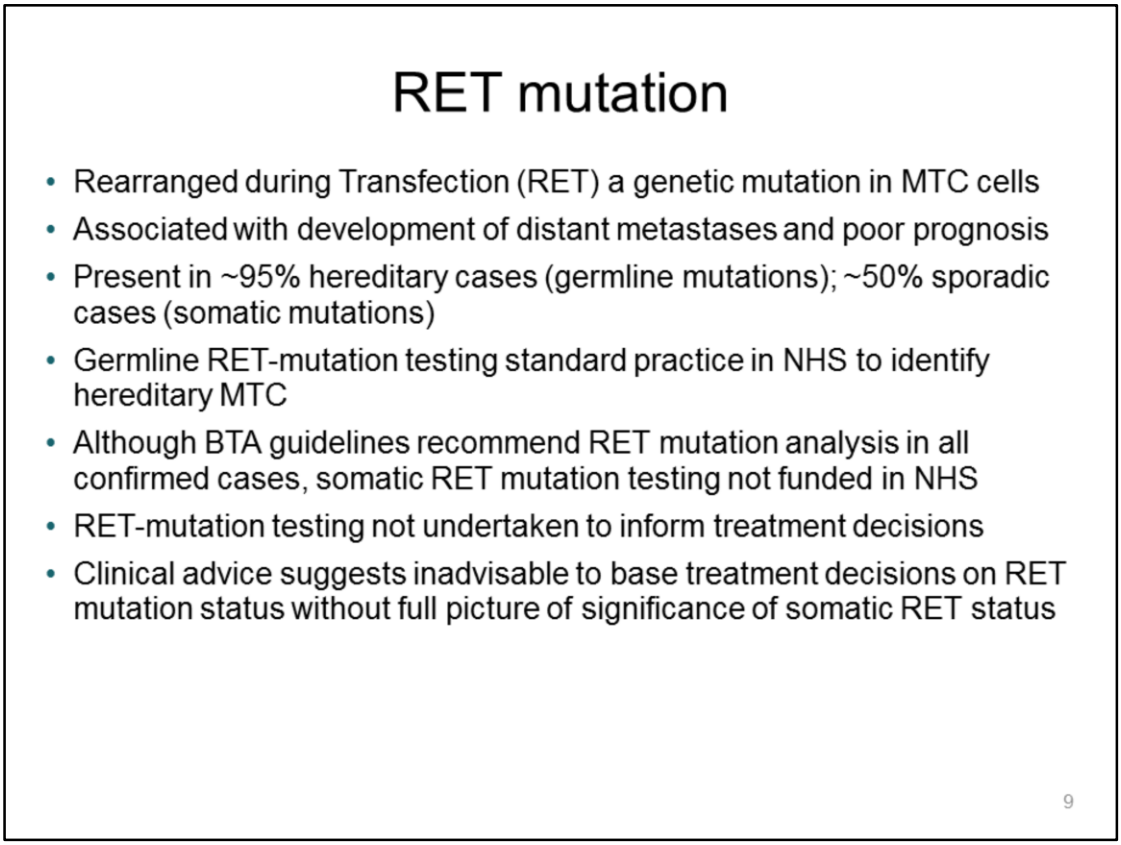
Source: Ipsen submission: page 6, Table 1, page 12, pages 22, 25, Table 2, page 27; Sanofi submission: pages 14, 16, 23, Table 9, pages 28-29

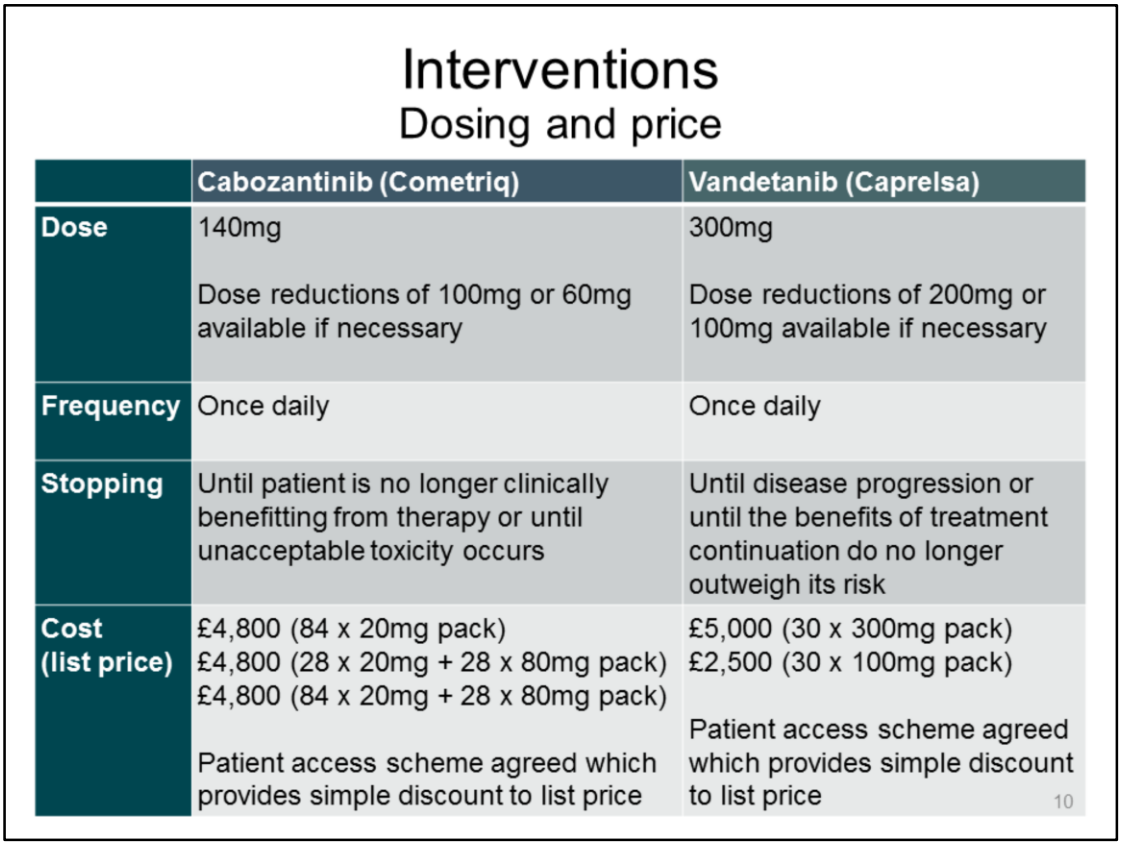
Vandetanib received its marketing authorisation in February 2012; Cabozantinib in March 2014

For information: vandetanib recently received a marketing authorisation for use in children over 5 *Source: Sanofi submission, page 10*



Source: AG report: pages 10, 55; Ipsen submission: page 22; Sanofi submission: pages 12, 25, 36

Germline RET is present at birth, whereas somatic RET occurs in the tumour. A patient can be germline RET negative yet have a RET positive tumour.
RET status of primary thyroid cancer may not be the same as that in metastases. Also, if primary tumour has been removed before metastases occurs, the mutation analysis may no longer be accurate.
Even if a patient is RET mutation negative, they may still get benefit from the drug targeting other mutations.



Interventions
Dosing and price

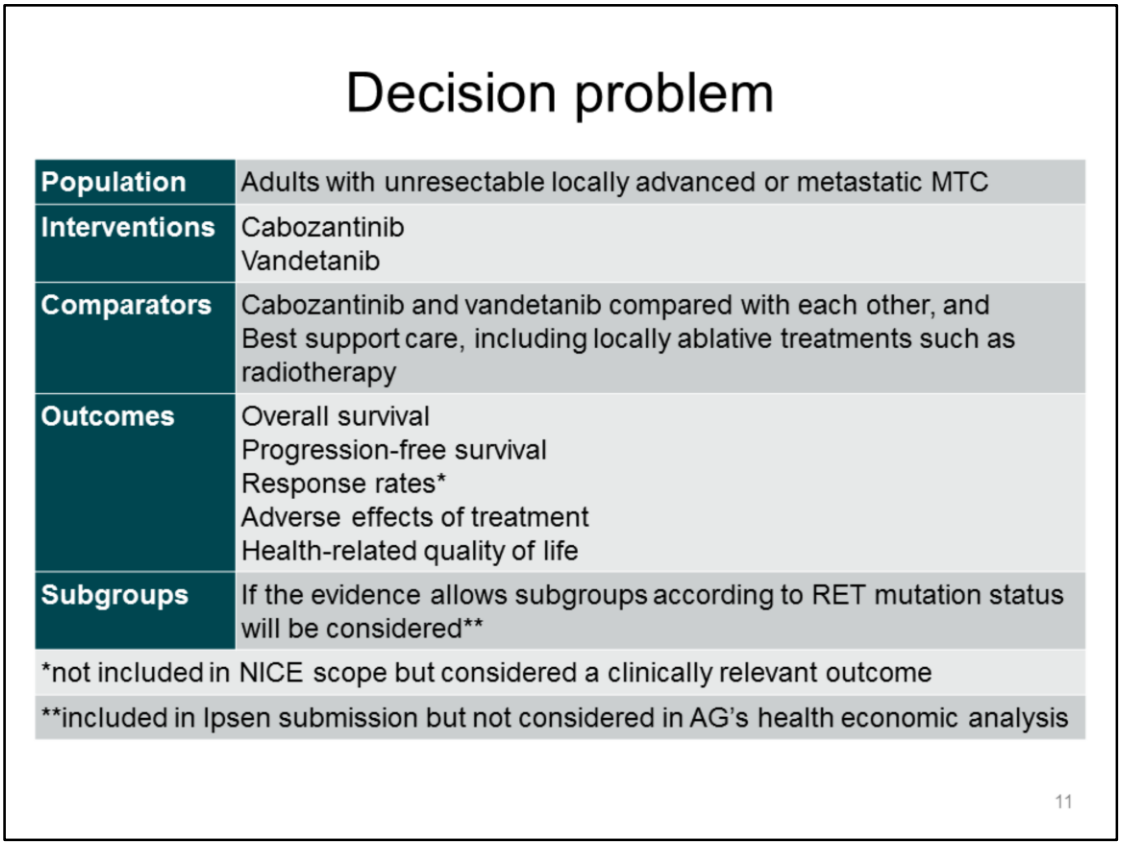
	Cabozantinib (Cometriq)	Vandetanib (Caprelsa)
Dose	140mg Dose reductions of 100mg or 60mg available if necessary	300mg Dose reductions of 200mg or 100mg available if necessary
Frequency	Once daily	Once daily
Stopping	Until patient is no longer clinically benefitting from therapy or until unacceptable toxicity occurs	Until disease progression or until the benefits of treatment continuation do no longer outweigh its risk
Cost (list price)	£4,800 (84 x 20mg pack) £4,800 (28 x 20mg + 28 x 80mg pack) £4,800 (84 x 20mg + 28 x 80mg pack) Patient access scheme agreed which provides simple discount to list price	£5,000 (30 x 300mg pack) £2,500 (30 x 100mg pack) Patient access scheme agreed which provides simple discount to list price

10

Source: Ipsen submission, Table 1, page 12, page 25, Table 2, page 27; Sanofi submission, page 23, Table 9, pages 28-29

Vandetanib SmPC: “QTc interval should be carefully assessed prior to initiation of treatment. In the event of common terminology criteria for adverse events (CTCAE) grade 3 or higher toxicity or prolongation of the ECG QTc interval, dosing with vandetanib should be at least temporarily stopped and resumed at a reduced dose when toxicity has resolved or improved to CTCAE grade 1. Due to the 19-day half-life, adverse reactions including a prolonged QTc interval may not resolve quickly.”

Cabozantinib SmPC: “It should be expected that a majority of patients treated with COMETRIQ will require one or more dose adjustments (reduction and/or interruption) due to toxicity. Patients should therefore be closely monitored during the first eight weeks of therapy. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of COMETRIQ therapy. Dose interruptions are recommended for management of CTCAE grade 3 or greater toxicities or intolerable grade 2 toxicities. 3
Dose reductions are recommended for events that, if persistent, could become serious or intolerable.



Decision problem

Population	Adults with unresectable locally advanced or metastatic MTC
Interventions	Cabozantinib Vandetanib
Comparators	Cabozantinib and vandetanib compared with each other, and Best support care, including locally ablative treatments such as radiotherapy
Outcomes	Overall survival Progression-free survival Response rates* Adverse effects of treatment Health-related quality of life
Subgroups	If the evidence allows subgroups according to RET mutation status will be considered**
*not included in NICE scope but considered a clinically relevant outcome	
**included in Ipsen submission but not considered in AG's health economic analysis	

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Source: NICE scope

Ipsen note that cabozantinib is positioned after radiotherapy and that radiotherapy is used for palliative care only, no direct comparisons with are radiotherapy available *Source: Ipsen submission: page 19*

Key trials

	EXAM (cabozantinib)	ZETA (vandetanib)
Design	Phase III international, multicentre, parallel-group double-blinded RCT	
Population	Patients with unresectable, locally advanced, metastatic and progressive MTC **(n=330)**	Patients with unresectable, locally advanced and metastatic MTC **(n=331)**
Intervention	Cabozantinib 140mg	Vandetanib 300mg
	. . . until disease progression or intolerable toxicity	
Comparator	Placebo	Placebo
1° outcome	Progression-free survival	
2° outcomes	Overall survival, objective response rate, duration of response, biomarker changes	
	Safety and tolerability	Health-related quality of life, disease control rate at 24 weeks, time to worsening of pain
Follow-up	Median 13.9 months	Median 24 months

12

Source: Ipsen submission, pages 16, 40-41
Source: Sanofi submission: pages 16, 41-42, Table 12, page 44, 45
Source: AG report: Table 2, page 27

EXAM: Across 90 sites in 23 countries (55.8% in Europe)

ZETA: 63 study sites in Europe, USA, Australia
Note: ZETA trial more inclusive than marketing authorisation for vandetanib

EXAM: Progression measured using modified RECIST (Response Evaluation Criteria in Solid Tumours), described as “operational clarifications intended to ensure accurate, consistent application of the criteria by multiple radiologists”
ZETA: Progression measured using standard RECIST

Tumour assessments evaluated by blinded independent review committee in both trials.

Baseline characteristics in trials

	EXAM		ZETA	
	Cabozantinib n=219	Placebo n=111	Vandetanib n=231	Placebo n=100
Performance status (EXAM: ECOG; ZETA: WHO)				
0	56%	51%	67%	58%
1-2	43%	50%	33%	42%
RET mutation status				
Positive	46%	52%	59%	50%
Negative	14%	9%	1%	6%
Unknown	40%	39%	40%	44%
Previous TKI therapy				
Yes	20%	22%	NR*	NR*
No	78%	78%	NR*	NR*
Unknown	2%	1%	NR*	NR*

13

Source: Ipsen submission: Table 4.2.2.1.1, page 45
Source: Sanofi submission: Table 14, page 48
Source: AG report: page 28, table 4, page 30

*Vandetanib only licensed TKI for MTC at time of trial

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ZETA trial crossover

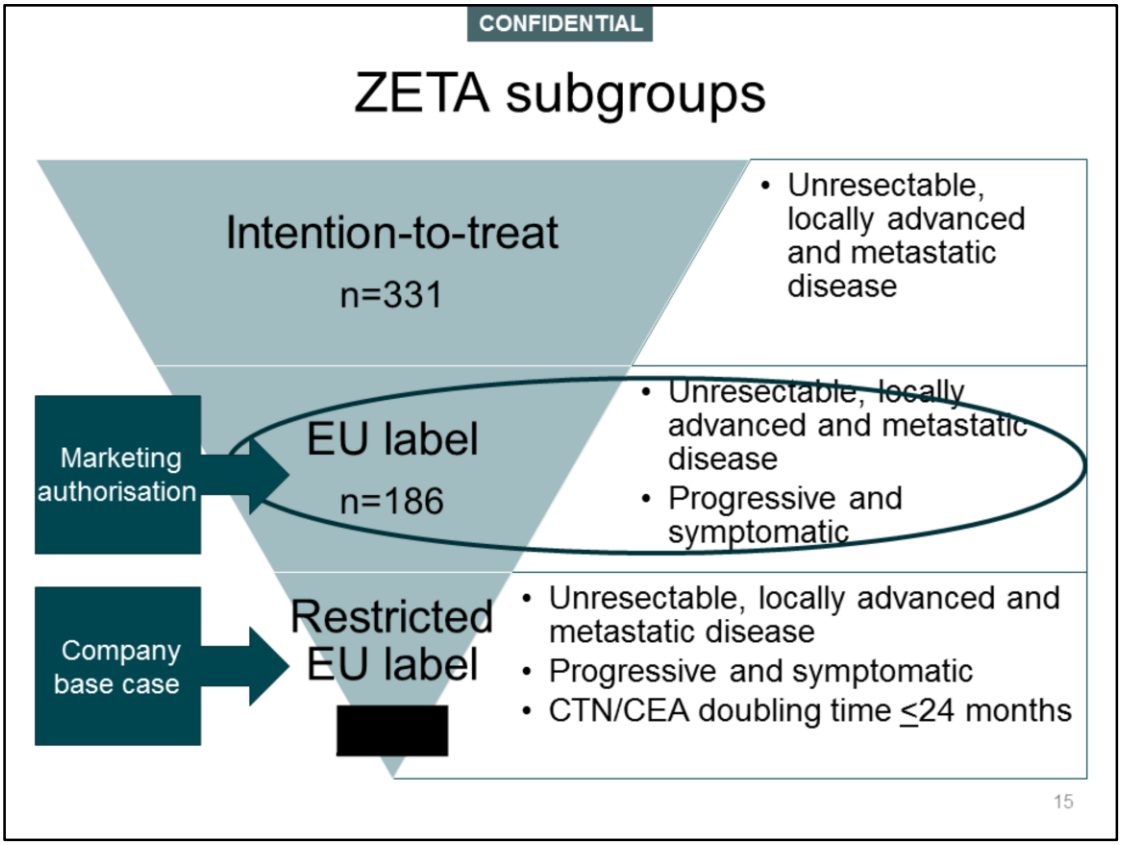
- Patients received open-label vandetanib at investigator-assessed progression, before confirmation by central review and results uncensored
- Central review PFS; OS results confounded (overestimate of placebo arm)
- OS data more likely to show impact of treatment with immediate vs delayed vandetanib rather than true comparison of vandetanib vs placebo
- Company tried to adjust for crossover but not successful; AG unable to adjust for crossover because no access to patient level data

Total proportion of patients receiving open-label vandetanib post-progression in intention-to-treat population and subgroups:

Vandetanib			Placebo		
ITT	EU label	Restricted	ITT	EU label	Restricted
47.2%	43.8%	[redacted]	79.0%	79.7%	[redacted]

14

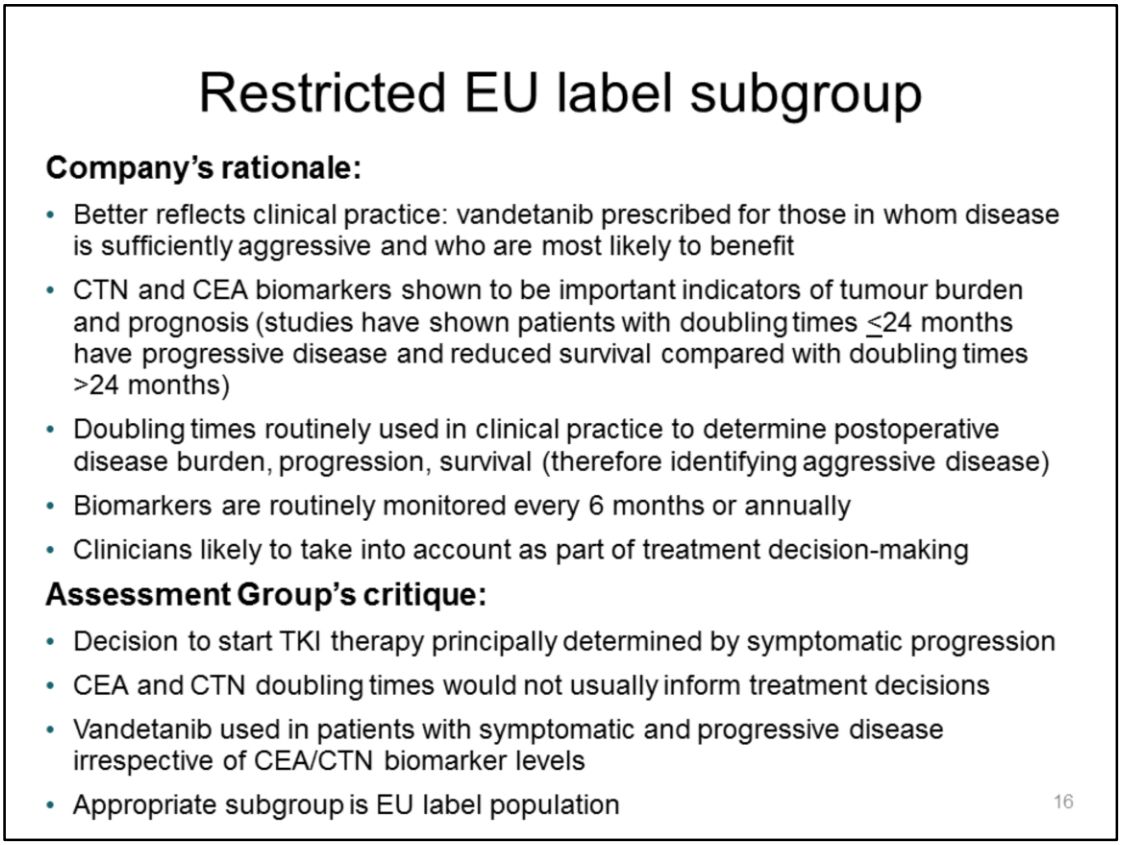
Source: AG report: pages 29-32, 62
Source: Sanofi submission: pages 16-17, 48, 50, 57



Progressive and symptomatic defined as:

- Progression within 12 months of diagnosis
- 1 or more symptoms (including pain score >4, ≥10 days of opioid use, diarrhoea, flushing, fatigue, pain, nausea, dysphagia, dysphonia, respiratory symptoms, weight loss)

Base case evidence obtained from post-hoc subgroup analysis.



Source: Sanofi submission: pages 9, 15, 30, 36, 41, 54-55
Source: Ipsen submission: page 21
Source: AG report: page 31

CTN = Calcitonin: A hormone produced by the parafollicular cells (C cells) of the thyroid gland
CEA = Carcinoembryonic antigen: A protein that might appear in the blood of people who have certain types of cancer

EXAM trial (cabozantinib) results

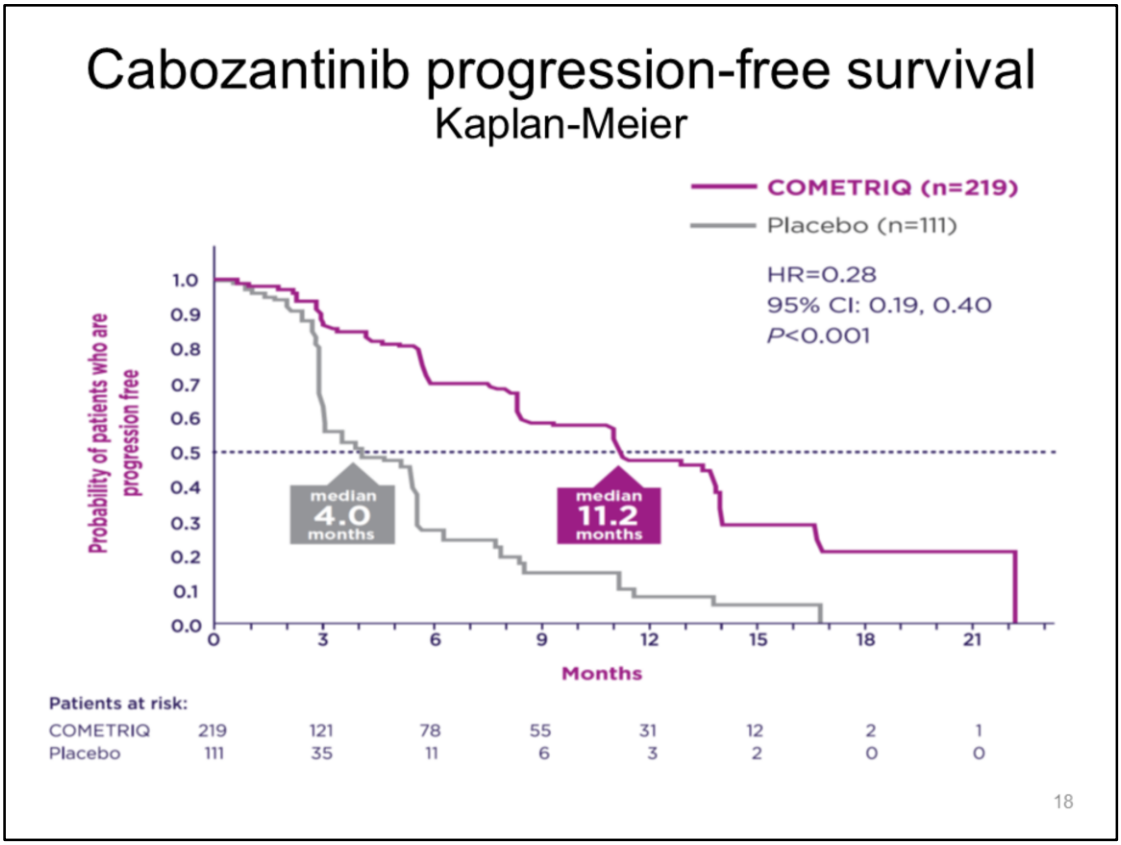
	Cabozantinib (n=219)	Placebo (n=111)	Hazard ratio
Median follow-up 13.9 months			
Median progression-free survival Independent Review Committee	**11.2 months**	**4.0 months**	**0.28 95% CI 0.19, 0.40 p<0.001**
Median progression-free survival Investigator-assessed	13.8 months	3.1 months	0.29 95% CI 0.21, 0.42 p<0.001
Median follow-up 52.4 months			
Median overall survival	26.6 months	21.1 months	0.85 95% CI 0.64, 1.12 p=0.2409
Objective response rate	28%	0%	p<0.001

17

Source: Ipsen submission: pages 17, 19, 39, 45, Figure D, page 46-48, pages 51-57
Source: AG report: Table 7, page 38, Table 12, page 42, Table 13, page 43

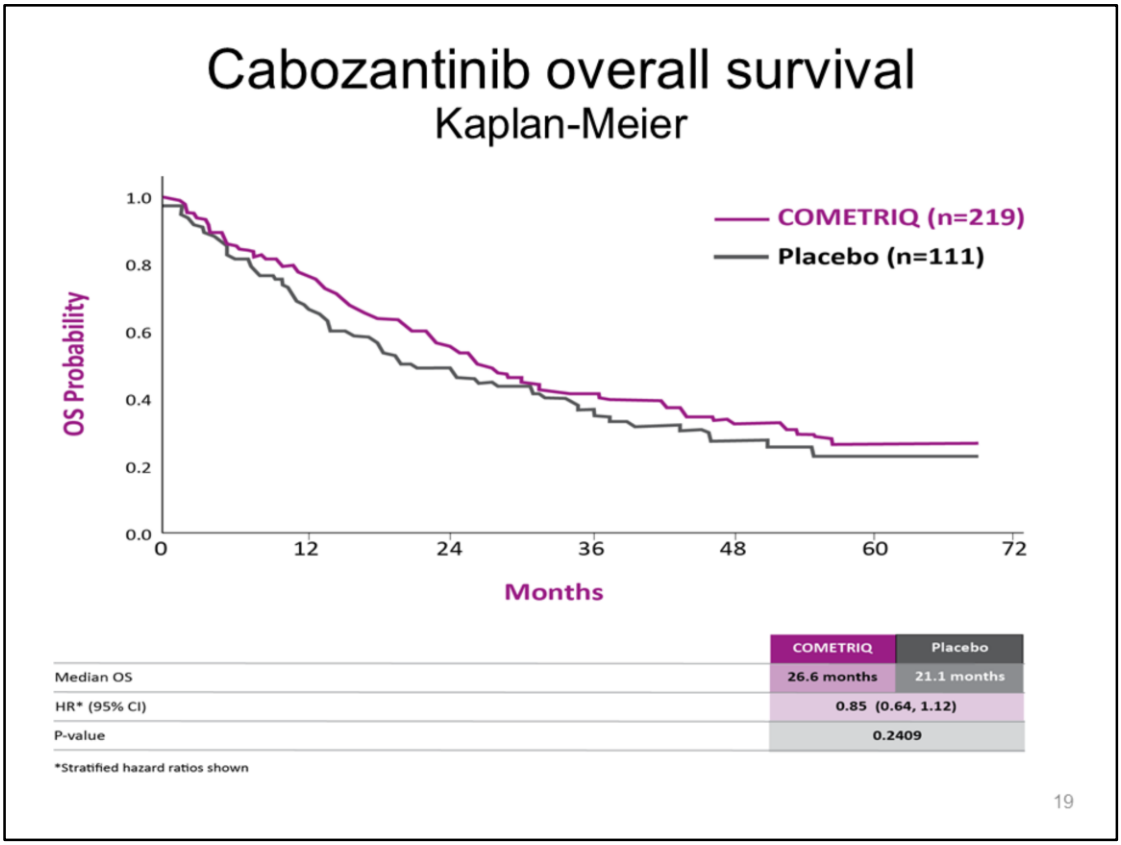
PFS analysis – data cut off June 2011. At this point 45% of patients in the cabozantinib arm were still receiving blinded study treatment; 14% in the placebo arm.
OS analysis – data cut off August 2014
ORR – assessed by IRC: Proportion of subjects with measurable disease achieving best overall response of confirmed complete response or confirmed partial response (all partial responses)

For results for secondary endpoints see *Ipsen submission: pages 47-49*



Source: Ipsen submission, Figure D, pages 18 and 46

PFS as assessed by Independent Review Committee



Source: Ipsen submission, Figure E, page 47

ZETA trial (vandetanib) results

Intention-to-treat population

	Vandetanib (n=231)	Placebo (n=100)	Hazard ratio
Median follow-up 24 months			
Median progression-free survival Central read	**30.5 months**	**19.3 months**	**0.46 95% CI 0.31, 0.69 p<0.001**
Median progression-free survival Site read	22.3 months	8.3 months	0.40 95% CI 0.27, 0.58 p<0.001
Median progression-free survival Central read excluding open-label vandetanib use	32.4 months	16.4 months	0.28 95% CI 0.18, 0.42 p<0.001
Median follow-up 105 months			
Overall survival	50.2% had died	52.0% had died	0.99 95% CI 0.72, 1.38 p=0.9750
Objective response rate	45.0%	13.0%	p<0.001

Source: Sanofi submission: pages 17, 45, 47-48, Table 15, page 49, Table 16, page 50
Source: AG report: Table 8, page 38, Table 12, page 42, Table 13, page 43

PFS analysis – data cut off July 2009. At this point 48% of patients in the vandetanib arm were still receiving blinded study treatment; 28% in the placebo arm.
OS analysis – data cut off September 2015
Central read PFS results are predicted medians (using Weibull extrapolation) because medians not reached.
Objective response rate = complete objective response plus partial response. Confounded by crossover: only 1 patient (1%) had a response in double-blinded period

For secondary endpoint results see *Sanofi submission: pages 45, 50*

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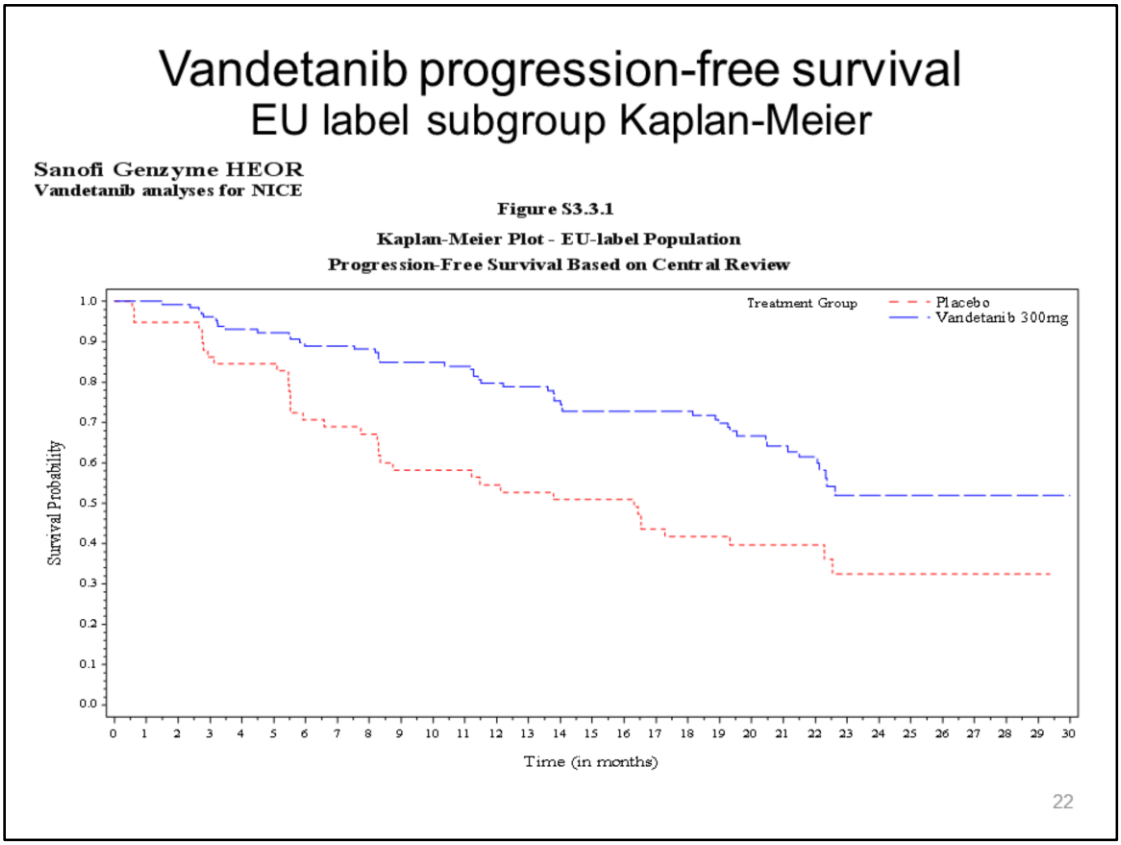
ZETA trial (vandetanib) results
EU label subgroup

	Vandetanib (n=126)	Placebo (n=60)	Hazard ratio
Median follow-up 24 months			
Median progression-free survival Central read	**28.0 months**	**16.4 months**	**0.47 95% CI 0.29, 0.77 p=0.0024**
Median progression-free survival Investigator-assessed	22.1 months	8.3 months	0.33 95% CI 0.20, 0.53 p<0.001*
Median progression-free survival Central read excluding open-label vandetanib use	30.1 months	11.1 months	0.32 95% CI 0.19, 0.54 p<0.001
Median follow-up 105 months			
Median overall survival	[redacted]	[redacted]	[redacted]
Objective response rate	43.7%	1.7%	p<0.0001

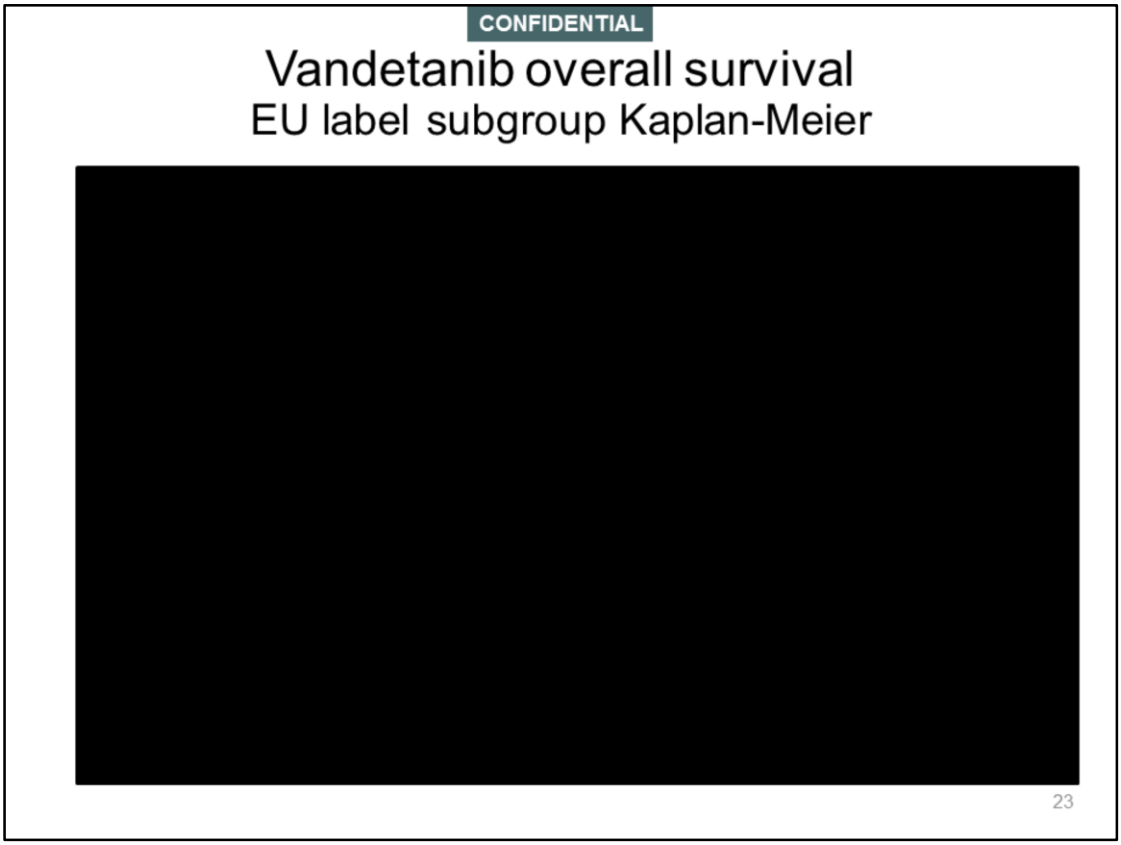
Source: Sanofi submission: pages 17, 18, Table 18, pages 53-54, Table 24, page 67
Source: AG report: Table 9, page 39, Table 12, page 42, Table 13, page 43

*AG reports a p value of 0.0226

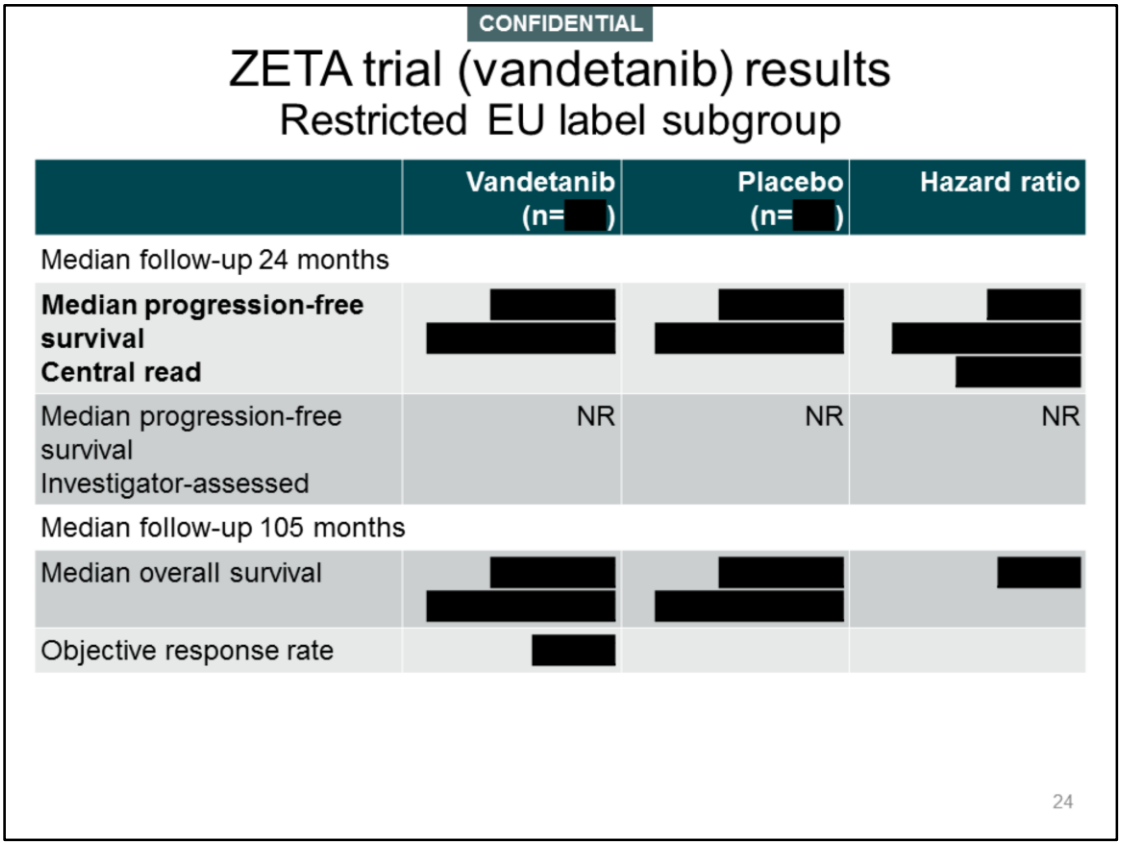
Central read PFS results are predicted medians (using Weibull extrapolation) because medians not reached.
Central read excluding open-label vandetanib use - Imputed PFS based on linear interpolation based on RECIST score prior to open-label vandetanib
OS is estimated median



Source: Sanofi appendix 6: Figure 1, page 52



Source: Sanofi appendix 6: Figure 2, page 54

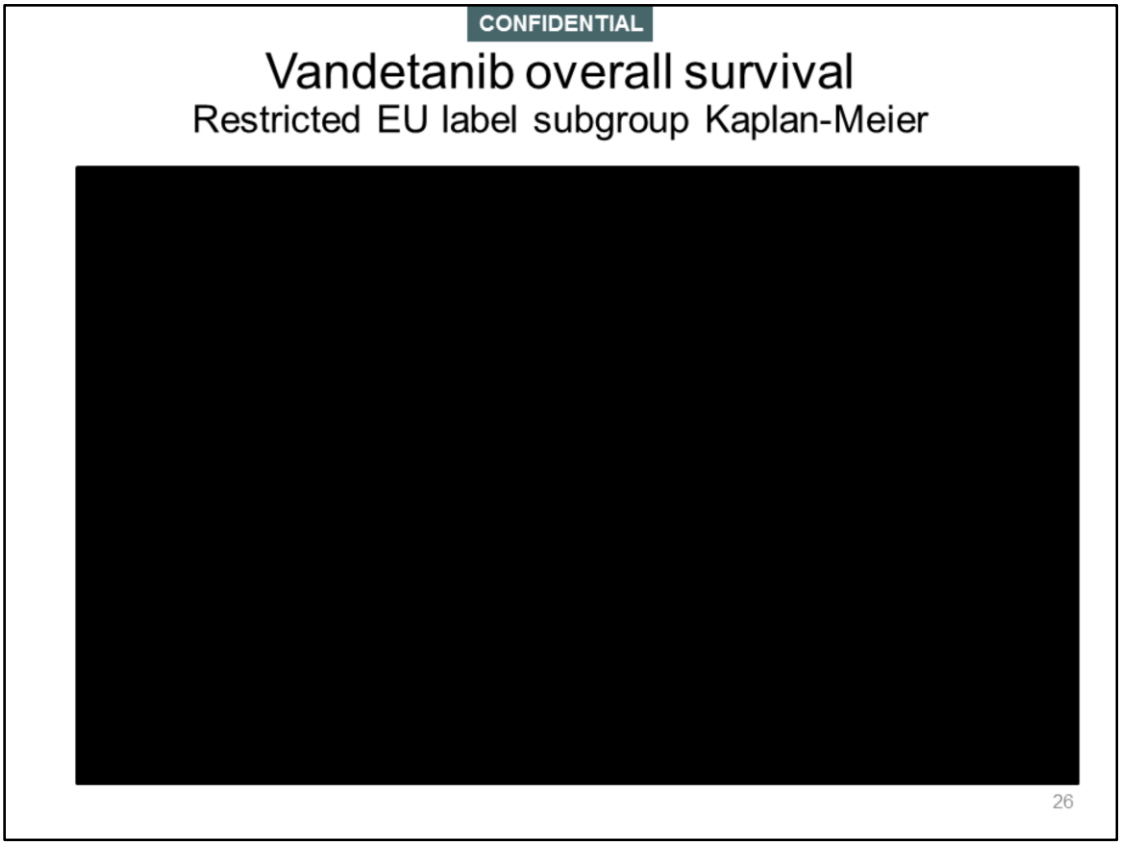


Source: Sanofi submission: 54-56, Table 24, pages 66-67
Source: AG report: Table 9, page 39, Table 12, page 42, Table 13, page 43

Mean survival time and its standard error underestimated because largest observation censored and estimation restricted to the largest event time
Site read PFS results the preferred outcome for the economic analysis because "better reflects real life practice" and median reached in both arms. *Source: Sanofi submission: page 49* although central read PFS is actually used in Sanofi's economic modelling.

Source: Sanofi submission: Figure 6, page 56

Based on central review



Source: Sanofi submission: Figure 7, page 58

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Trial results summary

EXAM (median follow-up 13.9 months)		ZETA EU label (median follow-up 24 months)		ZETA restricted EU label (med. follow-up 24 mths)	
Cabozantinib n=219	Placebo n=111	Vandetanib n=126	Placebo n=60	Vandetanib n=[redacted]	Placebo n=[redacted]
Progression-free survival (EXAM IRC-assessed; ZETA EU label and restricted EU label central read)					
11.2 months	4.0 months	28.0 months	16.4 months	[redacted]	[redacted]
HR 0.28 95% CI 0.19, 0.40 p<0.001		HR 0.47 95% CI 0.29, 0.77 p=0.0024		[redacted]	
Overall survival					
EXAM (median follow-up 52.4 months)		**ZETA EU label (median follow-up 105 months)**		**ZETA restricted EU label med. follow-up 105 mths**	
26.6 months	21.1 months	[redacted]	[redacted]	[redacted]	[redacted]
HR 0.85 95% CI 0.64, 1.12 p=0.2409		[redacted]		[redacted]	

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RET mutation subgroup analyses
(Progression free survival)

Mutation status	Cabozantinib		Placebo		HR (95% CI)	p value
	n	Median PFS	n	Median PFS		
RET-positive	107	60 weeks	62	20 weeks	0.23 (0.14, 0.38)	<0.0001
RET-negative	35	25 weeks	11	23 weeks	0.53 (0.19, 1.50)	0.2142
RET-unknown	77	48 weeks	38	13 weeks	0.30 (0.16, 0.57)	0.0001
RET M918T positive	81	61 weeks	45	17 weeks	0.15 (0.08, 0.28)	<0.0001
RAS-positive	13	47 weeks	3	8 weeks	0.15 (0.02, 1.10)	0.0317
RET-negative + RAS-negative	22	24 weeks	8	23 weeks	0.88 (0.24, 3.22)	0.8330

Vandetanib (intention-to-treat population)

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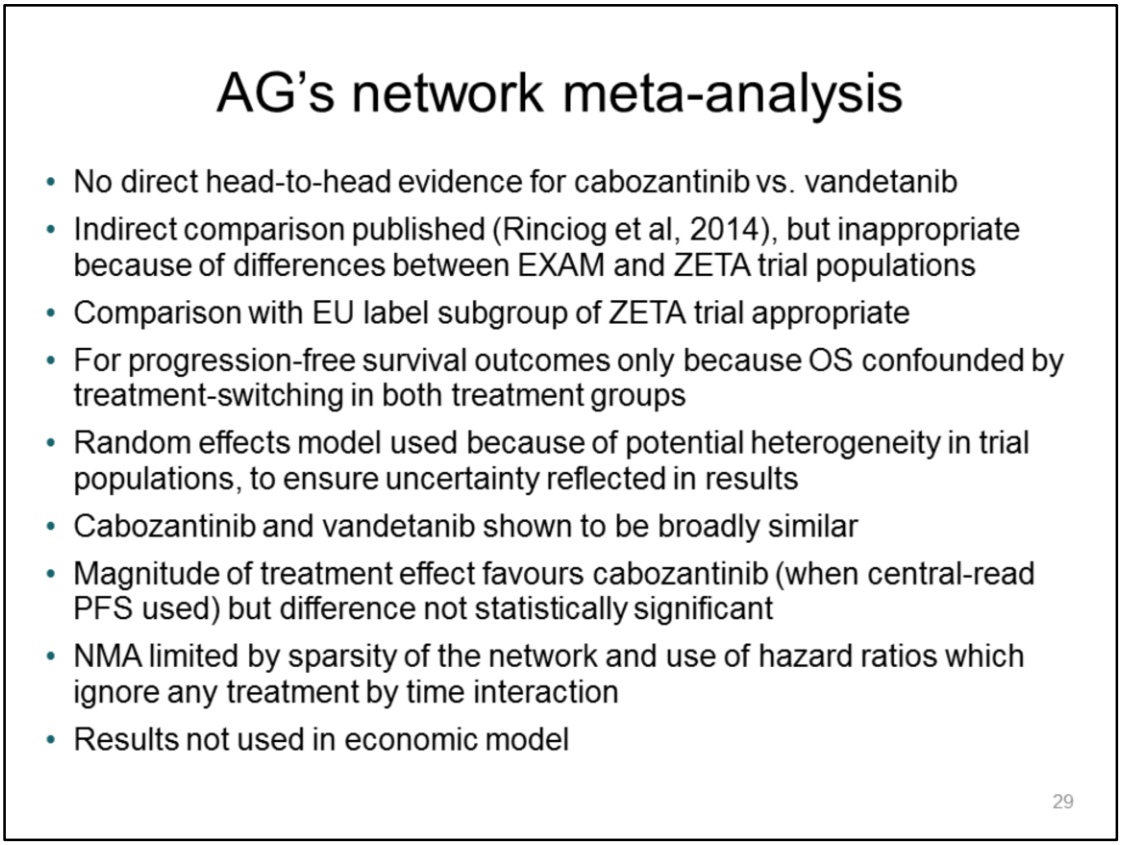
Source: Ipsen submission: page 7, page 20, Table 4.2.2.3, page 52
Source: Sanofi submission: Figure 4, page 51
Source: AG report: Table 11, Figure 3, page 41



Source: AG report: pages 51-3
Source: Ipsen submission: page 57
Source: Sanofi submission: Table 22, page 61, page 64

Valid NMA requires balance of treatment effect modifiers between trial populations
Patients in EXAM had confirmed disease progression; ZETA trial had a broader population
Results reported in Sanofi submission suggest progression may be a treatment modifier (greater effect seen in subgroup with progressed disease)

Differences in baseline characteristics in the 2 trial populations expected and do not invalidate indirect comparison
Clinical advisors suggested severity of disease was a treatment effect modifier, but because ECOG/WHO performance status at baseline was unavailable for ZETA EU label subgroup, balance could not be assessed (although subgroup analyses indicated consistent treatment effects according to performance status at baseline for both interventions).

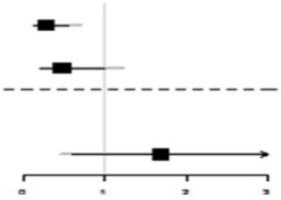
AG's network meta-analysis results

Investigator-read progression-free survival

Comparison	HR	(95% CrI)	(95% PrI)
placebo			
cabozantinib	0.29	(0.15,0.58)	(0.12,0.73)
vandetanib	0.33	(0.16,0.70)	(0.13,0.86)
cabozantinib			
vandetanib	1.14	(0.41,3.09)	(0.31,4.35)

Central-read progression-free survival

Comparison	HR	(95% CrI)	(95% PrI)
placebo			
cabozantinib	0.28	(0.14,0.56)	(0.11,0.71)
vandetanib	0.47	(0.22,0.99)	(0.18,1.23)
cabozantinib			
vandetanib	1.68	(0.61,4.62)	(0.45,6.48)



30

Source: AG report: Figures 5 and 6, page 54

Adverse effects

	EXAM Cabozantinib n=214	EXAM Placebo n=109	ZETA Vandetanib n=231	ZETA Placebo n=99
Duration of treatment	Median follow-up 10.8 mths		90.1 weeks	39.9 weeks
Any adverse event	100%	95.4%	99.6%	90.9%
Considered related to study drug	98.6%	74.3%	96.0%	NR
Any grade 3 or 4 adverse event	77.6%	33.9%	55.4%	24.2%
Any serious adverse event	53.3%	23.9%	30.7%	13.1%
Any adverse event leading to drug dose modification	87.4%	22.0%	49.4%	15.2%
Any adverse event leading to treatment discontinuation	23.4%	9.2%	12.1%	3.0%

Assessment Group comment: patients have substantial disease burden, demonstrated by adverse events and comorbidities in placebo arm and baseline data for EXAM and ZETA trial patients

31

Source: Ipsen submission: Table 4.2.2.7, pages 64-65, table 4.2.2.7.1, page 66, table 4.2.2.7.2, page 68.
Source: Sanofi submission: Table 33, pages 80-81
Source: AG report: pages 45-46

All reported using Common Terminology Criteria for Adverse Events

At time of analysis, 9.6% patients remained on cabozantinib; 0% on placebo
Most common SAEs mucosal inflammation, hypocalcaemia, pulmonary embolism, hypertension

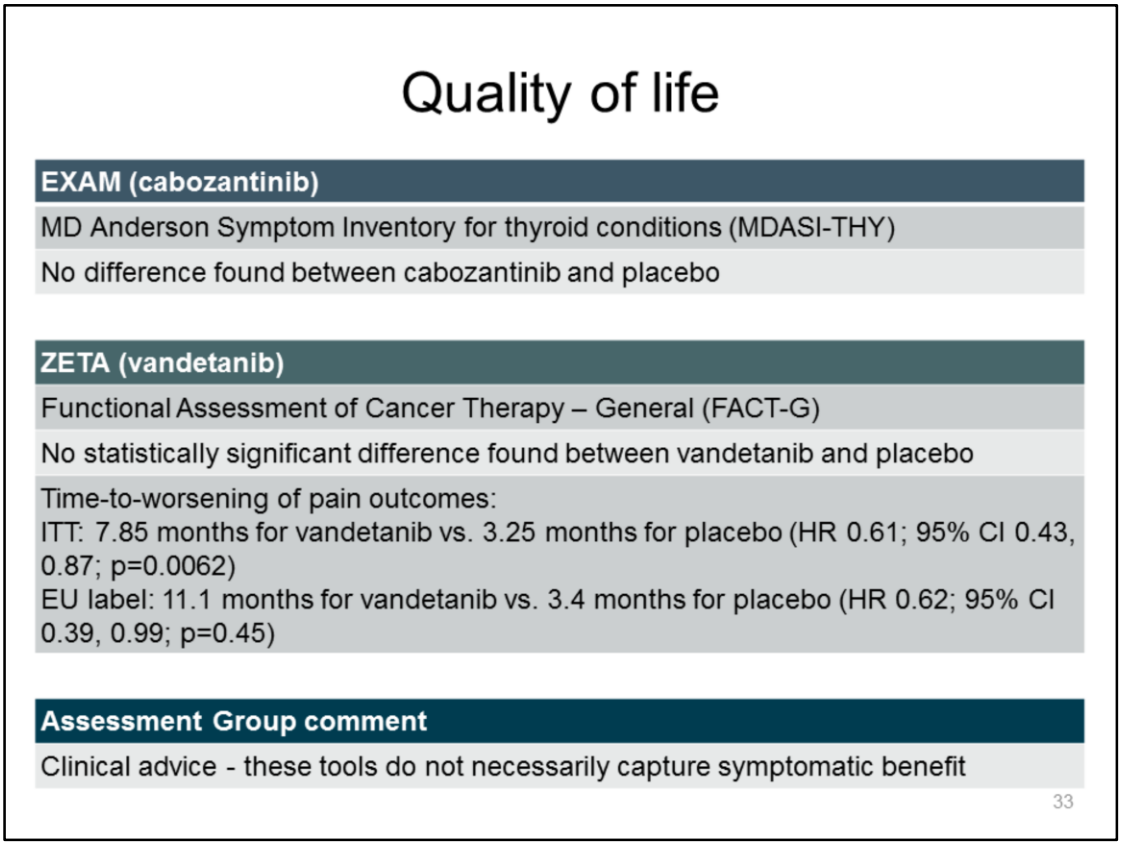
Adverse event data from ZETA ITT population used in economic model (results for EU label population also available in *Sanofi submission: Table 33, page 80*)

Dose modifications

EXAM population	Cabozantinib (n=214)	Placebo (n=109)
At least 1 dose delay	77.1%	-
At least 1 first level dose reduction	82.2%	11.0%
At least 1 second level dose reduction	45.5%	0.9%
ZETA ITT population	**Vandetanib (n=231)**	**Placebo (n=99)**
Dose reduction or interruption	49.4%	15.2%
Dose reduction	35.9%	3.0%
Dose interruption	47.2%	15.2%
ZETA EU label population	**Vandetanib (n=126)**	**Placebo (n=60)**
Dose reduction or interruption	-	-
Dose reduction	33%	3%
Dose interruption	-	-

32

Source: Ipsen submission, Table 4.2.2.7.3, page 69
Source: Sanofi submission: Table 33, page 79
Source: AG report: Table 20, page 50



Source: Ipsen submission: 39-40, 50
Source: Sanofi submission: page 51
Source: AG report: page 45, page 57

MDASI THY consists of 2 parts: 1) – Q1-9 covering 13 core cancer and treatment related symptoms with severity scored from 0 (not present) to 10 (symptom as bad as you can imagine it could be) and 2) Q20-5 evaluating how symptoms have interfered with patient's life in the previous 24 hours scored from 0 (no interference) to 10 (interfered completely). High MDASI score indicates presence of more symptoms. Difference in mean symptoms and intereference change over time between treatment groups, 0.5 (half of a SD of baseline values) effect size deemed clinically meaningful.

Results from FACT-G converted into health utilities for Sanofi's economic modelling

Clinical effectiveness summary

Assessment Group's critique

- EXAM low risk of bias; ZETA moderate to high risk of bias because of crossover design leading to confounding of outcomes data
- Different populations in 2 trials (EXAM progressive; ZETA less severe)
- EXAM trial and ZETA EU label subgroup populations comparable, and reflect patients likely to present in clinical practice in England
- Biomarkers (CTN/CEA) unlikely to be relevant when other criteria indicate progressive disease (e.g. RECIST, symptoms) – not used to inform decisions about starting TKI treatment
- Both drugs show significantly improved PFS compared with placebo
- Treatment effects of both broadly similar, but uncertainty in NMA results
- No significant survival benefit for either drug
- RET mutation testing not routinely undertaken to inform treatment choices so subgroup analyses not relevant
- No difference found in quality of life measurements
- Both drugs produced frequent adverse effects; more led to dose modification for cabozantinib than vandetanib

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Source: AG report, pages 54-58, 146

Cost effectiveness

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The economic models

NICE Reference case	Sanofi's model	Assessment Group's model
Type	Partitioned survival model	Partitioned survival model
Population	Restricted EU label	EU label Restricted EU label
Comparators	Best supportive care	Best supportive care Cabozantinib
Time horizon	20 years (lifetime)	20 years (lifetime)
Cycle length	1 month	1 month
Measure of health effects	QALYs	QALYs
Discounting of utilities and costs	3.5%	3.5%
Perspective	NHS/PSS*	NHS/PSS*
*PSS Costs not explicitly considered by Sanofi or included by Assessment Group		

36

Source: Sanofi submission: Table 36, pages 101-102
Source: AG report: Table 32, pages 76-77, Table 35, page 87

Sanofi's base case

Using list price, with errors corrected by AG

Technical programming errors corrected by Assessment Group related to:

- Proportion of patients discontinuing vandetanib before progression (company later corrected this in their submission)
- Duration over which QALY losses from adverse events applied (company later corrected this in their submission)

	Total		Incremental		ICER
	Costs	QALYs	Costs	QALYs	
Probabilistic					
Best supportive care	£138,915	2.19			
Vandetanib	£181,130	3.53	£42,215	1.34	**£31,546**
Deterministic					
Best supportive care	£132,292	2.13			
Vandetanib	£175,316	3.49	£43,024	1.36	**£31,731**

37

Source: AG report: Adapted from Table 31, page 74, page 83
Source: Sanofi submission: Table 49, pages 116-117

Deterministic sensitivity analysis showed the most influential parameters (of those assessed by Sanofi) related to:

- Probability of vandetanib continuation beyond progression
- Probability of treatment switching in BSC arm
- Vandetanib discontinuation parameter applied to vandetanib group during progression-free phase

AG's critique of Sanofi's model (1)

1. Relevance of restricted EU label population
   - In clinical practice vandetanib used in patients with symptomatic and progressive disease irrespective of CEA/CTN biomarker levels
   - Biomarkers used for monitoring, rather than informing treatment decisions
2. Not adjusting for continued vandetanib use/crossover post-progression
   - Survival data confounded because of treatment crossover
   - Use of vandetanib post-progression does not reflect usual clinical practice
   - Attempts made by Sanofi to adjust for crossover reported as unsuccessful
3. Likely overestimation of costs of vandetanib use post-progression
   - Post-progression vandetanib assumed to continue until death
   - Unlikely in reality – overestimates costs in both arms
4. Questionable implementation of vandetanib discontinuation parameter
   - Applied as fixed proportion of patients in pre-progression, resulting in vandetanib costs being less than post-progression in BSC arm
   - Lacks face validity (**significant impact on ICER when corrected**)

38

Source: AG report: pages 79-85

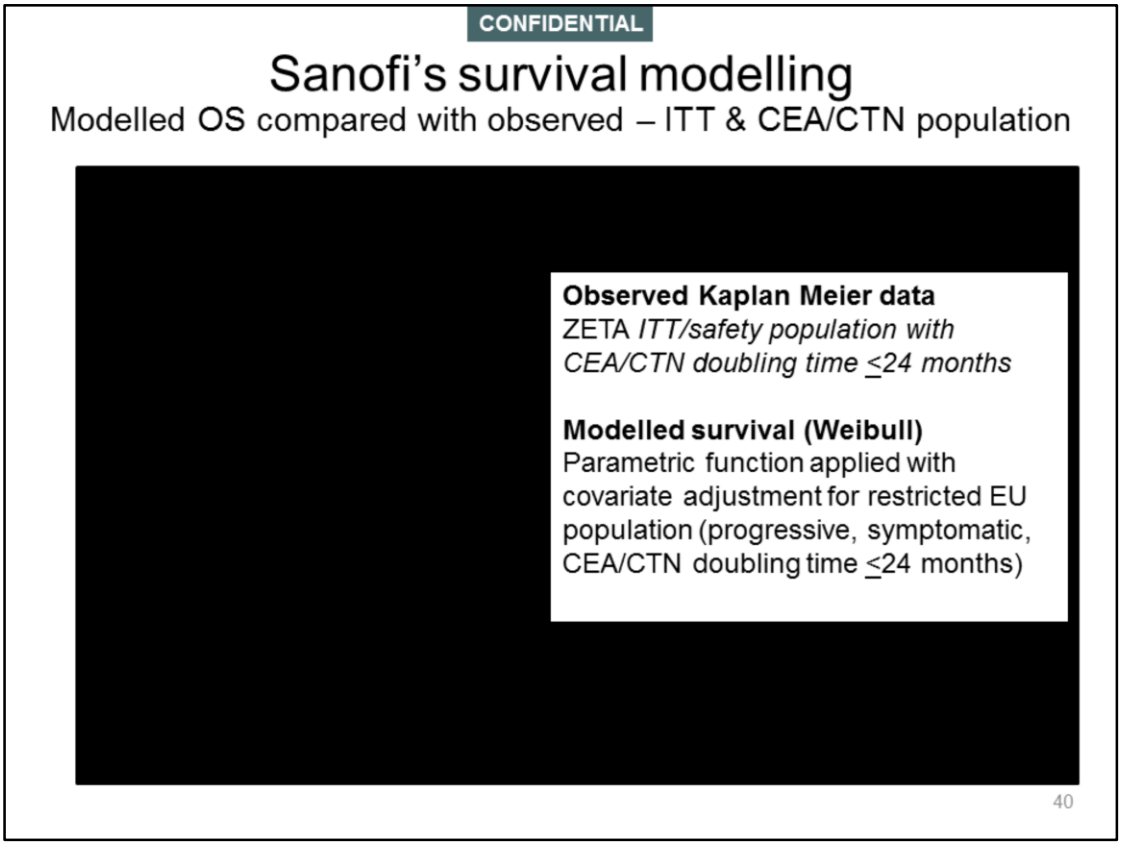
AG's critique of Sanofi's model (2)
Survival modelling

5. Robustness of covariate-adjusted survival modelling to reflect restricted EU label population
   - Parametric functions fitted to ZETA ITT population for PFS and safety population for OS with covariate adjustment to reflect restricted EU population (symptomatic, progressive disease with CTN/CEA doubling time ≤24 months). **More appropriate to fit parametric functions directly to population of interest.**
   - **Sanofi's interpretation of predicted and observed survival comparison is incorrect**. 2 different populations are being compared:
     - Observed survival: Kaplan-Meier ZETA ITT/safety population with CTN/CEA doubling time ≤24 months (not symptomatic or progressive)
     - Predicted survival: Parametric function applied with covariate adjustment to reflect restricted EU label population (symptomatic, progressive disease with CTN/CEA doubling time ≤24 months)

39

Source: AG report: pages 81-82

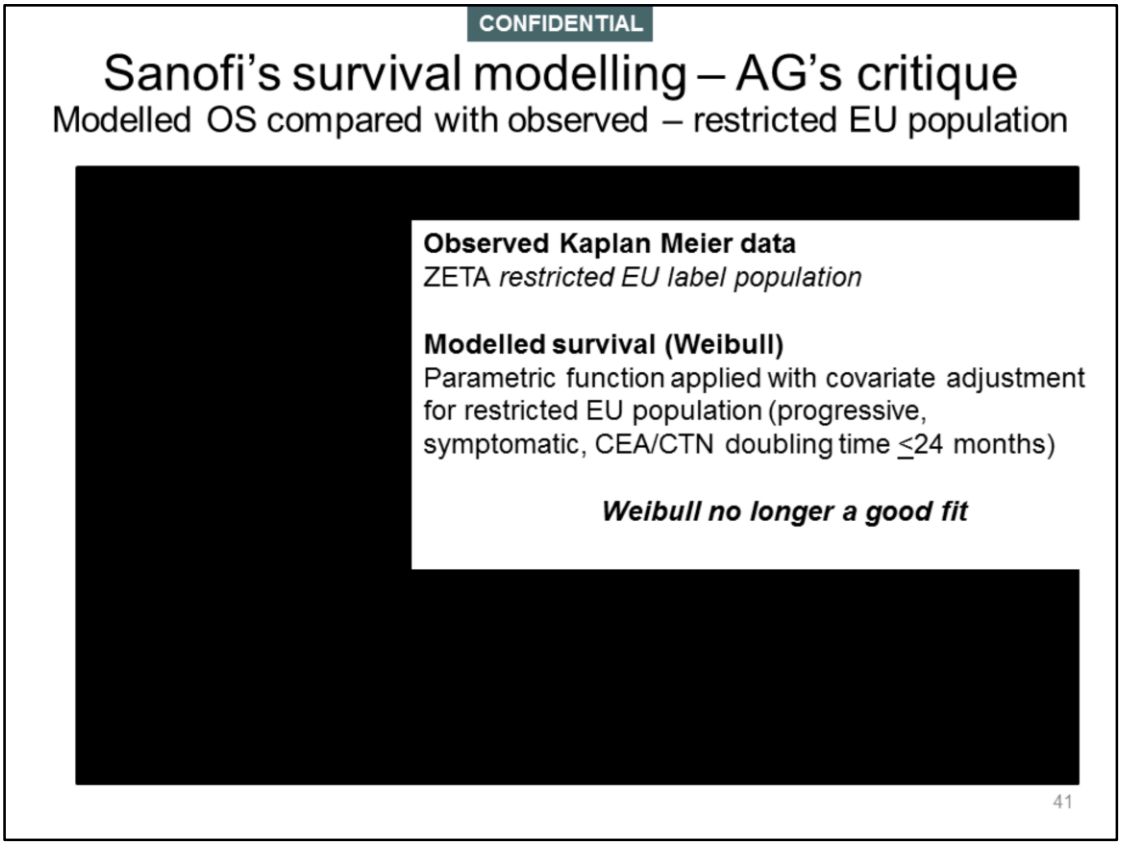
Assessment Group considers that fitting parametric functions to directly to a small population has no more potential for inaccuracy than the covariate approach.



Source: Sanofi submission: Figure 9, page 59, page 105
Source: AG report: page 82

Parametric functions fitted to available data with coefficients applied for 1)sympprog (presence of symptomatic and progressive disease) and 2)biomarker (CTN/CEA doubling time ≤24 months), i.e. Restricted EU population.

Weibull function selected because it "matches human mortality better in the long term".



Source: AG report: Figure 13, page 82

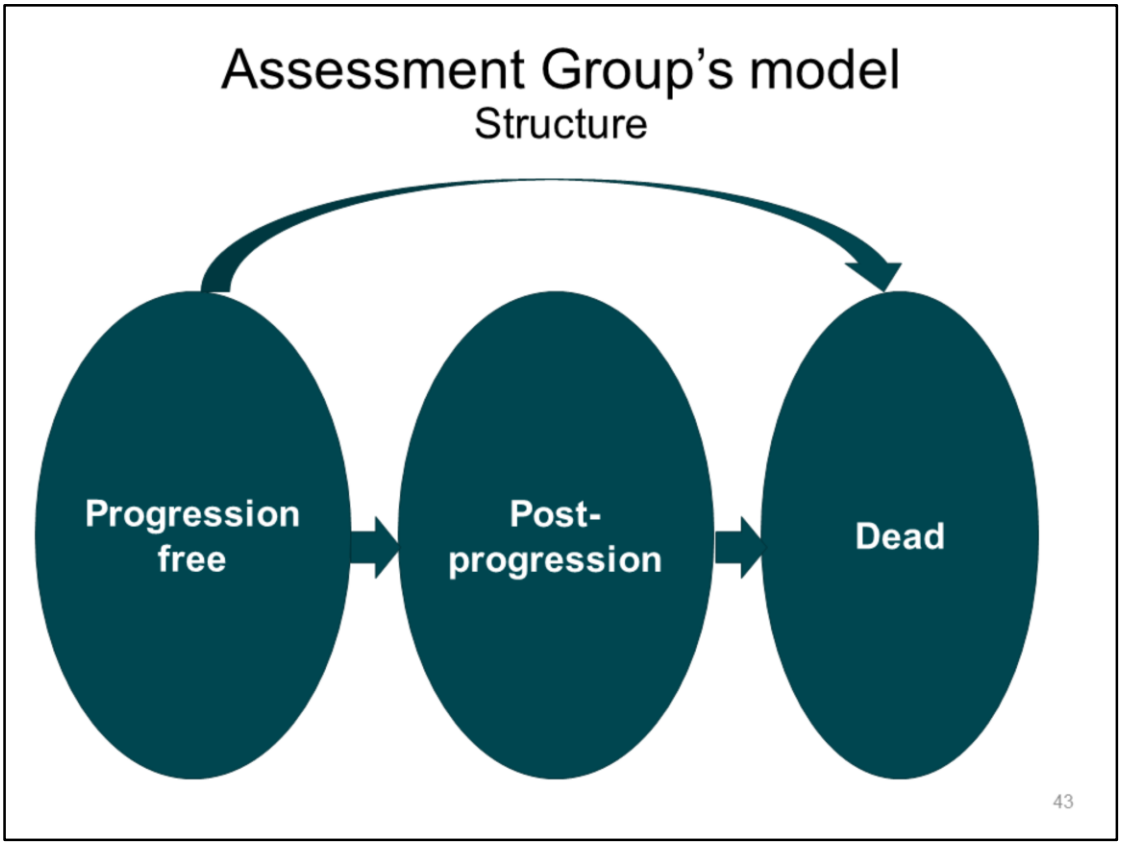
AG's critique of Sanofi's model (3)

6. Technical programming errors
   - Model not adjusted for logical inconsistencies
   - Proportion of patients discontinuing vandetanib pre-progression
   - Duration over which QALY losses from adverse events applied
7. Concerns regarding health utility parameters
   - FACT-G mapped to EQ-5D, but trial didn't use a preference-based measure
   - Beusterien study related to melanoma, so relevance to MTC unclear
   - More appropriate to use Fordham study because relates to thyroid cancer and health utilities valued using a preference-based measure
8. Limited exploration of uncertainty around survivor functions in DSA
9. Concerns regarding costings
   - BSC post-progression costs overestimated (**significant impact on ICER when corrected**)
   - Vandetanib monitoring costs underestimated
   - Adverse event costs overestimated

42

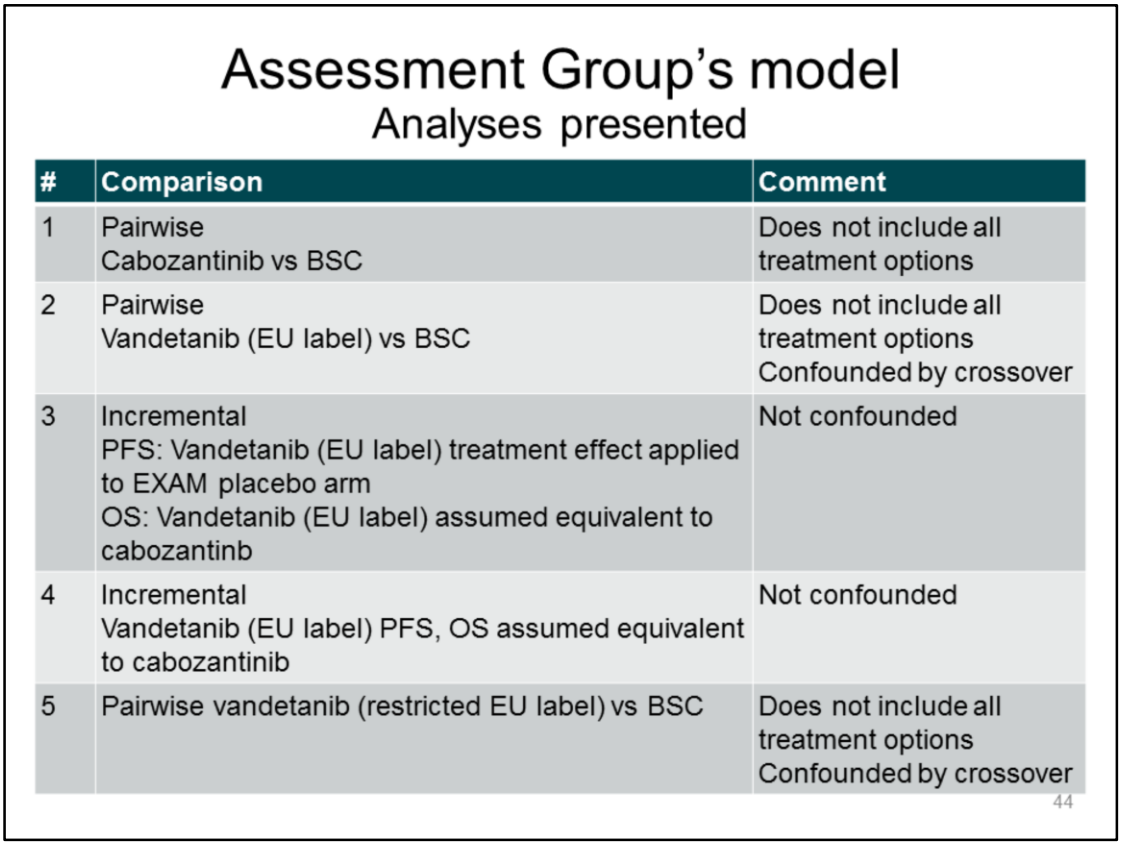
Source: AG report: pages 79-85, pages 70, 113

Sanofi later corrected 2 of the technical programming errors – proportion of patients discontinuing vandetanib pre-progression and duration over which QALY losses from adverse events applied.



Source: AG report: Adapted from Figure 14, page 88

Structure broadly similar Sanofi model: *Sanofi submission, page 87*



Assessment Group's model
Analyses presented

#	Comparison	Comment
1	Pairwise Cabozantinib vs BSC	Does not include all treatment options
2	Pairwise Vandetanib (EU label) vs BSC	Does not include all treatment options Confounded by crossover
3	Incremental PFS: Vandetanib (EU label) treatment effect applied to EXAM placebo arm OS: Vandetanib (EU label) assumed equivalent to cabozantinb	Not confounded
4	Incremental Vandetanib (EU label) PFS, OS assumed equivalent to cabozantinib	Not confounded
5	Pairwise vandetanib (restricted EU label) vs BSC	Does not include all treatment options Confounded by crossover

44

Source: AG report: page 86, Table 35, page 87

Cabozantinib could not be included in analysis 5 because equivalent covariate data (for symptomatic, progressive and CTN/CEA doubling times) not available from EXAM trial

Assessment Group's model
Structural assumptions

- Assumptions accepted in Sanofi model:
  - Modelling of costs and outcomes includes treatment switching and post-progression vandetanib use observed in ZETA, because attempts to adjust for crossover unsuccessful
  - Health related quality of life determined according to presence/absence of disease progression and incidence of grade 3/4 adverse events
  - Grade 3/4 adverse events impact on costs and health related quality of life; health losses assumed to be transient and resolved quickly (QALY loss only applied during first month)
  - Palliative care costs incurred only during final month of life
- BSC costs assumed to be the same in progression-free and post-progression states
- Health state resource use incurred during progression-free period assumed to differ between 3 treatment options
- Includes adjustments for logical inconsistencies

45

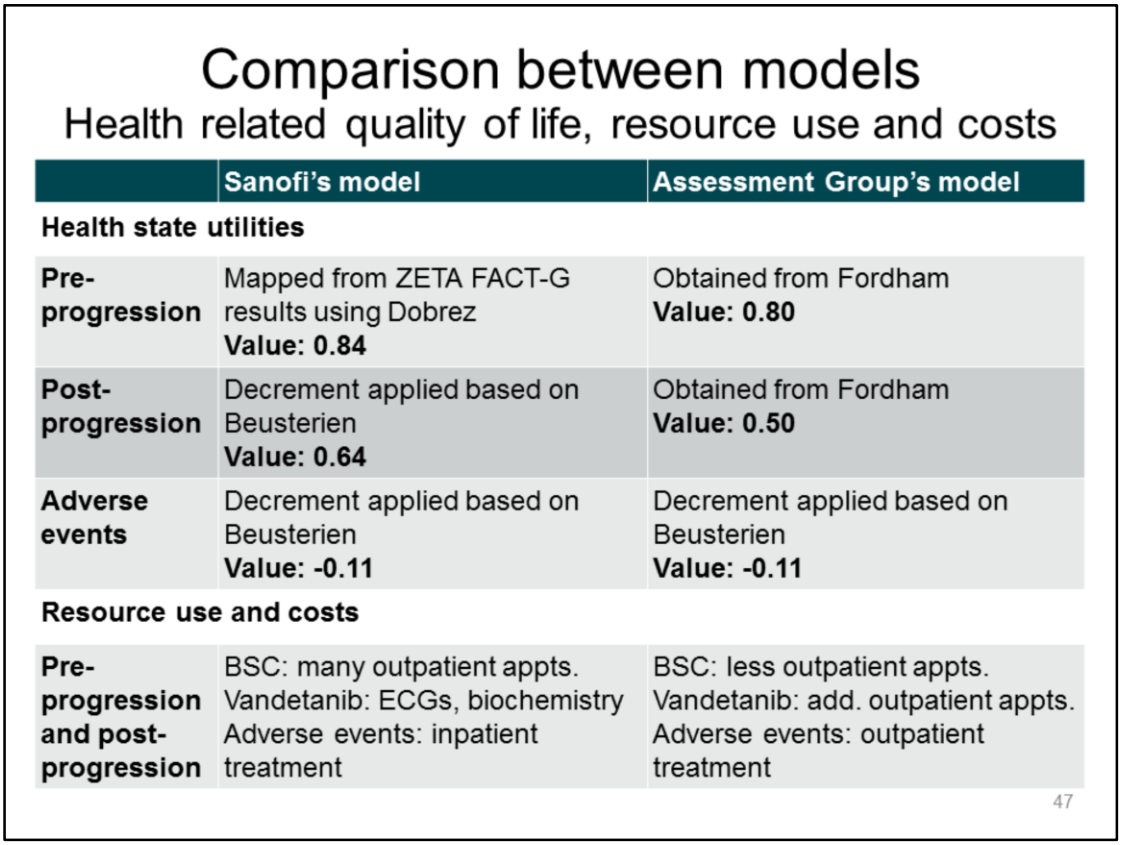
Source: AG report: pages 87-89

Comparison between models
Clinical parameters

	Sanofi's model	Assessment Group's model
Comparisons	Vandetanib vs BSC	Cabozantinib vs BSC Vandetanib vs BSC Full incremental analysis of all options
Trial evidence for OS and PFS outcomes	ZETA ITT/safety population	EXAM ITT ZETA EU label ZETA Restricted EU label
Survival modelling	Covariate-adjusted survivor functions fitted to ITT/safety dataset	Survivor functions fitted directly to data for relevant populations
Vandetanib discontinuation	Applied in full only to pre-progression vandetanib group, as fixed proportion of patients incurring no vandetanib costs	Half of total value applied to all patients receiving vandetanib in progression-free and post-progression states (where applicable).

46

Source: AG report: Adapted from Table 73, page 143



Comparison between models

Health related quality of life, resource use and costs

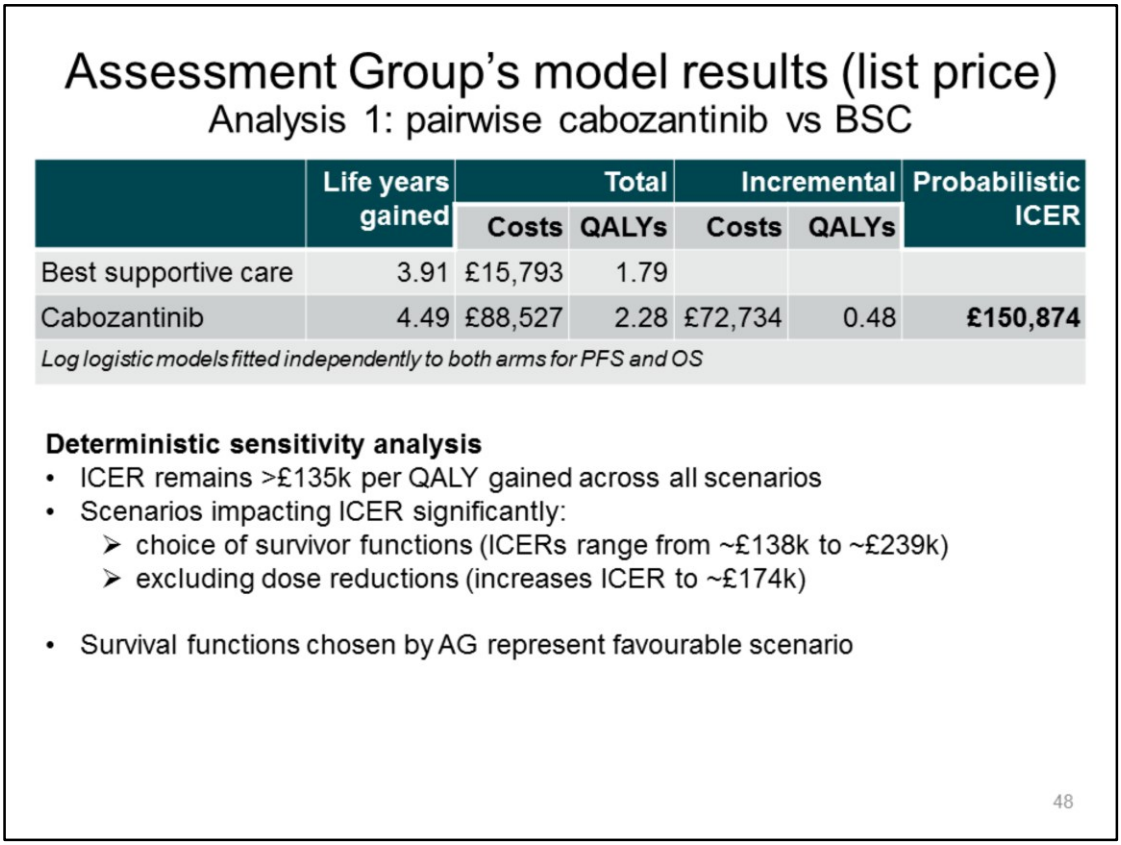
	Sanofi's model	Assessment Group's model
Health state utilities		
Pre-progression	Mapped from ZETA FACT-G results using Dobrez **Value: 0.84**	Obtained from Fordham **Value: 0.80**
Post-progression	Decrement applied based on Beusterien **Value: 0.64**	Obtained from Fordham **Value: 0.50**
Adverse events	Decrement applied based on Beusterien **Value: -0.11**	Decrement applied based on Beusterien **Value: -0.11**
Resource use and costs		
Pre-progression and post-progression	BSC: many outpatient appts. Vandetanib: ECGs, biochemistry Adverse events: inpatient treatment	BSC: less outpatient appts. Vandetanib: add. outpatient appts. Adverse events: outpatient treatment

47

Source: AG report: Table 23, page 65, Table 36, page 90, Table 46, pages 112-114
Source: Sanofi submission: pages 107-109

Dobrez: Algorithm to convert FACT-G responses to time trade-off (TTO) utilities. Based on directly elicited TTO utilities provided by patients with cancer for their health state at the time as well as the patients' responses to the FACT-G. 1,433 subjects with one of ten cancer diagnoses: breast (n=250), prostate (n=189), colon (n=170), non-small-cell lung (n=146), head and neck (n=164), non-Hodgkin's lymphoma (n=148), Hodgkin's lymphoma (n=38), small-cell lung (n=35), other known (n=288), and unknown primary cancer type (n=12).
Fordham: Vignettes developed for 7 health states based on results of a previous qualitative study in differentiated thyroid cancer. States included: (i) stable/no response; (ii) response (partial and complete); (iii) progressive disease; (iv) stable/no response with Grade 3 diarrhoea; (v) stable/no response with Grade 3 fatigue; (vi) stable/no response with Grade 3 HFS, and; (vii) stable/no response with Grades 1 and 2 alopecia. 100 members of UK general public participated in time trade-off (TTO) interviews to value the defined health states. Utility scores estimated directly from the raw interview response data and using regression analyses.
Beusterien: general population standard gamble study of societal preferences for

advanced melanoma health states



Assessment Group's model results (list price)

Analysis 1: pairwise cabozantinib vs BSC

	Life years gained	Total		Incremental		Probabilistic ICER
		Costs	QALYs	Costs	QALYs	
Best supportive care	3.91	£15,793	1.79			
Cabozantinib	4.49	£88,527	2.28	£72,734	0.48	**£150,874**

Log logistic models fitted independently to both arms for PFS and OS

Deterministic sensitivity analysis

- ICER remains >£135k per QALY gained across all scenarios
- Scenarios impacting ICER significantly:
  - choice of survivor functions (ICERs range from ~£138k to ~£239k)
  - excluding dose reductions (increases ICER to ~£174k)
- Survival functions chosen by AG represent favourable scenario

48

Source: AG report: Table 56, page 120, Table 57, page 121, page 122

See Table 58, page 122-23 for all scenario results included in deterministic sensitivity analysis

Assessment Group's model results (list price)

Analysis 2: pairwise vandetanib (EU label) vs BSC

	Life years gained	Total		Incremental		Probabilistic ICER
		Costs	QALYs	Costs	QALYs	
Best supportive care	7.58	£175,932	3.79			
Vandetanib	7.32	£255,677	4.02	£79,745	0.23	**£352,508**

Log logistic models fitted independently to both arms for PFS and OS

Deterministic sensitivity analysis

- ICER remains >£123k per QALY gained across all scenarios
- Scenarios impacting ICER significantly:
  - choice of survivor functions (ICERs range from ~£124k to vandetanib being dominated)
  - choice of utility values (alternatives can increase ICER to ~£822k and ~£1,532k)
  - assuming no vandetanib discontinuation (increases ICER to ~£378k)
  - excluding post-progression vandetanib costs (increases ICER to ~£752k)
- Survival functions chosen by AG represent neither most nor least favourable scenario

49

Source: AG report: Tables 59-60, page 124, page 125

See Table 61, page 126-7 for all scenario results included in deterministic sensitivity analysis

Assessment Group's model results (list price)

Analysis 3: incremental (vandetanib PFS treatment effect applied to EXAM; OS assumed equivalent)

	Life years gained	Total		Incremental		Probabilistic ICER
		Costs	QALYs	Costs	QALYs	
Best supportive care	3.91	£15,793	1.79			
Vandetanib	4.49	£67,968	2.17	£52,175	0.38	**£138,405**
Cabozantinib	4.49	£88,527	2.28	£20,559	0.11	**£195,593**

Single parametric model with covariate for treatment arm considered for ZETA EU label to obtain vandetanib treatment effect compared with placebo, which was then applied to EXAM placebo arm for PFS; log logistic model for PFS and OS

Deterministic sensitivity analysis

- ICER remains >£85k per QALY gained for vandetanib; >£148k for cabozantinb across all scenarios
- Scenarios impacting ICER significantly:
  - choice of survivor function (vandetanib ICERs range from ~£85k to extended dominance; cabozantinib ICERs range from ~£181k to ~£239k)
  - choice of utility values (alternatives can increase cabozantinib ICER to £380k)
  - assuming no vandetanib discontinuation (vandetanib extendedly dominated; cabozantinib ICER ~£148k)
- Survival functions chosen by AG represent neither most nor least favourable

50

Source: AG report: Table 62, page 127, Table 63, page 129

See Table 64, pages 129-130 for all scenario results included in deterministic sensitivity analysis

Assessment Group's model results (list price)

Analysis 4: incremental (PFS & OS assumed equivalent)

	Life years gained	Total		Incremental		Probabilistic ICER
		Costs	QALYs	Costs	QALYs	
Best supportive care	3.91	£15,793	1.79			
Vandetanib	4.49	£86,276	2.28	£70,482	0.49	**£144,841**
Cabozantinib	4.49	£88,527	2.28	-	-	**Dominated**

Log logistic models fitted independently to both arms for PFS and OS

Deterministic sensitivity analysis

- Cabozantinb remains dominated across all scenarios except where no vandetanib discontinuation
- Vandetanib ICER remains >£130k across all scenarios
- Scenarios impacting ICER significantly:
  - choice of survivor function (vandetanib ICERs range from ~£133k to ~£228k; cabozantinib dominated)
  - assuming no vandetanib discontinuation (increases vandetanib ICER to >£1.35m; cabozantinib ICER is ~£148k)
- Survival functions chosen by AG close to most favourable for vandetanib

51

Source: AG report: Tables 65-6, page 131, page 132

See Table 67, pages 133-4 for all scenario results included in deterministic sensitivity analysis

Assessment Group's model results (list price)

Analysis 5: pairwise vandetanib (restricted EU label) vs BSC

Represents Sanofi's base case analysis but with:

- Survivor models fitted directly to relevant observed data (see critique point 5)
- Different utilities, costs, discontinuation application (see critique points 4, 7, 9)

	Life years gained	Total		Incremental		Probabilistic ICER
		Costs	QALYs	Costs	QALYs	
Best supportive care	3.34	£96,759	1.83			
Vandetanib	6.50	£204,539	3.45	£107,780	1.61	**£66,779**

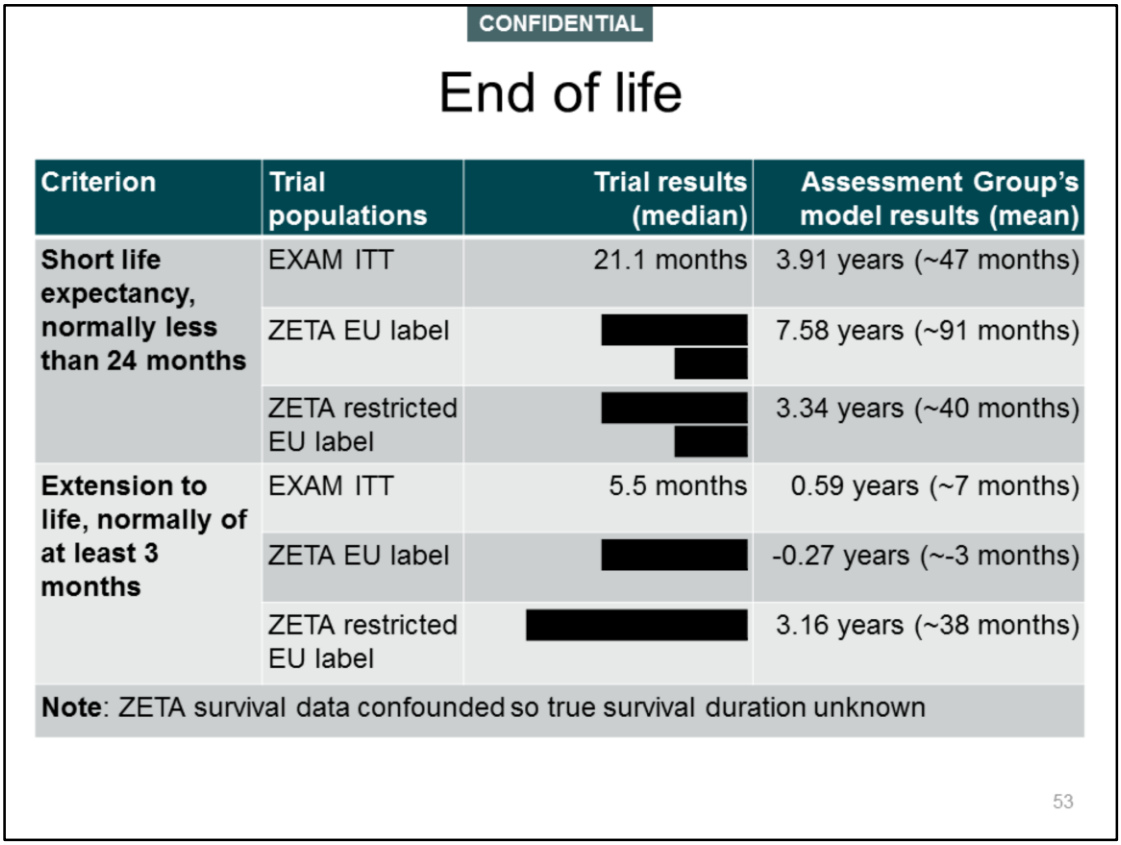
Individual log normal models for PFS; individual Gompertz models for OS

Deterministic sensitivity analysis

- ICER remains >£51k per QALY gained across all scenarios
- Scenarios impacting ICER significantly:
  - choice of survivor function (ICERs range from ~£51k to ~£71k)
  - choice of utility values (alternatives can reduce ICER to ~£61k)
  - excluding post-progression vandetanib costs (increases ICER to ~£84k)
  - assuming no vandetanib discontinuation (increases ICER to ~£76k)
- Survival curves used by AG represent neither most nor least favourable scenario[52]

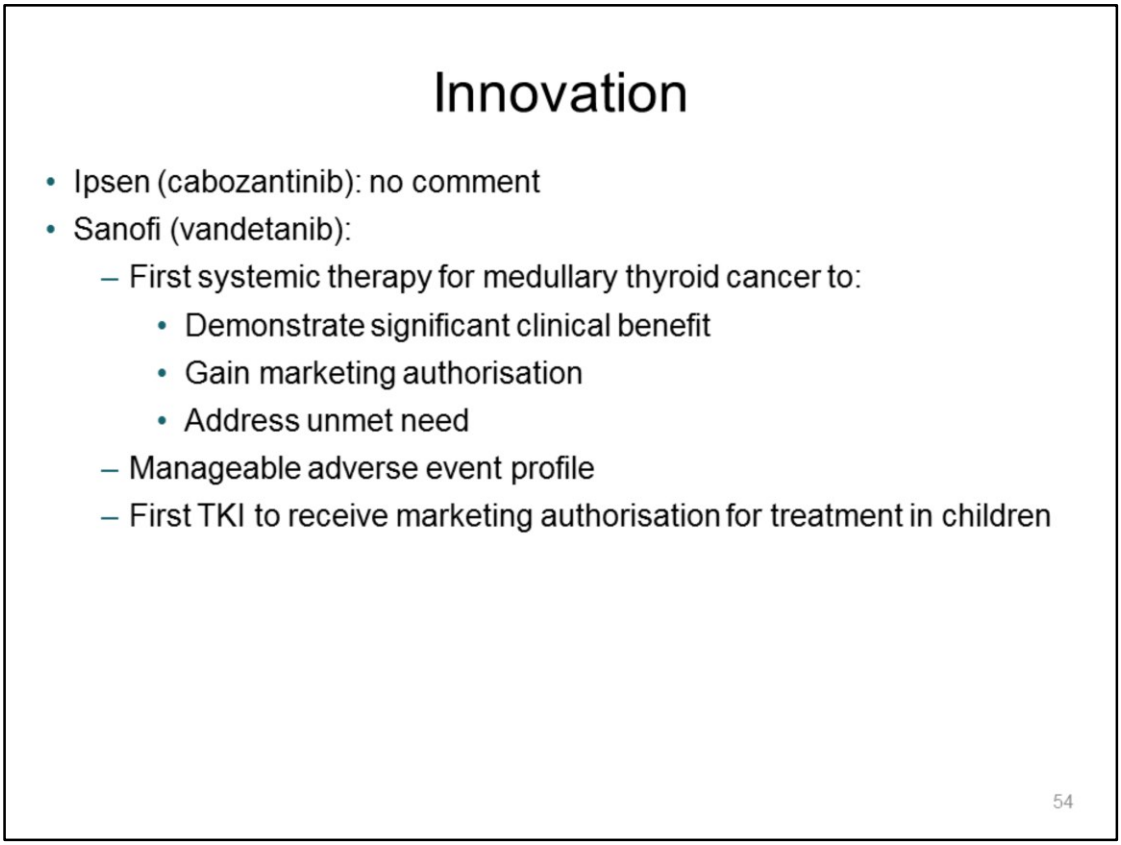
Source: AG report: Tables 68-9, page 135, page 136

See Table 70, pages 136-7 for all scenario results included in deterministic sensitivity analysis

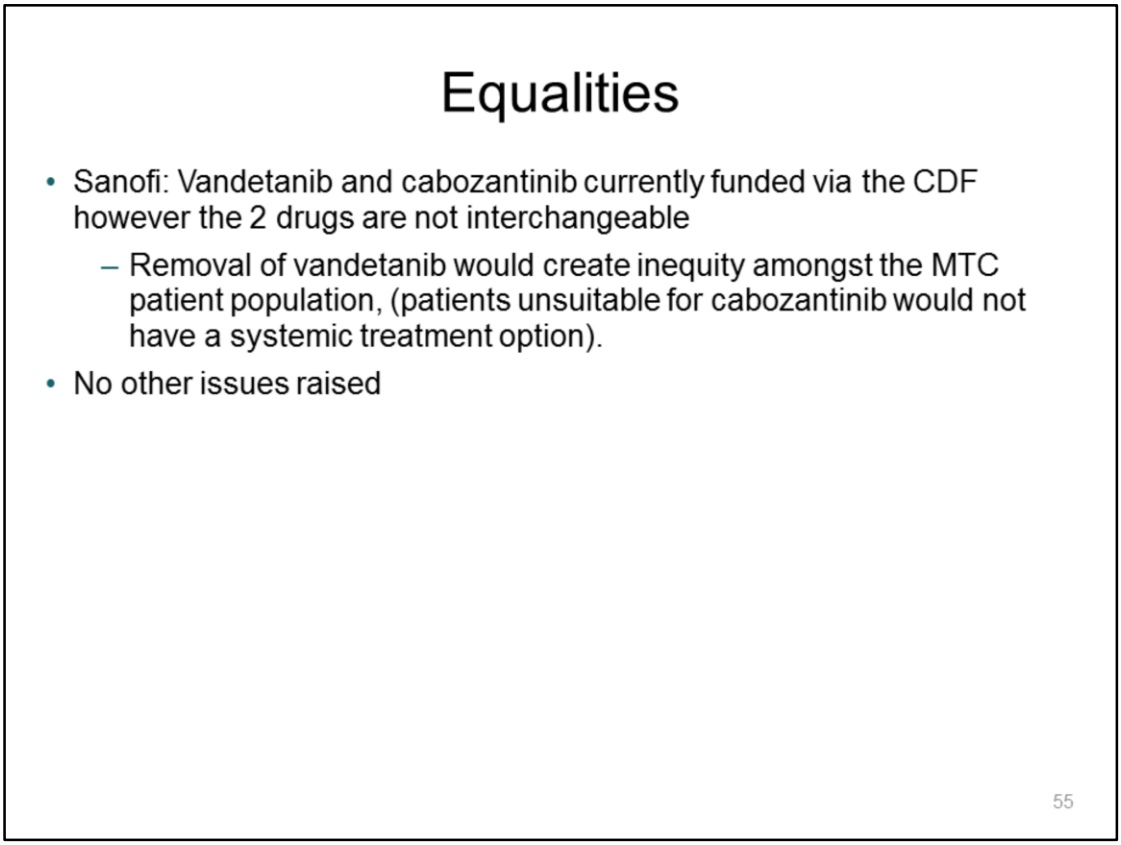


Source: Sanofi submission: page 89
Source: AG report: Table 74, pages 144-145

AG consider criteria for short life expectancy not met for both drugs, and criteria for extension to life met for cabozantinib and vandetanib restricted EU label population



Source: Sanofi submission, pages 31-2



Source: Sanofi submission: page 40

Key clinical effectiveness issues

- Which group of patients from the ZETA trial are the most appropriate in which to consider the clinical effectiveness of vandetanib: the EU label population or the restricted EU label population?
  - Is CTN/CEA doubling time an appropriate way to identify people in most need of treatment?
- Is RET mutation status an appropriate subgroup in which to consider clinical effectiveness?
- The impact of crossover on the ZETA trial results
- Is there evidence to show whether cabozantinib or vandetanib is more clinically effective than the other?
- Could 1 drug be used after the other in practice?
  - Approximately 20% in EXAM had a previous TKI; not reported in ZETA
  - Current CDF recommendations allow switching to the other TKI if toxicity occurs with one TKI.
  - Clinical advisors to AG consider there is value in having access to both TKIs.

56

Source: AG report: page 144

Key cost effectiveness issues

- The most appropriate population to assess vandetanib; EU label or restricted EU label
- The most appropriate model for decision-making for vandetanib: Sanofi or Assessment Group, main differences are:
  - Modelled population from ZETA (see slide 38)
  - Survival modelling method (see slides 39-41)
  - Health utilities data source (see slides 42, 47)
  - Application of vandetanib discontinuation parameter (see slide 38)
  - Costs (see slide 42)
- The most appropriate AG analyses for decision-making; pair-wise or fully incremental
- Are the end of life criteria met?

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Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence

Title: Cabozantinib and vandetanib for treating unresectable locally advanced or metastatic medullary thyroid cancer

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Rider on responsibility for report

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Paul Tappenden acted as the project lead. Ruth Wong undertook the electronic searches. Christopher Carroll and Eva Kaltenthaler undertook the systematic review of clinical effectiveness and safety evidence. Jean Hamilton conducted the statistical analysis. Paul Tappenden critiqued the health economic analysis submitted by Sanofi and developed the independent Assessment Group model. Laura Moss, Jonathan Wadsley and Sabapathy Balasubramanian provided clinical advice throughout the appraisal. All authors were involved in drafting and commenting on the final report.

About ScHARR

The School of Health and Related Research (ScHARR) is one of the four Schools that comprise the Faculty of Medicine at the University of Sheffield. ScHARR brings together a wide range of medical- and health-related disciplines including public health, general practice, mental health, epidemiology, health economics, management sciences, medical statistics, operational research and information science. It includes the Sheffield unit of the Trent Institute for Health Services Research, which is funded by NHS R&D to facilitate high-quality health services research and capacity development.

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1 DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

DEFINITION OF TERMS

Medullary thyroid cancer	A rare type of thyroid cancer that originates from the parafollicular cells (also called C cells) of the thyroid.
Calcitonin	A hormone produced by the parafollicular cells (C cells) of the thyroid gland.
Carcinoembryonic Antigen	A protein that might appear in the blood of people who have certain types of cancer.
Meta-analysis	A statistical method by which the results of a number of studies are pooled to give a combined summary statistic.
Network meta-analysis	A meta-analysis in which multiple treatments are compared using both direct comparisons of interventions within randomised controlled trials and indirect comparisons across trials based on a common comparator.
Extended dominance	A situation whereby the incremental cost-effectiveness ratio for a given treatment alternative is higher than that of the next more effective (non-dominated) comparator.
Simple dominance	A situation whereby an intervention is less effective and more expensive than its comparator.
Partitioned survival model	A model in which individuals reside in one of a series of mutually exclusive and jointly exhaustive health states. State membership is determined fully by a series of independently modelled non-mutually exclusive survival curves. A survival curve must be specified for each alive health state that describes time from *model start* (i.e. patient entry in to the model) to transiting to *any health state that is further along the sequence.*

Abbreviations

µg/L	Microgram/litre
AE	Adverse event
AIC	Akaike Information Criterion
ATA	American Thyroid Association
AWMSG	All Wales Medicines Strategy Group
BIC	Bayesian Information Criterion
BPI	Brief Pain Inventory
BSC	Best supportive care
CC	Complexity and comorbidity
CDF	Cancer Drugs Fund
CDSR	Cochrane Database of Systematic Reviews
CEA	Carcinoembryonic antigen
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CINAHL	Cumulative Index of Nursing and Allied Health Literature
CPCI	Conference Proceedings Citation Index
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
CT	Computerised tomography
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
CTN	Calcitonin
DARE	Database of Abstracts of Reviews of Effects
DICE	Discretely Integrated Condition Event
DSA	Deterministic sensitivity analysis
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGF	Epidermal growth factor
EMA	European Medicines Agency
EMBASE	*Excerpta Medica* dataBASE
EQ-5D	Euroqol 5-Dimensions
EU	European Union
FACT-G	Functional Assessment of Cancer Therapy - General
FDA	Food and Drug Administration
FLT3	Fms-like tyrosine kinase-3
FNAB	Fine-needle aspiration biopsy
GI	Gastrointestinal
HFS	Hand-foot syndrome
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IPCW	Inverse Probability of Censoring Weights
IPD	Individual patient data
IPE	Iterative Parameter Estimation
IRC	Independent review committee
ITT	Intention-to-treat
KDR	Kinase insert domain containing receptor
LYG	Life year gained
MDASI-THY	MD Anderson Symptom Inventory - Thyroid
MEDLINE	Medical Literature Analysis and Retrieval System Online
MEN	Multiple endocrine neoplasia
MeSH	Medical subject heading

mg	Milligram
MIBG	Iodine-123-meta-iodobenzylguanidine
(m)RECIST	modified Response Evaluation Criteria in Solid Tumour
MRI	Magnetic resonance imaging
MTC	Medullary thyroid cancer
N/a	Not applicable
NCT	National Clinical Trial
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
OLS	Ordinary least squares
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressive disease
PFLYG	Progression-free life year gained
PFS	Progression-free survival
pg/mL	Picograms per millilitre
pmol/L	Picomole/litre
PP	Post-progression
PPS	Post-progression survival
PPES	Palmarplantar erythrodysaesthesia syndrome
PrI	Prediction interval
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROM	Patient-reported outcome measure
PROSPERO	International prospective register of systematic reviews
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QTc	Corrected QT interval
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumour
RET	RE-arranged during Transfection
RPSFT	Rank Preserving Structural Failure Time
RTK	Receptor tyrosine kinase
SAE	Serious adverse event
SAS	Statistical Analysis System
SCI	Science Citation Index
s.d.	Standard deviation
s.e.	Standard error
SG	Standard gamble
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
TKI	Tyrosine kinase inhibitor
TSH	Thyroid stimulating hormone
TTO	Time trade-off
TWP	Time to worsening of pain
UK	United Kingdom
VEGF	Vascular endothelial growth factor
WHO ICTRP	World Health Organization International Clinical Trials Registry Portal
WTP	Willingness-to-pay

2 EXECUTIVE SUMMARY

2.1 Background

Thyroid cancer is the most common malignant endocrine tumour, but represents only about 1% of all malignancies. According to Cancer Research UK, 3,404 new diagnoses of thyroid cancer were reported in England in 2014: 966 cases (28%) were in males and 2,438 cases (72%) were in females. There are four main types of thyroid cancer: papillary, follicular, medullary and anaplastic. Medullary thyroid carcinoma (MTC) is a rare type of cancer that presents as a mass of tumours in the thyroid gland of the neck. MTC occurs in the parafollicular cells (also known as C-cells). There are four types of MTC: sporadic, multiple endocrine neoplasia (MEN) 2A and 2B and familial MTC; approximately 75% of cases of MTC are sporadic in nature. MTC is very rare and accounts for approximately 5% of all thyroid cancers. The estimated annual incidence of MTC is around 170 cases. Ten-year survival rates for patients with regional disease spread are reported to be around 75%, whilst survival estimates of 21%-40% have been reported for patients presenting with metastases at diagnosis (Stage IV disease). Patients with MTC typically present with a lump in the neck (which may represent a thyroid or lymph node mass) or distant metastases. The lumps are not usually associated with other symptoms but may occasionally cause dysphagia (difficulty or discomfort in swallowing) or dysphonia (difficulty in speaking). Symptoms might also relate to the effect of metastases, especially diarrhoea, flushing, dyspnoea and bone pain.

For many patients, surgery can be curative. Treatment options for patients with unresectable locally advanced or metastatic MTC include tyrosine kinase inhibitor (TKI) therapy and best supportive care (BSC), which typically comprises symptom control and palliative treatments such as radiotherapy and palliative surgery. Currently, vandetanib and cabozantinib are the modality of choice for inoperable progressive and symptomatic MTC. Both cabozantinib and vandetanib are currently available through the Cancer Drugs Fund (CDF) for the first-line treatment of symptomatic and progressive MTC. In 2016, [redacted] new patients initiated treatment with these therapies (vandetanib, n=[redacted]; cabozantinib, n=[redacted]).

The evidence presented within this assessment relates to two populations of patients with MTC: (1) patients with symptomatic and progressive disease (referred to as the "EU label population"), and; (2) patients with symptomatic and progressive disease with carcinoembryonic antigen (CEA) and calcitonin (CTN) doubling time ≤24 months (referred to as the "Restricted EU label population").

2.2 Aims

The aims of the assessment are:

1) To evaluate the clinical effectiveness and safety of cabozantinib and vandetanib within their marketing authorisations for treating unresectable locally advanced or metastatic MTC.
2) To estimate the incremental cost-effectiveness of cabozantinib and vandetanib compared with each other and BSC.

3) To identify key areas for primary research.
4) To estimate the overall cost in England.

2.3 Methods

Clinical effectiveness

A systematic review was conducted following standard methods. Systematic searches were undertaken in 10 electronic databases up to November 2016 to identify randomised controlled trials (RCTs) of cabozantinib and vandetanib for treating unresectable locally advanced or metastatic MTC. The quality of studies included in the review was assessed using the Cochrane Risk of Bias tool. Results were reported using narrative synthesis and were presented in a tabular format. In the absence of direct evidence comparing cabozantinib and vandetanib, a network meta-analysis (NMA) was performed using the ZETA EU label and EXAM intention-to-treat (ITT) populations.

Cost-effectiveness

A comprehensive search was undertaken to systematically identify economic evaluations of treatments for locally advanced or metastatic medullary thyroid cancer (MTC) and studies reporting on the health-related quality of life (HRQoL) of patients with locally advanced or metastatic thyroid cancer (including MTC as well as other more common forms of thyroid cancer). The submissions received by the National Institute for Health and Care Excellence (NICE) included one unpublished economic analysis of vandetanib versus BSC in the Restricted EU label population (symptomatic and progressive MTC with CEA/CTN doubling time ≤24 months) based on a partitioned survival structure implemented using the Discretely Integrated Condition Event (DICE) approach. The fully executable model used to undertake the analysis was also submitted to NICE. The model was scrutinised by the Assessment Group and the economic analysis was critically appraised using the key items contained within published checklists. Two errors were identified hence all submitted analyses were repeated by the Assessment Group using a corrected version of the company's model. The manufacturer of cabozantinib did not submit any economic evidence relating to this product.

In light of the absence of published evidence relating to the cost-effectiveness of vandetanib or cabozantinib, the absence of a submitted economic analysis of cabozantinib and concerns regarding the submitted economic analysis of vandetanib, the Assessment Group developed a *de novo* health economic model. The Assessment Group's model used a partitioned survival approach based on three health states: (i) progression-free; (ii) post-progression, and; (iii) dead. Costs and health utilities were assumed to differ according to the presence/absence of disease progression. The model parameters were informed by analyses of individual patient data (IPD) from the EXAM trial, replicated IPD from the ZETA trial, the submissions from Sanofi and Ipsen and data contained within subsequent clarification responses, as well as published literature, standard reference cost sources and expert judgement. The model was evaluated

across five sets of analyses from the perspective of the NHS and Personal Social Services (PSS) over a lifetime horizon. Four sets of analyses related to the evaluation of cabozantinib and/or vandetanib versus BSC in the EU label population (symptomatic and progressive MTC); the remaining analysis set evaluated vandetanib versus BSC in the Restricted EU label population (symptomatic and progressive MTC with CEA/CTN doubling time≤24 months). Costs and health outcomes were discounted at a rate of 3.5% per annum. Costs were valued at 2016/17 prices. Confidential Patient Access Schemes have been proposed for both products. All economic analyses within this report relate to the list prices of vandetanib and cabozantinib; separate analyses including price discounts are presented in confidential appendices to this report.

2.4 Results

Clinical effectiveness

The systematic review identified and included two placebo-controlled trials. The EXAM trial evaluated the efficacy and safety of cabozantinib in patients with unresectable locally advanced, metastatic and progressive MTC (n=330). The ZETA trial evaluated the efficacy and safety of vandetanib in patients with unresectable locally advanced or metastatic MTC (n=331). The two trials therefore assessed different populations because the ZETA trial inclusion criteria did not specify "progressive" disease: the ITT population in this trial therefore generally had less severe disease (there were more patients with potentially indolent disease). However, the ZETA trial did include a subgroup of patients with "progressive and symptomatic disease" (n=186), which formed the "EU label" population. Clinical advice received by the Assessment Group confirmed that this group was comparable with the EXAM ITT population.

In terms of efficacy, both cabozantinib and vandetanib significantly improved progression-free survival (PFS) compared with placebo. For the principal comparison between the EXAM ITT population and the ZETA EU label population, PFS was similar for cabozantinib versus placebo (investigator-read hazard ratio [HR] 0.29, 95% confidence interval [CI] 0.21-0.42, $p<0.001$; central review HR 0.28, 95% CI 0.19-0.40, $p<0.001$) and vandetanib versus placebo (investigator-read HR 0.33, 95% 0.2-0.53, $p=0.0226$; central review, excluding crossover patients, HR 0.47, $p=0.0024$, and including open-label populations, HR 0.32, $p<0.001$).

The NMA undertaken by the Assessment Group suggested that the treatment effects on PFS were broadly similar (vandetanib versus cabozantinib, HR 1.14, 95% credible interval [CrI] 0.41-3.09). The magnitude of the treatment effect was more favourable towards cabozantinib when the comparison was based on central-read PFS rather than investigator-read PFS (HR 1.68, 95% CrI 0.61-4.62), however, the difference between the two interventions was not statistically significant. The NMA was however limited by the sparsity of the network and the use of HRs which ignore any treatment by time interaction.

Based on the trial evidence, there was no significant benefit in terms of overall survival (OS) for either cabozantinib or vandetanib compared with placebo, although the data from the ZETA trial were subject to potential confounding due to open-label vandetanib use in the placebo group. Both cabozantinib ($p<0.001$) and vandetanib (ITT group, $p<0.001$ and EU label group, $p<0.0001$) demonstrated significantly better objective response rates (ORRs), as determined by modified or standard RECIST criteria, than placebo. Both cabozantinib ($p<0.001$) and vandetanib ($p<0.001$) also demonstrated significantly better CTN and CEA response rates than placebo. Both cabozantinib and vandetanib produced frequent adverse events (AEs). The overall incidence of any severe adverse event (SAE) in the EXAM trial was 42% in the cabozantinib arm compared with 23% in the placebo arm, whilst in the ZETA trial, the incidence of SAEs was 31% in the vandetanib arm compared with 13% in the placebo arm.

Cost-effectiveness

The corrected version of the company's model suggests that the probabilistic incremental cost-effectiveness ratio (ICER) for vandetanib versus BSC in the Restricted EU label population (symptomatic and progressive MTC with CEA/CTN doubling time≤24 months) is approximately £31,546 per quality-adjusted life year (QALY) gained. However, Assessment Group noted several concerns with this analysis, in particular: (1) the questionable relevance of the Restricted EU label population to current clinical practice; (2) the failure to adjust for open-label vandetanib use in both treatment groups of the ZETA trial; (3) the likely overestimation of the costs of vandetanib use in the post-progression state; (4) questionable assumptions regarding the amount of vandetanib received, and; (5) concerns regarding the robustness of the company's covariate-adjusted survival modelling in the Restricted EU label population. The Assessment Group considers that it is likely that the ICER for vandetanib is considerably higher than the estimates presented within the Sanofi submission to NICE.

Based on the Assessment Group's probabilistic analysis of cabozantinib versus placebo in the EU label (symptomatic and progressive) MTC population, the ICER for cabozantinib versus BSC is expected to be £150,874 per QALY gained. Within the EU label (symptomatic and progressive) MTC population of the ZETA trial, the Assessment Group's probabilistic analysis suggests that the ICER for vandetanib versus BSC is expected to be £352,508 per QALY gained. The fully incremental analysis of cabozantinib, vandetanib and BSC based on the EXAM ITT population and the vandetanib PFS treatment effect from the ZETA trial suggests that the ICER for vandetanib versus BSC is expected to be £138,405 per QALY gained whilst the ICER for cabozantinib versus vandetanib is expected to be £195,593 per QALY gained. Within the fully incremental analysis in which the PFS and OS outcomes for vandetanib were assumed to be equivalent to the cabozantinib group outcomes in the EXAM trial, cabozantinib is expected to be dominated, whilst the ICER for vandetanib versus BSC is expected to be £144,841 per QALY gained.

Within the Restricted EU label population (symptomatic and progressive MTC plus CEA/CTN doubling time ≤24 months), the ICER for vandetanib versus BSC is expected to be £66,779 per QALY gained.

2.5 Discussion

Two RCTs comparing active treatment with placebo were identified, one of cabozantinib (EXAM) and one of vandetanib (ZETA). The EXAM trial was at low risk of bias. The ZETA trial was at moderate or high risk of bias, principally as a consequence of the use of a crossover design that led to the potential confounding of outcomes data. There was no direct evidence comparing outcomes for cabozantinib or vandetanib against each other. Both cabozantinib and vandetanib demonstrated significant benefits compared with placebo in terms of PFS and appeared to be broadly similar in terms of efficacy, although neither has demonstrated significant OS benefit compared with placebo. Both cabozantinib and vandetanib produced frequent AEs, with substantial proportions of patients experiencing AEs that led to dose interruption or reduction.

The economic analyses undertaken by Sanofi and the Assessment Group are each limited by the evidence used to inform them. In particular, the use of open-label vandetanib in the placebo group of the ZETA trial is likely to have confounded OS outcomes. The Sanofi submission states that whilst attempts had been made to adjust for this potential confounding in OS using the Rank Preserving Structural Failure Time (RPSFT) approach, these were not successful. The Assessment Group did not have access to the underlying IPD (including data on relevant covariates), hence further attempts to adjust for treatment switching were not possible. Consequently, the pairwise analyses of vandetanib versus BSC may not be meaningful for decision-making. For this reason, the Assessment Group undertook fully incremental analyses based principally on the observed outcomes within the EXAM trial. Whilst these incremental analyses necessarily reflect potentially strong assumptions concerning transferable/equivalent treatment effects between vandetanib and cabozantinib, they are not subject to confounding due to post-progression vandetanib use. These analyses suggest that within the EU label population (symptomatic and progressive MTC), the ICERs for vandetanib and cabozantinib versus BSC are expected to be in excess of £138,000 per QALY gained. The analyses undertaken in the Restricted EU label population (symptomatic and progressive MTC plus CEA/CTN doubling time ≤24 months) suggest that the ICER for vandetanib versus BSC is expected to be more favourable but still remains greater than £66,000 per QALY gained; this latter analysis is also subject to potential confounding due to open-label vandetanib use.

The Assessment Group's economic analysis suggest that the NICE's criteria for life-extending therapies given at the end of life are not met for cabozantinib in the EU label population (symptomatic and progressive MTC) or for vandetanib in either the EU label population or the Restricted EU label population. There is however uncertainty surrounding the mean survival duration of patients who do not receive either cabozantinib or vandetanib.

2.6 Conclusions

In terms of efficacy, both cabozantinib and vandetanib significantly improved PFS compared with placebo. In the absence of direct evidence comparing the two interventions, an NMA was performed; this analysis suggests that the treatment effect of both drugs on PFS is broadly similar, although these findings depend on the assumption of comparability between the EXAM ITT population and ZETA EU label population and should be treated with caution due to the sparsity of the network. Neither cabozantinib nor vandetanib demonstrated significant OS benefits compared with placebo and both drugs produced frequent AEs.

Based on the economic analyses undertaken by the Assessment Group, the ICERs for cabozantinib and vandetanib versus BSC in the EU label population (symptomatic and progressive MTC) are greater than £138,000 per QALY gained. The analyses undertaken within the Restricted EU label population (symptomatic and progressive MTC with CEA/CTN doubling time≤24 months) suggest that the ICER for vandetanib versus BSC is expected to be more favourable but remains greater than £66,000 per QALY gained. The impact of statistically adjusting for open-label vandetanib use on the cost-effectiveness of vandetanib versus BSC is unknown.

3 BACKGROUND

3.1 Description of health problem

Incidence and prevalence

Thyroid cancer is the most common malignant endocrine tumour, but represents only about 1% of all malignancies.[1, 2] The disease is more common in females than males. According to Cancer Research UK, 3,404 new diagnoses of thyroid cancer were reported in England in 2014: 966 cases (28%) were in males and 2,438 cases (72%) were in females.[1] The age-standardised incidence rate of thyroid cancer is reported to be 7 per 100,000 persons in women and 3 per 100,000 persons in men.[1] The UK incidence rate is the 11th lowest in Europe for males and the 15th lowest for females. The median age at diagnosis is approximately 50 years.[3, 4]

There are four main types of thyroid cancer: papillary, follicular, medullary and anaplastic. Papillary and follicular thyroid cancer are the most common types of thyroid cancer and account for more than 90% of all cases.[3] Medullary thyroid carcinoma (MTC), the disease type considered within this appraisal, develops from the parafollicular cells (also known as C-cells) and commonly presents as a mass in the neck.[2] MTC is very rare and accounts for approximately 5% of all thyroid cancers,[2] although a lower frequency has been quoted by the American Thyroid Association (ATA) guidelines.[5] Anaplastic cancers, thyroid lymphomas and metastases to thyroid from other primary tumours are rarer than MTC; anaplastic thyroid cancer accounts for approximately 2% of all thyroid cancers.[3] MTC is reported to account for 3% of all thyroid cancers in adults and 10% of all thyroid cancers in children.[2] Based on 2014 estimates of disease incidence,[1] the number of new cases of MTC in England in any year would be in the order of around 170 individuals (5% of 3,404).

There are four types of MTC: sporadic; multiple endocrine neoplasia (MEN) 2 and 3 (formerly 2A and 2B; and familial medullary thyroid carcinoma (FMTC). Incidence rates for each type differs by age and gender.[1] Approximately 75% of cases of MTC are sporadic in nature, whilst the remaining 25% are genetically determined (MEN2, MEN3 and FMTC).[2, 3] The RE-arranged during Transfection (RET) oncogene is central to the development of sporadic and hereditary MTC.[5] Germline testing of the RET oncogene mutation is recommended for all confirmed cases of MTC in order to establish the possible hereditary basis for the disease within an individual and to facilitate the identification of family members who might be at risk.[2] Almost all patients with MEN2, MEN3 and FMTC have germline RET mutation, whilst approximately 40%-50% of patients with sporadic MTC have somatic RET mutations.[2, 5] Only germline RET mutation testing is routinely undertaken in the NHS.

Diagnosis and management

In more than 75% of cases, patients with MTC will typically present with a lump in the neck (which may represent a thyroid or lymph node mass) or distant metastases.[2] The lumps are not usually associated with

other symptoms but may occasionally cause dysphagia (difficulty or discomfort in swallowing) or dysphonia (difficulty in speaking).[2, 6] Symptoms might also relate to the effect of metastases, especially diarrhoea, flushing, dyspnoea and bone pain.

Diagnosis is usually made by using either fine needle aspiration cytology of a thyroid nodule or lymph node, or a core needle biopsy with ultrasound guidance, alongside biochemical investigations of serum-based biomarkers, especially calcitonin (CTN).[2, 3, 5, 7] CTN is the major product secreted by C cells:[5] CTN levels greater than 100 picograms per millilitre (pg/mL) are considered to have a 100% positive predictive value for the presence of MTC.[2, 3]

The disease is staged and, if appropriate, surgery is performed (usually total thyroidectomy and central +/- lateral neck dissection).[2, 8, 9] Patients with MTC may be classified into three groups: (1) patients with localised disease without evidence of metastases for whom surgical cure is possible; (2) patients with metastatic disease limited to the neck in which surgical cure might be possible, but is not always achieved, and; (3) patients with distant metastasis in which the disease has spread outside the neck and for whom surgery is not curative.[3] The only curative treatment for MTC therefore is complete surgical resection, but lymph node or systemic metastases are present at initial diagnosis in around half of cases of MTC[5] and resection is sometimes incomplete due to extensive lateral spread.[3, 4] Patients with unresectable locally advanced or metastatic MTC are the focus of this appraisal. For these patients, the treatment options are limited because MTC is relatively unresponsive to conventional doses of radiation therapy and to all tested chemotherapeutic regimens[2, 3, 5] (see Sections 3.2 and 3.3). Therefore, patients with symptomatic and progressive disease, according to the Response Evaluation Criteria in Solid Tumour (RECIST) criteria,[10] are the principal candidates for systemic treatment.[6]

Prognosis

Compared with other advanced solid tumours, MTC can be relatively indolent, but it can sometimes be aggressive: data indicate that survival is influenced by age and stage at diagnosis.[4, 5, 11] It has been reported that patients who are younger than 40 years of age at the time of diagnosis have a significantly higher adjusted survival rate than older patients[4, 12] and 10-year survival rates are reported to be up to 100% for Stage I disease, i.e. if tumours are confined to the thyroid gland.[4, 5, 9, 13] In the absence of progressive and symptomatic disease, health-related quality of life (HRQoL) can be maintained for months or years.[2, 6] However, reported 10-year survival rates decrease to about 75% with regional disease spread[3, 14] and range from 21%-40% for subjects with metastatic disease at diagnosis.[2, 3, 5] Distant metastases, which can affect multiple organs, most commonly the liver, lungs and bone, are reported to be present in between 7% and 23% of MTC cases at diagnosis.[3, 6] Just under half of all patients with sporadic MTC will present with Stage III or IV (advanced) disease.[5]

CTN and, to a lesser extent, carcinoembryonic antigen (CEA), are used as biological markers of post-operative MTC burden, progression and survival.[15] CEA levels are not specific to MTC and are less sensitive and less reliable than CTN for diagnosis, however, when measured alongside CTN they are considered to be potentially useful in assessing disease progression.[5, 15] Certain levels of CEA might indicate regional spread to draining lymph nodes or more distant spread to non-regional lymph nodes, but are particularly important as an indicator of disease progression.[3, 5] Studies have indicated that patients with CTN and CEA doubling times ≤24 months have more progressive disease and a reduced survival compared to patients with CTN and CEA doubling times of >24 months.[16-20] A 2005 study reported 5- and 10-year survival rates in MTC patients with post-operative CTN doubling times <6 months of 25% and 8%, respectively, compared with 92% and 37%, respectively, in patients with doubling times between 6 and 24 months. Within that study, the 10-year survival rate for patients with CTN doubling times greater than 24 months was 100%.[16]

3.2 Impact of health problem

3.2.1 Significance for patients

There is little published research concerning the impact of MTC on patients' HRQoL. As noted within the Ipsen submission to the National Institute for Health and Care Excellence (NICE),[21] most of the available HRQoL evidence is derived from studies of patients with other more common types of thyroid cancer. As noted in Section 3.1, MTC is associated with a number of symptoms which may impair patients' HRQoL including: the presence of a thyroid mass (usually a non-tender thyroid nodule or diffuse thyroid enlargement), cervical lymphadenopathy, airway compromise, pain, dysphagia and dysphonia. Diarrhoea is commonly seen in patients with advanced MTC due to hormonal excess caused by increased CTN secretion from the parafollicular cells; this may be debilitating and lead to problems with nutrition. Distant metastases may result in additional symptoms including spinal cord compression, bone fracture, bronchial obstruction and pain.[5] Debilitating symptoms associated with MTC (for example, severe diarrhoea) may lead to workplace absence and lost productivity.

3.2.2 Significance for the NHS

MTC is a very rare disease and for many patients, surgery can be curative, hence the population of patients with advanced or metastatic MTC eligible for treatment with vandetanib and cabozantinib is very small. However, given the list prices of the drugs and the lack of effective alternative treatments, the cost per patient treated may be considerable. Both vandetanib and cabozantinib are also associated with additional monitoring costs. The Summary of Product Characteristics (SmPC) for vandetanib[22] states the following:

"An ECG [electrocardiogram], and levels of serum potassium, calcium and magnesium and thyroid stimulating hormone (TSH) should be obtained at baseline, at 1, 3, 6 and 12 weeks after starting treatment and every 3 months for at least a year thereafter. This schedule should apply to the period after dose

reduction due to QTc prolongation and after dose interruption for more than two weeks. ECGs and blood tests should also be obtained as clinically indicated during this period and afterwards. Frequent ECG monitoring of the QTc interval should be continued.

Serum potassium, serum magnesium and serum calcium should be kept within normal range to reduce the risk of ECG QTc prolongation. Additional monitoring of QTc, electrolytes and renal function are required especially in case of diarrhoea, increase in diarrhoea/dehydration, electrolyte imbalance and/or impaired renal function. If QTc increases markedly but stays below 500 msec, cardiologist advice should be sought."[22]

The SmPC for cabozantinib[23] also recommends close monitoring during the first eight weeks of treatment:

"As most events can occur early in the course of treatment, the physician should evaluate the patient closely during the first eight weeks of treatment to determine if dose modifications are warranted. Events that generally have early onset include hypocalcaemia, hypokalaemia, thrombocytopenia, hypertension, palmarplantar erythrodysaesthesia syndrome (PPES), and gastrointestinal (GI) events (abdominal or mouth pain, mucosal inflammation, constipation, diarrhoea, vomiting)." [23]

One of the clinical advisors to the Assessment Group noted that whilst cardiac toxicity is less for cabozantinib compared with vandetanib, ECG monitoring may also be required.

3.3 Current service provision

3.3.1 Clinical guidelines

There are no clinical guidelines for the management of MTC. A NICE quality standard for head and neck cancer has recently been published,[24] however, this does not include the management of MTC.

3.3.2 Current NICE technology appraisal guidance

There is currently no NICE technology appraisal guidance for interventions for the treatment of unresectable locally advanced or metastatic MTC.

3.3.3 Current service cost

The current cost of managing MTC is uncertain. However, MTC is a very rare disease, with an estimated annual incidence for England of around 170 new patients. Prescribing data from the Cancer Drugs Fund (CDF) indicates that in 2016, [redacted] new patients received vandetanib and [redacted] new patients received cabozantinib. The data from 2015 indicate very similar prescribing levels, with [redacted] new patients starting vandetanib and [redacted] patients starting cabozantinib (personal communication: Professor Peter Clark, Chair of CDF). Based on current prescribing levels, the cost of treating new MTC patients with cabozantinib and

vandetanib for one year (assuming full dose and excluding any discontinuation) is approximately £1.96million.

3.3.4 Variation in services and uncertainty about best practice

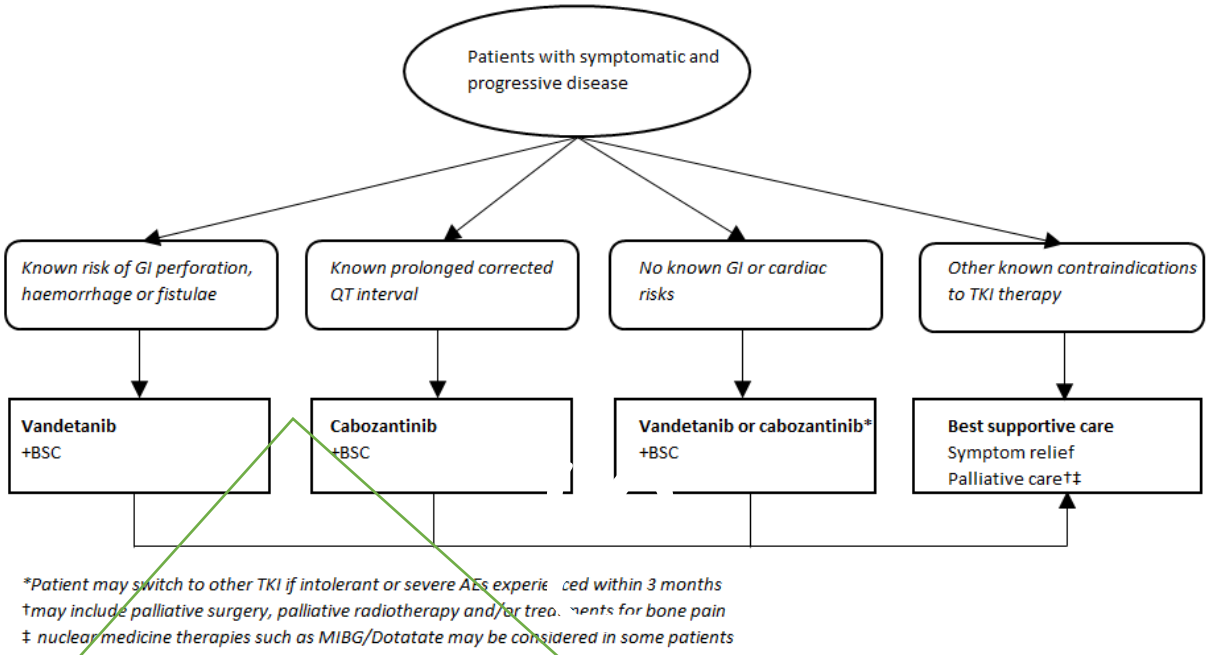
Clinical advisors to the Assessment Group noted that whilst the indications set out in the marketing authorisations for cabozantinib and vandetanib[22, 23] relate to patients with progressive disease, this may be determined on the basis of radiographic evidence or the presence of symptomatic disease. They also noted that elsewhere in Europe, clinicians often initiate treatment earlier on the basis of imaging, whereas clinicians in the UK tend to consider symptomatic progression as the more important timepoint at which to initiate palliative treatment.

The SmPCs for both vandetanib and cabozantinib state that *"For patients in whom Rearranged during Transfection (RET) mutation status is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision."*[22, 23] Clinical advisors to the Assessment Group noted that all patients should have an assessment of their germline RET status to check if their disease is sporadic or genetic. This is however, different to checking if the tumour expresses RET (somatic RET mutation testing). In the UK, it is not routine practice to check the tumour (either primary or metastases) for RET mutations. Whilst clinicians do not currently have routine access to mutation analysis, this may change in the future. The clinical advisors warned that the RET status of the primary thyroid cancer may not reflect the mutation landscape in the metastases and that it would be inadvisable to base recommendations about the use of vandetanib and cabozantinib in the NHS on RET mutation status without a full and accurate picture of the significance of somatic RET status. Furthermore, the clinicians commented that the thyroid primary may have been removed many years before metastases develop, hence at the time of relapse, the mutation analysis may no longer be accurate. Furthermore, as cabozantinib and vandetanib have multiple targets, whilst a patient may be RET mutation negative in the metastases they may still obtain a treatment response by virtue of other mutations that are targeted by the individual drug received.

3.3.5 Current treatment pathway

A summary of the treatment pathway, as developed by the Assessment Group, is presented in Figure 1; for patients who are ineligible to receive cabozantinib or vandetanib, treatment is likely to be comprised of palliative treatments. Both cabozantinib and vandetanib are currently available on the CDF as first-line treatments for unresectable, locally advanced or metastatic MTC.[25] The CDF indication for each therapy is the same, as shown in Box 1.

Figure 1: Current treatment pathway for adults with symptomatic and progressive MTC



Box 1: CDF indication for cabozantinib and vandetanib for the treatment of locally advanced or metastatic MTC[25]

The first-line treatment of MTC where all the following criteria are met:

- Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
- Histologically confirmed, unresectable, locally advanced or metastatic MTC
- 1st line indication
- Progressive and symptomatic disease
- *For cabozantinib:* No previous tyrosine kinase inhibitor therapy unless intolerant of vandetanib within 3 months of starting therapy and toxicity which cannot be managed by dose delay or dose modification and in the absence of disease progression on vandetanib
- *For vandetanib:* No previous tyrosine kinase inhibitor therapy unless intolerant of cabozantinib within 3 months of starting therapy and toxicity which cannot be managed by dose delay or dose modification and in the absence of disease progression on cabozantinib.

3.4 Description of technology under assessment

3.4.1 Interventions considered in the scope of this report

This assessment includes two interventions: cabozantinib and vandetanib.

Cabozantinib

Cabozantinib has an EU marketing authorisation for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC. The SmPC for cabozantinib[23] states that for patients in whom RET mutation status is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision. Cabozantinib is administered orally at a recommended dose of 140mg once daily, taken as one 80mg capsule and three 20mg capsules. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.[23] Cabozantinib is available in packs of: (1) 80 x 20mg capsules; (2) 28 x 20mg capsules and 28 x 80mg capsules, or; (3) 84 x 20mg capsules and 28 x 80mg capsules. The list price for cabozantinib is £4,800 per pack. A confidential Patient Access Scheme (PAS) has been proposed cabozantinib.

Vandetanib

Vandetanib has an EU marketing authorisation for the treatment of aggressive and symptomatic MTC in patients with unresectable locally advanced or metastatic disease (including children and adolescents aged 5 years and older).[22] The SmPC for vandetanib[22] states that for patients in whom RET mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision. Vandetanib is administered orally at a recommended dose of 300mg once a day. Vandetanib may be administered until disease progression or until the benefits of treatment continuation no longer outweigh its risk, taking into account the severity of adverse events (AEs) in relation to the degree of clinical stabilisation of the tumour status.[22] Vandetanib is available in packs of: (1) 30 x 100mg tablets (cost per pack=£2,500), and; (2) 30 x 300mg tablets (cost per pack=£5,000). A confidential PAS has also been proposed for vandetanib.

3.4.2 Mode of action

Cabozantinib

Cabozantinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumour growth and angiogenesis, pathologic bone remodeling, and metastatic progression of cancer. Cabozantinib was evaluated for its inhibitory activity against a variety of kinases and was identified as an inhibitor of MET (hepatocyte growth factor receptor protein) and VEGF (vascular endothelial growth factor) receptors. In addition, cabozantinib inhibits other tyrosine kinases including RET, the GAS6 receptor (AXL), the stem cell factor receptor (KIT), and Fms-like tyrosine kinase-3 (FLT3).[23]

Vandetanib

Vandetanib is a potent inhibitor of vascular endothelial growth factor receptor-2 (VEGFR-2 also known as kinase insert domain containing receptor [KDR]), epidermal growth factor receptor (EGFR) and RET tyrosine kinases. Vandetanib is also a sub-micromolar inhibitor of vascular endothelial receptor-3 tyrosine kinase. Vandetanib inhibits VEGF-stimulated endothelial cell migration, proliferation, survival and new

blood vessel formation in *in vitro* models of angiogenesis. In addition, vandetanib inhibits epidermal growth factor (EGF)-stimulated EGF receptor tyrosine kinase in tumour cells and endothelial cells. Vandetanib inhibits EGFR-dependent cell proliferation and cell survival *in vitro*. Vandetanib also inhibits both wild type and the majority of mutated, activated forms of RET, and significantly inhibits the proliferation of MTC cell lines *in vitro*. *In vivo* vandetanib administration reduced tumour cell-induced angiogenesis, tumour vessel permeability, tumour microvessel density, and inhibited tumour growth of a range of human xenograft tumour models in athymic mice. Vandetanib also inhibited the growth of MTC xenograft tumours *in vivo*. The precise mechanism of action of vandetanib in locally advanced or metastatic MTC is unknown.[22]

3.4.3 Current usage in the NHS

As noted in Section 3.3.3, both cabozantinib and vandetanib are currently available for use through the CDF. Given the rarity of MTC, total prescribing rates of these products are low: in 2016, [redacted] new patients were prescribed cabozantinib or vandetanib through the CDF.

4 DEFINITION OF THE DECISION PROBLEM

This assessment evaluates the clinical effectiveness and cost-effectiveness of cabozantinib and vandetanib within their marketing authorisations for treating unresectable or metastatic MTC. Vandetanib holds an EU marketing authorisation for the treatment of aggressive and symptomatic MTC in patients with unresectable locally advanced or metastatic MTC. Vandetanib is indicated in adults, children and adolescents aged 5 years and older.[22] Cabozantinib holds an EU marketing authorisation for the treatment of adult patients with progressive, unresectable locally advanced or metastatic MTC.[23] The SmPCs for each product state that for patients in whom RET mutation status is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision.[22, 23]

4.1 Decision problem

In line with the final NICE scope,[26] the decision problem is specified as follows:

Population

- Adults with unresectable locally advanced or metastatic MTC.

In December 2016, the marketing authorisation for vandetanib was extended to include children and adolescents aged 5 years or over;[22] this population is beyond the scope of this appraisal.[26] Clinical advisors to the Assessment Group note that the incidence of unresectable locally advanced or metastatic MTC in children and adolescents aged 5 years or over is expected to be extremely low.

Interventions

- Cabozantinib (oral, Cometriq®, Ipsen)
- Vandetanib (oral, Caprelsa®, Sanofi)

Relevant comparators

Cabozantinib and vandetanib are compared with:

- Each other
- BSC.

Outcomes

The following outcomes are included in the assessment.

- Overall survival (OS)
- Progression-free survival (PFS)
- Response rates
- Adverse effects of treatment
- Health-related quality of life (HRQoL).

Whilst response rates were not included in the final NICE scope,[26] this outcome has been included in the assessment as it is a clinically relevant endpoint within the key trials considered within this report.[27, 28]

Subgroups

The final NICE scope[26] states *"If the evidence allows subgroups according to RET mutation status will be considered."* Based on the guidance of the clinical advisors to the Assessment Group (see Section 3.3.4), RET mutation status has not been considered within the health economic analysis presented within this report.

4.2 Overall aims and objectives of assessment

The aims of the assessment are:

1) To evaluate the clinical effectiveness and safety of cabozantinib and vandetanib within their marketing authorisations for treating unresectable locally advanced or metastatic MTC.
2) To estimate the incremental cost effectiveness of cabozantinib and vandetanib compared with each other and BSC.
3) To identify key areas for primary research.
4) To estimate the overall cost in England.

5. ASSESSMENT OF CLINICAL EFFECTIVENESS

This section presents a summary and critique of relevant studies on the efficacy and safety of cabozantinib (Cometriq®, XL184) and vandetanib (Caprelsa®, ZD6474) for the treatment of unresectable locally advanced or metastatic MTC. The systematic review was conducted and reported following the general principles outlined in 'Systematic Reviews: CRD's guidance for undertaking reviews in health care' and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and checklist.[29,30] The protocol for this review has been registered with, and is available from, the PROSPERO database (registration number CRD42016050403, available from: http://www.crd.york.ac.uk/PROSPERO/).

5.1 Methods for reviewing effectiveness

5.1.1 Inclusion criteria

The inclusion criteria for the reviews are described in Table 1. These criteria are in accordance with the decision problem set out in the final NICE scope.[26]

Table 1: Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	Participants with unresectable locally advanced or metastatic MTC, aged 18 years or older. Studies with populations broader than unresectable locally advanced or metastatic MTC will be considered only if data for the relevant study population are available and are reported separately.	Studies conducted in paediatric populations
Interventions	• Cabozantinib (oral) • Vandetanib (oral)	
Comparators	Interventions will be compared with each other and against BSC (including locally ablative treatments such as radiotherapy).	
Outcomes	The following outcomes will be included in the assessment: • Overall survival (OS) • Progression-free survival (PFS) • Response rates • Adverse effects of treatment • Health-related quality of life (HRQoL)	
Study design	Randomised controlled trials (RCTs) are to be included in the clinical effectiveness systematic review. If no relevant RCTs are identified for an intervention, non-randomised comparative studies would be considered for inclusion. Non-randomised comparative studies are also to be included, where necessary, as a source of additional evidence (e.g., regarding AEs related to the interventions).	Pre-clinical or biologic studies as well as studies of animal models will be excluded. The following publication types will not be considered for inclusion in the review and synthesis, although the reference lists of reviews and guidelines will be checked for additional relevant trials: narrative reviews, systematic reviews, clinical guidelines, editorials, letters, opinion pieces, and abstracts with insufficient details to assess study quality or results.
Language	Searches were not limited by language.	n/a

HRQoL - health-related quality of life; RCT - randomised controlled trial; n/a - not applicable

5.1.2 Searches

A comprehensive literature search was undertaken to systematically identify randomised controlled trials (RCTs) and systematic reviews (for the identification of additional trials) of the clinical effectiveness of cabozantinib and vandetanib for the treatment of unresectable locally advanced or metastatic MTC.

The following electronic databases were searched from inception to November 2016:

- MEDLINE: Ovid, 1946 to present MEDLINE in Process: Ovid, 1946 to present
- MEDLINE Epub Ahead of Print: Ovid, 1946 to present
- CINAHL: EBSCO, 1982 to present
- EMBASE: Ovid, 1980 to present
- Cochrane Database of Systematic Reviews (CDSR): Wiley Interscience, 1996 to present,
- Cochrane Controlled Trials Register (CENTRAL): Wiley Interscience, 1995 to present
- Database of Abstracts of Reviews of Effects (DARE): Wiley Interscience, 1995 to 2015
- Health Technology Assessment Database (HTA): Wiley Interscience, 1995 to present
- Web of Science: Science Citation Index (SCI): Thomson Reuters, 1900 to present
- Conference Proceedings Citation Index (CPCI): Thomson Reuters, 1990 to present.

In order to identify ongoing or recently completed studies, trial registers were searched using the World Health Organization's International Clinical Trials Registry Portal (WHO ICTRP) which regularly compiles and updates data from more than 15 clinical trial registers (http://apps.who.int/trialsearch/, date accessed: 2nd November 2016).

Searches were not limited by language or publication date and were not restricted to published research only. Search terms included Medical Subject Heading (MeSH) terms and free text synonyms for MTC combined with an RCT or systematic reviews study design filter. The search strategy was designed to be deliberately broad in order to capture all intervention studies within the MTC population, i.e. studies of cabozantinib and vandetanib as well as additional evidence for possible comparators, including BSC and radiotherapy as such studies may be used to inform indirect comparisons. The MEDLINE search strategy is presented in Appendix 1.

In order to identify additional studies, reference lists of relevant studies, systematic reviews, clinical guidelines and submissions to regulatory authorities and advisory bodies (All Wales Medicines Strategy Group [AWMSG]; Scottish Medicines Consortium [SMC]; European Medicines Agency [EMA]; and the US Food and Drug Administration [FDA]) were examined. In addition, company submissions to NICE related to the interventions within the scope of this review were examined. Citation searches of

key included studies using the Web of Science database were also conducted. Clinical advisors to the Assessment Group provided advice on whether any relevant studies were missing from the search results.

A comprehensive database of relevant published and unpublished articles was constructed using EndNote® software.

5.1.3 Study selection and data extraction

Following standard systematic review processes, two reviewers (CC and EK) independently screened all titles and abstracts using the eligibility criteria outlined in Table 1; full papers were retrieved for any publication which was deemed by a reviewer to be potentially includable. The two reviewers independently screened all full texts to identify studies that satisfied the inclusion criteria. Any discrepancies between reviewers were resolved through discussion. Results were reported in text, tables and a PRISMA flowchart. Data extraction was performed by one reviewer (CC) and was independently checked for errors against the original and published trial reports by the second reviewer (EK). Any discrepancies were resolved through discussion. Results were reported in text and tables.

5.1.4 Quality assessment

For the RCT evidence, critical appraisal of included trials was conducted by one reviewer (CC) using the Cochrane Risk of Bias tool;[31] this was checked by a second reviewer (EK) and any discrepancies were resolved through discussion.

5.1.5 Evidence synthesis

Details of the included RCTs, including population characteristics, interventions, comparators and outcomes, were tabulated and discussed in a narrative review. On account of the small number of included studies, with just one study contributing evidence for each of the interventions, pairwise meta-analysis was not appropriate. In the absence of direct evidence comparing cabozantinib and vandetanib, a network meta-analysis (NMA) was performed using the ZETA EU label and EXAM intention-to-treat (ITT) populations (see Section 5.3).

5.2 Results

5.2.1 Quantity and quality of research available

The details of the study selection process are outlined in the PRISMA flowchart (see Figure 2). The search identified 1,581 references after de-duplication, of which 1,516 were excluded because they did not satisfy the eligibility criteria. The full texts of 65 studies were retrieved to assess eligibility; 38 of these studies were excluded for the following reasons: absence of a control arm (n=17); review (n=6); letter/commentary (n=6); wrong population (n=5); wrong intervention (n=2); animal study or a

duplicate (n=1 each). A list of excluded full papers, with reasons, is provided in Appendix 2. This included two single-arm studies of vandetanib in children and adolescents with unresectable locally advanced or metastatic MTC as a result of MEN type 2 (one published study[32] and one ongoing study - NCT00514046). These studies may be relevant to the extension to the marketing authorisation for vandetanib;[22] however, this population is beyond the scope of this appraisal.

There were five potentially relevant controlled trials of comparator interventions, principally other tyrosine kinase inhibitors (TKIs), one of which ended prematurely due to recruitment issues (NCT01736878); the remaining four studies are ongoing (NCT01270321, NCT01625520, NCT01788982, NCT02586350). There is also one published retrospective study comparing MTC patients who received radioactive iodine (ROI) therapy against those whose did not.[33] As a result, there was no appropriate additional controlled trial evidence of other potential comparators to cabozantinib or vandetanib (for example, radiotherapy) which may have been used to inform an NMA.

The final result was 27 publications and protocols relating to five randomised controlled studies. For cabozantinib, this included 13 publications relating to the Phase III EXAM trial[28] (NCT00704730), which compared cabozantinib 140mg/day with placebo, and two publications relating to the ongoing EXAMINER trial (NCT01896479), which compares cabozantinib 140mg/day with cabozantinib 60mg/day and seeks to recruit 188 participants (expected completion date: March 2018).[34] For vandetanib, this included 10 publications relating to the Phase III ZETA trial[27] (NCT00410761), which compares vandetanib 300mg/day with placebo, and two publications relating to two ongoing vandetanib trials: NCT01496313 for vandetanib 300mg/day versus vandetanib 150mg/day, and NCT00923247 for vandetanib versus vandetanib plus bortezomib.

No additional relevant papers or studies were identified from the reference lists of included studies or reviews, from citation searching of the key publications for the EXAM or ZETA trials. The clinical advisors to the Assessment Group were satisfied that no other relevant studies were missing.

The two pivotal Phase III trials, EXAM and ZETA, were international, multicentre, placebo-controlled trials. The characteristics of the EXAM and ZETA trials are presented in Table 2.

The clinical evidence submitted to NICE by the manufacturers of cabozantinib[21] and vandetanib[35] included data from six studies. All of these studies were identified by the search for this review, but only four studies satisfied the review eligibility criteria: for cabozantinib, the EXAM trial and ongoing EXAMINER trial; and for vandetanib, the ZETA trial and the ongoing trial NCT01496313. The submissions also included data from a Phase I, non-controlled, single-arm cabozantinib, dose-escalation trial, which included a subset of relevant MTC patients[36] (NCT00215605); a controlled study to assess

the addition of an outreach programme to vandetanib treatment;[37] and two "real world", non-controlled, single-arm vandetanib studies[38, 39] (NCT01945762). All of these studies were identified by the search but were excluded from this review because they did not satisfy the eligibility criteria: they were either single-arm cohort studies without a control group or the intervention evaluated in the trial did not relate to either cabozantinib or vandetanib (see Appendix 2).

Figure 2: **PRISMA flowchart**

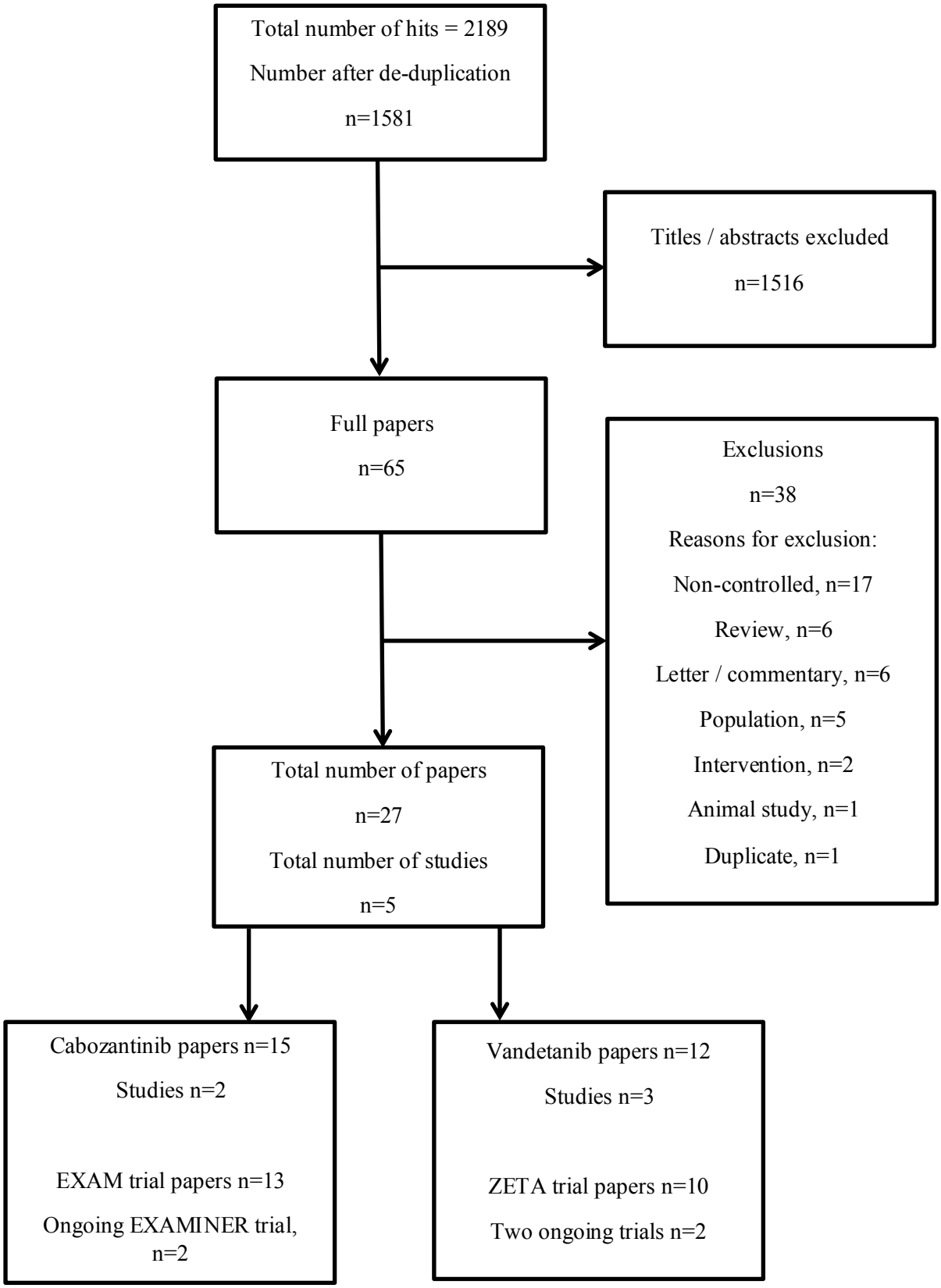


Table 2: **Characteristics of included RCTs**

Study	**Cabozantinib: EXAM trial[28]**	**Vandetanib: ZETA trial[27]**
Design	International (including Europe), multi-centre, Phase III, parallel-group, double-blind RCT	International (including Europe), multi-centre, Phase III, parallel-group, double-blind RCT
Follow-up	13.9 months (median); range 3.6-32.5 months	24 months (median)
Population*	Eligible patients were adults with histologically confirmed, unresectable, locally advanced, or metastatic MTC. Patients were required to have radiographic disease progression per mRECIST guidelines at screening compared with an image obtained within the prior 14 months. Documentation of progressive disease (PD) to establish eligibility was by independent review in 89.4% of patients, and by investigator assessment in the remaining patients Exclusion criteria: Included: prior systemic anticancer therapy within four weeks or significant cardiac, hematopoietic, hepatic, or renal dysfunction. There was no limit on prior therapy, including exposure to other TKIs.	Eligible patients were adults who had measurable, unresectable locally advanced or metastatic, hereditary or sporadic MTC. Submission of a tumour sample was required except for patients with hereditary MTC who had a documented germline RET mutation. Other key inclusion criteria were WHO performance status of 0 to 2 and serum CTN level $\geq$500 pg/mL Exclusion criteria: Included: administration of chemotherapy and/or radiation therapy within four weeks before random assignment, or significant cardiac, hematopoietic, hepatic, or renal dysfunction.
Intervention	Cabozantinib 140mg (freebase equivalent) taken orally once per day until either intolerable toxicity or disease progression per mRECIST. Dose holds and up to two dose-level reductions (to a minimum dose of 60mg per day) were allowed.	Vandetanib 300mg taken orally once per day until disease progression
Comparator	Placebo	Placebo
Outcomes	Primary end point: PFS (assessed every 12 weeks until progression) Secondary end points: OS; Objective response rate (ORR); RET mutation status; CTN; CEA AEs measured using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE)	Primary end point: PFS (assessed every 12 weeks until progression) Secondary end points: OS; ORR and duration of response; disease control rate at 24 weeks; RET mutation status; CTN; time to worsening of pain; CEA AEs measured using the National Cancer Institute's CTCAE

MTC - medullary thyroid cancer; PD - progressive disease; mRECIST - modified Response Evaluation Criteria in Solid Tumours; TKI - tyrosine kinase inhibitor; WHO - World Health Organization; RET - RE-arranged during Transfection; PFS – progression-free survival; OS - overall survival; ORR - objective response rate; CEA - carcinoembryonic antigen

* Some additional criteria are detailed in the protocols for cabozantinib (https://clinicaltrials.gov/ct2/show/record/NCT00704730) and vandetanib (https://clinicaltrials.gov/ct2/show/NCT00410761)

The inclusion and exclusion criteria of the two trials were virtually identical, with the exception that the cabozantinib EXAM trial participants were required to have radiographic evidence of progressive disease (PD) at baseline. This was not an eligibility criterion for the vandetanib ZETA trial: the number of participants with "aggressive and symptomatic disease" at baseline is reported to be 56% (186/331).[40] The cabozantinib trial had a median follow-up of 13.9 months compared with 24 months for the vandetanib trial. The two trials had common primary (PFS) and secondary (OS, ORR, RET mutation status, CTN and CEA) endpoints. The cabozantinib trial assessed quality of life using the MD Anderson Symptom Inventory for thyroid conditions (MDASI-THY), whilst the vandetanib trial also assessed disease control rate and measured quality of life using the Functional Assessment of Cancer Therapy – General (FACT-G) tool and time to worsening of pain (TWP). It is noteworthy that the MDASI-THY and TWP were both listed in the protocols but were not reported in the publications of the EXAM trial (only in the Clinical Study Reports [CSRs]), whilst the FACT-G assessment was not listed in any publication of the ZETA trial, but its results were reported in the Sanofi company submission (CS).[35]

The definitions of PFS used within both trials were similar (see Table 3) and both trials employed a central committee to confirm investigator assessments. However, the EXAM trial used the modified RECIST (mRECIST) criteria and employed a blinded independent review committee (IRC), whilst the ZETA trial used the standard RECIST criteria and it is unclear whether or not the central review was blinded.

Table 3: **Definitions of PFS**

	EXAM trial[28]	**ZETA trial[27]**
Definition of PFS	PFS was calculated as the time from random assignment to the earlier of documented PD per mRECIST (based on radiographic tumour assessments performed by a blinded IRC) or death due to any cause.	PFS was defined from the date of random assignment to the date of objective progression or death (by any cause in the absence of progression within three months of the last evaluable RECIST assessment). PFS was determined from objective tumor measurements. Tumor assessments "were categorized by the investigator by using RECIST v1.0… Responses were confirmed by central review of separate assessments performed at least four weeks apart."

PD - progressive disease; (m)RECIST - (modified) Response Evaluation Criteria in Solid Tumours; IRC - Independent Radiology Review Committee

The EXAM and ZETA trials had 330 and 331 participants respectively (see Table 4). Both trials randomised patients 2:1 to receive the active drug or placebo, respectively. In terms of baseline characteristics, the two arms of the cabozantinib EXAM trial are generally well-balanced with the possible exceptions of: Eastern Cooperative Oncology Group (ECOG) performance status of 0 (56.2% in the cabozantinib arm vs 50.5% in the placebo arm), the proportion who had received prior systemic therapy for MTC (37% vs 42%, respectively) and positive RET mutation status (46.1% vs 52.3%),

indicating that the control group might have had more severe disease. RET mutation status was unknown in 39% of patients due to missing sequence data or the presence of a mutation of unknown significance.[28] The two arms of the vandetanib ZETA trial are also generally well-balanced, albeit with higher proportions of participants in the control arm than the treatment arm also potentially having more severe disease on account of a WHO performance status of 1-2 (42% for placebo vs 33% for vandetanib) and having involvement of two or more organs (92% vs 87%, respectively).

Comparing the two trials, the vandetanib ZETA trial included substantially greater proportions of patients with hereditary disease (12% in the vandetanib arm compared with 6% in the cabozantinib intervention arm) and patients with a performance status of 0 (67% in the vandetanib arm compared with 56% in the cabozantinib arm). However, the principal difference between the EXAM and ZETA trial populations concerns the presence of progressive disease (PD): participants in the EXAM trial were required to have evidence of PD, whilst participants in the ZETA trial were not. The two ITT populations are therefore sufficiently different to invalidate a standard indirect comparison.

In both trials, patients discontinued study treatment if there was evidence of disease progression or toxicity. The ZETA trial used an additional cross-over design.[27] During the randomised phase, if there was disease progression based on investigator assessment, patients discontinued study treatment but were offered the opportunity to receive vandetanib post-progression as un-blinded open-label treatment until normal discontinuation criteria applied (e.g. toxicity or progression).[27] In the vandetanib arm during the randomised stage of the trial, 120/231 (52%) discontinued treatment due to progression or toxicity (compared with 55% in the cabozantinib trial[28]), but 44 of these 120 patients (37%) continued to receive vandetanib in the open-label phase. In the placebo arm of the ZETA trial, 71/99 (72%) discontinued “treatment” due to progression or toxicity (compared with 86% in the cabozantinib trial), and 58 of these 71 patients (82%) then “crossed-over” to receive vandetanib in the open-label phase. All efficacy and safety data reported below are from the crossover phase of the trial, unless otherwise stated. This raises issues of confounding for some of the outcomes data from the ZETA trial.

Table 4: **Participants' baseline characteristics from the EXAM and ZETA trials**

Study	**EXAM trial[28]**		**ZETA trial[27]**	
Total	**n=330**		**n=331**	
Intervention	**Cabozantinib 140mg n=219**	**Placebo n=111**	**Vandetanib 300mg n=231**	**Placebo n=100**
Male, n (%)	151 (69)	70 (63)	134 (58)	56 (56)
Age, years Median (range)	55 (20-86)	55 (21-79)	51* (NR)	53* (NR)
Disease type, n (%)				
Hereditary	12 (6)	8 (7)	28 (12)	5 (5)
Sporadic or unknown	207‡ (95)	103 (93)	203 (88)	95 (95)
Locally advanced	NR		14 (6)	3 (3)
Metastatic	NR		217 (94)	97 (97)
RET mutation status, n (%)				
Positive	101 (46)	58 (52)	137 (59)	50 (50)
Negative	31 (14)	10 (9)	2 (1)	6 (6)
Unknown	87 (40)	43 (39)	92 (40)	44 (44)
Performance status, n (%) (ECOG / WHO)				
0	123 (56)	56 (51)	154 (67)	58 (58)
1-2	95 (43)	55 (50)	77 (33)	42 (42)
No. of organs involved†				
0-1	28 (13)	15 (14)	29 (13)	8 (8)
≥2	191 (87)	96 (87)	202 (87)	92 (92)
Prior systemic therapy for MTC	81 (37)	47 (42)	90 (39)	42 (42)
Prior thyroidectomy	201 (92)	104 (94)	NR	
Prior anticancer therapy	85 (39)	48 (43)	NR	
Prior TKI, n (%)			NR	
Yes	44 (20)	24 (22)		
No	171 (78)	86 (78)		
Unknown	4 (2)	1 (1)		

**Mean; †excluding thyroid; ‡ discrete data for sporadic disease are reported for the EXAM trial (191/291=88%), which is higher than the proportion of patients usually presenting with sporadic disease (75%).[27, 28] Note: All decimals rounded up to the nearest whole number.*

ECOG - Eastern Cooperative Oncology Group; RET - Rearranged during Transfection; MTC - medullary thyroid cancer; NR - Not reported

The marketing authorisation for vandetanib states that it is indicated *"for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease."*[22] The terms "aggressive" and "symptomatic" are not defined in the licence, but were defined *post hoc* (see below). The Sanofi CS for vandetanib[35] presents PFS and OS outcomes data from *post hoc* analyses on two pre-planned sub-populations within the ZETA trial (and as such are more restrictive than the overall population recruited to this trial):

- Patients with unresectable, locally advanced or metastatic MTC and whose disease is 'progressive *and* symptomatic' (defined as having "documented progression 12 months prior to enrolment and at least one of the following symptoms at baseline: pain score > 4, ≥10mg/day opioid use, diarrhoea, flushing, fatigue, pain, nausea, dysphagia, dysphonia, respiratory symptoms, and weight loss."[40] This corresponds to the "EU label" or "progressive and symptomatic" population (n=186) referred to within the Sanofi CS.[35] In the *post hoc* analyses conducted by the company, the data reported by Kreissl *et al* could not be replicated exactly and the number reported is n=190 for PFS and n=189 for OS data in the Sanofi CS (see Sanofi CS,[35] Appendix 6, Tables 5 and 7, respectively). Numbers from the published Kreissl *et al* analyses are used throughout the clinical effectiveness section, while the cost-effectiveness section is based on the slightly larger subgroup defined for the purposes of the NICE submission.
- Patients with unresectable, locally advanced or metastatic MTC whose disease is "progressive and symptomatic" (as above) *and* which is 'aggressive', i.e. with CTN *and* CEA doubling time of <24 months from screening. This is the so-called "Restricted EU label population" (n=[redacted]) presented in the Sanofi CS. The Sanofi CS claims that *"This population closely reflects UK clinical practice for TKI treatment"* (CS,[35] page 11 and page 54). However, clinical advice received by the Assessment Group suggests that CTN and CEA monitoring would not usually inform decisions about whether to commence TKI therapy, as this is principally determined by radiographic evidence of progression and symptoms.

The data presented for these groups are partly unpublished (only the PFS and ORR data for the EU label population are published[40]) and are reported here because they are used to inform the health economic model developed by the Assessment Group. The baseline characteristics of these subgroups are presented in Table 5, together with the comparable baseline data for the EXAM trial ITT population. Despite the EXAM ITT population being "progressive" and the EU label ZETA trial population being "progressive and symptomatic", clinical advice received by the Assessment Group confirmed that these two populations were comparable.

It should also be noted that within the EU label population [redacted] of patients in the intervention group continued to receive vandetanib in the open-label phase, whilst [redacted] of patients in the placebo arm

"crossed-over" to receive open-label vandetanib (see Sanofi clarification response,[41] question 3). In the Restricted EU label population, [redacted] of patients in the intervention group continued to receive vandetanib in the open-label phase, whilst [redacted] of patients in the placebo arm "crossed-over" to receive open-label vandetanib (Sanofi CS,[35] pages 17 and 63). All efficacy and safety data reported below for this group are from the cross-over phase of the trial, unless otherwise stated. This raises issues of confounding for some of the trial data, including for the Restricted EU label population.

Table 5: **Participants' baseline characteristics in the cabozantinib 'progressive' and the vandetanib EU-label and Restricted EU label populations**

Study	**EXAM trial: 'progressive'[28]**		**ZETA trial: EU label, 'progressive and symptomatic'**		**ZETA trial: Restricted EU label, 'progressive, symptomatic and with CTN/CEA criteria'**	
Total	n=330		n=186		[redacted]	
Intervention	Cabozantinib 140mg n=219	Placebo=111	Vandetanib 300mg n=126	Placebo n=60	Vandenatib 300mg	Placebo
Male, %	69	69	63	65	[redacted]	
Age, years Median	55	55	53.1	53.9	[redacted]	
Disease type, %						
Hereditary	6	7	8.7	3.3	[redacted]	
Sporadic	95	93	50.8	46.7	[redacted]	
Locally advanced	NR		5.6	1.7	[redacted]	
Metastatic	NR		94.4	98.3	[redacted]	
RET mutation status, %						
Positive	46.1	52.3	59.5	50.0	[redacted]	
Negative	13.2	9.0	0.8	10.0	[redacted]	
Unknown	39.7	38.7	39.7	40.0	[redacted]	
Prior systemic therapy for MTC	37	42	35.7	48.3	[redacted]	

(reproduced from Sanofi CS, Tables 17 and 19 and Wells 2012[27])
RET - Rearranged during Transfection; MTC - medullary thyroid cancer

The risk of bias in the EXAM and ZETA trials was assessed using the Cochrane risk of bias tool (see Table 6). These assessments made use of the protocols (published and unpublished), the trial publications, and unpublished CSRs for each trial.

The Assessment Group considers the EXAM trial to be of generally good quality, being assessed at a low risk of performance, detection and attrition bias on account of measures to ensure blinding and the management of drop-outs. It is at unclear risk of selection bias because full details of the randomisation and allocation concealment processes were absent from the documents identified from the searches or from those made available during this appraisal. It was at a moderate risk of reporting bias on account of the failure to report the results of some outcomes in published documents, and at moderate risk of other bias due to potential conflicts of interest and the failure to control for the possible treatment effect modifier of CTN and CEA doubling time.

Overall, the Assessment Group considers that the ZETA trial was at a moderate to high risk of bias across most domains. As with the EXAM trial, the likelihood of attrition bias was considered to be low and the risk of selection bias was unclear. However, there was a moderate risk of reporting and other bias due to the presence of selective reporting and some potential conflicts of interest, although *post hoc* analyses were conducted on the potential treatment effect modifier of CTN and CEA doubling time. In contrast to the EXAM trial, performance bias and detection bias were assessed as moderate to high because there was a lack of detail on blinding procedures and certain outcomes and their results were potentially confounded by the inclusion of open-label, cross-over patients within the analysis.

Table 6: **Risk of bias assessment (Cochrane tool) of included RCTs**

Risk of bias	Criteria	EXAM trial (Cabozantinib)[28]	ZETA trial (Vandetanib)[27]
Selection bias	Random sequence generation and allocation concealment	UNCLEAR "Patients were randomly assigned in a 2:1 ratio to receive cabozantinib or placebo in a double-blinded fashion and were stratified by age (≤65 years,>65 years) and prior TKI treatment (yes, no)." Protocols (manuscript supplement and published NCT record) and unpublished CSR[42] (Section 9.4.3) provide no further details on how randomisation was conducted.	UNCLEAR Patients recruited to this multicenter phase III study were randomly assigned in a 2:1 ratio to receive oral vandetanib at a starting dose of 300 mg/d or placebo until disease progression. The published protocol (NCT), published CSR, which accompanied the full publication,[27] and an earlier unpublished CSR,[43] provide no further details on how randomisation was conducted. It is only mentioned in a later CSR[44] (October 2014) that, "The biostatistics group within AstraZeneca was responsible for generating the randomization scheme. The randomization scheme was produced by a computer software program that incorporated a standard procedure for generating random numbers. The specific methods used to assign subjects to treatment groups are described in Section 5.2.1 of the Clinical Study Protocol." (Section 5.4.3). Independent randomisation does not appear to have been conducted.
Performance bias	Blinding of participants and personnel	LOW "Double-blind" reported but not described in publications, but unpublished CSR details who was blinded and the manner in which the placebo was "indistinguishable" from the active treatment (Section 9.4.7 of the unpublished CSR).[42] There was no evaluation of blinding.	MODERATE to HIGH "Double-blind" reported but not described. Published CSR and unpublished CSRs state: "placebo to match vandetanib." The CSR from October 2014[44] states that, "methods for ensuring blinding and the procedures for unblinding the study are described in Section 5.4 of the CSP." These details could not be verified (as they were not reported in any available protocol). Therefore, there was no evaluation of blinding and insufficient detail was provided regarding how blinding was guaranteed. A number of outcomes were also potentially confounded by the inclusion of data from the open-label (unblinded), cross-over stage within the trial (e.g. OS and safety outcomes, as well as post-progression PFS and ORR).

Risk of bias	Criteria	EXAM trial (Cabozantinib)[28]	ZETA trial (Vandetanib)[27]
Detection bias	Blinding of outcome assessment	LOW "Tumor assessments were performed by a blinded IRC to determine response and/or progression for the primary efficacy analyses..." The primary outcome, PFS, was assessed by a blinded and independent radiology review committee [IRC].	MODERATE "Tumor assessments were categorized by the investigator by using Response Evaluation Criteria in Solid Tumors v1.0 (RECIST). Responses were confirmed by central review of separate assessments performed at least 4 weeks apart. RECIST assessments derived from an independent central review of patient scans were the basis for the primary analysis."[27] The majority of trial documents do not state whether the confirmatory "independent central review" was blinded. This is only stated in an unpublished CSR from July 2011,[43] where the PFS efficacy results are described as being "based on an independent, blinded central review" (page 180) (repeated in the Sanofi CS, page 41). This information does not appear elsewhere in available protocols, other CSRs or publications. The CSR accompanying the main publication[27] and the unpublished CSR of July 2011[43] are the only documents to indicate that the RECIST criteria applied in the ZETA trial were "modified"; this is detailed in the unpublished CSR as being based on "particular radiographic characteristics, hypodense lesions, and calcified lesions." (page 48) A number of outcomes are also potentially confounded by the inclusion of open-label, cross-over patients within the analysis (e.g. OS, ORR, AEs)
Attrition bias	Incomplete outcome data	LOW There were high levels of attrition (discontinuation of treatment) but the assumption was that disease had progressed from the point at which data were censored: "The primary analysis of PFS was event driven … and included all randomly assigned patients (i.e., the intention-to-treat population)... all patients except the first 138 to experience an event were censored in the	LOW There were high levels of attrition (discontinuation of treatment) but the assumption is that disease had progressed from the point at which data are censored: "Analyses of PFS and overall survival were conducted by using the log-rank test (unadjusted model with treatment factor only) in the intention-to-treat population... Patients who had not progressed or who had died at the time of analysis were censored at the time of their last evaluable RECIST assessment...If a patient had not progressed according to the central read when the patient started to

Risk of bias	Criteria	EXAM trial (Cabozantinib)[28]	ZETA trial (Vandetanib)[27]
		PFS analysis, contributing time-to-event data until the date of censoring"[28]	receive open label treatment, the open label assessments were included in the derivation of these endpoints."[27]
Reporting bias	Selective reporting	MODERATE The primary and principal secondary outcomes (OS, ORR) are reported, but some outcomes listed in the protocol that accompanied the publication[28] were not reported in the publication or its related data supplement, only in the unpublished CSR (e.g. Section 11.4.4.2 and 12.1.6).[42] These are the patient-reported outcome MDASI-Thyroid module, plus two "safety endpoints": ECOG performance status and concomitant medications.	MODERATE All of the outcomes reported in the protocol were reported in the publication or the published CSR[27], except the FACT-G quality of life measure, which was not listed in the published protocols and was only reported in an unpublished CSR from October 2014[44] (data were not reported, only a summary finding). Time to Worsening Pain [TWP] was listed in the protocol, but results only appear in the published and unpublished CSRs.
Other bias		MODERATE Many declared conflicts of interests among the authors. There were reported differences between the two trial arms in the prognostic factors CTN and CEA, although in the publication "these baseline values were judged to be not meaningfully different"[28]. However, CTN and CEA doubling time is a potential confounder and is neither controlled for (e.g. by stratification) nor assessed[15].	MODERATE Many declared conflicts of interests among the authors. "The principal investigator in collaboration with the study sponsor, AstraZeneca, designed the clinical trial. The sponsor provided funding and organizational support, collected and managed the data, and performed the statistical analysis." CTN and CEA doubling time were assessed as confounders[19] (and Sanofi CS,[35] Figure 4, page 51).

Note: All quotations are taken from the full trial publications

PD - progressive disease; PFS – progression-free survival; OS - overall survival; ORR - objective response rate; IRC - independent radiology review committee; CSR - clinical study report; CTN - calcitonin; CEA - carcinoembryonic antigen; PROMS - patient reported outcome measure; MDASI - MD Anderson Symptom Inventory; (m)RECIST - (modified) Response Evaluation Criteria In Solid Tumours; ECOG PS - Eastern Cooperative Oncology Group Performance Status; FACT-G - Functional Assessment of Cancer Therapy – General.

5.2.2 Assessment of effectiveness

In the EXAM trial, at data cut-off (15th June 2011), the median duration of follow-up was 13.9 months. At this timepoint, 98/219 (45%) in the cabozantinib arm were still receiving blinded study treatment, whilst only 15/111 (14%) in the placebo arm were still receiving blinded study treatment.[28] In the ZETA trial, at data cut-off (July 2009), the median duration of follow-up was 24 months. At this timepoint, 111/231 (48%) in the vandetanib arm were still receiving blinded study treatment, while only 28/100 (28%) in the placebo arm were doing so.[27]

5.2.2.1 Progression-free survival (PFS)

Both pivotal trials reported PFS as their primary outcome using similar definitions and was based on tumour measurements performed at screening and every 12 weeks. Both treatments resulted in a significantly reduced risk of progression. For cabozantinib, the hazard ratio (HR) for PFS was reported to be 0.28 (95% confidence interval [CI] 0.19 to 0.40; $p<0.001$) by central review and 0.29 (95% CI 0.21 to 0.42; $p<0.001$) by investigator-read[28, 45] (see Table 7).

Table 7: **EXAM trial median PFS duration (months)**

EXAM n=330[28]			
Assessed by	**Cabozantinib n=219**	**Placebo n=111**	**HR**
Central review	11.2	4.0	0.28 (95% CI 0.19-0.40, $p<0.001$)
Investigator	13.8	3.1	0.29 (95% CI 0.21-0.42, $p<0.001$)

HR – hazard ratio

For vandetanib, the HR for PFS was reported to be 0.46 (95% CI 0.31 to 0.69; $p<0.001$) by central review of all patients (ITT population), 0.28 (95% CI 0.18 to 0.42; $p<0.001$) by central review excluding open-label patients, and 0.40 (95% CI 0.18 to 0.42; $p<0.001$) by investigator-read[27] (see Table 8).

Table 8: **ZETA trial ITT population median PFS duration (months)**

ZETA ITT population n=331[27]			
Assessed by	**Vandetanib n=231**	**Placebo n=100**	**HR**
*Central review (ITT population)	30.5	19.3‡	0.46 (95% CI 0.31-0.69, $p<0.001$)
*Central review (excluding open-label)	32.4	16.4‡	‡0.28 (95% CI 0.18-0.42, $p<0.001$**)
Investigator (all patients, ITT population)	22.3	8.3‡	0.40 (95% CI 0.27-0.58, $p<0.001$)

**Weibull model predicted median because median not reached; ‡ CS only ** 0.27, 95% CI 0.18-0.41, p<0.001[27]*
HR – hazard ratio; CI – confidence interval; ITT – intention-to-treat

In *post hoc* analysis, PFS was also calculated for the EU label (n=186) and Restricted EU label [redacted] populations. For the vandetanib EU label population, the HR for PFS was reported to be 0.47 (95% CI 0.29 to 0.77; p=0.0024) for all patients by central review[35] and 0.33 (95% CI 0.20 to 0.53; p=0.0226) by investigator-read for all patients.[40] The HR by central review but excluding open-label patients[40] was reported to be 0.32 (95% CI 0.19 to 0.54; p<0.001, see Table 9). According to the Sanofi CS (page 55),[35] the median PFS for the Restricted EU label group was [redacted] in the placebo arm compared with [redacted] in the vandetanib arm [redacted].

Table 9: **ZETA trial EU label populations median PFS duration (months)**

EU label population n=186[35, 40]			
Assessed by	**Vandetanib n=126**	**Placebo n=60**	**HR**
*Central review (all patients)‡	28.0	16.4	0.47 (95% CI 0.29-0.77; p=0.0024)
*Central review (excluding open-label)§	30.1	11.1	0.32 (95% CI 0.19-0.54; p<0.0001)
Investigator §	22.1	8.3	0.33, †(95% 0.2-0.53; p=0.0226)
Restricted EU label population [redacted][35]			
	Vandetanib	Placebo [redacted]	HR
[redacted]	[redacted]	[redacted]	[redacted]

**Weibull model predicted median because median not reached; † Confidence intervals only provided in Sanofi CS, Tables 18 and 22, which also states p<0.0001 for this HR. ‡ CS only § Kreissl 2014.*
HR – hazard ratio; NR: Not reported

The investigator-read risk of progression, compared with placebo, for the comparable EXAM (n=331) and ZETA EU label (n=186) populations was HR 0.29 (95% CI 0.21 to 0.42; p<0.001) for cabozantinib, and HR 0.33 (95% CI 0.2 to 0.53; p=0.0226), for vandetanib, respectively.

The proportion of randomised patients progressing was similar in the treatment and placebo groups across the two trials. The EXAM trial publication (Elisei *et al*[28]) states that 57/219 (26%) of patients randomised to cabozantinib had progressed at follow-up compared with 67/111 (60%) in the placebo group. The ZETA trial publication (Wells *et al*[27]) reported data on 124 patients who progressed: 73/231 (32%) of patients randomised to vandetanib had progressed (previously reported as 37% at 24 months[46]) and 51/100 (51%) randomised to placebo had progressed.[27]

Within the EXAM trial, the Kaplan-Meier estimates for the proportion of patients alive and progression-free at 1 year was reported to be 47.3% for cabozantinib compared with 7.2% for placebo.[28] Within the ZETA trial, the proportion of patients in the ITT population alive and progression-free at 6 months was reported to be 91% for vandetanib compared with 74% for placebo.[47]

Subgroup analyses according to pre-specified subgroups were conducted for PFS for both cabozantinib and vandetanib. For both interventions, all subgroups demonstrated a beneficial effect with treatment (HR <1.0) although 95% CIs indicated non-statistically significant treatment effects for some small subgroups, as may be expected. Subgroups were considered including gender, performance status, and number of previous anticancer regimens or other TKIs received and response to those therapies.[27, 28, 45, 48, 49] The Ipsen CS for cabozantinib reported that PFS was also prolonged in a subgroup of cabozantinib patients (n=34) who had received prior vandetanib (median PFS, months 12.8 for cabozantinib and 2.8 for placebo, and ORR 28%, where prior vandetanib use reported).[21] PFS for cabozantinib was also consistent across subgroups according to age and the presence of bone metastases[28] and PFS for vandetanib was not sensitive to ethnicity.[27]

Subgroup analyses based on RET mutation status (as specified in the final NICE scope[26]) were also conducted for the EXAM trial. Details of the number of patients in each of these groups within the EXAM trial are presented in Table 10. As shown in

Table 11, cabozantinib was associated with a beneficial effect compared with placebo for all subgroups tested, although the treatment effect was not statistically significant at the 95% level (p=0.21) for the RET negative subgroup, and PFS improvement was least pronounced in the small subset of RET-mutation–negative patients who were also RAS-mutation negative).[50, 51]

Table 10: **RET mutation status in the EXAM trial[28, 50]**

	Patients (%) (Sherman 2016)		
RET mutation subgroup	**Total (n=330)**	**Cabozantinib arm (n=219)**	**Placebo arm (n=111)**
Positive	NR (51.2)	46.1 (48.9)	52.3 (55.9)
Negative	NR (13.9)	14.2 (16.0)	9.0 (9.9)
Unknown	NR (34.8)	39.7 (35.2)	38.7 (34.2)
RET M918T status			
Positive	NR (38.2)	34.2 (37.0)	38.7 (40.5)
Negative	NR (32.4)	30.6 (34.2)	27.0 (28.8)
Unknown	NR (29.4)	35.2 (28.8)	34.2 (30.6)

RET – REarranged during Transfection

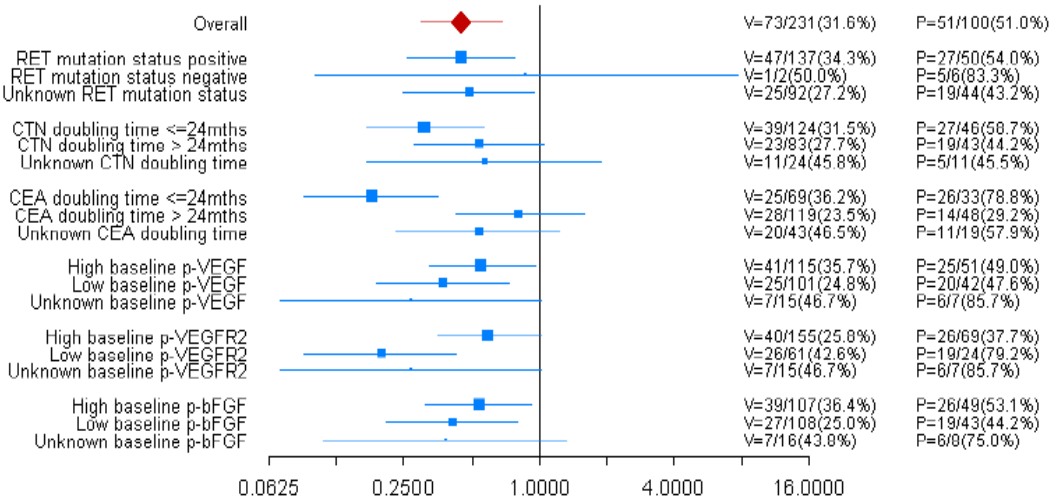
Table 11: **PFS by RET mutational status in *post hoc* analysis of EXAM trial (Ipsen CS,[21] adapted from Sherman *et al*[50])**

Mutation status	Cabozantinib		Placebo		HR (95% CI)	*p*-value
	N	Median PFS (weeks)	N	Median PFS (weeks)		
RET-positive	107	60	62	20	0.23 (0.14, 0.38)	<0.0001
RET-negative	35	25	11	23	0.53 (0.19, 1.50)	0.2142
RET-unknown	77	48	38	13	0.30 (0.16, 0.57)	0.0001
RET M918T positive	81	61	45	17	0.15 (0.08-0.28)	<0.0001
RAS-positive	13	47	3	8	0.15 (0.02, 1.10)	0.0317
RET-negative + *RAS*-negative	22	24	8	23	0.88 (0.24, 3.22)	0.8330

RET – REarranged during Transfection; HR - hazard ratio; CI – confidence interval; PFS – progression-free survival; N - number

With respect to vandetanib, the Sanofi CS states that, *"subgroups relating to two different definitions for "aggressive disease" were included in a pre-specified subgroup analysis: calcitonin (CTN) doubling time (DT) ≤24 months and CEA DT ≤24 months"* (Sanofi CS,[35] Section 4.3, page 45). Subgroup analyses by these criteria were reported in this CS and the unpublished CSR.[43] These found that all subgroups demonstrated a beneficial effect for PFS (HR <1.0) with a statistically significant treatment effect observed for patients with a CTN doubling time of ≤24 months and patients with a CEA doubling time of ≤24 months (see Figure 3).

Figure 3: PFS according to subgroups in the ZETA trial (reproduced from Sanofi CS[35], Figure 4, page 51 and unpublished Astra Zeneca CSR dated July 2011[43])



5.2.2.2 Overall Survival (OS)

The authors of the EXAM trial paper reported that there was no statistically significant difference between cabozantinib and placebo based on an interim analysis.[28] According to a recent abstract

(2015),[52] the EXAM trial was designed with 80% power to detect an HR of 0.667 for the secondary endpoint of OS. A final analysis was conducted after 218 deaths (the trial required 217 deaths for the analysis[28]) at a median follow-up of 52.4 months.[52] The estimated median OS was 26.6 months for cabozantinib compared with 21.1 months for placebo (stratified HR=0.85; 95% CI 0.64 to 1.12), which was not statistically significantly different (p=0.241, see Table 12).[52]

Table 12: **OS median duration (months)**

EXAM n=330 [52]		
Cabozantinib n=219	**Placebo n=111**	**HR**
26.6	21.1	0.85 (95% CI 0.64-1.12; p=0.2409)
ZETA ITT population n=331[27]		
Vandetanib n=231	**Placebo n=100**	**HR**
NR	NR	0.99 (95% CI 0.72-1.38, p=0.9750)
EU label population n=189[53]*		
Vandetanib n=126	**Placebo n=60**	**HR**
[redacted]	[redacted]	[redacted]
Restricted EU label population [redacted][53]*		
Vandetanib [redacted]	**Placebo** [redacted]	**HR**
[redacted]	[redacted]	[redacted]

**Survival time was originally reported in years but has been converted to months.*
HR – hazard ratio; ITT – intention-to-treat; CI – confidence interval

For the 215 (65%) patients with known positive or negative RET mutations in the EXAM trial,[50] median OS was 31.6 months in the cabozantinib arm compared with 24.8 months in the placebo arm (HR=0.79; 95% CI 0.54 to 1.17; p=0.240).[54] For the 126 patients with known RET M918T positive mutations, median OS was 44.3 months for cabozantinib compared with 18.9 months for placebo (HR=0.60; 95% CI 0.38 to 0.94; p=0.026).[52, 54] Subgroups of patients lacking RET mutations or lacking RET M918T showed no increase in OS.[52, 54] The secondary endpoint of improved OS was not met because the difference between arms was not statistically significant in the ITT population.[52]

The data on OS from the ZETA trial were immature, which reported a non-significant interim result (HR=0.89; 95% CI 0.48 to 1.65; p-value not reported)[27] and the intention to conduct a final analysis when 50% of patients had died. Numbers of patients who had died at data cut-off (31 July 2009) were reported in the published CSR[27]: 32/231 (14%) in the vandetanib arm compared with 16/100 (16%) in the placebo arm, p=0.7115[27] (and Sanofi, CS,[35] page 49). In the final analysis set (data cut-off 7th September 2015), there remained no survival benefit: 50% of patients randomised to vandetanib had died compared with 52% of patients randomised to placebo (HR=0.99; 95% CI 0.72 to 1.38; p=0.975), although the placebo group included patients who had crossed-over to vandetanib in the un-blinded stage of the trial, thereby potentially confounding these results (Sanofi CS,[35] page 49).

For the ZETA EU label population, the estimated median OS was [redacted] for vandetanib compared with [redacted] for placebo [redacted].

According to the Sanofi CS[35] (page 55 and Table 20), the median OS for the Restricted EU label group was [redacted] in the placebo arm compared with [redacted] in the vandetanib arm [redacted]

5.2.2.3 Response rate

The end point of objective response rate (ORR) was reported in both trials, including complete and partial response, and was determined using the stated RECIST criteria[27, 28] (see Table 13). In the EXAM trial (n=312 for this outcome), no patients had a complete response. Twenty eight percent of patients had a partial response in the cabozantinib arm compared with 0% in the placebo arm (p<0.001), with a median estimated duration of response of 14.6 months (95% CI 11.1 to 17.5 months)[28] and similar rates for RET mutation positive and negative subgroups.[45, 48]

Table 13: **Objective response rates**

Trial	**Percentage with response**			**Estimated or predicted duration of response (months)**
EXAM n=312	**Cabozantinib**	**Placebo**	***p*-value**	
	28	0	<0.001	14.6
ZETA	**Vandetanib**	**Placebo**	***p*-value**	
ZETA n=331 (ITT)	45	13	<0.001	22
ZETA n=186 (EU label)†	43.7	1.7	<0.0001	NR

† "symptomatic and progressive" patients only, pre-crossover[40]; NR: Not reported.

In the full publication of the ZETA trial (n=331 for this outcome), the ORR was 45% in the vandetanib group compared with 13% in the placebo group (p<0.001), with a predicted median duration of response of 22 months.[27] Within an earlier abstract, the odds ratio (OR) was reported to be 5.4 compared with placebo (95% CI 2.99 to 10.79, p<0.0001).[55] It should be noted that 12/13 patients in the placebo group only had a response when they crossed-over to vandetanib in the open-label phase of the trial.[27, 46] The OR was reported to be 45.7 (p<0.0001) compared with placebo for the EU label patients (n=186) in the ZETA trial before any crossovers occurred.[40] The Sanofi CS[35] (Table 24, page 67) states that 43.7% of these patients had a response in this vandetanib group (n=126), compared with [redacted] in the Restricted EU label vandetanib group [redacted]. Small numbers of RET-negative patients were deemed to render findings from the subgroup analysis of the EU label group inconclusive, although other analyses did suggest that M918T mutation-positive patients had a better response to vandetanib than M918T mutation-negative patients.[27] The Sanofi CS also stated that higher proportions of patients with a CTN or CEA doubling-time of less than 24 months (47% and 54% respectively) achieved ORR compared

with patients with a doubling time of greater than or equal to 24 months (40% and 37%) (Sanofi CS,[35] page 51).

5.2.2.4 CTN and CEA response

Serum levels of CTN and CEA are recognised indicators of tumour burden and prognosis.[15, 17, 56] In both the EXAM and ZETA trials, CTN and CEA were evaluated from serum samples at baseline and, at the most, every 12 weeks after initiation of treatment, to coincide with radiologic tumour assessments; response was calculated as a percentage change compared with baseline.[27, 28] In the EXAM trial, the cabozantinib and placebo groups did not have statistically significantly different baseline levels of CTN or CEA, but at 12 weeks follow-up, evaluated patients in the cabozantinib group had statistically significantly better responses compared with placebo: levels of both biomarkers decreased in the treatment group and increased in the placebo group (see Table 14).[28, 57, 58]

Table 14: **EXAM trial CTN and CEA response rates**

Trial	**Biomarkers**	**Mean (s.d.)**		
EXAM		**Cabozantinib**	**Placebo**	***p*-value**
Baseline	CTN n=330	6,370 pmol/L (11,332 pmol/L)	8,846 pmol/L (15,722 pmol/L)	0.27*
	CEA n=330	736 µg/L (3,555µg/L)	1,108 µg/L (5,168 µg/L)	0.58*
		Percentage change, mean (SD)		
Week 12	CTN n=201	-45.2 (60.71)	+57.3 (115.4)	<0.001
	CEA n=241	-23.7 (58.21)	88.7 (182)	<0.001

**Welsh's t-test*

CTN – calcitonin; CEA – carcinoembryonic antigen; s.d. – standard deviation

In the ZETA trial, higher, statistically significant percentages of patients receiving vandetanib achieved a CTN and CEA response (69% and 52% respectively) compared with patients receiving placebo (3% and 2%) (see Table 15).[27, 35]

Table 15: **ZETA trial CTN and CEA response rates**

Trial	**Biomarkers**	**Percentage of patients with a response**		**OR**
ZETA		**Vandetanib**	**Placebo**	
Follow up not reported*	CTN n=331	69	3	72.9 (95% CI 26.2-303.2; p<0.001)
	CEA n=331	52	2	52 (95% CI 16.0-320.3; p<0.001)

**Full analysis set follow-up is 24 months*

CTN – calcitonin; CEA – carcinoembryonic antigen; OR – odds ratio

5.2.2.5 Lesion size

Lesion size was only measured and reported within the EXAM trial. In order to be included, patients needed measureable disease at baseline and at least one subsequent assessment.[28] One hundred and eighty of 219 cabozantinib patients and 89/111 placebo patients satisfied these criteria. Ninety four percent of these cabozantinib patients, and 27% of these placebo patients, had a detectable decrease in target lesion size.[28] Elisei *et al*[28] also noted that there was a "generally linear relationship" in the reductions in lesion size and both CTN and CEA levels.

5.2.2.6 MD Anderson Symptom Inventory (MDASI-THY)

The MDASI-THY module was the only patient-reported outcome measure (PROM) used in the EXAM trial and data on this outcome were reported only in the unpublished CSR.[42] Data were also provided by the company at the request of the Assessment Group. The analysis was exploratory and was evaluated at screening and every 12 weeks (±5 days) to disease progression, coinciding with tumour assessments. The tool measured clinical symptoms such as pain, fatigue, nausea, diarrhoea and mood, with higher scores indicating more symptoms. The CSR reported (Section 11.4.4.2) that although no formal statistical testing was performed, *"there was no apparent difference between treatment arms in change from baseline to 2011 data cut off analysis for this exploratory endpoint"*, though it was stated that there were only data for 75% of participants at week 12, with declining numbers for subsequent assessments.[42]

5.2.2.7 FACT-G and Time to worsening of pain (TWP)

These outcomes were only measured and reported for the ZETA trial; the details and results only appear in the published and unpublished CSR,[27, 43] although data were also provided by Sanofi at the request of the Assessment Group. The CSR states that quality of life was measured using the FACT-G instrument[43] and that, overall, scores between the two arms were similar. TWP was a composite endpoint, derived from opioid analgesic use and the worst pain item of the Brief Pain Inventory (BPI). The ZETA trial reported a significantly longer median TWP for vandetanib (7.85 months) compared with placebo (3.25 months): HR=0.61; 95% CI 0.43 to 0.87 (p=0.0062) in the published CSR.[27] In the EU label population, TWP was 11.1 months in the vandetanib arm, compared with 3.4 months in the placebo arm (HR=0.62; 95% CI 0.39 to 0.99; p=0.45).[35]

5.2.3 Safety outcomes

In order to be considered for safety outcomes, patients had to receive at least one dose of the study drug.[27, 28]

5.2.3.1 Any adverse event

The EXAM trial safety data were taken from the trial publications or the final datasets where available: the EXAM Final Analysis Set of August 2014, provided in the Ipsen CS for cabozantinib (median

follow-up of 10.8 months),[21] and the ZETA final Safety Analysis Set, provided in the Sanofi CS for vandetanib[35] and the unpublished CSR of 2011 (median total exposure 90.1 weeks for vandetanib compared with 39.9 weeks for placebo).[43] Seven patients are missing from the EXAM safety population data, therefore n=214 for cabozantinib rather than n=219 in the ITT population, and n=109 for placebo rather than n=111.

AEs were very common in both trials. Overall, 100% of patients were affected by at least one AE in the cabozantinib arm of the EXAM trial, and 99.6% of patients were affected by at least one AE in the vandetanib arm of the ZETA trial, 96% of which were attributed to vandetanib by the investigator.[27] Both trials reported many AEs affecting $\geq$10% and <20% of patients: dry skin, insomnia, abdominal pain, dermatitis acneiform, cough, nasopharyngitis, prolonged ECG QT (as defined by the National Cancer Institute CTCAE), alopecia, pain in extremity, dyspnea, arthralgia, dizziness, oral pain, dry mouth, dysphagia, cough, muscle spasms, dyspepsia, erythema, and glossodynia.[27, 28]

Given their high frequency, only the most common AEs, i.e. those affecting $\geq$20% of patients in any trial arm, are presented in

Table 16. The most common AEs for cabozantinib were diarrhoea (63%), hand foot syndrome (50%), decreased weight (48%), decreased appetite (46%), nausea (43%) and fatigue (41%).[28]

Similarly, the most common AEs for vandetanib were diarrhoea (56%), decreased appetite (21%), nausea (33%) and fatigue (24%). In addition, there was a high incidence of rash (45%), hypertension (32%) and headache (26%), but low or no incidence of hand foot syndrome.[27, 46] Hypertension is a known AE for TKIs.[59, 60] The incidence of diarrhoea in vandetanib treatment for MTC appears to be similar to other cancers,[61] but the rates of any grade or high grade rash and hypertension appear to be higher for vandetanib in MTC patients than in most other cancer patients,[62, 63] which might be due to longer treatment duration.[63]

Table 16: **Common adverse events (any grade) reported for >20% of patients in any arm of the EXAM or ZETA trials (figures rounded up to the nearest whole number)**

Adverse event	**EXAM trial (% with event)**		**ZETA trial (% with event)**	
	Follow-ups: 10.8 months (median)*		90.1 weeks†	39.9 weeks†
	Cabozantinib (n=214)	**Placebo (n=109)**	**Vandetanib (n=231)**	**Placebo (n=99)**
Overall	100*	95*	97 (Wells CSR[27])	91 (Wells CSR[27])
Diarrhoea	63	33	56	26
Hand foot syndrome	50	2	-	-
Decreased weight	48	10	10	9
Decreased appetite	46	16	21	12
Nausea	43	21	33	16
Fatigue	41	28	24	23
Dysgeusia	34	6	-	-
Hair colour changes	34	1	-	-
Hypertension	33	5	32	5
Stomatitis	29	3	-	-
Constipation	27	6	-	-
Haemorrhage	25	16	-	-
Vomiting	24	2	14	7
Mucosal inflammation	23	4	-	-
Asthenia	21	15	14	11
Dysphonia	20	9	-	-
Rash	19	10	45	11
Headache	18	8	26	9
Acne	-	-	20	5
Back pain	15	11	9	20

*Blank cells indicate not reported or <10%. * Ipsen CS, 2017 from final analysis of August 2014. †Median duration of exposure: Sanofi CS, Table 33 and CSR 2011, Table 40.*
CSR – clinical study report

It should be noted that patients with MTC have a substantial disease burden. This is demonstrated by the AEs and comorbidities in the placebo arm and baseline data for EXAM and ZETA trial patients (see

Table 16), and especially those in the EXAM trial, with radiographic evidence of progressive disease[64] as presented in Table 17. The majority of symptoms were of Grade 1 and 2 severity.

Table 17: Percentage of patients with reported symptoms at baseline in the EXAM trial

Symptoms	% of patients (n=330)
Pain	46.1
Diarrhoea	39.7
Fatigue	25.8
Dysphonia	23.0
Dyspnoea	16.1
Cough	12.1
Dysphagia	9.1
Anorexia	7.0
Weight loss	5.5
Flushing	4.2

5.2.3.2 Grade ≥3 and serious adverse events (SAEs)

AEs of Grade 3 or above reported for ≥2% of patients are presented in

Table 18. The most common Grade ≥3 AEs for cabozantinib were diarrhoea (16%), hand foot syndrome (HFS, 13%), fatigue (9%) and hypertension (8%), asthenia (6%) and decreased weight (5%) and appetite (5%).[28, 45] These appear to be consistent with other anti-VEGF TKIs and the open-label cabozantinib studies.[65-68] However, it should be noted that the incidence and severity of HFS reported in the EXAM trial is lower than that reported in other cabozantinib trials for the treatment of other solid malignancies.[69]

The most common Grade ≥3 AEs for vandetanib were also diarrhoea (11%), hypertension (9%), fatigue (6%) and decreased appetite (4%), but also rash (4%) and prolonged ECG QT (8%). An exploratory study of a subset of the ZETA trial patients has indicated potential benefits of vandetanib in terms of weight and muscle loss.[70-72] This study also identified significant toxicities in the presence of higher mean vandetanib plasma concentration, the most frequent toxicities being asthenia Grade 3 (36%), prolongation of the QTc interval (25%), and cutaneous symptoms (11%).[71] Vandetanib is one of only two TKIs (the other being sunitinib) identified as being associated with prolonged QTc.[73]

Table 18: Grade 3 or higher adverse events reported for ≥2% of patients in any arm of the EXAM or ZETA trials (all figures rounded-up to the nearest whole number)

Adverse event	EXAM trial (% with event)		ZETA trial (% with event)	
	Follow-ups: 10.8 months (median)*		90.1 weeks†	39.9 weeks†
	Cabozantinib (n=214)	**Placebo (n=109)**	**Vandetanib (n=231)**	**Placebo (n=99)**
Overall	69 (78*)	33	55 (CSR, Langmuir) 61 (Kreissl)	24 (CSR and Kreissl)
Diarrhoea	16	2	11	2

Hand foot syndrome	13	0	-	-
Fatigue	9	3	6	1
Hypertension	8	1	9	0
Asthenia	6	2	3	1
Decreased weight	5	0	-	-
Decreased appetite	5	1	4	0
Dysphagia	4	1	-	-
Abdominal pain	3	1	-	-
Haemorrhage	3	1	-	-
Dyspnoea	2	10	1	3
Back pain	2	1	0	3
Mucosal inflammation	3	0	-	-
Vomiting	2	1	-	-
Rash	1	0	4	1
Headache	1	0	-	-
Syncope	-	-	0	2
Prolonged ECG QT	-	-	8	1

*Blank cells indicate not reported or <2%. NR: * Ipsen CS, 2017 from final analysis of August 2014. †Median duration of exposure: Sanofi CS, Table 33 and Astra Zeneca 2011, Table 46.*

Serious adverse events (SAEs), as defined by the National Cancer Institute's CTCAE,[74] affected more patients receiving cabozantinib (42.1% or 53% depending on source) compared with those receiving placebo (22.9% or 24%) in the EXAM trial.[21, 28] SAEs that occurred in ≥2% of patients in any arm of the EXAM trial are presented in

Table 19. The overall incidence of any SAE in the ZETA trial was 31% in the vandetanib arm compared with 13% in the placebo arm.[27]

Table 19: **Serious adverse events ≥2% in any arm in the EXAM trial[28] or ZETA trial (Sanofi CS, Table 33[35] and Astra Zeneca CSR 2011, Table 50[43])**

Adverse event	**EXAM trial (% with event)**		**ZETA trial**	
	Follow-ups: 10.8 months (median)*		90.1 weeks†	39.9 weeks†
	Cabozantinib (n=214)	**Placebo (n=109)**	**Vandetanib (n=231)**	**Placebo (n=99)**
Overall	42.1 (53*)	22.9 (24*)	30.7	13.1
Mucosal inflammation	2.8	0	2.2	0
Hypocalcaemia	2.8	0	1.3	0
Pulmonary embolism	2.3	0	NR	NR
Hypertension	2.3	0	1.3	0
Diarrhoea	NR	NR	2.2	

** Ipsen CS, 2017 from final analysis of August 2014. †Median duration of exposure: Sanofi CS, Table 33.*

Grade 5 AEs occurring within 30 days of the last dose were reported in more cabozantinib patients than placebo patients (7.9% compared with 7.3%).[28] A number of these Grade 5 AEs were specified as being related to cabozantinib: fistula, respiratory failure, haemorrhage, sepsis/multi-organ failure, sudden death, cardiopulmonary failure and "death, not other specified." At 52.4 months follow-up, the most common SAEs (≥2%) were pneumonia (4.2% of those receiving cabozantinib experienced this event),

pulmonary embolism (3.3%), mucosal inflammation (2.8%), hypocalcaemia (2.8%), hypertension, dysphagia, dehydration and lung abscess (2.3% each).[75]

5.2.3.3 Adverse events leading to discontinuation or dose interruption/reduction

AEs leading to dose reductions/interruptions and/or discontinuation of treatment were reported for both trials (see

Table 20). There were similar proportions of patients across the two trials who discontinued treatment due to AEs (16% or 23% for cabozantinib and 12% for vandetanib), however there was a higher percentage of patients experiencing AEs leading to dose interruption or reduction on cabozantinib (65%) than on vandetanib (35%).[27,28] A later abstract detailing this outcome for the EXAM trial reported that dose reduction to manage AEs was performed for 82% of patients treated with cabozantinib[34], which increased again to 87% in the final analysis.[21] The percentages of patients experiencing AEs leading to dose interruption (17%) or discontinuation (8%) were also higher in the placebo arm of the cabozantinib trial[28] than in the placebo vandetanib trial (3% for dose interruption and 3% for discontinuation). High rates of dose reduction and discontinuation have also been reported for a retrospective study of 15 patients with progressive MTC on cabozantinib.[49]

Table 20: Dose interruption or discontinuation rates in the EXAM and ZETA trials (from Sanofi CS[35] unless stated)

EXAM trial	**Cabozantinib (n=214)**	**Placebo (n=109)**
Dose interruption due to AE[28]	65%	17%
Discontinuation due to AE[28]	16% (23*)	8% (9*)
Dose interruption or reduction	87%	22%
Dose reduction*	79%	9%
ZETA trial	**Vandetanib (n=231)**	**Placebo (n=99)**
Dose interruption†	47%	15%
Discontinuation due to AEs[27]	12%	3%
Dose interruption or reduction	49%	15%
Dose reduction[27]	35%	3%
EU-label only (Sanofi CS, Table 33)†	**Vandetanib (n=126)**	**Placebo (n=60)**
Discontinuation due to AEs	12%	2%
Dose reduction	33%	3%

**Data from Sanofi CS, 2017, page 73 only. †From Sanofi CS, Table 33.*
CS - company submission

5.2.3.4 Deaths

In the EXAM trial, at data cut-off, 30% of patients (65/214) had died in the cabozantinib arm compared with 28% (30/109) in the placebo arm. Twenty three percent (15/65) of deaths in the cabozantinib arm were attributable to AEs compared with 20% (6/30) in the placebo arm;[28] other deaths were attributable to disease progression. Full details of the AEs leading to death were not reported.[28] By the final analysis (August 2014), the figures had increased to 65% (138/214) in the cabozantinib arm compared with 70% (76/109) in the placebo arm, with deaths deemed to be treatment-related remaining at 4-5% for cabozantinib and 1% for placebo at both the interim and final analysis.[21]

During the randomised phase of the ZETA trial, five patients who received vandetanib experienced AEs leading to death. Reasons given were: aspiration pneumonia, respiratory arrest, respiratory failure, staphylococcal sepsis and, in one patient, arrhythmia and acute cardiac failure. Instances of gastroenteritis and GI haemorrhage led to deaths in two patients in the placebo group.[27] The number of deaths reported at safety follow-up was 10 (4.3%) in the vandetanib group compared with 6 (6.1%) in the placebo group, although two of the deaths in the vandetanib group did not have MTC as either the primary or secondary cause; no such deaths were recorded in the placebo group.[43]

5.2.3.5 Supplementary safety evidence

The Sanofi CS[35] also presented safety data from two additional published studies[37, 39] and one ongoing study (NCT01496313); the data from this third, ongoing study are unpublished. The findings on the most frequent AEs and SAEs, and the incidence and type of AEs, were all similar to the ZETA trial for the 300mg vandetanib dose. Dose interruption and reduction rates were also similar, except for higher rates in a trial arm that included additional monitoring through an outreach programme.[37] Only the 'real

world' study of 68 MTC patients treated with vandetanib in France[39] had a markedly higher incidence of death (42% compared to 12% or less in the other studies for the 300mg vandetanib dose) and AE-related discontinuations (27% compared with 15% or less) than the other studies or the ZETA trial. These trials had similar or shorter duration of follow-up to the ZETA trial, but were not subject to potential confounding due to crossover.

5.3 Network meta-analysis

5.3.1 Justification for conducting a network meta-analysis

In the absence of head-to-head evidence comparing cabozantinib and vandetanib, an indirect comparison using an NMA was considered. An indirect comparison has previously been published as an abstract[76] and is presented in the Ipsen CS;[21] however, due to the differences between the ITT population of the EXAM and ZETA trials, this analysis was not deemed appropriate for formal consideration within this assessment. The validity of the NMA depends on the assumption that there is no difference in the distribution of trial-level treatment effect modifiers between the populations in the two trials. This is unlikely to be the case for the ITT populations of the ZETA and EXAM trials, in particular, because patients in the EXAM trial had confirmed disease progression, whilst the ZETA trial recruited a broader population of patients with no requirement for established disease progression. HRs for the effectiveness of vandetanib compared with placebo for investigator-assessed PFS in the ZETA trial were reported for the symptomatic and progressive subgroup (n=186, HR=0.33; 95% CI 0.20 to 0.53) and the full analysis set excluding symptomatic and progressive patients (n=139, HR=0.49; 95% CI 0.27 to 0.58) within the Sanofi CS.[35] This suggests that progression may be a treatment effect modifier, with a greater treatment effect observed for the subgroup with confirmed progression (though a statistically significant difference between the two groups cannot be inferred).

Despite differences in the ITT populations, the Assessment Group considered an NMA based on the EU label subgroup of the ZETA population to be appropriate. There was a marked difference in the median PFS in the control groups of the two studies (EXAM – 4.0 months, ZETA EU label - 16.4 months [by central review]), however differences in baseline characteristics of the included studies due to differences in study protocols are to be expected and do not invalidate an indirect comparison. For an NMA to be valid, it is important that there is not an imbalance in treatment effect modifiers. Clinical advisors to the Assessment Group identified severity of disease as an important potential treatment effect modifier. Information on ECOG/WHO performance status at baseline was not available for the ZETA EU label population and so balance across the two studies could not be assessed. However, subgroup analyses indicated consistent treatment effects according to performance status at baseline for both interventions,[27, 28] hence there was no evidence to rule out an NMA on this basis. Clinical advice received by the Assessment Group suggested that the ZETA EU label and EXAM ITT populations could be considered to be broadly comparable.

5.3.2 Methods for the network meta-analysis

An NMA was conducted by the Assessment Group to provide an indirect comparison between cabozantinib and vandetanib for central-read PFS and investigator-read PFS. For OS, the HRs for both treatment groups are confounded by treatment switching; an NMA was therefore not conducted for this outcome as it would not provide a meaningful comparison.

The network diagram is presented in Figure 4 and data contributing to the NMA are presented in Table 21. Analyses were conducted using a Bayesian random effects model, as described by Dias *et al*.[77] Given that there is potential heterogeneity between the trials, a random effects model was considered to be most appropriate so that this uncertainty is appropriately reflected in the estimated treatment effects. There was insufficient information to estimate the between-study variance from the data alone, hence a weakly informative prior was used for this parameter (log normal -2.56, 1.742 based on the recommendation in Turner *et al*.[78]) which has median of 0.08 and 95% range of 0.003 to 2.34 on the untransformed scale. This prior was also truncated such that the ratio of the upper and lower 95% CI of the prior does not exceed 10, based on advice from Speigelhalter *et al*[79] and Smith *et al*[80] that the between-study treatment effects are unlikely to vary by more than an order of magnitude.

Analyses were conducted in the freely available software packages WinBUGS[81] and R[82] using the R2Winbugs interface package.[83] Convergence to the target posterior distributions was assessed using the Gelman-Rubin statistic, as modified by Brooks and Gelman,[84] for two chains with different initial values. For all outcomes, a burn-in of 50,000 iterations of the Markov chain was used with a further 20,000 iterations retained to estimate parameters. There was no evidence of high autocorrelation between successive iterations of the Markov chain.

It should be noted that the results from the NMA are not used to inform the health economic model developed by the Assessment Group (see Section 6.2). The NMA utilises HRs, which are averaged estimates of treatment effect, and their use in the health economic model would be appropriate only if the hazards are proportional over the entire extrapolation period. However, the Assessment Group's health economic model considers a broader range of parametric functions, not all of which conform to the proportional hazards assumption, hence the use of HRs from the NMA would not be appropriate. Instead, estimation of the treatment effects and baseline model is conducted using the same parametric model type (see Section 6.2.3.2.), conforming to the recommendation in Guyot *et al*.[85]

Figure 4: **Network diagram for NMA**

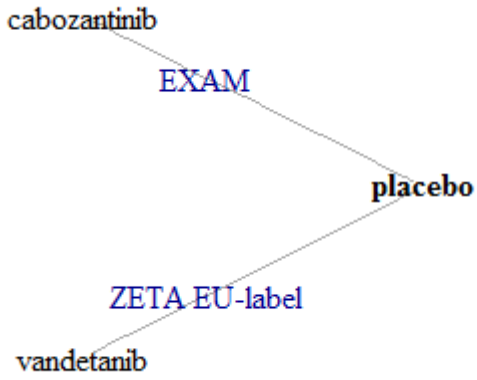


Table 21: **Data for the NMA on PFS**

Study	**Treatment**	**Comparator**	**PFS HR (95% CI)**	
			Investigator-read	**Central-read**
EXAM n=330 (Elisei *et al* 2013)	Cabozantinib	Placebo	0.29 (0.21-0.42)	0.28 (0.19-0.40)
ZETA EU Label n=186 (Kreissl *et al* 2014)	Vandetanib	Placebo	0.33 (0.20-0.53)	0.47 (0.29-0.77)

CI – confidence interval

5.3.3 Results of the network meta-analysis

The results of the NMA are shown in Figure 5 for investigator-read PFS and Figure 6 for central-read PFS, respectively. Based on investigator-read PFS, the results of the two treatments are broadly similar (vandetanib vs cabozantinib HR=1.14; 95% credible interval [CrI] 0.41 to 3.09). The magnitude of the treatment effect is more favourable towards cabozantinib when the comparison is based on central-read PFS (HR=1.68; 95% CrI 0.61 to 4.62) however the difference between the two interventions is not statistically significant.

Figure 5: **Results of the NMA for investigator-read PFS**

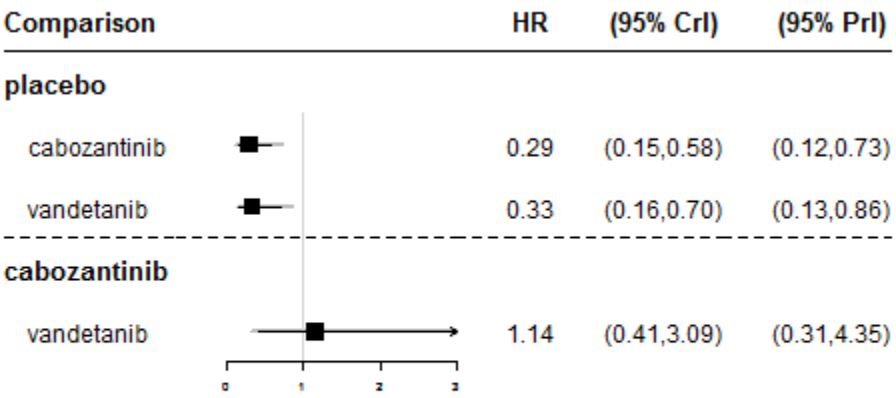
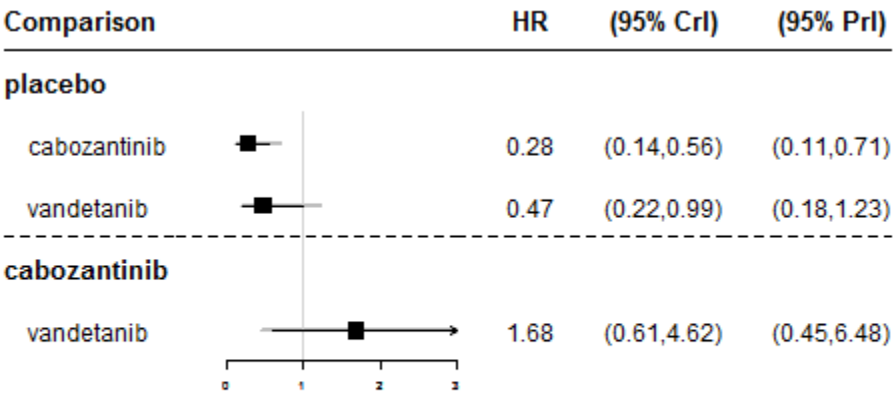


Figure 6: **Results of the NMA for central-read PFS**



5.4 Discussion

The systematic review of the clinical effectiveness evidence identified two placebo-controlled RCTs. The EXAM trial evaluated the efficacy and safety of cabozantinib in patients with unresectable locally advanced or metastatic and progressive MTC (n=330). The ZETA trial evaluated the efficacy and safety of vandetanib in patients with unresectable locally advanced or metastatic MTC (n=331). The EXAM trial was at low risk of bias across most domains (although the risk of selection bias was unclear because the method of randomisation was not explicitly reported), whilst the ZETA trial was at a moderate to high risk of bias across a number of domains; in particular, the method of randomisation was not described and several outcomes were confounded by the inclusion of open-label, cross-over patients within analyses.

The two trials assessed different populations: the EXAM trial (n=330) only included patients with unresectable locally advanced or metastatic and progressive MTC, whilst the ZETA trial inclusion criteria (n=331) did not specify the requirement for patients to have "progressive" disease: the ITT population in the latter trial therefore generally had less severe disease (there were more patients with potentially indolent disease). The more progressive and severe disease of EXAM trial patients is evidenced by the between-trial baseline differences in Performance Status (see Table 4) and the relatively shorter duration of PFS for the patients in the placebo arm of the EXAM trial. However, published abstracts and the Sanofi CS[35] provided data on a subgroup of the ZETA ITT population, i.e. those with "progressive and symptomatic disease" (n=186) - the EU label population. Despite slight differences in definition (e.g. the explicit requirement for defined symptoms in the ZETA EU label subgroup), clinical advice received by the Assessment Group confirmed that the EXAM trial and ZETA trial "progressive and symptomatic" (EU label) populations are comparable. Clinical advice also confirmed that these populations reflect patients who are likely to present in clinical practice in England. The Sanofi CS also presented data on a Restricted EU label subgroup from the ZETA trial [redacted], which was composed of "progressive and symptomatic" patients who also had "aggressive" disease, defined as a CTN and CEA doubling time of less than 24 months. CTN and CEA doubling time is an acknowledged prognostic factor for MTC[15, 17, 56] and was not controlled for in the EXAM trial. However, clinical advice received by the Assessment Group suggests that these biomarkers are unlikely to be relevant in the presence of other criteria indicating progressive disease (e.g. RECIST criteria and symptoms), and whilst they might be used to determine whether treatment is still working, they would not be used to inform decisions about whether to initiate TKI treatment.

In terms of efficacy, both cabozantinib and vandetanib significantly improved PFS compared with placebo. For the principal comparison between the EXAM ITT population and the ZETA EU label population, PFS was similar for cabozantinib (investigator-read HR=0.29; 95% CI 0.21 to 0.42, p<0.001; central review HR=0.28; 95% CI 0.19 to 0.40, *p*<0.001) and vandetanib (investigator-read HR=0.33; 95% CI 0.2 to 0.53, *p*=0.0226; central review excluding crossover patients HR=0.47; 95% CI 0.29 to 0.77, *p*=0.0024; including open-label populations HR=0.32, 95% CI 0.19 to 0.54, *p*<0.001, see Section 5.2.2.1). The difference in PFS between vandetanib and placebo was [redacted] for the Restricted EU label population [redacted].[35] Subgroup analyses demonstrated a favourable treatment effect for all subgroup categories. The publications and company submissions also presented data for PFS based on RET-mutation status, but clinical advice received by the Assessment Group indicated that germline RET-mutation status testing is conducted in the NHS in England only for the purpose of identifying patients with hereditary MTC. Somatic and other RET-mutation testing is not routinely undertaken to inform treatment choices. Subgroup analyses reported in the Sanofi CS and the unpublished ZETA CSR found that patients with a CTN or CEA doubling time of less than 24 months had a PFS response to vandetanib that was more pronounced than

patients with a doubling time of greater than 24 months and those in whom the doubling time is unknown.[35, 43]

The NMA suggests that the PFS effects for the two treatments are broadly similar (vandetanib vs cabozantinib PFS HR=1.14; 95% CrI 0.41 to 3.09). The magnitude of the treatment effect is more favourable towards cabozantinib when the comparison is based on central-read PFS rather than investigator-read PFS (HR=1.68; 95% CrI 0.61 to 4.62), but the difference between the two interventions was not statistically significant. In the absence of direct evidence comparing the two interventions, the results of the NMA provide a useful comparison but should be interpreted with caution for the following reasons. Owing to the sparsity of the network, it was necessary to use a weakly informative prior for the between-study variance. This was considered to be more realistic than assuming that the between-study heterogeneity would be zero (i.e. taking a fixed effects approach) however the results are subject to the suitability of the prior and the resulting credible and prediction intervals are relatively wide, representing genuine uncertainty in the network. Furthermore, the NMA utilises HRs, which are averaged estimates of treatment effect, and ignore any potential treatment-by-time interaction. Alternative methods that allow the relative treatment effects to vary over time have been proposed, including the use of fractional polynomials.[86] The Assessment Group did not deem this approach to be necessary as the results of the NMA are used to judge the comparative effectiveness of the interventions over the observed trial period and have not been used to inform the health economic model (see Section 6.2).

Based on the available trial evidence, there was no significant survival benefit in terms of OS for either cabozantinib or vandetanib compared with placebo, although the data from the vandetanib ZETA trial were confounded by crossover. In the EXAM trial, the estimated median OS was 26.6 months for cabozantinib compared with 21.1 months for placebo (stratified HR=0.85; 95% CI 0.64 to 1.12; p=0.241).[52] Within this study, the only significant difference in OS was found for 126 patients with known RET M918T positive mutations: the median OS was 44.3 months for cabozantinib compared with 18.9 months for placebo (HR=0.60; 95% CI 0.38 to 0.94; p=0.026). In the ZETA trial, the reported OS for the ITT population was 50% for vandetanib compared with 52% for placebo (HR=0.99; 95% CI 0.72 to 1.38; p=0.975), although the placebo group included patients who had crossed-over to vandetanib in the open-label stage of the trial, thus potentially confounding these results.[35] According to the Sanofi CS, the median OS for the Restricted EU label group was [redacted] in the placebo arm compared with [redacted] in the vandetanib arm [redacted].

Both cabozantinib (p<0.001) and vandetanib (ITT group, p<0.001 and EU label group, p<0.0001) demonstrated significant benefits compared with placebo in terms of ORR, as determined by RECIST

criteria. Both cabozantinib ($p<0.001$) and vandetanib ($p<0.001$) also demonstrated significantly better CTN and CEA response rates than placebo.

The two trials also conducted exploratory assessments of patients' quality of life using instruments that evaluated various criteria, including symptoms: the MDASI-THY in the EXAM trial and the FACT-G in the ZETA trial. However, no difference was found between the treatment or placebo arms at follow-up in either trial. Clinical advice received by the Assessment Group suggested that these tools did not necessarily capture symptomatic benefit produced by improved PFS or response on treatment.

Both cabozantinib and vandetanib produced frequent AEs. Based on the EXAM trial, the most common AEs for cabozantinib were diarrhoea (63%), hand foot syndrome (50%), decreased weight (48%) and appetite (46%), nausea (43%) and fatigue (41%). The most common AEs for vandetanib were diarrhoea (56%), decreased appetite (21%), nausea (33%) and fatigue (24%); in addition, there was a high incidence of rash (45%), hypertension (32%) and headache (26%), and low or no incidence of hand foot syndrome. Hypertension is a known AE for TKIs.[59, 60] The incidence of rates of rash and hypertension appear to be higher for vandetanib in MTC patients than in most other cancer patients,[62, 63] which might be due to a longer treatment duration.[63]

The most common Grade ≥3 AEs for cabozantinib, as reported from the EXAM trial, were diarrhoea (16%), HFS (13%), fatigue (9%) and hypertension (8%), asthenia (6%) and decreased weight (5%) and appetite (5%). These appear to be consistent with other anti-VEGF TKIs and the open-label cabozantinib studies. The most common Grade ≥3 AEs for vandetanib, as reported for the ITT population from the ZETA trial, were diarrhoea (11%), hypertension (9%), fatigue (6%) and decreased appetite (4%), however rash (4%) and prolonged ECG QT (8%) were also common. An exploratory study also identified significant toxicities in the presence of higher mean vandetanib plasma concentration, the most frequent toxicities being asthenia Grade 3 (36%), prolongation of the QTc interval (25%), and cutaneous symptoms (11%).[71] Vandetanib is one of only two TKIs (the other being sunitinb) identified as being particularly associated with prolonged QTc interval.[73]

Similar proportions of patients across the two trials discontinued treatment due to AEs (16% for cabozantinib and 12% for vandetanib), but a higher percentage of patients experienced AEs leading to dose interruption or reduction on cabozantinib (65%) than on vandetanib (35%). A later abstract detailing this outcome for the EXAM trial reported that dose reduction to manage AEs was performed for 82% of patients treated with cabozantinib, which increased again to 87% in the final analysis. The percentages of patients experiencing AEs leading to dose interruption or discontinuation were also higher in the placebo arm of the cabozantinib EXAM trial (17% for dose interruption and 8% for discontinuation) than in the vandetanib ZETA trial (3% and 3% respectively). High rates of dose

reduction and discontinuation have also been reported for a retrospective study of 15 patients with progressive MTC on cabozantinib.[49] The authors of the EXAM trial acknowledged the high rate of dose interruption with cabozantinib 140mg:[28] the EXAMINER trial has therefore been developed to assess the efficacy and safety of a lower dose of cabozantinib (60mg) compared with the current standard dose (140mg) (NCT01896479).

Finally, in the EXAM trial, up to 5% of deaths were reported as being treatment-related for cabozantinib and 1% for placebo.[21] During the randomised phase of the ZETA trial, 2% patients who received vandetanib (5/231) experienced AEs leading to death. The reasons given were: aspiration pneumonia, respiratory arrest, respiratory failure, staphylococcal sepsis and, in one patient, arrhythmia and acute cardiac failure.[27] Instances of gastroenteritis and GI haemorrhage lead to deaths in two patients in the placebo group.[27]

6 ASSESSMENT OF COST-EFFECTIVENESS

This section presents a systematic review of existing economic evaluations of treatments for locally advanced or metastatic MTC, a summary and critique of economic analyses submitted by the manufacturers of vandetanib and cabozantinib together with details of the methods and results of a *de novo* health economic analysis undertaken by the Assessment Group.

6.1 Systematic review of existing cost-effectiveness evidence

6.1.1 Review of existing economic evaluations - methods

A comprehensive search was undertaken to systematically identify economic evaluations of treatments for locally advanced or metastatic MTC and studies reporting on the health-related quality of life (HRQoL) of patients with locally advanced or metastatic thyroid cancer (including MTC as well as other more common forms of thyroid cancer). In anticipation of the likely dearth of relevant evidence, the Assessment Group's search strategy was designed to be intentionally broad.

The following electronic databases were searched from inception to 3rd November 2016:

- MEDLINE: Ovid, 1946 to present
- MEDLINE in Process: Ovid, 1946 to present
- MEDLINE Epub Ahead of Print: Ovid, 1946 to present
- CINAHL: EBSCO, 1982 to present
- EMBASE: Ovid, 1980 to present
- Health Technology Assessment Database (HTA), 1995 to present
- NHS Economic Evaluation Database (NHS EED), 1995 to 2015
- Web of Science Citation Index: Thomson Reuters, 1899 to present
- Conference Proceedings Citation Index (CPCI): Thomson Reuters, 1990 to present.

The search strategy was comprised of MeSH or Emtree Thesauri terms and free-text synonyms for "thyroid cancer." Searches were translated across databases and were not limited either by language or publication date. The search strategies are presented in Appendix 1. Search filters designed to identify economic evaluations and HRQoL studies were applied in MEDLINE and other databases, where appropriate. Reference and citation searching of included papers was also undertaken.

Potentially includable studies were sifted by title and abstract by one reviewer (PT). In keeping with the breadth of the search strategy, the inclusion criteria were also defined broadly and the sifting process followed an inclusive approach in order to maximise sensitivity. Given that the cost-effectiveness search also identified studies relating to health utilities (for example, those used within models), and the HRQoL search also identified health economic evaluation studies, the results of both searches were

sifted together using a common set of inclusion criteria (see Box 2). Whilst the inclusion criteria for the review of existing economic evaluation studies was specific to MTC, HRQoL studies were considered to be potentially includable if they were undertaken in patients with MTC or other types of thyroid cancer (papillary, follicular, Hürthle cell carcinoma).

Box 2: Inclusion criteria for review of published economic evaluations and health utility data

Inclusion criteria

- Comparative economic evaluations of interventions for the treatment of locally advanced or metastatic MTC
- Studies reporting preference-based health utilities relating to any type of thyroid cancer

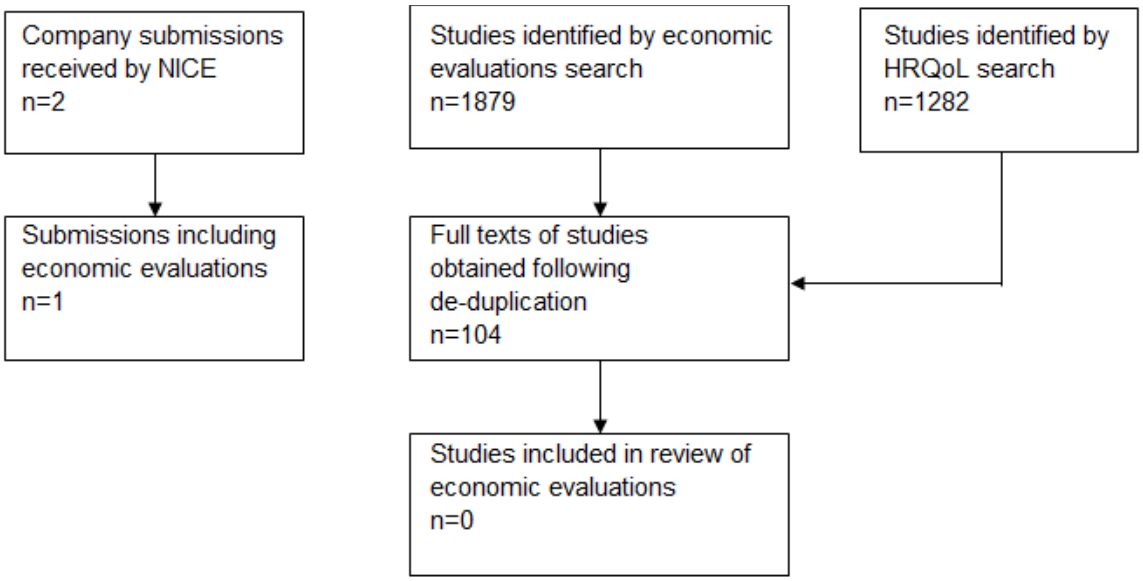
Exclusion criteria

- Studies evaluating diagnostic/staging interventions e.g. fine needle aspiration biopsy (FNAB) (unless the study specifically mentions utilities for advanced/metastatic disease or reports QALYs)
- Partial economic analyses e.g. costing studies
- Editorials
- Reviews
- Clinical studies which do not report costs
- Letters and commentaries
- Non-English language

6.1.2 Review of existing economic evaluations - results

Figure 7 presents the study selection results. Before de-duplication, the searches yielded 3,161 citations (HRQoL search=1,282 studies; economic evaluation search=1,879 citations). Following the initial sift, 3,057 of these studies were excluded. Full texts of the remaining 104 potentially includable studies were retrieved for further examination. However, none of these studies contained an economic evaluation of treatments for MTC, hence all studies were excluded from the review. In addition, none of these studies reported health utilities for patients with locally advanced or metastatic MTC. One study reported health utilities for patients with radioactive iodine-refractory differentiated thyroid cancer (Fordham *et al*[87]); this study is discussed in further detail in Section 6.2.3.3.

Figure 7: Study selection results



6.1.3 Review of models submitted by the companies

The Sanofi submission[35] includes a health economic evaluation of vandetanib for the treatment of locally advanced or metastatic MTC together with a fully executable health economic model. The Ipsen submission[21] does not include any economic evidence for this appraisal.

6.1.3.1 Scope of the Sanofi economic evaluation

The Sanofi CS[35] presents the methods and results of a model-based economic evaluation of vandetanib for the treatment of MTC, based largely on analyses of a subgroup of the ZETA trial. The scope of the company's model is summarised in

Table 22. The model assesses the incremental cost-effectiveness of vandetanib versus BSC over a lifetime (20-year) time horizon from the perspective of the NHS. Cost-effectiveness is expressed in terms of the incremental cost per quality-adjusted life year (QALY) gained. The population considered within the company's model relates to the "Restricted EU label population": i.e. patients with aggressive and symptomatic unresectable locally advanced or metastatic MTC, defined as: progressive (documented progression within 12 months prior to enrolment) and symptomatic (at least one symptom at baseline, including pain score > 4, ≥10 days of opioid use, diarrhoea, flushing, fatigue, pain, nausea, dysphagia, dysphonia, respiratory symptoms, weight loss) plus CTN and CEA doubling times within 24 months of screening.[35] The Assessment Group notes that this population is narrower than the indication permitted by the EMA marketing authorisation for vandetanib;[22] a health economic analysis of the broader licensed population is not presented within the CS.[35] Costs and health outcomes are discounted at a rate of 3.5% per annum. The company's economic analysis includes a Patient Access Scheme (PAS) which takes the form of a simple price discount for vandetanib. The results presented within this report use the list price for vandetanib; the results of the Sanofi model including the PAS

are presented within a confidential appendix to this report (Confidential Appendix 4). Costs were valued at 2015/16 prices.

It is important to note from the outset that a substantial proportion of patients ([redacted]) in the Restricted EU label population who were allocated to the placebo arm of the ZETA trial switched to open-label vandetanib (either post-progression or in any patient following a protocol amendment in January 2010, see Sanofi clarification response,[41] question A2). In addition, a proportion of patients ([redacted]) in the Restricted EU label population who were allocated to the intervention group continued to receive open-label vandetanib following disease progression. Whilst the company attempted to adjust for treatment switching using the Rank Preserving Structural Failure Time (RPSFT) method, this was not successful (see Sanofi CS,[35] pages 98-99), hence the estimates of OS for both modelled treatment groups are unadjusted and thus remain potentially confounded by the use of open-label vandetanib. As the potential impact of open-label vandetanib use could not be addressed, the company's model includes the estimated costs of post-progression vandetanib use within both the intervention and comparator treatment groups. The economic comparison made by the company's model is therefore vandetanib including continued use in some patients post-progression versus BSC with vandetanib use in most patients post-progression. The Assessment Group notes that this may not be useful for decision-making; the same issue also applies to the two pairwise comparisons of vandetanib versus BSC undertaken using the Assessment Group model (see Section 6.2).

The Assessment Group also notes that two errors were identified within the company's original submitted model; these related to: (i) the duration over which QALY losses due to AEs are applied, and (ii) inputs relating to the proportion of patients who discontinue vandetanib prior to disease progression (see Section 6.1.3.6). All results presented within this report include corrections to these errors.

Table 22: **Sanofi model scope**

Population	The Restricted EU label population for vandetanib - patients with aggressive and symptomatic unresectable locally advanced or metastatic MTC defined as progressive (documented progression within 12 months prior to enrolment) and symptomatic (at least one symptom at baseline, including pain score > 4, ≥10 days of opioid use, diarrhoea, flushing, fatigue, pain, nausea, dysphagia, dysphonia, respiratory symptoms, weight loss) plus CTN and CEA doubling times within 24 months of screening.
Intervention	Vandetanib 300mg/day* (with post-progression continuation of vandetanib in [redacted] of patients).
Comparator	BSC (with switch to vandetanib 300mg/day post-progression in [redacted] of patients).
Analysis type	Cost-utility analysis
Economic outcome	Incremental cost per QALY gained
Perspective	NHS
Time horizon	20 years (lifetime)
Discount rate	3.5% per annum for health outcomes and costs

** Dose adjustments, treatment interruption and treatment discontinuation are included for patients receiving vandetanib*
MTC – medullary thyroid cancer; QALY – quality-adjusted life year; NHS – National health Service; mg - milligram

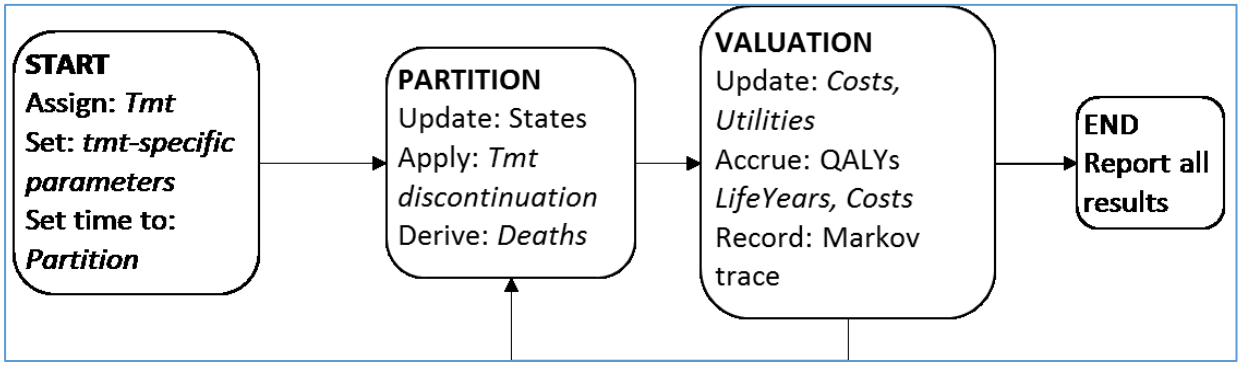
6.1.3.2 Sanofi model structure

The economic analysis presented by Sanofi takes the form of a cohort-level partitioned survival model implemented using the Discretely Integrated Condition Event (DICE) simulation methodology[88] (see Figure 8). The model includes 3 health states: (i) progression-free; (ii) post-progression, and; (iii) dead. The model operates as follows. At any time *t*, the probability that a patient allocated to treatment group *k* is alive is given by $S(t)_{OS}\_k$, whilst the probability that a patient allocated to treatment group *k* is alive and progression-free is given by $S(t)_{PFS}\_k$. The probability that a patient is alive following disease progression is calculated as the difference between the two survivor functions: $S(t)_{OS}\_k$ - $S(t)_{PFS}\_k$ for any time *t*. Given the presence of censoring, parametric survivor functions were fitted to Kaplan-Meier curves for OS and PFS from the ITT/safety populations of the ZETA trial including adjustment for two covariates: (1) "sympprog" (presence of symptomatic and progressive disease), and; (2) "biomarker" (CEA and CTN doubling time ≤24 months). Weibull functions were selected to model both OS and PFS, assuming independent (non-proportional) hazards between treatment groups. The DICE routine is evaluated using a monthly cycle length over a 20-year lifetime horizon and includes a half cycle correction to account for the timing of events.

The model assumes that health utility is determined by the presence/absence of disease progression, with higher utilities applied to the progression-free state. In addition, a once-only QALY loss is applied to each group to account for the incidence of Grade 3/4 AEs.

The model includes the following resource costs: (i) vandetanib drug acquisition costs; (ii) monitoring for patients receiving vandetanib; (iii) BSC costs; (iv) palliative care costs, and; (v) costs associated with managing AEs.

Figure 8: **Schematic of the Sanofi DICE model (reproduced from the Sanofi CS[35])**



The model employs the following structural assumptions:

- HRQoL is determined according to the presence/absence of disease progression and the incidence of Grade 3/4 AEs.
- PFS and OS are modelled using Weibull functions assuming independent (non-proportional) hazards.
- Survival models were fitted to the overall ITT population for PFS and the safety population for OS including covariate adjustments to reflect the characteristics of the Restricted EU label population.
- No adjustment is made to account for logical inconsistencies (i.e. where $S(t)_{PFS} > S(t)_{OS}$).
- The modelling of costs and health outcomes includes the level of open-label vandetanib use (either post-progression or in any patient following the January 2010 protocol amendment[41]) observed in the ZETA trial.
- AEs are assumed to impact upon both costs and HRQoL. According to the Sanofi CS, AE impacts on HRQoL apply only during the first month of the time horizon. This aspect of the model is subject to a programming error (see Section 6.1.3.6) and was corrected by the company in their clarification response[41] (question A18).
- Palliative care costs are assumed to be incurred only during the final month of life.

6.1.3.3 Evidence used to inform the company's model

Table 23 summarises the evidence used to parameterise the company's model. The derivation of these parameters and their evidence sources are discussed in further detail below.

Table 23: **Company's model parameters and evidence sources**

Parameter group	Evidence source	
Progression-free survival	Parametric survival models fitted to ZETA ITT population PFS data and subsequently adjusted by setting coefficients for covariates "SympProg" and [redacted] to 100%.[35]	
Overall survival	Parametric survival models fitted to ZETA safety population OS data and subsequently adjusted by setting coefficients for covariates "SympProg" and [redacted] to 100%.	
Health utilities	*Progression-free state:* FACT-G scores for progression-free state observed in ZETA trial mapped to the 3-level Euroqol 5-Dimensions (EQ-5D) instrument using algorithm reported by Dobrez *et al*.[89] *Post-progression state:* Calculated using utility multiplier (0.766) for post-progression versus pre-progression using general population standard gamble (SG) study of societal preferences for advanced melanoma health states reported by Beusterien *et al.*[90] *Disutility due to AEs:* Disutility for any Grade 3/4 AE taken from Beusterien *et al* advanced melanoma SG study.[90]	
Time spent receiving vandetanib	*Vandetanib group*	*BSC group*
	(a) Pre-progression: Percentage of PFS time spent receiving 300mg/200mg/100mg/ interrupted dose based on the Restricted EU label population of the ZETA trial.[35, 53] An additional constant discontinuation probability ([redacted]) is also assumed.[35]	*(b) Pre-progression:* Not applicable.
	(c) Post-progression: Same as (a) but without additional constant discontinuation probability.	*(d) Post-progression:* Same as (a) but without additional constant discontinuation probability.
Probability of receiving vandetanib whilst in post-progression state	Based on observed continuation proportion in the vandetanib group of the Restricted EU label population from the ZETA trial ([redacted]).[35]	Based on observed switching proportion in the placebo group of the Restricted EU label population from the ZETA trial ([redacted]).[35]
Vandetanib acquisition cost	Sanofi CS[35]	
Monitoring resource use	Resource use related to ECGs and phlebotomy during the first and subsequent years of use based on the SmPC for vandetanib.[22]	
AE incidence	Grade 3/4 AEs observed within full safety population of the ZETA trial.[35, 43]	
BSC resource use	Assumption	
AE management costs	NHS Reference Costs 2015/16[91]	
BSC costs	NHS Reference Costs 2015/16[91]	
Palliative chemotherapy costs	NHS Reference Costs 2015/16[91]	
Palliative care costs	Curtis and Burns[92]	

ITT – intention-to-treat; PFS – progression-free survival; FACT-G – Functional Assessment of Cancer Therapy – General; EQ-5D – Euroqol 5-Dimensions; SG – standard gamble; AE – adverse event; SmPC – Summary of Product Characteristics; mg - milligram

Overall survival

OS was defined as the time from randomisation to death or the last date at which the subject was known to be alive.[35] The analyses of OS used individual patient data (IPD) for all patients who received randomised treatment (the safety population) including follow-up to the 7th September 2015 data cut-off. As noted in Section 6.1.3.1, the Sanofi CS states that whilst attempts were made to adjust for treatment switching using the RPSFT method, this was unsuccessful (see Sanofi CS,[35] pages 98-99). As such, the OS data used in the model remain subject to potential confounding as they include the use of open-label vandetanib in both treatment groups. With respect to this issue, the company states: *"the OS data are more likely to show the impact of treatment with immediate vs delayed vandetanib, rather than be a true comparison of vandetanib vs placebo."* (Sanofi CS, [35] page 63). Parametric survival models (Weibull, log normal, log logistic, exponential and gamma functions) were fitted to the available data including two covariates: (1) "sympprog" (presence of symptomatic and progressive disease), and; (2) "biomarker" (CEA and CTN doubling time ≤24 months) using the LIFEREG procedure in SAS. In order to reflect the Restricted EU label population within the model, the coefficients for both covariates were set equal to 100%. Statistical goodness-of-fit was assessed using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC). The CS states that the plausibility of the long-term projections for each model were also assessed, although the CS does not provide details regarding who undertook this assessment or whether any external data were used to inform these judgements. The company's subsequent clarification response states that assessments of clinical plausibility involved an expert clinician, the statistical consultants and the modelling team (Sanofi clarification response,[41] question A15).

The observed and predicted OS curves are presented in Figure 9, based on the comparison presented in both the Sanofi CS and the model. As the CS includes only a comparison of the Weibull function against the empirical Kaplan-Meier data, the Assessment Group digitised the Kaplan-Meier data and plotted the predictions of the covariate-adjusted Weibull, log normal and log logistic OS functions for the purposes of comparison. The Assessment Group considers this comparison of observed and predicted OS to be inappropriate as the population represented by the observed Kaplan-Meier data is not the same as the population reflected by the modelled functions (the observed data reflect the safety population with the CTN/CEA biomarker but without aggressive and progressive disease, see Section 6.1.3.6). The corresponding AIC/BIC statistics for all five parametric models are presented in Table 4; the lowest values are shown in bold.

With respect to the vandetanib group, the AIC and BIC were lowest for the log normal model, whilst for the placebo group, the AIC and BIC were lowest for the gamma model. The CS states that the Weibull function was selected for use in the base case analysis as, in this instance, this function *"matches human mortality better in the long term"* (Sanofi CS,[35] page 105). The impact of uncertainty

surrounding the choice of parametric function for PFS and OS was partially explored in the sensitivity analyses.

Figure 9: **Observed and predicted OS – data from ITT with CTN/CEA biomarker versus Sanofi model predictions for Restricted EU label population (Kaplan-Meier data digitised by Assessment Group)**

Table 24: AIC and BIC statistics from Sanofi covariate-adjusted analysis of ZETA trial observed OS

Model	AIC	BIC
Vandetanib		
Weibull		
Log normal		
Log logistic		
Exponential*		
Gamma*		
Placebo		
Weibull		
Log normal		
Log logistic		
Exponential*		
Gamma*		

** Not reported in CS - obtained from company's model*
AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion

Progression-free survival

PFS was defined as the time from randomisation to documented progression based on central review or death.[35] The Sanofi CS (page 101) notes that whilst the use of central-read PFS is subject to confounding due to crossover, using this endpoint mirrors the per protocol endpoints of the ZETA trial. The analyses of PFS used IPD for all randomised patients available at the date of the initial data cut-off, as reported in the original CSR of 6 July 2011.[43] As with the company's analysis of OS, parametric survival models (Weibull, log normal, log logistic, exponential and gamma functions) were fitted to the available PFS data including two covariates: (1) "sympprog" (presence of symptomatic and progressive disease), and; (2) "biomarker" (CEA and CTN doubling time ≤24 months) using the LIFEREG procedure in SAS. In order to reflect the Restricted EU label population, the coefficients for both covariates were set equal to 100%. Statistical goodness-of-fit was assessed using the AIC and the BIC. The CS states that the plausibility of the long-term projections for each model was also assessed; the company's clarification response states that this exercise involved an expert clinician, the statistical consultants and the modelling team (Sanofi clarification response,[41] question A15).

The observed and predicted PFS curves are presented in Figure 10, based on the observed central review PFS Kaplan-Meier curves for the Restricted EU label population presented in Figure 6 of the CS (see Sanofi CS,[35] page 56). As the CS includes only a comparison of the Weibull function against the empirical Kaplan-Meier PFS curves, the Assessment Group digitised the Kaplan-Meier data and plotted the predictions of the covariate-adjusted Weibull, log normal and log logistic PFS functions for the purposes of comparison. The Assessment Group notes that the Kaplan-Meier curves used to compare model-predicted versus observed PFS within the Sanofi CS and those presented in the company's model are not the same as the cumulative survival probabilities differ considerably; the reasons for these differences are unclear. The corresponding AIC/BIC statistics for all five parametric models are presented in Table 25; the lowest values are shown in bold.

The AIC and BIC were lowest for the log normal model for the vandetanib group, whilst the AIC and BIC were lowest for the exponential model for the placebo group. The CS states that *"As there is no clear, clinical expectation for the PFS over the long-term, Weibull was also selected in the base case for consistency"* (Sanofi CS[35] page 105). The impact of uncertainty surrounding the choice of parametric function for PFS and OS was partially explored in the sensitivity analyses.

Figure 10: **Observed and predicted PFS – data from Restricted EU label population PFS in Sanofi CS Figure 6 versus Sanofi model predictions for Restricted EU label population (Kaplan-Meier data digitised by Assessment Group)**

Table 25: **AIC and BIC statistics from Sanofi's covariate-adjusted analysis of ZETA trial observed PFS**

Model	AIC	BIC
Vandetanib		
Weibull		
Log normal		
Log logistic		
Exponential*		
Gamma*		
Placebo		
Weibull		
Log normal		
Log logistic		
Exponential*		
Gamma*		

** Not reported in CS - obtained from company's model*
AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion

Health-related quality of life

The health utility values applied in the Sanofi model are summarised in Table 26.

Table 26: **HRQoL parameters used in the Sanofi model**

Health state	Value	Source
Progression-free	0.84	FACT-G mapped to EQ-5D using Dobrez *et al*[89]
Post-progression	0.64	Derived by applying progressive disease to stable disease multiplier from Beusterien *et al*[90] to pre-progression utility from ZETA FACT-G mapping exercise
Disutility any Grade 3/4 AE	-0.11	Beusterien *et al*[90]

FACT-G – Functional Assessment of Cancer Therapy – General; EQ-5D – Euroqol 5-Dimensions; AE – adverse event

The ZETA trial assessed HRQoL using the FACT-G instrument;[43] the trial did not include the use of a preference-based HRQoL instrument. Within the model, the health utility score associated with the progression-free state was estimated by mapping FACT-G scores for patients who were progression-free in the ZETA trial to the 3-level EQ-5D using a published ordinary least squares (OLS) algorithm reported by Dobrez *et al*.[89] This mapping exercise produced a mean utility score for the progression-free state of 0.84.

The Sanofi CS notes that within the ZETA trial, post-progression FACT-G data were available for only 62 patients (27%). Rather than applying the mapping approach used for the progression-free state, the health utility score for the post-progression state was instead estimated using a utility multiplier for the states of post-progression versus pre-progression derived from a general population SG study of societal preferences for advanced melanoma states reported by Beusterien *et al*.[90] Within this study, the ratio of progressive disease utility to stable disease utility was 0.766 (0.59/0.77); applying this multiplier to the company's estimated utility score for the progression-free state leads to an estimated post-progression utility score of 0.64 (0.84 x 0.766). The disutility associated with any Grade 3/4 AEs was also derived from the Beusterien *et al* advanced melanoma valuation study (disutility=-0.11). The same disutility was assumed to apply to each type of AE.

Time spent receiving vandetanib

Table 27 presents the percentage of time spent receiving each dose level of vandetanib during the progression-free period divided by the total pre-progression time on treatment, calculated from data for the Restricted EU label population.[35, 53] This distribution is applied within the vandetanib group to determine the amount of time spent receiving treatment in the progression-free state. The Sanofi CS[35] (page 103) notes that: *"Patients whose cancer had not yet progressed were allowed, nevertheless, to discontinue treatment. These treatment discontinuations were addressed by applying the relevant proportion to the patients not having progressed in each cycle" (21.9%)."* This value was later

corrected by the company (corrected value=[redacted]). Whilst the wording of the CS implies that all patients start treatment on vandetanib and a proportion of patients subsequently discontinue treatment during each cycle, this discontinuation parameter is instead applied as a fixed proportion of patients in the progression-free state who do not receive vandetanib (and therefore do not incur any costs of vandetanib treatment). The appropriateness of this parameter is unclear. The distribution of vandetanib use shown in Table 27 is also applied in the post-progression state for the proportions of patients who switch to or continue to receive vandetanib post-progression in each treatment group, albeit without the vandetanib discontinuation parameter. As a consequence, patients receive more vandetanib per cycle during the post-progression phase compared within the pre-progression phase; it is unclear whether this reflects an error or an unreasonable assumption.

Table 27: **Use of vandetanib during progression-free period**

Dose	Percentage of PFS time receiving vandetanib*
300mg (full dose)	66.3%
200mg dose	16.5%
100mg dose	15.5%
Interrupted	1.7%

** Also applied to post-progression states in both treatment groups*
PFS – progression-free survival; mg – milligram

Probability of receiving vandetanib in the post-progression state

Based on the experience of the ZETA trial[35, 53] (specifically with respect to the Restricted EU label population), the model assumes that [redacted] of patients in the vandetanib group continue to receive vandetanib post-progression, whilst [redacted] of patients in the BSC group cross over to receive vandetanib post-progression. Clinical advisors to the Assessment Group noted that the use of vandetanib post-progression does not reflect usual clinical practice in England.

Vandetanib acquisition cost

The acquisition costs of vandetanib are summarised in Table 28, based on the current prices listed in the British National Formulary (BNF).

Table 28: **Vandetanib acquisition costs according to pack size**

Intervention	Cost per pack (30 tablets)	Annual cost (assuming full dose)
Vandetanib 300mg tab	£ 5,000	£60,875.00
Vandetanib 100mg tab	£ 2,500	£30,437.50

mg - milligram

Monitoring costs

Resource use estimates were based on the monitoring regimen detailed in the SmPC for vandetanib.[22] Unit costs were derived from NHS Reference Costs 2015/16[91] (see Table 29). Due to the inclusion of the costs associated with post-progression vandetanib use in the BSC group, these monitoring costs are applied in both groups (to the proportion of patients who initially receive/continue vandetanib in the intervention group and to the proportion of patients who switch from BSC to vandetanib in the comparator group). Whilst the monitoring costs are presented within the CS as being dependent on the time since starting treatment, this time dependence is captured only in the progression-free state for the intervention group. The lower "subsequent years" cost is applied to the proportion of patients continuing or switching to vandetanib post-progression (see Sanofi CS,[35] page 111). The company states that this approach was deemed to be conservative (see Sanofi clarification response,[41] question A20), although the Assessment Group notes that the impact on the incremental cost-effectiveness ratio (ICER) is likely to be small.

Table 29: Vandetanib monitoring costs assumed in the Sanofi model

Resource item	Unit cost	Frequency/year		Total cost	
		Year 1	Subsequent years	Year 1	Subsequent years
EY51Z ECG monitoring or stress testing (directly accessed diagnostic services)	£ 40.00	8	4	£ 320.00	£ 160.00
DAPS04 Clinical biochemistry; DAPS08 Phlebotomy; DAPS05 Haematology	£ 7.00	8	4	£ 56.00	£ 28.00
DAPS09 Other (TSH)	£ 3.00	8	4	£ 24.00	£ 12.00

AE management costs

The company's model includes any Grade 3/4 AEs that occurred in ≥2% of patients in either treatment group. Table 30 presents the Grade 3/4 AE incidence rate and associated management costs included in the company's model. The incidence of any Grade 3/4 AEs was taken from the safety population of the ZETA trial[27] (derived directly from the Wells *et al*[27] trial publication). Unit costs associated with the management of AEs were derived from NHS Reference Costs 2015/16.[91] In response to a request for clarification from the Assessment Group, the company clarified that the AE data for the safety population were used because the equivalent data for the Restricted EU label population were not available at the time of the submission (see Sanofi clarification response,[41] question A11). The model applies the total AE cost once during the first model cycle. The Assessment Group notes that all NHS Reference Cost codes assume that the patient is treated in an elective inpatient setting; given that these costs are associated with the management of AEs (i.e. non-elective), this is inappropriate but is likely to have only a negligible impact upon the model results.

Table 30: **Incidence and costs associated with Grade 3/4 AEs**

AE type	Unit cost	Vandetanib	BSC	NHS Reference Cost 2015/16 HRG code[91]
Diarrhoea	£1,102.00	11%	2%	FZ91M Non-malignant GI tract disorders without interventions, with CC score 0–2
Hypertension	£982.00	9%	0%	EB04Z Hypertension
ECG QT prolonged	£1,014.00	8%	1%	EB07E Arrhythmia or conduction disorders, with CC score 0–3
Fatigue	£0.00	6%	1%	n/a
Decreased appetite	£1,512.00	4%	0%	FZ49H Nutritional disorders without interventions, with CC score 0–1
Rash	£1,078.00	4%	1%	JD07K Skin disorders without interventions, with CC score 0–1
Asthenia	£0.00	3%	1%	n/a
Dyspnoea	£896.00	1%	3%	DZ19N Other respiratory disorders without interventions, with CC score 0–4
Back pain	£1,510.00	0%	3%	HC32K Low back pain without interventions, with CC score 0–2
Syncope	£1,067.00	0%	2%	EB08E Syncope or collapse, with CC score 0–3
Weighted AE cost	-	**£413.42**	**£136.48**	-

HRG – healthcare resource group; AE – adverse event; ECG – electrocardiogram; CC – complexity and comorbidity

Palliative care costs

The company's model includes a cost of £5,775 for palliative care derived from the Personal Social Services Research Unit (PSSRU)[92] and £827 for palliative chemotherapy given at the end of life, based on NHS Reference Costs 2015/16.[91] This cost is applied for the last month prior to death. As these costs are common to both groups, and because virtually all patients die within the time horizon (>98.7% patients), the only differences in these costs between the two treatment groups is a consequence of discounting.

6.1.3.4 Model evaluation methods

The headline results presented in the Sanofi CS[35] are based on the deterministic version of the model. Uncertainty surrounding model parameters was explored using deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA). The company's probabilistic results were estimated from 1,000 Monte Carlo samples. Uncertainty was represented using tornado diagrams, cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs).

6.1.3.5 Sanofi model results

Sanofi central estimates of cost-effectiveness (excluding PAS, including error corrections)

Table 31 presents the company's base case estimates of cost-effectiveness using the list price for vandetanib. Based on the probabilistic version of the company's model, vandetanib is expected to

generate an additional 1.34 QALYs at an additional cost of £42,215 compared with BSC; the ICER for vandetanib versus BSC is expected to be £31,546 per QALY gained. The deterministic version of the model produces a slightly higher ICER of £31,731 per QALY gained.

Table 31: **Sanofi base case estimates of cost-effectiveness (excluding PAS)**

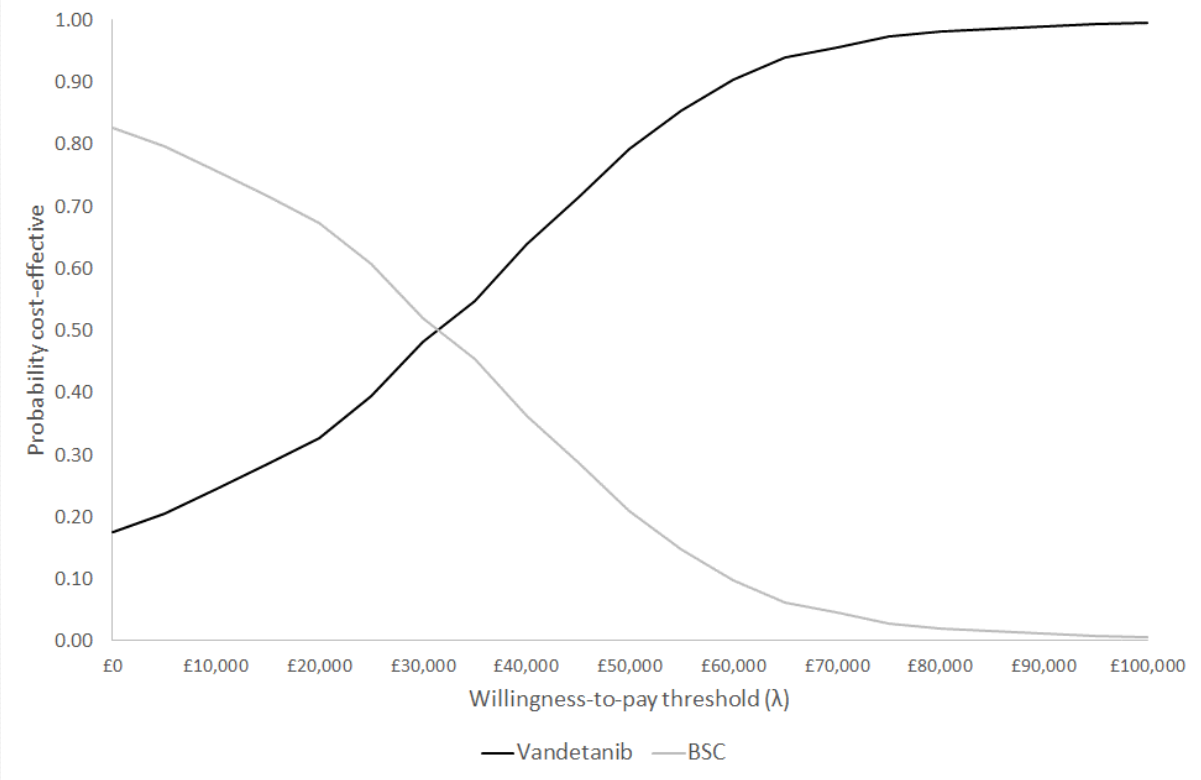
Option	Absolute		Incremental		
	QALYs	Costs	QALYs	Costs	ICER
Probabilistic model					
Vandetanib*	3.53	£181,130	1.34	£42,215	**£31,546**
BSC*	2.19	£138,915	-	-	-
Deterministic model					
Vandetanib*	3.49	£175,316	1.36	£43,024	**£31,731**
BSC*	2.13	£132,292	-	-	-

** Includes post-progression vandetanib costs*
BSC – best supportive care; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

Sanofi probabilistic sensitivity analysis results

Figure 11 presents the CEACs for vandetanib and BSC, generated by the Assessment Group using the corrected version of the Sanofi model. The CEAC indicates that assuming willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained, the probability that vandetanib produces more net benefit than BSC is approximately 0.33 and 0.48, respectively.

Figure 11: **Cost-effectiveness acceptability curves generated using the Sanofi model – vandetanib versus BSC (re-drawn by the Assessment Group)**

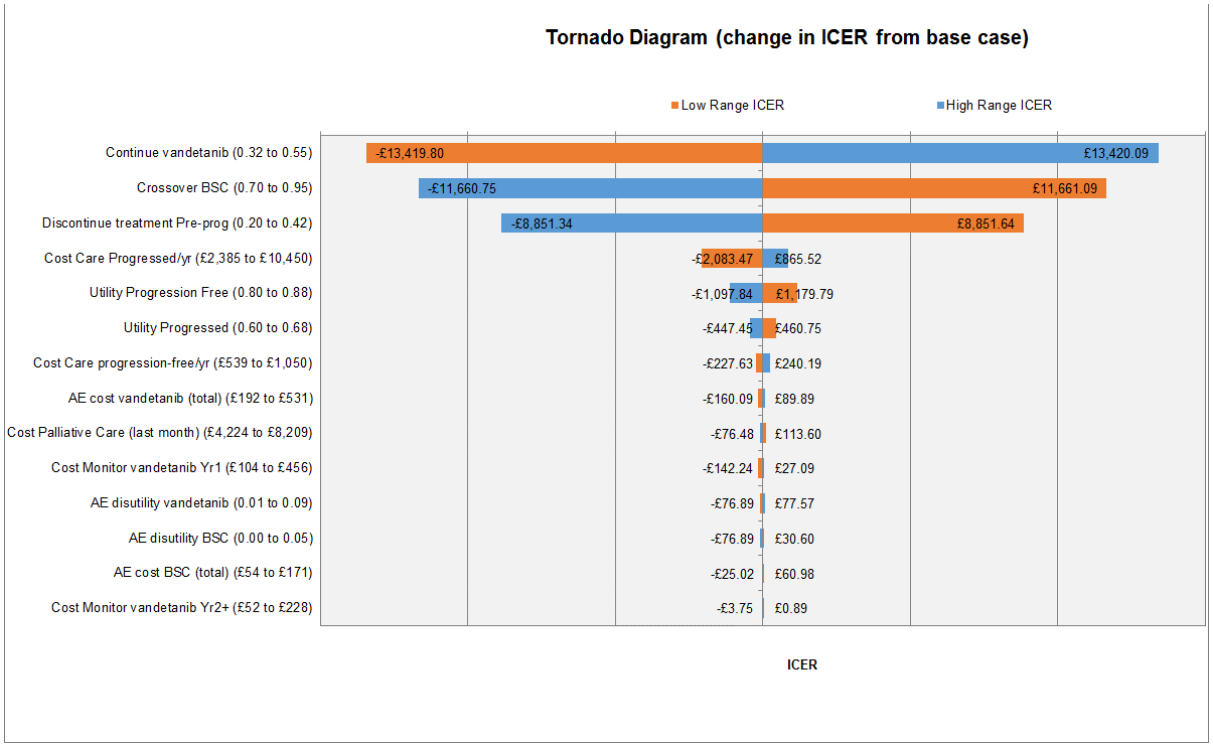


BSC – best supportive care

Sanofi deterministic sensitivity analysis results

Figure 12 presents the results of the company's DSAs. The most influential parameters (of those assessed by the company) relate to the probability of vandetanib continuation beyond progression, the probability of treatment switching in the BSC group and the vandetanib discontinuation parameter applied to the vandetanib group during the progression-free phase. The use of the log logistic and log normal functions for PFS and OS (analyses not shown in Figure 12) did not have a substantial impact upon the ICER for vandetanib versus BSC (log normal PFS and OS ICER=£37,227 per QALY gained; log logistic PFS and OS ICER=£28,879 per QALY gained). It should be noted that a higher proportion of vandetanib patients are alive at 20-years (>8%) using these functions compared with the Weibull model (<2%).

Figure 12: **DSA results generated using the Sanofi model (reproduced from Sanofi model)**



** Note: Tornado plot shows absolute change to base case ICER*

6.1.3.6 Critical appraisal of the economic analysis presented by Sanofi

Methods for reviewing the company's economic evaluation and health economic model

The Assessment Group adopted a number of approaches to explore, interrogate and critically appraise the economic evaluation submitted by Sanofi and the underlying health economic model upon which this was based. These approaches included:

- An assessment of the extent to which the model adheres to the NICE Reference Case[93]
- Consideration of key items contained within published economic evaluation and health economic modelling checklists[94, 95] to critically appraise the model and associated analysis.

- Scrutiny of the model and discussion of issues identified amongst the members of the Assessment Group.
- Double-programming of the deterministic version of the Sanofi model to fully assess the logic of the company's model structure, to draw out any unwritten assumptions and to identify any apparent errors in the implementation of the model.
- Examination of the correspondence between the description of the model reported within the CS[35] and the executable model.
- Replication of the base case results, PSA and scenario analysis presented within the Sanofi CS.[35]
- Where possible, checking of Sanofi model parameter values against the original data sources.
- The use of expert clinical input to judge the clinical credibility of the company's economic evaluation and the assumptions underpinning the model.

Adherence of the company's economic analysis to the NICE Reference Case

Table 32 summarises the extent to which the economic analysis submitted by Sanofi adheres to the NICE Reference Case.[93]

Table 32: **Adherence of the company's economic analysis to the NICE Reference Case**

Element	Reference case	Assessment Group comments
Defining the decision problem	The scope developed by NICE	The analysis is partially in line with the decision problem set out in the final NICE scope. The two key deviations are: (1) The economic analysis relates specifically to the Restricted EU label population, that is, patients with aggressive and symptomatic unresectable locally advanced or metastatic MTC defined as progressive (documented progression within 12 months prior to enrolment) and symptomatic (at least one symptom at baseline, including pain score > 4, ≥10 days of opioid use, diarrhoea, flushing, fatigue, pain, nausea, dysphagia, dysphonia, respiratory symptoms, weight loss) plus CTN and CEA doubling times ≤24 months. No economic analysis is presented for the broader licensed population. (2) Cabozantinib is not included as a comparator.
Comparator(s)	As listed in the scope developed by NICE	The company's model compares vandetanib versus BSC. However, estimates of OS are not adjusted for continued post-progression vandetanib use or switching from placebo to vandetanib post-progression, or any pre-progression open-label vandetanib use permitted following the January 2010 protocol amendment to the ZETA trial. Cabozantinib is not considered within the economic analysis. Locally ablative therapies such as radiotherapy are not explicitly considered.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The model includes direct health effects.

Element	Reference case	Assessment Group comments
Perspective on costs	NHS and PSS	The Sanofi model adopts an NHS perspective. PSS costs are not explicitly considered.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The economic evaluation takes the form of a cost-utility analysis. Results are presented in terms of the incremental cost per QALY gained for vandetanib versus BSC.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	A lifetime (20-year) time horizon is adopted.
Synthesis of evidence on health effects	Based on systematic review	The company did not undertake a systematic review of clinical effectiveness evidence.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Within the progression-free state, health utility was estimated by mapping from the FACT-G collected in the ZETA trial to the EQ-5D. The health utility multiplier for the post-progression state and for the disutility associated with AEs was based on an SG study of societal preferences for advanced melanoma states reported by Beusterien *et al*.[90] A disutility for any Grade 3/4 AE is included based on Beusterien *et al*.[90]
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No equity weighting is applied.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource use estimates were based on data from the ZETA trial, expert opinion and assumptions. Unit costs were taken from NHS Reference Costs 2015/16.[91]
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Costs and health outcomes are discounted at a rate of 3.5% per annum.

The two main deviations from the NICE Reference Case concern the exclusion of cabozantinib as a comparator and the population considered within the economic analysis (the Restricted EU label

population). The Assessment Group also notes that the clinical evidence and health utilities were not identified using systematic review methods. These issues are discussed further in Section 6.1.3.6.

Model verification

The Assessment Group reproduced the deterministic version of the company's DICE model using a simple partitioned survival approach implemented in Microsoft Excel. Table 33 compares the results generated by the company's submitted model and the Assessment Group's double-programmed model (including corrections detailed in critical appraisal point 6). As shown in the table, the results generated by the two models are very similar. The Assessment Group is confident that the model has been implemented by the company as intended.

Table 33: **Comparison of DICE model results and double-programmed Assessment Group partitioned survival model**

	Company's model			**Assessment Group's double-programmed model**		
Outcome	**Vandetanib**	**Placebo**	**Incremental**	**Vandetanib**	**Placebo**	**Incremental**
LYGs	4.84	3.10	1.74	4.84	3.10	1.74
PFLYGs*	2.07	0.77	1.30	2.07	0.77	1.30
QALYs	3.49	2.13	1.36	3.49	2.13	1.36
Treatment costs, pre-progression	£75,766.71	£0.00	£75,766.71	£75,817.76	£0.00	£75,817.76
Treatment costs, post-progression	£68,490.03	£106,330.94	-£37,840.91	£68,490.35	£106,317.39	-£37,827.04
Monitoring costs	£653.86	£385.80	£268.06	£646.21	£385.75	£260.46
AE costs	£409.32	£136.48	£272.84	£409.32	£136.48	£272.84
Cost of BSC	£24,506.37	£19,521.81	£4,984.56	£24,506.45	£19,519.65	£4,986.80
Palliative care costs	£5,489.93	£5,916.92	-£426.99	£5,574.17	£6,004.49	-£430.31
Total costs	£175,316.22	£132,291.95	£43,024.27	£175,444.26	£132,363.76	£43,080.50
ICER	-	-	**£31,730.99**	-	-	**£31,636.28**

**undiscounted*

LYG – life year gained; PFLYG – progression-free life year gained; QALY – quality-adjusted life year; BSC – best supportive care; ICER – incremental cost-effectiveness ratio

Summary of main issues identified within the critical appraisal

Box 3 presents a summary of the main issues surrounding the company's health economic analysis. These issues are discussed in further detail below.

Box 3: Main issues identified by the Assessment Group

1. Relevance of the Restricted EU label population
2. Failure to adjust for continued vandetanib use and BSC switching to vandetanib post-progression
3. Likely overestimation of costs of vandetanib use in post-progression state
4. Questionable implementation of the vandetanib discontinuation parameter
5. Robustness of covariate-adjusted survival modelling to reflect the Restricted EU label population
6. Technical programming errors
7. Concerns regarding health utility parameters
8. Limited exploration of uncertainty surrounding survivor functions
9. Concerns regarding costings

(1) Relevance of the Restricted EU label population

The company's health economic analysis is limited to the "Restricted EU label" population, based on the argument that this reflects the current use of vandetanib in clinical practice in England. In response to a request for clarification from the Assessment Group (see clarification response,[41] question A3), the company stated:

"In developing the submission, we consulted with two UK clinical experts to discuss management of MTC in practice. Factors which determined the need for systemic treatment were speed of progression, tumour burden/size and symptoms. CTN/CEA doubling are known markers of poor prognosis and more aggressive disease. SanofiGenzyme re-analysed the ZETA trial population and considered the patients who were symptomatic, had progressed within 12 months and with CTN/CEA doubling <24 months most closely reflected UK clinical expert opinion. This approach is within the intent of the EU label where benefit outweighs the risk by using local clinical approaches to identify those most in need of treatment."

However, clinical advisors to the Assessment Group disagree with this assertion and instead suggest that in clinical practice vandetanib is used in patients with symptomatic and progressive disease irrespective of CEA/CTN biomarker levels. The clinical advisors also noted that CTN is an unstable measure and that the presence of disease progression (which is likely to also be accompanied by symptomatic disease) is more useful for informing treatment decisions. The advisors further noted that whilst CEA and CTN are routinely measured in patients with MTC, these biomarkers are typically used to monitor patients whilst they are receiving treatment (to assess whether treatment is working), rather than to determine whether treatment should be initiated. The clinical advisors also noted that patients with symptomatic and progressive disease would also likely have CEA/CTN doubling times ≤24

months. As noted previously, the CS does not contain a health economic analysis of vandetanib within the broader population indicated by its marketing authorisation.[22] The clinical advisors did however agree that the company's interpretation of what constitutes "progressive and symptomatic" disease (see Section 5) is clinically appropriate.

(2) Failure to adjust for continued vandetanib use and BSC switching to vandetanib post-progression

The Sanofi CS states that whilst attempts were made to account for treatment switching in the ZETA trial using the RPSFT method, these were reported to have been unsuccessful. In response to a request for clarification (see clarification response,[41] question A2), the company stated *"RPSFT failed to undo bias as the method looks for the effect sizes needed so that the two survival curves match if they are given the same treatment, if the curves never separate, or don't separate enough because crossover happens too early or before sufficient events occur in placebo (as was the case in ZETA), the curves will match up with effects very close to the null. This was the result obtained in the analyses."* Based on the company's description, it seems likely that the RPSFT model did work as it would be expected to given its assumptions, but the company describe the approach failing as it showed a null treatment effect. The company's clarification response also provides further details regarding other treatment switching adjustment methods considered by the company (the Iterative Parameter Estimation [IPE], Inverse Probability of Censoring Weights [IPCW] and 2-stage methods), however, these methods were not implemented. Consequently, the OS data for the BSC group remain subject to potential confounding due to treatment switching. Clinical advisors to the Assessment Group noted that the continued use of vandetanib beyond disease progression does not reflect usual clinical practice in England, hence the survival outcomes observed in the intervention group reflect an atypical treatment pathway. However, one clinical advisor suggested that if imaging showed a mixed response with the largest or most symptomatic/problematic lesions being stable and some other lesions progressing, vandetanib may still be continued; the advisor did however note that this scenario is uncommon. Consequently, the Assessment Group notes that the results generated by the company's model may not be meaningful for the purposes of decision-making.

(3) Likely overestimation of costs of vandetanib use in post-progression state

The company's model includes a single progression event which corresponds to the partition between the progression-free and post-progression health states. As such, patients who receive vandetanib post-progression in either the intervention or the comparator group are assumed to continue to do so until death. In reality, these patients could experience a second progression event prior to death and such progression would likely trigger a clinical decision to discontinue vandetanib. This is not reflected in the company's model. The Assessment Group accepts that due to the failure of the crossover adjustment attempts, it is reasonable to include the costs of the drug in both groups, however, assuming that all post-progression treatment continues indefinitely will likely lead to the overestimation of the costs of

vandetanib in both groups. This bias strongly favours the intervention group as a considerably higher proportion of patients receive vandetanib post-progression within the BSC group (proportion of patients on treatment post-progression: BSC [redacted] vs. vandetanib [redacted]; post-progression drug costs: BSC £106,331 vs. vandetanib £68,490). Removing the costs of vandetanib received post-progression in both groups increases the deterministic ICER from £31,731 per QALY gained to £59,740 per QALY gained. This same concern also applies to the pairwise comparisons of vandetanib versus BSC undertaken using the Assessment Group model.

(4) Questionable implementation of the vandetanib discontinuation parameter

Whilst the company's model includes dose reductions (including treatment interruptions) for patients receiving vandetanib in both groups as per the ZETA trial (see Table 27), a further discontinuation parameter is also applied only to those patients in the vandetanib group during the progression-free phase. This parameter is applied as a fixed proportion of patients who incur no vandetanib costs ([redacted]) during any model cycle whilst patients in the intervention group are progression-free. As a consequence of this parameter, together with the long post-progression phase (see critical appraisal point 3), the pre-progression vandetanib acquisition costs in the intervention group are less than the post-progression vandetanib costs in the BSC group (vandetanib pre-progression drug costs £75,767 vs BSC post-progression drug costs £106,331). This lacks face validity and it is unclear whether the company's omission of this parameter from post-progression cost calculations was intentional. Setting this parameter equal to zero increases the ICER from £31,731 to £57,266 per QALY gained.

(5) Robustness of covariate-adjusted survival modelling to reflect the Restricted EU label population

The Sanofi CS[35] (page 57) states that *"it was not possible to fit a parametric regression model to the observed K-M data… due to relatively sparse data in the restricted population producing K-M curves with long steps would lead to inaccurate estimates of the median survival function when extrapolated for the economic model."* Instead, the company used the ITT and safety datasets for PFS and OS, respectively, and fitted curves including covariates for symptomatic and progressive disease and for the CEA/CTN biomarker. The Assessment Group considers that it would have been more appropriate to fit parametric functions directly to the data relating to the population of interest (the Restricted EU label population, vandetanib group [redacted], placebo group [redacted]) as these are the most relevant data available to estimate PFS and OS in this subgroup. Whilst the CS explains that the Kaplan-Meier curves feature large steps between events due to the small sample size, it is not clear that this would lead to more inaccurate estimates of median survival in the Restricted EU label population than those produced by fitting a covariate-adjusted model to the broader EU label population. It should be noted that the model fit statistics (AIC/BIC) presented by the company reflect how well each parametric model with covariates fits the data observed for the entire ITT/safety population, and so the model with lowest AIC/BIC does not necessarily indicate the best fit to the population of interest.

The Assessment Group has further concerns regarding the company's interpretation of their covariate-adjusted survival modelling. Figure 9 of the Sanofi CS[35] (page 59) presents a comparison of the covariate-adjusted Weibull OS model against the empirical Kaplan-Meier curves from the ZETA trial (see Figure 9) and states: *"These parameterised curves appear to underestimate the benefit of vandetanib in the CTN/CEA doubling population from the ITT dataset (Figure 7), even without undoing crossover. There is uncertainty regarding how well this function would fit the 'true' survival curves in the CTN/CEA doubling population from the EU label dataset with cross over undone."* However, the comparison of predicted and observed OS probabilities represented in this comparison relate to two different populations: the covariate-adjusted Weibull model relates to the Restricted EU label population, whilst the observed Kaplan-Meier curves relate to the ZETA ITT population with CEA and CTN doubling time ≤24 months (excluding the progressive population characteristics). Figure 13 shows the company's Weibull OS model fitted against the relevant Kaplan-Meier curve for the Restricted EU label subgroup (plotted by the Assessment Group). As shown in the figure, the company's Weibull model does not provide a good visual fit to either the vandetanib or BSC group data.

Figure 13: **Corrected comparison of company's predicted versus observed OS (Kaplan-Meier Restricted EU label population)**

(6) Technical programming errors

According to the CS[35] (page 107), the disutility for AEs was intended to be applied during the first cycle only (1 month duration). However, the DICE event used to calculate disutilities in each group does not include a time adjustment, hence this disutility is applied to the whole first year of the model. This reflects a programming error which exaggerates the QALY loss in both groups; given that the incidence of AEs is higher for vandetanib, the error produces a small bias in favour of the BSC comparator group. This issue was later corrected by the company in their clarification response[41] (question A18). During the appraisal process, the company also highlighted a further error relating to the vandetanib discontinuation parameter; this was originally reported to be [redacted] but was later corrected to [redacted]. Correcting these two errors reduces the company's original deterministic ICER from £40,363 to £31,731 per QALY gained.

The Assessment Group also notes that the model does not include any adjustment for logical inconsistency (i.e. where the cumulative survival probability for PFS is greater than that for OS at a given timepoint). This does not affect the company's deterministic base case Weibull functions for OS and PFS. However, this issue is evident in scenarios in which other parametric functions are used (for example, if the log normal function is used for PFS and the Weibull function is used for OS). This leads to a situation whereby the health state population of the post-progression state becomes negative (see

Table 34). This issue could have been resolved by conditioning the PFS function to be equal or lower than the OS function.

Table 34: **Health state populations by year, PFS=log normal, OS=Weibull (logically inconsistent results highlighted in bold)**

Year	BSC group			Vandetanib group		
	OS Weibull	PFS log normal	PPS state population (OS minus PFS)	OS Weibull	PFS log normal	PPS state population (OS minus PFS)
0	1.000	1.000	0	1.000	1.000	0
1	0.768	0.322	0.446	0.886	0.737	0.149
2	0.575	0.171	0.404	0.760	0.516	0.244
3	0.424	0.107	0.317	0.640	0.378	0.262
4	0.310	0.074	0.236	0.533	0.287	0.246
5	0.224	0.054	0.17	0.439	0.225	0.214
6	0.162	0.041	0.121	0.359	0.180	0.179
7	0.116	0.032	0.084	0.291	0.147	0.144
8	0.082	0.026	0.056	0.235	0.121	0.114
9	0.058	0.021	0.037	0.188	0.102	0.086
10	0.041	0.017	0.024	0.150	0.086	0.064
11	0.029	0.015	0.014	0.119	0.074	0.045
12	0.020	0.012	0.008	0.094	0.064	0.03
13	0.014	0.011	0.003	0.074	0.055	0.019
14	0.010	0.009	0.001	0.058	0.049	0.009
15	**0.007**	**0.008**	**-0.001**	0.045	0.043	0.002
16	**0.005**	**0.007**	**-0.002**	**0.035**	**0.038**	**-0.003**
17	**0.003**	**0.006**	**-0.003**	**0.027**	**0.034**	**-0.007**
18	**0.002**	**0.006**	**-0.004**	**0.021**	**0.030**	**-0.009**
19	**0.002**	**0.005**	**-0.003**	**0.016**	**0.027**	**-0.011**
20	**0.001**	**0.004**	**-0.003**	**0.012**	**0.024**	**-0.012**

BSC – best supportive care; OS – overall survival; PFS – progression-free survival; PPS – post-progression survival

(7) Concerns regarding health utility parameters

The CS does not include details of a systematic review of utility estimates in MTC or other types of thyroid cancer. The means through which the company identified the Beusterien *et al* study,[90] which is used to inform the post-progression utility multiplier and the disutility for Grade 3/4 AEs, are unclear from the Sanofi CS. The Assessment Group also notes that the Beusterien *et al*[90] study relates to advanced melanoma health states, hence its relevance to MTC is unclear. Whilst the Sanofi CS[35] (page 114) states that there are *"insufficient data available for alternative estimates"*, such statements are difficult to qualify without undertaking a formal systematic review of the available evidence. However, as shown in the company's DSAs, these parameters do not have a marked impact on the cost-effectiveness of vandetanib within the Restricted EU label population (see Figure 12).

(8) Limited exploration of uncertainty surrounding survivor functions

The CS includes only limited consideration of uncertainty surrounding the range of potentially plausible survivor functions for PFS or OS. Whilst a number of parametric functions were fitted to the available data for PFS and OS, only the impact of the log logistic and log normal functions for both PFS and OS

(together) were explored within the company's DSAs (see Section 6.1.3.5). It should also be noted that whilst the company's executable model includes the parameters for five alternative survivor functions, only the Weibull, log logistic and log normal curves can be selected as options. The reasons for this are unclear.

(9) Concerns regarding costings

Clinical advisors to the Assessment Group noted several concerns regarding the company's cost assumptions.

(i) *Monitoring costs.* Whilst the company's model includes the costs associated with ECGs to monitor patients whilst receiving vandetanib, these costs should also include consultant-/nurse-led outpatient appointments (typically at a frequency of around 12 consultant-led visits and 4 nurse-led visits per year).

(ii) *BSC costs in post-progression state.* The company's assumption of 36.5 outpatient appointments per year (one appointment every 10 days) whilst patients are receiving BSC is unrealistically high. Clinical advisors to the Assessment Group suggested that a more reasonable estimate would be around 6 appointments per year.

(iii) *Costs of managing AEs.* Clinical advisors to the Assessment Group believe that the costs of managing some of the Grade 3/4 events included in the company's model are implausibly high. As noted in Section 6.1.3.3, the unit costs assumed for these events all assume that the episode is elective, which is by definition, incorrect. The clinical advisors suggested that the incidence of prolonged QT interval, hypertension, decreased appetite and rash would most likely be managed by discontinuing vandetanib. Hypertension would likely require the prescription of antihypertensive drugs.

6.1.3.7 Discussion of existing evidence relating to the cost-effectiveness of cabozantinib and vandetanib for the treatment of locally advanced or metastatic MTC

The systematic review of existing economic evaluations did not identify any relevant published studies. The manufacturer of cabozantinib did not submit any economic evidence relating to this product. The manufacturer of vandetanib (Sanofi) submitted a *de novo* model-based health economic evaluation of vandetanib versus BSC in the Restricted EU label population (patients with symptomatic and progressive disease with CEA/CTN doubling time ≤24 months). An economic analysis for the broader licensed population was not presented. The corrected version of the company's submitted model suggests that the probabilistic ICER for vandetanib versus BSC is approximately £31,546 per QALY gained. The Assessment Group notes several concerns relating to the company's submitted model, in particular: (1) the questionable relevance of the Restricted EU label population to current clinical practice; (2) the failure to adjust for open-label vandetanib use in both treatment groups; (3) the likely overestimation of the costs of vandetanib use in the post-progression state; (4) questionable assumptions

regarding the amount of vandetanib received, and; (5) concerns regarding the robustness of the company's covariate-adjusted survival modelling to reflect the Restricted EU label population. The Assessment Group considers that it is likely that the ICER for vandetanib is considerably higher than the estimates presented within the Sanofi CS.

6.2 Independent Assessment Group model

6.2.1 Model scope

The scope of the Assessment Group's analysis is summarised in Table 35. The Assessment Group's analyses are presented across two populations of patients with locally advanced or metastatic MTC: (i) patients with progressive and symptomatic disease (the EU label population for vandetanib), and (ii) the Restricted EU label population for vandetanib. Within the broader symptomatic and progressive population, pairwise economic comparisons are made for cabozantinib versus BSC based on the ITT population of the EXAM trial[28] (AG Analysis 1) and for vandetanib versus BSC based on the *post hoc* EU label (symptomatic and progressive) subgroup of the ZETA trial[35, 53] (AG Analysis 2). It should be noted that these analyses are limited in that they do not include all relevant treatment options. As the Assessment Group did not have access to the underlying IPD (including data on relevant covariates) from the ZETA trial, it was not possible to implement statistical adjustments to account for open-label vandetanib use in either treatment group, or to adjust for other potential baseline imbalances in the subgroup. Consequently, the comparison of vandetanib versus BSC is subject to potential confounding. In order to provide more meaningful estimates of the cost-effectiveness of vandetanib and cabozantinib, two sets of fully incremental analyses of all options are also presented. The first of these (AG Analysis 3) uses the EXAM trial data for cabozantinib and BSC and applies the PFS treatment effect for vandetanib versus placebo from the ZETA trial EU label subgroup to the EXAM placebo group baseline; OS is assumed to be the same for both TKIs (equivalent to the cabozantinib arm in the EXAM trial). The second incremental analysis (AG Analysis 4) assumes that PFS and OS outcomes for vandetanib are equivalent to those for cabozantinib. Whilst these incremental analyses necessarily reflect potentially strong assumptions concerning transferable/equivalent treatment effects between vandetanib and cabozantinib, they are not subject to potential confounding caused by post-progression vandetanib use within the clinical data. A further pairwise comparison (AG Analysis 5) is also presented which evaluates vandetanib versus BSC within the Restricted EU label population (patients with symptomatic and progressive MTC with CEA/CTN doubling time ≤24 months); as equivalent covariate data were not available from the EXAM study, cabozantinib could not be included within this analysis. Across all five sets of analyses, cost-effectiveness is evaluated in terms of the incremental cost per QALY gained from the perspective of the NHS and Personal Social Services (PSS) over a 20-year (lifetime) horizon. Costs and health outcomes were discounted at a rate of 3.5% per annum.[93] Costs were valued at 2016/17 prices.

Table 35: **Assessment Group model scope**

Population	**EU label population: Symptomatic and progressive MTC**	**Restricted EU label population: Symptomatic and progressive MTC with CEA/CTN doubling time ≤24 months**
Intervention(s)	• Vandetanib • Cabozantinib	• Vandetanib
Comparator	BSC	
Outcomes	Incremental cost per QALY gained	
Economic comparisons	*AG Analysis 1:* Pairwise economic evaluation of cabozantinib versus BSC in the EXAM ITT population *AG Analysis 2:* Pairwise economic evaluation of vandetanib versus BSC in the ZETA EU label population *AG Analysis 3:* Fully incremental analysis based on EXAM ITT population with vandetanib PFS treatment effect applied to EXAM placebo baseline, vandetanib OS assumed equivalent to cabozantinib OS *AG Analysis 4:* Fully incremental analysis based on EXAM ITT population assuming PFS and OS are equivalent for vandetanib and cabozantinib	*AG Analysis 5:* Pairwise economic evaluation of vandetanib versus BSC in the ZETA Restricted EU label population
Perspective	NHS and PSS*	
Time horizon	20 years	
Cycle length	1 month	
Discount rate	3.5% for health outcomes and costs	

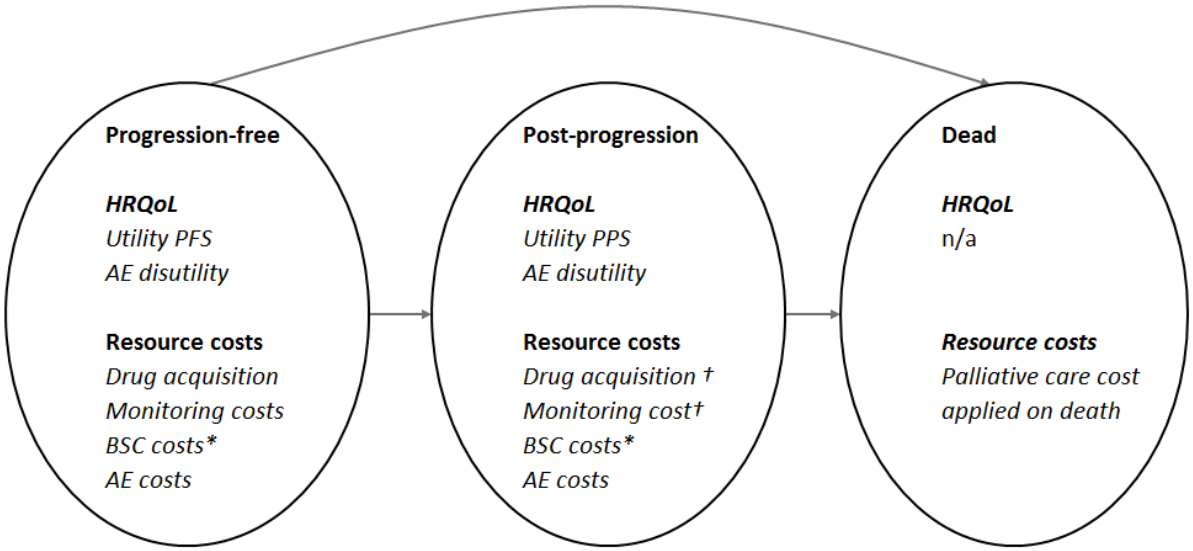
** PSS costs not explicitly included*
CEA – carcinoembryonic antigen; CTN – calcitonin; BSC – best supportive care; QALY – quality-adjusted life year; ITT – intention-to-treat; PFS – progression-free survival; OS – overall survival; NHS – National Health Service; PSS – Personal Social Services

6.2.2 Model structure

The structure of the Assessment Group's model is presented in Figure 14. As shown in the diagram, the Assessment Group model structure is broadly similar to that adopted within the Sanofi model (see Section 6.1.3.2). The Assessment Group model adopts a partitioned survival approach, based on three health states: (i) progression-free; (ii) post-progression, and; (iii) dead. For any time *t*, the probability that a patient is alive and progression-free is given by the cumulative survival probability for PFS, whilst the probability that a patient is alive is given by the cumulative survival probability for OS. The probability that a patient is in the post-progression state is given by the difference between the cumulative survival probabilities for PFS and OS for any time *t*. The model includes an adjustment for logical inconsistency whereby if the probability of PFS is greater than OS, PFS is constrained to reflect the lower OS probability. As with the Sanofi model, HRQoL is defined according to the presence or absence of disease progression and a separate QALY loss is applied to account for the incidence of

Grade 3/4 AEs during the first model cycle. The model includes costs associated with drug acquisition, health state costs incurred whilst receiving cabozantinib and vandetanib (consultant-led outpatient visits, nurse-led outpatient visits, ECGs, blood tests, and computerised tomography [CT] scans), costs associated with managing Grade 3/4 AEs, BSC-related costs (consultant-led outpatient visits, CT scans, magnetic resonance imaging [MRI] scans, specialist palliative care visits, palliative radiotherapy, palliative surgery and bisphosphonates for bone metastases) and end-of-life care costs.

Figure 14: **Assessment Group model structure**



** Applies only to patients not receiving vandetanib/cabozantinib*

† Applies only to open-label vandetanib costs within pairwise comparisons of vandetanib vs BSC

The model employs the following structural assumptions:

- HRQoL is assumed to be determined according to the presence/absence of disease progression and the incidence of Grade 3/4 AEs.
- The model includes an adjustment to account for logical inconsistencies (i.e. where $S(t)_{PFS} > S(t)_{OS}$).
- In the pairwise comparisons of vandetanib versus BSC (see Table 35, AG Analyses 2 and 5), the modelling of costs and health outcomes includes the level of treatment switching and continued vandetanib use post-progression observed in the ZETA trial subgroups. This was included as the company's attempts to adjust for treatment switching and treatment continuation post-progression were reported to have been unsuccessful (see Section 6.1.3.6).
- Grade 3/4 AEs are assumed to impact upon both costs and HRQoL. Health losses resulting from AEs are assumed to be transient and resolved quickly: a QALY loss is applied during the first model cycle only (1 month duration).

- As patients receiving BSC, by definition, have progressed disease, the costs associated with BSC are assumed to be the same in both the progression-free and post-progression states.
- Health state resource use (including additional TKI monitoring requirements) incurred during the progression-free period are assumed to differ between the three treatment options.
- Palliative care costs are incurred only during the final month of life.

6.2.3 Evidence used to inform the model's parameters

6.2.3.1 Summary of evidence sources used to inform the Assessment Group model

Table 36 summarises the evidence sources used to inform the Assessment Group's health economic model. These evidence sources are discussed in further detail in the subsequent sections.

Table 36: **Evidence used to inform the Assessment Group model**

Parameter group	Evidence source
Progression-free survival	*Pairwise comparisons of TKI versus BSC (AG Analyses 1, 2 and 5)* Parametric PFS functions fitted to IPD from the EXAM and ZETA trials.* *Incremental comparison of all options including a differential PFS treatment effect between vandetanib and cabozantinib (AG Analysis 3)* Parametric PFS functions fitted to IPD from the EXAM trial. Vandetanib PFS effect derived using treatment effect parameter from combined model using ZETA IPD (applied to the EXAM ITT placebo arm as the baseline). *Incremental comparison of all options assuming equivalent effectiveness for TKIs (AG Analysis 4)* Parametric PFS functions fitted to IPD from the EXAM trial. Vandetanib outcomes assumed to be equivalent to cabozantinib outcomes.
Overall survival	*Pairwise comparisons of TKI versus BSC (AG Analyses 1, 2 and 5)* Parametric OS functions fitted to IPD from the EXAM and ZETA trials (includes potential confounding due to switching/continuation post-progression for vandetanib comparisons).* *Incremental comparisons of all options (AG Analyses 3 and 4)* Parametric OS functions fitted to IPD from the EXAM trial ITT population. Vandetanib outcomes assumed to be equivalent to cabozantinib outcomes.
Health utilities	*Progression-free and post-progression health state* Derived from time trade-off (TTO) study utility valuation in radioactive iodine-refractory differentiated thyroid cancer (Fordham *et al.*[87]). *Disutility due to AEs* Disutility for any Grade 3/4 AE taken from general population SG study of societal preferences for advanced melanoma health states (Beusterien *et al*[90]).
Time spent receiving vandetanib	Based on proportion of PFS time spent on each dose level (or interrupted treatment) for relevant subgroup in ZETA.[35, 41, 53] Vandetanib dose distribution also applied to post-progression vandetanib use (in AG Analyses 2 and 5 only). Includes vandetanib pre-progression discontinuation parameter in both progression-free and post-progression states.
Time spent receiving cabozantinib	Based on proportion of PFS time spent on each dose level (or interrupted treatment) within the EXAM trial.[28]
Probability of receiving vandetanib whilst in post-progression state	Treatment switching/continuation proportions observed in relevant subgroups of ZETA.[35, 41] Vandetanib dose distribution also applied to post-progression use.
Drug acquisition costs	BNF[96]
AE incidence	Derived from EXAM and ZETA trial publications[27, 28]
Health state resource use	Personal communication: Dr Jon Wadsley and Dr Laura Moss
BSC resource use	Personal communication: Dr Jon Wadsley and Dr Laura Moss
Health state unit costs	NHS Reference Costs 2015/16[91]
AE management costs	NHS Reference Costs 2015/16[91] Weighted mean of all non-elective excess bed days.
BSC costs	NHS Reference Costs 2015/16[91]
Palliative care and palliative chemotherapy costs	NHS Reference Costs 2015/16[91] and Curtis and Burns[92]

** Data from the ZETA trial were reconstructed IPD rather than raw trial data*
TKI – tyrosine kinase inhibitor; BSC – best supportive care; PFS – progression-free survival; IPD – individual patient data; OS – overall survival; AE – adverse event; TTO – time trade-off; SG – standard gamble; BNF – British National Formulary

6.2.3.2 Time to event analysis using individual patient data

Table 37 summarises the use of the time-to-event data from the ZETA and EXAM trials within the Assessment Group model.

Table 37: **Summary of time-to-event data used in Assessment Group model**

Outcome	**EU label population: Symptomatic and progressive MTC**				**Restricted EU label population: Symptomatic and progressive MTC with CEA/CTN doubling time ≤24 months**
	AG Analysis 1: Cabozantinib versus BSC (pairwise)	**AG Analysis 2: Vandetanib versus BSC (pairwise)**	**AG Analysis 3: All options – vandetanib PFS treatment effect from joint model**	**AG Analysis 4: All options – cabozantinib and vandetanib equivalent**	**AG Analysis 5: Vandetanib versus BSC (pairwise)**
Progression-free survival					
Cabozantinib PFS	Cabozantinib arm, EXAM ITT	N/a	Cabozantinib arm, EXAM ITT	Cabozantinib arm, EXAM ITT	N/a
Vandetanib PFS	N/a	Vandetanib arm, ZETA EU label	Treatment effect from ZETA EU label applied to EXAM placebo arm	Assumed same as cabozantinib arm, EXAM ITT	Vandetanib arm, ZETA Restricted EU label
BSC PFS	Placebo arm, EXAM ITT	Placebo arm, ZETA EU label	Placebo arm, EXAM ITT	Placebo arm, EXAM ITT	Placebo arm, ZETA Restricted EU label
Overall survival					
Cabozantinib OS	Cabozantinib arm, EXAM ITT	N/a	Cabozantinib arm, EXAM ITT	Cabozantinib arm, EXAM ITT	N/a
Vandetanib OS	N/a	Vandetanib arm, ZETA EU label	Assumed same as cabozantinib arm, EXAM ITT	Assumed same as cabozantinib arm, EXAM ITT	Vandetanib arm, ZETA Restricted EU label
BSC OS	Placebo arm, EXAM ITT	Placebo arm, ZETA EU label	Placebo arm, EXAM ITT	Placebo arm, EXAM ITT	Placebo arm, ZETA Restricted EU label
Treatment switching					
Includes switching/ continued vandetanib costs?	N/a	Yes	No	No	Yes

BSC – best supportive care; CEA – carcinoembryonic antigen; CTN - calcitonin; ITT – intention-to-treat; PFS – progression-free survival; OS – overall survival; N/a – not applicable

Data used to inform time to event analysis

The comparison of cabozantinib versus placebo was based on IPD relating to the full population of the EXAM trial (cabozantinib N=219, placebo N=111); these data were supplied by Ipsen for both PFS and OS.[97]

The comparison of vandetanib to placebo was based on *post hoc* subgroups of patients enrolled into the ZETA trial; the EU label population (vandetanib N=[redacted], placebo=[redacted] for PFS, placebo=[redacted] for OS) and the Restricted EU label population (vandetanib N=[redacted], placebo N=[redacted]). Owing to concerns regarding the intellectual propriety rights of the patient-level dataset, Sanofi was unable to provide the original IPD collected during the trial. Instead, Kaplan-Meier curves for each population and outcome were provided by Sanofi.[41] The supplied Kaplan-Meier curves were digitised using Engauge Digitizer[98] and IPD were then reconstructed from the digitised curves using the algorithm reported by Guyot *et al*.[99] This method maps the digitised curves back to time-to-event data by finding numerical solutions to the inverted Kaplan-Meier equations. There are four variations on the method depending on the amount of information supplied. For both of the ZETA subgroups (EU label and Restricted EU label) and outcomes (PFS and OS), both the number at risk tables and the total numbers of events were supplied by Sanofi, thereby allowing the most accurate variation of the algorithm to be used. In addition, as the sample sizes of the subgroups are fairly small and there are a small number of events which can be readily identified from the Kaplan-Meier survival curves, the resulting reconstructed IPD are likely to provide a good approximation of the original dataset.

Methods for time to event analysis

For each dataset, model selection was conducted following the process described in the NICE Decision Support Unit Technical Support Document No. 14.[100] Log cumulative hazard plots were produced to assess the type of hazards observed in the trial in order to help inform which types of parametric function may be considered appropriate. For all analyses except for AG Analysis 4, individual models were fitted to data for each treatment group, thereby avoiding unnecessarily restrictive assumptions of proportional hazards or constant acceleration factors. The AIC and BIC were examined to assess the comparative internal validity of competing models. The final choice of models for the economic analysis was made on the basis of fit to the observed data as well as consideration of the clinical plausibility of competing candidate models, based on judgements elicited from one clinical expert (JW). The final model selections used to inform the health economic model are presented in Table 43.

In order to inform the fully incremental analyses of cabozantinib, vandetanib, and BSC (AG Analysis 3), a single parametric model with a covariate indicating treatment arm was considered for PFS in the EU label population of the ZETA trial. As discussed in Section 5.2.1 and 5.3.1, this population is considered to be broadly comparable to that of the EXAM trial. Fitting a combined model provides a

treatment effect for vandetanib compared to placebo (either an HR or constant acceleration factor, depending on the parametric model). This can then be applied to the baseline model (taken to be the placebo arm in the EXAM trial) in order to approximate the absolute effect for a vandetanib treatment group in the chosen baseline population. The estimated HR from the NMA (see Section 5.3) was not used as it is generally recommended that estimation of the treatment effects and baseline follows a consistent modelling procedure.[85] Furthermore, the use of HRs would not be appropriate for the accelerated failure time models as these not make the assumption of proportional hazards.

Curve fitting was conducted in R[82] using the 'flexsurv' package.[101] The 'muhaz' package was used to estimate the empirical hazard function.[102] Exponential, Weibull, Gompertz, log normal, log logistic, gamma, and generalised gamma models were considered. The more flexible generalised F distribution was also considered, however, for some of the analyses the model fitting algorithm failed to converge; in these cases, the Assessment Group considered that the Generalised F model would not be appropriate. Goodness-of-fit information is provided for all considered models.

Cabozantinib versus BSC, EXAM ITT population (used in AG Analyses 1, 3 and 4)

PFS

The analysis of PFS for cabozantinib versus placebo was based on IPD from the full population of the EXAM trial (cabozantinib N=219, placebo N=111, Figure 15) provided by Ipsen. Empirical diagnostic plots are provided in Appendix 3. Visual inspection of the empirical hazard function plot indicates potentially different behaviours between the two treatment arms. Visual inspection of the log-log plot of cumulative survival versus time indicates that the exponential model may not be appropriate as the gradient is not close to 1.0; the remaining standard parametric models were deemed suitable for consideration.

Measures of comparative internal validity are presented in Table 38. Plots of the fitted models against the empirical Kaplan-Meier PFS curves are presented in Figure 17 (cabozantinib) and Figure 18 (placebo). For the placebo arm, the log logistic model provided the best fit to the observed data according to both the AIC and BIC (AIC=308.71, BIC=314.13), although the log normal model also provided a good fit to the data (AIC=311.48, BIC=316.90). For the cabozantinib arm, the Weibull model provided the best fit according to both the AIC and BIC (AIC= 579.70, BIC=586.48), although the BIC was similar for several models.

OS

The analysis of OS for cabozantinib versus placebo was based on IPD from the full population of the EXAM trial (cabozantinib N=219, placebo N=111, Figure 16) provided by Ipsen. Log cumulative hazard plots are provided in Appendix 3 Figure 39. Visual inspection of the empirical hazard function

indicates that the observed hazard is approximately constant for both trial arms, and visual inspection of the log-log plot of cumulative survival versus time indicates a gradient of approximately 1.0, suggesting that the exponential model may be appropriate in this case.

Measures of comparative internal validity are presented in Table 38. Plots of the fitted models against the empirical Kaplan-Meier OS curves are presented in Figure 19 (cabozantinib) and Figure 20 (placebo). Based on AIC and BIC statistics for the placebo arm, the log logistic and exponential models provided the best fit (log logistic AIC=708.31, BIC=713.73; exponential AIC=709.58, BIC=712.29). Findings were similar for the cabozantinib arm: the log logistic model provided the best fit to the observed data according to the AIC (1343.69) and the exponential model provided the best fit according to the BIC (1348.42).

Figure 15: EXAM ITT population PFS

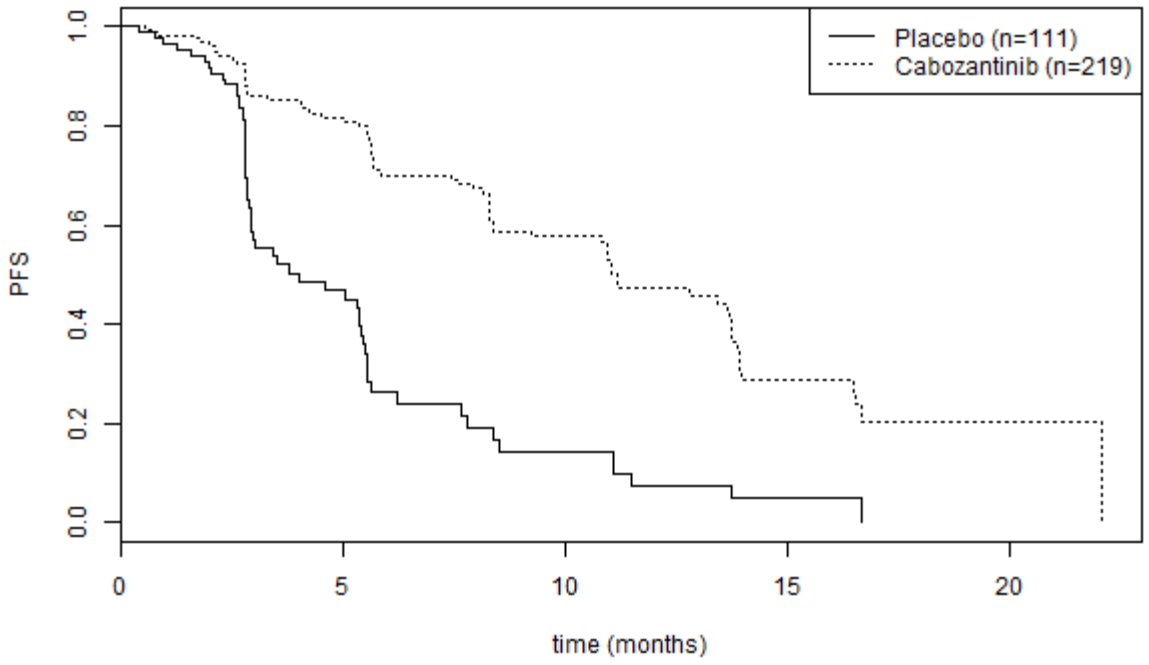


Figure 16: EXAM ITT population OS

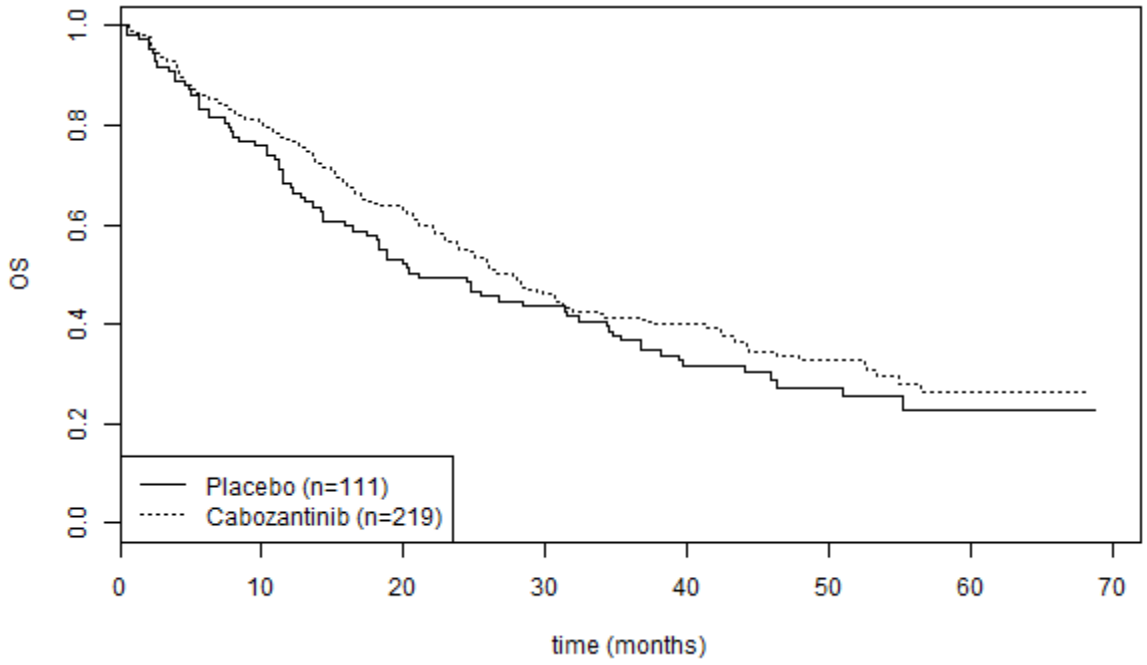


Table 38: **Model fit statistics - EXAM ITT population, individual models for each treatment arm, PFS and OS**

		Placebo		Cabozantinib	
		AIC	**BIC**	**AIC**	**BIC**
PFS	**exponential**	338.71	341.42	599.32	602.71
	Weibull	320.19	325.61	**579.70**	**586.48**
	Gompertz	333.52	338.94	582.76	589.54
	log normal	311.48	316.90	584.68	591.46
	log logistic	**308.71**	**314.13**	583.59	590.37
	gamma	314.44	319.86	580.06	586.84
	generalised gamma	313.16	321.28	581.68	591.85
	generalised F	failed to converge		583.69	597.24
		AIC	**BIC**	**AIC**	**BIC**
OS	**exponential**	709.58	**712.29**	1345.03	**1348.42**
	Weibull	711.35	716.77	1346.97	1353.75
	Gompertz	709.88	715.29	1346.48	1353.26
	log normal	708.80	714.22	1344.34	1351.12
	log logistic	**708.31**	713.73	**1343.69**	1350.47
	gamma	711.54	716.95	1346.76	1353.54
	generalised gamma	710.22	718.34	1345.03	1355.19
	generalised F	712.18	723.01	1347.03	1360.59

Figures in bold indicate best fitting model (lowest AIC/BIC).

PFS – progression-free survival; OS – overall survival; AIC – Akaike Information Criterion; BSC – best supportive care

Figure 17: **EXAM ITT population, PFS, cabozantinib group (extrapolation up to 10 years)**

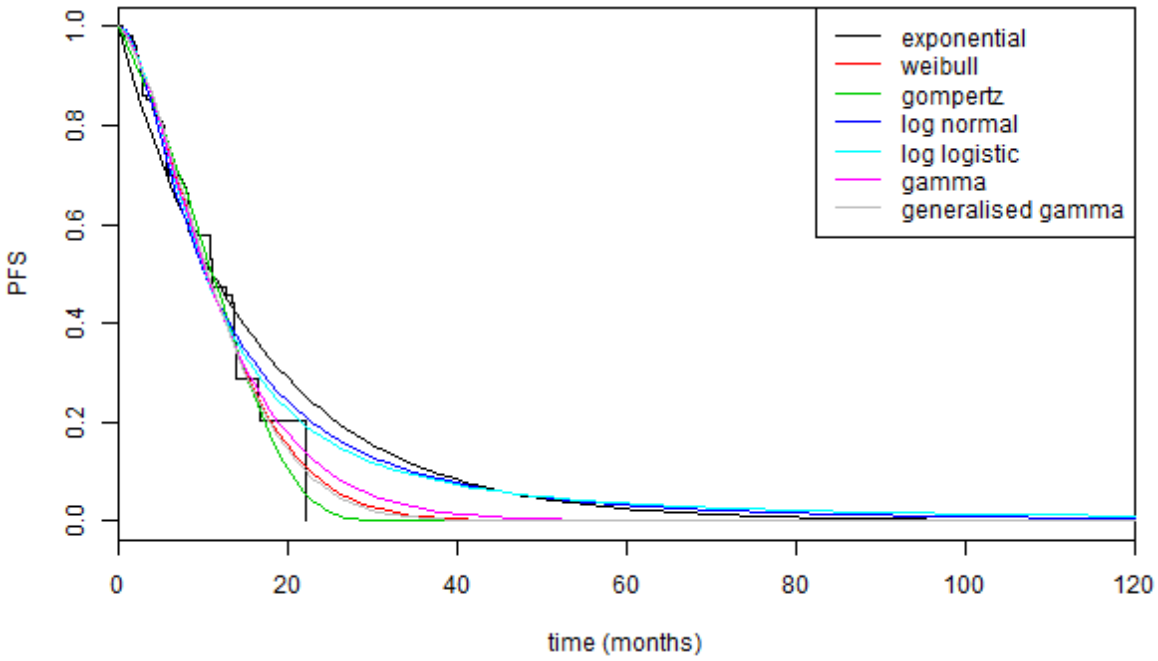


Figure 18: **EXAM ITT population, PFS, placebo group (extrapolation up to 10 years)**

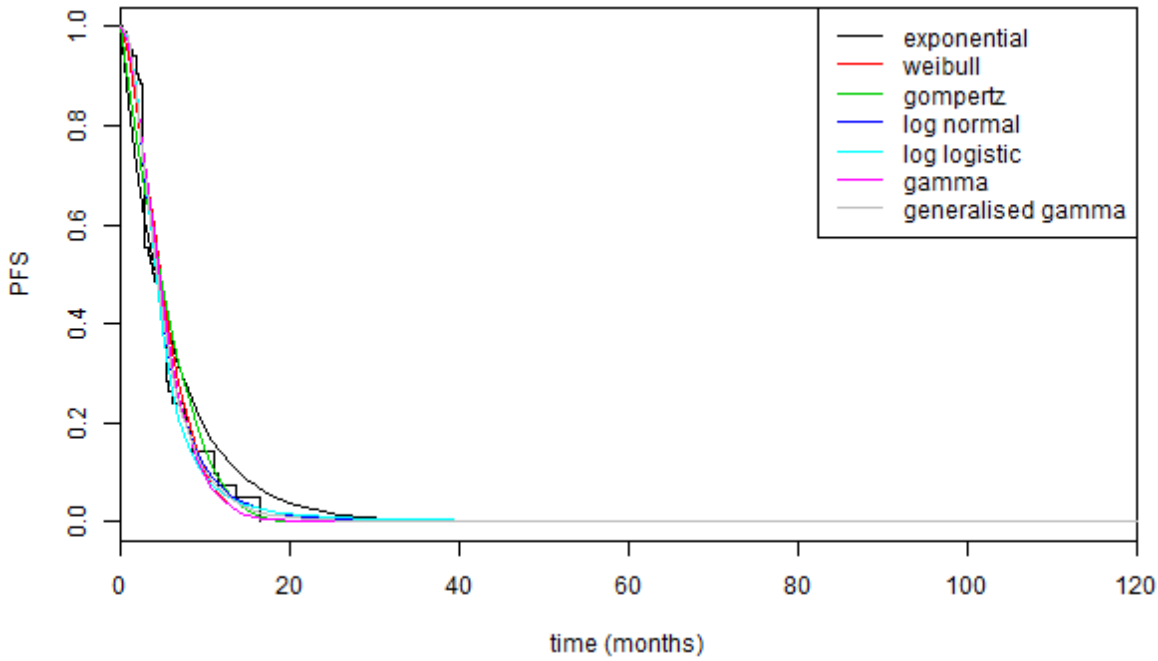


Figure 19: **EXAM ITT population, OS, cabozantinib group (extrapolation up to 20 years)**

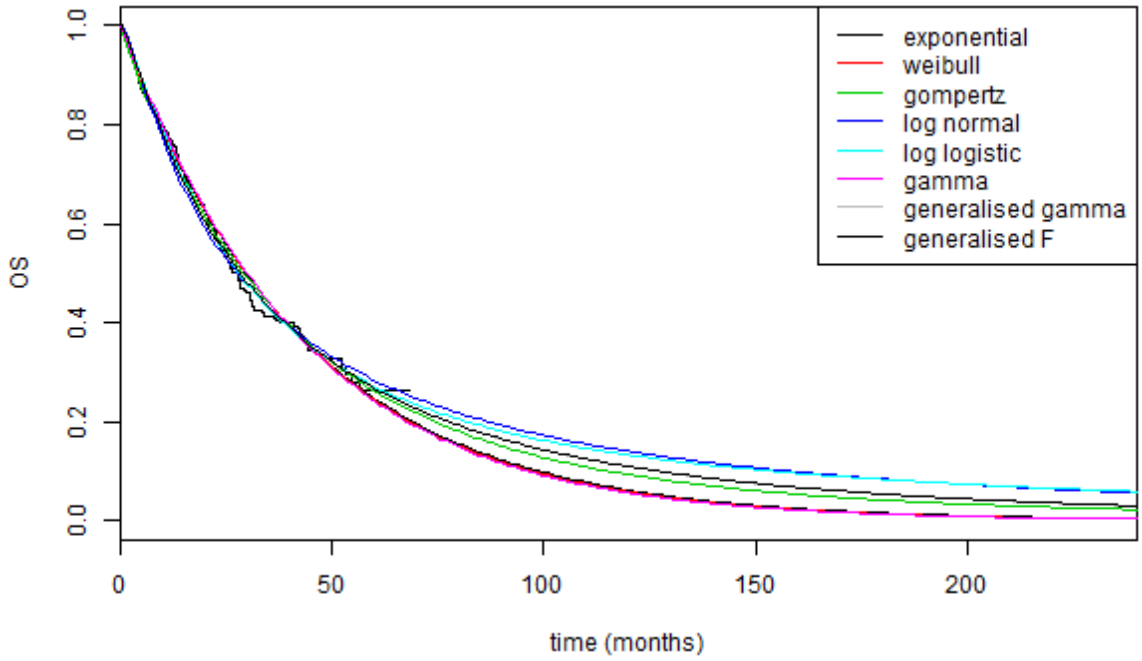
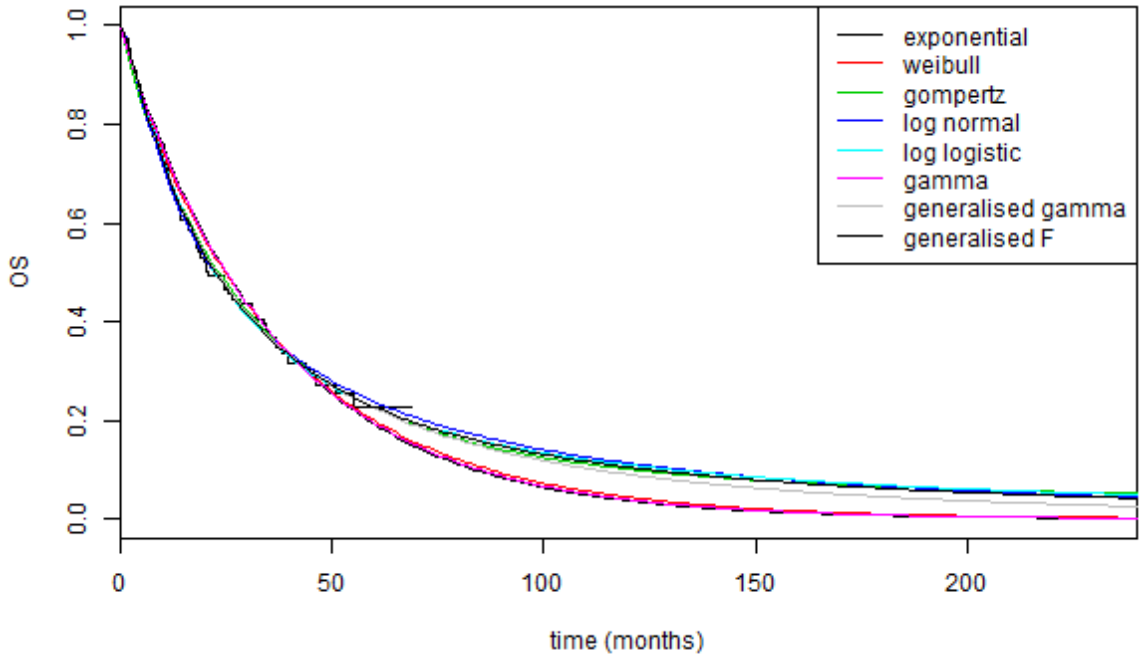


Figure 20: **EXAM ITT population, OS, placebo group (extrapolation up to 20 years)**



Vandetanib versus BSC, ZETA EU label population (used in AG Analysis 2)

PFS

The analysis of PFS for vandetanib versus placebo was based on Kaplan-Meier curves for the EU label population of the ZETA trial (vandetanib N=[redacted], placebo N=[redacted]). The Kaplan-Meier curves provided by Sanofi[41] are presented in Figure 21. The number of observed events was [redacted] in the vandetanib arm and [redacted] in the placebo arm (Sanofi CS appendices,[53] Table 5, page 51). The replicated Kaplan-Meier curves appear consistent with the reported data (see Appendix 3,

Figure 41): the replicated median PFS time of [redacted] months for placebo is close to the value reported from the observed data (median 16.4, N=60 from Kriessl *et al*[40]). Median PFS was not reached for the vandetanib arm.

Log cumulative hazard plots are provided in Appendix 3

Figure 43. Visual inspection of the empirical hazard function indicates that the observed hazard is approximately constant for both trial arms, and visual inspection of the log-log plot of cumulative survival versus time indicates a gradient of approximately 1.0 for the placebo arm, thereby suggesting that the exponential model may be an appropriate model choice.

Measures of comparative internal validity are presented in

Table 39. Plots of the fitted models against the empirical PFS data are presented in Figures in *bold indicate best fitting model (lowest AIC/BIC)*

PFS – progression-free survival; OS – overall survival; AIC – Akaike Information Criterion; BSC – best supportive care

Figure 22 (vandetanib) and

Figure **23** (placebo). For the placebo arm, the exponential model provided the best fit to the observed data according to both AIC and BIC (AIC=296.49, BIC=298.58). For the vandetanib arm, the gamma model provided the best fit to the observed data according to both AIC and BIC (AIC=467.93, BIC=473.66), however differences in the goodness-of-fit statistics across models were generally small, giving little justification to discriminate between models on this basis.

OS

The analysis of OS for vandetanib was based on Kaplan-Meier curves for the EU label population of the ZETA trial (vandetanib N=[redacted], placebo N=[redacted]). The Kaplan-Meier curves provided by the company are shown in

Figure 24; the number of events observed was [redacted] in the vandetanib arm and [redacted] in the placebo arm (Sanofi CS appendices,[53] Table 7, page 53). The replicated Kaplan-Meier curves appear consistent with the reported data (see Appendix 3

Figure 42): the replicated median OS times of [redacted] months for placebo and [redacted] months for vandetanib are close to the estimates reported from the observed data (placebo median=[redacted], vandetanib median=[redacted], from Kreissl *et al*[40] 2014).

Log cumulative hazard plots are provided in Appendix 3

Figure 44. Visual inspection of the empirical hazard function indicates that the observed hazard is approximately constant for both trial arms, and visual inspection of the log-log plot of cumulative survival versus time indicates a gradient of approximately 1.0 for both treatment models, thereby suggesting that the exponential model may be appropriate.

Measures of comparative internal validity are presented in

Table 39. Plots of the fitted models against the empirical Kaplan-Meier OS curves are presented in Figure 25 (vandetanib) and Figure 26 (placebo). For the placebo arm, the exponential model provided the best fit to the observed data (AIC=421.65, BIC=423.73). For the vandetanib arm, the log normal model provided the best fit to the observed data (AIC=847.27, BIC=853.01), however differences in the AIC and BIC were generally small, thereby giving little justification to discriminate between models on this basis.

Figure 21: **ZETA EU label population PFS**

Table 39: **Model fit statistics - ZETA EU label population, individual models for each treatment, PFS and OS**

		Placebo		Vandetanib	
		AIC	**BIC**	**AIC**	**BIC**
PFS	**exponential**	**296.49**	**298.58**	471.89	474.76
	Weibull	298.48	302.67	467.96	473.69
	Gompertz	298.05	302.24	468.95	474.69
	log normal	296.85	301.04	468.52	474.26
	log logistic	296.80	300.99	468.57	474.31
	gamma	298.43	302.62	**467.93**	**473.66**
	generalised gamma	298.76	305.05	469.92	478.53
	generalised F	300.24	308.62	failed to converge	
		AIC	**BIC**	**AIC**	**BIC**
OS	**exponential**	**421.65**	**423.73**	851.75	854.62
	Weibull	422.13	426.29	851.32	857.05
	Gompertz	422.37	426.52	853.57	859.31
	log normal	425.21	429.36	**847.27**	**853.01**
	log logistic	423.24	427.39	847.62	853.36
	gamma	422.21	426.37	850.40	856.14
	generalised gamma	424.11	430.34	849.20	857.80
	generalised F	425.97	434.28	850.91	862.38

Figures in bold indicate best fitting model (lowest AIC/BIC)
PFS – progression-free survival; OS – overall survival; AIC – Akaike Information Criterion; BSC – best supportive care

Figure 22: **ZETA EU label population, vandetanib group, PFS (extrapolation up to 10 years)**

Figure 23: ZETA EU label population, placebo group, PFS (extrapolation up to 10 years)

Figure 24: ZETA EU label population OS

Figure 25: **ZETA EU label population, vandetanib group, OS (extrapolation up to 20 years)**

Figure 26: **ZETA EU label population, placebo group, OS (extrapolation up to 20 years)**

Vandetanib versus BSC, Restricted EU label population, ZETA trial (used in AG Analysis 5)

PFS

The analysis of PFS for vandetanib versus placebo was based on Kaplan-Meier curves for the EU label population of the ZETA trial (vandetanib N=[redacted], placebo N=[redacted]). The provided by Sanofi are shown in Figure 27; the number of progression events observed was [redacted] in the vandetanib arm and [redacted] in the placebo arm. The replicated Kaplan-Meier curves appear consistent with the reported data (see Appendix 3,

Figure 45): the replicated median PFS times of [redacted] months for the placebo arm and [redacted] months for the vandetanib arm are close to the estimates reported from the observed data (placebo median=[redacted] months, vandetanib median=[redacted] months, from Sanofi CS Appendix 6[53]).

Log cumulative hazard plots are presented in Appendix 3,

Figure 46. Measures of comparative internal validity are presented in Table 40. Plots of the fitted models against the empirical Kaplan-Meier OS curves are presented in Figure 28 (vandetanib) and

Figure 29 (placebo). For the placebo arm, the log logistic model provided the best fit to the observed data according to the AIC (89.55), whilst the exponential model provided the best fit according to the BIC (90.54). For the vandetanib arm, the log normal model provided the best fit according the AIC (132.60), whilst the exponential model provided the best fit according to the BIC (134.30), however differences in the AIC and BIC statistics were generally small, thereby giving little justification to discriminate between models on this basis.

OS

The analysis of OS for vandetanib was based on Kaplan-Meier curves for the Restricted EU label population within the ZETA trial (vandetanib N=[redacted], placebo N=[redacted]). The Kaplan-Meier curves provided by Sanofi are shown in

Figure 30; the number of progression events observed was [redacted] in the vandetanib arm and [redacted] in the placebo arm. The replicated Kaplan-Meier curves appear consistent with the reported estimates (see Appendix 3, Figure 47): the median PFS times of [redacted] months for placebo and [redacted] months for vandetanib are close to the estimates reported from the observed data (placebo median=[redacted] months, vandetanib median=[redacted] months, from Sanofi CS Appendix 6[53]).

Log cumulative hazard plots are provided in Appendix 3

Figure 48. Measures of comparative internal validity are presented in Table 40. Plots of the fitted models against the empirical Kaplan-Meier OS curves are presented in

Figure 31 (vandetanib) and

Figure 32 (placebo). For the placebo arm, the Gompertz model provided the best fit to the observed data according to both the AIC and BIC (AIC=150.44, BIC=152.11). For the vandetanib arm, the exponential model provided the best fit to the observed data according to both the AIC and the BIC (AIC=212.75, BIC=214.21).

Figure 27: **ZETA Restricted EU label population PFS**

Table 40: **Model fit statistics, ZETA Restricted EU label population, individual models for each treatment, PFS and OS**

		Placebo		Vandetanib	
		AIC	BIC	AIC	BIC
PFS	exponential	89.71	**90.54**	132.83	**134.30**
	Weibull	91.64	93.31	134.63	137.56
	Gompertz	91.48	93.14	134.79	137.72
	log normal	89.62	91.29	**132.60**	135.53
	log logistic	**89.55**	91.22	133.60	136.53
	gamma	91.43	93.10	134.44	137.38
	generalised gamma	91.57	94.07	133.70	138.10

	generalised F	92.83	96.16	135.70	141.56
		AIC	**BIC**	**AIC**	**BIC**
OS	**exponential**	152.90	153.74	**212.75**	**214.21**
	Weibull	153.02	154.69	214.74	217.67
	Gompertz	**150.44**	**152.11**	214.23	217.16
	log normal	158.84	160.51	212.96	215.89
	log logistic	158.34	160.00	213.19	216.12
	gamma	153.95	155.62	214.68	217.61
	generalised gamma	152.19	154.69	214.92	219.32
	generalised F	154.19	157.52	216.92	222.79

Figures in bold indicate best fitting model (lowest AIC/BIC).
PFS – progression-free survival; OS – overall survival; AIC – Akaike Information Criterion; BSC – best supportive care

Figure 28: **ZETA Restricted EU label population, vandetanib group, PFS (extrapolation up to 20 years)**

Figure 29: **ZETA Restricted EU label population, placebo group, PFS (extrapolation up to 20 years)**

Figure 30: **ZETA restricted EU label population OS**

Figure 31: **Restricted EU label population, vandetanib group, OS (extrapolation up to 20 years)**

Figure 32: **Restricted EU label population, placebo group, OS (extrapolation up to 20 years)**

Combined model used to estimate PFS treatment effect for vandetanib and BSC (used in AG Analysis 3)

The analysis of PFS for vandetanib versus placebo used to inform AG Analysis 3 utilised the Kaplan-Meier curves for the ZETA EU label population (vandetanib N=[redacted], placebo N=[redacted]); these curves were provided by Sanofi and reconstructed by the AG as described in the previous sections.

Visual inspection of the log-log plot of cumulative survival versus time (Appendix 3,

Figure 43) suggests that the proportional hazards assumption may be considered valid for the observed period, and the use of a single model with a treatment indicating covariate is therefore appropriate.

Measures of comparative internal validity are presented in Table 41. The log normal model provided the best fit to the observed data according to both the AIC and BIC (AIC=764.25, BIC=773.99). Figure 33 presents plots of the reconstructed survival data for both the placebo and vandetanib groups.

Table 41: **ZETA EU label model fit statistics and treatment effect estimates (HR or AFT factor) for single parametric models, PFS**

	PH/AFT	model fit		treatment effect		
		AIC	BIC	β	SE(β)	HR/AFT*
exponential	PH	768.38	774.87	[redacted]	[redacted]	[redacted]
Weibull	PH	767.30	777.04	[redacted]	[redacted]	[redacted]
Gompertz	PH	768.80	778.54	[redacted]	[redacted]	[redacted]
log normal	AFT	**764.25**	**773.99**	[redacted]	[redacted]	[redacted]
log logistic	AFT	764.57	774.31	[redacted]	[redacted]	[redacted]
gamma	AFT	766.55	776.29	[redacted]	[redacted]	[redacted]
generalised gamma	AFT	766.09	779.08	[redacted]	[redacted]	[redacted]

β : coefficient on analysis scale. Figures in bold indicate best fitting model (lowest AIC/BIC).
AIC – Akaike Information Criterion; BSC – best supportive care; PH – proportional hazards; AFT – accelerated failure time; SE – standard error; HR – hazard ratio

Figure 33: **PFS ZETA EU label population, joint model, extrapolation up to 10 years. Solid line- placebo, dashed line- intervention**

Within the health economic model, the treatment effect covariate (shown in Table 41) is applied to the baseline model (taken to be the placebo arm in the EXAM trial ITT population) in order to approximate the absolute effect for a vandetanib treatment group in the chosen baseline population.

For parametric models in the proportional hazards family (exponential, Weibull, Gompertz), the estimated treatment effect represents an HR. For parametric models in the accelerated failure time family (log normal, log logistic, gamma, generalised gamma and generalised F), the estimated treatment

effect represents an acceleration factor (AF). These parameters are applied to the survivor function of the baseline PH/AFT model as follows.

PH models

Given a survivor function for the placebo arm, $S_P(t)$, and an HR r for treatment (vandetanib) compared with placebo, the survivor function for the vandetanib arm, $S_V(t)$, is obtained using:

$$S_V(t) = S_P(t)^r.$$

Further detail can be found in Collett *et al*.[103]

AFT models

Given an acceleration factor of θ in the treatment arm (vandetanib) compared with placebo, the survivor function for the vandetanib arm is given by:

$$S_V(t) = S_P(\theta t)$$

where, $\theta = \exp(-\beta x)$ and β is the coefficient on the analysis scale. Applying the coefficients presented in Table 41, we have $\boldsymbol{S_V(t) = S_P}(\exp(-\beta x)\, \boldsymbol{t})$**.** If $\theta > 1$, then events in the treatment arm happen more quickly than in the control arm (assuming a negative outcome, this favours the control). If $\theta < 1$, then events in the treatment arm happen less quickly than in the control arm (assuming a negative outcome, this favours the treatment).

Model selection

The clinical plausibility of the competing survivor functions for each analysis was assessed using clinical opinion. Clinical advisors were asked to select their preferred model(s) on the basis of visual fit to the data within the observed trial period and the clinical plausibility of the extrapolated portion of each curve. Clinicians were allowed to select more than one preferred model and were asked to provide justification for their preferences. The responses from the first clinical advisor are presented in

Table 42. The second clinical advisor felt unable to complete the model selection exercise. The Assessment group's selected base case survivor functions for each analysis are presented in

Table 43.

Table 42: **Clinical advisor's preferred survivor functions**

Population	Advisor #1 (JW)	
	Preferred curve	**Justification**
EU label population: Symptomatic and progressive MTC		
EXAM ITT, PFS, cabozantinib	Log logistic	*"There is a tail to account for small proportion of patients with extended PFS but best fit at earlier time points"*
EXAM ITT, PFS, placebo	Log logistic	*"Appears to most closely fit observed data"*
EXAM ITT, OS, cabozantinib	Log logistic or log normal	*"Good fit with observed data at early time points and both allow for a small proportion of long term survivors"*
EXAM ITT, OS, placebo	Gompertz, log logistic or log normal	*"All have good fit at early time points and allow for possibility of long term survival for a small number of patients"*
ZETA EU label, PFS, vandetanib	Log logistic	*"Good fit at early time points and allows for a small proportion of long term PFS patients"*
ZETA EU label, PFS, placebo	Log logistic, log normal, Gompertz	*"Good fit at early time points and allow for small proportion of patients without progression at later time points"*
ZETA EU label, OS, vandetanib	Log normal or log logistic	*"Appears to give best fit to early data"*
ZETA EU label, OS, placebo	Log logistic	*"Good fit with early data and allows for a small proportion of long term survivors"*
Restricted EU label population: Symptomatic and progressive MTC with CEA/CTN doubling time≤24 months		
ZETA EU label, PFS, vandetanib	Log logistic, log normal and Gompertz	*"Allow for a small but realistic proportion of long term survivors - too many long term PF patients with exponential model"*
ZETA EU label, PFS, placebo	log normal, log logistic, Gompertz	*"Close fit to early data and realistic, small number of longer term PF survivors"*
ZETA EU label, OS, vandetanib	Log logistic, log normal, Gompertz	*"Good fit with early data and realistic number of longer term survivors"*
ZETA EU label, OS, placebo	Gompertz	*"Closest fit to early data and realistic upper limit of 100 months OS for this poor prognosis group"*

MTC – medullary thyroid cancer; ITT – intention-to-treat; PFS – progression-free survival; OS – overall survival

Table 43: **Survivor functions used in Assessment Group base case analysis**

Population	Selected curve	Justification
Cabozantinib versus BSC, EXAM ITT population (used in AG Analyses 1, 3 and 4)		
EXAM ITT, PFS, cabozantinib	Log logistic	Selected based on clinical justification of long-term survivors. The AIC and BIC for the log logistic function are higher than the best fitting model (Weibull). It should be noted that outcomes predicted by the log logistic function are more favourable than those of the Weibull model.
EXAM ITT, PFS, placebo	Log logistic	Selected based on clinical opinion and on the basis of consistency with model used for the intervention group. There is a cluster of models which appear to provide a very similar visual fit to the data during the observed period of the trial. The log logistic is also the best fitting model in terms of the AIC and BIC.
EXAM ITT, OS, cabozantinib	Log logistic	Log logistic and log normal provide a similar fit. The log logistic is the best fitting model in terms of the AIC (the exponential provides the best fit according to the BIC).
EXAM ITT, OS, placebo	Log logistic	Clinician's selected models (log logistic, Gompertz and log normal) all provide a similar visual fit to the data. Log logistic is the best fitting model in terms of AIC and is consistent with the choice of model used for the intervention group.
Vandetanib versus BSC, ZETA trial, EU label population (used in AG Analysis 2)		
ZETA EU label, PFS, vandetanib	Log logistic	Reflects clinician's choice, justified in terms of proportion of long-term survivors. The gamma model gives the best fit in terms of both AIC and BIC but the log logistic is very similar.
ZETA EU label, PFS, placebo	Log logistic	Clinicians' choices (log logistic, log normal and Gompertz) are within a cluster of very similar models. The log logistic model does not provide the best AIC or BIC (the best-fitting model is the exponential), however the differences between the three candidate curves are small. Log logistic model selected on basis of consistency with the intervention arm.
ZETA EU label, OS, vandetanib	Log logistic	Of the two candidate curves (log logistic and log normal), the log normal model provides best fit to observed data. Log logistic model selected for consistency with the comparator arm and is very similar in terms of AIC/BIC.
ZETA EU label, OS, placebo	Log logistic	Reflects clinician's choice, justified in terms of proportion of long-term survivors.
Vandetanib versus BSC, ZETA trial, Restricted EU label population (used in AG Analysis 5)		
ZETA Restricted EU label, PFS, vandetanib	Log normal	Predicted outcomes are very similar for all three candidate models (log logistic, log normal and Gompertz). Log normal model selected due to best AIC.
ZETA Restricted EU label, PFS, placebo	Log normal	Log normal selected for consistency with the intervention arm, and very similar to log logistic model in terms of AIC.
ZETA Restricted EU label, OS, vandetanib	Gompertz	Selected on basis of consistency with comparator arm.
ZETA Restricted EU label, OS, placebo	Gompertz	Models selected on basis of clinical justification (proportion of long-term survivors). Gompertz model has best AIC/BIC.

ITT – intention-to-treat; PFS – progression-free survival; OS – overall survival; AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion

6.2.3.3 Health-related quality of life

The Assessment Group's systematic searches for HRQoL evidence identified only one published study which reports health utilities for states of progression-free and post-progression in patients with thyroid cancer (Fordham *et al*[87]). Within this study, the authors developed vignettes for seven health states based on the results of a previous qualitative study in differentiated thyroid cancer.[104] These states included: (i) stable/no response; (ii) response (partial and complete); (iii) progressive disease; (iv) stable/no response with Grade 3 diarrhoea; (v) stable/no response with Grade 3 fatigue; (vi) stable/no response with Grade 3 HFS, and; (vii) stable/no response with Grades 1 and 2 alopecia. One hundred members of the UK general public participated in time trade-off (TTO) interviews to value the defined health states. Utility scores were estimated directly from the raw interview response data and using regression analyses. The results of the TTO valuations are presented in Table 44.

Table 44: **Utility values reported by Fordham *et al*[87]**

Health state	Observed mean utility*		Unadjusted†		Adjusted‡	
	Mean utility (s.d.)	95% CI	Utility value	95% CI	Utility value	95% CI
Best state – stable/no response	0.80 (0.19)	0.77, 0.84	0.86	0.83, 0.90	0.87	0.84, 0.91
Response to therapy	0.86 (0.15)	0.83, 0.89	+0.04	0.01, 0.07	+0.4	0.01, 0.07
Progressive disease	0.50 (0.28)	0.45, 0.56	-0.37	-0.43, -0.31	-0.35	-0.41, -0.29
Diarrhoea	0.42 (0.29)	0.36, 0.48	-0.48	-0.54, -043	-0.47	-0.52, -0.41
Fatigue	0.72 (0.24)	0.67, 0.77	-0.08	-0.13, -0.04	-0.08	-0.12, 0.04
Hand and foot syndrome	0.52 (0.30)	0.46, 0.58	-0.35	-0.42, -0.29	-0.34	-0.40, 0.028
Alopecia	0.75 (0.21)	0.71, 0.79	-0.05	-0.09, -0.01	-0.05	-0.08, 0.01

** Mean observed TTO health state utilities.*
† Derived from reduced parameter model (health states only)
‡ Adjusted for educational qualification level and EQ-5D-3L (usual activities and anxiety/depression) ratings using UK norms.
s.d. – standard deviation; CI – confidence interval

Owing to the lack of published evidence relating to the HRQoL associated with thyroid cancer states, the Assessment Group also explored the health utility values considered within previous thyroid cancer drug submissions to the SMC and the AWMSG.

Table 45 summarises the health utilities assumed within these submissions.

Table 45: **Health utility values applied in other UK thyroid cancer submissions**

Body	Drug	Indication	Health utility values
SMC	Lenvatinib[105]	Adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine	Derived from Fordham *et al*.[87] Stable disease 0.80 Response: 0.86 Progressive disease: 0.50 Utility decrements of -0.042 for lenvatinib and -0.117 for sorafenib applied for AEs (diarrhoea, fatigue, hand and foot syndrome, alopecia)
SMC	Sorafenib[106]	Patients progressive, locally advanced or metastatic, differentiated thyroid carcinoma, refractory to radioactive iodine	Utilities derived from EQ-5D data from DECISION study:[107] Sorafenib, progression-free: 0.72 BSC, progression-free: 0.80 Post-progression (both groups): 0.64
SMC	Cabozantinib[108]	Adult patients with progressive, unresectable locally advanced or metastatic MTC	Published trial data in thyroid cancer (not specified) in which SF-36 outcomes had been converted to utilities by mapping to EQ-5D and converting to SF-6D values for the non-progressed and progressed states. Progression-free: 0.796 Post-progression: 0.624
AWMSG	Vandetanib[109]	Patients with aggressive and symptomatic unresectable locally advanced or metastatic MTC	FACT-G scores collected in the ZETA study mapped to TTO values. Pre- and post-progression utility values not reported. Disutilities for AEs based on Beusterien *et al*[90] (values of −0.11 and −0.13 assumed)
AWMSG	Cabozantinib[110]	Adult patients with progressive, unresectable, locally advanced or metastatic MTC	For the base case analysis, utility values were taken from two published studies in thyroid cancer, albeit in patients with less severe disease than the progressive MTC population (sources and values not specified). Utility decrements for AEs were derived from the published literature (also not specified).

SMC – Scottish Medicines Consortium; AWMSG – All Wales Medicines Strategy Group; EQ-5D – Euroqol 5-Dimensions; SF-6D – Short Form 6-Dimensions; AE – adverse event; TTO – time trade-off; MTC – medullary thyroid cancer

The health utilities assumed in the Assessment Group base case analysis are summarised in Table 46. Health utilities associated with the absence/presence of disease progression were based on the study reported by Fordham *et al* as this study specifically relates to thyroid cancer states and health utilities were valued using a preference-based measure (TTO).[87] The disutility associated with Grade 3/4 AEs was based on the lower value reported by Beusterien *et al*[90] (disutility=-0.11). Uncertainty surrounding these parameters was modelled using beta distributions. Alternative utility values based on the cabozantinib the sorafenib SMC submissions[106, 108] are explored within the sensitivity analyses.

Table 46: **Health utilities used in Assessment Group model**

Health state	Mean (95% CI)	Beta distribution parameters		Source
		α	β	
Progression-free	0.80 (0.77, 0.84)	400.61	100.15	
Post-progression	0.50 (0.45, 0.56)	158.24	158.24	Fordham *et al*[87]
Disutility AEs	-0.11 (s.e.=0.02)	26.81	216.94	Beusterien *et al*[90]

AE – adverse event

6.2.3.4 Adverse event rates

The probability of experiencing Grade 3/4 AEs was taken directly from the EXAM and ZETA trial publications (each based on the ITT study populations, see Table 47).[27, 28] Within the incremental comparisons (AG Analyses 3 and 4), the AE rates for the BSC group were assumed to reflect those observed in the placebo group of the EXAM trial. AEs were assumed to have a duration of 1 month.

Table 47: **Grade 3/4 adverse event rates assumed in the Assessment Group model**

Treatment group	Pairwise comparison – cabozantinib versus BSC (AG Analysis 1)	Pairwise comparison – vandetanib versus BSC (AG Analyses 2 and 5)	Incremental comparisons – all options (AG Analyses 3 and 4)
Cabozantinib	0.94	n/a	0.94
Vandetanib	n/a	0.45	0.45
Placebo	0.24	0.14	0.24

BSC – best supportive care

6.2.3.5 Treatment switching/continuation parameters (AG Analyses 2 and 5 only)

As noted in Section 6.1.3.1, Sanofi applied the RPSFT approach in an attempt to adjust for the high level of treatment switching which occurred within the ZETA trial.[35] However, the company's attempts were reported to have been unsuccessful, hence the available OS data for vandetanib which are used in the pairwise comparisons of vandetanib versus BSC in the symptomatic and progressive MTC population and the Restricted EU label MTC population remain subject to potential confounding (AG Analyses 2 and 5). In order to allow for a fairer comparison, the Assessment Group included the costs associated with treatment switching and vandetanib continuation post-progression in the pairwise analyses of vandetanib versus BSC. The number of patients who received vandetanib post-progression in each arm of each subgroup of the ZETA trial was provided by Sanofi (see

Table 48).

Table 48: **Proportion of patients who switched to vandetanib or continued vandetanib post-progression**

Parameter	EU label population: Symptomatic and progressive MTC			Restricted EU label population: Symptomatic and progressive MTC with CEA/ CTN doubling time ≤24 months		
	Proportion	Continued PP	Not continued PP	Proportion	Continued PP	Not continued PP
Proportion vandetanib group continuing vandetanib PP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion BSC group switching to vandetanib PP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MTC – medullary thyroid cancer; CEA – carcinoembryonic antigen; CTN – calcitonin; BSC – best supportive care PP – post-progression

6.2.3.6 Resource use and costs

Drug acquisition

Table 49 presents the drug acquisition costs for cabozantinib and vandetanib based on their current list prices.[96] As shown in the table, the cost of cabozantinib is the same for all dose packs. Both vandetanib and cabozantinib have separate agreed PAS schemes. The results of the Assessment Group's economic analysis including the PAS discounts for vandetanib and cabozantinib are presented in a confidential appendix to this report (see Confidential Appendix 5).

Table 49: Drug acquisition costs – vandetanib and cabozantinib

Item	Price per pack	Annual cost at full dose
Cabozantinib 84 x 20mg capsules (2 level dose reduction)	£4,800.00	£62,614.29
Cabozantinib 28 x 20 mg and 28 x 80mg combination (1 level dose reduction)	£4,800.00	£62,614.29
Cabozantinib 84 x 20 mg and 28 x 80mg combination (full dose)	£4,800.00	£62,614.29
Vandetanib 30 x 300mg tab	£5,000.00	£60,875.00
Vandetanib 30 x 100mg tab	£2,500.00	£30,437.50

mg – milligram

6.2.3.7 Time spent receiving cabozantinib and vandetanib

Table 50 presents the proportion of PFS time spent receiving each dose of cabozantinib within the EXAM trial.[97] Table 51 presents the proportion of PFS time spent receiving each dose of vandetanib within the ZETA trial subgroups.[35,41] As these data are multinomial in nature, uncertainty was modelled using a Dirichlet distribution with minimally informative priors.

Table 50: **Cabozantinib – proportion of PFS time spent at dose level**

Dose	Mean proportion	Dirichlet parameters	
		Days on dose	Total PFS days
Cabozantinib 140mg	[redacted]	[redacted]	[redacted]
Cabozantinib 100mg	[redacted]	[redacted]	[redacted]
Cabozantinib 60mg	[redacted]	[redacted]	[redacted]
Cabozantinib interrupted dose	[redacted]	[redacted]	[redacted]

PFS – progression-free survival; mg – milligram

Table 51: **Vandetanib – proportion of PFS time spent at dose level**

Dose	Mean proportion	Dirichlet parameters	
		Days on dose	Total PFS days
EU label population: Symptomatic and progressive MTC			
Vandetanib 300mg	0.73	76,994.70	106105.13
Vandetanib 200mg	0.13	13,806.45	106105.13
Vandetanib 100mg	0.13	13,550.78	106105.13
Vandetanib interrupted dose	0.02	1,753.20	106105.13
Restricted EU label population: Symptomatic and progressive MTC with CEA/CTN doubling time≤24 months			
Vandetanib 300mg	0.66	13,769.93	20,746
Vandetanib 200mg	0.17	3,433.35	20,746
Vandetanib 100mg	0.15	3,214.20	20,746
Vandetanib interrupted dose	0.02	328.73	20,746

PFS – progression-free survival; mg – milligram

The model also includes a further parameter to reflect those patients who discontinued vandetanib prior to disease progression ([redacted] in the Restricted EU label population and 22.31% in the broader EU label population). Whilst these patients could have discontinued treatment at any time, assuming that they incur no drug costs (i.e. discontinued at Day 0) is likely to bias the model in favour of vandetanib (see Section 6.1.3.6, critical appraisal point 4). In contrast to the assumption taken within the Sanofi model, the Assessment Group assumed that these patients incur half of the total cost of vandetanib during the progression-free phase (hence the discontinuation parameter was divided by two). Uncertainty surrounding this parameter was modelled using a beta distribution.

6.2.3.8 Cost of managing Grade 3/4 AEs

The cost associated with managing Grade 3/4 AEs was assumed to require a single non-elective bed day. The unit cost per AE was assumed to reflect the weighted mean cost of a non-elective excess bed day, based on the NHS Reference Costs 2015/16[91] (mean cost=£298.41). Uncertainty surrounding this parameter was modelled using a normal distribution, assuming that the standard error was equal to 15% of the mean (s.e.=£44.76).

6.2.3.9 BSC costs

Resource use for patients receiving cabozantinib, vandetanib and BSC was estimated using expert opinion (see Table 52 and Table 53). Clinical advice received by the Assessment Group suggested that

the resource use associated with BSC is likely to be the same for both the pre-progression and post-progression states as these patients have, by definition, progressed disease. Conversely, total health state resource use associated with cabozantinib and vandetanib was assumed to be time-dependent in order to account for the monitoring requirements associated with the TKIs. With respect to the pairwise comparisons of vandetanib versus BSC (AG Analyses 2 and 5), patients who switch from BSC to vandetanib post-progression are assumed to incur the "subsequent years" costs for vandetanib; this assumption was also made in the Sanofi model.

One clinical expert (JW) provided resource use estimates (central estimates, minimums and maximums); these were then verified and augmented with additional components by a second clinical expert (LM). As the elicited information relates to ranges and some of the distributions are highly skewed, uncertainty surrounding these parameters was represented using triangular distributions. The experts' central estimates were taken to be the mode of the distribution; means were calculated as (*lower limit+mode+upper limit*)/3. The number of ECGs, CT scans, and blood tests were not associated with uncertain ranges and were thus held as fixed values within the probabilistic analysis.

Table 52: **Annual BSC resource use included in the Assessment Group model**

Resource item	**Visits/items per year**
	Progression-free and post-progression states
Consultant outpatient visits	6 (2-12)
CT scans	2 (0-4)
MRI scan	1 (0-2)
Community palliative care support	12 (0-20)
Palliative radiotherapy	2 (fixed)
Bisphosphonates for bone metastases	0.6 (fixed)*
Palliative surgery	0.03 (fixed)

** Assumed to reflect monthly IV regimen for 5% of patients, also costed to include outpatient visit*
CT – computerised tomography; MRI – magnetic resonance imaging

Table 53: **Total annual health state resource use for cabozantinib and vandetanib included in the Assessment Group model**

Resource item	**Cabozantinib**		**Vandetanib**	
	Year 1	**Subsequent years***	**Year 1**	**Subsequent years***
Consultant-led outpatient visits	12 (4-16)	6 (4-12)	12 (4-16)	6 (4-12)
Nurse-led outpatient visits	4 (0-6)	6 (0-6)	4 (0-6)	6 (0-6)
ECG	0	0	12	6
Blood tests	12	6	12	6
CT scan	4	4	4	4

** AG Analysis 2 and 5 – subsequent years costs applied to patients receiving vandetanib in the post-progression state irrespective of time since model entry*
ECG – electrocardiogram

6.2.3.10 Cost of palliative care

The costs associated with palliative care and palliative chemotherapy are applied at the point of death to all patients. These costs were based on the same data used in the Sanofi model,[35] which were, in turn, derived from the NHS Reference Costs 2015/16[91] and the PSSRU.[92] A total cost of £6,602.52 is applied per patient.

6.2.3.11 Unit costs

Table 54 summarises the unit costs included in the Assessment Group model.

Table 54: **Unit costs applied in the Assessment Group model**

Unit	Cost	Standard error	Source
Consultant-led outpatient visit (medical oncology)	£162.84	£6.48	NHS Reference Costs 2015/16,[91] Consultant-led, non-admitted face to face attendance, follow-up WF01A
Nurse-led outpatient (medical oncology)	£99.97	£8.46	NHS Reference Costs 2015/16,[91] Non-consultant-led, non-admitted face to face attendance, follow-up, WF01A
CT scan	£136.50	£7.13	NHS Reference Costs 2015/16,[91] Outpatient, complex CT scan, RD28Z
MRI scan	£161.93	£3.68	NHS Reference Costs 2015/16[91] Outpatient, MRI scan of two or three areas, without contrast, RD04Z
ECG	£207.98	£29.16	NHS Reference Costs 2015/16,[91] outpatient (medical oncology), electrocardiogram monitoring or stress testing, EY51Z
Blood test	£3.37	£0.26	NHS Reference Costs 2015/16,[91] directly accessed pathology, phlebotomy, DAPS08
Palliative care nurse visit	£91.83	£4.81	NHS Reference Costs 2015/16,[91] specialist nursing, palliative/respite care, adult, face to face, N21AF
Palliative radiotherapy (per fraction)	£104.77	£7.47	NHS Reference Costs 2015/16,[91] outpatient, deliver a fraction of treatment on a megavoltage machine, SC22Z
Palliative surgery	£3,363.82	£70.08	NHS Reference Costs 2015/16,[91] elective inpatient, thyroid procedures with CC score 0-1, KA09E
Bisphosphonates for bone metastases (4mg/100ml infusion bags)*	£150.00	n/a	BNF[96] Zerlinda 4mg/100ml infusion bags (Actavis UK Ltd)
Palliative care (last month of life)	£5,775.52	£866.33†	PSSRU[92] palliative care costs (assumes equal weighting between child and adult inpatient and outpatient)
Palliative chemotherapy (last month of life)	£827.00	£124.05†	Sanofi CS[35] (based on NHS Reference Costs 2015/16,[91] other, procure chemotherapy drugs for regimens in band 1-10, SB01Z-SB10Z
Cost managing AEs	£298.41	£44.76†	NHS Reference Costs 2015/16,[91] weighted mean of all non-elective excess bed days, AA22C-YR55Z

** Assumed to be given during additional outpatient appointment; † s.e. assumed to be 15% of mean*
ECG – electrocardiogram; CT – computerised tomography; MRI – magnetic resonance imaging; AE – adverse event

6.2.4 Model evaluation methods

Uncertainty was evaluated using PSA and DSA. PSA was undertaken using simple Monte Carlo sampling methods (2,000 samples). The choice of distribution assumed for each parameter group is summarised in Table 55. The results of the PSA are presented as CEACs. DSAs were undertaken to explore the impact of alternative assumptions regarding discount rates, choices of parametric survivor functions, disutilities associated with AEs, and resource use and cost assumptions.

Table 55: **Distributions used in probabilistic sensitivity analysis**

Parameter group	Distribution	Comments
Time to event outcomes (PFS and OS)	Normal/multivariate normal	Sampled via Cholesky decomposition using variance-covariance matrices for each parametric model.
Vandetanib PFS treatment effect (AG Analysis 3 only)	Normal (log scale)	Treatment effect parameters (HRs and acceleration factors) derived from joint models fitted to ZETA subgroup data
Grade 3/4 AE rates	Beta	Distribution parameters based on total number of AEs reported in ITT population
Vandetanib switching/continuation parameters	Beta	Distribution parameters based on numbers continuing/not continuing in ZETA subgroups
Health state utilities	Beta	Derived using method of moments
Disutility for Grade 3/4 AEs	Beta	Derived using method of moments
Drug dose distributions for cabozantinib and vandetanib	Dirichlet	Includes minimally informative priors, specified in days
Proportion of patients discontinuing vandetanib prior to progression	Beta	Distribution parameters based on observed data for ZETA subgroups
BSC resource use (outpatient visits, CT scans, MRI scans and community palliative care support)*	Triangular	Distribution selected to reflect expert's beliefs.
Vandetanib and cabozantinib health state resource use†	Triangular	Distribution selected to reflect expert's beliefs
Drug acquisition costs	Fixed	-
Unit costs	Normal	s.e. derived from interquartile ranges
Palliative care costs	Normal	s.e. assumed to be 15% of mean
AE costs	Normal	s.e. assumed to be 15% of mean

** IV bisphosphonates, palliative radiotherapy and palliative surgery held fixed*
† Resources related to monitoring held fixed (ECGs, CT scans and blood tests)
PFS – progression-free survival; OS – overall survival; AE – adverse event; BSC – best supportive care; CT – computerised tomography; MRI – magnetic resonance imaging; HR – hazard ratio; ITT – intention-to-treat; s.e. – standard error

6.2.5 Model validation

The Assessment Group adopted a number of approaches to ensure the credibility of the model. These included: scrutiny of the implemented model coding and formulae by two modellers, black box testing, double-programming of the deterministic base case for all pairwise comparisons, checking the accuracy

of all model inputs against the original sources, consultation with clinical experts, peer review of the model assumptions by clinical experts and peer review of the report by two third-party modellers (see acknowledgements).

6.2.6 Assessment Group model results

This section presents the results based on the Assessment Group model for each of the five sets of analyses.

Analysis 1: EU label population (symptomatic and progressive MTC), cabozantinib versus BSC (pairwise)

Table 56 presents the results of the pairwise comparison of cabozantinib versus BSC within the EU label (symptomatic and progressive) MTC population. Disaggregated life years gained (LYGs), QALYs and costs are presented in

Table 57. Based on the probabilistic version of the Assessment Group's model (assuming the log logistic function for both PFS and OS), cabozantinib is expected to generate 0.48 additional QALYs at an additional cost of £72,734 compared with BSC; the ICER for cabozantinib versus BSC is expected to be £150,874 per QALY gained. The deterministic version of the model (based on point estimates of parameters) produces similar results (deterministic ICER=£148,169 per QALY gained). The disaggregated results show that a considerable amount of the OS gain in both groups is accrued in the post-progression state.

Table 56: **Analysis 1, EU label population (symptomatic and progressive MTC), cabozantinib versus BSC (pairwise), central estimates of cost-effectiveness (PFS=log logistic, OS=log logistic for both options)**

Probabilistic model					
Option	**QALYs**	**Costs**	**Inc. QALYs**	**Inc. costs**	**ICER**
Cabozantinib	2.28	£88,527	0.48	£72,734	**£150,874**
BSC	1.79	£15,793	-	-	-
Deterministic model					
Cabozantinib	2.27	£87,960	0.49	£72,287	**£148,169**
BSC	1.79	£15,672	-	-	-

Inc. – incremental; BSC – best supportive care; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

Table 57: Analysis 1, EU label population (symptomatic and progressive MTC), cabozantinib versus BSC (pairwise), disaggregated LYGs, QALYs and costs

Outcomes (undiscounted)	Cabozantinib	BSC
LYGs	4.49	3.91
LYGs in progression-free state	1.39	0.45
LYGs in post-progression state	3.10	3.46
Total QALYs	2.66	2.09
Total QALYs in progression-free state	1.10	0.36
Total QALYs in post-progression state	1.55	1.73
Total cost	£95,307	£18,063
Total cost in progression-free state	£79,788	£1,417
Total cost in post-progression state	£15,519	£16,647
Modelled probability alive at 20-years	0.06	0.05

BSC – best supportive care; LYG – life year gained; QALY – quality-adjusted life year

Figure 34 presents incremental CEACs for the pairwise comparison of cabozantinib versus BSC within the EU label (symptomatic and progressive) MTC population. Assuming a WTP threshold (λ) of £30,000 per QALY gained, the probability that cabozantinib produces more net benefit than BSC is zero.

Figure 34: Analysis 1, EU label population (symptomatic and progressive MTC), cabozantinib versus BSC (pairwise), cost-effectiveness acceptability curves (PFS=log logistic, OS=log logistic for both options)

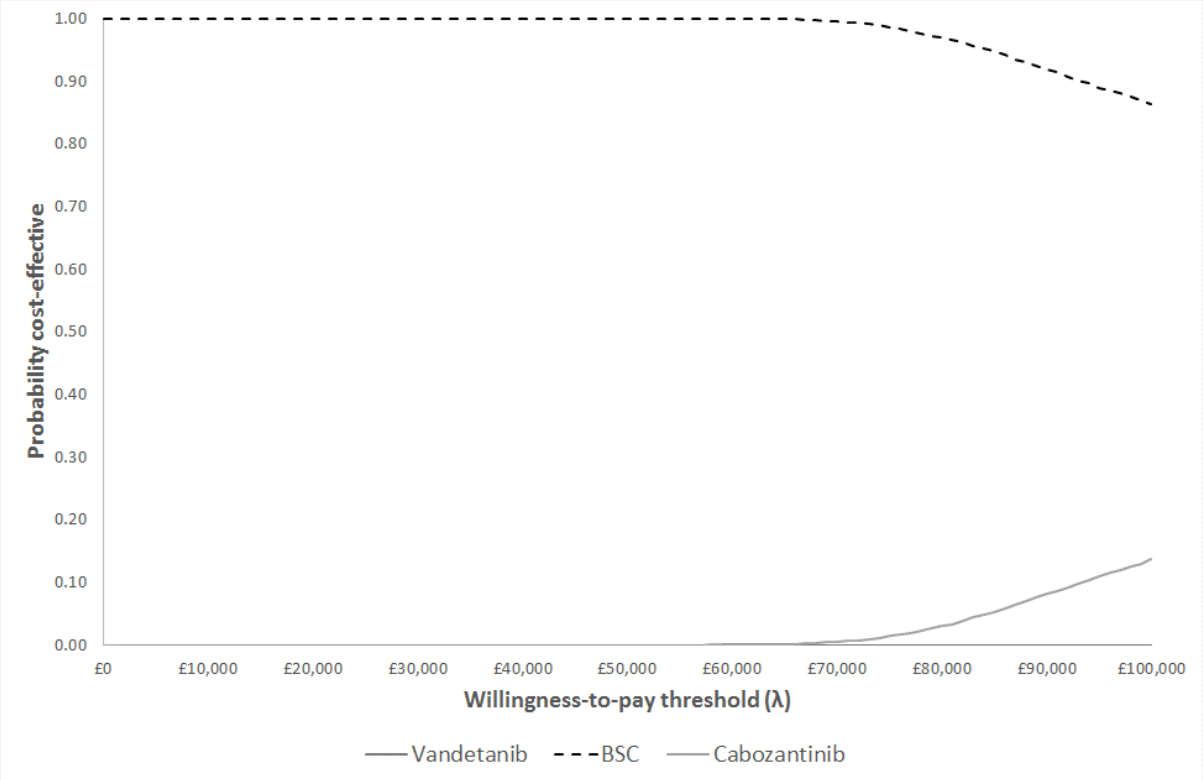


Table 58 presents the results of the DSAs for the pairwise comparison of cabozantinib versus BSC within the EU label (symptomatic and progressive) MTC population. As shown in the table, the ICER remains in excess of £135,000 per QALY gained across all scenarios. The alternative scenarios regarding health utilities, AE impacts and health state resource use do not have a marked impact upon the cost-effectiveness of cabozantinib. The exclusion of dose reductions for cabozantinib increases the ICER to £174,297 per QALY gained. The choice of survivor functions for PFS and OS produces ICERs for cabozantinib versus BSC in the range £138,259 to £239,141 per QALY gained; the curves used in the Assessment Group base case analysis (PFS=log logistic, OS=log logistic) are close to the most favourable scenario.

Table 58: **Analysis 1, EU label population (symptomatic and progressive MTC), cabozantinib versus BSC (pairwise), deterministic sensitivity analysis results**

Scenario	Inc. QALYs	Inc. costs	ICER
Base case	0.49	£72,287	£148,169
Undiscounted health outcomes and costs	0.57	£77,243	£135,531
Sanofi CS utilities	0.47	£72,287	£154,582
DECISION study utilities	0.43	£72,287	£166,890
Cabozantinib SMC utilities	0.44	£72,287	£165,816
AE disutility doubled	0.48	£72,287	£150,159
AE disutility halved	0.49	£72,287	£147,194
AE management costs doubled	0.49	£72,498	£148,601
AE management costs halved	0.49	£72,182	£147,954
Health state resource use doubled	0.49	£72,959	£149,546
Health state resource use halved	0.49	£71,951	£147,481
No cabozantinib dose reductions	0.49	£85,034	£174,297
Curve choice: PFS - exponential; OS - exponential	0.45	£71,195	£158,030
Curve choice: PFS - exponential; OS - Weibull	0.42	£71,012	£170,550
Curve choice: PFS - exponential; OS - Gompertz	0.31	£70,525	£227,293
Curve choice: PFS - exponential; OS - log normal	0.47	£71,298	£150,146
Curve choice: PFS - exponential; OS - log logistic	0.46	£71,251	£153,284
Curve choice: PFS - exponential; OS - gamma	0.43	£71,061	£166,964
Curve choice: PFS - Weibull; OS - exponential	0.38	£55,213	£147,111
Curve choice: PFS - Weibull; OS - Weibull	0.34	£55,035	£161,300
Curve choice: PFS - Weibull; OS - Gompertz	0.24	£54,530	£232,034
Curve choice: PFS - Weibull; OS - log normal	0.40	£55,345	£138,424
Curve choice: PFS - Weibull; OS - log logistic	0.39	£55,297	£141,864
Curve choice: PFS - Weibull; OS - gamma	0.35	£55,093	£157,191
Curve choice: PFS - Gompertz; OS - exponential	0.36	£52,776	£147,369
Curve choice: PFS - Gompertz; OS - Weibull	0.32	£52,593	£162,336
Curve choice: PFS - Gompertz; OS - Gompertz	0.22	£52,105	£239,141
Curve choice: PFS - Gompertz; OS - log normal	0.38	£52,879	£138,259
Curve choice: PFS - Gompertz; OS - log logistic	0.37	£52,831	£141,855
Curve choice: PFS - Gompertz; OS - gamma	0.33	£52,642	£157,984
Curve choice: PFS - log normal; OS - exponential	0.46	£70,719	£152,833
Curve choice: PFS - log normal; OS - Weibull	0.43	£70,551	£164,542
Curve choice: PFS - log normal; OS - Gompertz	0.32	£70,024	£217,141
Curve choice: PFS - log normal; OS - log normal	0.49	£70,909	£145,511

Scenario	Inc. QALYs	Inc. costs	ICER
Curve choice: PFS - log normal; OS - log logistic	0.48	£70,834	£148,443
Curve choice: PFS - log normal; OS - gamma	0.44	£70,617	£161,210
Curve choice: PFS - log logistic; OS - exponential	0.47	£72,176	£152,470
Curve choice: PFS - log logistic; OS - Weibull	0.44	£72,008	£163,867
Curve choice: PFS - log logistic; OS - Gompertz	0.33	£71,481	£214,567
Curve choice: PFS - log logistic; OS - log normal	0.50	£72,342	£145,282
Curve choice: PFS - log logistic; OS - log logistic*	0.49	£72,287	£148,169
Curve choice: PFS - log logistic; OS - gamma	0.45	£72,070	£160,627
Curve choice: PFS - gamma; OS - exponential	0.39	£57,437	£147,094
Curve choice: PFS - gamma; OS - Weibull	0.36	£57,260	£160,678
Curve choice: PFS - gamma; OS - Gompertz	0.25	£56,743	£226,874
Curve choice: PFS - gamma; OS - log normal	0.42	£57,582	£138,733
Curve choice: PFS - gamma; OS - log logistic	0.41	£57,535	£142,051
Curve choice: PFS - gamma; OS - gamma	0.37	£57,318	£156,755

** Assessment Group base case curve choice*

Inc. – incremental; BSC – best supportive care; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; PFS – progression-free survival; OS – overall survival

Analysis 2: EU label population (symptomatic and progressive MTC), vandetanib versus BSC (pairwise)

Table 59 presents the results of the pairwise comparison of vandetanib versus BSC within the EU label (symptomatic and progressive) MTC population. It should be noted that this analysis is subject to potential confounding due to the open-label use of vandetanib in the ZETA trial, hence post-progression vandetanib costs are included for both treatment groups. Disaggregated LYGs, QALYs and costs are presented in Table 60. Based on the probabilistic version of the Assessment Group's model (assuming the log logistic function for both PFS and OS), vandetanib is expected to generate 0.23 additional QALYs at an additional cost of £79,745 compared with BSC; the ICER for vandetanib versus BSC is expected to be £352,508 per QALY gained. The deterministic version of the model yields a lower ICER of £336,896 per QALY gained. The disaggregated results indicate that based on the log logistic model, OS is expected to be higher in the BSC group compared with the vandetanib group: this is likely to be a consequence of confounding due to open-label vandetanib use in the placebo group (see Figure **24**). It is also noteworthy that based on the selected OS functions, a similar proportion of patients in each group (11-12%) are still alive at 20-years due to the tails of the modelled curves; additional analyses undertaken by the Assessment Group indicate that the ICER for vandetanib versus BSC remains stable over longer time horizons (ICER using a 30-year time horizon, excluding any general population mortality constraints = £345,284 per QALY gained).

Table 59: **Analysis 2: EU label population (symptomatic and progressive MTC), vandetanib versus BSC (pairwise), central estimates of cost-effectiveness (PFS=log logistic, OS=log logistic for both options)**

Probabilistic model					
Option	**QALYs**	**Costs**	**Inc. QALYs**	**Inc. costs**	**ICER**
Vandetanib	4.02	£255,677	0.23	£79,745	**£352,508**
BSC	3.79	£175,932	-	-	-
Deterministic model					
Vandetanib	4.02	£255,114	0.23	£79,044	**£336,896**
BSC	3.78	£176,070	-	-	-

Inc. – incremental; BSC – best supportive care; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

Table 60: Analysis 2: EU label population (symptomatic and progressive MTC), vandetanib versus BSC (pairwise), disaggregated LYGs, QALYs and costs

Outcomes (undiscounted)	**Vandetanib**	**BSC**
LYGs	7.32	7.58
LYGs in progression-free state	4.00	2.70
LYGs in post-progression state	3.32	4.89
Total QALYs	4.85	4.60
Total QALYs in progression-free state	3.20	2.16
Total QALYs in post-progression state	1.66	2.44
Total cost	£305,003	£223,755
Total cost in progression-free state	£216,263	£8,131
Total cost in post-progression state	£88,740	£215,624
Modelled probability alive at 20-years	0.11	0.12

BSC – best supportive care; LYG – life year gained; QALY – quality-adjusted life year

Figure 35 presents incremental CEACs for the pairwise comparison of vandetanib versus BSC within the EU label (symptomatic and progressive) MTC population. Assuming a WTP threshold (λ) of £30,000 per QALY gained, the probability that vandetanib produces more net benefit than BSC is approximately 0.01.

Figure 35: **Analysis 2: EU label population (symptomatic and progressive MTC), vandetanib versus BSC (pairwise), cost-effectiveness acceptability curves (PFS=log logistic, OS=log logistic for both options)**

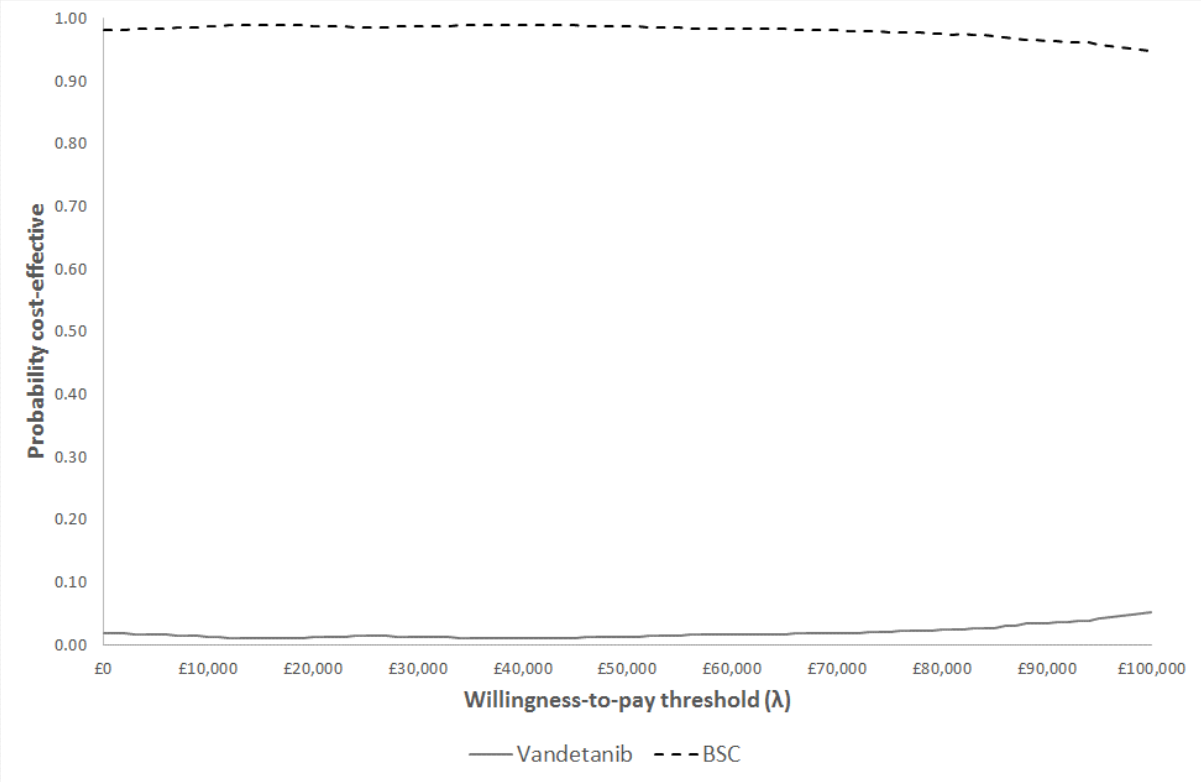


Table 61 presents the results of the DSAs for the pairwise comparison of vandetanib versus BSC within the EU label (symptomatic and progressive) MTC population. Across the range of DSAs considered, the ICERs for vandetanib versus BSC remain above £123,000 per QALY gained. In several scenarios in which the Gompertz function is used to model PFS, vandetanib is expected to be dominated by BSC. The DSAs indicate that the choice of utility values used in the base case analysis produce a considerably more favourable ICER for vandetanib versus BSC compared with the alternative sources identified. The scenarios surrounding health state resource use assumptions do not substantially alter the ICER, however the exclusion of post-progression vandetanib costs in both groups produces a marked increase in the ICER for vandetanib (ICER=£752,136 per QALY gained). In addition, setting the vandetanib discontinuation parameter equal to zero leads to an increase in the ICER for vandetanib (ICER=£378,272 per QALY gained). The choice of survival curves produce ICERs for vandetanib versus BSC ranging from £123,723 per QALY gained to dominated; the parametric survivor functions selected for use in the Assessment Group's base case do not represent the most optimistic case for vandetanib, nor do they represent they least favourable.

Table 61: **Analysis 2: EU label population (symptomatic and progressive MTC), vandetanib versus BSC (pairwise), deterministic sensitivity analysis results**

Scenario	Inc. QALYs	Inc. costs	ICER
Base case	0.23	£79,044	£336,896
Undiscounted health outcomes and costs	0.25	£81,248	£320,133
Sanofi CS utilities	0.10	£79,044	£822,117
DECISION study utilities	0.05	£79,044	£1,532,109
Cabozantinib SMC utilities	0.07	£79,044	£1,161,487
AE disutility doubled	0.23	£79,044	£340,951
AE disutility halved	0.24	£79,044	£334,904
AE management costs doubled	0.23	£79,134	£337,283
AE management costs halved	0.23	£78,998	£336,702
Post-progression vandetanib costs excluded	0.23	£176,468	£752,136
Vandetanib discontinuation parameter equal to zero	0.23	£88,751	£378,272
Health state resource use doubled	0.23	£80,593	£343,500
Health state resource use halved	0.23	£78,269	£333,593
No vandetanib dose reductions	0.23	£85,802	£365,703
Curve choice: PFS - exponential; OS - exponential	0.46	£59,484	£130,328
Curve choice: PFS - exponential; OS - Weibull	0.46	£62,545	£137,196
Curve choice: PFS - exponential; OS - Gompertz	0.59	£72,938	£123,723
Curve choice: PFS - exponential; OS - log normal	0.39	£49,372	£128,083
Curve choice: PFS - exponential; OS - log logistic	0.37	£49,310	£134,230
Curve choice: PFS - exponential; OS - gamma	0.43	£60,268	£139,406
Curve choice: PFS - Weibull; OS - exponential	0.22	£37,245	£165,924
Curve choice: PFS - Weibull; OS - Weibull	0.22	£40,327	£179,916
Curve choice: PFS - Weibull; OS - Gompertz	0.36	£50,707	£141,776
Curve choice: PFS - Weibull; OS - log normal	0.15	£27,155	£176,631
Curve choice: PFS - Weibull; OS - log logistic	0.14	£27,093	£199,768
Curve choice: PFS - Weibull; OS - gamma	0.20	£38,051	£189,697
Curve choice: PFS - Gompertz; OS - exponential	-0.08	£53,486	Dominated
Curve choice: PFS - Gompertz; OS - Weibull	-0.08	£56,486	Dominated
Curve choice: PFS - Gompertz; OS - Gompertz	0.07	£64,762	£969,254
Curve choice: PFS - Gompertz; OS - log normal	-0.15	£43,375	Dominated
Curve choice: PFS - Gompertz; OS - log logistic	-0.17	£43,313	Dominated
Curve choice: PFS - Gompertz; OS - gamma	-0.11	£54,271	Dominated
Curve choice: PFS - log normal; OS - exponential	0.39	£97,481	£249,691
Curve choice: PFS - log normal; OS - Weibull	0.39	£100,596	£257,665
Curve choice: PFS - log normal; OS - Gompertz	0.53	£110,381	£209,110
Curve choice: PFS - log normal; OS - log normal	0.32	£87,433	£273,140
Curve choice: PFS - log normal; OS - log logistic	0.30	£87,371	£289,324
Curve choice: PFS - log normal; OS - gamma	0.37	£98,325	£267,980
Curve choice: PFS - log logistic; OS - exponential	0.32	£89,180	£275,834
Curve choice: PFS - log logistic; OS - Weibull	0.32	£92,278	£285,560
Curve choice: PFS - log logistic; OS - Gompertz	0.46	£101,633	£218,981
Curve choice: PFS - log logistic; OS - log normal	0.25	£79,106	£312,992
Curve choice: PFS - log logistic; OS - log logistic*	0.23	£79,044	£336,896
Curve choice: PFS - log logistic; OS - gamma	0.30	£90,002	£300,416
Curve choice: PFS - gamma; OS - exponential	0.28	£41,060	£147,850
Curve choice: PFS - gamma; OS - Weibull	0.28	£44,151	£159,114
Curve choice: PFS - gamma; OS - Gompertz	0.41	£54,525	£132,686
Curve choice: PFS - gamma; OS - log normal	0.21	£30,979	£149,603
Curve choice: PFS - gamma; OS - log logistic	0.19	£30,917	£163,617

Scenario	Inc. QALYs	Inc. costs	ICER
Curve choice: PFS - gamma; OS – gamma	0.25	£41,875	£164,911

** Assessment Group base case curve choice*
Inc. – incremental; BSC – best supportive care; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; PFS – progression-free survival; OS – overall survival

Analysis 3: EU label population (symptomatic and progressive MTC), fully incremental analysis of all options using vandetanib PFS treatment effect from combined model, central estimates of cost-effectiveness

Table 62 presents the results of the fully incremental analysis of all options within the EU label (symptomatic and progressive) MTC population based on the EXAM trial baseline together with the PFS treatment effect derived from the EU label population of ZETA trial. It should noted that this analysis assumes that OS for vandetanib is equal to that of cabozantinib, which given the increased hazard rate/acceleration factor for PFS may be seen to be optimistic for vandetanib. Disaggregated LYGs, QALYs and costs are presented in

Table 63. Based on the probabilistic version of the model (assuming the log logistic function for both PFS and OS), the ICER for vandetanib versus BSC is expected to be £138,405 per QALY gained, whilst the ICER for cabozantinib versus vandetanib is expected to be £195,593 per QALY gained. The deterministic version of the model produces similar results (vandetanib versus BSC ICER = £134,817 per QALY gained; cabozantinib versus vandetanib ICER = £195,053 per QALY gained). The disaggregated results indicate that a considerable amount of the OS gain for all options is accrued in the post-progression state.

Table 62: Analysis 3: EU label population (symptomatic and progressive MTC), fully incremental analysis of all options using vandetanib PFS treatment effect from combined model, central estimates of cost-effectiveness (PFS=log logistic, OS=log logistic for all options)

Probabilistic model					
Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
Cabozantinib	2.28	£88,527	0.11	£20,559	**£195,593**
Vandetanib	2.17	£67,968	0.38	£52,175	**£138,405**
BSC	1.79	£15,793	-	-	-
Deterministic model					
Cabozantinib	2.27	£87,960	0.11	£21,094	**£195,053**
Vandetanib	2.16	£66,866	0.38	£51,193	**£134,817**
BSC	1.79	£15,672	-	-	-

Inc. – incremental; BSC – best supportive care; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

Table 63: Analysis 3: EU label population (symptomatic and progressive MTC), fully incremental analysis of all options using vandetanib PFS treatment effect from combined model, disaggregated LYGs, QALYs and costs

Outcomes (undiscounted)	Cabozantinib	Vandetanib	BSC
LYGs	4.49	4.49	3.91
LYGs in progression-free state	1.39	0.96	0.45
LYGs in post-progression state	3.10	3.54	3.46
Total QALYs	2.66	2.53	2.09
Total QALYs in progression-free state	1.10	0.76	0.36
Total QALYs in post-progression state	1.55	1.77	1.73
Total cost	£95,307	£71,105	£18,063
Total cost in progression-free state	£79,788	£54,284	£1,417
Total cost in post-progression state	£15,519	£16,820	£16,647
Modelled probability alive at 20-years	0.06	0.06	0.05

BSC – best supportive care; LYG – life year gained; QALY – quality-adjusted life year

Figure 36 presents incremental CEACs for the pairwise comparison of cabozantinib, vandetanib and BSC within the EU label (symptomatic and progressive) MTC population, including the PFS treatment effect for vandetanib from the ZETA trial. Assuming a WTP threshold (λ) of £30,000 per QALY gained, the probability that either cabozantinib or vandetanib produces more net benefit than BSC is zero.

Figure 36: Analysis 3: EU label population (symptomatic and progressive MTC), fully incremental analysis of all options using vandetanib PFS treatment effect from combined model, cost-effectiveness acceptability curves (PFS=log logistic, OS=log logistic for all options)

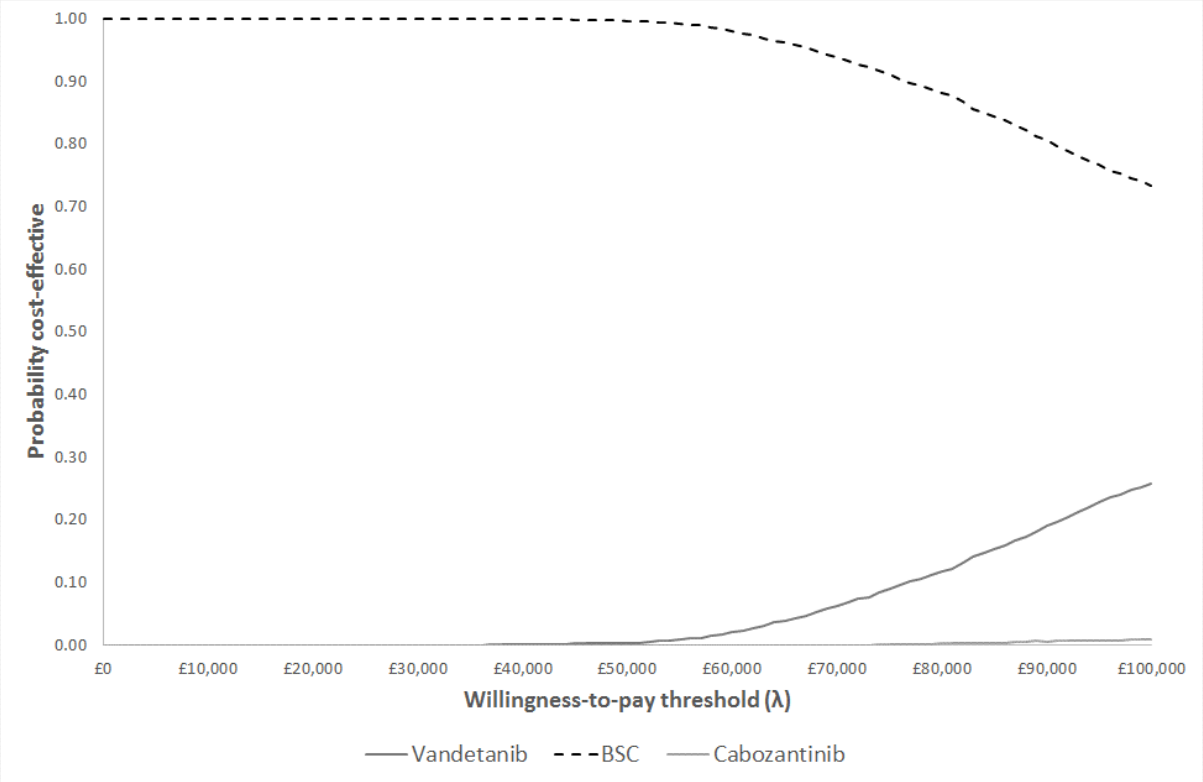


Table 64 presents the results of the DSAs for the fully incremental analyses of cabozantinib, vandetanib and BSC within the EU label (symptomatic and progressive) MTC population, including the PFS treatment effect for vandetanib from the ZETA trial. Across the range of DSAs considered, the ICERs for vandetanib remain above £85,000 per QALY gained, whilst the ICERs for cabozantinib remain above £148,000 per QALY gained. In several scenarios in which the Gompertz function is used to model OS, vandetanib is ruled out of the analysis due to extended dominance. The DSAs indicate that the choice of utility values used in the base case analysis produces a considerably more favourable ICER for cabozantinib compared with the alternative sources identified. The scenarios surrounding alternative health state resource use assumptions do not substantially alter the ICER. Setting the vandetanib discontinuation parameter equal to zero leads to a situation in which vandetanib is ruled out due to extended dominance; the ICER for cabozantinib versus BSC is estimated to be £148,169 per QALY gained. The choice of survival curves produce ICERs for vandetanib in the range £85,217 per QALY gained to extendedly dominated and ICERs for cabozantinib in the range £180,985 to £239,141 per QALY gained. The parametric survivor functions selected for use in the Assessment Group's base case do not represent the most optimistic case for either drug, nor are they the least favourable.

Table 64: Analysis 3: EU label population (symptomatic and progressive MTC), fully incremental analysis of all options using vandetanib PFS treatment effect from combined model, disaggregated LYGs, deterministic sensitivity analysis results

Scenario	Cabozantinib ICER (versus next best comparator)	Vandetanib ICER (versus next best comparator)
Base case	£195,053 (vs VAN)	£134,817 (vs BSC)
Undiscounted health outcomes and costs	£192,555 (vs VAN)	£119,397 (vs BSC)
Sanofi CS utilities	£298,889 (vs VAN)	£128,932 (vs BSC)
DECISION study utilities	£379,753 (vs VAN)	£135,577 (vs BSC)
Cabozantinib SMC utilities	£351,244 (vs VAN)	£136,191 (vs BSC)
AE disutility doubled	£203,651 (vs VAN)	£135,495 (vs BSC)
AE disutility halved	£191,021 (vs VAN)	£134,480 (vs BSC)
AE management costs doubled	£196,428 (vs VAN)	£134,980 (vs BSC)
AE management costs halved	£194,366 (vs VAN)	£134,735 (vs BSC)
Vandetanib discontinuation parameter equal to zero	£148,169 (vs BSC)	Ext dom
Health state resource use doubled	£173,521 (vs VAN)	£142,718 (vs BSC)
Health state resource use halved	£205,819 (vs VAN)	£130,866 (vs BSC)
No vandetanib or cabozantinib dose reductions	£273,909 (vs VAN)	£145,927 (vs BSC)
Curve choice: PFS - exponential; OS - exponential	£204,220 (vs VAN)	£147,531 (vs BSC)
Curve choice: PFS - exponential; OS - Weibull	£204,220 (vs VAN)	£162,113 (vs BSC)
Curve choice: PFS - exponential; OS - Gompertz	£227,293 (vs BSC)	ext dom
Curve choice: PFS - exponential; OS - log normal	£204,220 (vs VAN)	£138,620 (vs BSC)
Curve choice: PFS - exponential; OS - log logistic	£204,220 (vs VAN)	£142,141 (vs BSC)
Curve choice: PFS - exponential; OS - gamma	£204,220 (vs VAN)	£157,880 (vs BSC)
Curve choice: PFS - Weibull; OS - exponential	£197,918 (vs VAN)	£133,290 (vs BSC)
Curve choice: PFS - Weibull; OS - Weibull	£197,908 (vs VAN)	£150,033 (vs BSC)
Curve choice: PFS - Weibull; OS - Gompertz	£232,034 (vs BSC)	ext dom
Curve choice: PFS - Weibull; OS - log normal	£197,873 (vs VAN)	£123,454 (vs BSC)

Scenario	Cabozantinib ICER (versus next best comparator)	Vandetanib ICER (versus next best comparator)
Curve choice: PFS - Weibull; OS - log logistic	£197,873 (vs VAN)	£127,303 (vs BSC)
Curve choice: PFS - Weibull; OS - gamma	£197,895 (vs VAN)	£145,084 (vs BSC)
Curve choice: PFS - Gompertz; OS - exponential	£207,886 (vs VAN)	£135,751 (vs BSC)
Curve choice: PFS - Gompertz; OS - Weibull	£207,886 (vs VAN)	£152,470 (vs BSC)
Curve choice: PFS - Gompertz; OS - Gompertz	£239,141 (vs BSC)	ext dom
Curve choice: PFS - Gompertz; OS - log normal	£207,886 (vs VAN)	£125,894 (vs BSC)
Curve choice: PFS - Gompertz; OS - log logistic	£207,886 (vs VAN)	£129,755 (vs BSC)
Curve choice: PFS - Gompertz; OS - gamma	£207,886 (vs VAN)	£147,537 (vs BSC)
Curve choice: PFS - log normal; OS - exponential	£204,639 (vs VAN)	£142,355 (vs BSC)
Curve choice: PFS - log normal; OS - Weibull	£204,672 (vs VAN)	£155,650 (vs BSC)
Curve choice: PFS - log normal; OS - Gompertz	£217,141 (vs BSC)	ext dom
Curve choice: PFS - log normal; OS - log normal	£204,981 (vs VAN)	£134,340 (vs BSC)
Curve choice: PFS - log normal; OS - log logistic	£204,897 (vs VAN)	£137,538 (vs BSC)
Curve choice: PFS - log normal; OS - gamma	£204,722 (vs VAN)	£151,833 (vs BSC)
Curve choice: PFS - log logistic; OS - exponential	£194,919 (vs VAN)	£139,808 (vs BSC)
Curve choice: PFS - log logistic; OS - Weibull	£194,936 (vs VAN)	£153,657 (vs BSC)
Curve choice: PFS - log logistic; OS - Gompertz	£214,567 (vs BSC)	ext dom
Curve choice: PFS - log logistic; OS - log normal	£195,113 (vs VAN)	£131,503 (vs BSC)
Curve choice: PFS - log logistic; OS - log logistic*	£195,053 (vs VAN)	£134,817 (vs BSC)
Curve choice: PFS - log logistic; OS - gamma	£194,966 (vs VAN)	£149,667 (vs BSC)
Curve choice: PFS - gamma; OS - exponential	£180,990 (vs VAN)	£97,633 (vs BSC)
Curve choice: PFS - gamma; OS - Weibull	£180,990 (vs VAN)	£122,911 (vs BSC)
Curve choice: PFS - gamma; OS - Gompertz	£226,874 (vs BSC)	ext dom
Curve choice: PFS - gamma; OS - log normal	£180,985 (vs VAN)	£85,217 (vs BSC)
Curve choice: PFS - gamma; OS - log logistic	£180,985 (vs VAN)	£89,881 (vs BSC)
Curve choice: PFS - gamma; OS - gamma	£180,989 (vs VAN)	£114,798 (vs BSC)

** Assessment Group base case curve choice*

Inc. – incremental; BSC – best supportive care; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; PFS – progression-free survival; OS – overall survival; VAN – vandetanib.

Analysis 4: EU label population (symptomatic and progressive MTC), cabozantinib and vandetanib assumed equivalent

Table 65 presents the results of the fully incremental analysis of all options within the EU label (symptomatic and progressive) MTC population, assuming equivalent PFS and OS outcomes for cabozantinib and vandetanib, using time-to-event data from the EXAM trial. Disaggregated LYGs, QALYs and costs are presented in Table 66. Based on the probabilistic version of the model (assuming the log logistic function for both PFS and OS), cabozantinib is expected to be dominated; this is a consequence of the more favourable Grade ≥3 AE profile and the slightly lower total RDI-adjusted drug costs for vandetanib. The probabilistic ICER for vandetanib versus BSC is estimated to be £144,841 per QALY gained. The deterministic version of the model produces a similar result (deterministic ICER=£142,279 per QALY gained). The disaggregated results indicate that a considerable proportion of the total OS gain for all options is accrued in the post-progression state.

Table 65: **Analysis 4: EU label population (symptomatic and progressive MTC), cabozantinib and vandetanib assumed equivalent, central estimates of cost-effectiveness (PFS=log logistic, OS= log logistic for all options)**

Probabilistic model					
Option	**QALYs**	**Costs**	**Inc. QALYs**	**Inc. costs**	**ICER**
Vandetanib	2.28	£86,276	0.49	£70,482	**£144,841**
Cabozantinib	2.28	£88,527	-	-	**dominated**
BSC	1.79	£15,793	-	-	-
Deterministic model					
Vandetanib	2.28	£85,736	0.49	£70,063	**£142,279**
Cabozantinib	2.27	£87,960	-	-	**dominated**
BSC	1.79	£15,672	-	-	-

Inc. – incremental; BSC – best supportive care; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

Table 66: Analysis 4: EU label population (symptomatic and progressive MTC), cabozantinib and vandetanib assumed equivalent, disaggregated LYGs, QALYs and costs

Outcomes (undiscounted)	**Cabozantinib**	**Vandetanib**	**BSC**
LYGs	4.49	4.49	3.91
LYGs in progression-free state	1.39	1.39	0.45
LYGs in post-progression state	3.10	3.10	3.46
Total QALYs	2.66	2.66	2.09
Total QALYs in progression-free state	1.10	1.11	0.36
Total QALYs in post-progression state	1.55	1.55	1.73
Total cost	£95,307	£92,909	£18,063
Total cost in progression-free state	£79,788	£77,390	£1,417
Total cost in post-progression state	£15,519	£15,519	£16,647
Modelled probability alive at 20-years	0.06	0.06	0.05

BSC – best supportive care; LYG – life year gained; QALY – quality-adjusted life year

Figure 37 presents incremental CEACs for the pairwise comparison of vandetanib versus BSC within the EU label (symptomatic and progressive) MTC population for the analysis in which PFS and OS outcomes are assumed to be equivalent for both drugs. Assuming a WTP threshold (λ) of £30,000 per QALY gained, the probability that either cabozantinib or vandetanib produces more net benefit than BSC is zero.

Figure 37: **Analysis 4: EU label population (symptomatic and progressive MTC), cabozantinib and vandetanib assumed equivalent, cost-effectiveness acceptability curves (PFS=log logistic, OS=log logistic for all options)**

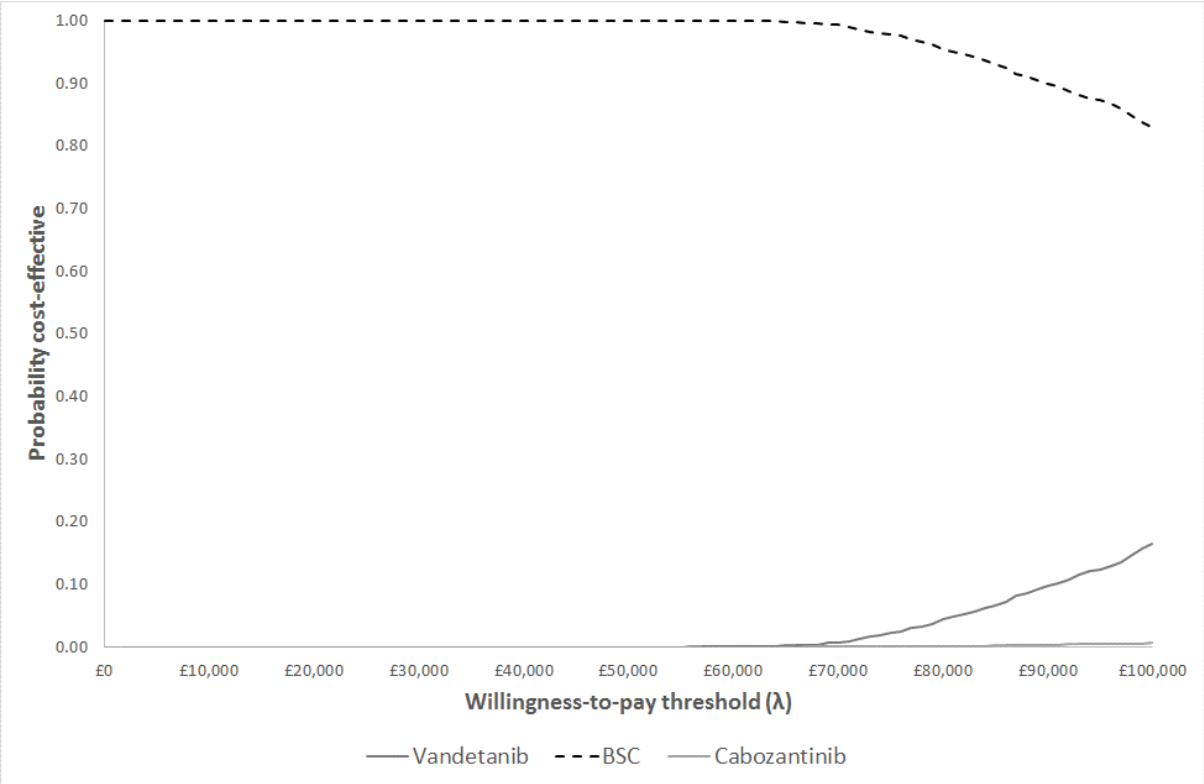


Table 67 presents the results of the DSAs for the fully incremental analysis of all options based on the assumption of equivalent PFS and OS outcomes for cabozantinib and vandetanib, using time-to-event outcomes data from the EXAM trial. Cabozantinib remains dominated across all scenarios, except the scenario in which the vandetanib discontinuation parameter is set equal to zero; in this scenario, the ICER for cabozantinib versus BSC is estimated to be £148,169 per QALY gained, whilst the ICER for vandetanib versus cabozantinib is estimated to be in excess of £1.35million per QALY gained. Across the remaining scenarios, the ICER for vandetanib versus BSC remains greater than £130,000 per QALY gained. The DSAs indicate that the choice of utility values and assumptions regarding AE impacts and health state resource use do not have a marked impact on the conclusions of the analysis. The choice of survival curves produces ICERs for vandetanib versus BSC in the range £132,998 to £227,918 per QALY gained; the parametric survivor functions selected for use in the base case Assessment Group's base case are close to the most favourable scenario for vandetanib.

Table 67: **Analysis 4: EU label population (symptomatic and progressive MTC), cabozantinib and vandetanib assumed equivalent, deterministic sensitivity analysis results**

Scenario	Cabozantinib ICER (versus next best comparator)	Vandetanib ICER (versus next best comparator)
Base case	Dominated	£142,279 (vs BSC)
Undiscounted health outcomes and costs	Dominated	£130,280 (vs BSC)
Sanofi CS utilities	Dominated	£148,377 (vs BSC)
DECISION study utilities	Dominated	£160,069 (vs BSC)
Cabozantinib SMC utilities	Dominated	£159,049 (vs BSC)
AE disutility doubled	Dominated	£142,831 (vs BSC)
AE disutility halved	Dominated	£142,005 (vs BSC)
AE management costs doubled	Dominated	£142,405 (vs BSC)
AE management costs halved	Dominated	£142,217 (vs BSC)
Vandetanib discontinuation parameter equal to zero	£148,169 (vs BSC)	£1,354,088 (vs CABO)
Health state resource use doubled	Ext dom	£148,745 (vs BSC)
Health state resource use halved	Dominated	£139,047 (vs BSC)
No vandetanib or cabozantinib dose reductions	Dominated	£154,164 (vs BSC)
Curve choice: PFS - exponential; OS - exponential	Dominated	£151,561 (vs BSC)
Curve choice: PFS - exponential; OS - Weibull	Dominated	£163,420 (vs BSC)
Curve choice: PFS - exponential; OS - Gompertz	Dominated	£216,938 (vs BSC)
Curve choice: PFS - exponential; OS - log normal	Dominated	£144,080 (vs BSC)
Curve choice: PFS - exponential; OS - log logistic	Dominated	£147,058 (vs BSC)
Curve choice: PFS - exponential; OS - gamma	Dominated	£160,026 (vs BSC)
Curve choice: PFS - Weibull; OS - exponential	Dominated	£141,362 (vs BSC)
Curve choice: PFS - Weibull; OS - Weibull	Dominated	£154,796 (vs BSC)
Curve choice: PFS - Weibull; OS - Gompertz	Dominated	£221,301 (vs BSC)
Curve choice: PFS - Weibull; OS - log normal	Dominated	£133,120 (vs BSC)
Curve choice: PFS - Weibull; OS - log logistic	Dominated	£136,386 (vs BSC)
Curve choice: PFS - Weibull; OS - gamma	Dominated	£150,910 (vs BSC)
Curve choice: PFS - Gompertz; OS - exponential	Dominated	£141,640 (vs BSC)
Curve choice: PFS - Gompertz; OS - Weibull	Dominated	£155,804 (vs BSC)
Curve choice: PFS - Gompertz; OS - Gompertz	Dominated	£227,918 (vs BSC)
Curve choice: PFS - Gompertz; OS - log normal	Dominated	£132,998 (vs BSC)
Curve choice: PFS - Gompertz; OS - log logistic	Dominated	£136,411 (vs BSC)
Curve choice: PFS - Gompertz; OS - gamma	Dominated	£151,689 (vs BSC)
Curve choice: PFS - log normal; OS - exponential	Dominated	£146,684 (vs BSC)
Curve choice: PFS - log normal; OS - Weibull	Dominated	£157,787 (vs BSC)
Curve choice: PFS - log normal; OS - Gompertz	Dominated	£207,458 (vs BSC)
Curve choice: PFS - log normal; OS - log normal	Dominated	£139,734 (vs BSC)
Curve choice: PFS - log normal; OS - log logistic	Dominated	£142,517 (vs BSC)
Curve choice: PFS - log normal; OS - gamma	Dominated	£154,630 (vs BSC)
Curve choice: PFS - log logistic; OS - exponential	Dominated	£146,363 (vs BSC)
Curve choice: PFS - log logistic; OS - Weibull	Dominated	£157,175 (vs BSC)
Curve choice: PFS - log logistic; OS - Gompertz	Dominated	£205,085 (vs BSC)
Curve choice: PFS - log logistic; OS - log normal	Dominated	£139,536 (vs BSC)
Curve choice: PFS - log logistic; OS - log logistic*	Dominated	£142,279 (vs BSC)
Curve choice: PFS - log logistic; OS - gamma	Dominated	£154,103 (vs BSC)
Curve choice: PFS - gamma; OS - exponential	Dominated	£141,316 (vs BSC)
Curve choice: PFS - gamma; OS - Weibull	Dominated	£154,181 (vs BSC)
Curve choice: PFS - gamma; OS - Gompertz	Dominated	£216,482 (vs BSC)

Scenario	Cabozantinib ICER (versus next best comparator)	Vandetanib ICER (versus next best comparator)
Curve choice: PFS - gamma; OS - log normal	Dominated	£133,382 (vs BSC)
Curve choice: PFS - gamma; OS - log logistic	Dominated	£136,532 (vs BSC)
Curve choice: PFS - gamma; OS - gamma	Dominated	£150,469 (vs BSC)

** Assessment Group base case curve choice*
BSC – best supportive care; ICER – incremental cost-effectiveness ratio; PFS – progression-free survival; OS – overall survival; CABO - cabozantinib

Analysis 5: Restricted EU label population (symptomatic and progressive MTC with CEA/CTN doubling time ≤24 months), vandetanib versus BSC (pairwise)

Table 68 presents the results of the pairwise comparison of vandetanib versus BSC for the Restricted EU label population (symptomatic and progressive MTC plus CEA/CTN doubling time ≤24 months). Disaggregated LYGs, QALYs and costs are presented in Table 69. This analysis closely reflects the economic analysis presented within the Sanofi CS,[35] but includes: survival models fitted directly to the observed data for the ZETA trial Restricted EU label subgroup; alternative assumptions regarding the vandetanib discontinuation parameter; different health state costs, and; different utility values. It should also be noted that this analysis is subject to potential confounding due to the open-label use of vandetanib, hence post-progression vandetanib costs are included in both treatment groups. Based on the probabilistic version of the Assessment Group's model (assuming the log normal function for PFS and the Gompertz function for OS), vandetanib is expected to generate 1.61 additional QALYs at an additional cost of £107,780 compared with BSC; the ICER for vandetanib versus BSC is expected to be £66,779 per QALY gained. The deterministic version of the model yields a slightly lower ICER of £65,184 per QALY gained. The disaggregated results indicate that the majority of the incremental OS gain for vandetanib is accrued in the progression-free state. It is also noteworthy that based on the selected Gompertz OS function, around 12% of the vandetanib cohort are still alive at 20-years due to the tail of the modelled curve. Additional analyses undertaken by the Assessment Group indicate that the ICER for vandetanib versus BSC is similar over longer time horizons (ICER using a 30-year time horizon, excluding any general population mortality constraints = £63,357 per QALY gained). However, the Assessment Group consider that the level of survival at 20 years may be an overestimate and that the true ICER for vandetanib may therefore be higher than £67,000 per QALY gained. The impact of assuming alternative OS functions is explored within the sensitivity analyses (see Table 70).

Table 68: Analysis 5: Restricted EU label population (symptomatic and progressive MTC with CEA/CTN doubling time ≤24 months), vandetanib versus BSC (pairwise), central estimates of cost-effectiveness (PFS=log normal, OS=Gompertz for both options)

Probabilistic model					
Option	**QALYs**	**Costs**	**Inc. QALYs**	**Inc. costs**	**ICER**
Vandetanib	3.45	£204,539	1.61	£107,780	**£66,779**
BSC	1.83	£96,759	-	-	-
Deterministic model					
Vandetanib	3.46	£205,457	1.64	£106,762	**£65,184**
BSC	1.82	£98,695	-	-	-

Inc. – incremental; BSC – best supportive care; QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio

Table 69: Analysis 5: Restricted EU label population (symptomatic and progressive MTC with CEA/CTN doubling time ≤24 months), vandetanib versus BSC (pairwise), disaggregated LYGs, QALYs and costs

Outcomes (undiscounted)	**Vandetanib**	**BSC**
LYGs	6.50	3.34
LYGs in progression-free state	3.15	0.97
LYGs in post-progression state	3.35	2.37
Total QALYs	4.19	1.96
Total QALYs in progression-free state	2.52	0.78
Total QALYs in post-progression state	1.67	1.18
Total cost	£245,641	£108,236
Total cost in progression-free state	£161,051	£2,956
Total cost in post-progression state	£84,591	£105,279
Modelled probability alive at 20-years	0.12	0.00

BSC – best supportive care; LYG – life year gained; QALY – quality-adjusted life year

Figure 38 presents incremental CEACs for the pairwise comparison of vandetanib versus BSC within the Restricted EU label MTC population. Assuming a WTP threshold (λ) of £30,000 per QALY gained, the probability that vandetanib produces more net benefit than BSC is approximately 0.02.

Figure 38: **Analysis 5: Restricted EU label population (symptomatic and progressive MTC with CEA/CTN doubling time ≤24 months), vandetanib versus BSC (pairwise),**

cost-effectiveness acceptability curves (PFS=log normal, OS=Gompertz for both options)

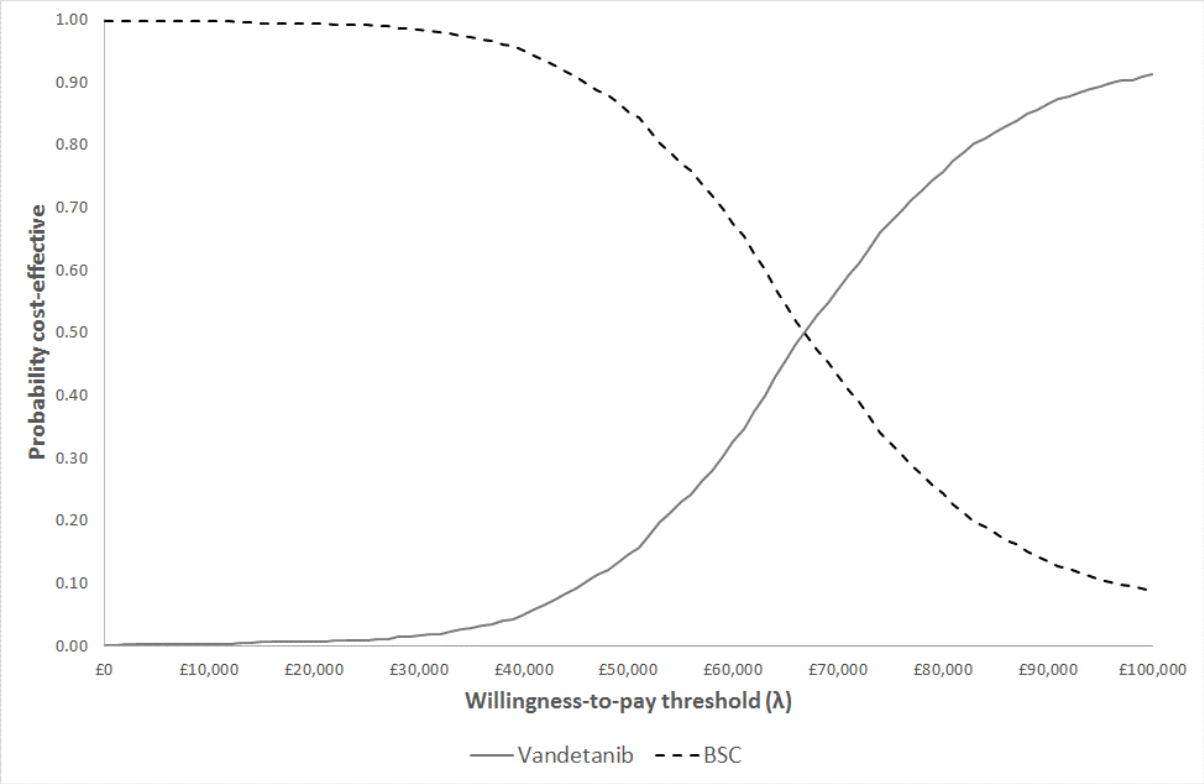


Table 70 presents the results of the DSA for the pairwise comparison of vandetanib versus BSC within the Restricted EU label population. As shown in the table, the ICER remains in excess of £51,000 per QALY gained across all scenarios. The DSAs indicate that the choice of utility values used in the base case analysis produces a slightly less favourable ICER for vandetanib versus BSC within this population compared with the alternative sources identified. The alternative assumptions regarding health state resource use and AEs do not have a marked impact upon the cost-effectiveness of vandetanib. In this population, excluding the post-progression vandetanib costs increases the ICER to £84,438 per QALY gained. Setting the vandetanib discontinuation parameter equal to zero increases the ICER to £76,352 per QALY gained. The choice of survival curves produces ICERs for vandetanib versus BSC in the range £51,194 to £71,128 per QALY gained; the curves used in the Assessment Group base case analysis (PFS=log normal, OS=Gompertz) represent neither the most favourable nor the least favourable scenario for vandetanib within the Restricted EU label population.

Table 70: **Analysis 5: Restricted EU label population (symptomatic and progressive MTC with CEA/CTN doubling time ≤24 months), vandetanib versus BSC (pairwise), deterministic sensitivity analysis results**

Scenario	Inc. QALYs	Inc. costs	ICER
Base case	1.64	£106,762	£65,184

Scenario	Inc. QALYs	Inc. costs	ICER
Undiscounted health outcomes and costs	2.23	£137,406	£61,584
Sanofi CS utilities	1.76	£106,762	£60,576
DECISION study utilities	1.69	£106,762	£63,186
Cabozantinib SMC utilities	1.68	£106,762	£63,683
AE disutility doubled	1.64	£106,762	£65,295
AE disutility halved	1.64	£106,762	£65,128
AE management costs doubled	1.64	£106,853	£65,239
AE management costs halved	1.64	£106,717	£65,156
Post-progression vandetanib costs excluded	1.64	£138,298	£84,438
Vandetanib discontinuation parameter equal to zero	1.64	£125,054	£76,352
Health state resource use doubled	1.64	£115,552	£70,551
Health state resource use halved	1.64	£102,367	£62,500
No vandetanib dose reductions	1.64	£116,928	£71,390
Curve choice: PFS - exponential; OS - exponential	1.30	£81,931	£63,007
Curve choice: PFS - exponential; OS - Weibull	1.30	£82,041	£63,165
Curve choice: PFS - exponential; OS - Gompertz	1.50	£90,264	£60,296
Curve choice: PFS - exponential; OS - log normal	1.28	£73,914	£57,821
Curve choice: PFS - exponential; OS - log logistic	1.06	£56,920	£53,857
Curve choice: PFS - exponential; OS - gamma	1.27	£80,262	£63,172
Curve choice: PFS - Weibull; OS - exponential	1.25	£77,205	£61,602
Curve choice: PFS - Weibull; OS - Weibull	1.25	£77,316	£61,765
Curve choice: PFS - Weibull; OS - Gompertz	1.45	£85,538	£58,993
Curve choice: PFS - Weibull; OS - log normal	1.23	£69,188	£56,193
Curve choice: PFS - Weibull; OS - log logistic	1.01	£52,195	£51,687
Curve choice: PFS - Weibull; OS - gamma	1.22	£75,537	£61,739
Curve choice: PFS - Gompertz; OS - exponential	1.40	£99,812	£71,119
Curve choice: PFS - Gompertz; OS - Weibull	1.41	£99,165	£70,439
Curve choice: PFS - Gompertz; OS - Gompertz	1.61	£106,531	£66,060
Curve choice: PFS - Gompertz; OS - log normal	1.38	£91,856	£66,516
Curve choice: PFS - Gompertz; OS - log logistic	1.16	£74,863	£64,564
Curve choice: PFS - Gompertz; OS - gamma	1.38	£97,861	£71,128
Curve choice: PFS - log normal; OS - exponential	1.44	£98,830	£68,718
Curve choice: PFS - log normal; OS - Weibull	1.44	£98,899	£68,821
Curve choice: PFS - log normal; OS – Gompertz*	1.64	£106,762	£65,184
Curve choice: PFS - log normal; OS - log normal	1.42	£90,824	£64,128
Curve choice: PFS - log normal; OS - log logistic	1.19	£73,831	£61,791
Curve choice: PFS - log normal; OS - gamma	1.41	£97,169	£68,989
Curve choice: PFS - log logistic; OS - exponential	1.44	£100,247	£69,779
Curve choice: PFS - log logistic; OS - Weibull	1.44	£99,816	£69,348
Curve choice: PFS - log logistic; OS - Gompertz	1.64	£107,120	£65,132
Curve choice: PFS - log logistic; OS - log normal	1.41	£92,230	£65,198
Curve choice: PFS - log logistic; OS - log logistic	1.19	£75,237	£63,056
Curve choice: PFS - log logistic; OS - gamma	1.41	£98,433	£69,923
Curve choice: PFS - gamma; OS - exponential	1.25	£76,695	£61,206
Curve choice: PFS - gamma; OS - Weibull	1.25	£76,806	£61,368
Curve choice: PFS - gamma; OS - Gompertz	1.45	£85,028	£58,651
Curve choice: PFS - gamma; OS - log normal	1.23	£68,678	£55,789
Curve choice: PFS - gamma; OS - log logistic	1.01	£51,685	£51,194
Curve choice: PFS - gamma; OS - gamma	1.22	£75,027	£61,334

* *Assessment Group base case curve choice*

BSC – best supportive care; ICER – incremental cost-effectiveness ratio; PFS – progression-free survival; OS – overall survival

6.3 Budget impact analysis

Table 71 presents a budget impact analysis for cabozantinib and vandetanib based on year-on-year drug acquisition costs predicted using the Assessment Group model. The budget impact analysis makes the following assumptions:

- The analysis considers only the acquisition costs of the drugs; other resource use components are excluded.
- The analysis includes prevalent (surviving) and incident (new) patients.
- Cumulative costs for surviving patients remaining progression-free and on treatment (based on the log logistic PFS models) are considered over a period of 10 years. The costs of post-progression vandetanib use are excluded from the analysis.
- The analysis assumes a constant eligible incident population of [redacted] MTC patients per year, based on the current use of the drugs on the CDF.
- The maximum annual budget impact is calculated using the total incident and prevalent cohort at 10-years.

The maximum annual budget impact for cabozantinib within the symptomatic and progressive population is expected to be around £2.35million. The maximum budget impact for vandetanib within the symptomatic and progressive population is expected to be around £5.53million; the costs of vandetanib in the Restricted EU label population are expected to be lower.

Table 71: Budget impact analysis – cabozantinib and vandetanib, EU label (symptomatic and progressive) MTC population

Budget impact – cabozantinib, symptomatic and progressive MTC population (based on EXAM ITT PFS, log logistic model)											
	Cohort year	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Entry year	**1**	£1,293,225	£488,370	£214,984	£118,396	£74,784	£51,564	£37,756	£28,878	£22,828	£18,518
	2	-	£1,293,225	£488,370	£214,984	£118,396	£74,784	£51,564	£37,756	£28,878	£22,828
	3	-	-	£1,293,225	£488,370	£214,984	£118,396	£74,784	£51,564	£37,756	£28,878
	4	-	-	-	£1,293,225	£488,370	£214,984	£118,396	£74,784	£51,564	£37,756
	5	-	-	-	-	£1,293,225	£488,370	£214,984	£118,396	£74,784	£51,564
	6	-	-	-	-	-	£1,293,225	£488,370	£214,984	£118,396	£74,784
	7	-	-	-	-	-	-	£1,293,225	£488,370	£214,984	£118,396
	8	-	-	-	-	-	-	-	£1,293,225	£488,370	£214,984
	9	-	-	-	-	-	-	-	-	£1,293,225	£488,370
	10	-	-	-	-	-	-	-	-	-	£1,293,225
Total annual cost		**£1,293,225**	**£1,781,595**	**£1,996,579**	**£2,114,975**	**£2,189,759**	**£2,241,323**	**£2,279,080**	**£2,307,958**	**£2,330,786**	**£2,349,304**
Budget impact – vandetanib, symptomatic and progressive MTC population (based on ZETA EU label subgroup PFS, log logistic model)											
	Cohort year	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Entry year	**1**	£1,465,575	£1,087,458	£775,968	£568,666	£432,204	£339,574	£274,328	£226,761	£191,027	£163,483
	2	-	£1,465,575	£1,087,458	£775,968	£568,666	£432,204	£339,574	£274,328	£226,761	£191,027
	3	-	-	£1,465,575	£1,087,458	£775,968	£568,666	£432,204	£339,574	£274,328	£226,761
	4	-	-	-	£1,465,575	£1,087,458	£775,968	£568,666	£432,204	£339,574	£274,328
	5	-	-	-	-	£1,465,575	£1,087,458	£775,968	£568,666	£432,204	£339,574
	6	-	-	-	-	-	£1,465,575	£1,087,458	£775,968	£568,666	£432,204
	7	-	-	-	-	-	-	£1,465,575	£1,087,458	£775,968	£568,666
	8	-	-	-	-	-	-	-	£1,465,575	£1,087,458	£775,968
	9	-	-	-	-	-	-	-	-	£1,465,575	£1,087,458
	10	-	-	-	-	-	-	-	-	-	£1,465,575
Total annual cost		**£1,465,575**	**£2,553,033**	**£3,329,001**	**£3,897,667**	**£4,329,872**	**£4,669,446**	**£4,943,774**	**£5,170,534**	**£5,361,561**	**£5,525,045**

6.4 Discussion

The Assessment Group's systematic review of existing economic evaluations did not identify any relevant published studies.

The manufacturer of cabozantinib did not submit any economic evidence relating to this product.

The manufacturer of vandetanib submitted a *de novo* model-based health economic evaluation of vandetanib versus BSC in the Restricted EU label population (symptomatic and progressive MTC plus CTN/CEA doubling times ≤24 months). An economic analysis for the broader licensed population was not presented. The corrected version of Sanofi's partitioned survival model suggests that the probabilistic ICER for vandetanib versus BSC is approximately £31,546 per QALY gained. The Assessment Group notes several concerns relating to the company's submitted model, in particular: (1) the questionable relevance of the Restricted EU label population to current clinical practice, (2) the failure to adjust for open-label vandetanib use in both treatment groups; (3) the likely overestimation of the costs of vandetanib use in the post-progression state; (4) questionable assumptions regarding the amount of vandetanib received, and (5) concerns regarding the robustness of the company's covariate-adjusted survival modelling to reflect the Restricted EU label population. The Assessment Group considers that the ICER for vandetanib is likely to be considerably higher than the estimates presented within the Sanofi CS.

In light of concerns regarding the economic analysis submitted by Sanofi and the absence of any economic evidence for cabozantinib, the Assessment Group developed a *de novo* health economic model. The Assessment Group's model was evaluated across five sets of analyses from the perspective of the NHS and PSS over a lifetime horizon. Four sets of analyses of cabozantinib and/or vandetanib versus BSC were undertaken in the EU label (symptomatic and progressive) MTC population and one set of analyses of vandetanib versus BSC was undertaken in the Restricted EU label population (symptomatic and progressive MTC with CTN/CEA doubling times ≤24 months). Costs and health outcomes were discounted at a rate of 3.5% per annum. Costs were valued at 2016/17 prices. The Assessment Group's model used a partitioned survival approach based on three health states: (i) progression-free; (ii) post-progression, and; (iii) dead. Costs and health utilities were assumed to differ according to the presence/absence of disease progression. The model parameters were informed by analyses of IPD from the EXAM trial, replicated IPD from the ZETA trial, the submissions from Sanofi and Ipsen and data contained within subsequent clarification responses, as well as published literature, standard reference cost sources and expert judgement. The results of the Assessment Group's economic analysis are summarised in Table 72.

Table 72: **Summary of Assessment Group cost-effectiveness results**

Analysis No.	Description	Probabilistic ICER	Probability cost-effective at λ=£30,000 per QALY gained	ICER range from alternative parametric survivor functions
AG Analysis 1	Pairwise economic evaluation of cabozantinib versus BSC in the EXAM ITT population	£150,874 per QALY gained	Cabozantinib=0.00	£138,259 to £239,141 per QALY gained
AG Analysis 2	Pairwise economic evaluation of vandetanib versus BSC in the ZETA EU label population	£352,508 per QALY gained	Vandetanib=0.01	£123,723 per QALY gained to dominated
AG Analysis 3	Fully incremental analysis based on EXAM ITT population with vandetanib PFS treatment effect applied to EXAM placebo baseline, vandetanib OS assumed equivalent to cabozantinib OS	Vandetanib vs BSC =£138,405 per QALY gained Cabozantinib vs vandetanib =£195,593 per QALY gained	Vandetanib=0.00 Cabozantinib=0	Vandetanib vs next best comparator=£85,217 per QALY gained to extendedly dominated Cabozantinib vs next best comparator=£180,985 to £239,141 per QALY gained
AG Analysis 4	Fully incremental analysis based on EXAM ITT population assuming PFS and OS are equivalent for vandetanib and cabozantinib	Cabozantinib=dominated Vandetanib vs BSC=£144,841 per QALY gained	Cabozantinib=0.00 Vandetanib=0.00	Cabozantinib=dominated to dominated Vandetanib=£132,998 to £227,918 per QALY gained
AG Analysis 5	Pairwise economic evaluation of vandetanib versus BSC using ZETA Restricted EU label population	£66,779 per QALY gained	Vandetanib=0.02	£51,194 to £71,128 per QALY gained

ITT – intention-to-treat; BSC – best supportive care; PFS – progression-free survival; OS – overall survival; ICER – incremental cost-effectiveness ratio; QALY – quality-adjusted life year

AG Analysis 1: EU label population (symptomatic and progressive MTC), pairwise economic evaluation of cabozantinib versus BSC

Based on the Assessment Group's probabilistic model (assuming the log logistic function for both PFS and OS), the ICER for cabozantinib versus BSC is expected to be £150,874 per QALY gained. The DSAs indicate that the Assessment Group's base case is close to the most favourable scenario.

AG Analysis 2: EU label population (symptomatic and progressive MTC), pairwise economic evaluation of vandetanib versus BSC

Based on the probabilistic version of the Assessment Group's model (assuming the log logistic function for both PFS and OS), the ICER for vandetanib versus BSC is expected to be £352,508 per QALY gained. The DSAs indicate that the Assessment Group's base case does not represent the most optimistic case for vandetanib, nor does it reflect the most pessimistic scenario.

AG Analysis 3: EU label population (symptomatic and progressive MTC), fully incremental analysis, vandetanib PFS treatment effect applied to EXAM placebo baseline, vandetanib OS assumed equivalent to cabozantinib OS

Within this analysis, the ICER for vandetanib versus BSC is expected to be £138,405 per QALY gained, whilst the ICER for cabozantinib versus vandetanib is expected to £195,593 per QALY gained. The DSAs indicate that the Assessment Group's base case represents neither the most favourable nor the least favourable scenario for either drug.

AG Analysis 4: EU label population (symptomatic and progressive MTC), fully incremental analysis, PFS and OS outcomes assumed equivalent for vandetanib and cabozantinib

Based on the probabilistic version of the model (assuming the log logistic function for both PFS and OS), cabozantinib is expected to be dominated; this is a consequence of the more favourable Grade ≥3 AE profile and the slightly lower total RDI-adjusted drug costs for vandetanib. The probabilistic ICER for vandetanib versus BSC is expected to be £144,841 per QALY gained. The DSAs indicate that the Assessment Group's base case represents one of the more favourable scenarios for vandetanib.

AG Analysis 5: Restricted EU label population (symptomatic and progressive MTC plus CEA/CTN doubling time ≤ 24 months), pairwise economic evaluation of vandetanib versus BSC

Based on the probabilistic version of the Assessment Group's model (assuming the log normal function for PFS and the Gompertz function for OS), the ICER for vandetanib versus BSC is expected to be £66,779 per QALY gained. The DSAs indicate that the Assessment Group's base case represents neither a highly favourable nor a highly unfavourable scenario for vandetanib.

Table 73 highlights the key differences between the Assessment Group's model and the Sanofi model. Whilst the two models are very similar in terms of their structure and definition of parameters, the key differences between the analyses relate to: (i) the scope of the economic comparisons; (ii) the time-to-event data used to inform the analyses (covariate-adjusted ITT/safety dataset versus actual subgroup data); (iii) the source of health utility values, (iv) assumptions regarding the costs associated with BSC, and; (v) assumptions regarding the costs of vandetanib in patients who discontinue therapy prior to disease progression.

Table 73: Key differences between the Sanofi model and the Assessment Group model

Element of economic analysis	Sanofi model	Assessment Group model
Comparisons	Vandetanib versus BSC	Cabozantinib versus BSC Vandetanib versus BSC Full incremental analysis of all options
Trial evidence used to inform time-to-event outcomes	ZETA ITT/safety population	EXAM ITT, ZETA EU label, ZETA Restricted EU label
Structure	Partitioned survival model. No adjustment for logical inconsistency	Partitioned survival model. Includes adjustment for logical inconsistency
Survival modelling approach	Covariate-adjusted survivor functions fitted to ITT/safety dataset	Survivor functions fitted directly to data for relevant populations
Health state utilities	Mapped utilities for progression-free state, decrement for post-progression based on Beusterien *et al*[90]	Health state utilities derived from Fordham *et al*[87]
Costing approach	Different costs for BSC in progression-free and post-progression states.	Same costs for BSC in progression-free and post-progression states. Additional resource use components included for patients receiving TKIs and for those receiving BSC.
Vandetanib discontinuation parameter	Applied in full only to pre-progression vandetanib group	Half of total value applied to all patients receiving vandetanib in progression-free and post-progression states (where applicable).

BSC – best supportive care; ITT – intention-to-treat; TKI – tyrosine kinase inhibitor

7 ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

7.1 Additional monitoring requirements

Vandetanib and cabozantinib are associated with additional monitoring requirements, particularly during the first three months after initiating treatment (see Section 3.2.2.) These additional monitoring requirements impose additional costs on the NHS over and above the costs of drug acquisition. However, given the small population of MTC patients eligible to receive vandetanib and cabozantinib, these additional resource requirements are expected to be negligible.

7.2 Current availability of cabozantinib and vandetanib for MTC

Both vandetanib and cabozantinib are currently available for the treatment of symptomatic and progressive MTC through the CDF. The current CDF recommendations for each TKI allow for the use of the other TKI for patients in whom toxicity occurs provided that: (i) switching to the other TKI takes place within 3 months of starting the initial TKI; (ii) the toxicity cannot be managed by dose delay or dose modification, and; (iii) the patient has not experienced disease progression on the initial TKI. In addition, given the different AE profiles of cabozantinib and vandetanib and special warnings listed within their SmPCs,[22, 23] some patients will not be able to receive both therapies. The clinical advisors to the Assessment Group consider that there is value in having access to both TKIs for this reason.

7.3 End-of-life considerations

NICE's end-of-life supplementary advice should be applied in the following circumstances and when the criteria referred to below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

Table 74 presents the undiscounted LYGs predicted by the Assessment Group's base case model (see Section 6.2.3.2). As shown in the table, the expected mean survival in the placebo group of the EXAM trial and the subgroups of the ZETA trial is greater than 24 months. This conclusion remains consistent irrespective of the choice of parametric model used to represent OS. However, it should be noted that the analyses of the OS data for the ZETA subgroups remain confounded by open-label vandetanib use, hence the true survival duration in this population is unknown. The analyses suggest that the criterion relating to >3 months life extension is likely to be met for cabozantinib in the EU label (symptomatic and progressive) MTC population and for vandetanib within the Restricted EU label population (symptomatic and progressive MTC with CEA/CTN doubling time ≤24 months).

Table 74: Undiscounted survival estimates used in the Assessment Group model

Outcome	EXAM safety population		ZETA symptomatic and progressive		ZETA symptomatic and progressive with CEA/CTN biomarker	
	Cabozantinib	BSC	Vandetanib	BSC	Vandetanib	BSC
Assessment Group base case OS (undiscounted LYGs)	4.49	3.91	7.32	7.58	6.50	3.34
Incremental OS gain (undiscounted LYGs)	0.59		-0.27		3.16	

BSC – best supportive care; CEA – carcinoembryonic antigen; CTN – calcitonin; OS – overall survival; LYG – life year gained

8 DISCUSSION

8.1 Statement of principal findings

The systematic review of the clinical effectiveness evidence identified two relevant placebo-controlled RCTs: the EXAM trial, which evaluated cabozantinib (n=330) and the ZETA trial, which evaluated vandetanib. The EXAM trial was at low risk of bias across most domains, whilst the ZETA trial was at a moderate to high risk of bias across a number of domains. The two trials assessed different populations (the ZETA trial inclusion criteria did not specify "progressive" disease), but ZETA did include a subgroup with "progressive and symptomatic disease" (n=186), which formed the "EU label" population. This group and the EXAM ITT population were considered to be comparable. In terms of efficacy, both cabozantinib and vandetanib significantly improved PFS compared with placebo. In the absence of direct evidence comparing the two interventions, an NMA was performed, which suggested that the results of the two treatments were broadly similar in terms of PFS, although these findings must be treated with caution due to the sparsity of the network.

Both cabozantinib and vandetanib also demonstrated significant benefits compared with placebo in terms of ORR, as determined by RECIST criteria. However, there was no significant OS benefit for either cabozantinib or vandetanib compared with placebo, although the data from the vandetanib trial were subject to potential confounding due to open-label vandetanib use in both groups. The two trials also conducted exploratory assessments of patients' quality of life using instruments that evaluated various criteria, but no difference was found between the treatment or placebo arms at follow-up in either trial. Clinical advice received by the Assessment Group suggested that these tools did not necessarily capture symptomatic benefit produced by improved PFS or response to treatment. Both cabozantinib and vandetanib produced frequent AEs, with similar types and rates of Grade ≥3 AEs, except for higher rates of HFS (13%) for cabozantinib, and prolonged ECG QT (8%) for vandetanib. Similar proportions of patients across the two trials discontinued treatment due to AEs, but a higher percentage of patients experienced AEs leading to dose interruption or reduction on cabozantinib than on vandetanib.

Based on the Assessment Group's probabilistic analysis of cabozantinib versus placebo in the EU label (symptomatic and progressive) MTC population, the ICER for cabozantinib versus BSC is expected to be £150,874 per QALY gained. Within the EU label (symptomatic and progressive) MTC population of the ZETA trial, the Assessment Group's probabilistic analysis suggests that the ICER for vandetanib versus BSC is expected to be £352,508 per QALY gained. The fully incremental analysis of cabozantinib, vandetanib and BSC based on the EXAM ITT population and the vandetanib PFS treatment effect from the ZETA trial suggests that the ICER for vandetanib versus BSC is expected to be £138,405 per QALY gained whilst the ICER for cabozantinib versus vandetanib is expected to be £195,593 per QALY gained. Within the fully incremental analysis in which the PFS and OS outcomes

for vandetanib were assumed to be equivalent to the cabozantinib group outcomes in the EXAM trial, cabozantinib is expected to be dominated, whilst the ICER for vandetanib versus BSC is expected to be £144,841 per QALY gained. Within the Restricted EU label population (symptomatic and progressive MTC plus CEA/CTN doubling time ≤24 months), the ICER for vandetanib versus BSC is expected to be £66,779 per QALY gained.

The Assessment Group's economic analysis suggest that the NICE's criteria for life-extending therapies given at the end of life are not met for cabozantinib in the EU label population (symptomatic and progressive MTC) or for vandetanib in either the EU label population or the Restricted EU label population (symptomatic and progressive MTC with CEA/CTN doubling time ≤24 months).

8.2 Strengths and limitations of the assessment

The key strengths of this assessment are as follows:

- The Assessment Group's economic evaluation includes fully incremental analyses of cabozantinib, vandetanib and BSC within the symptomatic and progressive MTA population.
- The health economic model developed by the Assessment Group uses a simple partitioned survival approach which directly uses the available data on PFS and OS from the EXAM and ZETA trials. This model structure is very similar to that used within the Sanofi model.
- The Assessment Group's economic analysis includes a thorough assessment of uncertainty surrounding the impact of using alternative parametric functions for PFS and OS based on models fitted directly to data for the relevant population/subgroup under consideration. This is particularly important given that the choice of parametric functions has been informed by only one clinical expert; it is possible that other clinical experts may have selected different preferred curves.

The main weaknesses of the assessment are largely a consequence of weaknesses and gaps in the clinical evidence base:

- The Assessment Group did not have access to IPD from the ZETA trial; instead, PFS and OS outcomes were replicated using a published algorithm. Whilst the accuracy of this replication is likely to be good, this process may have introduced a small loss of accuracy relative to using the IPD directly.
- The ITT populations for the EXAM trial and the ZETA trials are notably different. The analyses of the ZETA trial subgroups have been defined *post hoc* and may be subject to confounding due to differences in baseline characteristics.
- The OS data for the ZETA trial are subject to potential confounding due to open-label vandetanib use. Sanofi's attempts to adjust OS estimates using the RPSFT approach were

reported to be unsuccessful. As a consequence, the pairwise economic comparisons of vandetanib versus BSC (presented by both Sanofi and the Assessment Group) may be of limited relevance for decision-making. Conversely, the Assessment Group's incremental analyses make potentially strong assumptions concerning transferable/equivalent treatment effects between vandetanib and cabozantinib.

- The systematic review of HRQoL evidence did not identify any relevant published health valuation studies relating specifically to the MTC population.

8.3 Uncertainties

The key uncertainties associated with this evaluation are:

- Quality of life gains as a result of PFS and related-symptom management. These have not been adequately explored in the literature.
- The comparative effectiveness and cost-effectiveness of cabozantinib and vandetanib compared with each other and compared with BSC.
- The incremental OS benefits associated with vandetanib in patients with symptomatic and progressive MTC and in patients with the additional CEA/CTN biomarker. Other outcomes, e.g. safety, are also subject to potential confounding.
- Treatment duration in patients who discontinue TKI therapy prior to disease progression.
- The impact of locally advanced or metastatic MTC on HRQoL, as measured using a preference-based utility instrument.
- The relative AE profiles of vandetanib and cabozantinib within the symptomatic and progressive MTC population.

8.4 Other relevant factors

The number of patients that would be eligible for these treatments is very small. In 2016, [redacted] patients initiated treatment using cabozantinib (n=[redacted]) or vandetanib (n=[redacted]).

9 CONCLUSIONS

The systematic review of the clinical effectiveness evidence identified two relevant placebo-controlled RCTs: the EXAM trial, which evaluated cabozantinib (n=330) and the ZETA trial, which evaluated vandetanib (n=331). The two trials assessed different MTC populations (the ZETA trial inclusion criteria did not specify "progressive" disease), but ZETA did include a subgroup with "progressive and symptomatic disease" (n=186), which formed the "EU label" population. This group and the EXAM ITT population were considered to be comparable. Both cabozantinib and vandetanib demonstrated significant benefits compared with placebo in terms of PFS and appear to be broadly similar in terms of efficacy, although neither drug has demonstrated significant OS benefit compared with placebo. Both cabozantinib and vandetanib produced frequent AEs, with substantial proportions of patients experiencing AEs that led to dose interruption or reduction.

Based on the Assessment Group's probabilistic analysis of cabozantinib versus placebo in the EU label (symptomatic and progressive) MTC population, the ICER for cabozantinib versus BSC is expected to be £150,874 per QALY gained. Within the EU label (symptomatic and progressive) MTC population of the ZETA trial, the Assessment Group's probabilistic analysis suggests that the ICER for vandetanib versus BSC is expected to be £352,508 per QALY gained. The fully incremental analysis of cabozantinib, vandetanib and BSC based on the EXAM ITT population and the vandetanib PFS treatment effect from the ZETA trial suggests that the ICER for vandetanib versus BSC is expected to be £138,405 per QALY gained whilst the ICER for cabozantinib versus vandetanib is expected to be £195,593 per QALY gained. Within the fully incremental analysis in which the PFS and OS outcomes for vandetanib were assumed to be equivalent to the cabozantinib group outcomes in the EXAM trial, cabozantinib is expected to be dominated, whilst the ICER for vandetanib versus BSC is expected to be £144,841 per QALY gained. Within the Restricted EU label population (symptomatic and progressive MTC plus CEA/CTN doubling time ≤24 months), the ICER for vandetanib versus BSC is expected to be £66,779 per QALY gained.

The Assessment Group's economic analysis suggest that the NICE's criteria for life-extending therapies given at the end of life are not met for cabozantinib in the EU label population (symptomatic and progressive MTC) or for vandetanib in either the EU label population or the Restricted EU label population (symptomatic and progressive MTC with CEA/CTN doubling time ≤24 months).

9.1 Implications for service provision

The implications for service provision are minimal due to the rarity of the disease and due to the current availability of both therapies through the CDF.

9.2 Suggested research priorities

1. Primary research comparing the long-term clinical benefits of cabozantinib and vandetanib within relevant subgroups.
2. Analyses of existing evidence from the ZETA trial to investigate the impact of adjusting for open-label vandetanib use using appropriate statistical methods.
3. Studies assessing the impact of MTC on HRQoL using a preference-based measure such as the EQ-5D.

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11 APPENDICES

APPENDIX 1: Literature Search Strategies

Cost-effectiveness studies

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
3rd November 2016

#	Searches
1	exp Thyroid Neoplasms/
2	exp Goiter, Nodular/
3	(thyr?oid* adj5 (cancer* or neoplas* or carcinoma* or malignan* or tumor* or tumour* or adenocarcinoma*)).mp.
4	Thyroid Gland/
5	exp Neoplasms/
6	4 and 5
7	or/1-3,6
8	exp "Costs and Cost Analysis"/
9	Economics/
10	exp Economics, Hospital/
11	exp Economics, Medical/
12	Economics, Nursing/
13	exp models, economic/
14	Economics, Pharmaceutical/
15	exp "Fees and Charges"/
16	exp Budgets/
17	budget$.tw.
18	ec.fs.
19	cost$.ti.
20	(cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab.
21	(economic$ or pharmacoeconomic$ or pharmaco-economic$).ti.
22	(price$ or pricing$).tw.
23	(financial or finance or finances or financed).tw.
24	(fee or fees).tw.
25	(value adj2 (money or monetary)).tw.
26	quality-adjusted life years/
27	(qaly or qalys).af.
28	(quality adjusted life year or quality adjusted life years).af.
29	or/8-28
30	7 and 29

Embase 1974 to 2016 November 01
3rd November 2016

#	Searches
1	exp thyroid tumor/
2	exp nodular goiter/
3	(thyr?oid* adj5 (cancer* or neoplas* or carcinoma* or malignan* or tumor* or tumour* or adenocarcinoma*)).mp.
4	thyroid gland/
5	exp neoplasm/
6	4 and 5
7	or/1-3,6
8	Socioeconomics/
9	Cost benefit analysis/
10	Cost effectiveness analysis/
11	Cost of illness/
12	Cost control/
13	Economic aspect/
14	Financial management/
15	Health care cost/
16	Health care financing/
17	Health economics/
18	Hospital cost/
19	(fiscal or financial or finance or funding).tw.
20	Cost minimization analysis/
21	(cost adj estimate$).mp.
22	(cost adj variable$).mp.
23	(unit adj cost$).mp.
24	or/8-23
25	7 and 24

Web of Science® Core Collection
Science Citation Index Expanded (1900-)
Conference Proceedings Citation Index - Science (1990-)
3rd November 2016

#	Searches
# 1	TOPIC: ((thyr*oid* NEAR/5 (cancer* or neoplas* or carcinoma* or malignan* or tumor* or tumour* or adenocarcinoma*)))
# 2	TS=(cost* and (effective* or utilit* or benefit* or minimi*)) OR TS=(cost*) OR TI=(economic* or pharmacoeconomic* or pharmaco-economic*) OR TS=(price* or pricing*) OR TS=(financial or finance or finances or financed) OR TS=(fee or fees) OR TS=(value and (money or monetary)) OR TS=(economic*) OR TS=(economic* and (hospital or medical or nursing or pharmaceutical)) OR TS=("quality adjusted life year" or "quality adjusted life years") OR TS=(qaly or qalys) OR TS=(budget*)
# 3	#2 AND #1

Cochrane Database of Systematic Reviews (CDR): Wiley Online.
Health Technology Assessment Database (HTA): Wiley Online.
NHS Economic Evaluation Database (NHS EED): Wiley Online. 1995-2015
3rd November 2016

#	Searches
#1	MeSH descriptor: [Thyroid Neoplasms] explode all trees
#2	MeSH descriptor: [Goiter, Nodular] explode all trees
#3	(thyr*oid* near/5 (cancer* or neoplas* or carcinoma* or malignan* or tumor* or tumour* or adenocarcinoma*)):ti,ab,kw
#4	MeSH descriptor: [Thyroid Gland] this term only
#5	MeSH descriptor: [Neoplasms] explode all trees
#6	#4 and #5
#7	30-#3, #6

CINAHL 1982 to Present
3rd November 2016

#	Searches
S1	(MH "Thyroid Neoplasms+")
S2	(thyr?oid* N5 (cancer* or neoplas* or carcinoma* or malignan* or tumor* or tumour* or adenocarcinoma*))
S3	(MH "Thyroid Gland")
S4	(MH "Neoplasms+")
S5	S3 AND S4
S6	S1 OR S2 OR S5
S7	(MH "Costs and Cost Analysis+")
S8	(MH "Economics")
S9	(MH "Economics, Pharmaceutical")
S10	(MH "Fees and Charges+")
S11	(MH "Budgets")
S12	budget*
S13	cost*
S14	AB cost* and (effective* or utilit* or benefit* or minimi*)
S15	TI economic* or pharmacoeconomic* or pharmaco-economic*
S16	price* or pricing*
S17	financial or finance or finances or financed
S18	fee or fees
S19	value and (money or monetary)
S20	qaly or qalys
S21	quality adjusted life year or quality adjusted life years
S22	S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21
S23	S6 AND S22

Quality of life studies

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
3rd November 2016

#	Searches
1	exp Thyroid Neoplasms/
2	exp Goiter, Nodular/
3	(thyr?oid* adj5 (cancer* or neoplas* or carcinoma* or malignan* or tumor* or tumour* or adenocarcinoma*)).mp.
4	Thyroid Gland/
5	exp Neoplasms/
6	4 and 5
7	or/1-3,6
8	"Quality of Life"/
9	(qol or (quality adj2 life)).ab,ti.
10	(value adj2 (money or monetary)).tw.
11	value of life/
12	quality adjusted life year/
13	quality adjusted life.tw.
14	(qaly$ or qald$ or qale$ or qtime$).tw.
15	disability adjusted life.tw.
16	daly$.tw.
17	health status indicators/
18	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
19	(sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
20	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
21	(sf6D or sf 6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).tw.
22	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
23	(euroqol or euro qol or eq5d or eq 5d).tw.
24	(hql or hqol or h qol or hrqol or hr qol).tw.
25	(hye or hyes).tw.
26	health$ year$ equivalent$.tw.
27	health utilit$.tw.
28	(hui or hui1 or hui2 or hui3).tw.
29	disutilit$.tw.
30	rosser.tw.
31	(quality adj2 wellbeing).tw.
32	qwb.tw.
33	(willingness adj2 pay).tw.
34	standard gamble$.tw.
35	time trade off.tw.

36	time tradeoff.tw.
37	tto.tw.
38	letter.pt.
39	editorial.pt.
40	comment.pt.
41	38 or 39 or 40
42	or/8-37
43	42 not 41
44	7 and 43

Embase 1974 to 2016 November 01
3rd November 2016

#	Searches
1	exp thyroid tumor/
2	exp nodular goiter/
3	(thyr?oid* adj5 (cancer* or neoplas* or carcinoma* or malignan* or tumor* or tumour* or adenocarcinoma*)).mp.
4	thyroid gland/
5	exp neoplasm/
6	4 and 5
7	or/1-3,6
8	socioeconomics/
9	quality adjusted life year/
10	quality adjusted life.tw.
11	(qaly$ or qald$ or qale$ or qtime$).tw.
12	disability adjusted life.tw.
13	daly$.tw.
14	health survey/
15	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
16	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
17	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
18	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
19	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
20	(euroqol or euro qol or eq5d or eq 5d).tw.
21	(hql or hqol or h qol or hrqol or hr qol).tw.
22	(hye or hyes).tw.
23	health$ year$ equivalent$.tw.
24	health utilit$.tw.
25	(hui or hui1 or hui2 or hui3).tw.
26	disutili$.tw.
27	rosser.tw.
28	quality of wellbeing.tw.
29	qwb.tw.
30	willingness to pay.tw.
31	standard gamble$.tw.
32	time trade off.tw.
33	time tradeoff.tw.
34	tto.tw.
35	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36	7 and 35

Web of Science® Core Collection
Science Citation Index Expanded (1900-)
Conference Proceedings Citation Index - Science (1990-)
3rd November 2016

#	Searches
# 1	TOPIC: ((thyr*oid* NEAR/5 (cancer* or neoplas* or carcinoma* or malignan* or tumor* or tumour* or adenocarcinoma*)))
# 2	TS=(qol or "quality of life" or "quality adjusted life" or qaly* or qald* or qale* or qtime* or "disability adjusted life" or daly*)
# 3	TS=(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six) OR TS=(sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six) OR TS=(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve) OR TS=(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen) OR TS=(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty)
# 4	TS=(euroqol or euro qol or eq5d or eq 5d or hql or hqol or h qol or hrqol or hr qol or disutilit* or rosser "quality of wellbeing" or qwb or "willingness to pay" or "standard gamble*" or "time trade off" or "time tradeoff" or tto)
# 5	#4 OR #3 OR #2
# 6	#5 AND #1

Cochrane Database of Systematic Reviews (CDR): Wiley Online.
Health Technology Assessment Database (HTA): Wiley Online.
NHS Economic Evaluation Database (NHS EED): Wiley Online. 1995-2015
3rd November 2016

#	Searches
#1	MeSH descriptor: [Thyroid Neoplasms] explode all trees
#2	MeSH descriptor: [Goiter, Nodular] explode all trees
#3	(thyr*oid* near/5 (cancer* or neoplas* or carcinoma* or malignan* or tumor* or tumour* or adenocarcinoma*)):ti,ab,kw
#4	MeSH descriptor: [Thyroid Gland] this term only
#5	MeSH descriptor: [Neoplasms] explode all trees
#6	#4 and #5
#7	30-#3, #6

CINAHL 1982 to Present
3rd November 2016

#	**Searches**
S1	(MH "Thyroid Neoplasms+")
S2	(thyr?oid* N5 (cancer* or neoplas* or carcinoma* or malignan* or tumor* or tumour* or adenocarcinoma*))
S3	(MH "Thyroid Gland")
S4	(MH "Neoplasms+")
S5	S3 AND S4
S6	S1 OR S2 OR S5
S7	(MH "Quality of Life")
S8	TI (qol or (quality N2 life)) or AB (qol or (quality N2 life))
S9	TI value and TI (money or monetary) or AB value and AB (money or monetary)
S10	(MH "Economic Value of Life")
S11	(MH "Quality-Adjusted Life Years")
S12	TI (qaly* or qald* or qale* or qtime*) or AB (qaly* or qald* or qale* or qtime*)
S13	TI disability adjusted life or AB disability adjusted life
S14	TI daly* or AB daly*
S15	(MH "Health Status Indicators")
S16	TI (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six) or AB (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six)
S17	TI (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six) or AB (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six)
S18	TI quality adjusted life or AB quality adjusted life
S19	TI (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve) or AB (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve)
S20	TI (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen) or AB (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen)
S21	TI (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty) or AB (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty)
S22	TI (euroqol or euro qol or eq5d or eq 5d) or AB (euroqol or euro qol or eq5d or eq 5d)
S23	TI (hql or hqol or h qol or hrqol or hr qol) or AB (hql or hqol or h qol or hrqol or hr qol)
S24	TI (hye or hyes) or AB (hye or hyes)
S25	TI health* year* equivalent* or AB health* year* equivalent*
S26	TI health utilit* or AB health utilit*
S27	TI (hui or hui1 or hui2 or hui3) or AB (hui or hui1 or hui2 or hui3)
S28	TI disutilit* or AB disutilit*
S29	TI rosser or AB rosser
S30	TI quality N2 wellbeing or AB quality N2 wellbeing
S31	TI qwb or AB qwb

S32	TI willingness N2 pay or AB willingness N2 pay
S33	TI standard gamble* or AB standard gamble*
S34	TI time trade off or AB time trade off
S35	TI time tradeoff or AB time tradeoff
S36	TI tto or AB tto
S37	PT letter
S38	PT editorial
S39	PT comment
S40	S37 or S38 or S39
S41	S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36
S42	S41 NOT S40
S43	S6 AND S42

APPENDIX 2: Excluded studies with reasons

Single arm studies:

1. Anagnostou E, Saltiki K, Vasiliou V, et al. Experience from the administration of tyrosine kinase inhibitors (TKI) in patients with metastatic progressive medullary thyroid carcinoma (MTC) in a referral centre in Greece. European Thyroid Journal 2016; 5:75. doi: http://dx.doi.org/10.1159/000447416

2. Chougnet C, Schlumberger M, Isabelle B. Efficacy and toxicity of vandetanib for advanced medullary thyroid cancer treatment, the French experience. European Thyroid Journal 2014; 3: 77-78. doi: 10.1159/000365244

3. Chougnet CN, Borget I, Leboulleux S, et al. Vandetanib for the treatment of advanced medullary thyroid cancer outside a clinical trial: results from a French cohort. Thyroid 2015; 25(4): 386-91. doi: http://dx.doi.org/10.1089/thy.2014.0361

4. Kurzrock R, Atkins J, Wheler J, et al. Tumor marker and measurement fluctuations may not reflect treatment efficacy in patients with medullary thyroid carcinoma on long-term RET inhibitor therapy. Annals of Oncology 2013;24 (9): 2256-61. doi: http://dx.doi.org/10.1093/annonc/mdt177

5. Kurzrock R, Sherman SI, Ball DW, et al. Activity of XL184 (Cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer. J Clin Oncol 2011; 29(19): 2660-66. doi: http://dx.doi.org/10.1200/JCO.2010.32.4145

6. Marquez Fernandez E, Marmesat Rodas B, Quesada Sanz MP, et al. Use of vandetanib in medullary thyroid cancer. International Journal of Clinical Pharmacy 2016; 38 (6):587. doi: http://dx.doi.org/10.1007/s11096-015-0240-y

7. NCT00098345. Efficacy and Tolerability of ZD6474 in Patients With Thyroid Cancer, 2004.

8. NCT00358956. A Study To Assess ZD6474 (ZACTIMA™) Monotherapy In Locally Advanced or Metastatic Hereditary Medullary Thyroid Cancer, 2006.

9. NCT01661179. Evaluate the Safety and Tolerability of Vandetanib in Japanese Patients With Medullary Thyroid Carcinoma, 2012.

10. NCT01683110. Expanded Access of Cabozantinib in Medullary Thyroid Cancer, 2012.

11. NCT01945762. Observational Study to Evaluate Vandetanib in RET -/+ Patients With Metastatic Medullary Thyroid Cancer, 2013.

12. Robinson BG, Paz-Ares L, Krebs A, et al. Vandetanib (100 mg) in patients with locally advanced or metastatic hereditary medullary thyroid cancer. J Clin Endocrinol Metab 2010; 95(6): 2664-71. doi: http://dx.doi.org/10.1210/jc.2009-2461

13. Takahashi S, Tomomatsu J, Okamoto T, et al. Safety and tolerability of vandetanib in japanese patients (PTS) with medullary thyroid cancer (MTC): A phase i/ii open-label study. Thyroid 2015; 25: A273. doi: http://dx.doi.org/10.1089/thy.2015.29004.abstracts

14. Tiedje V, Locati LD, Kroiss M, et al. Cabozantinib therapy in medullary thyroid carcinoma patients outside a clinical trial. Thyroid 2015; 25: A266. doi: http://dx.doi.org/10.1089/thy.2015.29004.abstracts

15. Tiedje V, Ting S, Walter RF, et al. Prognostic markers and response to vandetanib therapy in sporadic medullary thyroid cancer patients. Eur 2016; 175(3): 173-80. doi: http://dx.doi.org/10.1530/EJE-16-0252
16. Wells SA, Jr., Gosnell JE, Gagel RF, et al. Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer. J Clin Oncol 2010; 28(5):767-72. doi: http://dx.doi.org/10.1200/JCO.2009.23.6604
17. Zhang L, Li S, Zhang Y, et al. Pharmacokinetics and tolerability of vandetanib in Chinese patients with solid, malignant tumors: an open-label, phase I, rising multiple-dose study. Clinical Therapeutics 2011;33(3):315-27. doi: http://dx.doi.org/10.1016/j.clinthera.2011.04.005

Reviews:

1. Belum VR, Serna-Tamayo C, Wu S, et al. Incidence and risk of hand-foot skin reaction with cabozantinib, a novel multikinase inhibitor: a meta-analysis. Clin Exp Dermatol 2016; 41(1): 8-15. doi: http://dx.doi.org/10.1111/ced.12694
2. Huo Z, Yu S, Hong S, et al. A systematic review and meta-analysis of the risk of diarrhea associated with vandetanib treatment in carcinoma patients. Onco Targets Ther 2016; 9: 3621-31. doi: http://dx.doi.org/10.2147/OTT.S96830
3. Qi WX, Shen Z, Lin F, et al. Incidence and risk of hypertension with vandetanib in cancer patients: A systematic review and meta-analysis of clinical trials. British Journal of Clinical Pharmacology 2013; 75(4): 919-30. doi: http://dx.doi.org/10.1111/j.1365-2125.2012.04417.x
4. Rinciog C, Myren KJ, Alden M, et al. An Indirect Treatment Comparison of Cabozantinib Verse Vandetanib in Progressive Medullary Thyroid Cancer (MTC). Value in Health 2014; 17(7): A616-17. doi: http://dx.doi.org/10.1016/j.jval.2014.08.2173
5. Rosen AC, Wu S, Damse A, et al. Risk of rash in cancer patients treated with vandetanib: systematic review and meta-analysis. J Clin Endocrinol Metab 2012; 97(4): 1125-33. doi: http://dx.doi.org/10.1210/jc.2011-2677
6. Thornton K, Kim G, Maher VE, et al. Vandetanib for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease: U.S. Food and Drug Administration drug approval summary. Clin Cancer Res 2012;18(14):3722-30. doi: http://dx.doi.org/10.1158/1078-0432.CCR-12-0411

Letters / commentaries:

1. Anonymous. Vandetanib (Caprelsa) for medullary thyroid cancer. Med Lett Drugs Ther 2012; 54(1381): 3-4.
2. Anonymous. Vandetanib: too dangerous in medullary thyroid cancer. Prescrire International 2012; 21(131): 233.

3. Baudry C, Paepegaey AC, Groussin L. Reversal of Cushing's syndrome by vandetanib in medullary thyroid carcinoma. New England Journal of Medicine 2013; 369(6): 584-86. doi: 10.1056/NEJMc1301428
4. Chatal JF, Kraeber-Bodéré F, Goldenberg DM, et al. Treatment of metastatic medullary thyroid cancer with vandetanib: need to stratify patients on basis of calcitonin doubling time...J Clin Oncol. 2012; 30(2): 134-41. J Clin Oncol 2012;30(17):2165-65.
5. Fuerst M. Medullary Thyroid Cancer: Cabozantinib Extends PFS in Patients with RET or RAS Mutations. Oncology Times 2013: 11-12.
6. Susman E. Cabozantinib Linked to Worrisome Weight Loss. Oncology Times 2015; 37(15):55-56.

Population:

1. Fox E, Widemann BC, Chuk MK, et al. Vandetanib in children and adolescents with multiple endocrine neoplasia type 2B associated medullary thyroid carcinoma. Clin Cancer Res 2013; 19(15): 4239-48. doi: http://dx.doi.org/10.1158/1078-0432.CCR-13-0071
2. NCT00514046. Vandetanib to Treat Children and Adolescents With Medullary Thyroid Cancer, 2007.
3. NCT01709435. Cabozantinib S-Malate in Treating Younger Patients With Recurrent or Refractory Solid Tumors, 2012.
4. NCT02867592. Cabozantinib-S-Malate in Treating Younger Patients With Recurrent, Refractory, or Newly Diagnosed Sarcomas, Wilms Tumor, or Other Rare Tumors, 2016.
5. Nguyen L, Holland J, Ramies D, et al. Effect of Renal and Hepatic Impairment on the Pharmacokinetics of Cabozantinib. Journal of Clinical Pharmacology 2016;56(9):1130-40. doi: http://dx.doi.org/10.1002/jcph.714.

Intervention:

1. Bastholt L, Kreissl MC, Fuhrer D, et al. Effect of an outreach programme on vandetanib safety in medullary thyroid cancer. European Thyroid Journal 2016; 5(3): 187-94. doi: http://dx.doi.org/10.1159/000448919
2. NCT02088645. 177Lu-PP-F11N for Receptor Targeted Therapy and Imaging of Metastatic Thyroid Cancer. 2014.

Animal study:

1. Lin H, Jiang X, Zhu H, et al. 2ME2 inhibits the activated hypoxia-inducible pathways by cabozantinib and enhances its efficacy against medullary thyroid carcinoma. Tumour Biology 2016;37(1):381-91. doi: http://dx.doi.org/10.1007/s13277-015-3816-1

Duplicate:

1. Anonymous. 37th Annual Meeting of the European Thyroid Association. European Thyroid Journal Conference: 37th Annual Meeting of the European Thyroid Association Leiden Netherlands Conference Start 2013; 2.

APPENDIX 3: Supplementary information to inform time to event analyses

Figure 39: ITT EXAM standard diagnostic plots for PFS

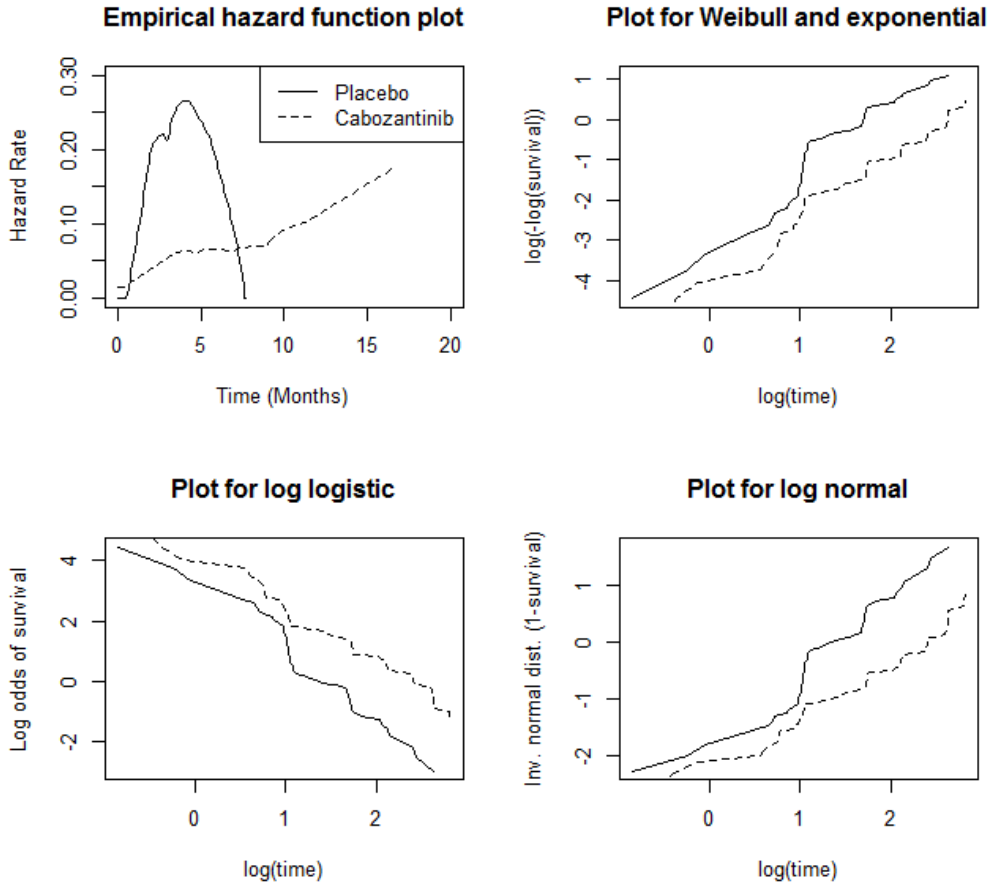


Figure 40: **ITT EXAM standard diagnostic plots for OS**

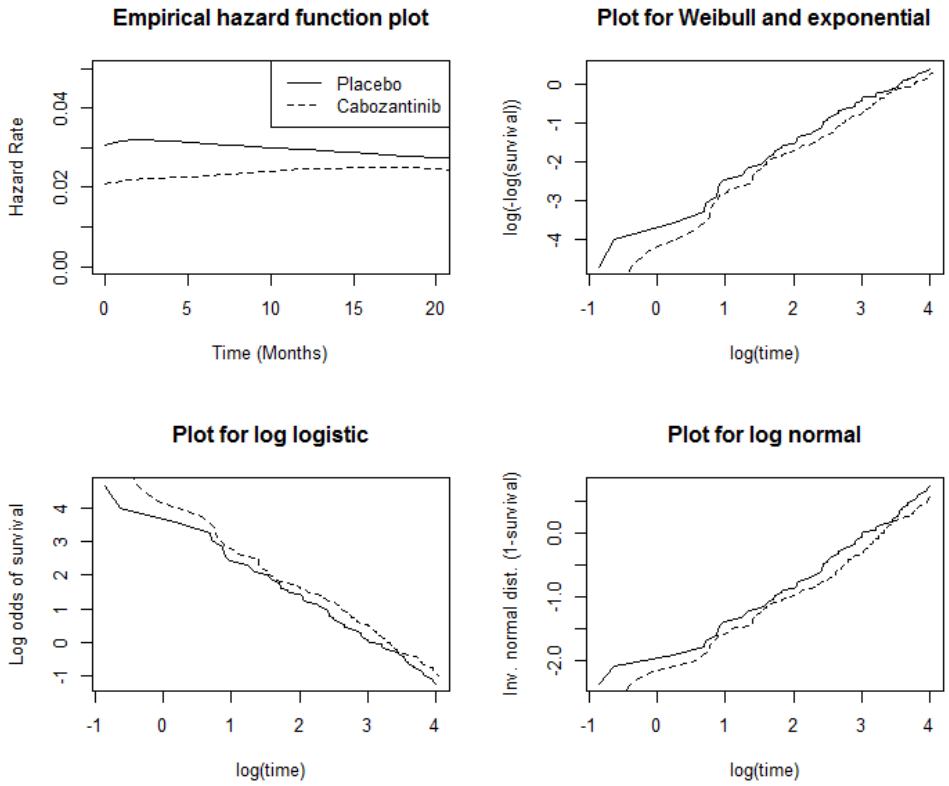


Figure 41: ZETA EU label Kaplan-Meier for PFS from reconstructed IPD

Figure 42: **ZETA EU label Kaplan-Meier for OS from reconstructed IPD**

Figure 43: **ZETA EU label, standard diagnostic plots for PFS**

Figure 44: **ZETA EU label, standard diagnostic plots for OS**

Figure 45: ZETA Restricted EU label Kaplan-Meier for PFS from reconstructed IPD

Figure 46: ZETA Restricted EU label, standard diagnostic plots for PFS

Figure 47: ZETA Restricted EU label Kaplan-Meier for OS from reconstructed IPD

Figure 48: ZETA Restricted EU label, standard diagnostic plots for OS

reduction due to QTc prolongation and after dose interruption for more than two weeks. ECGs and blood tests should also be obtained as clinically indicated during this period and afterwards. Frequent ECG monitoring of the QTc interval should be continued.

Serum potassium, serum magnesium and serum calcium should be kept within normal range to reduce the risk of ECG QTc prolongation. Additional monitoring of QTc, electrolytes and renal function are required especially in case of diarrhoea, increase in diarrhoea/dehydration, electrolyte imbalance and/or impaired renal function. If QTc increases markedly but stays below 500 msec, cardiologist advice should be sought."[22]

The SmPC for cabozantinib[23] also recommends close monitoring during the first eight weeks of treatment:

"As most events can occur early in the course of treatment, the physician should evaluate the patient closely during the first eight weeks of treatment to determine if dose modifications are warranted. Events that generally have early onset include hypocalcaemia, hypokalaemia, thrombocytopenia, hypertension, palmarplantar erythrodysaesthesia syndrome (PPES), and gastrointestinal (GI) events (abdominal or mouth pain, mucosal inflammation, constipation, diarrhoea, vomiting)." [23]

One of the clinical advisors to the Assessment Group noted that whilst cardiac toxicity is less for cabozantinib compared with vandetanib, ECG monitoring may also be required.

3.3 Current service provision

3.3.1 Clinical guidelines

There are no clinical guidelines for the management of MTC in the UK. A NICE quality standard for head and neck cancer has recently been published,[24] however, this does not include the management of MTC.

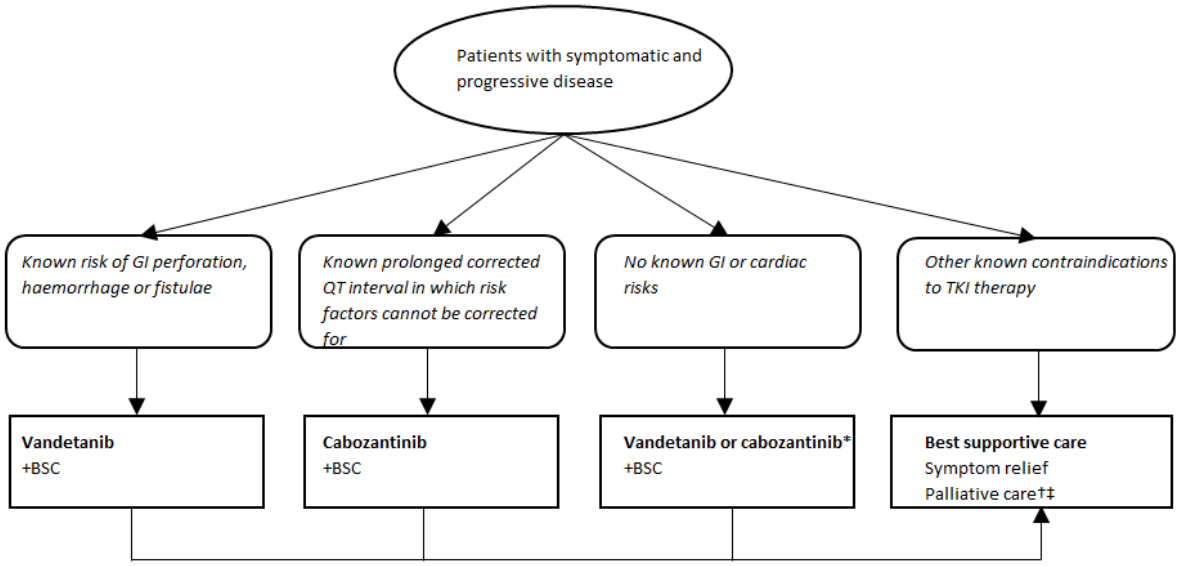
3.3.2 Current NICE technology appraisal guidance

There is currently no NICE technology appraisal guidance for interventions for the treatment of unresectable locally advanced or metastatic MTC.

3.3.3 Current service cost

The current cost of managing MTC is uncertain. However, MTC is a very rare disease, with an estimated annual incidence for England of around 170 new patients. Prescribing data from the Cancer Drugs Fund (CDF) indicates that in 2016, [redacted] new patients received vandetanib and [redacted] new patients received cabozantinib. The data from 2015 indicate very similar prescribing levels, with [redacted] new patients starting vandetanib and [redacted] patients starting cabozantinib (personal communication: Professor Peter Clark, Chair

Figure 1: Current treatment pathway for adults with symptomatic and progressive MTC



*Patient may switch to other TKI if intolerant or severe AEs experienced within 3 months. Note that the vandetanib licence is in aggressive and symptomatic disease, whilst the licence for cabozantinib is for progressive, unresectable locally advanced or metastatic MTC
†may include palliative surgery, palliative radiotherapy and/or treatments for bone pain
‡ nuclear medicine therapies such as MIBG/Dotatate may be considered in some patients

Box 1: CDF indication for cabozantinib and vandetanib for the treatment of locally advanced or metastatic MTC[25]

The first-line treatment of MTC where all the following criteria are met:

- Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
- Histologically confirmed, unresectable, locally advanced or metastatic MTC
- 1st line indication
- Progressive and symptomatic disease
- *For cabozantinib:* No previous tyrosine kinase therapy unless intolerant of vandetanib within 3 months of starting therapy and toxicity which cannot be managed by dose delay or dose modification and in the absence of disease progression on vandetanib
- *For vandetanib:* No previous tyrosine kinase therapy unless intolerant of cabozantinib within 3 months of starting therapy and toxicity which cannot be managed by dose delay or dose modification and in the absence of disease progression on cabozantinib.

3.4 Description of technology under assessment

3.4.1 Interventions considered in the scope of this report

This assessment includes two interventions: cabozantinib and vandetanib.

Cabozantinib and vandetanib for treating unresectable locally advanced or metastatic medullary thyroid cancer [ID56]

Assessment Report: Response from Ipsen to NICE.

Ipsen are broadly in agreement with the conclusions reached in the Assessment Report and have no further comments to add on the technical content of the report.

[redacted]
Ipsen Limited
190 Bath Road
Slough
SL1 3XE

Dear Meindert,

Thank you for the opportunity to provide comments on the Assessment Group's (AG) report for cabozantinib and vandetanib for treatment of unresectable locally advanced or metastatic medullary thyroid cancer [ID56].

We find the review group's assessment of the evidence and the methodology used in their report as fair and reasonable. However, Sanofi Genzyme would like to comment on the following factors which are important considerations in the light of the evidence on vandetanib:

Main points in response to the AG report

- MTC is an ultra-orphan disease
- Application of standard NICE CEA thresholds to rare diseases are not reasonable
- The restricted EU label approximates the patient population currently treated with vandetanib in UK clinical practise
- The value of data collection via the CDF/Return to CDF to confirm the patient population
- Economic modelling assumptions regarding cross-over and open label use of vandetanib
- Vandetanib meets the end of life (EOL) criteria
- Clinicians want two TKIs to have treatment options for patients
- Factual inaccuracies or statements needing context in AG report
- Comment on the economic model

MTC is an ultra-orphan disease

As stated in the assessment report (page 12) "MTC is a very rare disease and for many patients, surgery can be curative, hence the population of patients with advanced or metastatic MTC eligible for treatment with vandetanib and cabozantinib is very small". We completely agree with the assessment group's statement and would like to reiterate that the current prevalence of MTC in the EU is 0.7/10,000 and the incidence is 0.22/100,000 (1). MTC fulfils the criteria for an orphan indication in the European Union (EU) (prevalence of <5/10,000) (2).

There is no official definition for an ultra-orphan disease. However, based on an AG estimate of 170 patients with MTC in the UK, MTC meets the accepted criterion in England and Wales: a disease affecting less than 1000 patients or <1/50,000 (3-4). MTC has two distinct phases: an indolent phase where treatment strategy is watchful waiting; and an aggressive phase during which patients in the UK receive active treatment. Using estimates from the AG report, it is clear that most patients are managed with watchful waiting and only a small percentage are actually eligible for active treatment. The actual number of patients treated with either vandetanib or cabozantinib is very low (approximately [redacted] patients/year) and estimated budget impact of £2million/year.

Given the above, and to reiterate statements made by Sanofi Genzyme when this technology appraisal was scoped, we do not think this is a suitable topic for NICE multiple technology appraisal. When the drug received its marketing authorisation in 2012 the product was not scoped by NICE, presumably because it did not meet the criteria for NICE assessment. Of all processes available to NICE, the Highly Specialised Technology evaluation is a more equitable process to apply for a disease with such a small number of patients.

Application of standard NICE willingness to pay thresholds to rare diseases is not reasonable

We acknowledge that MTC does not meet the Highly Specialised Technology evaluation criteria. However, assessing either of the TKIs in the MTA against usual NICE efficiency thresholds of £20,000 - £30,000 would be unfairly punitive. The MTC population routinely treated in UK is likely to meet the End of Life Criteria and therefore that threshold should be available for the NICE committee's consideration. However, we think it would be more reasonable to apply the new HST threshold (£100,000 per QALY) to this assessment.

The restricted EU label reflects the patient population treated with vandetanib in UK clinical practise

As a company, Sanofi Genzyme believes that if a patient is deemed to be progressing, based on RECIST/imaging evidence and a clinical/patient decision is made that active treatment is suitable understanding the risk/benefits of the TKIs, the patient should be offered vandetanib or cabozantinib. We understand that in the UK treatment is reserved until the disease is aggressively progressing.

There is debate in the clinical literature regarding the optimal time to start tumour treatment in patients with advanced MTC. The size and number of tumour foci and the rate of change of tumour volume during watchful waiting may help identify the optimal time to commence treatment with vandetanib. The rate of change in serum levels of calcitonin (CTN) and/or carcinoembryonic antigen (CEA) may also be taken into account but should not be considered in isolation. Therefore, we accept the view of the clinical advisors that CTN/CEA doubling are not used routinely in clinical practice to determine treatment initiation and that radiographic imaging and symptoms are more likely to determine need for treatment irrespective of CTN/CEA biomarker levels. However, CTN/CEA are routinely monitored and it is well accepted that doubling times $\leq$24months is indicative of aggressive form of the disease, rapid deterioration and reduced survival compared to patients with doubling times >24months (AG Report page 12).

The EU label indication is open to interpretation but the intention is clear, that only those patients most in need should be treated:

"*In view of the associated risks, it is important to limit treatment with vandetanib to patients who are in real need for treatment, i.e. with a symptomatic-aggressive course of the disease. Either symptomatic disease or progressive disease alone is not enough to prompt the need of treatment with vandetanib. Rate of change in biomarker levels such as of calcitonin (CTN) and/or carcinoembryonic antigen (CEA) as well as the rate of change of tumour volume during watchful waiting might help to identify not only patients in need for treatment but also the optimal moment to commence treatment with vandetanib*."

Clinicians weigh up the risk-benefit of long term treatment against potentially rapid disease progression if left untreated and we believe that clinical judgement and rationale ensures that patients selected for active treatment are those patients who need it most. According to

page 84 of the AG report, the clinical advisors noted that patients with symptomatic and progressive disease "would also likely have CTN/CEA doubling times ≤24 months". So, although in clinical practice CTN and CEA doubling times are not factors formally required when determining TKI treatment initiation, it is highly likely that many/most patients initiating treatment (in the UK at least) will have doubling times less than 24 months.

So, we are not suggesting there *must* be additional criteria for CTN/CEA doubling times ≤24 months in practice for patients to be eligible for vandetanib. Instead we have used the available data from ZETA as a reasonable proxy for the UK patient population currently treated with vandetanib. It was our attempt to describe a cohort based on patients' need for treatment options, even though it means using a more restrictive interpretation of the EU label, that reflects UK practice and facilitates decision making. It is plausible that the true UK patient lies somewhere between the EU label and the restricted EU label populations that were both of which were post hoc definitions of the ZETA trial.

Proposed CDF data collection to confirm characteristics of the patient population

To reduce the uncertainty regarding which of the populations considered in the submission reflects the true MTC population in the UK treated with vandetanib, Sanofi-Genzyme would commit to collect baseline clinical characteristics data, including CTN/CEA doubling times, if this product were returned to the CDF. Collection of baseline demographic and clinical characteristics for treated patients will elucidate where on the range between EU label and restricted EU label, patients in the UK truly are.

Economic modelling assumptions regarding cross-over and open label use of vandetanib

The AG has rightly pointed out the limitation of the evidence package arising from the crossover to vandetanib treatment. As noted in our submission all outcomes are confounded by extensive crossover. Crossover occurred because it was considered unethical to deny access to a treatment, to patients on the placebo arm, which had demonstrated benefit. In the EU restricted population, [redacted] of those initially on placebo crossed over to vandetanib.

In addition, patients treated with vandetanib experience tumour shrinkage of most or at least some lesions and the tumour volume is thus lower than at baseline. When the disease stops responding to treatment, or at the turning point from disease control to disease progression, the tumour volume starts to increase but there may still be considerable time during which the tumour volume remains below that at baseline and clinicians may, thus, elect to continue treatment. Indeed, feedback from a clinical advisor (page 85) indicated that in some cases, the clinician may maintain patients on treatment if the observed progression is slow, or if the response to treatment is still evident in some lesions. The reasoning being that if treatment is interrupted progression will be unrestrained. Thus, many patients on vandetanib stayed on treatment after progression. In the EU restricted population, [redacted] of patients randomised to vandetanib continued open-label treatment.

As we noted in our submission we could not undo crossover statistically to produce clinically meaningful results and all outcomes are confounded by extensive crossover.

In the interest of reducing uncertainty or at the very least to demonstrate that statistically adjusting for crossover would be unsuccessful in this study Sanofi Genzyme repeats its offer to share the IPD data from ZETA with the AG so they can investigate the crossover issue.

Vandetanib meets the end of life (EOL) criteria

We challenge the conclusion that vandetanib does not meet NICE EOL criteria for the following reasons: 1) there are very limited overall survival data for MTC patients not treated with TKIs; 2) for the specific UK patient population, for which there is some uncertainty (EU label/restricted EU label), there are no robust overall survival estimates if not treated with TKIs; 3) the true clinical advantage of vandetanib over BSC was confounded by the crossover permitted in the ZETA trial.

In general, 10 year survival with MTC ranges from 21%-40% (AG report, page 11). Patients with aggressive disease defined with CTN/CEA doubling have poorer prognosis as highlighted above. In the EXAM study, the median OS of the placebo arm (which is not confounded by crossover to active treatment) is 21.1months. The AG concluded the EXAM population and the ZETA trial EU label population are equivalent. These may be the only data which reflects progression in symptomatic and progressive patients without treatment. In this trial, cross-over to cabozantinib was not allowed for patients randomised to placebo and patients who received any other subsequent anti-cancer therapies were censored at the time of the primary analysis. Overall, 52% of placebo patients and 33% of cabozantinib patients had some form of post-progression therapy, including 16% and 10% who went on to receive vandetanib. No data are available on mean OS (5).

Moreover, the National Cancer Database reported median overall survival less than 24 months in MTC patients with distant metastases (6). This comprehensive study includes data from 2968 patients with MTC diagnosed between 1998 and 2005, and is the only from few registry studies that we could identify reporting overall survival for MTC patients. Currently, it will be impossible to collect survival data as it will be unethical not to treat MTC patients as there are now 2 available alternatives to best supportive care approved.

In the ZETA EU restricted population, the median and mean OS estimates are not a true estimate of treatment benefit with vandetanib due to the extensive crossover. Instead the OS data are more likely to show the impact of treatment with immediate vs delayed vandetanib, rather than be a true comparison of vandetanib vs placebo. In the absence of meaningful OS data, progression-free survival data can provide information on efficacy. In EU restricted population, there was [redacted] months incremental benefit over placebo, ORR was 41.4%. As highlighted by the assessment report, the criterion relating to greater than 3 months life extension is likely to be met for vandetanib. Equally, the treatment is licensed and indicated for small patient population.

Therefore, on balance of available evidence, vandetanib can be considered to meet NICE EOL criteria, as the overall median survival of MTC with aggressive/progressive and symptomatic disease is <2 years and true treatment OS benefit of vandetanib is likely to be >3months.

For clinicians to have treatment options two TKIs are required

Prior to initiating therapy, a review of a patient's past medical history, current comorbidities, and medications would be conducted with an emphasis on the potential interactions and effects on treatment-related AEs. Therefore, there is a need for both vandetanib and cabozantinib as shown in Figure 1 of the AG report. Each drug has a different risk-benefit profile and patients' individual characteristics are taken into account when selecting appropriate treatment as neither drug are suitable for all patients with MTC.

As it can be expected that disease will become resistant to treatment in the long term, disease progression will be observed in time and it is important to have alternative therapies

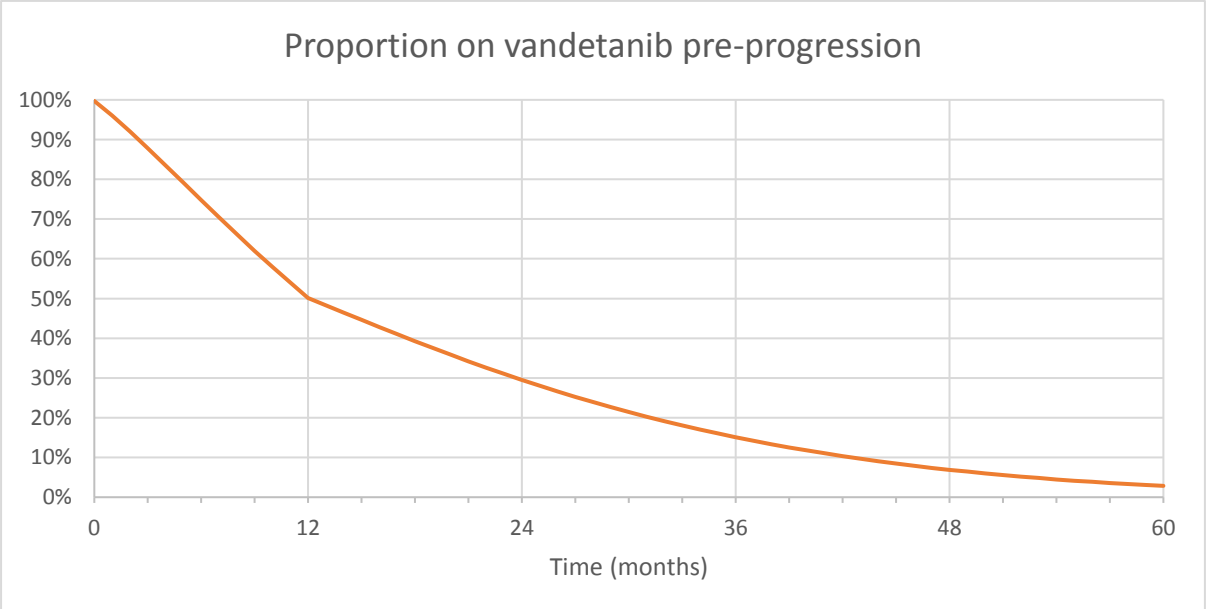
to offer. Vandetanib and cabozantinib are similar but still different enough to have a distinct mechanism of action and AE risk profile. This difference allows salvage therapy for patients that start progressing with the first line TKI.

Factual inaccuracies or statements without context in the AG report

- In discussion section 2.5 (page 8), the report states: “Both cabozantinib and vandetanib produced frequent AEs, with substantial proportions of patients experiencing AEs that led to dose interruption or reduction”
  The incidence of AEs observed in clinical trials, a period during which there's little experience with the tested drugs, would not correspond to the observation in current clinical practice. The post-marketing experience allowed a significant learning towards AEs management (prevention as well as treatment) (7-9). Since its approval in 2012, clinical experience and information collected on safety demonstrates a good benefit/safety profile on vandetanib.
- Figure 1, page 15. In general we agree with this treatment algorithm but have a few suggestions. Firstly there is a subtle difference in the wording of the indications for vandetanib and cabozantinib which can be reflected as footnote in the figure (vandetanib licence is in aggressive and symptomatic while cabozantinib is in progressive disease). The box which states ‘Known prolonged corrected QT interval’ is too broad as long QTc intervals may be prone for correction. Therefore we suggest adding "in which risk factors cannot be corrected".
- We would like to note an inaccuracy in page 87 of the report, “However, the comparison of predicted and observed OS probabilities represented in this comparison relate to two different populations: the covariate-adjusted Weibull model relates to the Restricted EU label population, whilst the observed Kaplan-Meier curves relate to the ZETA ITT population with CEA and CTN doubling time ≤24 months (excluding the progressive population characteristics)”. The KM curves include the progressive population characteristics.
- Incidence and prevalence (section 3.1/page 10) states: “Almost all patients with MEN2, MEN3 and FMTC have germline RET mutation, whilst approximately 40%-50% of patients with sporadic MTC have somatic RET mutations”. The percentage of 40%-50% is based on older data and at the time of diagnosis. More recent studies investigating RET mutations prevalence in advanced MTC show a much higher percentage of RET positive cases (approx. 90%) based on reference: Romei C et al. Low prevalence of the somatic M918T RET mutation in micro-medullary thyroid cancer. Thyroid 2012, 22:476–481.
- Section 3.3.1 (page 13) states: “There are no clinical guidelines for the management of MTC.” This should read: “There are no clinical guidelines for the management of MTC in the UK.” There are guidelines for MTC published from Spanish Society of Endocrinology (10) and American Thyroid Association (11); and the British Thyroid Association includes a chapter on MTC management (12).
- Cost of managing AEs (page 91). The view reflected here can be challenged. It is also likely that other options would be tried before discontinuing treatment e.g. Patient would be educated on minimizing side effects (i.e. use sunblock and moisturizing agents, to avoid rash; adapt diet, to avoid diarrhoea), recognizing the most common side effects symptoms so that symptomatic treatment can be initiated; and dose reduction will be considered if side effect symptomatic treatment is ineffective. Dose interruption will be the last resort. We request this point is discussed with clinical experts and text updated to reflect common practice.

- Time to treatment discontinuation (page 130). The only result available from ZETA on this aspect was the proportion of patients who discontinued treatment for reasons other than progression or death. In the company submitted model, we agree that it was an overestimate to apply this discontinuation probability as a fixed parameter in every cycle pre-progression and not at all post-progression. To address this, an additional analysis has been done linearly increasing the proportion discontinued from zero to reach the full amount after 1 year (see figure 1). We think this is more likely the case as discontinuations tended to occur early and disagree with the assumption made in the AG model that half the discontinuation rate would apply constantly over the entire pre-progression phase. In the individual simulation, the proportion can be converted to a hazard which is then used to estimate each individual's time to discontinuation. This hazard can also be applied in the same way to the patients who crossover to vandetanib at progression. In that analysis, the cost of treatment post-progression in those who crossover drops by nearly 15% but remains higher than the cost of vandetanib pre-progression because the period post-progression is longer than the pre-progression time.
- In its estimation of budget impact, the AG state that 5% of thyroid cases are MTC and reference the BTA guidelines. The BTA guidelines however state that 3% of cases are in adults with MTC. A recent audit by Wiltshire et al (2015) estimated approximately 253 cases of MTC (13).
- The budget impact section, section 7, requires more detail to understand how the AG have arrived at the cost impact to the NHS. We understand list prices have been used (vandetanib has lower drug acquisition cost) but cost over 5 years is higher on vandetanib than cabozantinib. However in section 3.3.3 (page 13) "Based on current prescribing levels, the cost of treating new MTC patients with cabozantinib and vandetanib for one year (assuming full dose and excluding any discontinuation) is approximately £1.96 million. This value is in line with our estimates assuming same number of patients would be treated with either drug. Please add further detail to this section along with the assumptions and limitation of the analysis.

Figure 1 Proportion on vandetanib treatment in the pre-progression phase.



Graph obtained using the company submitted model and the discontinued proportion linearly increasing from 0% to 31% (proportion obtained from ZETA). The proportion on treatment pre-progression also decreases because of tumour progression and death. Assumed no further discontinuation after progression in patients continuing vandetanib

Summary and conclusion

We believe the supporting evidence provided here and by the UK clinical advisors would suggest that it is plausible that those patients treated in practice are highly likely to have CTN/CEA doubling < 24 months as their tumour progresses from indolent to aggressive.

We urge the Committee to consider the balance of evidence on vandetanib, the expected ICERs using standard NICE reference case, the estimated patient population versus the patient need in this ultra-orphan disease. Denying access to one or both vandetanib or cabozantinib, particularly where the treatment options have already been available in the UK via the CDF and clinicians desperately want access to treatment options, creates a very unequitable situation for patient with this rare disease.

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Assessment consultation response – Assessment Group response to comments from Ipsen and Sanofi

Response to comments received from Ipsen

Comment	Assessment Group response
Ipsen are broadly in agreement with the conclusions reached in the Assessment Report and have no further comments to add on the technical content of the report.	No amendment required.

Response to comments received from Sanofi

Comment	Assessment Group response
MTC is an ultra-orphan disease As stated in the assessment report (page 12) "MTC is a very rare disease and for many patients, surgery can be curative, hence the population of patients with advanced or metastatic MTC eligible for treatment with vandetanib and cabozantinib is very small". We completely agree with the assessment group's statement and would like to reiterate that the current prevalence of MTC in the EU is 0.7/10,000 and the incidence is 0.22/100,000 (1). MTC fulfils the criteria for an orphan indication in the European Union (EU) (prevalence of <5/10,000) (2). There is no official definition for an ultra-orphan disease. However, based on an AG estimate of 170 patients with MTC in the UK, MTC meets the accepted criterion in England and Wales: a disease affecting less than 1000 patients or <1/50,000 (3-4). MTC has two distinct phases: an indolent phase where treatment strategy is watchful waiting; and an aggressive phase during which patients in the UK receive active treatment. Using estimates from the AG report, it is clear that most patients are managed with watchful waiting and only a small percentage are actually eligible for active treatment. The actual number of patients treated with either vandetanib or cabozantinib is very low (approximately [redacted] patients/year) and estimated budget impact of £2million/year. Given the above, and to reiterate statements made by Sanofi Genzyme when this technology appraisal was scoped, we do not think this is a suitable topic	The Assessment Group agrees that MTC is very rare. Cabozantinib and vandetanib have been assessed as part of a multiple technology appraisal as this is how the topic was scoped.

for NICE multiple technology appraisal. When the drug received its marketing authorisation in 2012 the product was not scoped by NICE, presumably because it did not meet the criteria for NICE assessment. Of all processes available to NICE, the Highly Specialised Technology evaluation is a more equitable process to apply for a disease with such a small number of patients.	
Application of standard NICE CEA thresholds to rare diseases are not reasonable We acknowledge that MTC does not meet the Highly Specialised Technology evaluation criteria. However, assessing either of the TKIs in the MTA against usual NICE efficiency thresholds of £20,000 - £30,000 would be unfairly punitive. The MTC population routinely treated in UK is likely to meet the End of Life Criteria and therefore that threshold should be available for the NICE committee's consideration. However, we think it would be more reasonable to apply the new HST threshold (£100,000 per QALY) to this assessment.	Cabozantinib and vandetanib have been assessed as part of a multiple technology appraisal as this is how the topic was scoped. Matters relating to the principles and process of decision-making should be taken up with NICE. As discussed on page 147 of the assessment report, the expected mean survival in the placebo group of the EXAM trial and the subgroups of the ZETA trial is greater than 24 months. This conclusion remains consistent irrespective of the choice of parametric model used to represent overall survival. However, as open-label vandetanib use has not been adjusted for, the true survival of the ZETA subgroups is not known.
The restricted EU label approximates the patient population currently treated with vandetanib in UK clinical practise As a company, Sanofi Genzyme believes that if a patient is deemed to be progressing, based on RECIST/imaging evidence and a clinical/patient decision is made that active treatment is suitable understanding the risk/benefits of the TKIs, the patient should be offered vandetanib or cabozantinib. We understand that in the UK treatment is reserved until the disease is aggressively progressing. There is debate in the clinical literature regarding the optimal time to start tumour treatment in patients with advanced MTC. The size and number of tumour foci and the rate of change of tumour volume during watchful waiting may help identify the optimal time to commence treatment with vandetanib. The rate of change in serum levels of calcitonin (CTN) and/or carcinoembryonic antigen (CEA) may also be taken into account but should not be considered in isolation. Therefore, we accept the view of the clinical advisors that CTN/CEA doubling are not used routinely in clinical practice to	The view of the clinical advisors to the AG was that these biomarkers are unlikely to be relevant in the presence of other criteria indicating progressive disease (e.g. RECIST criteria and symptoms), and whilst they might be used to determine whether treatment is still working, they would not be used to inform decisions about whether to initiate TKI treatment. On the basis of this clinical advice, it appears that the currently treated UK population is likely to be more reflective of the EU label population rather than the Restricted EU label population. It should also be noted that if the CEA/CTN doubling criteria were a requirement for treatment initiation, this would mean delayed treatment in some patients for 2 years or longer as well as the preclusion of treatment in some patients who have symptomatic and progressive disease who may obtain benefit but do not meet the CEA/CTN doubling time criterion.

determine treatment initiation and that radiographic imaging and symptoms are more likely to determine need for treatment irrespective of CTN/CEA biomarker levels. However, CTN/CEA are routinely monitored and it is well accepted that doubling times <24months is indicative of aggressive form of the disease, rapid deterioration and reduced survival compared to patients with doubling times >24months (AG Report page 12). The EU label indication is open to interpretation but the intention is clear, that only those patients most in need should be treated: "In view of the associated risks, it is important to limit treatment with vandetanib to patients who are in real need for treatment, i.e. with a symptomatic-aggressive course of the disease. Either symptomatic disease or progressive disease alone is not enough to prompt the need of treatment with vandetanib. Rate of change in biomarker levels such as of calcitonin (CTN) and/or carcinoembryonic antigen (CEA) as well as the rate of change of tumour volume during watchful waiting might help to identify not only patients in need for treatment but also the optimal moment to commence treatment with vandetanib." Clinicians weigh up the risk-benefit of long term treatment against potentially rapid disease progression if left untreated and we believe that clinical judgement and rationale ensures that patients selected for active treatment are those patients who need it most. According to page 84 of the AG report, the clinical advisors noted that patients with symptomatic and progressive disease "would also likely have CTN/CEA doubling times ≤24 months". So, although in clinical practice CTN and CEA doubling times are not factors formally required when determining TKI treatment initiation, it is highly likely that many/most patients initiating treatment (in the UK at least) will have doubling times less than 24 months. So, we are not suggesting there must be additional criteria for CTN/CEA doubling times ≤24 months in practice for patients to be eligible for vandetanib. Instead we have used the available data from ZETA as a reasonable proxy for the UK patient population currently treated with vandetanib. It was our attempt to describe a cohort based on patients' need for treatment options, even though it means using a more restrictive interpretation of the EU label, that reflects UK practice and facilitates decision making. It is plausible that the true UK patient lies somewhere between the EU label and the	

restricted EU label populations that were both of which were post hoc definitions of the ZETA trial.	
The value of data collection via the CDF/Return to CDF to confirm the patient population To reduce the uncertainty regarding which of the populations considered in the submission reflects the true MTC population in the UK treated with vandetanib, Sanofi-Genzyme would commit to collect baseline clinical characteristics data, including CTN/CEA doubling times, if this product were returned to the CDF. Collection of baseline demographic and clinical characteristics for treated patients will elucidate where on the range between EU label and restricted EU label, patients in the UK truly are	This may be a relevant consideration for the NICE Appraisal Committee. However, the Assessment Group notes that as a consequence of treatment switching in the placebo group of ZETA, together with the continued use of vandetanib beyond disease progression, a key uncertainty relates to the *relative* benefit of vandetanib versus BSC within the Restricted EU label population. It does not appear that the CDF proposition would be helpful in reducing this uncertainty as no information would be collected regarding outcomes for patients receiving BSC.
Economic modelling assumptions regarding cross-over and open label use of vandetanib The AG has rightly pointed out the limitation of the evidence package arising from the crossover to vandetanib treatment. As noted in our submission all outcomes are confounded by extensive crossover. Crossover occurred because it was considered unethical to deny access to a treatment, to patients on the placebo arm, which had demonstrated benefit. In the EU restricted population, [redacted] of those initially on placebo crossed over to vandetanib. In addition, patients treated with vandetanib experience tumour shrinkage of most or at least some lesions and the tumour volume is thus lower than at baseline. When the disease stops responding to treatment, or at the turning point from disease control to disease progression, the tumour volume starts to increase but there may still be considerable time during which the tumour volume remains below that at baseline and clinicians may, thus, elect to continue treatment. Indeed, feedback from a clinical advisor (page 85) indicated that in some cases, the clinician may maintain patients on treatment if the observed progression is slow, or if the response to treatment is still evident in some lesions. The reasoning being that if treatment is interrupted progression will be unrestrained. Thus, many patients on vandetanib stayed on treatment after progression. In the EU restricted population, [redacted] of patients randomised to vandetanib continued open-label treatment.	The use of open-label vandetanib is a significant problem for the interpretation of ZETA trial outcomes. The Assessment Group did request the IPD from ZETA during the clarification round. In response to this request, the company stated: *"Caprelsa is a rare disease medicine originally owned by AstraZeneca. Sanofi Genzyme entered into a definitive agreement with AstraZeneca in July 2015 to have access to this medicine.* [redacted] *therefore, we request a teleconference with NICE and the academic review group to discuss how best to take this request forward."* During the telephone call, the company was apprehensive about providing the IPD due to confidentiality/contract issues and it was instead agreed that Sanofi would provide requested Kaplan-Meier curves in aggregate form with N at risk tables. These unadjusted data were used in the Assessment Group model. At that point in time, both Sanofi and the Assessment Group considered this an acceptable solution. Sanofi's clarification response provides some detail around the alternative crossover methods considered and argues that the RPSFTM is the most appropriate approach. As noted in the assessment report (page 83), the Sanofi CS states that whilst attempts were made to account for treatment switching in the ZETA trial using the RPSFT method, these were reported to have been unsuccessful. In response to

As we noted in our submission we could not undo crossover statistically to produce clinically meaningful results and all outcomes are confounded by extensive crossover. In the interest of reducing uncertainty or at the very least to demonstrate that statistically adjusting for crossover would be unsuccessful in this study Sanofi Genzyme repeats its offer to share the IPD data from ZETA with the AG so they can investigate the crossover issue.	a request for clarification (see clarification response,41 question A2), the company stated *"RPSFT failed to undo bias as the method looks for the effect sizes needed so that the two survival curves match if they are given the same treatment, if the curves never separate, or don't separate enough because crossover happens too early or before sufficient events occur in placebo (as was the case in ZETA), the curves will match up with effects very close to the null. This was the result obtained in the analyses."* Based on the company's description, it seems likely that the RPSFT model did work as it would be expected to given its assumptions, but the company describe the approach failing as it showed a null treatment effect. Given that the company does not believe that alternative methods for adjusting for treatment switching are appropriate, and the RPSFTM approach did not produce a separation of the curves, the value of the Assessment Group repeating the RPSFTM approach appears to be limited (unless the method has been implemented incorrectly). With respect to the point about continuing vandetanib post-progression, one clinical advisor to the Assessment Group suggested that if imaging showed a mixed response with the largest or most symptomatic/problematic lesions being stable and some other lesions progressing, treatment with vandetanib may still be continued. However, as discussed in the assessment report, the advisor noted that this scenario is uncommon.
Vandetanib meets the end of life (EOL) criteria We challenge the conclusion that vandetanib does not meet NICE EOL criteria for the following reasons: 1) there are very limited overall survival data for MTC patients not treated with TKIs; 2) for the specific UK patient population, for which there is some uncertainty (EU label/restricted EU label), there are no robust overall survival estimates if not treated with TKIs; 3) the true clinical advantage of vandetanib over BSC was confounded by the crossover permitted in the ZETA trial. In general, 10 year survival with MTC ranges from 21%-40% (AG report, page 11). Patients with aggressive disease defined with CTN/CEA doubling have	We agree that there are limited OS data for MTC patients not treated with TKIs. The most appropriate data are likely to be those from the EXAM ITT placebo group, although we agree that some of these patients received post-progression therapies including TKIs. Data from ZETA are confounded by open-label vandetanib use and are therefore not particularly reliable. As noted in the assessment report, the modelled mean survival in the placebo group of the EXAM trial is greater than 24 months, irrespective of the choice of parametric model used. The lowest estimate for any curve is 3.03 years.

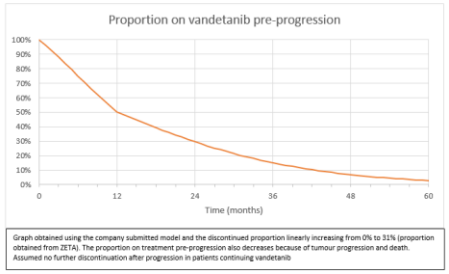
poorer prognosis as highlighted above. In the EXAM study, the median OS of the placebo arm (which is not confounded by crossover to active treatment) is 21.1months. The AG concluded the EXAM population and the ZETA trial EU label population are equivalent. These may be the only data which reflects progression in symptomatic and progressive patients without treatment. In this trial, cross-over to cabozantinib was not allowed for patients randomised to placebo and patients who received any other subsequent anti-cancer therapies were censored at the time of the primary analysis. Overall, 52% of placebo patients and 33% of cabozantinib patients had some form of post-progression therapy, including 16% and 10% who went on to receive vandetanib. No data are available on mean OS (5). Moreover, the National Cancer Database reported median overall survival less than 24 months in MTC patients with distant metastases (6). This comprehensive study includes data from 2968 patients with MTC diagnosed between 1998 and 2005, and is the only from few registry studies that we could identify reporting overall survival for MTC patients. Currently, it will be impossible to collect survival data as it will be unethical not to treat MTC patients as there are now 2 available alternatives to best supportive care approved. In the ZETA EU restricted population, the median and mean OS estimates are not a true estimate of treatment benefit with vandetanib due to the extensive crossover. Instead the OS data are more likely to show the impact of treatment with immediate vs delayed vandetanib, rather than be a true comparison of vandetanib vs placebo. In the absence of meaningful OS data, progression-free survival data can provide information on efficacy. In EU restricted population, there was [redacted] months incremental benefit over placebo, ORR was [redacted]. As highlighted by the assessment report, the criterion relating to greater than 3 months life extension is likely to be met for vandetanib. Equally, the treatment is licensed and indicated for small patient population. Therefore, on balance of available evidence, vandetanib can be considered to meet NICE EOL criteria, as the overall median survival of MTC with aggressive/progressive and symptomatic disease is <2 years and true treatment OS benefit of vandetanib is likely to be >3months.	The Assessment Group takes the view that means are more relevant than medians. This is particularly important in cases such as MTC where survival distributions are likely to be skewed due to the presence of long-term survivors. We also note that our report suggested that EXAM ITT population and the ZETA EU label population are comparable rather than equivalent. There are clearly differences in the placebo group outcomes between the two trials.

Clinicians want two TKIs to have treatment options for patients Prior to initiating therapy, a review of a patient's past medical history, current comorbidities, and medications would be conducted with an emphasis on the potential interactions and effects on treatment-related AEs. Therefore, there is a need for both vandetanib and cabozantinib as shown in Figure 1 of the AG report. Each drug has a different risk-benefit profile and patients' individual characteristics are taken into account when selecting appropriate treatment as neither drug are suitable for all patients with MTC. As it can be expected that disease will become resistant to treatment in the long term, disease progression will be observed in time and it is important to have alternative therapies to offer. Vandetanib and cabozantinib are similar but still different enough to have a distinct mechanism of action and AE risk profile. This difference allows salvage therapy for patients that start progressing with the first line TKI.	The clinical advisors to the Assessment Group consider that there is value in having access to both TKIs. The recommendations for the use of either or both of these therapies is within the remit of the Appraisal Committee, rather than the Assessment Group.

Factual inaccuracies raised by Sanofi

	Point of potential factual inaccuracy	**Assessment Group response**
1	In discussion section 2.5 (page 8), the report states: "Both cabozantinib and vandetanib produced frequent AEs, with substantial proportions of patients experiencing AEs that led to dose interruption or reduction" The incidence of AEs observed in clinical trials, a period during which there's little experience with the tested drugs, would not correspond to the observation in current clinical practice. The post-marketing experience allowed a significant learning towards AEs management (prevention as well as treatment) (7-9). Since its approval in 2012, clinical experience and information collected on safety demonstrates a good benefit/safety profile on vandetanib.	This is not factually inaccurate. The text refers to the experience of the trial rather than experience of using vandetanib in clinical practice.
2	Figure 1, page 15. In general we agree with this treatment algorithm but have a few suggestions. Firstly there is a subtle difference in the wording of the indications for vandetanib and cabozantinib which can be reflected as footnote in the figure (vandetanib licence is in aggressive and symptomatic while cabozantinib is in progressive disease). The box which states 'Known prolonged corrected QT interval' is too broad as	We agree. We have amended the figure.

	long QTc intervals may be prone for correction. Therefore we suggest adding "in which risk factors cannot be corrected".	
3	We would like to note an inaccuracy in page 87 of the report, "However, the comparison of predicted and observed OS probabilities represented in this comparison relate to two different populations: the covariate-adjusted Weibull model relates to the Restricted EU label population, whilst the observed Kaplan-Meier curves relate to the ZETA ITT population with CEA and CTN doubling time ≤24 months (excluding the progressive population characteristics)". The KM curves include the progressive population characteristics.	The company's comment does not appear to be correct – the curves presented in Figure 9 of the Sanofi CS do not relate to the Restricted EU label population. The correct KM curve for the Restricted EU label population is presented in Figure 30 of the assessment report. This is the appropriate curve for comparison with the company's modelled predictions (Restricted EU label population).
4	Incidence and prevalence (section 3.1/page 10) states: "Almost all patients with MEN2, MEN3 and FMTC have germline RET mutation, whilst approximately 40%-50% of patients with sporadic MTC have somatic RET mutations". The percentage of 40%-50% is based on older data and at the time of diagnosis. More recent studies investigating RET mutations prevalence in advanced MTC show a much higher percentage of RET positive cases (approx. 90%) based on reference: Romei C et al. Low prevalence of the somatic M918T RET mutation in micro-medullary thyroid cancer. Thyroid 2012, 22:476–481.	The figures cited in the assessment report accurately reflect the estimates given in the literature for sporadic MTC (which may not be advanced). The sources of these estimates (the BTA guidelines and the ATA guidelines) have been published more recently than the Romei study mentioned by Sanofi.
5	Section 3.3.1 (page 13) states: "There are no clinical guidelines for the management of MTC." This should read: "There are no clinical guidelines for the management of MTC in the UK." There are guidelines for MTC published from Spanish Society of Endocrinology (10) and American Thyroid Association (11); and the British Thyroid Association includes a chapter on MTC management (12).	We agree. We have amended the text.
6	Cost of managing AEs (page 91). The view reflected here can be challenged. It is also likely that other options would be tried before discontinuing treatment e.g. Patient would be educated on minimizing side effects (i.e. use sunblock and moisturizing agents, to avoid rash; adapt diet, to avoid diarrhoea), recognizing the most common side effects symptoms so that symptomatic treatment can be initiated; and	Both of the oncologists who provided advice to the Assessment Group considered these costs to be unrealistically high. The wording of the assessment report refers only to the view of our experts, rather than stating a point of fact. The text is therefore not factually inaccurate.

	dose reduction will be considered if side effect symptomatic treatment is ineffective. Dose interruption will be the last resort. We request this point is discussed with clinical experts and text updated to reflect common practice.	
7	Time to treatment discontinuation (page 130). The only result available from ZETA on this aspect was the proportion of patients who discontinued treatment for reasons other than progression or death. In the company submitted model, we agree that it was an overestimate to apply this discontinuation probability as a fixed parameter in every cycle pre-progression and not at all post-progression. To address this, an additional analysis has been done linearly increasing the proportion discontinued from zero to reach the full amount after 1 year (see figure 1). We think this is more likely the case as discontinuations tended to occur early and disagree with the assumption made in the AG model that half the discontinuation rate would apply constantly over the entire pre-progression phase. In the individual simulation, the proportion can be converted to a hazard which is then used to estimate each individual's time to discontinuation. This hazard can also be applied in the same way to the patients who crossover to vandetanib at progression. In that analysis, the cost of treatment post-progression in those who crossover drops by nearly 15% but remains higher than the cost of vandetanib pre-progression because the period post-progression is <u>longer</u> than the pre-progression time. **Figure 1 Proportion on vandetanib treatment in the pre-progression phase.**  Graph obtained using the company submitted model and the discontinued proportion linearly increasing from 0% to 31% (proportion obtained from ZETA). The proportion on treatment pre-progression also decreases because of tumour progression and death. Assumed no further discontinuation after progression in patients continuing vandetanib	With respect to those patients who discontinued vandetanib prior to progression with missing treatment duration data, it is not clear whether these discontinuations occurred early or late during the progression-free phase. Some of these patients discontinued due to AEs (and may be expected to have done so early), however some did not. In the absence of any information on this aspect of the ZETA trial, the company's analysis is not obviously more appropriate than the Assessment Group's analysis.

8	In its estimation of budget impact, the AG state that 5% of thyroid cases are MTC and reference the BTA guidelines. The BTA guidelines however state that 3% of cases are in adults with MTC. A recent audit by Wiltshire et al (2015) estimated approximately 253 cases of MTC (13).	The company is correct that the BTA cites estimates of 3% for adults, and 10% for paediatric patients. However, the text states that *approximately* 5% of thyroid cancers are MTC. The assessment report also states that lower estimates have been reported elsewhere. Based on the Wiltshire audit paper, this figure would be appear to be somewhat higher.
9	The budget impact section, section 7, requires more detail to understand how the AG have arrived at the cost impact to the NHS. We understand list prices have been used (vandetanib has lower drug acquisition cost) but cost over 5 years is higher on vandetanib than cabozantinib. However in section 3.3.3 (page 13) "Based on current prescribing levels, the cost of treating new MTC patients with cabozantinib and vandetanib for one year (assuming full dose and excluding any discontinuation) is approximately £1.96 million. This value is in line with our estimates assuming same number of patients would be treated with either drug. Please add further detail to this section along with the assumptions and limitation of the analysis.	The approximate cost estimate given in Section 3.3.3 assumes full dose and excludes discontinuation. These are crude assumptions. The budget impact analyses presented in Section 6.3 do not make these assumptions: instead, the expected costs predicted by the model in each year are applied to an initial population size of [redacted] patients including discontinuations as well as dose reductions and interruptions. The cumulative costs also assume a flat incidence rate of [redacted] new patients each year. The estimates given in Table 71 of the report should be easily calculable from the model.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Cabozantinib and vandetanib for treating unresectable locally advanced or metastatic medullary thyroid cancer ID56

Company evidence submission

Jan 2017

File name	Version	Contains confidential information	Date
COMETRIQ (Cabozantinib) MTA submission		**No**	**31/01/2017**

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1.0 Executive summary

Medullary thyroid cancer (MTC) is a rare cancer that arises from the parafollicular or C- cells of the thyroid gland (Leboulleux 2004; Schlumberger 2008). The incidence of thyroid cancer in England according to NCIN incidence figures based on sex, age and histological type is 1427 average cases per year for women, and 521 cases for men. Of these, 3% are classified as MTC in women (n=43), and 8%, in men (n=42), giving an estimate of 85 new cases of MTC per year in England (NCIN 2012).

While MTC accounts for a small proportion of thyroid cancer cases, the 10-year survival rate in patients with MTC is variable. Survival has been strongly associated with stage of disease; Surveillance, Epidemiology, and End Results (SEER) registry of 1252 MTC patients showed that compared to patients with local disease, patients with regional stage disease had a 2.69 times greater risk of dying and patients with distant disease had a 4.47 times greater risk of dying (Roman 2006). For patients with stages I, II, III, and IV MTC 10 year survival rates are 100%, 93%, 71%, and 21%, respectively (Wells 2015). MTC has a disproportionately severe impact because of a high rate of metastasis. In recent decades there has been no significant trend toward an earlier stage of disease at the time of diagnosis (Wells 2015). Distant metastases are already present in 7%–23% of MTC cases when patients are first diagnosed and are the main cause of death in patients with MTC (Schlumberger 2012a).

Treatment options are limited since surgical resection is often incomplete due to the extensive area requiring resection (Witt 2010; Tuttle 2014; Weitzman 2015). When resection is not considered appropriate high external beam radiation therapy (ERBT) may be considered for focal symptom control and more rarely may be used post resection, (Weitzman 2015, Tuttle 2014), but it is considered to generally have limited or no effect (Witt 2010). Traditional cytotoxic systemic chemotherapy, such as doxorubicin, has minimum efficacy in metastatic thyroid disease (Tuttle 2014; Weitzman 2015). Since MTC cells do not concentrate radioactive iodine (RAI) this is also of no significant benefit (Tuttle 2014).

Several studies indicate that activating mutations in the rearranged during transfection (RET) proto-oncogene have a central role in tumourigenesis, and that RET genetic alterations are detected (Moura 2009; Pinchot 2009; Wells 2015), in 95% and approximately 65% of patients with hereditary and sporadic MTC, respectively (Moura 2009, Weitzman 2015, Sherman 2016). Approximately 50-80% of tumours from patients with sporadic MTC harbour a somatic mutation at codon 918 of RET (M918T), which has been associated with more aggressive disease, development of distant metastases and poor prognosis (Elisei 2008; Kouvaraki 2005; Leboulleux 2004; Moura 2009; Schlumberger 2008; Wells 2015). One retrospective study attributes a 10 year survival rate of only 56% in patients with M918T mutation compared to 87% without this specific mutation (Schilling 2001).

COMETRIQ (cabozantinib) is a valuable therapeutic option for patients with documented progressive, advanced and metastatic MTC with distinctive targets of inhibition associated with the tyrosine kinase receptors of RET, vascular endothelial growth factor receptor 2 (VEGFR2) and MET (Yakes 2011; Elisei 2013; Sherman 2016; Viola 2016).

COMETRIQ has been shown to have potent activity toward VEGFR2, MET (only known ligand to hepatocyte growth factor (HGF)) and RET (Weitzman 2015), as well as strong activity against KIT, AXL and FLT3 (Yakes 2011; Weitzman 2015). The dysregulation of these receptor tyrosine kinases, found in human malignancies, have been identified as targets for tumour suppression by TKIs (Yakes 2011).

This profile of potent inhibition differs from vandetanib which inhibits endothelial growth factor receptor (EGFR), RET and VEGFR2 and 3, but not MET (Weitzman 2015; Viola 2016).

Cabozantinib, acting on multiple key pathways, produces anti-tumour and anti-angiogeneic effects, whilst not increasing tumour metastatic potential seen with some TKIs in preclinical models (Yakes 2011). It may be that the targeting of MET and VEGFR2 pathways at the same time may cut off metastatic escape pathways, and thus provide a more sustained anti-tumour effect (Yakes 2011; Weitzman 2015).

Recognising that MTC is a rare disease with prevalence below the threshold for orphan designation, the EMA approved an orphan designation for COMETRIQ in February 2009 (EMA 2009).

The key evidence to support the use of this agent comes from the pivotal trial “EXAM” which was the first randomised, double blind, placebo-controlled trial to demonstrate efficacy of a tyrosine kinase Inhibitor (TKI) in a rigorously selected population of 330 MTC patients with well-documented progressive disease, across 90 sites in 23 countries (55.8% in Europe) (Elisei 2013, CT.gov 2016).

This trial demonstrated a highly significant progression free survival (PFS) benefit of COMETRIQ, in both clinical and statistical terms. Patients receiving COMETRIQ had a 72% lower risk of experiencing disease progression compared with those in the placebo group and the median PFS was nearly 3-fold higher in the COMETRIQ arm compared with the placebo arm (11.2 months vs. 4.0 months, respectively, hazard ratio, 0.28; 95% CI, 0.19 to 0.40; P <0.001) (Elisei 2013; Tuttle 2014). In addition 47.3% of patients on cabozantinib vs 7.2% who received placebo were alive and progression free at 1 year (Elisei 2013).

In EXAM, COMETRIQ improved PFS in subjects who were RET-mutation positive (HR 0.24), negative (HR 0.47) and in patients with unknown RET status (HR 0.30) (although the CI for RET mutation negative subgroup crosses 1.0) (Elisei 2013).

ORR (IRC determined) was 28% in the cabozantinib arm (all partial responses) and 0% in the placebo arm (p<0.001). Objective tumour response was seen in patients with and without RET mutations (RET positive ORR 32%, RET negative ORR 25%) (Elisei 2013; Sherman 2016). Median estimated duration of response was 14.6 months (95% CI, 11.1, 17.5 months) (Elisei 2013).

Overall, at the final analysis (data cut off August 2014), 218 events had been recorded with median exposure to cabozantinib of 10.8 months (range 0.3-59.4) (Schlumberger 2015). The estimated median OS was 26.6 months for cabozantinib vs 21.1 months for placebo (stratified HR = 0.85; 95% CI 0.64-1.12; p = 0.2409). Thus, the study failed overall to meet the secondary endpoint of OS, with median OS 5.5 month longer with cabozantinib compared to placebo, not reaching significance in the ITT population, however as noted below those with RET M918T did show significant benefit in OS (Schlumberger 2015; Sherman 2016).

Although a statistically significant effect of COMETRIQ on OS was not demonstrated in the final analysis, the study was only powered to detect an increase in survival from 22 to 33 months, rather than minimum clinically meaningful improvement (Schlumberger 2015).

Most notably, in the final analysis (data cut off August 2014), a statistically significant treatment effect on OS was found in RET M918T-mutation–positive patients, where a 25-month gain in median OS for patients receiving COMETRIQ compared with those receiving placebo was observed (Schlumberger 2015).

Of the 215 (65%) patients with RET mutation status assigned in EXAM, 75% of these were positive for RET M918T in the primary efficacy study and showed statistically significant benefit in PFS (15.25 months cabozantinib vs 4.25 months placebo, HR 0.15 (95% CI; 0.08-0.28); p<0.0001), ORR (34%) and OS (44.3 months cabozantinib vs 18.9 months placebo, HR 0.60 (95% CI0.38-0.94; p=0.026) (Elisei 2013; Schlumberger 2015; Sherman 2016). In addition PFS benefit was demonstrated for RET mutation positive and RET mutation unknown patients (PFS 15 months cabozantinib vs 5 months placebo, HR 0.23 (95%CI; 0.14-0.38; p<0.001, ORR 32% and PFS 12 months cabozantinib vs 3.25 months placebo, HR 0.30 (95% CI; 0.16-0.57: p=0.0001, ORR 25% respectively) (Sherman 2016). Whilst RET negative population did not demonstrate statistically significant benefit between cabozantinib and placebo groups, this was probably due to the small size and unequal distribution of those in this group (PFS 6.25 months cabozantinib vs 5.75 months placebo, HR 0.53 (95% CI; 0.19-1.50; p=0.2142 (NS)) (Sherman 2016). Those with the RAS mutation (mutually exclusive to RET mutations), also demonstrated a positive benefit in tumour response (31%) and PFS (11.75 months cabozantinib vs 2 months placebo (HR 0.15; 95% CI, 0.02-1.10; p=0.0317). This subgroup had the small numbers (n=16 of which n=3 in placebo group) and no difference in median PFS between cabozantinib and placebo groups was demonstrated (Sherman 2016).

The data on the RET M918T positive patients supporting a correlation between prolonged PFS and improved OS among patients receiving COMETRIQ has been verified by Sherman et al. who noted greatest PFS benefit in those with RET M918T and RAS mutation positive status (Sherman 2016).

These findings indicate that COMETRIQ is effective in MTC patients regardless of their RET mutational status and should be considered as an alternative first line treatment option for all MTC patients (Elisei 2013; Tuttle 2014; Sherman 2016; Viola 2016).

Adverse events of COMETRIQ observed in the randomised, Phase III EXAM study were generally similar to those observed with other inhibitors of the VEGF pathway and other TKIs, and thus are familiar to physicians treating patients with advanced MTC. (Elisei 2013; Exelixis 2015; Colombo 2014; Kim 2016; Weitzman 2015)

Adverse events were generally manageable with supportive care and dose reductions and interruptions (Elisei 2013). Less frequent, but potentially life-threatening toxicities included GI perforations, and GI and non-GI fistulas and haemorrhage (Elisei 2013).

The challenge of managing patients with MTC, particularly those with progressive disease, was until relatively recently largely unmet. Due to the existence of tumour-escape pathways in MTC, agents are required for patients who progress despite initial treatment. There are currently two licensed medications indicated for progressive MTC, cabozantinib and vandetanib available in the UK. Both these treatments are recommended in a number of guidelines including, National Cancer Clinical Network (NCCN), American Thyroid Association (ATA), British Thyroid Association (BTA), European Thyroid Association (ETA), for locally advanced and metastatic MTC (Schlumberger (ETA) 2012, Tuttle 2014, BTA 2014, Wells 2015, Haddad 2016). The latest guidelines from NCCN give the use of these TKIs category 1 recommendation, based on high-level evidence, and uniform consensus that intervention is appropriate (Haddad 2016). Similarly, the BTA 2014 guidelines note that targeted therapies (cabozantinib and vandetanib) are the modality of choice for inoperable progressive and symptomatic disease (BTA 2014).

Both these therapies represent an advance in the treatment of advanced MTC, with a significant improvement over placebo in PFS and important secondary endpoints demonstrated with both in phase III clinical trials (Elisei 2013, Wells 2012). These recommendations are based principally on the EXAM (cabozantinib) and ZETA (vandetanib) clinical studies, however there are significant differences between these studies (Wells 2012, Elisei 2013, Viola 2016).

Notably, although patients who were symptomatic without evidence of progressive disease were enrolled in ZETA, the presence of disease progression was a fundamental inclusion criteria in EXAM (Wells 2012, Elisei 2013, Viola 2016). The longer median PFS observed in the

placebo groups in both studies (19.3 months in ZETA and 4.0 months in EXAM) demonstrates the different levels of severity of disease experience by the two trial patient populations (Viola 2016). Whilst ZETA did not require patients to have confirmed progressive disease at baseline, the licensed indication is limited to those meeting criteria for aggressive-symptomatic disease (VDB SmPC 2016).

Similarly, patients in ZETA who had disease progression were unblinded and could crossover to vandetanib in post-progression, open-label treatment (Wells 2012). This is in contrast to cabozantinib where no crossover was permitted once study treatment was discontinued (Elisei 2103).

MTC is heterogeneous with respect to the underlying mutations, so no single TKI is likely to be maximally potent across all MTC subtypes. Different TKIs also have differences in their receptor targets and adverse effect profiles that are important for clinicians to consider. Thus, there is a need for more than one TKI treatment option for patients with MTC.

1.1 Statement of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with unresectable locally advanced or metastatic medullary thyroid cancer	Appraisal of clinical effectiveness of cabozantinib and vandetanib in this group of patients. Estimated 85 new MTC patients per year.	Not all patients will have progressive disease, for which cabozantinib is indicated
Intervention	cabozantinib vandetanib	cabozantinib	
Comparator (s)	The interventions listed above will be compared with each other Best supportive care including locally ablative treatments such as radiotherapy	Information presented on the use of cabozantinib within its licensed indication for progressive, unresectable, locally advance or metastatic MTC.	The appropriate relevant comparators are: • vandetanib • palliative care <u>Radiotherapy</u> Based on its indication and current treatment guidelines, cabozantinib is positioned after surgery or radiotherapy: • It is licensed for use in patients with unresectable locally advanced or metastatic medullary thyroid cancer (SmPC 2016). • In this group of patients, current treatment guidelines recommend radiotherapy for palliative use only (BTA 2014) • No direct comparisons with radiotherapy are available

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • overall survival • progression-free survival • adverse effects of treatment	Limitations on availability of HRQoL data in this ultra-orphan group of patients means it is not possible to include this
Subgroups to be considered	If the evidence allows subgroups according to RET	RET mutation analysis RAS mutational status Prior TKI use	Data limited but presented on prior TKI use and RAS mutational status in addition to RET mutational status.
Special considerations including issues related to equity or equality	N/A	N/A	N/A

1.2 Description of the technology being appraised

Table 1 Technology being appraised

UK approved name and brand name	Cabozantinib capsule COMETRIQ®
Marketing authorisation/CE mark status	Conditional MA granted 21 March 2014 by EMA Orphan drug designation. Reimbursement via Cancer Drugs Fund
Indications and any restriction(s) as described in the summary of product characteristics	COMETRIQ, the (S)-malate salt of COMETRIQ (formerly known as XL184), is an orally bioavailable tyrosine kinase inhibitor. Its chemical name is N-(4-(6, 7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate. (Exelixis 2012). The Anatomical Therapeutic Chemical (ATC) code of COMETRIQ is L01XE. Cabozantinib is classified within the ATC pharmacotherapeutic class "Protein kinase inhibitors", a subcategory of "antineoplastic agents" which block the enzyme activity of protein kinases (WHO, 2016). Cabozantinib (COMETRIQ) is indicated for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma (MTC). For patients in whom Rearranged during Transfection (RET) mutation status is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision (European Medicines Agency, 2016)
Method of administration and dosage	Oral, capsule 140 mg daily, 100 mg daily or 60 mg daily
Differentiation of cabozantinib capsule and tablet	Cabozantinib tablet (Cabometyx®) is approved for second-line advanced renal cell cancer after first-line treatment with vascular endothelial growth factor-targeted therapy The results of the pharmacokinetics study of cabozantinib clearly state that COMETRIQ (cabozantinib) capsules and Cabometyx (cabozantinib) tablets are not bioequivalent and should not be used interchangeably (Nguygen 2016). In addition, the European Medicines Agency also confirmed "no interchangeability and non-bioequivalent." (EMA 2016a)

1.3 Summary of the clinical effectiveness analysis

The EU and US marketing authorisations for COMETRIQ within the respective indications for advanced MTC are based on efficacy, safety and tolerability results from the Phase III clinical trial EXAM (Study XL 184-301). Additional evidence supporting the efficacy, safety and tolerability of COMETRIQ in patients with MTC is provided by the Phase I study XL184-001. Both trials are summarised in the table below.

Table 4.1.1: Summary table of key COMETRIQ studies in MTC

Study	Patients	Interventions	Primary endpoints
XL184-001 Phase I, prospective, open-label, dose-escalation study	Advanced solid tumours, including MTC	13 dose levels with 2 different schedules of administration and formulations (suspension or capsules) of COMETRIQ	Safety, pharmacokinetics, and maximum-tolerated dose
EXAM Pivotal, Phase III, prospective, randomised, double-blind, placebo-controlled study	Unresectable, locally advanced, or metastatic MTC	• Cabozantinib 140mg (free base) capsule PO once daily • Placebo	Progression-free survival

Study XL 184-001 Phase I

Objective

Study XL184-001 (ClinicalTrials.gov Identifier NCT00215605) was a Phase I, non-randomised, open-label, dose-escalation study (Kurzrock 2011). This entry-into-humans study provided the initial data in 37 patients with MTC supporting the pivotal trial EXAM (Hart 2013).

The primary objectives of Study XL184-001 were to evaluate the safety and tolerability of COMETRIQ, including dose-limiting toxicity (DLT), to determine the maximum-tolerated dose (MTD) of COMETRIQ, and to evaluate pharmacokinetics (Kurzrock 2011). Secondary objectives

were to determine tumour response using RECIST criteria, pharmacodynamics, RET mutational status, and biomarker analyses (Kurzrock 2011).

Table 4.2.1.2: Response characteristics of patients with partial tumour response in Study XL184-001

Patient	Time to response, days	Duration of response, months
1	24	3.9
2	28	4.1
3	21	4.5
4	117	8.3
5	27	13.2
6	365	7.3*
7	24	18.3*
8	71	18.9*
9	85	33.9*
10	79	34.7*

*Active patient with continued confirmed partial response

The most frequent treatment-related adverse events of any grade were diarrhoea, fatigue, anorexia, and nausea, which occurred in more than 50% of patients receiving COMETRIQ 140 mg once daily continuously (Hart 2013). Grade 3 adverse events occurring in more than 10% of patients receiving the 140 mg daily dose included fatigue (13%), palmar-plantar erythrodysaesthesia (20%), and increased lipase level (18%). The only Grade 4 adverse event assessed as treatment-related was a single occurrence of pulmonary embolism (Kurzrock 2011, Hart 2013).

Frequently reported treatment-related adverse events observed in patients with MTC (Table 4.2.1.3) were reported as largely consistent with those in patients with other solid tumour diagnoses (Kurzrock 2011). The authors did however note that the incidence of all grades of hypertension (16%, including 2% grade 3) was lower than expected, compared with that of other TKIs, including motesanib and axitinib (Kurzrock 2011; Colombo 2014).

Sixteen (43%) of the 37 patients with MTC were previously treated with other TKIs. Three of the 10 responses occurred in patients with MTC in whom prior TKI therapies had failed, including those known to inhibit RET (e.g., vandetanib and sorafenib).

Responses were seen in both RET mutation positive and mutation negative tumours. Mutational analysis was carried out as part of the trial, and identified 15 patients with M918T, a RET mutation

associated with poor prognosis. Of these, 12 had a response or stable disease with COMETRIQ (Kurzrock 2011).

Clear progression was seen in only one patient with MTC, who had a functioning BRAF mutation (rare in this disease group), but no RET mutation. BRAF signalling occurs downstream of VEGFR, RET, and MET, which may account for the lack of response to COMETRIQ seen in this patient (Kurzrock 2011).

Substantial decreases in both calcitonin and carcinoembryonic antigen (CEA) were also measured in the majority of subjects with MTC in Study XL184-001. Reductions in serum calcitonin ranging from 3% to 99% below baseline were observed in 28 of 30 MTC patients with any measurable tumour shrinkage. Of the 28 patients with CEA data and measurable disease, 24 had a reduction in CEA ranging from 13% to 94% below baseline. However, no significant correlation was observed between the magnitude of tumour shrinkage and the magnitude of reduction in these biomarkers (Kurzrock 2011).

Overall, 18 patients experienced tumour shrinkage of 30% or more, including 17 (49%) of 35 patients with MTC with measurable disease. Additionally, 15 (41%) of 37 patients with MTC had stable disease (SD) for at least 6 months, resulting in SD for 6 months or longer or confirmed partial response in 68% of patients with MTC (Kurzrock 2011).

Summary

Although Study XL184-001 was not primarily an efficacy study and PFS was not assessed, the promising efficacy results supported further investigation of COMETRIQ 140 mg MTD in patients with MTC in Phase III trials (Kurzrock 2011).

Given the poor prognosis of MTC patients with progressive disease, the partial tumour responses observed in patients receiving COMETRIQ in Study XL184-001 were striking. It was particularly noteworthy that tumour regression was seen in patients with and without identified RET mutations. Authors concluded "…cabozantinib is active in patients with MTC, including those who harbour somatic *RET* mutations and are potentially at high risk for progression and death."

Study XL184-001 indicated COMETRIQ to have an acceptable safety profile (Kurzrock 2011) and established the MTD for the capsule formulation: 140 mg free-base COMETRIQ once daily (Hart 2013). The observed adverse event profile was generally similar to that of other TKIs (Kurzrock 2011; Colombo 2014).

Thus, Study XL184-001 suggested that COMETRIQ may be a valuable addition to the treatment options for advanced MTC, further supported by the observation of objective tumour response to COMETRIQ among patients in Study XL184-001 who had progressed on previous TKI therapy, including other RET and VEGFR2 inhibitors (Kurzrock 2011).

Study XL 184-301 (EXAM) Phase III

Objective

The efficacy of COMETRIQ in the treatment of MTC was established primarily by the international, multicentre, randomised, placebo-controlled, Phase III trial EXAM (**E**fficacy of **X**L184 in **A**dvanced **M**edullary Thyroid Cancer; Study XL184-301; ClinicalTrials.gov identifier NCT00704730) (Elisei 2013).

This study of patients with progressive unresectable, locally advanced or metastatic MTC was conducted at 90 sites in 23 countries (Elisei 2013).

The pre-specified primary endpoint was to compare the duration of progression free survival (PFS), adjusted for age and prior TKI status, in subjects assigned to receive COMETRIQ versus those assigned to receive placebo (Elisei 2013). Progression was determined by blinded radiographic assessments by the Independent Review Committee (IRC) in the intention-to-treat (ITT) population. The data cut-off date for this event-driven analysis was pre-specified as the date on which the 138th event occurred (this was attained on April 6th, 2011) (Elisei 2013).

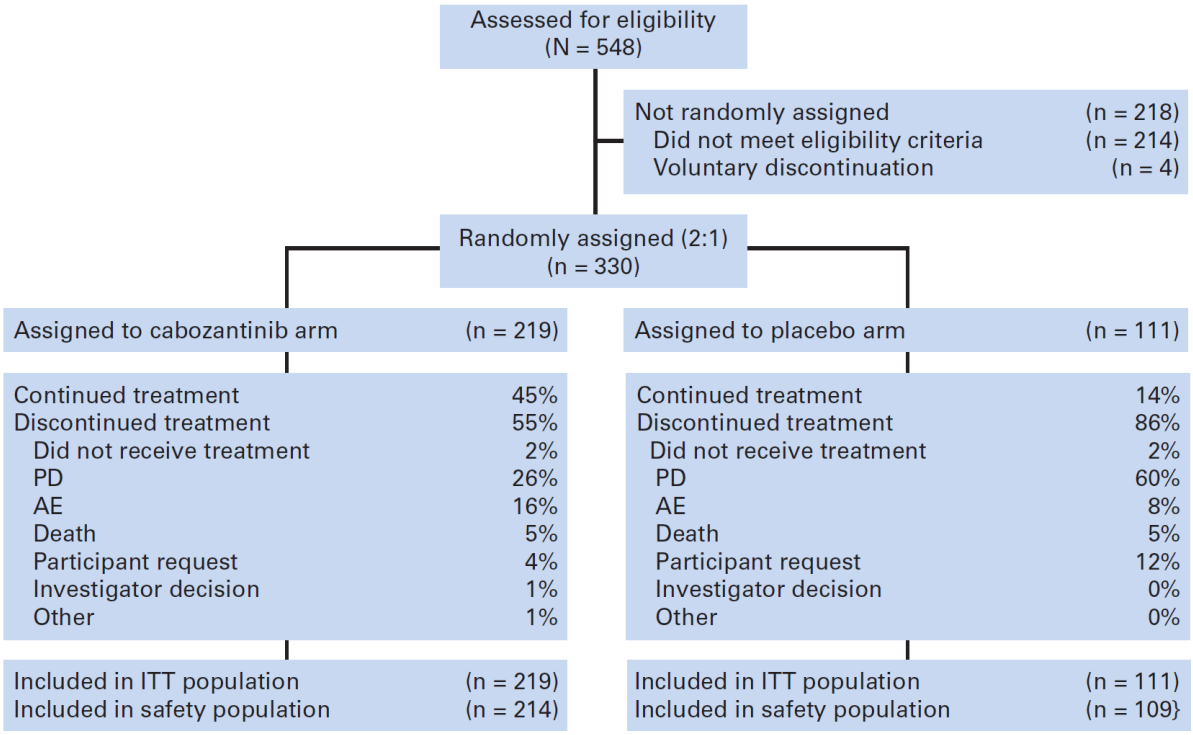
Secondary objectives of EXAM included evaluations of overall survival (OS), objective response rate (ORR), duration of response rate, changes in serum levels of calcitonin and carcinoembryonic antigen (CEA), and the potential relationship between RET mutation status and the efficacy of COMETRIQ (Exelixis 2015). Safety and tolerability were also assessed (Exelixis 2012; Elisei 2013; Exelixis 2015).

Subjects were randomised 2:1 to receive an orally administered regimen of either 140 mg COMETRIQ capsules once or placebo (Elisei 2013). Radiologic tumour assessments were to be performed every 12 weeks (± 5 days) from randomisation until disease progression as determined by the investigator using modified RECIST (mRECIST) criteria and tumour assessments were evaluated by a blinded Independent Radiology Review Committee (IRC) to determine response and/or progression.

Subjects remained in the treatment period until disease progression per mRECIST as determined by the investigator, as long as they did not experience unacceptable toxicity or did not meet other protocol-specified criteria (Elisei 2013).

The disposition of patients in EXAM is shown in Figure 4.2.1. The ITT population comprised 219 patients in the COMETRIQ arm and 111 patients in the placebo arm (Elisei 2013).

Figure C: CONSORT diagram of patient flow in the EXAM trial

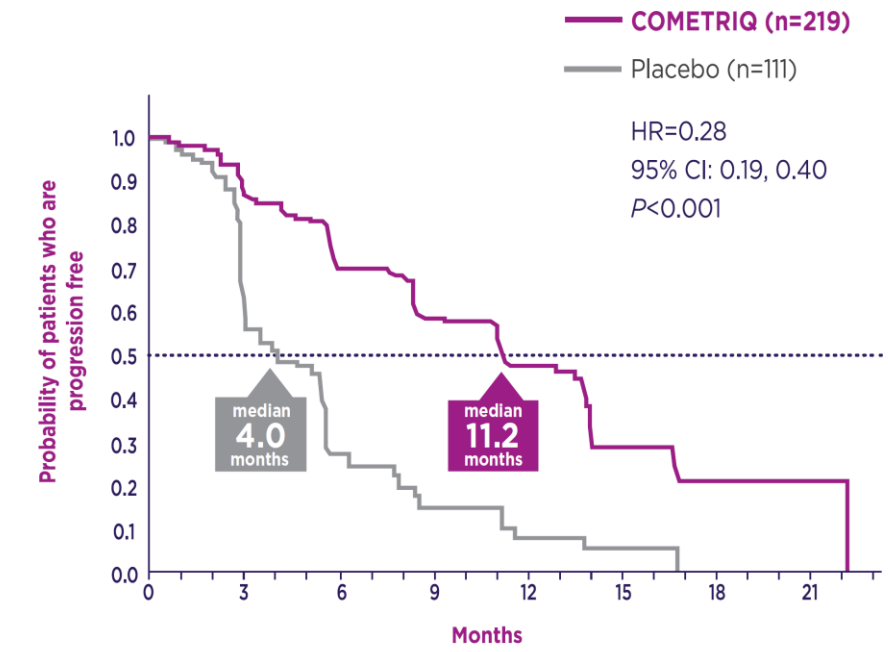


Elisei 2013

Results

The EXAM trial demonstrated a highly significant PFS benefit of COMETRIQ, in both clinical and statistical terms compared to placebo, in a population of 330 MTC patients with actively progressing disease (Elisei 2013). Patients receiving COMETRIQ had a 72% lower risk of experiencing disease progression compared with those in the placebo group (HR for PFS 0.28, 95% CI 0.19, 0.40, P<0.0001). The median PFS was nearly 3-fold higher in the COMETRIQ arm compared with the placebo arm (11.2 months vs. 4.0 months, respectively) (Elisei 2013).

Figure D Kaplan–Meier plot of PFS in EXAM through the date of the 138th IRC-adjudicated event



Patients at risk:

COMETRIQ	219	121	78	55	31	12	2	1
Placebo	111	35	11	6	3	2	0	0

	COMETRIQ	Placebo
EXAM – Primary endpoint: Progression Free Survival per IRC*	**% of patients**	
1 year PFS (estimates)	**47.3%**	**7.2%**
HR 95% CI	**0.28 (0.19, 0.40)**	

PFS= Progression-free survival *IRC= Independent Radiology Review Committee

Furthermore, the efficacy of COMETRIQ appeared to be positive across subgroups for any of the baseline and demographic parameters analysed (Elisei 2013). In particular, a similar PFS benefit was observed even in subjects who had undergone prior treatment with another TKI compared with TKI-naïve subjects (HR <0.5) (Elisei 2013), and PFS was also prolonged in the COMETRIQ arm compared with the placebo arm in the subgroup of patients (n=34) who had received prior vandetanib (median PFS, months 12.8 for cabozantinib and 2.8 for placebo, and ORR 28%, where prior vandetanib use reported) (Exelixis 2014).

Summary

In EXAM, COMETRIQ improved PFS in subjects who were RET-mutation positive (HR 0.24), negative (HR 0.47) and in patients with unknown RET status (HR 0.30) (although the CI for RET mutation negative subgroup crosses 1.0) (Elisei 2013). Furthermore, objective tumour response was seen in patients with and without RET mutations in EXAM (ORR RET positive 32% and RET negative 25%) (Elisei 2013).

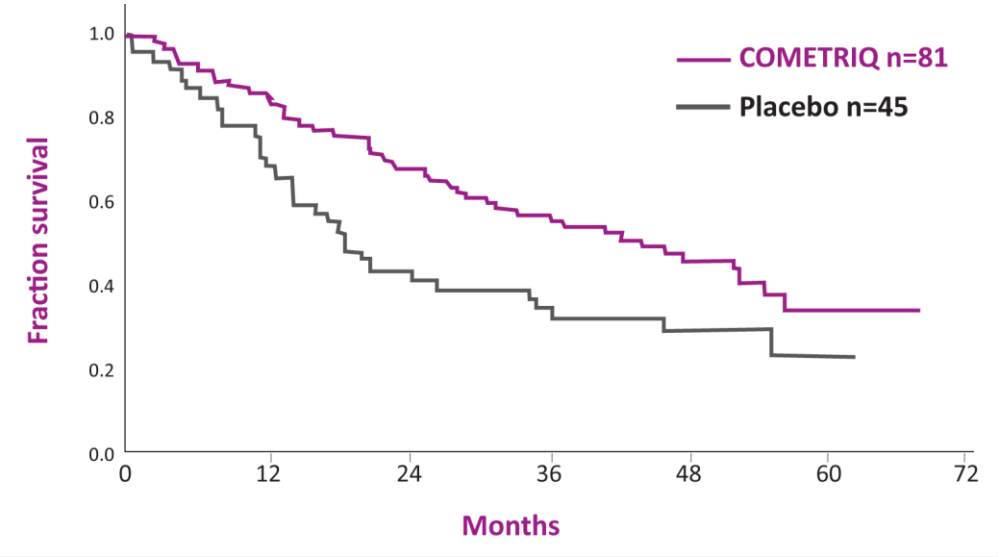
Additional evidence of clinical benefit was provided by a significant treatment effect of COMETRIQ on objective tumour response, with similar ORR regardless of whether or not patients had previously received prior TKI (Exelixis 2012).

In both the phase I and phase III studies reductions in calcitonin and CEA levels were observed. In contrast to the phase I study a clear correlation between change from baseline in levels of calcitonin and CEA, and change in tumour size, was demonstrated in the phase III study, which may be predictive of patient benefit (Elisei 2013).

A statistically significant effect of COMETRIQ on OS was not demonstrated in the interim analysis (data cut-off date June 2011) (Elisei 2013).

Final analysis of secondary endpoint, OS, was reported in a poster at ASCO meeting in 2015 following the data cut-off of 217 events had been reached. At this analysis 218 events had been recorded with median exposure of 52.4 months (Schlumberger 2015). The estimated median OS was 26.6 months for cabozantinib vs 21.1 months for placebo (stratified HR = 0.85; 95% CI 0.64-1.12; p = 0.241). Thus, the study failed overall to meet the secondary endpoint of OS, with median OS 5.5 month longer with cabozantinib compared to placebo, failing to reach significance in the ITT population (Schlumberger 2015).

Figure I Kaplan-Meier plot of OS by mutational status RET M918T subgroup (final analysis)



The OS, ORR and PFS improvement with cabozantinib was greatest, and statistically significant, in 126 patients with RET M918T mutations, with a 25.4 month increase in median OS (Figure l), 34% improvement in ORR and PFS HR of 0.15 compared to placebo (Table 4.2.2.3,2) (Schlumberger 2015).

Table 4.2.2.3.2: OS and PFS figures by mutational status RET M918T subgroup (final analysis)

	All Patients		RET M918T Positive		RET M918T Negative	
	COMETRIQ	Placebo	COMETRIQ	Placebo	COMETRIQ	Placebo
Median OS	26.6 months	21.1 months	44.3 months	18.9 months	20.2 months	21.5 months
OS HR (95% CI)	0.85 (0.64, 1.12)		0.60 (0.38, 0.95)		1.12 (0.70, 1.82)	
P-value	0.2409		0.0260		0.6308	
PFS HR (95% CI)	0.28 (0.19, 0.40)		0.15 (0.08, 0.28)		0.67 (0.37, 1.23)	
ORR	28%	0%	34%	0%	20%	0%

Adapted from Schlumberger 2015

Further analysis of the EXAM data showed that a subset of the RET-mutation–negative patients harboured a RAS mutation, and patients with RAS mutations showed PFS and tumour-response benefits to COMETRIQ treatment (Sherman 2016). Despite evidence for lower clinical benefit of COMETRIQ among RET- plus RAS-mutation–negative patients, the PFS hazard ratio of 0.88 (95% CI 0.24, 3.22) and the ORR of 21% indicated that COMETRIQ may have clinical activity in at least some patients in this subgroup (Sherman 2016).

These findings indicate that COMETRIQ can be used in MTC patients regardless of their RET mutational status.

Nevertheless, for patients in whom RET mutation status is not known or is negative, the possibility of lower clinical benefit should be taken into account before individual treatment decisions (SmPC 2016).

The short duration of PFS in the placebo group suggested that the subjects enrolled in EXAM had progressive disease and were in need of treatment (Elisei 2013). Supporting the ability of COMETRIQ to treat this population successfully, fewer patients receiving COMETRIQ than those receiving placebo switched to another cancer therapy following study drug discontinuation (18.3% vs. 43.2%, respectively) (Exelixis 2012).

Taken together, Study XL184-001 and EXAM consistently show a clinical benefit of COMETRIQ in MTC patients. The ORR of 28% in EXAM was supported by a similar objective response of 29% in the subjects with MTC and measurable disease in Study XL184-001 (Elisei 2013; Kurzrock 2011). In both studies, use of COMETRIQ reduced blood levels of calcitonin and CEA, biomarkers that have been shown to be important indicators of tumour burden and prognosis (Elisei 2013).

Adverse events of COMETRIQ observed in the randomised, Phase III EXAM study were generally similar to those observed with other inhibitors of the VEGF pathway and other TKIs, and thus are familiar to physicians treating patients with advanced MTC (Elisei 2013; Exelixis 2015; Colombo 2014; Kim 2016; Weitzman 2015).

Adverse events were generally manageable with supportive care and dose reductions and interruptions (Elisei 2013). Less frequent, but potentially life-threatening toxicities included GI perforations, and GI and non-GI fistulas and haemorrhage (Elisei 2013).

Thus, Study XL184-001 and EXAM provide evidence bridging from the pathophysiological rationale for treating advanced MTC with COMETRIQ in order to significant impact on clinically meaningful endpoints. Moreover, the significant effect of COMETRIQ on OS in the subgroup of patients in EXAM with a RET M918T mutation provides evidence that prolonged PFS is indeed associated with improved OS for this group of patients at least (Elisei 2013; EMA 2013; Schlumberger 2015).

2 The technology

2.1 Description of the technology

Approved name of medicine

Cabozantinib

COMETRIQ™, the (S)-malate salt of cabozantinib (formerly known as XL184), is an orally bioavailable tyrosine kinase inhibitor. Its chemical name is N-(4-(6,7-dimethoxyquinolin-4-yloxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate (Exelixis 2012)

Trade name

COMETRIQ

Therapeutic class

The Anatomical Therapeutic Chemical (ATC) code of COMETRIQ is L01XE. Cabozantinib is classified within the ATC pharmacotherapeutic class "Protein kinase inhibitors", a subcategory of "antineoplastic agents" which block the enzyme activity of protein kinases (WHO, 2016).

N.B. 175 mg malate salt is equivalent to 140 mg dose free base

Mechanism of action:

Cabozantinib is a tyrosine kinase inhibitor (TKI) with potent inhibitory action on three relevant pathways in MTC (Elisei 2013; Weitzman 2015).

COMETRIQ has been shown to have potent activity toward vascular endothelial growth factor receptor 2 (VEGFR2) and MET (only know ligand to hepatocyte growth factor (HGF), as well as strong activity against RET, KIT, AXL and FLT3 (Yakes 2011; Weitzman 2015). The dysregulation of these receptor tyrosine kinases, found in human malignancies, have been identified as targets for tumour suppression by TKIs (Yakes 2011).

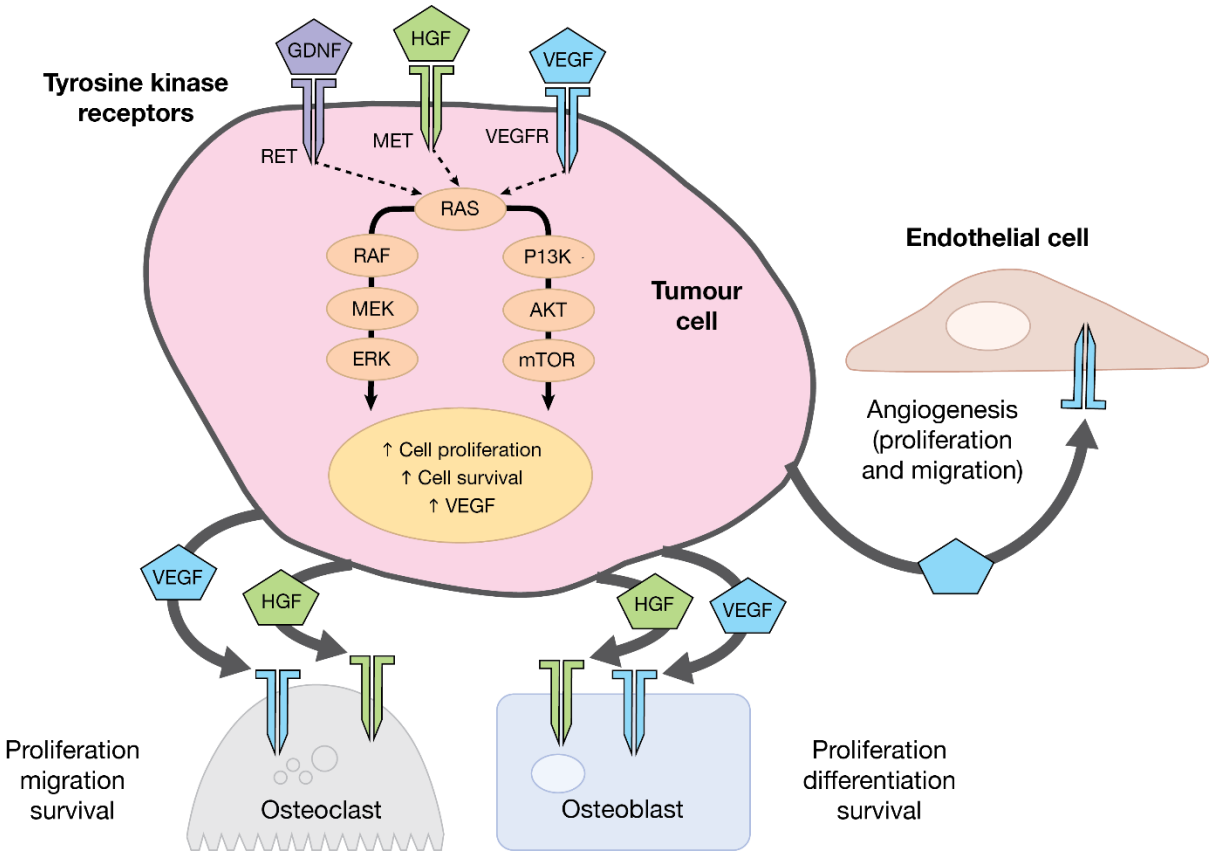
This profile of potent inhibition differs from vandetanib which inhibits endothelial growth factor receptor (EGFR), RET and VEGFR2 and 3, but not MET (Weitzman 2015; Viola 2016).

RET- activating mutations are the most common genetic alterations found in MTC cells (Viola 2016), with 95% of hereditary forms and 65% of sporadic forms having such mutations present

(Moura 2009; Sherman 2016). Recently RAS mutations have also been reported in MTC patients, RET and RAS being mutually exclusive in MTC cases (Viola 2016). The number of genetic mutations described for MTC continues to grow, with a significant proportion of MTCs still negative for known abnormalities (Viola 2016). However, RET M918T is a well recognised mutation, associated with development of distant metastasis and poor prognosis, present in approximately 50-80% of sporadic MTC cases (Sherman 2016).

Hepatocyte growth factor (HGF), MET and VEGFR2 and their receptors are overexpressed in MTC and other thyroid cancers (Viola 2016). These play an important role in the pathogenesis, progression and recurrence of these cancers (Viola 2016), with VEGFR and MET signalling dysregulation being widely recognised to be involved in tumourigenesis, angiogenesis, tumour invasion and survival (Yakes 2011).

Figure A Molecular pathways important in MTC and targets relevant to cabozantinib



Adapted from Weitzman and Cabanilas 2015

Abbreviations: MTC, medullary thyroid cancer; RET, rearranged during transfection; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Upregulation of MET is associated with the ability of tumours to evade antiangiogenic treatment (Weitzman 2015). In addition, osteoblasts and osteoclasts have MET and VEGF receptors

(Weitzman 2015). HGF, the only known ligand for the MET receptor, may be an important factor directing interaction between tumour cells and osteoblasts/osteoclasts and thus, simultaneous inhibition of MET and VEGF receptors may block progression of osteolytic and osteoblastic bone metastases (Weitzman 2015).

The inhibition of kinase activity by TKIs varies, with cabozantinib showing potent inhibition of the synergistic MET and VEGFR pathways, together with RET inhibition (Yakes 2011; Elisei 2013), leading, in mouse models, to dose dependent changes in tumour physiology, including; endothelial and cell apoptosis, disruption in tumour vasculature and increase in hypoxia (Yakes 2011).

It has been observed that in preclinical models using inhibitors which do not target MET the tumour burden/metastasis is increased (Yakes 2011). This has not been seen with cabozantinib in such models and is thought to be due to the targeting of both MET and VEGFR2 pathways simultaneously, preventing MET driven tumour escape (Yakes 2011).

By targeting RET, COMETRIQ may also inhibit tumour cell proliferation and survival through this pathway (Sherman 2016).

Cabozantinib therefore produces anti-tumour and anti-angiogeneic effects, whilst not increasing tumour metastatic potential seen with some TKIs in preclinical models (Yakes 2011). It may be that the targeting of MET and VEGFR2 pathways at the same time may cut off metastatic escape pathways, and thus provide a more sustained anti-tumour effect (Yakes 2011; Weitzman 2015).

2.2 Marketing authorisation/CE marking and health technology assessment

2.2.1 Regulatory status update:

Date UK licence granted	21st March 2014	Date of UK launch	2nd May 2014
Date EMA MA granted	21st March 2014		

2.2.2 Indication covered in this submission.

Cabozantinib (COMETRIQ®) is indicated for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma (MTC). For patients in whom Rearranged during Transfection (RET) mutation status is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision (European Medicines Agency, 2016)

2.2.3 Contraindications/restrictions:

Contraindications: Hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions: A number of conditions have been observed with COMETRIQ therapy and require caution, evaluation and/or discontinuation should they occur. These include: perforations, fistulas, and intra-abdominal abscesses; thromboembolic events; haemorrhage; wound complications; hypertension; osteonecrosis of the jaw (ONJ); palmar-plantar erythrodysaesthesia syndrome; proteinuria; reversible posterior leukoencephalopathy syndrome; prolongation of QT interval; concurrent administration of CYP3A4 inducers and inhibitors, P-glycoprotein substrates or MRP2 inhibitors.

Please refer to full Summary of Product Characteristics for full details (Appendix 1)

(European Medicines Agency, 2016)

2.2.4 Summary of product characteristics (SmPC)

Current SmPC dated December 2016 can be viewed in Appendix 1

2.2.5 European Public assessment report

Current EPAR (EMA/97103/2014) dated December 2013 can be found in Appendix 2

2.2.6 Regulatory authority information

COMETRIQ is subject to a conditional marketing authorisation. Periodic safety reports and a risk management plan are conditions required under this licence.

In addition a dose-comparison study (XL-184-401) (140 mg vs 60 mg) in 112 patients with hereditary or sporadic medullary thyroid cancer is being conducted and due March 2019.

(See Recommendations section 4 of CHMP Assessment Report EMA/97103/2014 - Appendix 2)

2.2.7 Regulatory approval outside the UK

COMETRIQ is approved for use in MTC by the EMA (21 March 2014) and by FDA (29 November 2012)

2.2.8 Other health technology assessments conducted

COMETRIQ was approved for use by the AWMSG in January 2015 (AWMSG 577).

COMETRIQ was assessed by the SMC and advice published March 2015. It is not recommended for use in Scotland (SMC 1022/15).

2.3 Administration and costs of the technology

Table 2 Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Capsule 20 mg Capsule 80 mg	SmPC
Acquisition cost (excluding VAT) *	Capsules, cabozantinib 84 x 20 mg pack: £4,800; 28 x 20 mg and 28 x 80 mg combination pack: £4,800; 84 x 20 mg and 28 x 80 mg combination pack: £4,800	BNF list price
Method of administration	Oral	SmPC
Doses	140 mg	SmPC
Dosing frequency	Once daily	SmPC
Average length of a course of treatment	Ongoing Dose interruptions may be used	
Average cost of a course of treatment	One month treatment £4,800	BNF list price
Anticipated average interval between courses of treatments	Continuous treatment	
Anticipated number of repeat courses of treatments	Median duration of exposure 10.8 months in EXAM	
Dose adjustments	Dose reduction down to minimum 60 mg may be made Dose interruptions may also be used	SmPC
Anticipated care setting	Secondary care initiation. Patients treated as outpatient	

Patient Access Scheme

The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of COMETRIQ. The level of the discount is commercial in confidence.

3 Health condition and position of the technology in the treatment pathway

Medullary thyroid cancer (MTC) is a rare cancer that arises from the parafollicular or C cells of the thyroid gland. The pathophysiology of MTC is well characterised (Ernani 2016). Most cases are associated with mutations of the proto-oncogene rearranged during transfection (RET*)*, which encodes a tyrosine kinase receptor that provides mitogenic and survival signals to parafollicular cells. Mutations affecting the downstream effector RAS and other tyrosine kinase receptors, including MET, EGFR, and VEGFR, have also been observed in patients with MTC. Different mutations are associated with different disease severity in MTC; in particular, the M918T mutation of RET has been established to be associated with poorer metastasis-free survival (Elisei 2013; Sherman 2016; Ernani 2016). MTC is either sporadic (~75%) or inherited (~25%) as an autosomal dominant disease (Ernani 2016).

While relatively indolent compared to other advanced solid tumours, MTC can be aggressive with 10-year survival rates of 21%-40% for subjects with metastatic disease at diagnosis (Wells 2015; Sherman 2016). The only curative treatment for MTC is complete surgical resection, however lymph node or systemic metastases are present at initial diagnosis around half of cases of MTC (Wells 2015) and resection is often incomplete due to extensive lateral spread (Ernani 2016; Roman 2006).

The National Cancer Intelligence Network (NCIN) note that the rate of new thyroid cancer cases has increased between the period 1990-1994 and 2006 -2010 (NCIN 2012). The increase has been sharper for women compared to men 1427 and 521 respectively (2006-10) (NCIN 2012). Latest figures from Cancer Research UK indicate that in England 2941 new cases of thyroid cancer occurred in 2014 (2115 women and 826 men), with an age standardised incidence of 5.7/100,000 (CRUK 2016). Medullary thyroid carcinoma accounts for approximately 3% of all adult thyroid cancers (BTA 2014) and thus based on 2014 figures the number of new cases that year of MTC in England would be expected to be in the order of 85 individuals.

More recently the American Thyroid Association Guidelines noted that MTC made up 1-2% of all thyroid cancers, lower than previously quoted, principally due to the increase in all thyroid cancers, but particularly papillary thyroid cancer (PTC) (Wells 2015).

There is a paucity of European data to support the prevalence and incidence of MTC since the available cancer surveillance databases that cover this region (including GLOBOCAN, EUCAN, and NORDCAN) report European data for all thyroid cancer cases combined, not separately for MTC and other subtypes.

EUCAN data for 2012 indicates that the incidence of thyroid cancer in the European Union (EU) was 6.5/100,000 (36,864 individuals) and in the UK 3.8/100,000 (2654 individuals) (EUCAN 2016). 1 year prevalence figures for the same year are noted as 31,255 for the EU and in the UK 1 year prevalence number is 2051 (EUCAN 2016). Cases of MTC are a small fraction (3%) of these overall adult thyroid cancer cases (BTA 2014).

In 2009 medullary thyroid carcinoma affected less than 0.7 in 10,000 people in the EU (EMA 2009). This was below the ceiling for orphan designation, which is 5 people in 10,000. Recognising that MTC is a rare disease the EMA approved orphan designation for COMETRIQ for the treatment of MTC on 6th February 2009 (EMA 2009).

While MTC accounts for a small proportion of thyroid cancer cases, the 10-year survival rate in patients with MTC is variable. For patients with stages I, II, III, and IV MTC 10 year survival rates are 100%, 93%, 71%, and 21%, respectively (Wells 2015). Distant metastases are already present in 7%–23% of MTC cases when patients are first diagnosed and are the main cause of death in patients with MTC (Schlumberger 2012a).

The primary treatment for MTC is extensive and meticulous surgical resection, however, due to the invasiveness of the disease and the frequent involvement of lateral spread - 80% of patients with one to 3 positive lymph nodes, surgical resection may be incomplete (Witt 2010; Ernani 2016). Treatment options are limited for those in whom distant disease occurs, as conventional cancer treatments such as cytotoxic chemotherapy are of minimal benefit (Ernani 2016).

There is a limited role for external-beam radiotherapy because the neuroendocrine-derived MTC is not responsive to either radioiodine or TSH-suppression, these options are not available for treatment of progressive metastatic MTC (Sippel 2008; Witt 2010, BTA 2014).

The current standard of care for adult patients with progressive, unresectable locally advanced or medullary thyroid carcinoma includes palliative radiotherapy, however targeted therapies are the modality of choice for inoperable progressive and symptomatic disease (BTA 2014). Indeed the American Thyroid Association (ATA) recommends TKIs targeting both RET and VEGFR in patients with significant tumour burden and symptomatic or progressive metastatic disease (Wells 2015).

In 2012, vandetanib was the first approved therapy in the EU to treat aggressive and symptomatic MTC. Vandetanib is a TKI that has been shown to inhibit RET, VEGFR2 and 3, and epidermal growth factor receptor pathways (Wells 2012; Kim 2016). The approval of vandetanib is based on the results of a single Phase 3, double-blind trial that randomised 331 patients with unresectable locally advanced or metastatic MTC to vandetanib 300 mg or placebo (Wells 2012). The study did not require patients to have confirmed progressive disease at baseline and thus vandetanib has not been tested in a group of patients that is most in need of therapy. Also, only a small number of subjects in that study were documented to be *RET* negative and a large number RET status was unknown. Thus efficacy could not be definitively assessed in these subgroups. Moreover, the

clinical use of vandetanib is limited by the prolongation of the QT interval with associated risk of sudden death. In that study, patients randomised to vandetanib showed a statistically significant improvement in progression free survival (PFS) when compared to those randomised to placebo (Wells 2012). An interim analysis of OS showed no treatment difference (Kim 2016).

There is widespread recognition of the unique circumstances of end-of-life care, and the agencies of several countries (including NHS England) have adopted more flexible reimbursement criteria for cancer drugs, accepting treatments with ICERs that may fall above the threshold applied to other diseases (Greenberg 2010).

Little published information is available on the health-related quality of life (HRQoL) of patients with MTC, as nearly all the evidence on HRQoL in thyroid cancer derives from studies in the more common subtypes, papillary and follicular thyroid cancer. The disease is well recognised to be associated with painful and bothersome symptoms that would negatively affect patient HRQoL, especially in advanced cases. For example, disease progression in the neck region can have a significant impact on HRQoL by causing substantial morbidity, including airway compromise, speech impairment, and difficulty in swallowing (Terezakis 2010). Other possible sequelae of progressive MTC that would impair HRQoL include spinal cord compression, fracture, and pain associated with bone lesions and bronchial obstruction (Wells 2015). In addition, diarrhoea—one of the main hormonally mediated complications of MTC—can be debilitating in terms of HRQoL as well as nutrition. Diarrhoea and/or pain are most often seen in patients with advanced MTC, particularly in those with hepatic metastases (Wells 2015). A key aspect to minimising impact on quality of life is the avoidance of hypothyroidism in patients with thyroid cancer, majority of whom will have extensive neck surgery (Borget 2007).

Although the overall economic burden of MTC on healthcare systems and society would be expected to be relatively low because of its rarity, the cost on a per-patient basis may be substantial. Unfortunately, there is a scarcity of published evidence on the societal and economic burden of any subtype of thyroid cancer, and none specifically related to MTC.

In addition to the direct medical cost of managing MTC, there are indirect costs of lost productivity and sick leave pay when symptoms related to thyroid cancer and its treatment prevent patients from being able to work (Borget 2007).

Guidance exists from NICE for improving outcomes in head and neck cancers (CSG6 Published November 2004) and quality standards in head and neck cancer are due this year. There is no NICE guidance on thyroid cancer treatment pathways generally, nor on MTC specifically (NICE website 2016).

The American Thyroid Association (ATA) guidelines note that cabozantinib or vandetanib can be used as single-agent first-line systemic therapy in patients with advanced progressive MTC (Grade A Recommendation) (Wells 2015). Both these treatments are recommended in a number of other

guidelines including, National Cancer Clinical Network (NCCN), , British Thyroid Association (BTA), European Thyroid Association (ETA), for locally advanced and metastatic MTC (Schlumberger (ETA) 2012,Tuttle 2014, BTA 2014, Wells 2015, Haddad 2016). The latest guidelines from NCCN give the use of these TKIs category 1 recommendation, based on high-level evidence, and uniform consensus that intervention is appropriate (Haddad 2016).

Similarly, the BTA 2014 guidelines note that targeted therapies (cabozantinib and vandetanib) are the modality of choice for inoperable progressive and symptomatic disease (BTA 2014).

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

PLEASE NOTE THAT ALL COMMERCIAL IN CONFIDENCE INFORMATION CONTAINED IN THIS SUBMISSION IS HIGHLIGHTED IN YELLOW

The EU and US marketing authorisations for COMETRIQ within the respective indications for advanced MTC are based on efficacy, safety and tolerability results from the Phase III clinical trial EXAM (Study XL 184-301). Additional evidence supporting the efficacy, safety and tolerability of COMETRIQ in patients with MTC is provided by the Phase I study XL184-001. Both trials are summarised in the table below.

Table 4.1.1 Summary table of key COMETRIQ studies in MTC

Study	Patients	Interventions	Primary endpoints
XL184-001 Phase I, prospective, open-label, dose-escalation study	Advanced solid tumours, including MTC	13 dose levels with 2 different schedules of administration and formulations (suspension or capsules) of COMETRIQ	Safety, pharmacokinetics, and maximum-tolerated dose
EXAM Pivotal, Phase III, prospective, randomised, double-blind, placebo-controlled study	Unresectable, locally advanced, or metastatic MTC	• Cabozantinib 140mg (free base) capsule PO once daily • Placebo	Progression-free survival

4.2 Description of the most relevant studies:

4.2.1 Study XL 184-001 Phase I

4.2.1.1 Summary of methodology

Objective

Study XL184-001 (ClinicalTrials.gov Identifier NCT00215605) was a Phase I, non-randomised, open-label, dose-escalation study (Kurzrock 2011). This entry-into-humans study provided the initial data in patients with MTC supporting the pivotal trial EXAM (Hart 2013).

The primary objectives of Study XL184-001 were to evaluate the safety and tolerability of COMETRIQ, including dose-limiting toxicity (DLT), to determine the maximum-tolerated dose (MTD) of COMETRIQ, and to evaluate pharmacokinetics (Kurzrock 2011). Secondary objectives were to determine tumour response using RECIST criteria, pharmacodynamics, RET mutational status, and biomarker analyses.

Methods

Pre-Treatment Period: Screening assessment with imaging studies to determine a subject's eligibility to participate was conducted within 30 days before the day of initial treatment (Day 1). Some screening assessments were required to be conducted within 14 days before the initial treatment and obviated the baseline assessment if performed within 72 hours before initial dose (Exelixis 2010).

Treatment Period: In this period of two, 2-week cycles, subjects were administered COMETRIQ either for five consecutive days followed by a nine-day observation period every two weeks (Intermittent 5 & 9) or on a once daily treatment schedule (Exelixis 2010).

Treatment Extension Period: During this period, in the absence of disease progression and unacceptable COMETRIQ-related toxicities, subjects could continue treatment with COMETRIQ in 2-week cycles for up to one year at the discretion of the investigator and beyond one year with the agreement of the sponsor. Treatment at the start of this period consisted of the same treatment schedule that the subject was on at the end of the Treatment Period (Exelixis 2010).

Post-Treatment Period: Subjects were to visit the study site 30 (± 4) days after the final dose of COMETRIQ for designated assessments (30-Day Follow-Up Visit). Additionally, 90 and 180 (± 15) days after the final dose of study drug or until death (if before Day 180), the investigator (or designee) was to obtain information including subsequent treatments, any severe adverse event (SAE) that was deemed by the investigator to be associated with COMETRIQ treatment, and, if applicable, date and cause of death (Exelixis 2010).

Study design

The study used a conventional “3+3” design for dose escalation. COMETRIQ was administered at escalating doses: as a powder-in-bottle (PIB) suspension formulation using a weight-based dose on an Intermittent 5 & 9 schedule, as a PIB formulation at a fixed dose on a once daily treatment schedule, or as capsules at a fixed dose on a once daily schedule.

Patient population

Study XL184-001 enrolled adult patients with histologically confirmed solid tumours or lymphomas that were metastatic or unresectable who were no longer responding to conventional therapies or who had disease for which no standard therapy existed (Kurzrock 2011). All patients were required to have an ECOG performance status score of 0 to 2 and life expectancy longer than 3 months. Exclusion criteria included receipt of chemotherapy or immunotherapy within 4 weeks, nitrosourea therapy within 6 weeks, radiotherapy or investigational agents within 30 days of the first dose of COMETRIQ, brain metastases, uncontrolled concomitant illness, or known HIV infection (Kurzrock 2011).

Based on early observations of clinical activity in subjects with MTC, enrolment in an expanded cohort of predominantly MTC patients administered 175 mg (equivalent to 140 mg free base) capsules once daily was subsequently initiated (Kurzrock 2011).

A total of 85 subjects with advanced malignancies were enrolled and treated, of whom 37 had MTC. Characteristics of these MTC patients are reported in Table 4.2.1.1.

Thirty-five of the 37 patients with MTC had measurable disease according to RECIST criteria. The majority of these patients received the MTD of 140 mg PO once daily (Hart 2013).

Table 4.2.1.1. Baseline demographic and clinical characteristics of the MTC patients in Study XL184-001

Adapted from Kurzrock 2011 TKI: tyrosine kinase inhibitor

Characteristic	MTC subgroup (n=37)
Age, (years)	
Median	55
Range	35–72
Sex	
Male	31
Female	6
Prior chemotherapy	
Patients, n	20
Median no of regimens (range)	2 (1-7)
Patients with prior TKI therapy, n*	16
RET mutational status[†]	31
Germline	3
Somatic	22
Unknown hereditary status	1[‡]
No mutations detected	5

*Including 12 patients who had prior RET inhibitors (vandetanib, motesanib, sorafenib, and AEE-788)

[†]Only activating mutations were scored in this analysis.

[‡]This patient had an activating mutation in tumour but no corresponding blood sample to determine hereditary status.

4.2.1.2 Efficacy results

The primary endpoint for this study is safety and tolerability which is covered later in this section (4.2.1.3).

Of the 35 patients with MTC and measurable disease, a confirmed objective response was achieved in 10 patients (29%, 95% CI 15%, 45%), each of whom had a partial response. (Kurzrock 2011). Five of the 10 responders had a partial response at the first radiologic assessment, and responses occurred most commonly at the 175 mg (140 mg free base) dose. Overall, 17 patients (49%) experienced a ≥30% decrease in the sum of tumour measurements compared with baseline measurements, including 7 patients without a confirmed response resulting either from lack of response based on the subsequent confirmatory scan or from study discontinuation before the subsequent scan (Kurzrock 2011).

Stable disease of at least 6 months' duration (range 6.4–31.1 months) was observed in 15 (41%) of the 37 patients with MTC (Kurzrock 2011). Stable disease for at least 6 months or confirmed partial response was observed in 25 (68%) of the 37 MTC patients.

Onset of tumour response in the MTC population was reported as early as Day 21 and as late as Day 365 (see Table 4.2.1.2). Median time to response was 49.5 days. The median duration of response had not been reached with a minimum of 17 months of follow-up (range 3.9–35 months) (Kurzrock 2011).

Table 4.2.1.2 Response characteristics of patients with partial tumour response in Study XL184-001

Patient	Time to response, days	Duration of response, months
1	24	3.9
2	28	4.1
3	21	4.5
4	117	8.3
5	27	13.2
6	365	7.3*
7	24	18.3*
8	71	18.9*
9	85	33.9*
10	79	34.7*

*Active patient with continued confirmed partial response

Sixteen (43%) of the 37 patients with MTC were treated with TKIs. Three of the 10 responses occurred in patients with MTC in whom prior TKI therapies had failed, including those known to inhibit RET (e.g. vandetanib and sorafenib) (Kurzrock 2011).

Responses were seen in both RET mutation positive and mutation negative tumours. Mutational analysis was carried out as part of the trial, and identified 15 patients with M918T, a RET mutation associated with poor prognosis for metastasis-free and overall survival. Of these, 12 had a response or stable disease with COMETRIQ (Kurzrock 2011).

Clear progression was seen in only one patient with MTC, who had a functioning BRAF mutation but no RET mutation. BRAF signalling occurs downstream of VEGFR, RET, and MET, which may account for the lack of response to COMETRIQ seen in this patient (Kurzrock 2011).

Substantial decreases in both calcitonin and CEA were also measured in the majority of subjects with MTC in Study XL184-001 (Kurzrock 2011). Reductions in serum calcitonin ranging from 3% to

99% below baseline were observed in 28 of 30 MTC patients with any measurable tumour shrinkage. Of the 28 patients with CEA data and measurable disease, 24 had a reduction in CEA ranging from 13% to 94% below baseline (Kurzrock 2011).

4.2.1.3 Safety results Study XL184-001

The maximum-tolerated dose (MTD) of the capsule formulation was defined as 140 mg once daily, based on dose limiting toxicities (DLTs) observed within the first 28 days of continuous daily dosing (Kurzrock 2011, Hart 2013). The once daily dosing was supported by the pharmacokinetic profile observed during the study.

Frequently reported treatment-related adverse events observed in patients with MTC (Table 4.2.1.3) were reported as largely consistent with those in patients with other solid tumour diagnoses (Kurzrock 2011).

The most frequent treatment-related adverse events of any grade were diarrhoea, fatigue, anorexia, and nausea, which occurred in more than 50% of patients receiving COMETRIQ 140 mg once daily continuously (Hart 2013). Grade 3 adverse events occurring in more than 10% of patients receiving the 140 mg daily dose included fatigue (13%), palmar-plantar erythrodysaesthesia (20%), and increased lipase level (18%). The only Grade 4 adverse event assessed as treatment-related was a single occurrence of pulmonary embolism (Kurzrock 2011, Hart 2013).

The adverse events observed in Study XL184-001 were generally similar to those seen with other TKIs targeting VEGF and RET, (Hart 2013). It was noted by the study authors however, that the incidence of all grades of hypertension (16%, including 2% grade 3) was lower than expected, compared with that of other TKIs, including motesanib and axitinib (Kurzrock 2011; Colombo 2014).

Summary of safety results

Study XL184-001 indicated COMETRIQ to have an acceptable safety profile (Kurzrock 2011) and established the MTD for the capsule formulation: 140 mg free-base COMETRIQ once daily (Hart 2013). The observed adverse event profile was generally similar to that of other TKIs (Kurzrock 2011; Colombo 2014).

Table 4.2.1.3 Treatment-related adverse events in XL184-001

Adverse Event	All patients (any dose; N=86*) n (%)	
	Grade 1/2	**Grade 3/4**
Diarrhoea	43 (50)	6 (7)
Fatigue	39 (45)	9 (10)
Decreased Appetite	40 (47)	1 (1)
Nausea	36 (42)	1 (1)
Palmar Plantar Erythrodysaesthesia	17 (20)	9 (10)
Rash	22 (26)	- (-)
Increased Aspartate Aminotransferase	19 (22)	3 (3)
Vomiting	21 (24)	- (-)
Mucosal Inflammation	20 (23)	1 (1)
Hair Colour Changes	19 (22)	- (-)
Increased Alanine Aminotransferase	16 (19)	3 (3)
Oral Pain	16 (19)	- (-)
Decreased Weight	13 (15)	5 (6)
Dysgeusia	14 (16)	- (-)
Hypertension	12 (14)	2 (2)
Dry Skin	10 (12)	- (-)
Peripheral Neuropathy	10 (12)	- (-)
Increased Lipase	4 (5)	9 (10)
Increased Blood Amylase	5 (6)	4 (5)

4.2.1.4 Summary XL184-001

Although Study XL184-001 was not primarily an efficacy study and PFS was not assessed, the promising efficacy results supported further investigation of the 140 mg MTD in patients with MTC in the Phase III trial (Kurzrock 2011).

Given the poor prognosis of MTC patients with progressive disease, the partial tumour responses observed in patients receiving COMETRIQ in Study XL184-001 were very encouraging. It was particularly noteworthy that tumour regression was seen in patients with and without identified RET mutations. Thus, Study XL184-001 suggested that COMETRIQ may be a valuable addition to the treatment options for advanced MTC, in consideration of the inconclusive results on PFS and objective responses to vandetanib among RET-negative patients in the ZETA trial (Wells 2012). This conclusion is further supported by the observation of objective tumour response to COMETRIQ among patients in Study XL184-001 who had progressed on previous TKI therapy (Kurzrock 2011).

4.2.2 Study XL 184-301 (EXAM) Phase III

4.2.2.1 Summary of methodology

Objective

The efficacy of COMETRIQ in the treatment of MTC was established primarily by the international, multicentre, randomised, placebo-controlled, Phase III trial EXAM (**E**fficacy of **X**L184 in **A**dvanced **M**edullary Thyroid Cancer; Study XL184-301; ClinicalTrials.gov identifier NCT00704730) (Elisei 2013)

The pre-specified primary endpoint was to compare the duration of progression free survival (PFS), adjusted for age and prior TKI status, in subjects assigned to receive COMETRIQ versus those assigned to receive placebo (Elisei 2013). Progression was determined by blinded radiographic assessments by the IRC in the intention-to-treat (ITT) population. The data cut-off date for this event-driven analysis was pre-specified as the date on which the 138th event occurred (this was attained on April 6th, 2011).

Secondary objectives of EXAM included evaluations of overall survival (OS), objective response rate (ORR), changes in serum levels of calcitonin and CEA, and the potential relationship between RET mutation status and the efficacy of COMETRIQ. Safety and tolerability were also assessed (Elisei 2013).

Patient self-assessment was reported on the MDASI Thyroid Module (MDASI-THY) which was evaluated as an exploratory endpoint. This was evaluated at screening and every 12 weeks (± 5 days) from randomisation until disease progression, in order to evaluate the most frequently

reported and most serious symptoms in patients with MTC. MDASI THY consists of 2 parts: 1) (Question 1-9) covering 13 core cancer and treatment related symptoms with severity scored from 0 (not present) to 10 (symptom as bad as you can imagine it could be); 2) (Questions 20-25) evaluating how symptoms have interfered with patient's life in the previous 24 hours scored from 0 (no interference) to 10 (interfered completely).

A high MDASI score indicates the presence of more symptoms (Exelixis 2012). In the evaluation of difference in mean symptoms and interference change over time between treatment groups, an effect size of 0.5 (half of a SD of baseline values) was deemed clinically meaningful (EMA 2013).

Method

Each subject's course consisted of the following periods:

Pre-Treatment: Screening evaluations were completed within 28 days before randomisation to determine the eligibility of subjects, including radiographically documented disease progression by mRECIST (Therasse et al 2000) compared to a radiologic assessment performed no more than 14 months previously. Some assessments, including physical examinations, Eastern Cooperative Oncology Group (ECOG) performance status (PS), haematology, serum chemistry, urine protein/creatinine ratio, urinalysis, and pregnancy tests, were repeated prior to treatment if the screening evaluations were performed more than seven days before the first dose of study treatment. Baseline subject self-assessment parameters and symptom burden were self-evaluated using the MDASI Thyroid Module.

Treatment: After confirmation of eligibility, subjects were randomised in a double-blinded fashion 2:1 to receive either a single oral daily dose of 175 mg XL184 (L-malate salt weight; 138 mg freebase equivalent weight) or placebo comparator, respectively. This period consisted of 4-week cycles. Radiologic tumour assessments were performed every 12 weeks (± 5 days) from randomisation until PD as determined by the investigator using mRECIST. Haematology and serum chemistry laboratory evaluations and vital signs assessments were conducted every two weeks during Cycles 1 and 2, and every four weeks starting with Cycle 3. Blood and tissue samples for biomarker analysis and blood samples for PK assessments were collected at specific protocol defined visits. At each study visit, evaluations of adverse events (AEs) and concomitant medication use were performed. Upon documented progression, using mRECIST as determined by the investigator or unacceptable toxicity or other protocol-specified criteria, the subject discontinued study treatment and entered the post-treatment period.

If study treatment was discontinued for reasons other than PD, the following efficacy and safety measures continued until documented tumour progression: tumour assessments; pharmacodynamics blood sampling; CTN, CEA, thyroid stimulating hormone (TSH), and free thyroxine (FT4) measurements; and MDASI Thyroid Module.

Post-Treatment: Thirty days (+7 days) after the last dose of study treatment, subjects returned to the study site for post-treatment assessments. The investigator obtained follow-up information, including survival status, every 12 weeks (± 15 days) after the last dose of study treatment.

The safety information from this study was reviewed by the Independent Data Monitoring Committee (IDMC) on an ongoing basis. The IDMC met quarterly to review unblinded data and, based on their review, made recommendations to the study sponsor as to whether or not it was safe to continue the study according to the protocol.

The Exelixis Safety Committee (ESC) conducted a blinded review of the XL184-301 safety data quarterly. The ESC is an internal Exelixis committee established to ensure a quarterly review of product safety data and consists of the medical monitor(s), the chief medical officer or vice president of clinical development, drug safety physician(s), and representatives from the following functional areas: regulatory affairs, biostatistics, and clinical development. The ESC reviewed all available safety data (AEs and SAEs) from all active XL184 (COMETRIQ) clinical studies to assess and monitor evolving safety trends, evaluate potential changes to clinical trial protocols based on safety analysis, and, ultimately, to safeguard subject safety. Results of the ESC quarterly reviews were shared with the IDMC. Tumour response and progression were assessed by the blinded IRC for the purpose of primary analyses of radiographic study endpoints.

Study design

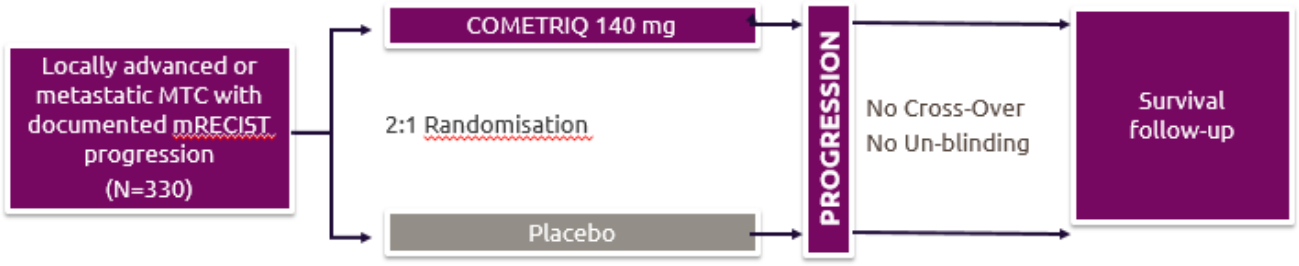
This study of patients with progressive unresectable, locally advanced or metastatic MTC was conducted at 90 sites in 23 countries.

Subjects were randomised 2:1 to receive an orally administered regimen of either 140 mg COMETRIQ capsules once or placebo (Elisei 2013). Radiologic tumour assessments were to be performed every 12 weeks (± 5 days) from randomisation until disease progression as determined by the investigator using modified RECIST (mRECIST) criteria, in which the original RECIST system was modified with operational clarifications intended to ensure accurate, consistent application of the criteria by multiple radiologists. Tumour assessments were evaluated by a blinded Independent Radiology Review Committee (IRC) to determine response and/or progression. The IRC comprised three board-certified radiologists: two primary radiologists independently read each case with the third radiologist serving as adjudicator if necessary.

Subjects remained in the treatment period until disease progression per mRECIST as determined by the investigator, as long as they did not experience unacceptable toxicity or did not meet other protocol-specified criteria (Elisei 2013). Switching to another systemic cancer therapy was allowed at the discretion of the investigator following discontinuation of study medication (COMETRIQ or placebo) (Exelixis 2012). Subjects receiving placebo were not allowed to switch to receive COMETRIQ (Elisei 2013).

Figure B Trial design EXAM study

Treatment until progression or unacceptable toxicity



Study endpoints

Primary: PFS per RECIST determined by IRC

Key secondary: Overall survival (OS), objective response rate (ORR) per RECIST

Adapted from Elisei 2013

Patient population

Inclusion and exclusion criteria for EXAM are presented in Table 4.2.2.1. In addition, at screening subjects were required to have radiographically documented disease progression by mRECIST compared to a radiologic assessment performed no more than 14 months previously (Exelixis 2012, Elisei 2013). This rigorous measure of disease progression has not previously been employed in studies in MTC patients, and was applied in EXAM in order to limit enrolment to patients in need of treatment.

Table 4.2.2.1 Inclusion and exclusion criteria in the EXAM trial

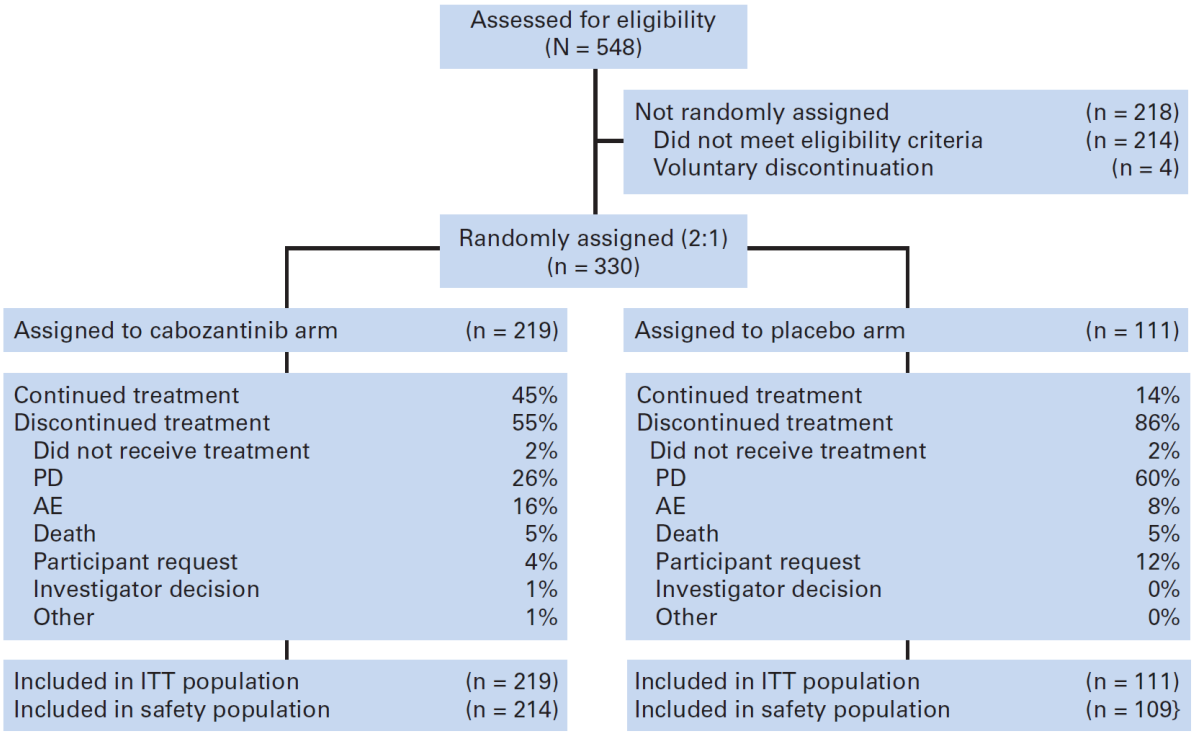
Inclusion criteria	Exclusion criteria
• Histologically confirmed diagnosis of MTC that was unresectable, locally advanced, or metastatic, and disease that was	• Prior systemic anti-tumour therapy within 4 weeks of randomisation (6 weeks for nitrosoureas or mitomycin C) • Radiation to ≥25% of bone marrow

measurable or non-measurable per mRECIST • Age ≥18 years • ECOG performance status ≤ 2 • Documented progressive disease • Recovered to CTCAE v3.0 Grade ≤1 from clinically significant AEs due to antineoplastic agents, investigational drugs, or other medications administered prior to randomisation • Absolute neutrophil count ≥1500/mm^3, platelets ≥100,000/mm^3, haemoglobin ≥9 g/dL, bilirubin ≤1.5× ULN (did not apply to subjects with Gilbert's syndrome), serum creatinine ≤1.5 mg/dL, and ALT and AST ≤2.5× ULN • Sexually active subjects: agreement to use medically accepted methods of contraception during the study and for 3 months following discontinuation of study treatments (except women not of childbearing potential and sterilised men) • No other diagnosis of malignancy (unless nonmelanoma skin cancer, carcinoma in situ of the cervix, or a malignancy diagnosed ≥2 years previously) and had no evidence of malignancy (unless nonmelanoma skin cancer or carcinoma in situ of the cervix) • Female subjects of childbearing potential: negative pregnancy test at screening	• Treatment with other investigational agents within 4 weeks of randomisation • Treatment with COMETRIQ • Brain metastases or spinal cord compression, unless completed radiation therapy ≥4 weeks prior to randomisation and stable without steroid and without anticonvulsant treatment for ≥10 days • History of clinically significant hematemesis or a recent history of haemoptysis of >2.5 ml of red blood or other signs indicative of pulmonary haemorrhage or evidence of endobronchial lesion(s) • Urine protein/creatinine (g/g) ratio ≥1 • Serious intercurrent illness or a recent history of serious disease • Pregnant or breastfeeding • Active infection requiring systemic treatment. • Known allergy or hypersensitivity to any of the components of study-drug formulations • Incapable of understanding and complying with the protocol or unable to provide informed consent

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; ULN: upper limit of normal range

The disposition of patients in EXAM is shown in Figure C. The ITT population comprised 219 patients in the COMETRIQ arm and 111 patients in the placebo arm (Elisei 2013).

Figure C CONSORT diagram of patient flow in the EXAM trial, data cut off 2011



As shown in Table 4.2.2.1.1, baseline characteristics were generally well balanced between the treatment arms in EXAM. The majority of subjects in both treatment groups were male, and most were ≤65 years of age (78.5% of subjects in the COMETRIQ arm vs. 77.5% of subjects in the placebo arm) (Elisei 2013).

The tumour RET mutational status was known in 60%–61% of subjects, and among those with known mutational status, 101 of 132 (77%) patients in the COMETRIQ arm and 58 of 68 (85%) patients in the placebo arm were RET mutation positive (Elisei 2013).

Several measures confirmed that subjects had advanced and progressive disease at baseline: all had documented radiographic disease progression, the vast majority had metastatic disease, nearly half had ECOG status of 1 or 2, and more than a third of patients had received prior systemic treatment for MTC. Approximately 1 in 5 subjects had previously received treatment with TKIs (Elisei 2013).

Table 4.2.2.1.1. Baseline demographic and clinical characteristics of patients in the EXAM trial

Characteristic	Cabozantinib (N=219)	Placebo (N=111)
Sex, n (%)		
Male	151 (68.9)	70 (63.1)
Female	68 (31.1)	41 (36.9)
Age, years		
Median (range)	55.0 (20–86)	55.0 (21–79)
>65	47 (21.5)	25 (22.5)
ECOG performance status, n (%)		
0	123 (56.2)	56 (50.5)
1-2	95 (43.4)	55 (49.5)
Tumour *RET* mutational status, n (%)		
Positive	101 (46.1)	58 (52.3)
Negative	31 (14.2)	10 (9.0)
Unknown	87 (39.7)	43 (38.7)
Subjects with prior systemic therapy for MTC, n (%)	81 (37.0)	47 (42.3)
Prior TKI status, n (%)		
Yes	44 (20.1)	24 (21.6)
vandetanib	25 (11.4)	9 (8.1)
No	171 (78.1)	86 (77.5)
Unknown	4 (1.8)	1 (0.9)

ECOG: Eastern Cooperative Oncology Group; MTC: medullary thyroid cancer; RET: rearranged during transfection; SD: standard deviation; TKI: tyrosine kinase inhibitor

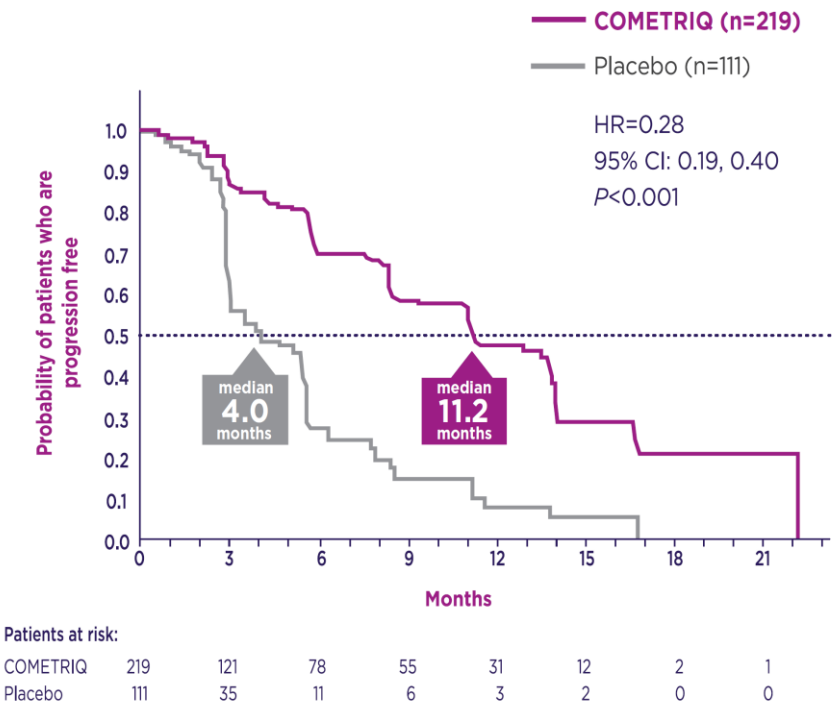
Elisei 2013

4.2.2.2 Efficacy Results

Progression free survival (PFS)

EXAM met its primary endpoint, demonstrating a large and statistically significant improvement in PFS for patients receiving COMETRIQ compared with those receiving placebo: with adjustment for age and prior TKI status, the HR was 0.28 (95% CI 0.19, 0.40; stratified log-rank P<0.001), an estimated 31.2-week (7.2-month) difference in the medians (Figure D) . The Kaplan-Meier estimate of the cumulative probability of subjects being event-free (alive and not yet progressed) at 12 months was 47.3% in the COMETRIQ arm and 7.2% in the placebo arm (Elisei 2013).

Figure D Kaplan–Meier plot of PFS in EXAM through the date of the 138th IRC-adjudicated event



Adapted from Elisei 2013

IRC: Independent Radiology Review Committee; PFS: progression-free survival

Median time to first dose modification (FMOD) in the COMTERIQ treatment group was approximately 30 days (XL184-301 ER 2012). A Kaplan-Meier analysis of PFS stratified by the time to FMOD (i.e. dose reduction or interruption) was performed. These data suggest that early dose modifications were not associated with a marked reduction in PFS (XL184-301 ER 2012).

Overall survival

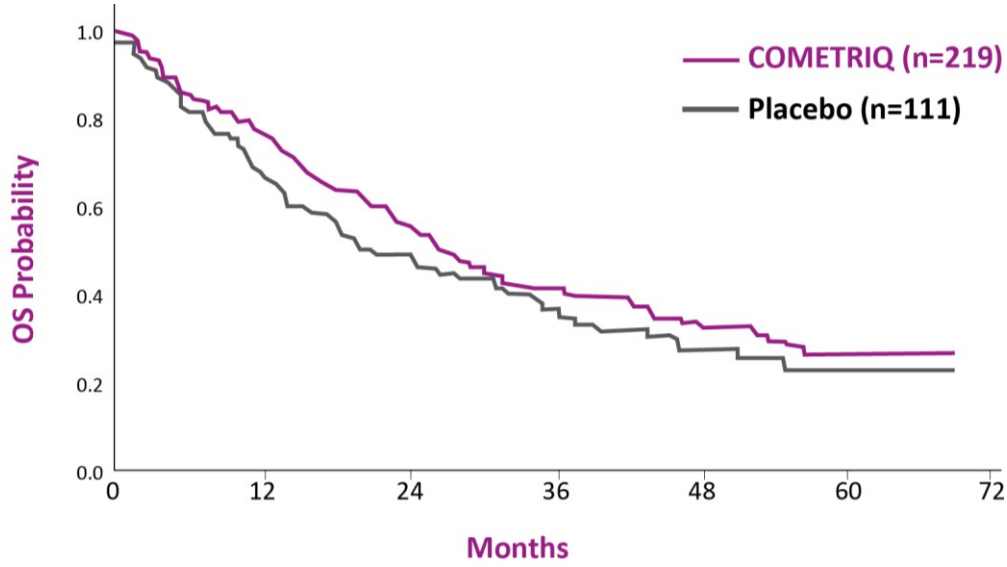
Pre-planned analysis of OS was conducted, when 44% of total events had occurred (data cut off June 15 2011). At this point no difference in OS was shown (Elisei 2013; Schlumberger 2015). An administrative analysis of OS was conducted with data up to June 15th, 2012, based on 162 (75%) of the 217 deaths required for the final analysis (Schlumberger 2015). This demonstrated a trend in favour of COMETRIQ, but statistical significance was not reached (HR 0.83) (Schlumberger 2015).

The final analysis was conducted when 218 deaths were recorded, data cut off 28 August 2014 (Schlumberger 2015).

In this final OS analysis, overall there was a trend for improvement in OS in the COMETRIQ arm, with a HR of 0.85 (95% CI: 0.64, 1.12; p=0.2409) (Schlumberger 2015). The median duration of OS was 26.6 months in the COMETRIQ arm and 21.1 months in the placebo arm (Schlumberger 2015).

MTC is a rare disease and it should be noted that the study was not designed to be large enough to provide high power to detect minimum clinically meaningful difference in the secondary endpoint of OS. Study size was chosen to provide reasonable power (80%) for a large (50%) improvement in OS (HR 0.667; improved median from 22 to 33 months) (Schlumberger 2015).

Figure E: Kaplan–Meier plot of OS in EXAM up to 28th August 2014 (final analysis)



	COMETRIQ	Placebo
Median OS	26.6 months	21.1 months
HR* (95% CI)	0.85 (0.64, 1.12)	
P-value	0.2409	

*Stratified hazard ratios shown

Additional analyses were conducted on subgroups including mutational status, which is covered later in section 4.2.2.3

Tumour response

A highly significant difference was observed for the pre-specified secondary endpoint of rate of objective responses confirmed with a follow-up tumour assessment at least 28 days later. (Elisei 2013). In the primary analysis of this endpoint, the ORR as determined by the IRC was 28% for subjects in the COMETRIQ arm (all were confirmed partial responses) and 0% for subjects in the

placebo arm (p<0.0001) (Table 4.2.2.2) Responses in the COMETRIQ group were durable, with a median duration of response of 14.6 months (95% CI 11.1, 17.5) (Elisei 2013).

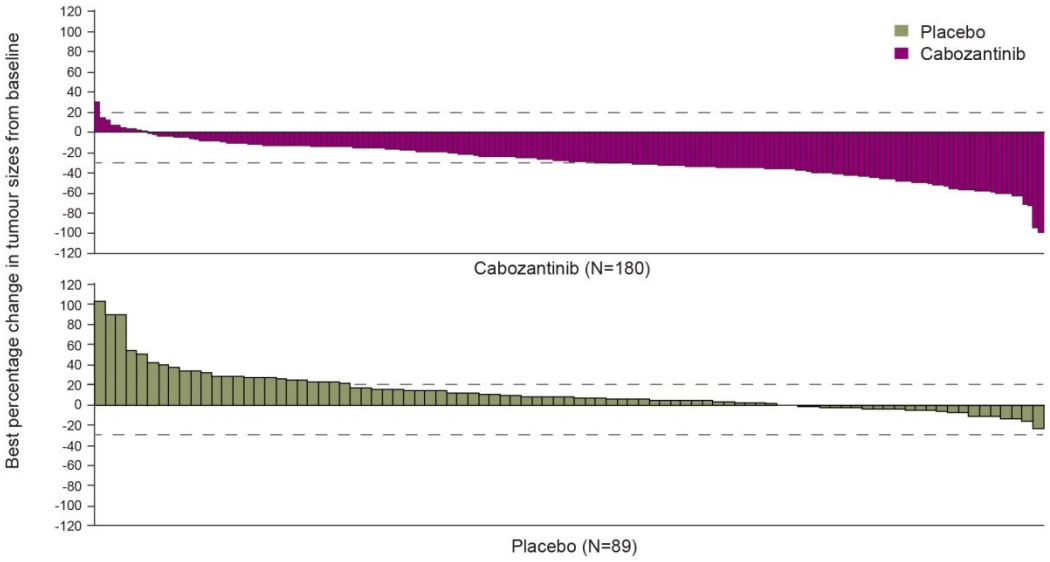
Table 4.2.2.2 Tumour response in subjects with measurable disease at baseline in EXAM

Subjects in ITT Population	Cabozantinib (N=219)	Placebo (N=111)
Subjects with measurable disease	208	104
Best overall response, n (%)*†		
Confirmed CR	0	0
Confirmed PR	58 (27.9)	0
Stable disease	100 (48.1)	52 (50.0)
Progressive disease	18 (8.7)	35 (33.7)
Unable to evaluate	5 (2.4)	1 (1.0)
Missing‡	27 (13.0)	16 (15.4)
ORR=CR+PR†§		
n (%)	58 (27.9)	0
95% CI	21.9%, 34.5%	NA
99% CI	20.2%, 36.6%	NA
P (stratified Cochran-Mantel-Haenszel test)¶	<0.0001	

Adapted from Exelixis 2012
* Best overall response determined by IRC using mRECIST criteria †Percentages are based on the number of subjects with measurable disease ‡No qualifying post-baseline assessment for overall response
§Proportion of subjects with measurable disease achieving best overall response of confirmed CR or confirmed PR
¶Stratification factors: age and prior TKI status
CI: confidence interval; CR: complete response; ITT: intention to treat; mRECIST: modified Response Evaluation Criteria in Solid Tumours; ORR: objective response rate; PR: partial response; TKI: tyrosine kinase inhibitor

Changes in the sum of the longest diameter of target lesions according to mRECIST criteria, as determined by the IRC, were available for 180 and 89 subjects who had measurable disease at baseline and at least one post-baseline assessment in the COMETRIQ arm and the placebo arm, respectively (Elisei 2013). Figure F displays this data indicating the vast majority of patients in COMETRIQ arm had a decrease in target lesions size (Elisei 2013).

Figure F Waterfall plot of best percentage change in size of target lesions from baseline in EXAM (IRC determined, ITT population)

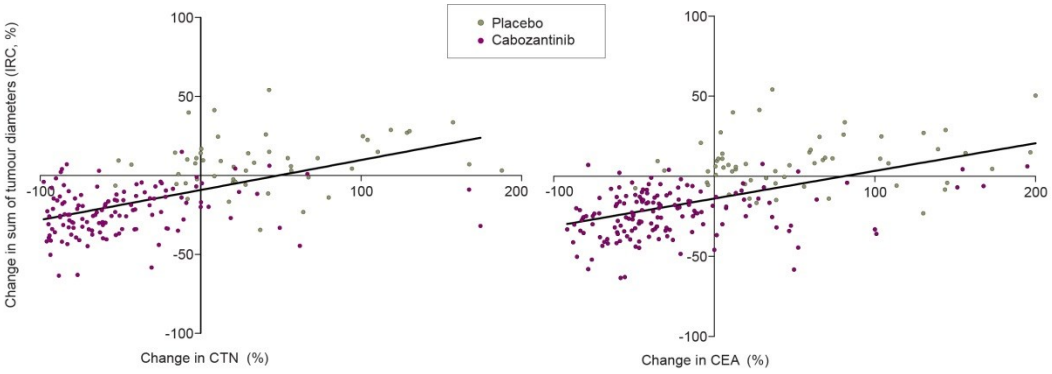


Adapted from Exelixis 2012 Bars represent individual patients

Biomarkers

Levels of serum calcitonin and CEA showed treatment-related reductions in the COMETRIQ arm and increases in the placebo arm (Elisei 2013), supporting the proposed mechanism of action for COMETRIQ. The relationship between decreases in levels for each of these biomarkers and change in tumour size in the COMETRIQ arm was found to be generally linear (Elisei 2013).

Figure G Correlation between changes in calcitonin or CEA and change in sum of tumour diameters at Week 12 in EXAM



Adapted from Elisei 2013 CEA: carcinoembryonic antigen; CTN: calcitonin

Patient reported outcomes

Subjects in EXAM self-assessed symptom burden using the MDASI-THY questionnaire as an exploratory objective for this study (Exelixis 2012). Although no formal statistical testing was performed there was no apparent difference between treatment arms in change from baseline to 2011 data cut off analysis for this exploratory endpoint (Exelixis 2012).

Subsequent cancer therapy

As reported from the final analysis (Table 4.2.2.2.1) subsequent cancer therapy was received by a lower proportion of subjects in the COMETRIQ arm than in the placebo arm: 44% versus 58%, respectively. Subsequent systemic cancer therapy, including cytotoxic chemotherapy and targeted agents, was received by 32% of subjects previously receiving COMETRIQ and 50% of those previously receiving placebo (Schlumberger 2015).

Table 4.2.2.2.1 Subsequent cancer therapy (final analysis)

Subjects in ITT Population	Cabozantinib N=219 n, (%)	Placebo N=111 n, (%)
Any subsequent anti-cancer therapy	97 (44.3)	64 (57.7)
Local therapy *	44 (20.1)	27 (24.3)
Systemic therapy	69 (31.5)	55 (49.5)
Cytotoxic agents	8 (3.7)	10 (9.0)
All TKIs [a]	59 (26.9)	46 (41.4)
Vandetanib	44 (20.1)	24(21.6)
Cabozantinib	5 (2.3)	9 (8.1)
Other TKI [b]	30 (13.7)	28 (25.2)
Targeted – other [c]	6 (2.7)	6 (5.4)
Other systemic [d]	3 (1.4)	8 (7.2)

Adapted from Schlumberger 2015 and Exelixis 2015 TKI: tyrosine kinase inhibitor

* Included radiation treatments, surgical resection, hepatic artery chemoembolism

[a] Included cediranib, erlotinib, lenvatinib, pazopanib, sorafenib, sunitinib

[b] refers to cabozantinib taken after discontinuation of study treatment

[c] Included everolimus, notch inhibitor labelled PJC-004

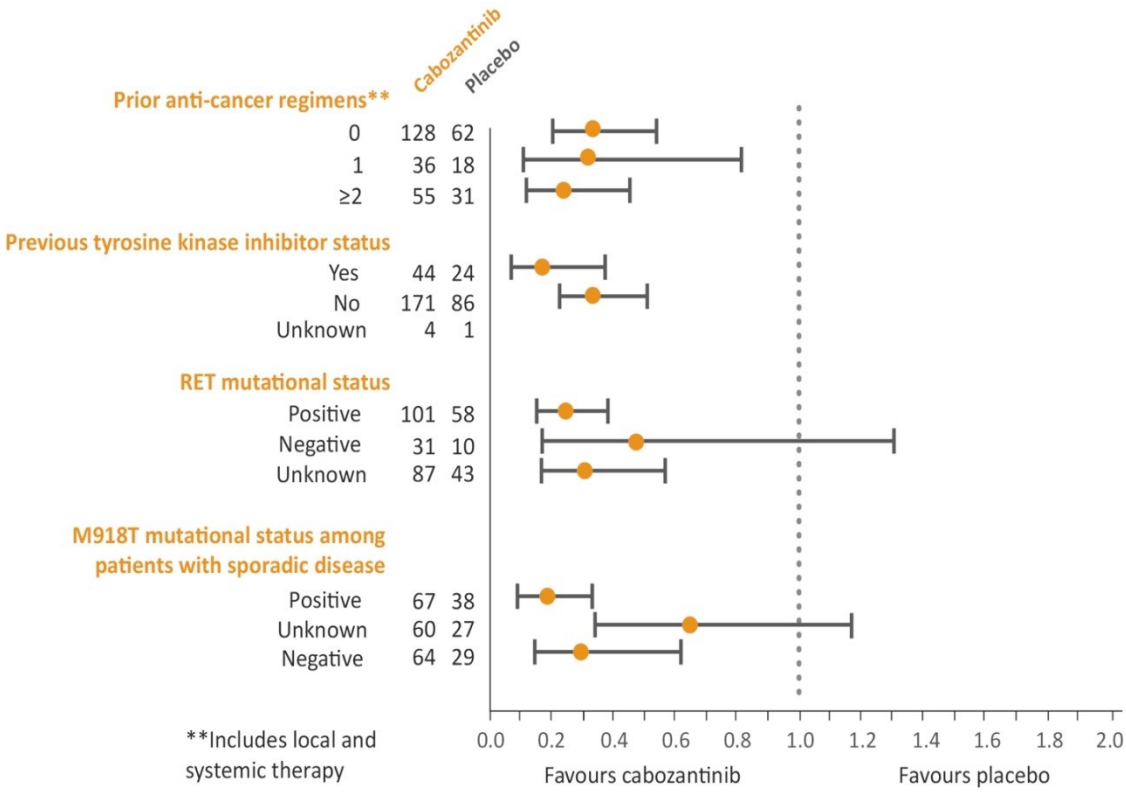
[d] Included interferon, PEG intron, Som 230 LAR, zoledronic acid

4.2.2.3 Subgroup analyses – RET mutation status

Progression free survival

Pre-specified subgroup analyses revealed that the significant improvement in PFS with COMETRIQ was highly robust (Elisei 2013). COMETRIQ treatment resulted in a consistent benefit across all of the baseline and demographic parameters; although the 95% CIs were wide in some smaller subgroups (as would be expected with small samples), all the point estimates across subgroups for prior treatment favoured COMETRIQ (Elisei 2013). Notably, the beneficial effect of COMETRIQ on PFS in EXAM was observed in all RET mutation subgroups (somatic or germline) status: positive, HR, 0.24; negative, HR, 0.47; unknown, HR 0.30), although for the RET mutation negative subgroup crosses 1.0 (Elisei 2013).

Figure H: Pre-specified subgroup analyses of IRC-adjudicated PFS in EXAM



Adapted from Elisei 2013

Activating mutations in the RET proto-oncogene have a central role in tumourigenesis and RET genetic alterations are detected in 95% of hereditary and 65% of sporadic MTC. In addition in sporadic MTC tumours that lack RET mutation often contain a mutation in RAS (also involved in tumourigenesis) (Sherman 2016). As a result there has been interest in subgroup analysis by these mutations (Schlumberger 2015; Sherman 2016).

Of those patients in the EXAM study who received COMETRIQ 37% were RET M918T mutation positive (Schlumberger 2015; Sherman 2016).

In the updated post hoc analyses that assessed PFS in patients on the basis of RET and RAS mutation status, PFS in RET-mutation–negative and RAS-mutation–positive patients was prolonged in patients receiving COMETRIQ compared with those receiving placebo (Sherman 2016). As shown in Table 4.2.2.3, PFS improvement was least pronounced in the small subset of RET-mutation–negative patients who were also RAS-mutation negative (n=33, 10% of total trial population), indicating that the PFS improvement observed for COMETRIQ treatment in RET-mutation–negative patients was partly attributable to patients harbouring RAS mutations (Schlumberger 2015; Sherman 2016).

Table 4.2.2.3: PFS in updated post hoc mutational analysis of EXAM data

Mutation status	Cabozantinib		Placebo		HR (95% CI)	P
	N	Median PFS (weeks)	N	Median PFS (weeks)		
RET-positive	107	60	62	20	0.23 (0.14, 0.38)	<0.0001
RET-negative	35	25	11	23	0.53 (0.19, 1.50)	0.2142
RET-unknown	77	48	38	13	0.30 (0.16, 0.57)	0.0001
RET M918T positive	81	61	45	17	0.15 (0.08-0.28)	<0.0001
RAS-positive	13	47	3	8	0.15 (0.02, 1.10)	0.0317
RET-negative + *RAS*-negative	22	24	8	23	0.8 8(0.24, 3.-22	0.8330

Adapted from Sherman 2016 CI: confidence interval; HR: hazard ratio; IRC: Independent Radiology Review Committee; PFS: progression-free survival

Kaplan-Meier estimates of PFS by RET mutation status also depict that where patients were RET mutation positive, RET mutation unknown or RAS gene positive there was a significant improvement in PFS (Sherman 2016). In those patients who were RET mutation negative the population was small and unequally distributed between cabozantinib and placebo groups and as a result no conclusions could be drawn regarding activity of COMETRIQ in this subpopulation (Sherman 2016).

Tumour response

ORR subgroup analyses showed that responses were observed in the COMETRIQ arm regardless of *RET* mutation status or M198T status in subjects with sporadic disease (Sherman 2016). In the updated post hoc analyses that assessed tumour response in EXAM on the basis of *RET* and *RAS* mutation status, tumour response rates between 22% and 32% were observed in all three *RET*-mutation subgroups (positive, negative, and unknown (Table 4.2.2.3.1) (Sherman 2016).

The 31% response rate for *RAS*-mutation–positive patients was also within this range. A response rate of 21% was observed in the *RET* and *RAS*-mutation–negative patients, providing evidence for clinical activity of COMETRIQ in this subgroup.

The greatest benefit in terms of response rate, as demonstrated by an ORR of 34%, was seen in those patients who were RET M918T mutation positive (Schlumberger 2015; Sherman 2016).

Table 4.2.2.3.1 Tumour response in updated post hoc mutational analysis of EXAM data

Mutation status	Patients with measurable disease (COMETRIQ arm)*	Tumour responses	Response rate, %
All COMETRIQ patients	208	58	28
RET-positive	101	32	32
RET-negative	32	7	22
RET-unknown	75	19	25
RET- M918T mutation positive	77	26	34
RAS-positive	13	4	31
RET-negative + no known *RAS* mutation	19	4	21

Adapted from Sherman 2016

*No tumour responses were measured in the placebo arm

Overall survival – RET M981T positive mutation status

In the final analysis that assessed OS in patients on the basis of *RET* M918T mutation status, among the subgroup of *RET* M918T-mutation–positive patients there was a 25.4 month gain in median OS for patients receiving COMETRIQ compared with those receiving placebo.

This OS benefit of COMETRIQ in *RET* M918T-mutation–positive patients was significant (P=0.0260), demonstrating a relationship between prolonged PFS and improved OS among patients receiving COMETRIQ (Table 4.2.2.3.2) (Sherman 2016).

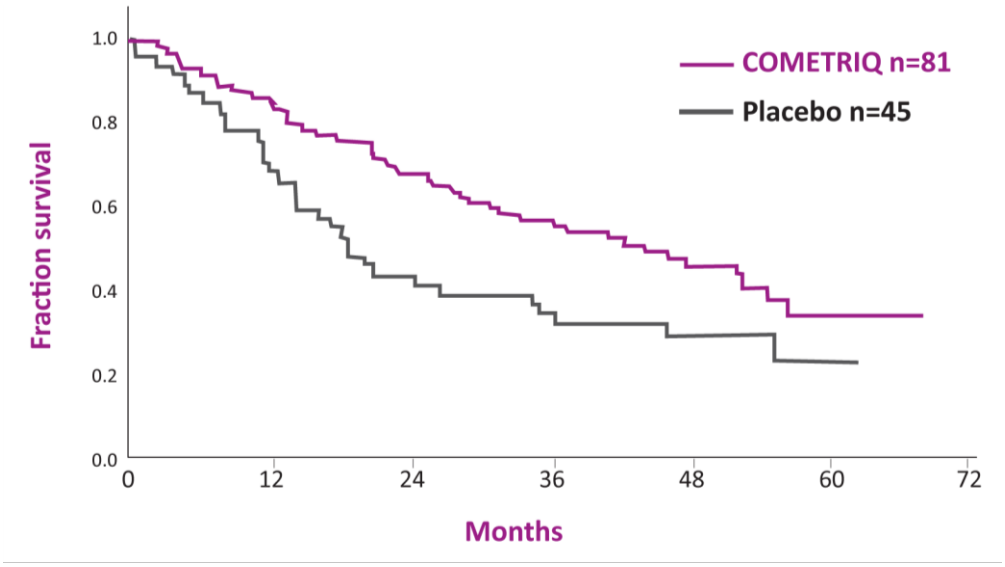
Table 4.2.2.3.2 OS and PFS figures by mutational status RET M918T subgroup (final analysis)

	RET M918T mutation positive		*RET* M918T mutation negative		All patients	
	Cabozantinib (N=81)	Placebo (N=45)	Cabozantinib (N=75)	Placebo (N=32)	Cabozantinib (N=219)	Placebo (N=111)
Median OS, months	44.3	18.9	20.2	21.5	26.6	21.1
OS HR (95% CI)	0.60 (0.38, 0.95)		1.12 (0.07, 1.82)		0.85 (0.64, 1.12)	
P value	0.0260		0.6308 (NS)		0.2409 (NS)	
PFS HR (95% CI)	0.15 (0.08, 0.28)		0.67 (0.37, 1.23)		0.28 (0.19, 0.40)	
ORR	34%	0%	20%	0%	28%	0%

Adapted from Schlumberger 2015

CI: confidence interval; HR: hazard ratio; NS: not statistically significant; OS: overall survival

Figure I Kaplan- Meier for OS stratified by RET M918T mutation positive status (final analysis)



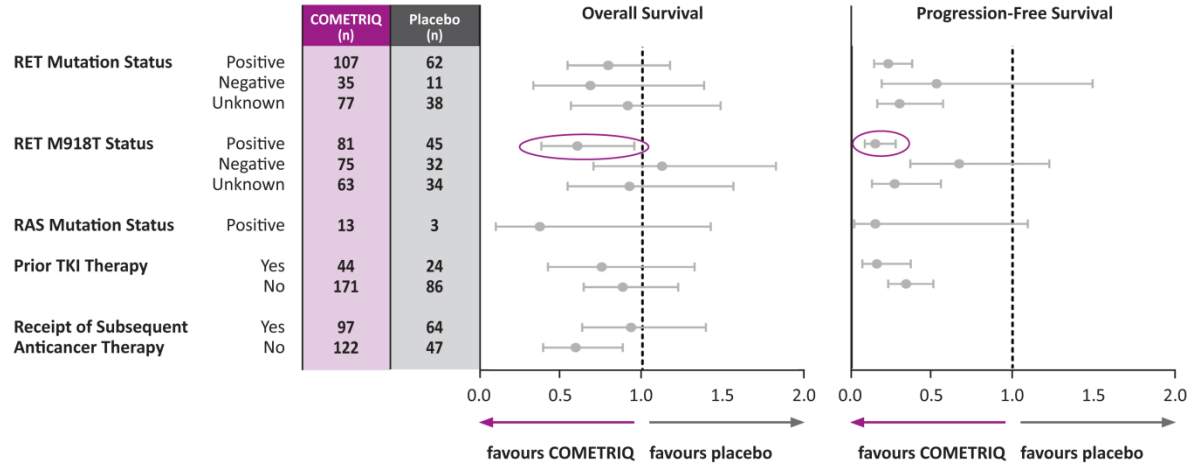
RET M918T Positive

	COMETRIQ	Placebo
Median OS	44.3 months	18.9 months
OS HR (95% CI)	0.60 (0.38, 0.95)	
P-value	0.0260	
PFS HR (95% CI)	0.15 (0.08, 0.28)	
ORR	34%	0%

Thus, the subgroup analyses demonstrated that treatment effect was most pronounced in the patients with RET M918T mutation, with median OS increase of 25.4 months over placebo and HR 0.60 (95% CI 0.38, 0.95), p=0.0260 (not adjusted for multiple subgroup analyses) in this subgroup (Schlumberger 2015; Sherman 2016).

This RET M918T subgroup also demonstrated the longest median PFS and highest objective response rate (Schlumberger 2015).

Figure J OS and PFS at final analysis by mutational status



Adapted from Schlumberger 2015

Subgroup analysis by prior TKI exposure

Only a small number of patients in EXAM were known to have previously received vandetanib (n=34). Prolonged PFS was observed in the COMETRIQ arm compared with the placebo arm regardless of whether patients were known to have previously received or not received vandetanib (Table 4.2.2.3.3) (Exelixis 2014).

Table 4.2.2.3.3 PFS in EXAM stratified by prior vandetanib use

Known receipt of prior vandetanib	Cabozantinib		Placebo	
	N	Median PFS (months)	N	Median PFS (months)
No	194	11.0	102	4.6
Yes	25	12.8	9	2.8

Adapted from Exelixis 2014 PFS: progression-free survival

Objective responses were also observed in the COMETRIQ arm regardless of whether patients were known to have previously received or not received vandetanib (Table 4.2.2.3.4). Of the 7 COMETRIQ-treated patients with tumour response in EXAM who had received prior treatment with vandetanib (Exelixis 2014).

Table 4.2.2.3.4 Tumour response in EXAM stratified by prior vandetanib use

Known receipt of prior vandetanib	Cabozantinib		Placebo	
	N	ORR, n (%)	N	ORR, n (%)
No	194	51 (26)	102	0
Yes	25	7 (28)	9	0

Reference: Exelixis 2014

ORR: objective response rate

4.2.2.4 Meta-analysis

No meta-analysis between COMETRIQ (cabozantinib) and vandetanib are available.

4.2.2.5 Indirect analysis

An indirect comparison between COMETRIQ and CAPRELSA (vandetanib) was reported as an abstract (Rinciog 2014). The objective of this study was to assess the relative efficacy in PFS and OS of cabozantinib vs vandetanib. Since there are no clinical trials directly comparing the two treatments, an adjusted indirect comparison (Bucher method) was used. Evidence on PFS for the two treatments was collected from the pivotal clinical trials in MTC. The analysis considered all patients and a subgroup of RET M918T mutation positive patients. Analysis focused on PFS due to lack of evidence for the vandetanib OS in the RET M918T mutation subgroup.

In the all patients analysis three different scenarios were explored: a log-rank model to ensure comparability with the vandetanib data; a Cox model stratified on age at randomization and prior TKI status; and a Cox model without stratifications.

In the subgroup analysis (log-rank model) PFS was estimated to increase by 65% with cabozantinib comparing to vandetanib (HR 0.35; 95% CI 0.14-0.87).

In the all-patients analysis the estimates were less conclusive: log-rank model (HR 0.72; 0.40-1.28), Cox model with stratifications (HR 0.61; 0.35-1.04), Cox model without stratifications (HR 0.66; 0.39-1.13).

The authors concluded the results showed a positive trend in favour of COMETRIQ in PFS and given the limited evidence a direct head-to-head comparison would be necessary to validate the study findings.

4.2.2.4 Efficacy Summary

The EXAM trial demonstrated a highly significant PFS benefit of COMETRIQ, in both clinical and statistical terms, in a population of MTC patients with actively progressing disease. Patients receiving COMETRIQ had a 72% lower risk of experiencing disease progression compared with those in the placebo group (HR for PFS 0.28, 95% CI 0.19, 0.40, P<0.001). (Elisei 2013). The median PFS was nearly 3-fold higher in the COMETRIQ arm compared with the placebo arm (11.2 months vs. 4.0 months, respectively) (Elisei 2013; Weitzman 2015).

Furthermore, the efficacy of COMETRIQ appeared to be consistent across subgroups for any of the baseline and demographic parameters analysed. In particular, a similar PFS benefit was observed even in subjects who had undergone prior treatment with another TKI compared with TKI-naïve subjects (Elisei 2013), and PFS was also prolonged in the COMETRIQ arm compared with the placebo arm in the subgroup of patients who had received prior vandetanib (Exelixis 2014). Despite evidence for lower clinical benefit of COMETRIQ among RET and RAS-mutation–negative patients, the PFS hazard ratio of 0.88 (95% CI 0.24, 3.22) and the ORR of 21% indicated that COMETRIQ may have clinical activity in at least some patients in this subgroup (Sherman 2016).

Additional evidence of clinical benefit was provided by a significant treatment effect of COMETRIQ on objective tumour response, with similar ORR regardless of whether or not patients had previously received vandetanib (Exelixis 2014), as well as a clear correlation between change in levels of calcitonin and CEA and change in tumour size (Elisei 2013).

Although a statistically significant effect of COMETRIQ on OS was not demonstrated in the final analysis, the study was only powered to detect and increase in survival from 22 to 33 months, rather than minimum clinically meaningful improvement (Schlumberger 2015). Notably, a statistically significant treatment effect on OS was found in RET M918T-mutation–positive patients (Sherman 2016).

The short duration of PFS in the placebo group suggested that the subjects enrolled in EXAM had progressive disease and were in need of treatment (Elisei 2013).

In its clinical trial programme in patients with MTC, COMETRIQ has demonstrated a clear clinical benefit. The pivotal trial EXAM was the first randomised, placebo-controlled trial to demonstrate efficacy of a TKI in a rigorously selected population of MTC patients with well-documented progressive disease (Elisei 2013).

In EXAM, COMETRIQ improved PFS in subjects who were RET-mutation positive, in those classified as RET-mutation negative, and in patients with unknown RET status. Furthermore, objective tumour response was seen in patients with and without RET mutations in both EXAM and Study XL184-001 (Elisei 2013; Kurzrock 2011).

These findings indicate that COMETRIQ can be used in MTC patients regardless of their RET mutational status. Further analysis of the EXAM data showed that a subset of the RET-mutation–

negative patients harboured a RAS mutation, and patients with RAS mutations showed PFS and tumour-response benefits of COMETRIQ treatment. Analysis indicated that the RET-mutation–negative subgroup is likely heterogeneous and contains subpopulations of patients who benefit from COMETRIQ treatment, including patients with RAS mutations. Nevertheless, for patients in whom RET mutation status is not known or is negative, the possibility of lower clinical benefit should be taken into account before individual treatment decisions are taken (SmPC 2016).

Taken together, Study XL184-001 and EXAM consistently show a clinical benefit of COMETRIQ in MTC patients. The ORR of 28% in EXAM was supported by a similar objective response of 29% in the subjects with MTC and measurable disease in Study XL184-001.

In both studies, use of COMETRIQ reduced blood levels of calcitonin and CEA, biomarkers that have been shown to be prognostic factors for disease progression. Thus, Study XL184-001 and EXAM provide evidence bridging from the pathophysiological rationale for treating advanced MTC with COMETRIQ to significant impact on clinically meaningful endpoints.

Moreover, the significant effect of COMETRIQ on OS in the subgroup of patients in EXAM with a RET M918T mutation provides evidence that prolonged PFS is indeed associated with improved OS (Elisei 2013; Schlumberger 2015).

Overleaf Table 4.2.2.4, an overview of the phase III EXAM trial is shown.

Table 4.2.2.4: Overview of phase III efficacy study of XL184 in patients with unresectable, locally advanced or metastatic MTC

Study identifier	**XL184-301**
Design	A Phase III, international, randomised, double-blinded efficacy study of XL184 in patients with unresectable, locally advanced or metastatic medullary thyroid cancer
Duration of main phase:	Patients remained in the Treatment Period until PD per mRECIST as determined by the investigator, as long as they did not experience unacceptable toxicity or did not meet other protocol-specified criteria.
Duration of Run-in phase:	N/A
Duration of Extension phase:	N/A
Hypothesis	Superiority
A total of 330 patients (219 cabozantinib and 111 placebo) were randomised (ITT population). Safety population comprised 323 patients (214 cabozantinib, 109 placebo) who had at least one dose of study drug and the per protocol population comprised 300 subjects (198 cabozantinib, 102 placebo)	
Treatments groups 175mg XL184 (COMETRIQ) (L-malate salt weight, 138 mg freebase equivalent weight)	**Treatment**: once per day (OD) oral administration **Duration**: Patients remained in the Treatment Period until PD per mRECIST as determined by the investigator, as long as they did not experience unacceptable toxicity or did not meet other protocol-specified criteria. Maintenance period then entered. **Number randomised**: 219
Placebo	**Treatment**: once per day oral administration **Duration**: Patients remained in the Treatment Period until PD per mRECIST as determined by the investigator, as long as they did not experience unacceptable toxicity or did not meet other protocol-specified criteria.
	Number randomised: 111

Endpoints and definitions	Primary endpoint	Progression Free survival PFS)	
Secondary endpoint	OS	Overall survival	
Secondary endpoint	ORR	Objective response rate	
Database lock	Maintenance phase from December 1 2014 Initial analysis data lock June 2011 Safety analysis and interim OS analysis data lock December 2011 Final analysis data lock 28 August 2014		
Results and Analysis			
Analysis description		**Primary Analysis**	
Intent to treat All patients who were randomised, regardless of whether any study treatment or the correct study treatment was administered. The analysis was conducted after at least 315 patients had been randomised and at least 138 progression events (non-censored radiographic progression per mRECIST as assessed by the IRC, or death) had occurred.			
Descriptive statistics and estimates	**Treatment group**	**XL184 (COMETRIQ)**	**Placebo**
	Number of patients	219	111
	Number of patients with measurable disease	208	104
Subjects in intent to treat (ITT) population at **initial analysis (June 2011 data cut off**) (*interim analysis for OS data cut off December 2011)	PFS Weeks (months)	48.6 (11.2)	17.4 (4)
	(95% CI)	(40.14, 59.71)	(12.86, 23.57)
	p-value	<0.0001	
	Hazard ratio (95% CI; stratified)	0.28 (0.19, 0.40)	
	OS* Number (%) patients		
	Censored	153 (69.9)	81 (73.0)
	Death	66 (30.1)	30 (27.0)
	OS* Median (Months)	21.1	N/A
	(95% CI)	(16.59, 28.52)	(17.41, N/A)
	p-value		
	ORR (ORR=CR+PR)	58 (27.9%)	0

	n (%) 95% CI	21.9%, 34.5% 20.2%, 36.6%	N/A N/A
	p-value	<0.0001	
No. of patients on study treatment as at June 2011 (Initial Report) n (%)		98/219 (44.7%)	15/111 (13.5%)
No. of patients on study treatment as at December 2011 (Safety Report) n (%)		65/219 (29.7%)	8/111 (7.2%)
Notes	This study went into maintenance phase Dec 2014. At final analysis (cut off August 2014) 21/219 patients only remained on cabozantinib and none on placebo. Data up to 15 June 2011 are contained in the main study publication (Elisei 2013)		
	Treatment group	**XL184 (COMETRIQ)**	**Placebo**
ITT cut off for OS (**administrative analysis**) 15 June 2012	Number of patients n (%)	219	111
	Median duration of survival (Months)	26.0	20.3
	Hazard ratio	0.83	
	Treatment group	**XL184 (COMETRIQ)**	**Placebo**
ITT population OS (secondary endpoint **final analysis**) at data cut off 28 August 2014	Number of patients n (%)	219	111
	Censored	78 (35.6)	34 (30.6)
	Death	141 (64.4)	77 (69.4)
	Median duration of survival (Months)	26.6	21.1
	95% CI	(23.2, 31.61)	21.1 (16.39, 32.36)
	Hazard ratio (95% CI; stratified)	0.85 (0.64, 1.12)	
	P value (stratified log-rank test)	0.2409	

OS by RET and RAS mutational status	Median duration of survival (months)	**XL184 (COMETRIQ)**	**Placebo**
	RET M918T positive	44.3	18.9
	Hazard ratio (95% CI)	0.60 (0.38, 0.94)	
	P value (log-rank)	0.0255	
	RET M918T negative	20.2	21.5
	Hazard ratio (95% CI)	1.12 (0.70, 1.82)	
	P value (log-rank)	0.6308	
	RET M918T unknown	26.2	31.4
	Hazard ratio (95% CI)	0.92 (0.54, 1.56)	
	P value (log-rank)	0.7577	
Notes	Treatment effect most pronounced in the subgroup of pts with RET M918T mutation where median OS was increased 25.4 months over placebo which was statistically significant. This subgroup also demonstrated longest median PFS and highest ORR.		
No. of patients on study treatment as at August 2014 (Final Report) n (%)		21/219 (9.6%)	0/111 (0%)
Final analysis Duration of exposure (months)	Mean (SD)	16.4 (15.8)	5.7 (6.1)
	Median	10.8	3.4
	Range	0.3 -59.4	0.4-40.5
Patients with at least one dose reduction (%)	1 level dose reduction	83	11
	2 level dose reduction	46	1
	25% patients received cabozantinib > 2 years (Schlumberger 2015)		

4.2.2.7 Safety and tolerability results EXAM: Phase III trial XL184-301

Treatment exposure and data cut offs

The XL 184-301 pivotal trial EXAM (Efficacy of XL184 in Advanced medullary Thyroid Cancer) provided a robust safety dataset, comprising 219 patients randomised to COMETRIQ and 111 to placebo (Elisei 2013).

At data cut off for the original Safety Addendum (31 December 2011), 29.7% (65/219) COMETRIQ-treated patients remained on treatment compared to 7.2% (8/111) placebo recipients (Exelixis 2015). The median duration of exposure to COMETRIQ was then 315 days (10.4 months) with 25% subjects having a duration of exposure of ≥ 468 days (15.4 months) (exelixis 2015). At further follow up with database cut off 28 August 2014 9.6% (21/219) COMETRIQ-treated patients remained on treatment compared with none (0/111) of the patients receiving placebo (Exelixis 2015). Median duration of exposure to COMETRIQ was then 329 days (10.8 months) with 25% having an exposure duration of ≥ 756 days (24.8 months) (Exelixis 2015).

The similarity of median exposure values reflects the fact that >50% of subjects had discontinued at the time of the Safety Addendum cut off (December 2011) (Exelixis 2015).

Subjects remained in the treatment period until disease progression per mRECIST as long as toxicity remained acceptable and no criteria for discontinuation as per protocol was not met (Exelixis 2015). Subjects could remain on study treatment beyond progression as long as investigator continued to see clinical benefit and they did not require subsequent anti-cancer therapy (Exelixis 2015).

Due to the low number of subjects remaining on study treatment between December 2011 data cut off and final analysis the saftey data is compared up to June 2011 cut off in Elisei et al. and up to December 2011 in the Safety Addendum. The final analysis data details the cabozantinib arm of the study up to 28 August 2014 and direct comparisons are not made due to differing level of exposure in the two arms (Exelixis 2015).

Adverse events

The frequencies of adverse events in EXAM reported in the earlier (2011) database cut off as well as final analysis are summarised in Table 4.2.2.7 (Exelixis 2015).

Most adverse events in each treatment group were judged by the investigator to be related to study drug (98.6% in COMETRIQ-treated subjects and 74.3% in placebo-treated subjects) (Exelixis 2012).

The proportion of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 events reported after December 2011 cut-off was higher among subjects who received COMETRIQ compared with subjects who received placebo (74.7% vs. 34.0%, respectively) (Exelixis 2012a).

Similarly, the incidence of serious adverse events was higher among subjects who received COMETRIQ compared with subjects who received placebo (45.8% vs 22.9%) (Exelixis 2012a).

However, adverse events led to permanent treatment discontinuation in both treatment groups: 23.4% in the COMETRIQ group and 9.2% in the placebo group (Exelixis 2015).

Table 4.2.2.7: Summary of adverse events in EXAM, by Grade 3 or 4 (≥2%), serious AEs and AEs leading to permanent treatment discontinuation in safety population final analysis (data cut-off Aug 2014)

Adverse event	Cabozantinib (N=214) n (%)	Placebo (N=109) n (%)
	Final analysis (Aug 2014)	
Any AE	214 (100)	104 (95.4)
Any CTCAE Grade 3 and Grade 4 AE	166 (77.6)	37 (33.9)
Any SAE	114 (53.3)	26 (23.9)
Any related SAE	84 (39.3)	7 (6.4)
Any AE leading to drug dose modification	187 (87.4)	24 (22.0)
Any AE leading to permanent treatment discontinuation	50 (23.4)	10 (9.2)

Adapted from Exelixis 2015

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

The adverse events occurring in ≥ 10% COMETRIQ-treated patients are shown in Table 4.2.2.7.1. Adverse events seen in ≥40% of patients were diarrhoea, palmar-plantar erythrodysaesthesia, decreased weight, decreased appetite, nausea, and fatigue (Elisei 2013)

Many of these adverse events are common symptoms in patients with advanced MTC, and were also frequent among patients in the placebo group of EXAM. Few of these adverse events led to study drug discontinuation (See Table 4.2.2.7).

Table 4.2.2.7.1: Adverse events occurring in ≥10% of COMETRIQ-treated patients in EXAM

Adverse event	Cabozantinib (N=214) n (%)	Placebo (N=109) n (%)
Number of subjects with ≥1 event	214 (100.0)	103 (94.5)
Diarrhoea	135 (63.1)	36 (33.0)
Palmar-plantar erythrodysaesthesia syndrome*	107 (50.0)	2 (1.8)
Weight decreased	102 (47.7)	11 (10.1)
Decreased appetite	98 (45.8)	17 (15.6)
Nausea	92 (43.0)	23 (21.1)
Fatigue	87 (40.7)	31 (28.4)
Dygeusia	73 (34.1)	6 (5.5)
Hair colour changes	72 (33.6)	1 (0.9)
Hypertension	70 (32.7)	5 (4.6)
Stomatitis	62 (29.0)	3 (2.8)
Constipation	57 (26.6)	6 (5.5)
Haemorrhage	54 (25.2)	17 (15.6)
Vomiting	52 (24.3)	2 (1.8)
Mucosal inflammation	50 (23.4)	4 (3.7)
Asthenia	45 (21.0)	16 (14.7)
Dysphonia	43 (20.1)	10 (9.2)
Rash	41 (19.2)	11 (10.1)
Dry skin	41 (19.2)	3 (2.8)
Headache	39 (18.2)	9 (8.3)
Oropharyngeal pain	38 (17.8)	5 (4.6)
Abdominal pain	36 (16.8)	7 (6.4)

Table 4.2.2.7.1 continued

Adverse event	Cabozantinib (N=214) n (%)	Placebo (N=109) n (%)
Alopecia	35 (16.4)	2 (1.8)
Pain in extremity	33 (15.4)	12 (11.0)
Back pain	32 (15.0)	12 (11.0)
Dyspnoea	29 (13.6)	19 (17.4)
Arthralgia	29 (13.6)	8 (7.3)
Dizziness	29 (13.6)	8 (7.3)
Oral pain	29 (13.6)	1 (0.9)
Dry mouth	28 (13.1)	9 (8.3)
Dysphagia	27 (12.6)	7 (6.4)
Cough	26 (12.1)	14 (12.8)
Muscle spasms	26 (12.1)	5 (4.6)
Dyspepsia	24 (11.2)	0
Insomnia	23 (10.7)	7 (6.4)
Erythema	23 (10.7)	2 (1.8)
Glossodynia	22 (10.3)	0

Adapted from Elisei 2013

Note Laboratory abnormalities are not included. * Hand-foot syndrome

In the EXAM publication serious adverse events (SAEs) were more frequent in cabozantinib versus placebo treated patients 42.1% (90/214) vs 22.9% (25/109). The most frequent serious adverse events (SAEs) seen in COMETRIQ-treated patients included mucosal inflammation, hypocalcaemia, pulmonary embolism, and hypertension (Elisei 2013).

Although adverse events and serious adverse events of hypertension were more frequent in the COMETRIQ group than in the placebo group, there were no events of hypertensive crisis or malignant hypertension in COMETRIQ-treated patients, whereas 1 placebo-treated subject had an event of hypertensive crisis (Exelixis 2012; Exelixis 2012a).

The later study report noted the same treatment-related SAEs at similar frequency to those documented earlier, no SAE increased by more than an incidence of 2 patients (Exelixis 2015). Table 4.2.2.7.2 notes these cumulative SAEs as noted in the final analysis.

Table 4.2.2.7.2 Related serious adverse event preferred terms (≥ 1%) of patients in COMETRIQ arm (final analysis)

Adverse event System organ class preferred term	Cabozantinib (N=214) n (%)	Placebo (N=109) n (%)
Number of subjects with at least one related SAE	84 (39.3)	7 (6.4)
Gastrointestinal disorders	22 (10.3)	1 (0.9)
Abdominal pain	3 (1.4)	0
Diarrhoea	3 (1.4)	1 (0.9)
Vomiting	3 (1.4)	0
Respiratory, thoracic, and mediastinal disorders	21 (9.8)	1 (0.9)
Pulmonary embolism	7 (3.3)	0
Acquired tracheo-oesphageal fistula	3 (1.4)	0
Infections and infestations	19 (8.9)	0
Peritonitis[a]	3 (1.4)	0
General disorders and administration site conditions	15 (7.0)	2 (1.8)
Mucosal inflammation	6 (2.8)	0
Fatigue	3 (1.4)	0
Metabolism and nutrition disorders	12 (5.6)	1 (0.9)
Hypocalcaemia	5 (2.3)	0
Dehydration	4 (1.9)	1 (0.9)
Vascular disorders	9 (4.2)	0
Hypertension	5 (2.3)	0
Investigation	8 (3.7)	2 (1.8)
Lipase increased	4 (1.9)	1 (0.9)
Blood and lymphatic disorders	5 (2.3)	1 (0.9)
Thrombocytopenia	3 (1.4)	0
Skin and subcutaneous tissue disorders	3 (1.4)	0
Palmar-plantar erythrodysaesthesia syndrome	3 (1.4)	0

Dose modifications

The overall incidence of AEs leading to study drug discontinuation at final analysis was 23.4% in the cabozantinib patients (Exelixis 2015). Adverse events were generally managed with concomitant medications and dose modifications (reductions or interruptions) (Elisei 2013). The proportion of COMETRIQ patients who had a least one dose reduction as of final analysis was 82.2% and at least one dose delay 77.1% (68.7% due to an AE), 45.8% required a second-level dose reduction (Exelixis 2015) (Table 4.2.2.7.3). Median time to first dose modification (at exposure response analysis) was 30 days (XL184-301 ER 2012).

Table 4.2.2.7.3 Dose reductions in safety population at final analysis (August 2014 cut-off)

	Cabozantinib (N=214) n (%)	Placebo (N=109) n (%)
Number of dose reductions per patient		
n	214	109
Mean	1.5 (1.04)	0.1 (0.35)
Median	1.0	0.2 0.0
Range	0-7	0.3 0-2
Number of patients with at least one		
1- Level dose reduction (n, %) [a]	176 (82.2)	12 (11.0)
2- Level dose reduction (n, %) [b]	98 (45.8)	1 (0.9)
Time to first level dose reduction (days)		
n	176	12
Mean (SD)	(80.1(122.66)	124.3 92.62)
Median	45.0	130.0
Range	2-1009	8-301
Time to second level dose reduction (days)		
n	98	1
Mean (SD)	155.3 (171.37)	127.0 (NA)
Median	85.0	127.0
Range	28-782	127-127

[a] A 1-level dose reduction was from 140 mg/day to 100 mg/day

[b] A 2-level dose reduction was from 100 mg/day to 60 mg/day

In the initial analysis the most frequent adverse events (≥10% of subjects in the COMETRIQ arm) leading to dose modifications, were palmar-plantar erythrodysaesthesia, diarrhoea, fatigue, decreased weight, decreased appetite and nausea (Elisei 2013). At final analysis lipase increased, palmar-plantar erythrodysaesthesia, hypocalcaemia, diarrhoea and renal failure noted as the most frequent causes (≥ 3 patients) (Exelixis 2015). The frequency of lipase increased as AE

resulting in discontinuation of study treatment was similar in both cabozantinib and placebo arms (5 (2.3%) and 3 (2.8%) respectively) (Exelixis 2015).

In the exposure analyses patient with lower plasma clearance were more likely to experience early dose reduction or interruption (XL184-301 ER 2012).

The median number of dose delays at final analysis per subject was 2 with a median duration of 4 days (Exelixis 2015).

Duration of exposure

While all patients in the COMETRIQ arm took 140 mg daily as their starting dose, at the final analysis the number of patients in the COMETRIQ arm who had a final recorded dose of 140 mg, 100 mg and 60 mg was 51, 69 and 92 respectively. This was similar to that seen at the Safety Addendum cut-off (December 2011) and reflected a few more dose reductions that occurred after this point (54, 71 and 89 patients being recorded on the 3 doses at that time) (Exelixis 2015).

Median duration of exposure was also similar at the two time points, with those on a final dose level 0f 60 mg having total median duration of exposure of 491.5 days at final analysis, reflecting continued extended treatment after second level dose reduction (Exelixis 2015).

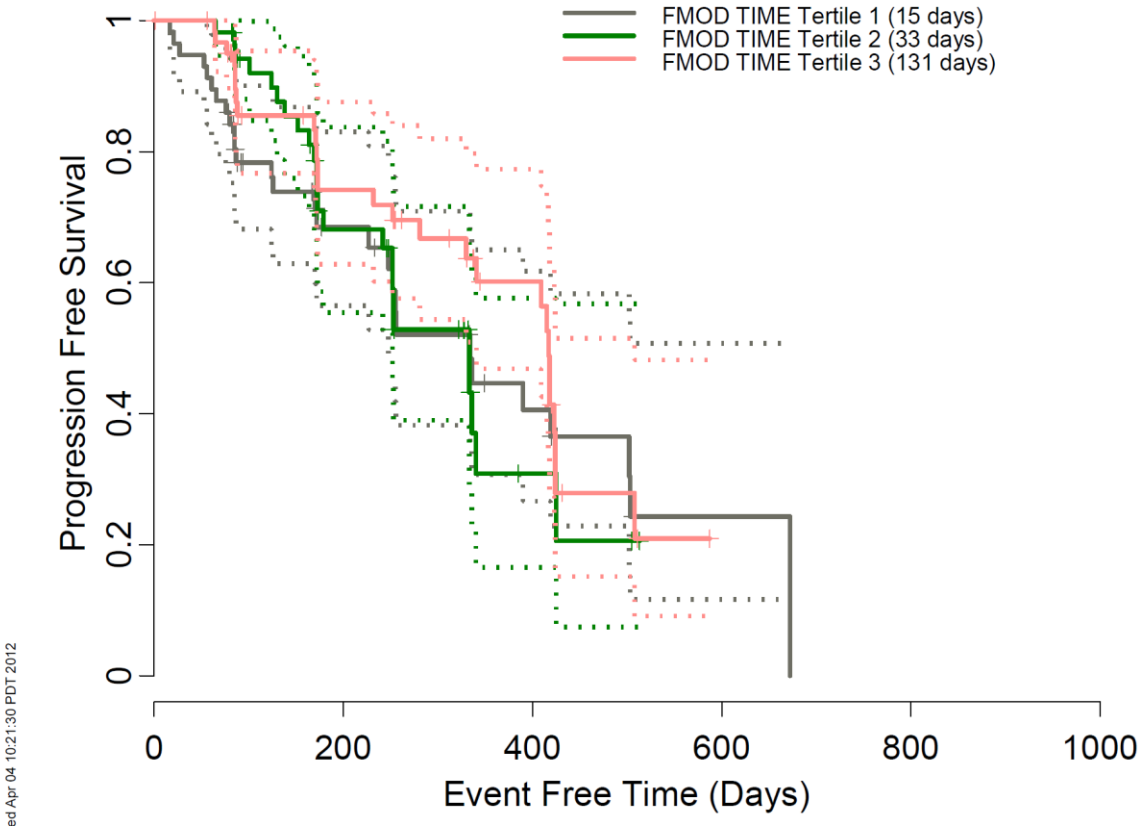
Table 4.2.2.7.4 Duration of exposure, in days, for patients for whom the last dose was 140 mg, 100 mg, 60 mg (safety population – final analysis)

		Cabozantinib (N=214)	Placebo (N=109)
140 mg	n	51 (23.8%)	98 (89.9%)
	Mean (SD)	315.4 (431.01)	169.2 (186.86)
	Median	168.00	103.0
	25%, 75%	31.0, 424.0	78.0, 183.0
	Min, max	8, 1633	11, 1232
100 mg	n	69 (32.2%)	10 (9.2%)
	Mean (SD)	392.5 (344.08)	219.3 (173.08)
	Median	306.0	153.5
	25%, 75%	119.0, 526.0	92.0, 337.0
	Min, max	15, 1438	15, 514
60 mg	n	92 (43.0%)	1 (0.9%)
	Mean (SD)	666.4 (526.60)	356.0 (N/A)
	Median	491.5	356.0
	25%, 75%	217.5, 1080.5	356.0, 356.0
	Min, max	37, 1808	356,356

Note. One patient in cabozantinib arm had a last dose of 40 mg which was not protocol specified. One patient on cabozantinib arm had an undetermined last dose due to error in reporting date of the last dose level. Duration of exposure: calculated in days as: date of last dose- date of first dose + 1

The Kaplan-Meier plot of PFS stratified by the time to first dose modification (tertiles) recorded in the exposure analysis, suggested that early dose modifications were not associated with a marked reduction in PFS (Figure K) (Exelixis 2012b).

Figure K PFS Kaplan-Meier curves stratified by time to first dose modification (FMOD) tertiles for cabozantinib treated patients



Dotted lines represent 95% CI

Further study of the effect of lower dose is being undertaken as one of the recommendations from the conditional licence approval (EMA 2013; CT.gov NCT01896479). (See section 4.2.3)

Adverse events related to VEGF pathway

Many of the adverse events observed in this study were consistent with those seen with other VEGF pathway antagonists (Elisei 2013; Kim 2016; Weitzman 2015). However, events of ≥Grade 3 severity associated with VEGF pathway inhibition were uncommon (Elisei 2013).

There was no occurrence of QTcF >500 ms in COMETRIQ-treated patients, and only a mild-to-moderate prolongation of QT interval was observed in the COMETRIQ group (10–15 ms increase from baseline on Day 29) (Exelixis 2012). There were no reports of torsades de pointes in any subjects enrolled in EXAM (Exelixis 2012a).

Deaths

The overall death rates at 2011 data cut off of were similar between the two treatment arms in EXAM: 65 (30.4%) in the COMETRIQ arm and 30 (27.5%) in the placebo arm (Table 4.2.2.7.5) (Exelixis 2012).

Table 4.2.2.7.5: Summary of deaths occurring up to the initial data cut-off date in EXAM (15 June 2011) and final analysis (28 August 2014 cut-off).

Survival Status	Cabozantinib (N=214) n (%)		Placebo (N=109) n (%)	
	Initial analysis	**Final analysis**	Initial analysis	**Final analysis**
Died during the study	65 (30.4)	138 (64.5)	30 (27.5)	76 (69.7)
Died ≤30 days after last dose	22 (10.3)	29 (13.6)	8 (7.3)	9 (8.3)
Progressive disease	10 (4.7)	13 (6.1)	5 (4.6)	6 (5.5)
Other	12 (5.6)	16 (7.5)	3 (2.8)	3 (2.8)
Not treatment-related	3 (1.4)	6 (2.8)	2 (1.8)	2 (1.8)
Possibly treatment-related	9 (4.2)	10 (4.7)	1 (0.9)*	1 (0.9)*
Died >30 days after last dose	43 (20.1)	109 (50.9)	22 (20.2)	67 (61.5)
Progressive disease	40 (18.7)	96 (44.9)	19 (17.4)	56 (51.4)
Other	3 (1.4)†	13 (6.1) ††	3 (2.8)‡	11 (10.1) ‡‡

Adapted from Exelixis 2012 & 2015

*An additional placebo-treated subject whose primary cause of death was reported as progressive disease was also reported by the investigator to have a possibly treatment-related Grade 5 adverse event of cardiopulmonary failure

†The cause of death was reported as probable pulmonary embolism in 1 subject and was unknown in 2 COMETRIQ-treated subjects; the relationship to study treatment was not assessed in these cases (Exelixis 2012)

†† In the cabozantinib arm, the cause of death was reported for one patient each: probable pulmonary embolism , acute pancreatitis, pulmonary insufficiency, acute kidney failure post-surgery, PD and cardio-respiratory insufficiency, haemorrhagic stroke, intestinal surgery, pseudomonas pneumonia, and was unknown in four subjects). The relationship to study treatment was not assessed in these cases. One patient had a reported cause of death of obstructive pyelonephritis which was classified as not related to study treatment and the cause of death was subsequently changed to PD in the SAE report (Exelixis 2015)

‡The cause of death was attributed to pneumonia in 1 placebo recipient and was unknown in 2 subjects; the relationship to study treatment was not assessed in these cases (Exelixis 2012)

‡‡ In the placebo arm, the cause of death was attributed to pneumonia in one subject and for one subject each: respiratory failure due to pneumonia, severe liver failure, intestinal obstruction, neoplastic cachexia and was unknown in six patients. The relationship to study treatment was not assessed in these cases.

Of these, 22 (10.3%) deaths among COMETRIQ-treated patients and 8 (7.3%) among placebo-treated subjects occurred up to 30 days after the last dose of study drug (Exelixis 2012). Regarding deaths not attributed to progressive disease and occurring within 30 days of the last dose of study drug, there were 12 (5.6%) in the COMETRIQ arm compared with 3 (2.8%) in the placebo arm (Exelixis 2012). The difference was largely accounted for by events commonly associated with VEGF pathway inhibition, including fistula formation and haemorrhage (Exelixis 2012).

The number of deaths observed in EXAM some three years later by August 2014 database cut off was 138 (64.5%) in the COMETRIQ arm and 76 (69.7%) in the placebo arm (Exelixis 2015).

29 (13.6%) patients died during the 30 days after last COMETRIQ dose, 5 occurred since the 2011 Safety Report. Primary cause of death was reported as disease progression in 2 patients; pulmonary insufficiency, general deterioration of condition and bronchopneumonia reported for the remaining 3 patients, none of which were deemed related to study treatment (Exelixis 2015).

4.2.2.8 Safety Summary

At the time of the final data cut-off (28 August 2014), none (0/111) of the patients randomised to the placebo arm compared with 9.6% (21/219) of subjects randomised to the cabozantinib arm remained on study treatment. This compared to the earlier analysis (data cut-off 31 December 2011), where 7.2% (8/111) of patients randomised to the placebo arm compared with 29.7% (65/219) of those in the cabozantinib arm remained on study treatment.

Due to the low number of placebo subjects remaining on study treatment during the period between the Safety Addendum report and the final analysis data cut-off, safety data was presented in detail for the cabozantinib arm only and in general, direct comparisons were not made due to the differences in exposure between arms. However, no new safety signals were observed in this longer term exposure to COMETRIQ.

At final analysis the median duration of exposure to cabozantinib was 329.0 days (10.8 months) in and 25% of subjects had a duration of exposure of at least 756.0 days (24.8 months). The corresponding data initial safety analysis (December 2011) was 315.0 days (10.4 months) for median duration of exposure and 25% of patients had a duration of exposure of at least 468.0 days (15.4 months). The similarity of the median values reflects that > 50% of subject had discontinued study treatment at the time of the initial analysis.

The proportion of cabozantinib-treated patients who had at least one dose reduction at final analysis was 82.2% which was similar to what was reported earlier (80.8%). The proportion of subjects who had at least one dose delay at final analysis (77.1%) was also similar to the value reported in the Safety Addendum (76.2%).

The overall incidence of AEs and Grade 3/4 AEs in the cabozantinib arm was similar to the incidence reported in the Safety Addendum (Final analysis vs Safety Addendum: incidence of 100% for all grades for both; 77.6% vs 74.7% for Grade 3/4).

The most frequent AEs (≥ 30%) reported were diarrhoea (70.1%), weight decreased (57.9%), palmar-plantar erythrodysaesthesia syndrome (52.8%), decreased appetite (49.1%), nausea (46.7%), fatigue (42.5%), dysgeusia (35.0%), hair colour changes (34.1%), and hypertension (32.7%). These are the same most frequent AEs that were observed at the earlier analysis and reported in the publication by Elisei et al.

In the final analysis the number of deaths observed was 138 (64.5%) in the cabozantinib arm and 76 (69.7%) in the placebo arm compared with 83 in the cabozantinib arm (38.8%), and 42 (38.5%) in the placebo arm. A total of 29 subjects (13.6%) died through 30 days after the last dose of cabozantinib treatment, and five of these deaths occurred since the data cut-off at end of 2011. Two of these subjects had a primary cause of death reported as disease progression, and three subjects had a primary cause of death reported as other than disease progression: pulmonary insufficiency, deterioration of general condition, and bronchopneumonia. None of these were deemed to be related to cabozantinib treatment.

The most frequently reported SAEs (≥ 2%) were pneumonia (4.2%), pulmonary embolism (3.3%), hypocalcaemia (2.8%), mucosal inflammation (2.8%), dehydration (2.3%), dysphagia (2.3%), hypertension (2.3%), and lung abscess (2.3%). Lung abscess was the only additional preferred term which reached the ≥ 2% threshold when compared to the most frequent events reported earlier. No SAE increased by more than an incidence of 2 subjects (0.9%) relative to SAEs reported at the 31 December 2011.

Between end August 2014 and the start of the Maintenance Phase on 01 December 2014, 5 SAEs were reported in 3 of the 21 subjects that remained on study treatment at the 28 August 2014 cut-off. One of the 5 events was determined to be related to study treatment. This was a case of squamous cell carcinoma that was reported in an 83-year old female subject who had a medical history of basal cell carcinoma of the skin.

The overall incidence of AEs leading to study drug dose modification in the cabozantinib arm through to 2014 data cut-off (87.4%) changed little from initial data cut off (86.9%). The most frequent AEs that lead to study drug dose modifications (≥ 10%) were palmar-plantar erythrodysaesthesia syndrome (29.0%), diarrhoea (27.6%), weight decreased (15.4%), fatigue (14.5%), decreased appetite (14.5%), nausea (14.0%), stomatitis (12.1%), asthenia (11.2%), and vomiting (10.3%). These are again the same most frequent AEs that led to study drug dose modifications reported earlier.

The overall incidence of AEs leading to study drug discontinuation was 23.4% in the cabozantinib arm. The most frequent AEs that led to study drug discontinuation in the cabozantinib arm (≥ 3 subjects) were lipase increased, palmar-plantar erythrodysaesthesia syndrome, hypocalcaemia, diarrhoea, and renal failure. Lipase increased was reported as an AE leading to treatment discontinuation at a similar frequency in the placebo arm (3 subjects (2.8%) placebo arm vs 5 patients (2.3%) in cabozantinib arm) (Exelixis 2015).

The adverse events of COMETRIQ observed in the randomised, Phase III EXAM study were generally similar to those observed with other inhibitors of the VEGF pathway and other TKIs, and

thus are familiar to physicians treating patients with advanced MTC. (Elisei 2013; Exelixis 2015; Colombo 2014; Kim 2016; Weitzman 2015)

Possible predisposing factors for these events were identified, including tumour invasion of the airway and other viscera (Exelixis 2012). Detailed evaluation of QTc in EXAM did not reveal a clinically significant QTc prolongation in the COMETRIQ arm (change in first 4 weeks from baseline in QT_C was 10–15 ms) (Exelixis 2012), and no patient experienced a QTc interval >500 ms (Elisei 2013).

Adverse events were generally manageable with supportive care and dose reductions and interruptions (Elisei 2013). Less frequent, but potentially life-threatening toxicities included GI perforations, and GI and non-GI fistulas and haemorrhage (Elisei 2013).

The level of dose reductions and dose interruptions seen (82.2% and 77.1% respectively) the majority within first few weeks of therapy, mean that monitoring of patient response is recommended particularly in the first eight weeks of treatment and adjustments made where necessary (SmPC 2016).

A Kaplan-Meier analysis of PFS stratified by the time to FMOD (i.e. dose reduction or interruption) was performed. These data suggest that early dose modifications were not associated with a marked reduction in PFS (Exelixis 2012b).

4.2.3 Ongoing studies

Further clinical study comparing 140 mg and 60 mg with PFS as primary endpoint is ongoing (CT.gov NCT01896479).

This study (EXAMINER) which aims to recruit 188 patients with progressive, metastatic MTC was initiated in December 2014 with final data cut off point September 2017 and trial is expected to be completed in March 2018.

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Appendices

Appendix 1 Summary of product characteristics

Appendix 2 EMA CHMP Assessment Report December 2013

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Vandetanib for treating unresectable locally advanced or metastatic medullary thyroid cancer (ID56)

SanofiGenzyme

Evidence submission

[02 February 2017]

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List of abbreviations and acronyms

AE	adverse event
ALT	alanine aminotransferase
AWMSG	All Wales Medicine Strategy Group
BMI	body mass index
BSC	best supportive care
CEA	carcinoembryonic
CI	confidence interval
CR	complete response
CTCAE	Common Terminology Critera for Adverse Events
CTN	calcitonin
CYP3A4	cytochrome P450 3A4
DCR	disease control rate
DOR	duration of response
EGFR	Epidermal growth factor receptor
GI	gastrointestinal
HR	hazard ratio
HTA	health technology assessment
ITT	intent-to-treat
KDR	kinase domain receptor
MEN2A	multiple endocrine neoplasia type 2A
MEN2B	multiple endocrine neoplasia type 2B
MKI	multikinase inhibitor
MTC	medullary thyroid cancer
OR	odds ratio
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
P-gp	P-glycoprotein
PI	prescribing information
PK	pharmacokinetic
PPES	palmar-plantar erythrodysesthesia syndrome
PR	partial response
QALY	quality-adjusted life year
QoL	quality of life
QTc	corrected QT interval
RECIST	Response Evaluation Criteria In Solid Tumors
REMS	Risk Evaluation of Mitigation Strategy
RET	REarranged during Transfection

SAE	serious adverse event
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results Program
SmPC	summary of product characteristics
TKI	tyrosine kinase inhibitor
TSH	thyroid stimulating hormone
TWP	time to worsening of pain
URTI	upper respiratory tract infection
VEGF	vascular endothelial growth factor
VEGFR-2	vascular endothelial growth factor receptor-2

1. Executive summary

Vandetanib, a selective tyrosine kinase inhibitor (TKI), is a clinically effective treatment that has become an established first-line treatment for advanced medullary thyroid cancer (MTC) in the UK since 2012, as recognised by the Cancer Drugs Fund. When reserved for patients with greatest need for urgent treatment (i.e. those with symptomatic and aggressive disease), vandetanib treatment results in significant progression-free survival in those who would otherwise have a life expectancy of less than 2 years. In this population of patients with aggressive disease, vandetanib is also cost-effective according to NICE thresholds. As an ultra-orphan disease, treatment with vandetanib is limited to approximately [redacted] patients per year with an estimated budget impact that does not exceed [redacted].

Medullary thyroid cancer (MTC)

MTC, a very rare type of cancer, arises in the parafollicular cells (C-cells) of the thyroid. It can spread to other organs including the lymph nodes, liver, lungs, bones and brain. The origin of MTC can be either inherited or sporadic. Patients may present early with local–regional disease, or locally advanced or metastatic disease. The disease is further described as being indolent or aggressive and symptomatic disease. If indolent, the general clinical approach is watch and wait as opposed to active treatment.

The prognosis for patients with locally advanced or metastatic MTC is poor with a reported 5-year survival rate of 25%.[1] A further study in the US reports 5- and 10-year survival rates of patient with distant metastases at diagnosis of 26% and 14% respectively.[2]

MTC and ultra-rare disease criteria

MTC fulfils the criteria for orphan indication in the European Union (EU) (prevalence of <5/10,000).[3] It also fulfills the accepted criteria for an ultra-orphan disease in the UK (i.e. affecting less than 1000 patients or <1/50,000).[4] SanofiGenzyme estimates that as of January 2017, there are 253 patients with MTC in the UK, of which [redacted] patients are currently receiving vandetanib treatment within the indicated label of aggressive and symptomatic MTC (the approved indication for vandetanib in Europe). A similarly small number of patients are receiving the other tyrosine kinase inhibitor (TKI) licensed for MTC, cabozantinib.

Vandetanib for the treatment of advanced MTC in England and Wales

In England, vandetanib is an established first-line treatment for MTC as recommended by the CDF since 2012/2013.[5] Cabozantinib is an alternative first line agent.[5 6] Both vandetanib and cabozantinib displace best supportive care (BSC), the previous clinical care pathway, and the CDF recommends availability of both TKIs, stating that clinicians should have the choice of one or other depending on the patient circumstances. The rationale for this recommendation is a consideration of the different evidence bases of the two drugs, including significant differences in safety profiles and the fact that patient tolerance was an important issue. The CDF concluded that both drugs should be available as they currently offer the only options for systemic therapy for MTC for patients who need active treatment.[5] Both vandetanib and cabozantinib displace BSC therefore, BSC is the appropriate comparator for vandetanib in this submission.

In clinical practice, vandetanib is only prescribed for patients in whom the disease is sufficiently aggressive (based on symptom burden and other markers of severity) to warrant active treatment and who are most likely to experience the greatest clinical benefit from systemic treatment. In making treatment decisions in this patient population based on disease severity, it is likely that a number of criteria are taken into account including symptom burden, time since Response Evaluation Criteria In Solid Tumors (RECIST) documented progression and serum tumour biomarkers (notably the rate of carcinoembryonic antigen [CEA] and calcitonin [CTN] doubling), which may determine increasing tumour burden and more rapidly deteriorating disease (Appendix 2).

This submission presents data on two populations. The licensed population for vandetanib has been defined post-hoc as progressive and symptomatic disease (referred to as the EU label population). The second population also included CTN and CEA doubling times less than 24 months (referred to as the restricted EU label population) as indicative of aggressive disease, as this is commonly used in clinical practice. Other assessments of disease may be used (tumour burden, RECIST criteria etc). Based on discussions with clinicians who treat patients suffering from MTC, SanofiGenzyme believes this restricted EU label subpopulation is most closely aligned with UK clinical practice of selecting patients in need of urgent treatment and reflects the patient population that are currently receiving treatment with vandetanib. However, while we have considered the CEA/CTN doubling times as a proxy marker of aggressive disease, aligning with UK clinical practice, in real life clinical setting factors including these biomarkers, tumour burden, symptoms, progression, patient

demographics, comorbid conditions and personal characteristics all contribute to treatment decision making.

It should be noted that this submission relates only to the use of vandetanib in adults according to the EU label and the restricted EU label criteria. However, SanofiGenzyme wishes to draw attention to the fact that vandetanib recently received a license for use in the paediatric population – the only TKI to have this marketing authorisation to date.[7]

1.1 Statement of decision problem

The decision problem is described in Table 1 over the page.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with unresectable locally advanced or metastatic medullary thyroid carcinoma.	Vandetanib is indicated for, "the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patient with unresectable locally advanced or metastatic disease", section 4.1 of the SPC.[8] Two populations are considered in this submission: • The **EU label population** defined as patients who progressed within 12 months of diagnosis and who had one from a list of symptoms (see section 4.8) • A **restricted EU label** subgroup of patients who, in addition to meeting the definition above, also have serum tumour biomarker CTN/CEA doubling times ≤24 months.	The population is refined in line with the EU label for vandetanib. The EU label wording has scope for interpretation: aggressive and symptomatic are not explicitly defined in the licence. As such we present two populations that would be within the EU label. The base case for the economic evaluation is the restricted EU label population. This reflects selection of patients in routine clinical practice in the UK, i.e., identifying patients with rapidly progressing disease using other criteria such as serum tumour biomarkers.
Intervention	Vandetanib	Vandetanib	
Comparator (s)	Cabozantinib Best supportive care (BSC)	BSC	Data were not available to formally compare vandetanib to cabozantinib. See Section 4.10 for comparison of the ZETA and EXAM studies. BSC is the most appropriate comparator.

Outcomes	Overall survival (OS) Progression-free survival (PFS) Adverse effects (AE) of treatment Health-related quality of life (HRQoL).	PFS OS AEs HRQoL	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Per the scope.	
Subgroups to be considered	If the evidence allows subgroups according to RET mutation status will be considered.	No subgroup analysis based on RET mutation status has been presented.	Although germline RET mutation testing is standard clinical practice, somatic RET mutation testing is not. Somatic RET mutation testing is not funded, and not used to guide treatment decisions in NHS England and Wales.
Special considerations including issues related to equity or equality		A very small number of patients in England and Wales with unresectable locally advanced or metastatic medullary thyroid cancer, that is aggressive and symptomatic, receive active treatment with TKIs. This is understood to be fewer than 60 patients in the UK/England each year. While NICE does not have orphan modifiers, we believe it is inappropriate	The access to vandetanib treatment that the CDF has allowed is in line with the vision of the UK Strategy for Rare Diseases.[10] It has meant that patients with this rare disease have had equitable access to an evidence based treatment, and allowed physicians to provide a patient centred approach to treatment. Removal of vandetanib or cabozantinib would be inequitable as patients with this very rare cancer would have no active treatment

		to assess a treatment for such a small patient population under standard efficiency cost/QALY measures. This product is not eligible for the Highly Specialised Technology (HST) process[9] as it is not a chronic condition and it is also deemed to be a subgroup of thyroid cancers. At launch vandetanib did not meet NICE's Topic Selection Criteria and was not referred for review. Vandetanib is currently funded via the CDF as a first-line treatment option. Cabozantinib is an alternative agent however the two drugs are not interchangeable. Removal of vandetanib as a treatment option would create inequity amongst the MTC patient population, and leave patients unsuitable for cabozantinib treatment without a valuable and effective systemic treatment.	choice.

1.2 Description of the technology being appraised

Table 2. Technology being appraised

UK approved name and brand name	CAPRELSA® (vandetanib)
Marketing authorisation/CE mark status	Vandetanib gained marketing authorisation in the European Union (EU) on 17 February 2012.[11]
Indications and any restriction(s) as described in the summary of product characteristics	Vandetanib is indicated for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease. Vandetanib is indicated in adults, children and adolescents aged 5 years and older. For patients in whom Rearranged during Transfection (RET) mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision. This submission is for the use of vandetanib in adults only.
Method of administration and dosage	The dose of vandetanib is 300mg administered orally once daily.[8] In the event of AE Grade 3 or higher toxicity, or prolongation of the ECG QTc interval, dosing of vandetanib should be stopped temporarily and resumed at a reduced dose upon resolution or improvement to Grade 1. The 300 mg, daily dose can be reduced to 200 mg (two 100 mg tablets), and then to 100 mg if necessary. In the ZETA ITT safety population 49.4% of vandetanib reported a dose reduction or interruption (section 4.12). In EU label population, more patients required dose reduction of vandetanib compared with placebo (41 [33%] versus 2 [3%]).[12]

1.3 Summary of the clinical effectiveness analysis

Regulatory approval of vandetanib

The regulatory assessment of vandetanib was based on the pivotal Phase 3 ZETA trial with the primary outcome progression free survival (PFS).[13] The licensed indication in Europe is:

> *"CAPRELSA® is indicated for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease." (Section 4.1[8])*

This population is more restrictive than the inclusion criteria for the ZETA trial.

The EMA considered the improvement in PFS, objective response rate (ORR), disease control rate (DCR) and patient reported outcomes (PROs) in the overall ZETA population to be important however, the risk of QT prolongation and associated clinical consequences, and renal risks associated with vandetanib also needed consideration. Consequently, the license statement reflects use in patients with rapidly deteriorating disease for which urgent treatment is required and the benefit of treatment outweighs the risk:

> *"In view of the associated risks, it is important to limit treatment with vandetanib to patients who are in real need for treatment, i.e. with a symptomatic-aggressive course of the disease. Either symptomatic disease or progressive disease alone is not enough to prompt the need of treatment with vandetanib. Rate of change in biomarker levels such as of calcitonin (CTN) and/or carcinoembryonic antigen (CEA) as well as the rate of change of tumour volume during watchful waiting might help to identify not only patients in need for treatment but also the optimal moment to commence treatment with vandetanib." (section 4.4[8]).*

The EU label wording, aggressive and symptomatic, was defined post-hoc as follows.[12] Patients had to have:

- Progressive: documented progression within 12 months prior to enrolment in the ZETA trial

and

- Symptomatic: at least one symptom at baseline, including pain score > 4, ≥10 days of opioid use, diarrhoea, flushing, fatigue, pain, nausea, dysphagia, dysphonia, respiratory symptoms, weight loss.

Vandetanib, developed by AstraZeneca and now marketed by SanofiGenzyme, was designated orphan drug status in 2006. This was withdrawn in 2010 at the request of AstraZeneca due to the prospect of a further indication in the treatment of non-small cell lung cancer (NSCLC). However, the marketing authorisation application for NSCLC was withdrawn and MTC remains the only licensed indication for vandetanib.[14] [15] While this product no longer has its regulatory orphan designation, vandetanib only has an indication for this ultra-orpahn disease.

ZETA trial

ZETA was a phase 3 trial conducted to demonstrate the safety and efficacy of vandetanib 300 mg versus placebo and included 331 patients with unresectable locally advanced or metastatic MTC and CTN levels ≥ 500 pg/mL.[13] The primary endpoint was PFS, with overall objective response rate (ORR), disease control rate (DCR) at 24 weeks, duration of response (DoR), time to worsening of pain (TWP) and overall survival (OS) as secondary endpoints. Biochemical response as measured by blood levels of CTN and CEA (markers of the level of aggressive disease) was also assessed. Health-related quality of life (HRQoL) was assessed using the FACT-G instrument. The PFS primary endpoint, ORR and DCR were based on centralized, independent blinded review of the imaging data.

Patients were treated with the randomised therapy until they reached objective disease progression based on an investigator's assessment; the blinded study treatment was then discontinued. Patients were then given the option to receive open-label vandetanib, prior to confirmation of the progression by central review of the imaging data. Thus, the ZETA trial design allowed placebo patients to “crossover” study arms and received open-label vandetanib treatment – at the time of investigator determined progression, prior to central review of the scans. Patients randomised to the vandetanib arm of the study were able to continue open-label treatment at that time, i.e., at the time of investigator determined progression, prior to central read of the scans.

While ethically appropriate, from a statistical point of view this study design is problematic for two reasons. The first is that PFS outcomes are confounded by crossover that occurred at time of investigator determined progression, but prior to confirmation by central review. The second is that the extensive crossover/continued, open-label, use of vandetanib post-progression, 79.0% in the placebo and arm and 47.2% in the vandetanib arm, confounded the OS result.[16]

EU label population

The EU label population (defined above) are derived from a post-hoc sub analysis of ZETA study in the population of patients with progressive and symptomatic disease.[12] In this population, 43.8% of patients randomised to vandetanib continued open-label treatment while 79.7% of those initially on placebo crossed over to vandetanib. The most obvious indication that cross-over affected the primary analysis is the 13% ORR in the placebo arm.[13] When data from patients receiving open label vandetanib was censored, the ORR with placebo dropped to 1%, which is much more typical for this patient population.[12] Open-label vandetanib also extended the PFS of both the vandetanib and placebo arms: when using centralised, independent blinded review of the imaging data, the median PFS is 28.0 months on vandetanib vs 16.4 months on placebo HR 0.47 (0.29, 0.77). When the investigator assessment of progression is used, to exclude the open label patients, the median values are 22.1 months and 8.3 months; HR 0.33 (0.2, 0.53).[12] In the EU label population, no difference in median OS was reported. However due to the crossover, the OS data are more likely to show the impact of treatment with immediate vs delayed vandetanib, rather than be a true comparison of vandetanib vs placebo.

Restricted EU label population

A further analysis has been completed on the population of patients within the ZETA trial with progressive and symptomatic disease defined above, and additional criteria for aggressive disease (CTN and CEA doubling times ≤24 months). As discussed above, this subpopulation is presented as an example of criteria that are used in clinical practice to select patients in most urgent need of treatment. We anticipate that this subpopulation most accurately reflects the patients that are currently treated with vandetanib in clinical practice in England and Wales.

In the ZETA trial, there were only [redacted] patients on vandetanib and [redacted] patients on placebo who met who met all criteria above. A significant benefit was observed in median PFS [redacted] on vandetanib arm versus [redacted] on placebo (p=0.01). However, the observed overall survival KM curves for this cohort overlapped and did not show separation due to extensive crossover: [redacted] of patients randomised to vandetanib continued open-label treatment while [redacted] of those initially on placebo crossed over to vandetanib. Again, due the crossover, the OS data are more likely to show the impact of treatment with immediate vs delayed vandetanib, rather than be a true comparison of vandetanib vs placebo.

The key results observed for the EU label population and the restricted EU label subgroup are described in Table 3.

Table 3. Clinical efficacy results for EU label and Restricted EU Label.

	Restricted EU label population (Appendix 6)		EU Label population (Appendix 6 and Kreissl et al, 2014[12])	
	Vandetanib N=[redacted]	Placebo N=[redacted]	Vandetanib N=126	Placebo N=60
Median PFS, months[a]	[redacted]	[redacted]	28.0[c]	16.4
Change vs placebo	[redacted]		11.6 months	
P value	[redacted]		0.002	
Median OS, years[b]	[redacted]	[redacted]	[redacted]	[redacted]
P Value	[redacted]		[redacted]	

MTC: medullary thyroid cancer; OS: overall survival PFS: progression-free survival; RECIST: Response Evaluation Criteria In Solid Tumors; SE: standard error. The mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.

a Median PFS based on central read PFS

b The median survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.c. Median not reached, the reported median is estimated based on a Weibull model

Vandetanib has a manageable adverse event (AE) profile well-evidenced by the low levels of discontinuation due to AEs in the vandetanib group (12% in both the safety analysis population and the aggressive and symptomatic population[12 13] from the ZETA trial despite a median duration of treatment of 90.1 weeks (safety analysis set; 88.6 weeks for the aggressive and symptomatic population[12]), combined with no significant differences from placebo on the FACT-G HRQoL measure, suggesting the AE profile is tolerable for patients overall.[13] The most commonly reported adverse events are diarrhoea, rash, nausea, hypertension, and headache.[8] QT related events were reported more frequently for vandetanib than placebo (15.6% vs. 4.0%) as such additional on-treatment monitoring is required.

Patient tolerance is an important issue for both vandetanib and cabozantinib, especially since indicated patients already have a high disease burden impacting their HRQoL. To date both vandetanib and cabozantinib have been included in the CDF as they are not suitable for use in all patients and could be considered as offering the only systemic therapy for MTC.[5]

Patient perspective

The [redacted] patients relevant to this submission are those with the most advanced MTC and therefore experience a significant disease burden and high level of symptoms, including pain, diarrhoea, nausea and fatigue, as well as the effects of metastases on specific organ

systems (including brain, lung, bones, liver and spinal cord). Together, these can substantially impair the patient's HRQoL.

In such patients, vandetanib has the potential to significantly delay the advancement of their disease, and thus to improve their HRQoL compared to the alternative BSC.

Vandetanib is an oral tablet self-administered once daily at home. Medical supervision of dosing is not required. Patients and physicians are well educated about and are closely monitored for QT prolongation as a requirement of the marketing authorisation.

Vandetanib: an innovative, highly specialised technology

Despite vandetanib no longer having an orphan drug designation, SanofiGenzyme believes strongly that consideration should still be given to the ultra-orphan disease state for which it is indicated, as well as the innovative aspects of the drug. The cost of vandetanib reflects the rarity of the disease it treats. We consider below how closely vandetanib aligns with the HST criteria (Table 4).[9]

Table 4. NICE HST prioritisation criteria.

Criteria	Vandetanib
The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS	[redacted] patients on commercial Caprelsa® as of January, 2017. Treatment in the UK occurs in 23 NHS centres.
The target patient group is distinct for clinical reasons	✓
The condition is chronic and severely disabling	Survival rates for EU label patients and restricted EU label patients are low, therefore the condition cannot be considered chronic.[17]
The technology is expected to be used exclusively in the context of a highly specialised service	Used in cancer centres
The technology is likely to have a very high acquisition cost	The acquisition cost reflects the rarity of the disease; however, the overall budget impact in England is manageable due to very few patients being affected by this rare disease and further being indicated for systemic treatment with vandetanib
The technology has the potential for life long use	Treatment with vandetanib continues until no further benefit or toxicity. It has the potential for life-long use, although the life expectancy of indicated patients is currently less than 2 years.
The need for national commissioning of the technology is significant	✓

Vandetanib and end-of-life (EOL) criteria

Table 5. Vandetanib and EOL criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Patients with unresectable locally advanced or metastatic medullary thyroid cancer have very short life expectancy if treated with only best supportive care. 5-year survival is reported to be 25%[1]; and median overall survival is 2–3 years in patients with distant metastatic disease.[11] In EXAM study, in which placebo arm was not confounded by cross over to active treatment, patients had median OS of 21.1 months.[18] The OS survival of the placebo arm in this study could be considered a proxy for patients who receive no active treatment and whose disease is reflection of natural progression of aggressive disease.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	In the restricted EU label population, subgroup of progressive and symptomatic with biomarker change, increase of more than 3 months are seen. Treatment with vandetanib results in difference of [redacted] months PFS over placebo (despite crossover effect) which drives an average of 1.7 LYG over BSC (see Section 5).
The treatment is licensed or otherwise indicated for small patient populations	There are currently [redacted] patients treated with vandetanib in England via CDF funding. Should NICE recommend vandetanib for routine use, we estimate that this number is likely to remain stable over the next 5 years (see section 6)

Equality issues

The access to vandetanib treatment that the CDF has allowed has meant that patients with this rare disease have had equitable access to an evidence-based treatment and allowed physicians to provide a patient-centred approach to treatment, in line with the vision of the UK Strategy for Rare Diseases.[10] Removing TKIs as a treatment option in advanced MTC would create inequity amongst the MTC patient population, and leave patients with no active treatment option.

To address equity issues around access to treatments for conditions with very few patients that do not meet all the criteria for HST assessment, we request some consideration beyond cost per QALY, efficiency assessment.

1.4 Summary of the cost-effectiveness analysis

A cost-effectiveness analysis for vandetanib compared with BSC alone is presented for patients with aggressive and symptomatic unresectable locally advanced or metastatic MTC defined as progressive (documented progression within 12 months prior to enrollment) and symptomatic (at least one symptom at baseline, including pain score > 4, ≥10 days of opioid use, diarrhoea, flushing, fatigue, pain, nausea, dysphagia, dysphonia, respiratory symptoms,

weight loss) plus CTN and CEA doubling times within 24 months of screening (i.e. the *restricted EU label population*).

A three-state, survival partition model was implemented using an Excel-based DICE simulation over a 20-year time horizon with a discount rate of 3.5% applied to benefits and costs. Inputs include drug acquisition costs for vandetanib (with a confidential discount applied), rates of grade 3 or 4 adverse events, monitoring costs associated with vandetanib, post-progression costs and palliative care costs applied in the last month prior to death.

Restricted EU label population

The restricted EU population as defined above was selected as the base case. This subpopulation is in line with the EU recommendation of selecting patients with the most urgent need for treatment and was shown in the ZETA study to have the most substantial clinical benefit and aligns with UK clinical practise.

Due to the small patient numbers ([redacted] patients on vandetanib and [redacted] on placebo) and overlapping overall survival curves and extensive crossover, we could not fit parametric curves needed to extrapolate the survival curve and estimate mean treatment benefit. Instead, to estimate the OS and PFS curves for this base case subpopulation, the parametric regressions fit to the entire study population were applied by considering the two characteristics symptomatic and progressive disease and speed of tumour biomarker increase, to create a regression equation that statistically modelled a population equivalent to the restricted EU population.

The incremental cost-effectiveness ratio (ICER) varies between [redacted] and [redacted]/QALY; and between [redacted] and [redacted]/LYG for the restricted EU label (base case), depending on the proportion who crossover from BSC or continue vandetanib post-progression, and the dose distribution afterwards.

No adjustment has been made for crossover, and thus the results underestimate the benefit of vandetanib. One key factor driving the ICERs is the proportion who crossover to vandetanib, and thus, the application of post-progression treatment costs to the BSC group. Despite this, the clinical benefit in this group of patients is almost 2 years (1.7 LYG).

In summary, the issue of crossover in a study conducted in an orphan disease at a time when there were no other active treatments, has highlighted the problem with applying standard cost-effectiveness methodology to very rare diseases with very small patient numbers. Vandetanib has been used in the UK since 2012 and to date there are only [redacted]

patients receiving treatment via CDF funding. This number is expected to remain fairly stable over next 5 years with estimated budget impact of [redacted]

Independent of the issues with the ZETA trial, the clinical benefit seen with vandetanib in prolonging OS in advanced and aggressive MTC is remarkable. Vandetanib offers patients with progressive and symptomatic MTC with CTN/CEA doubling ≤24 months an average survival gain of up 1.7 life-years for a drug cost of approximately [redacted]. In clinical practice, clinician and patients value the availability of having choice of treatment option and vandetanib should continue to be available as option for MTC in the UK, in line with UK strategy on rare disease.

Table 6. Incremental cost-effectiveness results

Technology (and comparators)	Total costs	Total life years	Total QALYs
BSC	£116,342	3.1	2.135
Vandetanib	[redacted]	4.8	3.491
Incremental	[redacted]	1.7	1.356
ICER			[redacted]

Conclusion

The clinical benefit seen with vandetanib in prolonging OS in advanced and aggressive MTC is remarkable, even when issues of cross-over with the ZETA trial are not addressed. In the patient population with the poorest survival outcomes, median OS has been reported to be less than two years, 21.1 month.[18] Vandetanib offers patients with progressive and symptomatic MTC who also have CTN/CEA doubling ≤24 months, a mean estimated survival gain of 1.7 life-years at a drug cost of approximately [redacted]. In clinical practice, clinicians and patients value having a choice in treatment options. Vandetanib should continue to be available as an option for MTC in the UK, in line with UK Strategy for Rare Diseases.[10]

2. Vandetanib

2.1 Description of the vandetanib

Brand name	CAPRELSA®
Approved name	Vandetanib
Therapeutic Class	Antineoplastic agent, protein kinase inhibitor

Mechanism of action

Vandetanib is an orally administered multi-targeted tyrosine kinase inhibitor (TKI). It is a potent inhibitor of vascular endothelial growth factor receptor-2 (VEGFR-2), epidermal growth factor receptor (EGFR) and REarranged during Transfection (RET) tyrosine kinases. Vandetanib also is a sub-micromolar inhibitor of VEGFR-3 and VEGFR-1. Inhibition of these tyrosine kinases suppresses tumour cell migration, proliferation, survival and angiogenesis mediated by these proteins. The precise mechanism of action of vandetanib in locally advanced or metastatic MTC is unknown.[8]

2.2 Marketing authorisation/CE marking and health technology assessment for vandetanib

Marketing authorisation

Vandetanib gained marketing authorisation in the EU on 17 February 2012.[11] It is currently marketed in 28 countries including the US where it was first approved by the Food and Drug Administration (FDA) in 2011. The EU indication for vandetanib is as follows:[8]

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

CAPRELSA® is indicated in adults, children and adolescents aged 5 years and older.

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

On the 16 December 2016, the EMA approved a license extension for the use of vandetanib in children and adolescents aged 5 years and older.[7] Only 2 to 3 children and adolescent patients are expected to receive treatment with this extension. Per the NICE scope, this submission is for the use of vandetanib in adults only.

Contraindications to vandetanib include: hypersensitivity to the active substance or to any of the excipients, congenital long QT syndrome, patients with a QTc interval over 480 msec, concomitant use of vandetanib with medicinal products known to also prolong the QT interval and/or induce Torsades de pointes and breastfeeding.[8]

Vandetanib, developed by AstraZeneca and now marketed by SanofiGenzyme, was designated orphan drug status in 2006. This was withdrawn in 2010 at the request of AstraZeneca due to the prospect of a further indication in the treatment of non-small cell lung cancer (NSCLC).[14] However, the marketing authorisation application for NSCLC was withdrawn and MTC remains the only licensed indication for vandetanib.

Regulatory assessment: *ZETA trial data vs. the EU label*

The regulatory assessment of vandetanib was primarily based on the pivotal Phase 3 ZETA trial with the primary outcome progression free survival (PFS).[13] However, the licensed indication in Europe, i.e. patients with aggressive and symptomatic, unresectable locally advanced or metastatic MTC, is more restrictive than the inclusion criteria of the ZETA trial and therefore represents a subgroup of the overall ZETA trial population.[12] It is important to note that the term 'aggressive' is used in the license instead of 'progressive' as the Committee for Medicinal Products for Human Use (CHMP) considered "progressive" to be ambiguous whilst the term 'aggressive' was likely to address the patient's condition with rapid deterioration and for which an urgent treatment is required.[11]

To evaluate the efficacy of vandetanib in a population representing a proxy for the EU label than the total trial population a post hoc subgroup analyses has been performed of ZETA trial in the population of patients with progressive and symptomatic disease, which was 56% of the trial population (126 of 231 vandetanib patients and 60 of 100 placebo patients).[12] 'Progressive' was defined as RECIST-documented progression within 12 months prior to enrolment. 'Symptomatic' was defined as at least one of the following symptoms at baseline: pain score >4; ≥10 mg/day opioid use; diarrhoea, flushing, fatigue, pain, nausea, dysphagia, dysphonia, respiratory symptoms and weight loss. This interpretation of the EU label has been presented as part of various HTA submission in Europe. The German reimbursement agency Gemeinsamer Bundesausschuss (G-BA) through its reviewing agency Institut für

Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) suggested that this subgroup definition was an adequate proxy for the EU label.[19]

The population indicated for treatment in the EU license does not directly correlate to a specific population within the ZETA trial and the definition of the target population above may be considered as one way of interpreting the indicated population.

From the discussion in the EPAR and statements in the SPC, it is clear that the regulators intended vandetanib use be restricted to patients who were in real need of treatment, in the symptomatic-aggressive phase of the disease where the patient's disease is rapidly deteriorating. Identifying the correlating patients in the ZETA trial could have been done a number of ways:

- RET mutation status
- serum tumour biomarkers CEA and CTN doubling speed
- symptom burden
- time since RECIST documented progression

A series of analyses have been done in the population that is symptomatic and progressive disease (EU label population) and are reported as part of the clinical evidence supporting vandetanib use (see section 4.8). In addition, this submission examines the patient population that meets three of these criteria: symptomatic, progressive disease and CEA/CTN doubling ≤24months (restricted EU label population). This subpopulation reflects patients that are currently treated with vandetanib in routine clinical practice in England. This group of patients are identified as those likely to achieve greatest benefit from treatment. As this definition reflects the approach to treatment of advanced MTC in the UK, and confers greatest clinical benefit it is presented as the base case for the pharmacoeconomic evaluation in Section 5.

However, there are potential analyses that have not yet been undertaken, for example patients with CEA/CTN doubling ≤24 months and symptomatic disease but no documented progression 12 months prior to enrollment. Similarly, patients with CEA/CTN doubling ≤24months and progressive disease but who were not symptomatic have not been examined. Given feedback from UK clinicians that they don't use RET mutation status to drive treatment decision making, RET status has not been further investigated.

Therefore, while SanofiGenzyme has considered the CEA/CTN doubling times as an additional marker of aggressive disease aligning with UK clinical practise, in reality, all four elements above and additional patient demographic and personal characteristics may drive decision making.

Benefit–risk balance

The European Public Assessment Report (EPAR)[11] discusses the benefit-risk balance for vandetanib in the desired patient sub-population (see previous section), which was considered positive overall and summarised in Table 7.

Table 7. Summary of EPAR discussion on vandetanib benefit-risk balance.[11]

Benefits	**Risks**
The superiority of vandetanib over placebo was clinically significant and quite consistent across all pre-planned subgroups. More benefit was seen in the subgroup of patients with biological markers (calcitonin [CTN] and carcinoembryonic antigen [CEA]) doubling time less than 24 months. There was uncertainty in the knowledge of beneficial effects in patients who were REarranged during Transfection (RET) mutation negative (RET M-).	Vandetanib has been shown to prolong QT interval and Torsades de pointes has been uncommonly reported. Vandetanib is a drug with a long half-life (19 days). A frequently observed symptom of MTC is diarrhoea. There is a further risk of dehydration and consequent renal impairment. Vandetanib has shown a deterioration of renal function (increased creatinine). Study 97 (NCT01496313) will provide additional safety and activity data on the use of vandetanib at a lower dose (150mg vs. 300mg). See Section 4.12.
Benefit–risk balance *In the overall population, improvement in progression-free survival (PFS), (objective response rate (ORR) and disease control rate (DCR) are of importance as well as a positive effect on some PRO. The management of the risk of QT prolongation and associated clinical consequences and renal risks associated with vandetanib are particularly important.* *The restriction of the indication to patients with symptomatic and aggressive disease allows (HCPs) to select patients who are at urgent need of treatment for medullary thyroid cancer. It is in this patient population that the benefits outweigh the important risks outlined.* Specific measures to further prevent and limit the concern over QT prolongation and the clinical consequences have been included in the SPC.[8]	

The CHMP granted a conditional marketing authorisation with the following requirements:[11]

- Submit periodic safety update reports (PSURs).
- Implement a risk management plan (RMP).
- Provide prescribing healthcare professionals (HCPs) with an educational pack including the SPC and package leaflet, educational materials for HCPs discussing the contraindications and cautions associated with QTc prolongation and patient alert cards (Appendix 1 annex).
- Provide comprehensive clinical data in MTC patients who are RET-mutation-negative (Caprelsa 104, NCT01945762, Section 4.14).

Health technology assessment

A summary of health technology assessments (HTA) in the UK is presented in Table 8. Vandetanib has not previously come under the NICE remit for technology appraisal possibly due to MTC affecting so few patients that the resulting impact on NHS England and Wales was not economically significant.

However, vandetanib has been assessed and included in the National Cancer Drugs Fund (CDF) since 2012 where it was the first TKI available for first line use in patients with symptomatic and aggressive MTC as per the licensed indication. In 2015, the panel reviewed currently available TKI drugs (vandetanib as well as the second-to-market cabozantinib [Cometriq®, produced by Exilexis Inc, San Francisco, USA and distributed in Europe by Ipsen, Paris, France]) and concluded as follows (see Section 4.13 for detailed background that underpinned their decision):[5]

"The CDF panel again decided that given these unusual circumstances of very different evidence bases and the fact that patient tolerance was an important issue, both drugs could be considered as offering the only systemic therapy for medullary thyroid cancer".

Table 8. Summary of vandetanib HTA

HTA Agency	Date of advice	Advice
CDF	2012	Document no longer available on NHS CDF website.
CDF[5]	2015	The treatment of medullary thyroid cancer where all the following criteria are met: 1. Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-

		cancer therapy; 2. Histologically confirmed, locally advanced and unresectable or metastatic medullary thyroid cancer; 3. Aggressive and symptomatic disease; 4. No previous tyrosine kinase therapy unless intolerant of cabozantinib within 3 months of starting therapy and toxicity which cannot be managed by dose delay or dose modification and in the absence of disease progression on cabozantinib
Scottish Medicines Consortium (SMC)[20]	June 2012	In the absence of a submission from the holder of the marketing authorisation vandetanib (CAPRELSA®) is not recommended for use within NHS Scotland. Indication under review: treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease.
All Wales Medicines Strategy Group (AWMSG)[4]	September 2014	Vandetanib (CAPRELSA®) is not recommended for use within NHS Wales for the treatment of aggressive and symptomatic medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. The case for cost-effectiveness has not been proven. AWMSG noted that it did not consider whether the treatment would have been cost-effective under ultra-orphan criteria.

2.3 Administration and costs of vandetanib

Table 9. Costs of vandetanib

	Cost	**Source**
Pharmaceutical formulation	100mg film coated tablet 300mg film coated tablet	SPC[8]
Acquisition cost (excluding VAT)*	The list price for vandetanib is: 100mg, 30 pack = £2500 300mg, 30 pack = £5000 A commercial agreement is in place with the CDF. [redacted]	BNF[21]
Method of administration	Oral administration	SPC[8]
Doses	300mg	SPC[8]
Dosing frequency	Once daily	SPC[8]
Average length of a course of treatment	Vandetanib may be administered until patients with MTC are no longer benefiting from treatment.[8] The median duration of treatment with vandetanib in the aggressive and symptomatic population in the ZETA trial was 88.6 weeks.	SPC[8] Kreissl 2014[12]
Average cost of a course of treatment	The cost of a course of vandetanib based on the EU label population at list price is £103,367, based on 300mg once daily for 88.6 weeks. [redacted]	SPC[8] Kreissl 2014[12]

	[redacted]. In the restricted EU label population, the average cost was estimated to be [redacted] (see section 5). However, since patients are treated until toxicity or until no further benefit the duration of a course and subsequently the cost, is variable. This cost per course is based on assumption of a patient not having any missed doses or dose reductions with the 300mg dose [redacted]. Therefore, it is the maximum cost to the NHS for the highest dose.	
Anticipated average interval between courses of treatments	Patients will not receive more than one course of vandetanib treatment.	SPC[8]
Anticipated number of repeat courses of treatments	Patients will not receive more than one course of vandetanib treatment.	SPC[8]
Dose adjustments	In the event of AE Grade 3 or higher toxicity, or prolongation of the ECG QTc interval, dosing of vandetanib should be stopped temporarily and resumed at a reduced dose upon resolution or improvement to Grade 1. The 300 mg, daily dose can be reduced to 200 mg (two 100 mg tablets), and then to 100 mg if necessary. In the ZETA ITT safety population 49.4% of vandetanib reported a dose reduction or interruption. In the EU label population, more patients required dose reduction of vandetanib compared with placebo (41 [33%] versus 2 [3%]) (section 4.12).	SPC[8] Wells 2012[13] Kreissl 2014[12]
Anticipated care setting	Patients self-administer vandetanib tablets at home, this does not require medical supervision. However, the ECGs and blood tests required upon initiation (as defined by the SPC) take place in specialised MTC centres.	SPC[8]

2.4 Changes in service provision and management

Vandetanib has been in use in the UK since 2012, made available by the CDF and established in clinical practice. A positive NICE recommendation will not result in an increase in resource use or require additional infrastructure within the NHS. For the reasons listed below the impact of reimbursing vandetanib on the NHS is small.

Due to the rarity of MTC it is only treated at a few ([redacted]) specialised MTC centres within the UK where a very small number of patients ([redacted]) currently receive commercial Caprelsa®.

Vandetanib is an oral tablet self-administered by the patient at home.

The marketing authorisation does not require any diagnostic tests to identify the indicated population. In clinical practice, somatic RET mutation testing is not funded, thereby not routinely performed. Section 3 provides further information on RET mutation testing.

The identification of patients who will benefit the most from vandetanib treatment occurs within the realm of routine clinical practice. Beginning at diagnosis patients' biological tumour markers (CTN and CEA) are monitored 6 monthly or annually depending on disease burden and symptoms. Inevitably the progression rate of the disease will accelerate characterised by increased CTN and CEA doubling times and progressive symptoms. From this point patients are monitored at least 3 monthly to guide treatment decisions. Discussed further in Section 3, CTN and CEA are routine in disease monitoring and not specific to identifying patients for TKI treatment.

On-treatment monitoring and tests are required however these are already established in clinical practice. From the SPC, section 4.4 Special warnings and precautions for use:[8]

> *An ECG, and levels of serum potassium, calcium and magnesium and thyroid stimulating hormone (TSH) should be obtained at baseline, at 1, 3, 6 and 12 weeks after starting treatment and every 3 months for at least a year thereafter. This schedule should apply to the period after dose reduction due to QTc prolongation and after dose interruption for more than two weeks. ECGs and blood tests should also be obtained as clinically indicated during this period and afterwards. Frequent ECG monitoring of the QTc interval should be continued.*
>
> *Serum potassium, serum magnesium and serum calcium should be kept within normal range to reduce the risk of ECG QTc prolongation. Additional monitoring of QTc, electrolytes and renal function are required especially in case of diarrhoea, increase in diarrhoea/dehydration, electrolyte imbalance and/or impaired renal function. If QTc increases markedly but stays below 500 msec, cardiologist advice should be sought.*

No specific concomitant medications are required for vandetanib treatment. Patients may receive vandetanib in conjunction with additional palliative medication and treatments depending on the needs of the patient:[17]

- Managing diarrhoea using antimotility agents such as loperamide, or somatostatin analogues such as octreotide.

- Controlling pain using analgesics, including opiates and non-opiates, or palliative radiotherapy.

- Treating bone metastases with bisphosphonates such as zoledronic acid

2.5 Innovation

Vandetanib was an innovative step change in the treatment of unresectable locally advanced or metastatic MTC at the time of initial regulatory approval. Vandetanib was the first systemic therapy to demonstrate a significant clinical benefit, gain marketing approval and address a significant unmet need in the treatment of advanced MTC whilst maintaining a manageable tolerability profile. Surgery is currently the only curative option for MTC, but only provides palliative therapy in patients with unresectable locally advanced or metastatic disease. MTC is unresponsive to radiotherapy and chemotherapy has proven ineffective in advanced MTC, producing low response rates (15%–20%) and short durations of response.[22] Vandetanib is now established practice in many countries, has been widely used since first approval by the FDA in 2011 and improved the treatment landscape of advanced MTC.

Patients in the EU suitable for vandetanib must, in their clinicians' judgment, meet the criteria of aggressive and symptomatic disease. They are the most advanced patients with a significant tumour burden and increased symptoms, including pain, diarrhoea, nausea and fatigue, as well as the effects of metastasis on specific organ systems, which can substantially impair the patient's health-related quality of life (HRQoL).[13 18 22 23] The introduction of vandetanib in such patients has the potential to significantly delay the advancement of their disease, and thus to improve their HRQoL. Clinical evidence from the phase III ZETA trial, for the restricted EU label population (see section 4.8; progressive and symptomatic disease in line with the EU label, and with CTN and CEA doubling times ≤24 months) showed a PFS benefit [redacted] months and an OS benefit [redacted] years. In addition, [redacted] of these patients had an objective response.

Vandetanib has a manageable AE profile and requires additional monitoring due to the potential for prolonged QT interval, although this is rarely reported.[8] The low levels of discontinuation in the vandetanib group (12% in both the safety analysis population and the aggressive and symptomatic population[12 13] from the ZETA trial despite a median duration of treatment of 90.1 weeks (safety analysis set; 88.6 weeks for the aggressive and symptomatic population[12]), combined with no significant differences from placebo on the FACT-G QoL measure, suggest that on the whole, the AE profile is tolerable for patients.[13]

In addition, by dosing to individual patient tolerance, the starting dose of 300 mg can be reduced as necessary to manage side effects and to avoid discontinuing the drug, thus maintaining the maximum possible efficacy benefit over many months to years. At data cut-off for final overall survival (OS) analysis (7 September 2015),[24] there were 15 (4.5%) patients who were still receiving randomised treatment (14 [6.1%] on vandetanib versus only 1 [1.0%] on placebo). A further 49 (14.8%) patients were continuing open-label treatment at data cut-off for final OS (28 [12.1%] on vandetanib and 21 [21%] on placebo).

Further evidence of a manageable AE profile is provided by the French cohort study[25] (see Section 4.11) where patients were treated with vandetanib in routine clinical practice, outside the context of a controlled clinical trial, for a median time of 9.7 months. Enrolled patients had locally advanced or metastatic MTC with large tumor burden who had either symptomatic and/or progressive disease (more advanced disease compared to ZETA ITT population). All patients (n=60) reported experiencing an AE; however, only 16 (27%) patients discontinued treatment due to an AE and dose reduction was necessary in just 20 patients (33%).[25]

Vandetanib recently became the first TKI to receive CHMP positive opinion for a license extension for use in children and adolescents aged 5 years and over.[7] This is a step change in the treatment of advanced MTC in this age group and is expected to apply to only 2 or 3 patients per year.[26] Although the evidence for this license extension is not directly relevant to the NICE decision problem, it indicates from a regulatory standpoint that despite concerns previously raised in the conditional marketing authorisation for adults, vandetanib is a valuable treatment for MTC across a range of patients.

3. Health condition and position of the vandetanib in the treatment of medullary thyroid cancer

Disease background

MTC is an ultra-rare disease arising in the parafollicular cells (C-cells) of the thyroid and can spread to other organs including the lymph nodes, liver, lungs, bones and brain.[1] It occurs sporadically in 75% of cases and is inherited in the remaining 25%. Patients with sporadic MTC typically present with a lump in the neck or with dysregulation symptoms such as hair loss, difficulty concentrating, sleep disturbances, fatigue, weight change, palpitations, intolerance to cold or heat, constipation, depression or anxiety.[27] [28] Diarrhoea (which can be debilitating in advanced disease) and vasomotor flushing are common symptoms of MTC disease due to increased calcitonin (CTN) secretion from the parafollicular cells.[1] CTN, and to a lesser extent carcinoembryonic antigen (CEA), are used as biological markers that provide valid data regarding postoperative MTC burden, progression and survival.[29]

At initial diagnosis, patients may present early with local–regional disease, or locally advanced or metastatic disease. Just under half of the patients with sporadic MTC will present with Stage III or IV (advanced) disease.[22] Patients are further described as having indolent or aggressive and symptomatic disease. Seven to 23% of patients present with distant metastases; however, due to slow growing tumours or distant metastases limited to single organs patients may remain asymptomatic and non-progressive with a low tumour burden. HRQoL can be maintained for months to years in these patients.[1]

The patients relevant to this submission are those with aggressive and symptomatic locally advanced or metastatic MTC where the disease is incurable, chronic and disabling. The clinical burden is high in these patients with multiple life affecting symptoms from distant metastases in the lungs, bones (occur in 5–10% of patients causing severe pain requiring opiates[28]), liver dysfunction or spinal cord compression.

Treatment options are limited as MTC is relatively unresponsive to conventional doses of radiation therapy and to all tested chemotherapeutic regimens. The prognosis for patients with locally advanced or metastatic MTC is poor with a reported 5-year survival rate of 25%.[1] There is limited epidemiological information published for the specific subgroup of aggressive and symptomatic patients however the patient population recruited for the EXAM trial represents those indicated for TKI treatment in clinical practice (see section 4.10), and the final OS result of 21.1 months for the placebo arm can be used as an estimate of survival

without treatment in the aggressive and symptomatic subgroup.[30] Thus, the patients relevant to this submission have a life expectancy of less than 2 years.

A study analysing surgical outcomes of 2968 patients with MTC from 1998 to 2005 in the US National Cancer Database (NCDB) provides survival information based on the number of cervical lymph node metastases and distant metastases at diagnosis.[2] Patients with no cervical or distant metastases had 5- and 10-year survival rates of 95% and 86%, respectively.[2] At the other end of the disease spectrum, patients with >16 cervical metastases and no distant metastases (locally advanced disease) had 5- and 10-year survival rates of 68% and 48%. Only 26% and 14% of patients with distant metastases were alive at 5 and 10 years.[2] Without providing any information as to whether the study patients had aggressive disease or not based on CTN and CEA doubling times, these results demonstrate the poor prognosis of locally advanced and metastatic MTC patients.

The Surveillance, Epidemiology, and End Results Program (SEERS) by the US National Cancer Institute provides comprehensive information on cancer incidence and survival in the US.[31] A study of 1252 MTC patients in the SEER database diagnosed from 1973 to 2002 confirms MTC patients may survive many years with the disease (mean overall survival 8.6 years [0 to 29.7 years]). Overall survival differed by SEER stage as shown in Figure 1.[31] Tumours confined to the thyroid had the best 10-year survival rate at 95.6%, however prognosis worsened with regional and distant metastatic disease (75.5% and 40% surviving at 10 years, respectively). The SEERs distant metastases 40% 10-year survival rate is higher than the 5-year survival rates in advanced MTC patients used in this submission as patients with distant metastases, as explained above, may have indolent disease extending their survival.[31]

Figure 1. Ten-year, disease-specific survival by Surveillance, Epidemiology, and End Results (SEER) stage for patients with histologically confirmed medullary thyroid cancer, 1973–2002.

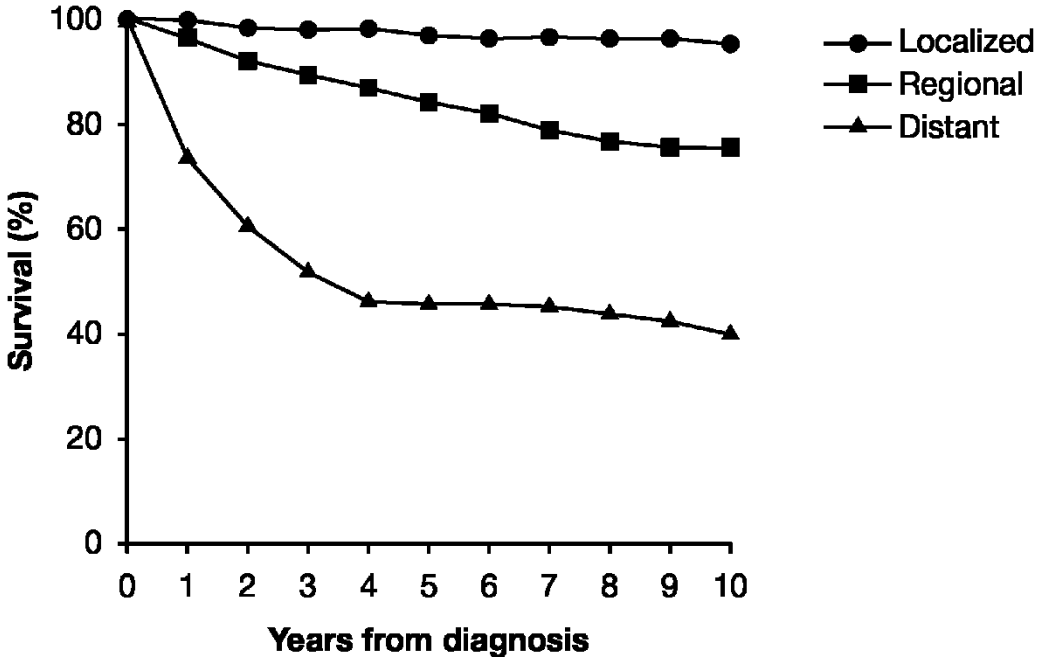


Figure adapted from Roman et al 2006.[31]

Incidence and prevalence

In the UK, 3% of all adult thyroid cancers are MTC.[32 33] During 2015–2016, an estimated 253 patients were diagnosed with MTC in UK hospitals.[17 34] Based on current usage of vandetanib in England [redacted] as of January 2017), 25% of MTC patients have aggressive and symptomatic disease. The current prevalence of MTC in the EU is 0.7/10,000 and the incidence is 0.22/100,000.[35] MTC fulfils the criteria for orphan indication in the European Union (EU) (prevalence of <5/10,000).[3] There is no official definition for an ultra-orphan disease however based on an estimated 253 patients with MTC in the UK, it meets the accepted criteria in England and Wales (a disease affecting less than 1000 patients or <1/50,000) and is an ultra-orphan disease.[36 37]

CTN and CEA doubling times

CTN is the major secretory product of neoplastic C cells. They also produce CEA and both molecules are the current tumour markers of MTC. Preoperative CTN levels help guide diagnosis and the extent of surgery required. Postoperative CTN levels correlate with MTC size, C cell hyperplasia, tumour or metastases size and loco-regional recurrence or persistent disease. CEA levels are not specific to MTC and are less sensitive and less reliable than CTN for diagnosis; however, when measured alongside CTN they may be

useful in assessing disease progression in patients diagnosed with MTC or who have undergone thyroidectomy.[22 29]

Doubling times of CTN and CEA are routinely used in clinical practice to determine postoperative MTC burden, progression and survival and thus identify patients with aggressive disease. Studies have shown that patients with CTN and CEA doubling times ≤24 months have progressive disease and a reduced survival compared to patients with CTN and CEA doubling times of >24 months.[38 39] One study reports 5- and 10-year survival rates in MTC patients with postoperative CTN doubling times <6 months of 25% and 8% respectively, compared to 92% and 37% respectively in those with doubling times between 6 and 24 months. All patients with CTN doubling times greater than 24 months were alive after 29.5 years at the end of the study.[38]

RET mutation testing

Point mutations in the RET proto-oncogene, ultimately impacting cell motility, proliferation, differentiation and survival, are responsible for most patients with hereditary MTC (germline mutations) and present in around half of the sporadic MTC cases (somatic mutations).[40] Somatic mutations occur in the tumour and are not present at birth. The British Thyroid Association Guidelines for the Management of Thyroid Cancer recommend RET mutation testing in all confirmed cases of MTC to establish the possible genetic basis for the disease within an individual or family member.[17] Germline RET mutation testing is standard practice in the NHS however somatic RET mutation testing of primary thyroid tumours or metastases is not. A patient can be germline-RET-mutation negative yet have a RET-mutation-positive tumour. Physicians do not have access to molecular profiling of MTC tumours (somatic testing not funded) and therefore cannot ascertain whether a patient will respond to TKIs which target RET.[4]

Treatment of MTC in England

The treatment pathway for MTC adapted from Grande et al (2015)[29] in consideration of the British Thyroid Association (BTA), European Thyroid Association (ETA) Guidelines and American Thyroid Association (ATA) is presented in

Figure 2.[1 17 22]

Figure 2. Treatment pathway for MTC.

Based on Grande et al (2015),[29] British Thyroid Association Guidelines (2014),[17] European Thyroid Association Guidelines (2012)[1] and the American thyroid Association Guidelines.[22]
BSC: best supportive care; CEA: carcinoembryonic antigen; CTN: calcitonin; EBRT: external beam radiation therapy.
[a]Based on 2015–2016 data of 253 patients were diagnosed with MTC in UK hospitals.[17 34]
[b]Based on SEERs data of locally advanced/metastatic disease.[31]
[c]Either vandetanib or cabozantinib is recommended first line depending on licensed indications, patient tolerability, physician experience.
[d]Annual drug acquisition cost incorporating discount.
[e]Annual drug acquisition cost sourced from Cabozantinib AWMSG ASAR.[41]
[f]National Cancer Drug Fund decision and summary document (2015).[5]
[g]Appendix 2: UK KOL feedback

Currently, there is no NICE guidance or pathway for this condition. Early stage, loco-regional disease is treated with complete or partial thyroidectomy, which can be curative. Recurrences are frequent and are often associated with, or precede, the discovery of distant metastases. Imaging and monitoring of biological markers (in particular CTN and CAE) are recommended until the disease is symptomatic and/or progressive (

Figure 2).[17]

Systemic treatment is recommended by BTA, ETA and ATA in advanced MTC patients with significant tumour burden and symptomatic or progressive disease according to RECIST criteria (

Figure 2). Both vandetanib and cabozantinib are first-line treatments in patients with symptomatic and/or progressive disease (according to their labels). Firstly, the choice of drug is based on the patient tolerability and licensed indications. In feedback received from two UK clinical experts, consideration is given to commencing TKIs provided the patient is of reasonable WHO PS and there are no significant comorbidities or contraindications (i.e. the clinician would assess patient's concomitant medications, comorbidities, potential drug toxicities and the impact of the site of the disease to select most appropriate first line therapy). (Appendix 2)

Prior to availability of vandetanib, BSC was the standard management for patients with advanced MTC, and this is still the case in patients where systemic treatment is not suitable. BSC is also used in conjunction with systemic treatment to provide symptom control (diarrhoea and pain), local treatments for distant metastases and palliative chemotherapy or radiation in suitable patients where necessary. Surgery is contemplated in advanced disease to decrease tumour burden, relieve symptoms and prevent complications.[22 29]

Vandetanib for the treatment of MTC in England and Wales

SanofiGenzyme anticipates vandetanib will be used in England and Wales first line in patients with unresectable locally advanced or metastatic MTC with aggressive and symptomatic disease, and CTN and CEA doubling times ≤24 months, i.e. those patients with the most aggressive disease. The [redacted] patients currently treated with vandetanib in England are likely to be those with most aggressive disease and therefore be similar to this restricted EU label population. It is expected that the size of this patient population will remain stable over the next 5 years. This population is in line with the EU label and reflects UK clinical practice on patient selection for TKI treatment.

In England, vandetanib is currently used first line as recommended by the CDF. Cabozantinib is an alternative first line agent.[5] Both vandetanib and cabozantinib displace BSC, and the CDF recommends availability of both TKIs; therefore, BSC is the appropriate comparator for vandetanib in this submission.

Significant clinical differences in the safety profiles of each drug mean that they are not suitable for use in all patients, as such both options should be available.[5] For example, vandetanib has been shown to prolong QTc interval and consequent Torsades de pointes are uncommonly reported.[8] On the other hand, cabozantinib has been shown to cause serious, and sometimes fatal, gastrointestinal (GI) perforations and fistulas as well as intra-abdominal abscesses.[42] If there are no issues precluding either drug, then treatment choice may be affected by drug cost and/or physician preference and experience.[5]

Vandetanib meets highly-specialised technology (HST) criteria

In 2013, The Department of Health published the UK Strategy for Rare Diseases, which aims to ensure that people living with a rare disease have the best quality of evidence-based care and treatment that the UK's health and social care systems, working with charities, researchers and industry, can provide. The Strategy statement contains the following information that is considered by SanofiGenzyme to be highly relevant to the appraisal of vandetanib:[10]

"So that patients with rare diseases get the most effective treatments, it is important that we have appropriate procedures for evaluating the benefits and costs of treatments as they become available. These procedures should be transparent and robust enough to be able to take account of the particular challenges that occur when evaluating treatments for rare diseases."

Based on this, SanofiGenzyme considers a multiple technology appraisal (MTA) to be an inappropriate method of evaluation for vandetanib. MTC is a rare disease fulfilling the criteria for orphan indication in the EU, and the accepted criteria for an ultra-orphan disease in the UK. Despite vandetanib no longer having an orphan drug designation, consideration should still be given to the ultra-rare disease state for which it is indicated, as well as its innovative aspects.

The cost of vandetanib reflects the rarity of the disease it treats. SanofiGenzyme accepts that it doesn't meet all the criteria for evaluation via the highly specialised technology (HST).[9] However, we suggest that to assess it under standard efficiency measure of cost per QALY is inequitable.

Table 10. NICE HST prioritisation criteria.

Criteria	Vandetanib
The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS;	[redacted] patients on commercial Caprelsa® as of January, 2017 Treatment in only [redacted] NHS centres
The target patient group is distinct for clinical reasons;	✓
The condition is chronic and severely disabling;	Survival rates for EU label patients and restricted EU label patients are low, therefore the condition cannot be considered chronic
The technology is expected to be used exclusively in the context of a highly specialised service;	✓
The technology is likely to have a very high acquisition cost;	The acquisition cost reflects the rarity of the disease; however, the overall budget impact in England is small due to very few patients being affected by this rare disease and further being indicated for systemic treatment with vandetanib
The technology has the potential for life long use;	Treatment with vandetanib continues until no further benefit or toxicity. It has the potential for life-long use, although the life expectancy of indicated patients is currently less than 2 years.
The need for national commissioning of the technology is significant.	✓

Equality issues

The access to vandetanib treatment that the CDF has allowed has meant that patients with this ultra-orphan disease have had equitable access to an evidence based treatment, and allowed physicians to provide a patient centred approach to treatment – in line with the vision of the UK Strategy for Rare Diseases.[10] Removing vandetanib as a treatment option in advanced MTC would create inequality amongst the MTC patient population, and leave patients unsuitable for cabozantinib treatment without a valuable and effective systemic treatment.

Furthermore, a recommendation for the use of either systemic treatment dependent on RET mutation status could also result in inequality and is not clinically valid – RET mutation status is not currently used to guide treatment decisions in the NHS in England and Wales. Vandetanib and cabozantinib both inhibit RET tyrosine kinase and although inadequately-powered sub-analyses based on mutation status have been done, somatic RET mutation analyses are not funded by the NHS and therefore not routinely performed in MTC patients.

To address equity issues around access to treatments for conditions with very few patients that do not meet all the criteria for HST assessment, we request some consideration beyond cost per QALY, efficiency assessment, for example orphan modifiers or some discretion in decision making.

4. Clinical effectiveness

The evidence supporting the clinical effectiveness of vandetanib within its labelled indication are derived from a post-hoc sub analysis of ZETA study. ZETA was a phase 3 trial conducted to demonstrate the safety and efficacy of vandetanib 300 mg versus placebo and included 331 patients with unresectable locally advanced or metastatic MTC and CTN levels ≥ 500 pg/mL. The vandetanib EU label reflects a subgroup of patients considered by the regulators (EMA) who are in urgent need of treatment and in whom the benefits of treatment outweighed the risks: these patients are defined as having symptomatic and aggressive disease.[11]

The primary objective of the ZETA study was to demonstrate an improvement in progression-free survival (PFS) with vandetanib compared to placebo, using centralised, blinded independent review of radiological images.[13] Treatment was continued until disease progression or unacceptable toxicity. The secondary endpoints included overall objective response rate (ORR), disease control rate (DCR) at 24 weeks, duration of response (DoR), time to worsening of pain (TWP) and overall survival (OS). Biochemical response as measured by blood levels of CTN and CEA (markers of the level of aggressive disease) was also assessed, and HRQoL was assessed using the FACT-G instrument.

The PFS primary endpoint, ORR and DCR were based on centralized, independent blinded review of the imaging data. Patients were treated with the randomised therapy until they reached objective disease progression based on the investigator's assessment, the blinded study treatment was then discontinued and patients were given the option to receive open-label vandetanib prior to confirmation of the progression event by central review. Patients randomised to placebo in the ZETA trial could cross-over to vandetanib at the time of investigator determined progression, prior to central review of the scans. Therefore, unless adjusted for crossover, results based on central review are confounded by patients receiving open-label vandetanib treatment after primary analysis was completed. This study design leads to a potential overestimation of the PFS and OS estimates in the placebo arms, a factor recognised by the EMA in its review of the trial data, where it was noted that cross-over at progression leads to an OS comparison between populations that differ mainly by the fact that vandetanib has been proposed early (experimental group) or later on, at progression (placebo arm). Analyses based on investigator assessment exclude crossover to active treatment as these assessments were taken prior to crossover.

For completeness, we present results on the ITT population initially. However, SanofiGenzyme recognises that the EU label cohort (i.e. aggressive and symptomatic) is the relevant starting point for review in this appraisal. SanofiGenzyme has further narrowed its focus on those patients with aggressive and symptomatic MTC and high rates of CTN and CEA doubling times (referred to as restricted EU label population), representing those patients with the most aggressive disease (data from these patients form the basis of the pharmacoeconomic modelling). This population of patients most closely aligns with UK clinical practise, as patients are selected for treatment with vandetanib based on those most likely to achieve greatest clinical benefit.

In this section, we discuss in further detail the limitations of the ZETA trial with respect to issues associated with centrally read assessments versus investigator assessment, as well as crossover leading to active treatment on both arms and therefore the post-progression use of vandetanib. These are all important factors to consider when interpreting the study results, particularly the primary endpoint (PFS) as well as the outcomes driving the economic analyses in section 5 (focussing on OS).

4.1 Identification and selection of relevant studies

No systematic literature was undertaken in the development of this submission. SanofiGenzyme confirms that there are no other relevant studies done outside of our companies that are relevant to the use of vandetanib in aggressive and symptomatic patients with MTC. A signed statement that all relevant data have been disclosed accompanies this submission.

4.2 Relevant randomised controlled trials

One relevant study is presented in support of this submission: the ZETA trial (Table 11).[12 13] As mentioned above, although the ZETA trial studied the effects of vandetanib in patients with unresectable, locally advanced or metastatic MTC, the EU indication is for a specific subset of patients, those with aggressive and symptomatic MTC. Consequently, the data supporting the regulatory approval and therefore this submission come from a post-hoc sub-analyses that was not pre-specified.[12] A similar analysis was undertaken by the CDF in its evaluation when it adopted vandetanib.[5]

The table below lists the publications and data sources associated with the overall ITT analyses and the post-hoc sub-analyses for the EU cohort of aggressive and symptomatic MTC patients in ZETA.

The key features of the ZETA study are briefly described in sections 4.1 to 4.7, and focus on the sub-group analysis specific to the restricted EU label in section 4.8. The full original analysis is available in the ZETA study report.[16]

Table 11. Description of the ZETA trial populations and subanalyses that support the pharmacoeconomic analysis of vandetanib in the restricted EU label population EU, plus their sources

Trial	Population	Intervention and comparator	Data source(s)	Key evidence reported
ZETA (study 58) ITT analyses	Patients with unresectable, locally advanced or metastatic MTC	Vandetanib 300 mg vs placebo	Wells 2012[13] Clinical study report[16]	PFS, Interim OS, ++
ZETA (study 58) ITT analyses	Patients with unresectable, locally advanced or metastatic MTC	Vandetanib 300 mg vs placebo	Clinical study report[16]	Final OS
ZETA (study 58) - EU label cohort, post-hoc analyses (1)	Patients with unresectable, locally advanced or metastatic MTC and whose disease is aggressive and symptomatic	Vandetanib 300 mg vs placebo	Kreissl 2014[12] Appendix 6 Manuscript planned for submission to Journal of Clinical Oncology in 2017	PFS, etc Final OS, PFS Cross over impact
ZETA (study 58) EU label cohort, post-hoc analyses (2)	Patients with unresectable, locally advanced or metastatic MTC and whose disease is aggressive and symptomatic and with CTN & CEA doubling <24 months of screening	Vandetanib 300 mg vs placebo	Data on file (Appendix 6)	Final OS, PFS Cross over impact

4.3 Summary of methodology of ZETA

The primary objective of the ZETA study was to demonstrate an improvement in PFS with vandetanib 300 mg compared with placebo.[13] The main features of the trial methodology are given in Table 12.

Table 12. Trial methodology in the Phase III ZETA study

Trial	Zeta (study 58)
Locations	International
Trial design	Randomised, double-blind, placebo controlled, multicentre, Phase III
Eligibility criteria for participants	Inclusion: • Provision of written informed consent. • Female or male aged 18 years and over. • Previously confirmed histological diagnosis of measurable, unresectable locally advanced or metastatic hereditary or sporadic MTC. • World Health Organization performance status (WHO PS) 0 to 2. • CTN ≥500 pg/mL (conventional units) or ≥146.3 pmol/L (international standard units) • All patients (other than those with hereditary MTC who had a documented germline RET mutation) had to submit a tumour sample for testing. Exclusion: • The last dose of prior chemotherapy or radiation therapy was received less than 4 weeks prior to randomization. Significant cardiac, hematopoietic, hepatic, or renal dysfunction
Settings and locations where data were collected	63 study sites in 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.
Trial drugs	Vandetanib (300 mg, OD), placebo
Cross over to open label treatment	The decision to discontinue randomized treatment for objective progression and eligibility to receive open-label vandetanib was made at the sites, based on the sites' RECIST assessments. After disease progression, all patients (both active and placebo) were discontinued from randomized treatment and given the option to be unblinded or begin open-label treatment with vandetanib 300 mg treatment (or receive a permanently reduced dose, if applicable). Patients were evaluated until objective disease progression was assessed by the investigator at the study site in real time and followed for survival. Patients who received open label vandetanib continued to have scans performed and send to Independent Review. After the report of the primary analysis all patients were offered to be unblended and receive open label therapy. After that amendment, only patients who were still on randomized therapy had scans performed and send to independent review. Safety was based on the frequency, Common Terminology Criteria for AEs (CTCAE) grade, and type of AEs; clinically significant laboratory abnormalities, or changes in vital signs, including ECG changes, and ophthalmologic findings.
Primary outcomes	Progression free survival (PFS) Progression was defined per modified RECIST criteria. All imaging

	scans were assessed for progression and response by a central imaging review ('central read'), independent of the sponsoring company. Although individual sites also made RECIST evaluations, the centralized RECIST assessments were used for the primary analysis of PFS and secondary objective efficacy endpoints
Secondary/tertiary outcomes	Objective response rate (ORR), disease control rate (DCR) and duration of response (DOR); overall survival (OS); calcitonin (CTN) and carcinoembryonic antigen (CEA) responses; time to worsening of pain (TWP); pharmacokinetics; pharmacokinetics-pharmacodynamics; safety and tolerability.
Pre-planned subgroups	Before unblinding of study data occurred, subgroup analyses were pre-specified for PFS. Subgroups relating to two different definitions for "aggressive disease" were included in a pre-specified subgroup analysis: CTN doubling time ≤24 months and CEA doubling time ≤24 months (as used in the economic model).

* Patients were randomized, in a non-stratified fashion, 2:1 to receive either vandetanib 300 mg or placebo until experiencing disease progression or unacceptable toxicity or withdrawing from trial

4.4 Statistical analysis and definition of study groups in ZETA

The study was designed to have a power of more than 80% to detect a hazard ratio (HR) less than 0.5 at a 5% significance level.

Analyses of PFS and OS were conducted using a log-rank test (unadjusted model with treatment factor only) in the intention-to-treat (ITT) population. ORR and DCR were analyzed using logistic regression. To account for the endpoint not being reached at the time of analysis, DOR was determined using a Weibull model. For CTN and CEA levels, a complete response represented a normalization of levels; partial response and progressive disease represented a decrease or increase, respectively, of at least 50% from baseline. TWP was defined as the time to either a worsening of the worst pain score of ≥2 points on the brief pain index, or an increase of ≥10 mg/day in the use of opioids (morphine or morphine equivalents), analyzed using a log-rank test.

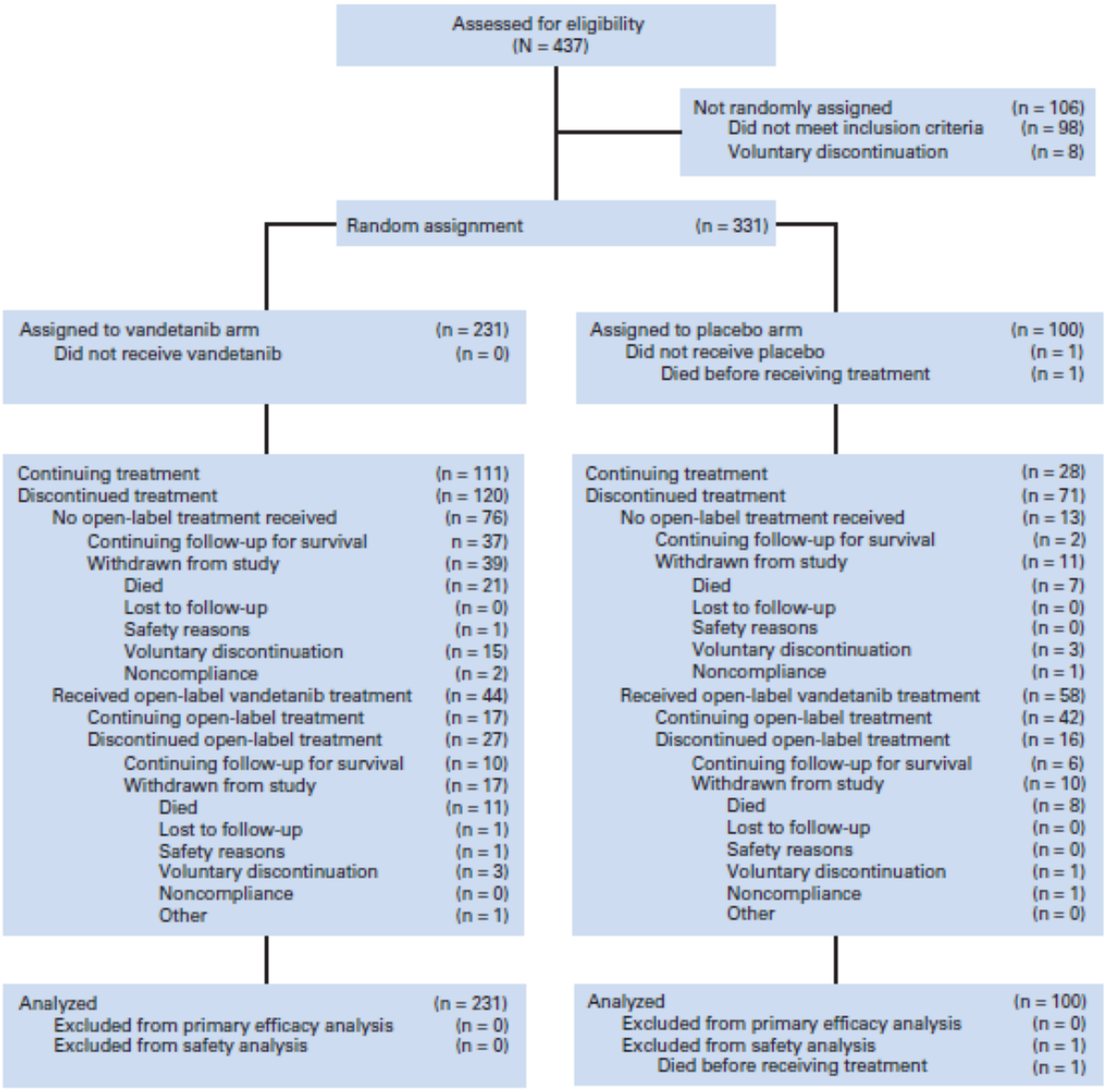
A nominal 2-sided significance level of 5% was used for all analyses, with the exception of OS where the significance level was adjusted to 0.02% to account for an initial analysis at the time of the PFS analysis. The final OS analysis was planned to occur after at least 50% of the patients have died[13] and this analysis was complete early in 2016.[24]

4.5 Participant flow in ZETA

The first patient was enrolled on 7 December 2006 and the last patient was enrolled in the trial on 21 November 2007. The date of data cut-off for estimation of the primary endpoint

(PFS) the trial was 31 July 2009. Patient flow is summarized in the Consort flow diagram (Figure 3). A second data analysis for OS was planned for 7 September 2015.

Figure 3. Patient flow in the Phase III ZETA trial of vandetinib in MTC (first data assessment, July 2009).[13]



SOURCE: Wells et al (2012)[13]

4.6 Quality assessment of ZETA

The quality assessment of the ZETA study is summarized in Table 13. Quality assessment results for the ZETA study.

Table 13. Quality assessment results for the ZETA study.

	ZETA
Was randomisation carried out appropriately?	YES
Was the concealment of treatment allocation adequate?	YES in the double-blind phase NO in the open-label phase
Were the groups similar at the outset of the study in terms of prognostic factors?	YES
Were the care providers, participants and outcome assessors blind to treatment allocation?	YES in the double-blind phase NO in the open-label phase
Were there any unexpected imbalances in drop-outs between groups?	NO
Is there any evidence to suggest that the authors measured more outcomes than they reported?	NO
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	YES

4.7 Clinical effectiveness results of the relevant randomised controlled trials

Here we report the data for the ITT population as originally defined for the ZETA trial. Please be aware that the specific sub-analysis supporting the EU label is given in section 4.8.

Study population: This study included 331 patients (231 vandetanib, 100 placebo; ITT population), aged 18 to 84 years, who were randomized at 63 study sites in 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. All 331 patients were included in the ITT analysis, and 330 were included in the safety analysis. Patients had a mean age of 51.5 years (50.7 vs. 53.4 years in the vandetanib and placebo groups, respectively), 57.4% were male (58% vs. 56%), 95.2% were Caucasian (94.4% vs. 97.0%), 90.3% had undergone thyroidectomy pre-study (89.6% vs. 92.0%), 94.6% of patients had stage IVC disease (93.5% vs. 97.0%), 45.0% of patients had a medical history of diarrhoea (43.3% vs. 49.0%), 15.4% had a history of fatigue (15.6% vs. 15.0%), and 20.5% of patients (21.6% vs. 18.0%) had previously received chemotherapy.

The majority of patients had sporadic (not hereditary) MTC, and more than half of the patients had no prior systemic therapy for MTC.[13] As shown in Table 14, the treatment arms were well balanced with regard to patient demographics and clinical characteristics.[13]

Table 14. Summary of demographic characteristics (ITT population).[13]

Baseline characteristics		**Vandetanib 300 mg (N=231)**	**Placebo (N=100)**
Age (years)	Mean	50.7	53.4
Male gender, n (%)	Male	134 (58.0)	56 (56.0)
WHO performance status	0	154 (67)	58 (58)
	1	67 (29)	38 (38)
	2	10 (4)	4 (4)
Disease type	Hereditary	28 (12)	5 (5)
	Sporadic or unknown	203 (88)	95 (95)
Prior systemic therapy for MTC	1 or more	90 (39)	42 (42)
RET mutation status	Positive	137 (59)	50 (50)
	Negative	2 (1)	6 (6)
	Unknown	92 (40)	44 (44)

MTC=medullary thyroid cancer; WHO=World Health Organization.

A statistically significant improvement in 'central read' PFS was observed for vandetanib versus placebo (HR: 0.46; 95% CI: 0.31,0.69) (Table 15). However, in total, 51 patients (15.4%) received open-label vandetanib before progression was documented by 'central read' (23 [10%] in the vandetanib arm and 28 [28%] in the placebo arm). Therefore, two sensitivity analyses were performed (Table 15):

- 'Central read' PFS assessment controlling for open label vandetanib exposure prior to PFS.
- 'Site read' PFS.

This sensitivity analysis indicated that the results using the 'site read' version of PFS were supportive of those of the primary analysis with 'central read', i.e. they demonstrated consistency between 'central read' PFS and 'site read' PFS assessments.

The 'site read' PFS and the unadjusted 'central read' PFS show a substantial and statistically significant benefit for vandetanib over placebo with an increase in median PFS of respectively 14.0 months and 11.2 months (Table 15). The analysis of 'central read' assessment with adjustment for cross-over prior to progression predicts the highest gain in

median PFS (16.0 months; Table 15). For the economic evaluation (section 5) the 'site read' PFS is the preferred outcome since it better reflects real life practice than the 'central read'. Moreover, the data are most robust (median PFS is reached in both arms). Compared to the 'central read' assessment (either without or with controlling for cross-over), the 'site read' PFS represent a conservative data set as illustrated by the slightly smaller gain in median PFS.

It is worth noting that the PFS results, and presumably other endpoints, for the ITT population in the ZETA trial appear to have been influenced by the presence of indolent disease. Overall, the site-read PFS in the placebo arm was 8.3 months. However, when the EU label population was excluded, OFS in the placebo arm increased to 19.3 months.

Table 15: PFS results in the overall population of the ZETA trial

Full ZETA Cohort PFS assessment	Median PFS (months)			Hazard ratio (95% CI)	P value
	Vandetanib (n=231)	Placebo (n=100)	Difference		
Central read	30.5	19.3	11.2	0.46 (0.31,0.69)	<0.0001
Central read controlling for cross-over[1]	32.4	16.4	16.0	0.28 (0.18,0.42)	<0.0001
Site read	22.3	8.3	14.0	0.40 (0.27,0.58)	<0.0001

ORR: A statistically significant improvement in ORR (complete objective response plus partial response) for vandetanib vs. placebo (odds ratio [OR]=5.48; 95% CI: 2.99, 10.79; P<0.0001), with 45.0% and 13.0% of patients, respectively, having an objective tumour response. Of the 13 patients in the placebo group who had an objective tumour response, only 1 patient had a response that began during the double-blind period; the remaining 12 responders in the placebo group had a response that began after the patient began receiving open-label vandetanib. The odds ratio for ORR for vandetanib versus placebo excluding open label vandetanib was 76.91; 95% CI: 16.68, 1366; P <0.0001.

OS: In the initial analysis performed after 48 deaths (15%) had occurred, there was no statistically significant difference between vandetanib and placebo on OS (HR=0.89; 99.98% CI: 0.28, 2.85; P=0.7115). The significance level for this first analysis was 0.02%, with corresponding 99.98% CIs presented. The assessment of OS was confounded by the use of subsequent therapy, as patients in the placebo arm who discontinued randomized treatment were unblinded and given the option to take open-label vandetanib. The influence of indolent disease, as described for the PFS data, should also be considered.

For the primary analysis of final OS (data cut-off of 7 September 2015), there was no statistically significant difference between vandetanib and placebo for OS (HR 0.99, 95% CI 0.72, 1.38, p=0.9750) (Table 16).[24]

Table 16. Summary of primary analysis of OS for final OS analysis (full analysis set).[24]

		Treatment effect (vandetanib:placebo)			
Randomised treatment	**N**	**Events, n (%)**	**OS hazard ratio***	**95.002% CI**	**2-sided P value**
Vandetanib, 300 mg	231	116 (50.2)	0.99	0.72, 1.38	0.9750
Placebo	100	52 (52.0)			

CI: confidence interval; OS: overall survival
*A hazard ratio <1.00 favours vandetanib over placebo.
The analysis was performed using a log rank test with treatment as the only factor.

However, it must be noted that in this study, 58/71 (81.7%) placebo-treated participants who discontinued randomized study drug received open-label vandetanib, including 52 (of 56) who discontinued due to tumour progression. Thus, with respect to the OS endpoint, the ZETA study does not, in reality, compare vandetanib to placebo but rather vandetanib with a 'watch and wait' strategy whereby vandetanib is initiated after RECIST progression.

Biochemical response rate: CTN and CEA (ITT population)[11]

Biochemical response rates for CTN and CEA, markers of activity of vandetanib in MTC, were evaluated as secondary efficacy endpoints in the pivotal ZETA study as pre-specified sub-analyses. CR was defined as complete normalization of the CTN level (≤10 pg/ml for men and ≤5 pg/ml for women) /CEA level (2.5 pg/ml) confirmed by a repeat assessment >4 weeks later. PR was defined as decrease in the CTN/CEA level of at least 50% from baseline confirmed by a repeat assessment >4 weeks later.

In the pivotal ZETA study, there was a statistically significant difference between vandetanib and placebo arm for both CTN and CEA response:

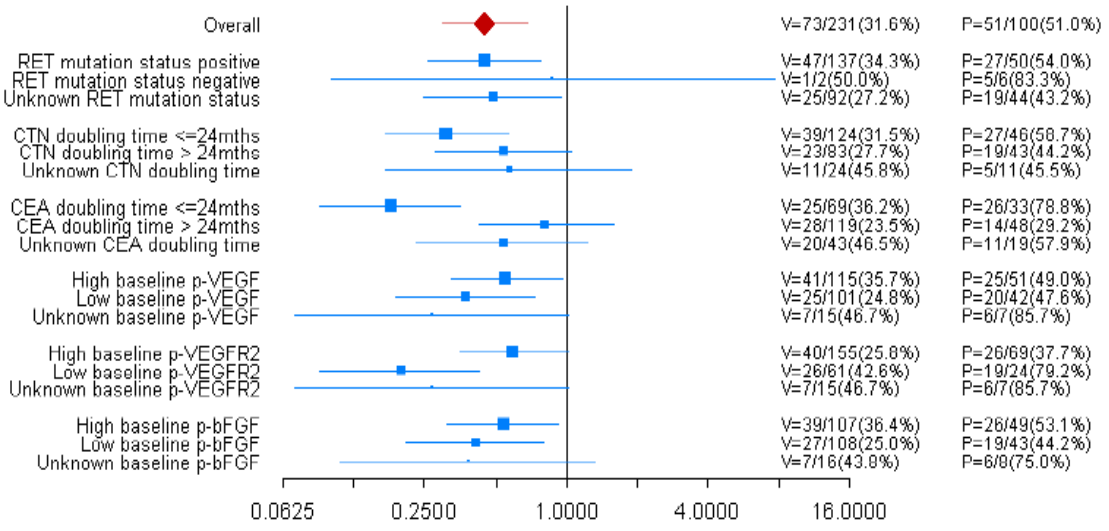
- CTN (CR plus PR): OR 72.86, 95% CI (26.22, 303.2), p<0.0001
- CEA (CR plus PR): OR 52.03, 95% CI (15.95, 320.3), p<0.0001.

CTN doubling time ≤ 24 months and CEA doubling time ≤24 months are known to be markers of poor prognosis and more aggressive disease. In ZETA, the efficacy of vandetanib on PFS was more marked in comparison with placebo in patients with CTN doubling time ≤ 24 months and CEA doubling time ≤24 months (statistically significant difference versus placebo in these subgroups) (Figure 4). As the global interaction test was not statistically significant at the 1% level (p=0.177), unplanned post hoc individual

interaction tests were performed with a 10% significance level for all factors included in the forest plots.

Additionally, the percentage of patients with ORR was higher in patients with CEA doubling time ≤24 months at baseline compared with CEA doubling time >24 months: 53.6% versus 37% respectively. The percentage of patients with ORR was higher in patients with CTN doubling time ≤24 months at baseline compared with CTN doubling time >24 months: 46.8% vs. 39.8 % respectively. CEA and CTN doubling times and tumour size have been linked to the rate of objective progression in MTC.

Figure 4. Pre-specified PFS sub-analyses in the ZETA study (ITT population).[16]



Quality of life was measured using the FACT-G instrument. Overall, scores between the two arms were similar. However, time-to-worsening pain (TWP) showed a statistically significant advantage for vandetanib compared with placebo (HR=0.61; 95% CI: 0.43, 0.87; P=0.0062).[16] In the EU label population, TWP was 11.1 months in the vandetanib arm, compared with 3.4 months in the placebo arm (HR=0.62, 95% CI 0.39, 0.99; P=0.45).[12]

4.8 Post-hoc subgroup analysis supporting the economic modelling

This section presents the post hoc analyses of the ZETA data used to support the economic modelling in section 5. Progressive and symptomatic MTC with biomarker change is the patient population expected to reflect UK clinical practise and is base case for this submission (referred to as restricted EU Label). Efficacy data for patients with aggressive

and symptomatic unresectable locally advanced or metastatic MTC is also presented as this subgroup as it was performed as a post-hoc analysis to support the EU label.

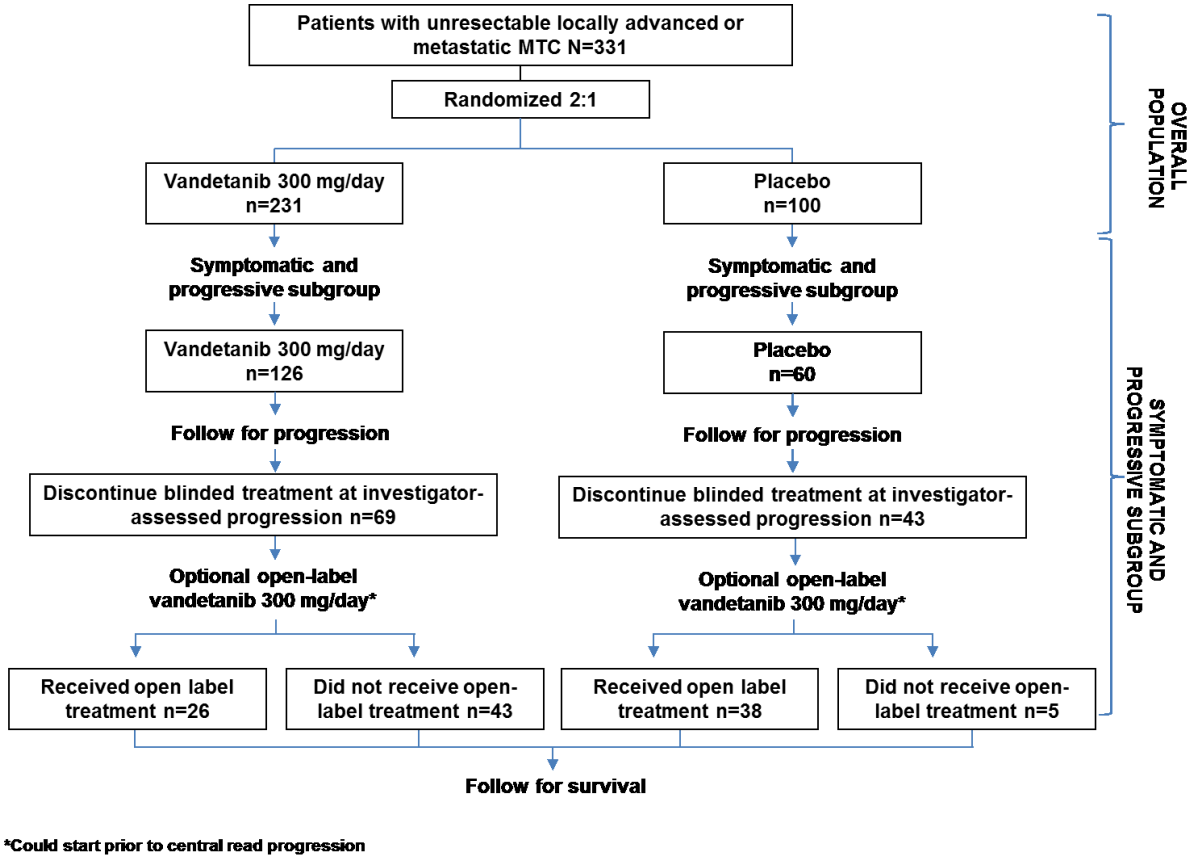
EU label population: Progressive and symptomatic patients

In the EU, vandetanib is specifically licensed for aggressive and symptomatic MTC in patients with unresectable, locally advanced or metastatic disease defined as progressive (documented progression within 12 months prior to enrollment) and symptomatic (at least one symptom at baseline, including pain score > 4, ≥10 days of opioid use, diarrhoea, flushing, fatigue, pain, nausea, dysphagia, dysphonia, respiratory symptoms, weight loss).

The regulatory history relating to the indication versus the ZETA trial population is described in section 2. Although patients in the ZETA trial were required to have unresectable, locally advanced or metastatic disease, there were no specific provisions to ensure that the disease was considered “aggressive”. Consequently, post hoc analyses have focused on subpopulations from this trial.

In the post-hoc analysis, “symptomatic and aggressive” included 186 patients out of the total trial population of 331, and was defined as documented progression 12 months prior to enrollment and at least one of the following symptoms at baseline: pain score > 4, ≥10 mg/day opioid use, diarrhea, flushing, fatigue, pain, nausea, dysphagia, dysphonia, respiratory symptoms, and weight loss.[12] Patient disposition in this subgroup is outline in Figure 5. The baseline characteristics and demographics of the symptomatic and aggressive group are outlined in Table 17, and are generally comparable to the demographics in the overall ITT population (Table 14).

Figure 5. Patient disposition in the subgroup of patients with symptomatic and progressive MTC from the ZETA trial.



*Could start prior to central read progression

Table 17. Baseline characteristics and patient demographics in post-hoc analysis of symptomatic and progressive ZETA patients.[12]

	Vandetanib 300 mg (n=126)	Placebo (n=60)
Male	63%	65%
Mean age, years	53.1	53.9
Locally advanced disease Metastatic disease	5.6% 94.4%	1.7% 98.3%
No prior systemic therapy for MTC ≥1 prior therapy for MTC	64.3% 35.7%	51.7% 48.3%
Hereditary disease Sporadic or unknown disease	8.7% 50.8%	3.3% 46.7%
RET mutation positive RET mutation negative RET mutation status unknown	59.5% 0.8% 39.7%	50.0% 10.0% 40.0%

MTC=medullary thyroid cancer.

After investigator assessment of progression, some patients underwent cross-over and received open-label vandetanib. In these cases, two methods were used to assess PFS excluding open-label vandetanib use after investigator assessed progression:[12] investigator-assessed PFS (based on RECIST criteria and generally considered to be closest to real-world practice) and 'central read' PFS excluding open-label vandetanib use with imputed

PFS based on a linear interpolation based on the RECIST score prior to open-label vandetanib.

Our analysis confirmed that the benefits of vandetanib vs. placebo in patients with aggressive and symptomatic disease (HR 0.47; 95% CI: 0.29, 0.77; P =0.0024) were similar to those observed in the overall population (HR=0.46; 95% CI: 0.31, 0.69; P=0.0001). The modelled median PFS benefit was also similar, with an improvement of 12 months (28 months in the vandetanib group vs.16 months in the placebo group) in progressive and symptomatic patients, compared with an improvement of 11 months in the overall population (30.5 months compared to 19.3 months, respectively). In the post-hoc sub-analysis, controlling for open-label vandetanib resulted in much shorter PFS in the placebo arm (Table 18).[12]

Table 18. PFS for progressive and symptomatic disease controlling for open label vandetanib.

	Median PFS, months Events, n (%)			
	Vandetanib (n=126)	**Placebo (n=60)**	**HR (95% CIs)**	***P* value**
Primary analysis	28.0 (46)	16.4 (35)	0.47 (0.29, 0.77)	0.0024
Central read, excluding open-label vandetanib with imputed PFS	30.1 (40)	11.1 (35)	0.32 (0.19, 0.54)	<0.0001
Investigator RECIST assessments	22.1 (62)	8.3 (41)	0.33 (0.2, 0.53)	<0.0001

Restricted EU label population

This subpopulation is a subset of the EU Label and is defined as patients with aggressive, progressive and symptomatic unresectable locally advanced or metastatic MTC as progressive (documented progression within 12 months prior to enrollment) and symptomatic (at least one symptom at baseline, including pain score > 4, ≥10 days of opioid use, diarrhoea, flushing, fatigue, pain, nausea, dysphagia, dysphonia, respiratory symptoms, weight loss) and with CTN and CEA doubling times ≤24 months at screening. This population closely reflects UK clinical practice for TKI treatment. Feedback received from two UK KOLs indicated that several methods are used to identify patients in need of

systemic treatment, one of which would include tumour markers CTN and CEA (Appendix 2) as their doubling times within 24 months are known to be markers of poor prognosis and more aggressive disease.[11]

In this cohort, there were [redacted] patients on vandetanib and [redacted] patients on placebo. The mean age on the vandetanib arm was [redacted] and [redacted] on the placebo arm (Appendix 6).

Table 19. Baseline characteristics and patient demographics in post-hoc analysis restricted EU Label population in ZETA

	Vandetanib ([redacted])	Placebo ([redacted])
Male	[redacted]	[redacted]
Mean age, years	[redacted]	[redacted]
Locally-advanced disease	[redacted]	[redacted]
Metastatic Disease	[redacted]	[redacted]
Prior Systemic Therapy for MTC	[redacted]	[redacted]
Hereditary disease	[redacted]	[redacted]
Sporadic disease	[redacted]	[redacted]
Unknown disease	[redacted]	[redacted]
RET mutation status	[redacted]	[redacted]
Positive	[redacted]	[redacted]
Negative	[redacted]	[redacted]
Unknown	[redacted]	[redacted]

The median PFS in the placebo arm was [redacted] compared with [redacted]. The median OS in the placebo arm was [redacted] compared with [redacted] for vandetanib. [redacted] patient in the vandetanib arm had a complete response, [redacted] had a partial response and [redacted] had stable disease by the end of treatment. [Appendix 5 and 6].

The mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.

Figure 6. KM curve for progression-free survival (based on central review): Restricted EU label population.

Table 20. Restricted EU label population: Results for PFS, OS (Appendix 6).

	Restricted EU label population	
	Vandetanib 300mg	Placebo
PFS, months[a]		
Change vs placebo		
P value		
Median OS, years		
Change vs placebo		
P Value		

MTC: medullary thyroid cancer; OS: overall survival PFS: progression-free survival; RECIST: Response Evaluation Criteria In Solid Tumors; SE: standard error. The mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time. [a] Median PFS (SE) reported for restricted EU Label based on centrally read images

In preparation for the NICE submission SanofiGenzyme undertook a series of post-hoc analyses to understand the data most relevant to the Decision Problem. In doing so SanofiGenzyme have replicated the EU label population analysis presented above.[12] The data reported in the Kreissl et al poster[12] could not be replicated exactly. In addition, exploratory analysis looked at the population of patients in the ZETA trial that had rapid

serum tumour biomarker doubling: CTN CEA doubling ≤24months. We understood this doubling time in CTN/CEA to represent a population of patients with MTC who had even more aggressive disease. This population was explored both as a subset of the ITT population and as a subset of the EU label population. In this case the definition of the EU label was in line with the Kreissl analysis.[12]

Figure 7 below show the K-M curve for the CTN/CEA patients that are a subset of the ITT population of the ZETA trial. The K-M curve shows clear and maintained separation of the arms in the trial. No crossover has been undone in these results.

Figure 8 below shows the K-M curve for the CTN/CEA patients that are a subset of the EU label population analysed from the ZETA trial. The K-M curve for this population might be imprecise as there are few patients i.e., fewer than [redacted] in one particular arm. Therefore, basing survival estimates on such small patient numbers would be very imprecise. Therefore, we used a regression model to estimate survival probabilities. This method borrows strength from events in the ZETA trial i.e., patients that were progressive, symptomatic and had rapid biomarker doubling. This is described in detail in Section 5.2 Model Execution. The OS data outputs from this regression model are those used to populate the economic model.

This population is very small: [redacted] vandetanib patients and [redacted] placebo patients. The difference in survival probability, curve separation, at the end of the observed data for both populations is about 0.3. We did attempt to undo cross-over in this population, applying the DSU recommended methods however, it was not possible to undo crossover in this population, in part because crossover appears to have occurred so early in this placebo arm.

This left us with a number of issues: 1) we can't submit on a patient population outside of the EU label - although this licence definition was not specified in the label but is an interpretation of the label wording – which means we need to consider the smaller population; 2) we can't undo crossover in the population we are interested in (see above); 3) because we can't undo crossover in this population, it was not possible to fit a parametric regression model to the observed K-M data; 4) due to relatively sparse data in the restricted

population producing K-M curves with long steps would lead to inaccurate estimates of the median survival function when extrapolated for the economic model.

Figure 7. Restricted EU Label population - Kaplan-Meier Plot Overall Survival.

Figure 8. ITT population with CTN/CEA doubling ≤24 months - Kaplan-Meier Plot Overall Survival

To estimate the OS and PFS curves for this base case subpopulation, the parametric regressions fit to the entire study population were applied by considering the two characteristics symptomatic and progressive disease and speed of tumour biomarker

increase, to create a regression equation that statistically modelled a population equivalent to the restricted EU population - see section 5.2 for more details.

Figure 9 presents the observed curve used in the economic model presented in section 5, superimposed with modelled survival curves. It is this parametric survival function that drives overall survival in the economic model. These parameterised curves appear to underestimate the benefit of vandetanib in the CTN/CEA doubling population from the ITT dataset (

Figure 7), even without undoing crossover. There is uncertainty regarding how well this function would fit the 'true' survival curves in the CTN/CEA doubling population from the EU label dataset with cross over undone.

Figure 9 Comparison of modelled (smooth solid line) with observed (dashed step line) overall survival (OS) in the restricted EU label population.

4.9 Meta-analysis

Currently, there is one Phase III trial supporting the use of vandetanib according to the EU label. Therefore, it is not possible to undertake a meta-analysis at this time.

4.10 Indirect and mixed treatment comparisons

NICE has identified cabozantinib as a comparator in this appraisal, as part of this submission, however SanofiGenzyme have not undertaken any indirect or mixed treatment comparisons to this treatment for two main reasons.

- Firstly, although the indicated population for both drugs appear similar (see below), there are in fact significant differences in the registration trials and evidence underpinning the labelled indication for each drug, which makes formal comparison impossible without access to individual patient-level data for both drugs. However, we do acknowledge that a single indirect comparison has been reported in the literature, which we will discuss below.
- Secondly, both drugs have been available in the UK via the CDF since license (2012 for vandetanib and 2014 for cabozantinib) and are not interchangeable. In clinical practice, both drugs are considered to have similar efficacy but differ on the basis of side effects, restrictions on concomitant medications and monitoring requirements, thus supporting the need for both treatment options to continue to be available for this rare patient population.[5]

We will discuss each of these elements in turn and will propose a pragmatic approach to the decision problem in this appraisal.

ZETA study (vandetanib) vs EXAM study (cabozantinib)

Study population

The ZETA study recruited a broad population of patients who had a previously confirmed histological diagnosis of unresectable, locally advanced or metastatic hereditary or sporadic MTC, with a WHO (World Health Organization) performance status 0–2. Patients were required to have serum calcitonin levels >500pg/ml, but there was no requirement for documentation of progressive disease.[13]

The EXAM study had patients that had histologically confirmed diagnosis of unresectable, locally advanced or metastatic MTC with an ECOG (Eastern Cooperative Oncology Group) performance status ≤2 and documented worsening of disease (progressive disease) confirmed by RECIST criteria at screening compared with a previous CT scan or MRI image done within 14 months of screening.[18]

As can be seen in Table 21, the indication for cabozantinib reflects the patients entered into EXAM, whereas for vandetanib, the indications are more restricted, both compared with cabozantinib and in relation to the trial design of ZETA.

Table 21. Side-by-side comparison of EU indications for vandetanib and cabozantinib.

Region	Vandetanib Indications	Cabozantinib Indications
EU/ UK	Vandetanib is indicated for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease.	Cabozantinib is indicated for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma.

The key driver of these restrictions was the occurrence of QT prolongation within ZETA and reports of torsades du pointes in the broader patient safety database. The fact that the ZETA trial was conducted at a time when there were no approved effective therapies for MTC meant that the regulatory authorities felt the need to approve a drug that showed such a clear benefit in terms of PFS. However, because in some patients MTC can be an indolent disease, they didn't want to expose otherwise 'healthy' patients to the risks of QT prolongation and so they restricted the label to those patients who really needed treatment.

From the sub-group analyses reported by Kreissl et al (2014),[12] we know that of the 331 patients entered into ZETA, 186 had symptomatic and progressive disease. Progressive disease was used as an alternative to aggressive disease and based on documented progression 12 months prior to enrolment. To be classified as symptomatic, patients had to have at least one of the following symptoms at baseline: pain score > 4, ≥10 mg/day opioid use, diarrhoea, flushing, fatigue, pain, nausea, dysphagia, dysphonia, respiratory symptoms, and weight loss.

In-house data shows that of the remaining patients, 139 were neither symptomatic nor progressive (i.e. had indolent MTC). In patients with indolent disease, disease progression may not be seen for many months/years, even without treatment. As a result, these patients are likely to have impacted the median PFS in both the vandetanib and placebo arms. Based on investigator assessment, the median PFS in patients with indolent non-symptomatic or non-progressive disease is markedly longer than in the full analysis set or the symptomatic/progressive sub-group (Table 22).

Table 22. PFS by Investigator Assessment, based on symptomatic and progressive patients compared with a cohort excluding symptomatic/progressive patients.[12 13]

Patient Cohort	Vandetanib	Placebo	HR (95% CI), p-value
Full Analysis Set (n=331)	22.3 months	8.3 months	0.4 (0.27–0.58), <0.0001
Symptomatic and Progressive (n=186)	22.1 months	8.3 months	0.33 (0.2–0.53), <0.0001
Excluding Symptomatic and Progressive (n=139)	NC	19.3 months	0.49 (0.27–0.91), p=0.0226

NC: not calculated

Prior therapies

Prior therapy was allowed in both studies although it is likely that the types of therapies used were different due to the treatment options available at the time of trial (i.e. not routine use of TKIs in ZETA whereas vandetanib was available to patients in the EXAM trial). In EXAM, 40% of patients had received at least one prior therapy and 25% had received >2. Overall, forty percent of patients had received prior anticancer therapy, and 21% received prior TKI treatment including 11% who had received prior vandetanib. Twenty-five percent had two or more systemic therapies (24% cabozantinb; 28% placebo).

In the ZETA trial, approximately 40% of patients had also received 1 or more prior therapies, although details are not available for how many received two or more. Details of the types of therapies received are not described, although it is likely that most patients received chemotherapy, as there were only a limited number of clinical trials ongoing at the time with TKIs in MTC, and agents such as sorafenib and sunitinib were only recently available for renal cell cancer and cabozantinib was only in Phase I trials.

Looking at the forest plots for both agents, it appears that the statistically significant improvement in PFS in ITT population was seen irrespective of line of therapy, although the impact of prior TKI therapy on the outcomes with cabozantinib are not shown.[13 18]

Post-progression therapies

In ZETA, at the time of data cut-off, 93 of 123 patients who had progressed (i.e., 76% of progressed patients) elected to receive open label vandetanib: 41/67 patients (61%) from the vandetanib arm and 52/56 patients (93%) of placebo patients.[13]

As a result, the OS data are more likely to show the impact of treatment with immediate vs delayed vandetanib, rather than be a true comparison of vandetanib vs placebo.

However, in the EXAM trial, cross-over to cabozantinib was not allowed, although patients could receive other post-progression therapies. Overall, 64% of placebo patients and 35% of cabozantinib patients received some form of post-progression therapy, including 16% and 10% in the two trial arms, respectively, who went on to receive vandetanib. Although these were censored at the time of the primary analysis and therefore did not impact the primary PFS analysis, it cannot be excluded that this analyses may be biased due to informed censoring, and thus impacted the result. Informed censoring usually leads to a longer observed PFS. The extensive use of post-progression therapy in the placebo arm is likely to impact the OS outcome.

Cross-over

In the EXAM trial, cross-over to cabozantinib was not allowed for patients randomised to placebo and patients who received any other subsequent anti-cancer therapies were censored at the time of the primary analysis.

In contrast, patients randomised to placebo in the ZETA trial could cross-over to vandetanib at the time of investigator determined progression, prior to central review of the scans and there was no censoring of data from patients crossing over to vandetanib in the placebo group. In ZETA, among 123 patients who developed tumour progression and were eligible to receive open-label treatment, 10% of vandetanib patients and 28% of placebo patients received open label treatment before central review and this was not censored at the time of the primary analysis.[13] In addition of the 100 patients on placebo, 79 received open label therapy as at final OS data cut, compared to 47.2% of vandetanib patients. As a result, the data for the primary PFS analysis in ZETA was confounded by patients receiving open-label vandetanib.[13] In the restricted EU label subpopulation, [redacted] of patients randomized to vandetanib continued open-label treatment while [redacted] of those initially on placebo crossed over to vandetanib.

The most obvious indication that cross-over affected the primary analysis is the 13% ORR in the placebo arm. When data from patients receiving open label vandetanib was censored, the ORR with placebo dropped to 1%, which is much more typical for this patient population.[12] Open-label vandetanib also extended the PFS of both the vandetanib and placebo arms: when the open-label patients are included the median PFS values are 30.5 months (estimated) and 19.3 months.[13] When the investigator assessment of progression is used, to exclude the open label patients, the median values are 22.3 months and 8.3 months.[12]

SanofiGenzyme wishes to include mention of the US Food and Drug Administration (FDA) analysis of the ZETA trial. It is common for the FDA to do its own analysis of submitted data as a process of verification. Specifically, for the ZETA trial, the FDA considered it to be appropriate to censor patients at the last RECIST assessment prior to discontinuation of the randomised drug, thereby excluding data from patients receiving open label vandetanib. In addition, the FDA censored patients at day 1 if they had no measurable disease at entry and also censored patients who received radiation therapy during the study (these patients were not censored in the primary analysis).

As a result of the differences in censoring, the PFS data in the US label, per the FDA analysis, for vandetanib versus placebo were 'not reached' (range 22.6 to 'not evaluable') versus 16.4 (8.3 to 19.7) months (HR: 0.35 [95% CI 0.24, 0.53]; P<0.0001). In addition, given the toxicity of vandetanib (principally QT prolongation) and the long natural history of the disease, the FDA felt that it was not appropriate to treat patients with indolent disease for potentially prolonged periods of time. As a result, data were analysed from patients who were symptomatic (HR: 0.31 [95% CI 0.19, 0.53] in favour of vandetanib; P<0.0001) and in patients who had progressed <6 months prior to enrollment (HR: 0.41 [95% CI 0.25, 0.66] in favour of vandetanib; P<0.0001). Data from both analyses were comparable with the ITT analysis.

Published indirect comparison

We are aware that an adjusted ITC was presented at the 2014 meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR),[43] involving an author from Sobi, the distributor of cabozantinib in the EU, Switzerland, Norway, Russia, and Turkey. This analysis, based on the ZETA and EXAM trials, found a positive trend in PFS in favor of cabozantinib in the subgroup of patients positive for the RET M918T mutation (HR 0.35; 95% CI 0.14 to 0.87).[43] In the overall patient population, the HR ranged from 0.61 to 0.72, depending on the analysis scenario.[43] The authors caution that these findings are based on limited evidence, and it should be noted that RET status is not routinely tested or funded by the NHS.[13 18] However, given the differences discussed above between the two trials, comparison of this kind should be interpreted with caution.

Summary

In summary, the differences in the trial population (Table 23), impact of prior and post-progression therapies and, most importantly, the cross-over allowed in the ZETA study make

it inappropriate to formally compare the two treatments, in the absence of head-to-head trials comparing vandetanib with cabozantinib.

Table 23. Key summary characteristics of the ZETA and EXAM trials

Characteristic	Vandetabib ZETA trial[13]	Cabozantinib EXAM trial[18]
Patient population	Measurable, unresectable, locally advanced or metastatic, hereditary or sporadic MTC	Histologically confirmed, unresectable, locally advanced or metastatic MTC with documentation of progressive disease within the previous 14 months
Previous TKI treatment, n (%)	N/A	25 (11.4%)
PS 1 or 2, n (%)	77 (33%)	95 (43.4%)
Crossover design	Yes	No

Application in clinical practice

According to the BTA guidelines,[17] targeted therapies are considered the modality of choice for inoperable progressive and symptomatic disease. Both vandetanib and cabozantanib are recommended based on their efficacy advantage over placebo,[13 18] and in particular in advanced, progressive and symptomatic disease where there are no other treatment options.[44 45]

The choice of initial drug is based on the toxicity profiles and licensing indications. In feedback received from two UK clinical experts, consideration is given to commencing TKIs provided the patient is of reasonable WHO PS and there are no significant comorbidities or contraindications (i.e. clinician would assess patient's concomitant medications, comorbidities and potential drug toxicities in order to select most appropriate first line therapy).

Most adverse events are those typically associated with inhibition of EGFR or VEGF receptors however each drug is associated with unique side-effect profile and restrictions based on concomitant medications and comorbidites (see section 4.12 and section 4.13)

Vandetanib has been associated with QT prolongation that has rarely led to torsades de pointes, and sudden death. As a result of this, EMA have placed some restrictions on the use of vandetanib. In the EU,[8] the risk of QTc prolongation and torsades de Pointes are highlighted, and patients treated with vandetanib must be given the patient alert card and be informed about the associated risks. On the other hand, cabozantinib has been associated with serious AEs such as perforations and fistulas, and haemorrhage. Gastrointestinal

perforations occurred in 3% and fistula formation in 1% of cabozantinib-treated patients.[8] Severe haemorrhage, including haemoptysis and gastrointestinal haemorrhage, which has sometimes been fatal, occurred in 3% of cabozantinib-treated patients. Patients should be monitored for signs and symptoms of bleeding.

The recommended dose of cabozantinib is 140 mg once daily (one 80mg and three 20mg capsules), and it is recommended that patients do not eat for at least 2 hours before and at least 1 hour after administration. The SmPC states that it should be expected that the majority of patients will require one or more dose adjustments (reduction [79%] and/or interruptions [72%]) due to toxicity. Patients should therefore be closely monitored during the first eight weeks of therapy.[42]

In terms of efficacy, in its review and re-reviews of both drugs, the CDF said it was not known whether one drug was superior to the other in terms of efficacy and "given these unusual circumstances of very different evidence bases and the fact that patient tolerance was an important issue, both drugs could be considered as offering the only systemic therapy for medullary thyroid cancer".[5] The CDF further commented that some comorbidities might result in one drug being preferred to the other drug and that if patients that did not have a comorbidity or tolerance issue which directed treatment to the other drug then the cheapest drug should be selected.[5]

Table 24 presents the efficacy results from the phase 3 trials for vandetanib and cabozantinib. The vandetanib data are presented for the full EU label population (subgroup of patients with progressive and symptomatic disease) and for the restricted EU label population (subgroup of patients with aggressive, progressive and symptomatic disease and CTN and CEA doubling within <24months), using central-assessed PFS (i.e. including data from patients who crossed over to vandetanib after progression on placebo). Only the overall response rates for the EU label population (43.7%) are reported for patients excluding the open-label scans.

Note that these data are from non–head-to-head comparisons and should be interpreted with caution. What appears the most likely interpretation of these results is that it is inappropriate to compare the two trials in this way.

Table 24: Efficacy data from the ZETA subgroups and EXAM trials

Endpoint	Vandetanib EU label population[12]	Vandetanib restricted EU label population	Cabozantinib (EXAM trial)[18]
Median PFS, months	28.0 (n=126)*	[redacted]*	11.2 (n=219)
Change vs placebo	11.6 months	[redacted]	7.2 months
P Value	*P*=0.0024	[redacted]	*P*<0.001
ORR, %	43.7%** (n=126)	[redacted]	28% (n=312)

CI=confidence interval; HR=hazard ratio; NR: not reported; ORR=objective response rate; PFS=progression-free survival.

*based on central read PFS. **based on excluding open label scans.

Therefore, based on UK clinical opinion (Appendix 2) and view of the CDF,[5] it may be reasonable to accept that both drugs have comparable efficacy but with differing side effect profile thus supporting the need for both treatment options for patients. Further, in cases where there are no restrictions to use of one drug over the other, the cheapest drug may be considered.[5]

In the economic section (section 5), the base case considers the cost-effectiveness of vandetanib to BSC as no formal comparison could be made with cabozantinib. However, based on the general views presented above, in the economic section we also present a simple cost comparison as an exploratory analysis. In this secondary analysis, vandetanib and cabozantinib both treatments are compared solely on the basis of drug acquisition cost, adverse events and monitoring costs.

4.11 Non-randomised and non-controlled evidence

SanofiGenzyme is aware of only one study of vandetanib in a non-randomised, non-controlled setting that is relevant to this submission. This was a French cohort study of patients in a routine practice setting (Table 25).[25]

Table 25. Relevant non-randomised and non-controlled evidence.

Objective	Population	Intervention	Comparator	Primary study reference	Justification for inclusion
To describe the toxicity profile and efficacy of vandetanib treatment when given outside any trial	68 locally advanced or metastatic MTC patients with either documented progression within 12 months or symptoms in France	vandetanib	NA	Chougnet 2015[25]	Provides evidence for the use of vandetanib in patients in the routine clinical practice. Patients were in close agreement with the EMA label.

Between August 2010 and February 2012, data were collected for 68 patients with MTC who received vandetanib in France. Selection criteria for treatment were based on international guidelines at the time of the study and were in agreement with the ongoing indications specified in the EMA label. Eight patients were excluded from the analysis: two patients who were treated for a cancer type that was not a MTC (one follicular thyroid cancer and one malignant teratoma), three patients who had already been treated with vandetanib in the phase III ZETA trial, and three patients who did not receive vandetanib (two patients died before initiation of treatment and one patient finally refused to be treated with vandetanib). The remaining 60 patients constituted the basis of the present analysis. The baseline characteristics are presented in Table 26.[25]

Most patients included in the study had advanced and progressive or symptomatic disease. They had similar characteristics to those included in controlled trials with vandetanib in terms of age and spread of disease, but had most likely a more severe clinical picture. Patient characteristics were in close agreement with the EU label.[25]

Table 26. French cohort study – baseline patient characteristics.

Patient characteristics		n (%)
N		60
Mean age		58 years
Age range		11–83 years
Male		39 (65)
Baseline ECOG		
	0 or 1	51 (85)
	2 or 3	7 (12)
	Unknown	2 (3)
Disease type		
	Sporadic	48 (80)
	Hereditary	6 (10)
	Unknown	6 (10)
Locally advanced MTC		4 (7)
Distant metastases		56 (93)
Presence of metastasis		
	Liver	32 (53)
	Mediastinal lymph nodes	47 (78)
	Lung	32 (53)
	Bones	39 (65)
	Neck	40 (67)
	Other sites	14 (23)
Number organs involved excluding thyroid		
	0 or 1	11 (18)
	≥2	49 (82)
Prior systemic therapy for MTC		
	0	49 (82)
	≥1	11 (18)

The median follow-up was 20 months, the median duration of treatment was 9.7 months (range 0.3 to 36), and 15 patients remained on treatment at the end of data collection. The median PFS observed was 16.1 months (Table 27).[25]

A complete response was observed in 1 patients (2%), partial response in 12 patients (20%), stable disease (SD) in 33 patients (55%), SD that was longer than 23 weeks in 23 patients (38%), and progressive disease (PD) in 7 patients (12%). Thirteen patients experienced a clinical improvement in their symptoms (decrease of diarrhoea or local cervical discomfort) after one month of treatment.[25]

Table 27. French cohort study – efficacy results.

Results		n (%)
Median follow up		20 months
Median duration of treatment		9.7 months
Treatment duration range		0.3–36 months
Discontinued due to disease progression		25 (42)
Dose reduction		
	Yes	20 (33)
	No	38 (63)
	Unknown	2 (4)
Best tumour response (n=53)		
	Complete	1 (2)
	Partial	12 (20)
Stable disease		33 (55)
Stable disease longer than 23 weeks		23 (38)
Progressive		7 (12)
Serum CTN decreased >50% (n=50)		33 (70)
Serum CEA decreased >50% (n=41)		19 (46)
Median PFS		16.1 months
Deaths at end of data collection		25
Median time to death (range)		12 month (0.3–26 months)

The adverse events results are presented in the combined adverse events table in section 4.12 (Table 33). Any grade AEs were common, with all patients experiencing at least one during therapy (Table 33). The most common AEs seen in this study were skin toxicity, diarrhoea, and asthenia. There was one death from vandetanib-induced cardiac toxicity.

In this trial, the number of discontinuations due to AEs (27%) was higher than the 12% reported in ZETA (Table 33). This may reflect the use of vandetanib by physicians relatively inexperienced in the use of the drug compared with use in a clinical trial setting, or it may suggest different patient populations between the trials. The likelihood of the patient populations being different, is supported by the data on duration of treatment; in this French ATU study median duration of treatment was 9.7 months (approximately 45 weeks), whereas in ZETA the duration was 90.1 weeks for the vandetanib treated patients and 39.9 weeks with placebo. This suggests that the ZETA patients appear to have more indolent disease.

This is the first report on the use of vandetanib in routine clinical practice outside the context of a controlled clinical trial. Enrolled patients had locally advanced or metastatic MTC with large tumor burden who had either symptomatic and/or progressive disease (more advanced disease compared to ZETA ITT population). The authors acknowledge the results for PFS and ORR differ from the ZETA trial and suggest this may not be significant or related in part

to the selection of patients or the assessment of efficacy. In conclusion, vandetanib showed effectiveness in advanced MTC and that the AE profile is manageable.

Quality assessment

Chougnet (2015) is an observational study[25]; the aspects for quality assessment of a randomised controlled trial are mostly not applicable (Table 28). In France, there was an opportunity to collect safety data on the use of vandetanib in real-life practice in all MTC patients who were given the drug under the umbrella of a temporary use authorisation (ATU). All patients treated with the drug under the ATU were selected for treatment according to the indications of the EMA label, were registered, then treated and followed according to local practices based on the recommendations of a multidisciplinary board. The study is a retrospective analysis of all patients who were enrolled in the vandetanib ATU in France. It's relevance to clinical practice in the UK has been discussed above.

Table 28. Quality assessment results for Chougnet 2015

	Chougnet 2015[25]
Was randomisation carried out appropriately?	NA – study included one treatment arm
Was the concealment of treatment allocation adequate?	NA – study was observational
Were the groups similar at the outset of the study in terms of prognostic factors?	NA – study included one treatment arm
Were the care providers, participants and outcome assessors blind to treatment allocation?	No
Were there any unexpected imbalances in drop-outs between groups?	NA – study included one treatment arm
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

4.12 Adverse reactions

Safety and tolerability data from the pivotal ZETA trial formed the basis of the regulatory submission and are presented in this section along with further evidence for the EU label population, i.e. patients with aggressive and symptomatic unresectable locally advanced or metastatic MTC, and from an additional two randomised studies.[16 46 47] There is limited data available for adverse reactions for the restricted EU label population. Adverse event data from the ITT Safety population is used for pharmacoeconomic modelling (Section 5). SanofiGenzyme expects the safety and tolerability of vandetanib when used in the restricted

EU label population to be consistent with the overall and EU label populations discussed here and summarised in Table 33.

Safety from ZETA ITT population

Results from the ZETA ITT safety population are summarised in Table 33. The median duration of total exposure was longer in the vandetanib group than in the placebo group (90.1 weeks vs. 39.9 weeks, full safety analysis population).[16] Nearly all patients in both groups experienced at least one AE (99.6% vandetanib vs. 90.9% placebo). More patients treated with vandetanib than placebo had at least one dose reduction or interruption (49.4% vs. 15.2%), grade 3 or higher AE (55.4% vs. 24.2%) and serious AEs (30.7% vs. 13.1%). A higher percentage of vandetanib patients discontinued the study due to AEs (12.1% vs. 3.0%; OR: 4.41; 95% CI: 1.31, 14.8). The percentage of reported fatal AEs was similar in both treatment arms (2.2% vandetanib vs. 2.0% placebo).

The most commonly reported adverse events are diarrhoea, rash, nausea, hypertension, and headache.[8] Diarrhoea, also a frequent symptom of MTC, was reported in 56% of vandetanib patients at all grades and was treated with standard medical care.[16] It was the most common grade 3 or higher AE reported in vandetanib patients (10.8%). Routine anti-diarrhoeals and frequently monitoring of QTc and electrolytes are recommended. Vandetanitb should be stopped in severe diarrhoea (grade 3 or higher) and resumed at a reduced dose upon improvement.[8]

QT related events were reported more frequently for vandetanib than placebo (15.6% vs. 4.0%). Vandetanib 300 mg was associated with a substantial and concentration dependent QTc prolongation (mean 28 msec, median 35 msec) which most often first occurred in the initial 3 months of treatment but continued to first occur after this time. Eighteen patients (7.8%) treated with vandetanib developed protocol-defined QTc prolongation grade 3 or higher. There were no reports of Torsades de pointes in the ZETA trial although it has been uncommonly reported in patients treated with vandetanib 300mg.[8 13] Frequent monitoring of ECG and electrolytes is required in patients treated with vandetanib to manage the risk of QT prolongation and the associated clinical consequences.[8]

Safety from the EU label symptomatic and aggressive subgroup analysis

Table 33 shows that the reported safety variables for the “symptomatic and progressive” subgroup are similar to those for the ITT safety population.[12]

[redacted]The most frequently reported AEs in vandetanib patients were [redacted]

- Seventy-seven patients (61%) receiving vandetanib and 14 patients (24%) receiving placebo reported AEs of grade ≥3
- A total of 16 patients discontinued treatment during the randomised phase as a result of an AE: 15 patients (12%) receiving vandetanib and one patient (2%) receiving placebo.

Safety and tolerability in comparison to cabozantinib

The ZETA and EXAM trials are not directly comparable due to differences in patient populations and trial design as already discussed in section 4.10 and section 4.13. Safety concerns were identified for both drugs in their respective trials which explain why neither drug is suitable for use in all MTC patients. The choice of one drug over another depends on patient circumstances including but not limited to cardiac and GI comorbidities.

Appendix 3 presents a side by side comparison of key safety data from both trials. Below is a summary of the key points for consideration.

- The most frequent adverse reactions of any grade associated with cabozantinib (experienced by at least 20% of patients) included diarrhoea, palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome, PPES), weight decreased, decreased appetite, nausea, fatigue, dysgeusia, hair colour changes, hypertension, stomatitis, constipation, vomiting, mucosal inflammation, asthenia, and dysphonia.[42]
- Patients treated with cabozantinib in EXAM had a high rate of dose reductions (79% vs. 9%) and interruptions (65% vs.17%) compared to placebo.[48]
- The most frequently reported Grade 3 or higher AEs are similar for vandetanib and cabozantinib. Key differences are QTc prolongation (8%) for vandetanib and PPES (13%) and GI perforation (3%) for cabozantinib.[13 48]
- Serious GI perforations and fistulas (sometimes fatal), intra-abdominal abscesses, GI haemorrhage and haemoptysis have been observed with cabozantinib treatment. Patients should be monitored for signs and symptoms of bleeding.[42]
- Five patients treated with cabozantinib experienced QTc prolongation (grade 1 and 2) in EXAM.[48] The SPC for cabozantinib states that periodic monitoring with on-treatment

ECGs and electrolytes should be considered for patients receiving cabozantinib with a history of QTc prolongation, in patients who are taking antiarrhythmics, or in patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances.[42]

Study of vandetanib plus patient outreach

Bastholt *et al* studied the role of a patient outreach programme on the tolerability of vandetanib in patients undergoing treatment for advanced or metastatic MTC (Table 29).[46]

Table 29. Summary of the vandetanib plus patient outreach study.

Objective	Population	Intervention	Comparator	Primary study reference	Justification for inclusion
Assess the effect of a patient outreach program on safety outcomes in patients receiving vandetanib.	205 patients with unresectable, locally advanced or metastatic MTC, performance status of 0 to 2 (WHO or Eastern Cooperative Oncology Group [ECOG]).	Vandetanib 300mg with outreach programme.	Vandetanib 300mg without outreach programme support.	Bastholt 2015[46]	Provides further evidence of tolerabilty for the use of vandetanib in patients in routine clinical practice.

This randomised, open-label, multicenter trial assessed the effect of a patient outreach program on safety outcomes in patients receiving vandetanib, who have previously confirmed, unresectable, locally advanced or metastatic MTC, and who have performance status of 0 to 2 (WHO or Eastern Cooperative Oncology Group [ECOG]), and in whom no standard therapy is available.[46] Patients were followed for 12 months unless meeting any criteria for discontinuation. The primary endpoint was the percentage of time a patient experiences ≥1 AE of CTCAE grade ≥2 during the first 12 months of treatment with vandetanib. If the patient discontinues prior to the 12-month time point for any reason, this endpoint will be the time a patient experienced at least one AE of CTCAE grade ≥2 as a percentage of the time the patient was receiving vandetanib.

A total of 205 patients were randomised to either vandetanib 300mg with (n=103) or without (n=102) the outreach program. The demographic characteristics in the overall population were well balanced between treatment arms. Overall, 194 (94.6%) patients had undergone

surgical and medical procedures, with 191 (93.2%) patients having undergone thyroidectomy. The mean duration of treatment in the vandetanib outreach arm was slightly longer than the vandetanib control arm (14.13 months vs. 13.87 months).

Results

The percentage of time (standard deviation [SD]) patients experienced grade ≥2 AEs was 51.7% (35.5%) in patients on vandetanib with the outreach program and 45.2% (36.3%) in the vandetanib group. This difference was not statistically significant (t statistic 1.29; 95% CI 3.44% - 16.37%; p = 0.199).[46]

Dose interruptions occurred in 112 (54.6%) patients (60.8% of the outreach group vs. 48.5% of the vandetanib control group) and dose reductions occurred in 82 (40.0%) patients (43.1% of the outreach group vs. 36.9% of the vandetanib control group). See combined AE table (Table 33).

Most patients reported at least one AE: 101 (99%) in the outreach arm vs. 93 (90.3%) in the vandetanib control arm. The most frequently reported AEs were diarrhoea, hypertension, rash and nausea. AEs of CTCAE grade 3 or higher were reported in 54 (52.9%) patients in the outreach arm versus 47 (45.6%) patients in the vandetanib control arm. The most frequently reported AEs of CTCAE grade 3 or higher were hypertension (16.7% vs. 10.7%), diarrhoea (6.9% vs. 2.9%), prolonged QT (3.9% vs. 4.9%), fatigue (2.0% vs. 2.9%) and rash (2.9% vs. 1.9%) (Table 33)

A total of 27 (26.5%) of patients in the vandetanib outreach arm and 30 (29.1%) of the vandetanib control reported a SAE (Table 33). The most frequently reported SAE was hypertension, which was reported by 2 patients in each group. AEs with an outcome of death were reported in 6 (2.9%) patients, 4 patients in the outreach arm and 2 patients in the vandetanib control arm (Table 33).

AEs were managed through the use of standard medical care, dose reduction, dose interruption, or permanent discontinuation of the treatment. The number of patients who discontinued treatment because of AEs was small (5.4%).

Strengths and limitations

This was a randomised study with a relatively large sample size considering the rarity of MTC. The trial population recruited for this study is similar to that expected in clinical practice. The types and severity of AEs were generally similar in both treatment arms and

consistent with the known safety profile of vandetanib and the mechanism of action of VEGFR and EGFR inhibition.

As the study was open-label, the primary endpoint result may be subject to ascertainment bias associated with the more frequent patient contact in the outreach arm. The number of patients who reported at least one AE was slightly larger for those patients participating in the outreach programme than for those who did not take part in the programme (99 vs. 90%). The possibility that intervention in this study could have encouraged participants to be more aware of their signs and symptoms, thereby increasing the likelihood of reporting of an AE, cannot be discounted.

Study 97

The Study 97 was designed to study the efficacy and safety of a low dose of vandetanib (150 mg; Table 30).[47]

Table 30. Description of Study 97.

Objective	Population	Intervention	Comparator	Primary study reference	Justification for inclusion
Assess the efficacy and safety of vandetanib 150mg and vandetanib 300mg.	81 patients with unresectable locally advanced or metastatic MTC with progressive or symptomatic disease.	Vandetanib 300mg	Vandetanib 150mg	Data on file (CSR and addendum)[47]	Provides further evidence confirming the tolerabilty of vandetanib 300mg.

This was a randomised, double-blind, international study to evaluate the safety and efficacy of vandetanib 150 and 300 mg/day in patients with unresectable locally advanced or metastatic MTC with progressive or symptomatic disease. The study is complete and due to be published soon.

The study consisted of a 14-month double-blind randomised phase (Part A) and an unblinded phase (Part B) where safety data was collected up to 2 years or 60 days following discontinuation if prior to 2 years. A total of 81 patients were randomised to receive study treatment: 40 in the vandetanib 150 mg group and 41 in the vandetanib 300 mg group. All

randomised patients received study treatment. The 2 treatment groups were generally balanced at baseline with respect to demographic and baseline characteristics. A total of 61 patients received 4 doses of open label vandetanib in Part B (100mg, 150mg, 200mg and 300 mg).

Efficacy results

Part A evaluated best objective response (BOR) and response duration. The results presented in Table 31.

Table 31. Study 97 – Part A, BOR and response duration (Full analysis set).

	BOR	Vandetanib 150mg N=40	Vandetanib 300mg N=41
Response, n (%)[a]	Total	[redacted]	[redacted]
	CR	[redacted]	[redacted]
	PR	[redacted]	[redacted]
Duration of response, Median (95% CI)[b]		[redacted]	[redacted]
Non-response, n (%)	Total	[redacted]	[redacted]
	Stable disease[c]	[redacted]	[redacted]
	Progressive disease	[redacted]	[redacted]
	Non-evaluable[d]	[redacted]	[redacted]

[a]The BOR was derived from the post-baseline assessments of objective tumour response within 14 months after randomisation, using the hierarchy CR>PR>SD>PD>NE.
[b]Duration of response was the time from the first documentation of CR/PR until the date of progression, or the last evaluable RECIST assessment for patients that did not progress or did not progress within 14 months of randomisation.
[c]Stable disease = Stable disease recorded at least 8 weeks after the date of randomisation.
[d]Patients with no available RECIST assessment were included as 'Non-Evaluable'

Safety

Part A and Part B evaluated the safety of both doses of vandetanib. These results are presented in Table 33.

[redacted]

Conclusions

The clinical benefit of vandetanib 300mg has already been established.

[redacted]

Quality Assessment

The study by Bastholt et al (2015)[46] was open label and the potential for bias has been discussed (Table 32). The randomisation process was conducted appropriately and both arms were similar in baseline characteristics and prognostic factors. An ITT analysis was performed with no evidence of unreported outcomes. There were no unexpected imbalances in drop outs.

Study 97[47] was appropriately randomised and blinded in Part A and Part B was open label (Table 32). An ITT analysis was performed with no evidence of unreported outcomes. There were no unexpected imbalances in drop outs and the study arms were similar for baseline characteristics and prognostic factors.

Table 32. Quality assessment results for Bastholt 2015 and Study 97.

	Bastholt 2015[46]	**Study 97[47]**
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	NA – study was open label	Yes Part A NA Part B – open label
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	No – study was open label	Yes Part A NA Part B – open label
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

Table 33. Combined safety results for vandetanib.[12 13 16 25 46 47]

	ZETA ITT Safety		EU label		Chougnet 2015[a]	Bastholt 2015[b, c]		Study 97 – A		Study 97 – B			
						Outreach	Control	Double blind vandetanib		Open label vandetanib			
	Vandetanib 300mg	Placebo	Vandetanib 300mg	Placebo	Vandetanib 300mg	Vandetanib 300mg	Vandetanib 300mg	150mg	300mg	100mg	150mg	200mg	300mg
n, (%)	N=231	N=99	N=126	N=60	N=60	N=103	N=102	N=40	N=41	N=5	N=9	N=8	N=39
Duration of treatment	90.1 weeks	39.9 weeks	88.6 weeks	37.1 weeks	9.7 months	14.1 months	13.9 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any AE	230 (99.6)	90 (90.9)			60 (100.0)	101 (99.0)	93 (90.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE	71 (30.7)	13 (13.1)				27 (26.5)	30 (29.1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths	5 (2.2)	2 (2.0)			25 (41.7)	4 (3.9)	2 (1.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dose reduction or interruption	114 (49.4)	15 (15.2)											
Dose Reduction	83 (35.9)[f]	3 (3.0)[f]	14 (33)	2 (3)	20 (33.3)	NR (43.1)	NR (36.9)	[redacted]	[redacted]				
Dose Interruption	109 (47.2)	15 (15.2)				NR (60.8)	NR (48.5)	[redacted]	[redacted]				
Discontinued - AE related	28 (12.1)	3 (3.0)	15 (12)	1 (2)	16 (26.7)	NR (5.4)[j]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued - Disease progression related					25 (41.7)					[redacted]	[redacted]	[redacted]	[redacted]
AE Grade 3 or higher	125 (55.4)	24 (24.2)	77 (61)	14 (24)	25 (42)	54 (52.9)	47 (45.6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Most frequent Grade 3 or higher AEs[g]												
Diarrhoea	25 (10.8)	2 (2.0)	4 (6.7)	NR (6.9)	NR (2.9)	1 (2.5)	2 (4.9)					
Hypertension	17 (7.4)	0 (0)	2 (3.3)	NR (16.7)	NR (10.7)	[redacted]						
QTc prolonged	18 (7.8)	1 (1.0)	3 (5.0)	NR (3.9)	NR (4.9)	[redacted]						
Fatigue	13 (5.6)	1 (1.0)	3 (5.0)[h]	NR (2.0)	NR (2.9)							
Decreased appetite	9 (3.9)	0 (0)										
Rash	8 (3.5)	0 (0)	6 (10.0)[i]	NR (2.9)	NR (1.9)							
Asthenia	6 (2.6)	1 (1.0)										
Dyspnoea	3 (1.3)	3 (3.0)										
Back pain	1 (0.4)	3 (3.0)										
Syncope	0 (0)	2 (2.0)										
Photosensitiviy			2 (3.3)									
Nausea/vomiting			2 (3.3)									
Dermatitis anceiform												
Hypocalcaemia												
Hyponatraemia												
Spinal cord compression												

AE = adverse event, SAE = serious AE, NR = not reported

[a] Adverse events were graded according to National Cancer Institute Common Terminology Criteria of Adverse Events, version 4, after reading the patient's file. Percentages are expressed for intention to treat (60 patients).

[b] Some AE are only reported as percentages, patient numbers are unknown.

[c] The results include AEs with an onset date on or after the first dose and up to and including 60 days following the last dose. If the patient remained on the study medication after 12 months, only new SAEs were collected until 60 days after the last dose of the study medication.

[d] Percentages are calculated from number of patients who received treatment in Part B.

[redacted]

[f] A patient can be dose reduced more than once, but will be counted only once at each reduced dose. Original dose level 300mg daily, 1st dose reduction to 200mg daily, 2nd dose reduction to 100mg daily.

[g] ZETA ITT and Bastholt 2015 Grade 3 or higher AEs occurring at an incidence ≥2% in either arm, Chougnet 2015 occurring at an incidence ≥3%, Study 97 Part A occurring at an incidence of ≥5% in either arm, Study 97 Part B occurring at an incidence of ≥5% in vandetanib 300mg arm and EU label population no information is available for individual AEs Grade 3 or higher.

[h] Fatigue/asthenia

[i] Rash/folliculitis/dry skin

[j] AE related treatment discontinuations were not reported for each individual arm, total result presented.

Overview of vandetanib safety in relation to the decision problem

The safety and tolerability of vandetanib compared to placebo assessed in clinical trials demonstrated vandetanib was generally well tolerated.[13 49] Further evidence from a French observational study representing "real world" use, Bastholt 2015 and Study 97 showed no unexpected safety issues.[25 46 47]

Adverse events associated with vandetanib treatment are consistent with its pharmacological action as an inhibitor of VEGFR and EGFR, and can be managed with standard clinical practice, or by stopping or reducing the dose. The management of the risk of QT prolongation and associated clinical consequences are particularly important and addressed in the marketing authorisation.[8]

The higher AE rate for vandetanib compared to placebo in the ZETA trial must be viewed in the context of the overall rates of adverse reactions in both treatment groups, the good manageability of the majority of adverse reactions, the lengthy therapeutic period with vandetanib, and considering the severity of the disease. By dosing to tolerance, the starting dose of 300 mg can be reduced as necessary to manage side effects and to avoid discontinuing the drug, maintaining the maximum possible efficacy benefit over many months to years.

Patient tolerance is an important issue for both vandetanib and cabozantinib, especially since indicated patients already have a high disease burden impacting their QoL. To date both vandetanib and cabozantinib have been included in the CDF as they are not suitable for use in all patients and could be considered as offering the only systemic therapy for MTC.[5]

4.13 Interpretation of clinical effectiveness and safety evidence

There is a strong scientific rationale for the use of vandetanib in patients with MTC, based on the inhibition of key molecular targets (RET, vascular endothelial growth factor receptor [VEGFR]-2, and epidermal growth factor receptor [EGFR]), all of which play a role in the pathogenesis of MTC. Analyses of relevant subgroups in ZETA support the benefits of vandetanib in populations analogous to the indicated population of patients with aggressive and symptomatic MTC and in particular those with short doubling times for CEA and CTN, who might benefit most from treatment with vandetanib.

In this section we address a number of elements of the narrative that supports this submission for vandetanib per the EU label: high level of unmet need; vandetanib and cabozantinib are both options for patients with MTC; multiple PFS data cuts for vandetanib;

vandetanib PFS analysis and routine clinical practice; ORR results; vandetanib and cabozantinib safety profiles; CDF scoring and evaluation of vandetanib and cabozantinib; cross-over and implications for placebo data; the role of RET mutation in clinical decision making and sequencing vandetanib and cabozantinib.

High level of unmet need

Vandetanib was the first systemic therapy to demonstrate a significant clinical benefit, gain marketing approval and address a significant unmet need in the treatment of advanced MTC whilst maintaining a manageable tolerability profile. Prior to vandetanib BSC was the standard management of advanced MTC patients, and this is still the case in patients where systemic treatment is not suitable. Surgery is currently the only curative option for MTC, but only provides palliative therapy in patients with unresectable locally advanced or metastatic disease. MTC is unresponsive to radiotherapy and chemotherapy has proven ineffective in advanced MTC, producing low response rates (15%–20%) and short durations of response.[22] The patients relevant to this submission are the most advanced patients with a significant disease burden and increased symptoms, including pain, diarrhoea, nausea, and fatigue, as well as the effects of metastasis on specific organ systems (including brain, lung, bones, liver and spinal cord) which can substantially impair the patient's QoL. They have a life expectancy of less than 2 years.[18] In such patients vandetanib has the potential to significantly delay the advancement of their disease, and thus to improve their QoL compared to the alternative best supportive care.

Vandetanib and cabozantinib are both options for patients with MTC

SanofiGenzyme does not consider cabozantinib to be a comparator to vandetanib, but instead agrees with the opinion of the CDF that both drugs should be available. There have been no head-to-head trials comparing vandetanib with cabozantinib, and due to the different study designs and patient populations in ZETA and EXAM it is inappropriate to compare across studies (see below and section 4.10).

Given the differing tolerability profiles of vandetanib and cabozantinib, the underlying baseline characteristics and comorbidities of each patient need to be taken into consideration by the physician when choosing the appropriate therapy for a patient.

Vandetanib and cabozantinib safety profiles

Due to the different study designs and patient populations, it is not appropriate to directly compare the tolerability profile of vandetanib and cabozantinib in the absence of a head to head trial.

The safety profile of vandetanib has been reported for over 2000 patients with MTC as well as across a range of other tumour types. Most of the adverse events (AEs) are those typically associated with inhibition of EGFR or VEGF receptors and grade 3/4 AEs consist principally of diarrhoea, hypertension, QT prolongation and fatigue.[8 11]

In the ZETA study, 31 out of 331 patients discontinued treatment during the randomized phase because of an adverse event: 28 (12%) receiving vandetanib and 3 (3%) receiving placebo. The most common adverse events leading to discontinuation of vandetanib were asthenia (1.7%) and rash (1.3%). More patients required dose reduction of vandetanib compared with placebo for adverse events or QTc prolongation (35% v 3%).[16]

Adverse events such as diarrhoea, rash, nausea, and hypertension occurred in more than 30% of patients receiving vandetanib with the most frequently reported grade 3/4 AEs being diarrhea (11%), hypertension (9%), QT prolongation (8%) and fatigue (6%).[11]

In the EXAM study, 16% (35 of 214) of cabozantinib-treated patients and 8% (9 of 109) of placebo-treated patients discontinued treatment due to an adverse event.[18] Six percent (12 of 214) discontinued cabozantinib treatment for reasons other than PD, AE, or death; 11 of these patients had ongoing AEs at the time of treatment discontinuation, although AEs were not reported as the primary reason for treatment discontinuation in these patients. In addition, 65% (140 of 214) and 17% (19 of 109) had dose interruptions due to AEs, while 79% (169 of 214) of cabozantinib-treated patients and 9% (10 of 109) of placebo patients had dose reductions. In patients receiving cabozantinib, two dose reductions were required in 41% of patients. The median time to first dose reduction was 43 days, and to first dose interruption was 33 days.

The most frequently reported grade 3 or 4 AEs with cabozantinib were diarrhea (15.9%), palmarplantar erythrodysesthesia (12.6%), and fatigue (9.3%). AEs including hypertension, hemorrhage, fistula formation, and GI perforation, occurred more frequently among cabozantinib-treated patients.[18]

Vandetanib has been associated with QT prolongation that has rarely led to Torsades de pointes, and sudden death. Within ZETA, 19 patients randomised to vandetanib experienced QT prolongation (there were no reports of Torsades du pointes).[16] As a result the US and EU prescribing information contain information to manage this and minimise the risk. The availability of the REMS in the US, and the RMP in Europe, may make it easier to use vandetanib as it provides detailed guidance to improve safety.

In the EU, where vandetanib has a black triangle warning, an ECG, and levels of serum potassium, calcium and magnesium and thyroid stimulating hormone (TSH) should be obtained at baseline, at 1, 3, 6 and 12 weeks after starting treatment and every 3 months for at least a year thereafter. Frequent ECG monitoring of the QTc interval should be continued. Serum potassium, serum magnesium and serum calcium should be kept within normal range to reduce the risk of ECG QTc prolongation.[8]

In the US, the advice is similar. it is recommended that ECGs should be obtained to monitor the QT interval at baseline, and then at 2–4 weeks and 8–12 weeks after starting treatment, and every 3 months thereafter. In the event of QT prolongation, treatment should be interrupted and re-started at a lower dose level when the QT interval returns to normal. In order to minimise the occurrence of QT prolongation and Torsades du points, the FDA also recommend that hypocalcaemia, hypokalemia and hypomagnesaemia should be corrected prior to vandetanib administration and should be periodically monitored.

In order to ensure physicians are aware of the guidance on QT prolongation, they should review the vandetanib educational materials and be certified to participate in the restricted distribution (REMS) programme. They only need to register for this once and not for each patient individually.

Cabozantinib in also associated with serious adverse events, as described above. In the US, the Prescribing Information carries a black box warning as the drug has been associated with perforations, fistulas, and hemorrhage. It is recommended that cabozantinib should be discontinued if perforations or fistulas occur and patients should be monitored for signs and symptoms of bleeding.[8] Likewise, in Europe, cabozantinib has a black triangle warning for safety issues.

In addition, it should be expected that a majority of patients treated with cabozantinib will require one or more dose adjustments (reduction and/or interruption) due to toxicity.[42] The

EU SmPC recommends that patients should therefore be closely monitored during the first eight weeks of therapy:[42]

> *As most events can occur early in the course of treatment, the physician should evaluate the patient closely during the first eight weeks of treatment to determine if dose modifications are warranted.*
>
> *The occurrence of some serious adverse reactions (like GI fistula) might be dependent on the cumulative dose and might present in a later stage of treatment.*
>
> *Dose reductions and dose interruptions occurred in 79% and 72%, respectively, of cabozantinib-treated patients in the pivotal clinical trial. Two dose reductions were required in 41% of patients. The median time to first dose reduction was 43 days, and to first dose interruption was 33 days.*

Based on the EU SmPC,[42] patients receiving cabozantinib should also be monitored for QT prolongation. Section 4.4 states:

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

Given the differing tolerability profiles of vandetanib and cabozantinib, the underlying baseline characteristics and comorbidities of each patient need to be taken into consideration by the physician when choosing the appropriate therapy for a patient.

CDF scoring and evaluation of vandetanib and cabozantinib

The CDF has previously reviewed vandetanib and cabozantinib, with an updated review of vandetanib in 2015. At the time of the original cabozantinib assessment, the CDF awarded that drug an overall score of 3B (PSF: 4; OS: 0; QoL: 0; Toxicity: -1; unmet need: 0), compared with a score of 6B for vandetanib (PSF: 7; OS: 0; QoL: 0; Toxicity: -1; unmet

need: 0). The difference in favour of vandetanib was due to the score for PFS. Following the reassessment in 2015, the overall score for vandetanib was increased to 9B (PSF: 7; OS: 0; QoL: 1; Toxicity: -2; unmet need: 3). The CDF assessment report at that time only recorded the individual scores, unchanged from the original assessment, but without an unmet need or overall score.[5 6]

The role of RET mutation in clinical decision making

In England and Wales, vandetanib is indicated for patients with aggressive and symptomatic MTC in patients with unresectable locally advanced metastatic disease. The EU label also states that "for patients in whom RET mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision."[8]

The indication for the use of vandetanib does not specify the need for *RET* mutation testing. The benefits in PFS from the ZETA trial ITT population were statistically significant in the subgroup of patients who were *RET* M+, and *RET* unknown. The data for *RET* negative patients appear less favourable for vandetanib, although there were only 8 patients with RET M- tumours (2 patients in the vandetanib arm). It should also be noted that RET mutation analysis is not currently funded by the NHS and therefore is not undertaken. Therefore, clinical decision making is not currently influenced by RET mutations status.

Sequencing vandetanib and cabozantinib

There is no established RCT data assessing the efficacy of vandetanib following cabozantinib.

Within the ZETA trial, approximately 40% of patients had received 1 or more prior therapies. Although details of the types of therapies received are not described,[16] it is likely that most patients received chemotherapy, as there were only a limited number of clinical trials ongoing at the time with TKIs in MTC, and agents such as sorafenib and sunitinib were only recently available for renal cell cancer. Cabozantinib was only in Phase I trials at that stage.

The EXAM trial started almost two years after the ZETA trial, and in this trial 20% of patients had received prior TKI therapy (including 11% who received prior vandetanib). Data from the Forest plot of the primary publication,[18] show that the drug significantly improved PFS irrespective of the number of lines of therapy, although the data specifically relating to prior use of TKIs or vandetanib are not reported.

Summary and conclusions

SanofiGenzyme has identified a subgroup of patients who, based on pre-specified sub-analyses and post hoc analyses of data from the ZETA trial in response to regulatory requests, are likely to experience maximum clinical benefit from vandetanib: those patients with aggressive, progressive and symptomatic MTC with biomarker (CTN and CEA) changes (described throughout as the restricted EU label population). Data for these patients form the focus of the pharmacoeconomic evaluation in section 5.

The choice of comparator for vandetanib is BSC, rather than the other licensed TKI, cabozantinib. Based on the view of clinical experts as well as the recommendations of treatment guidelines and the guidance of the CDF, both vandetanib and cabozantinib should be available for the small number of patients with advanced MTC for whom there are no other treatment options. Further, in the absence of an appropriately-powered, randomized, controlled head-to-head study of the two drugs, there are clear clinical justifications for not undertaking a direct comparison of data from the ZETA and EXAM trials, including the impact of crossover in the ZETA trial on outcomes in the placebo group, the levels of indolent disease in the ZETA trial versus EXAM study, and the impact of prior and post-progression treatments.

Table End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Patients with unresectable locally advanced or metastatic medullary thyroid cancer have very short life expectancy if treated with only best supportive care. 5-year survival is reported to be 25%[1]; and median overall survival is 2–3 years in patients with distant metastatic disease.[1] In EXAM study, in which placebo arm was not confounded by cross over to active treatment, patients had median OS of 21.1 months.[18] The OS survival of the placebo arm in this study could be considered a proxy for patients who receive no active treatment and whose disease is reflection of natural progression of aggressive disease.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	In the restricted EU label population, subgroup of progressive and symptomatic with biomarker change, increases of more than 3 months are seen. Treatment with vandetanib results in difference of 14.9 months PFS over placebo (despite crossover effect) which drives a 1.7 LYG over BSC (see section 5).
The treatment is licensed or otherwise indicated for small patient populations	There are currently [redacted] patients treated with vandetanib in England via CDF funding. Should NICE recommend vandetanib for routine use, we estimate that this number is likely to remain stable over the next 5 years (see section 6).

4.14 Ongoing studies

In addition to the ZETA trial and its sub-analyses in line with the EU label described in section 4, there are four other trials of vandetanib relevant to its use in the treatment of symptomatic and aggressive MTC (Table 34).

Table 34. Summary of completed and ongoing studies from which additional evidence will become available for vandetanib in the treatment of symptomatic and aggressive MTC (as of 31 January 2017)

Study (& CT.gov identifier)	Study name	Study numbers	Status	Key dates
ZETA NCT00410761	An International, Phase III, Randomized, Double-Blinded, Placebo-Controlled, Multi-Center Study to Assess the Efficacy of ZD6474 (ZACTIMA™) Versus Placebo in Subjects With Unresectable Locally Advanced or Metastatic Medullary Thyroid Cancer Publication of Primary Endpoint: Wells SA, Jr., Robinson BG, Gagel RF *et al*. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *J Clin Oncol* 2012;30:134-141.	n=331	This study is ongoing, but not recruiting participants (Completed for primary outcome)	Publication of follow-up data expected Q3/Q4 2017
Caprelsa 104 NCT01945762	European, Observational, Prospective Study to Evaluate the Benefit/Risk of Vandetanib in RET Mutation Negative and Positive Patients With Symptomatic, Aggressive, Sporadic, Unresectable, Locally Advanced/Metastatic Medullary Thyroid Cancer	n=80	This study is currently recruiting participants.	Estimated study completion date October 2018 Publication plan to be confirmed

5. Cost effectiveness

Summary and key points

A cost-effectiveness analysis of vandetanib compared with best supportive care (BSC) in the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease who also have serum tumour biomarker (CTN/CEA) doubling of ≤24 months is presented from the perspective of the NHS in England and Wales.

Complete overall survival data from the ZETA trial are not available: patients were still alive at the most recent data cut. Thus, to allow projections to the entire population across a longer time horizon, a survival partition model was developed including parametric extrapolation. This model was implemented using an Excel-based DICE simulation. The DICE cohort model enabled us to address the decision problem for the restricted EU label cohort.

The model uses data derived from the ZETA study to estimate most inputs. The time horizon of 20 years is used to ensure coverage of the entire survival curve and a discount rate of 3.5% is applied to benefits and costs, in line with the NICE reference case. Inputs include drug acquisition costs for vandetanib (with a confidential discount applied), rates of grade 3 or 4 adverse events, monitoring costs associated with vandetanib, post-progression costs and palliative care costs applied in the last month prior to death

The DICE model addresses the decision problem for the restricted EU label cohort: Patients with aggressive and symptomatic unresectable locally advanced or metastatic MTC defined as progressive (documented progression within 12 months prior to enrollment) and symptomatic (at least one symptom at baseline, including pain score > 4, ≥10 days of opioid use, diarrhoea, flushing, fatigue, pain, nausea, dysphagia, dysphonia, respiratory symptoms, weight loss) plus CTN and CEA doubling times within 24 months of screening.

This subset of patients reflects patients currently treated with TKIs in England, i.e., patients identified clinically as having most potential to benefit from active treatment. This also reflects the licence recommendation of selecting patient with most urgent need of treatment. It should be noted that this subset of patients included [redacted] patients on vandetanib and [redacted] patients on placebo. We acknowledge that these patients' numbers give rise to uncertainty in the estimates presented in this section, however, this is not

unusual in very rare diseases.

A very high proportion of patients randomised to both vandetanib and placebo arms in the trial went on to receive open-label vandetanib in post-progression disease. In the restricted EU population over 80% of the placebo arm crossed-over and received open-label vandetanib. Because of this, a number of post-hoc analyses, data manipulation/extrapolations and modelling approaches have been undertaken to support this submission.

Depending on the proportion who crossover from BSC or continue vandetanib post-progression, and the dose distribution afterwards, the incremental cost-effectiveness ratio (ICER) varies between [redacted]; and between [redacted] and [redacted] for the restricted EU label (base case). No adjustment is made for the crossover in these results and thus underestimates the treatment benefit of vandetanib over placebo. Despite this, the clinical benefit in this group of patients is almost 2 years (1.730 LYG).

The analyses presented in section 5 are associated with degree of uncertainty due to the extensive cross-over that could not be undone statistically. However, the clinical benefit in the restricted EU label population is clear. Independent of crossover, vandetanib results in remarkable improvement in OS.

5.1 Published cost-effectiveness studies

A simple pragmatic search in PubMed was performed based on article titles for cost-effectiveness studies in MTC using search terms ‘cost’, ‘economic’, ‘value’ and MTC or vandetanib or carbozantinib or BSC. No prior economic models in MTC were identified from the literature. Therefore, a *de novo* model was prepared to provide an assessment of the likely economic implications of using vandetanib per its licensed indication.

5.2 De novo analysis

Patient population

The base case population for this economic analysis is the **restricted EU label population.** Defined in the clinical section, see section 4.8 this is the population of patients with aggressive and symptomatic unresectable locally advanced or metastatic MTC defined as progressive (documented progression within 12 months prior to enrollment) and symptomatic (at least one symptom at baseline, including pain score > 4, ≥10 days of opioid use, diarrhoea, flushing, fatigue, pain, nausea, dysphagia, dysphonia, respiratory symptoms, weight loss) plus CTN and CEA doubling times within 24 months of screening.

This population reflects patients in treated in the UK who are those with most potential to benefit from active TKI treatment, as treatment is reserved for patients with rapidly progressing disease. Feedback received from two UK KOLs indicated that several methods are used to identify patients in need of systemic treatment, one of which includes assessment of the tumour markers CTN and CEA (Appendix 2) as their doubling times within 24 months are known markers of poor prognosis and more aggressive disease.[11]

Model structure

The model uses the simple survival partitioning technique commonly applied in oncology health technology assessments, with 1 month cycles. In this approach, the cohort is subdivided into three states: progression-free, progressed and dead. It is assumed (in accordance with the randomized clinical trial) that all patients begin in the progression-free state. Portions of the population are then transferred to the other two states by calculating the proportion who are still alive using the OS function, and the proportion who have not yet progressed using the PFS function; the difference between the two is the proportion in the progressed state. At each apportioning, values (in terms of quality of life and costs) are applied to each state and the resulting accruals are accumulated as outputs. This happens cyclically until the end of the time horizon.

This survival partition model was implemented using DICE simulation.[50] Training has been offered to the academic review group and the NICE technical team. The DICE simulation is an approach that involves two fundamental concepts: *Events* and *Conditions*:

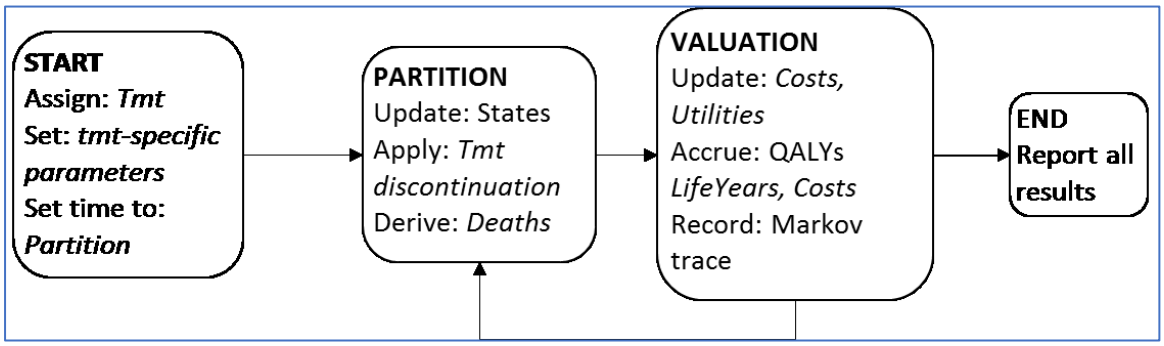
- An event in a DICE model reflects any aspect of the problem that happens at a point in time and has consequences.
- Conditions reflect aspects of the problem that persist over time (e.g., states).

The three states in this model are represented using a condition for each one: *Progression-free*, *Progressed*, and *Dead*. The level of each condition represents the proportion of the initial cohort in that state at any one time (i.e., the reading from the OS and PFS curves and the subtraction to obtain *Progressed* proportion). Other conditions keep track of the proportion of patients on treatment, the parameters of the survival functions, the utilities and various costs, inputs related to adverse events (AE) and the components of time.

The full set of conditions is listed on the Conditions worksheet in a table (See Appendix 4) that has two active columns: the first displays each condition's unique name and the second contains its initial level (if known at the start, for many it is set to zero because it is initialized during the run in the *Start* event).

There are four events in the model: *Start*, *Partition*, *Valuate*, and *End* (Figure 10). These are listed at the top of the Events worksheet, together with their initial time of occurrence and the name of the table that specifies their consequences. Each *Event* table contains rows that list the type of item (event, condition, or output) affected, its unique name and an expression, written as plain text[1] that articulates the consequence (e.g., the expression |OverallSurvival|-|ProgressionFree|[2] computes the proportion in *Progressed* state at this time).

Figure 10. Schematic of DICE simulation.



The *Start* event (see Appendix 4) happens at the beginning of simulation time (*Time*=0). It starts by assigning treatment (initially BSC alone, then vandetanib plus BSC) to all patients in the *Progression-Free* state and initializes all conditions that are specific to treatment. Everyone is assumed to begin on treatment (i.e., *OnTmt* is set to 100%). The conditions pertaining to the occurrence of AEs are also initialized. The *Partition* event is then set to occur at *Cycle* time.

[1] Of note, since the expressions are written as text, Excel will not detect syntax errors or other kinds of mistakes (e.g., referring to a non-existent named range, forgetting a parenthesis) that it would normally be able to flag as problems. If changes are made, the expressions must be carefully verified.
[2] The pipes | | identify Conditions

The survival partitioning is implemented in the *Partition* event, which occurs at the end of each cycle. In this event, the OS function is read at that time or at the mid-point of the cycle just ending if half-cycle correction is on. The same is done for the PFS function. These proportions are used to compute the fraction who have progressed. Before deriving the proportion who died, the number dead at the beginning of the cycle is stored in order to compute the number of deaths occurring in the cycle (to assign palliative care cost). The proportions in each state who are still on treatment are computed and the *Partition* event then calls the *Valuation* event.

In the *Valuation* event, the current utility is computed as the weighted average of the progression-free and progressed utilities. The same is done for the cost of care. The cost of monitoring patients on vandetanib is applied as appropriate, depending on whether it is during the first or subsequent years. The outputs are then updated by adding the cycle time weighted by the utility or cost, as appropriate, and suitably discounted. The ongoing PFS and OS curves are recorded for the outputs.

Before triggering the next *Partition* event, the time horizon is checked: if it has been reached, the *End* event is called. The *End* event stops execution for that intervention.

Model execution

The model execution (i.e., reading of the event tables and carrying out each expression) is implemented in MS Excel® using a simple macro written in Visual Basic for Applications (VBA). The macro steps through each row of each event table and executes whatever the expression specifies. The macro does this by converting each text expression into an MS Excel® formula. This is done one at a time to ensure sequential execution. The loop continues until the *End* event is encountered, at which point, results stored in *Output* conditions are displayed. The macro is generic to all models as the specifics of a particular model are given in the *Conditions* and *Event* tables, not in the VBA code. By clicking on the simulate icon  in the Excel ribbon, the macro is called. There is nothing else for the user to do. If any of the inputs are changed, then the model is rerun by clicking  again

VBA interacting with an MS Excel® spreadsheet is very slow. This is a problem when running analyses (e.g., probabilistic sensitivity analyses [PSA]) where several thousand executions of the model may be required. To speed up execution, the macro reads in all *Conditions* into memory and executes the instructions tabulated in the *Events* without using the spreadsheet itself for calculations. This version of the macro, EviDICE, is also written in VBA and is provided in an xlam file that is called whenever the model file is opened.

A replication is one realization of the model for all interventions. Multiple replications may be executed to make up one model run for PSA. In each run, the macro checks that all required tables exist; all expressions are in proper MS Excel syntax; all conditions referred to in *Event* tables are listed in the *Conditions* table; all ranges referred to in the expressions exist; and all outputs called in the event tables exist in the output table. It then reads into memory all constants from the *Constants* table (e.g., YearLength) in worksheet Run; all context inputs from the *Context* table (e.g., Time Horizon, discount rates) in Inputs; all *Conditions*, reserving memory to contain each one's level at any time and setting its initial level as recorded in Conditions. It sets up the first replication by resetting all variables, the replication counter to 1 and the IntervNum to 1 for the first intervention. The *AllEvents* table in Events is then read in and the initial event times are evaluated; the first event to happen is identified (always the *Start* event), and the corresponding event table is found. The "consequences" in the *Expressions* column are evaluated in the order they appear (i.e., row by row) and the resulting value is assigned to the item named in the second column. Each assignment of a level during simulation can optionally be logged to a text file. The macro then finds the next event to happen and the corresponding event table and evaluates its list of "consequences" as was done for the first event. This is repeated until the *End* event is called. When this happens, the simulation stops and reports the results for that intervention to a log sheet (if that option is selected). The process is repeated for the next intervention, and then for the next replication, until the specified number of replications has been run.

DICE simulation has been presented extensively[51 52] and used in more than 12 decision-analytic models [publications pending].[53]

Cycles: The model carries out all calculations in regular cycles. In the base case, the cycle is set to one month. The survival functions are read at the midpoint of each cycle to provide a better approximation ("half-cycle correction") to the continuous curves.

Time horizon: The time horizon is set to 20 years. This is meant to be long enough to capture most of the effects (i.e., approximately lifetime) in this disease that has a high mortality.

Log: All aspects of model execution are logged to a text file which can be opened with any text editor (Figure 11).

Figure 11. Extract from model execution log.

```
Event: Partition; Time: 2.416667;  Current Age: 47.42
  Event time update: Partition; Next time: 2.5
  Condition update: ReadTime = 867.46875
  Condition update: OverallSurvival = 0.581769
  Condition update: ProgressionFree = 0.060462
  Condition update: Progressed = 0.521307
  Condition update: PreviousDead = 0.405968
  Condition update: Dead = 0.418231
  Condition update: OnTmt = 0.054965
  Condition update: OnTmtPostProgress = 0.411833
  Event time update: Valuate; Next time: 2.416667
Event: Valuate; Time: 2.416667;  Current Age: 47.42
  Event time update: Valuate; Next time: 100000000001.417
  Condition update: UtilityCur = 0.384425
  Condition update: CostCurCare = 4261.592699
  Condition update: CostCurMonitor = 0.0
  Output update: ContinuousAccumulator LifeYears; assigned value: 0.5818; output current value: 1.791
  Output update: ContinuousAccumulator ProgressionFreeLY; assigned value: 0.0605; output current valu
  Output update: ContinuousAccumulator QALYs; assigned value: 0.3844; output current value: 1.3055
  Output update: ContinuousAccumulator AccCostTmt; assigned value: 0.0; output current value: 0.0
  Output update: ContinuousAccumulator AccCostTmtPD; assigned value: 21309.7838; output current value
  Output update: ContinuousAccumulator AccCostMonitor; assigned value: 0.0; output current value: 0.0
  Output update: ContinuousAccumulator AccCostCare; assigned value: 4261.5927; output current value:
  Output update: DiscreteAccumulator AccCostPall; assigned value: 80.9667; output current value: 2655
  Output update: ContinuousAccumulator AccCostAEs; assigned value: 0.0; output current value: 11.3733
  Output update: RecordOutput TotalCost; assigned value: 51785.3399; output current value: 51785.3399
  Output update: RecordOutput OSshare; assigned value: 0.5818; output current value: 0.5818
  Output update: RecordOutput PFSshare; assigned value: 0.0605; output current value: 0.0605
Event: Partition; Time: 2.5;  Current Age: 47.50
  Event time update: Partition; Next time: 2.583333
  Condition update: ReadTime = 897.90625
  Condition update: OverallSurvival = 0.569719
```

Survival functions: To implement the survival partitioning, two functions are required, one for PFS and another for OS. These functions specify the proportion of patients still progression-free and the proportion still alive, respectively. They were obtained by fitting parametric distributions to the observed times of progression and of death, based on the data at the final cut-off. Each function is defined by two parameters, *intercept* and *scale* (using the parametrization adopted by SAS, which was employed for the fittings). In the Inputs worksheet, *Context* table, the user can select from several distributional forms that were fit to the data:

Weibull: $S_t = e^{-\left[\left(e^{-intercept}t\right)^{1/scale}\right]}$, written as an Excel expression:

Exp(-((exp(-|OSintercept|)*|ReadTime|)^(1/|OSscale|)))

Log normal: $S_t = 1 - \Phi\left[\frac{\ln(t) - intercept}{scale}\right]$, written as an Excel expression:

1-NORM.S.DIST((LN(|ReadTime|)-|OSintercept|)/|OSscale|,TRUE)

Log logistic: $S_t = \frac{1}{1+\left[e^{-(intercept)}t\right]^{1/scale}}$, written as an Excel expression:

1/(1+(exp(-|OSintercept|)*|ReadTime|)^(1/|OSscale|))

For the corresponding PFS fits, OSintercept and OSscale are replaced with PFSintercept and PFSscale. Details of the statistical methods used for fitting the functions are provided in Appendix 5.

The base case analyses are for the **restricted EU label population** (i.e., progressive and symptomatic MTC with biomarker change) of the ZETA study, a subset of the EU label (see section 5.2.1). Other parameters (dose distribution and crossover) are also adjusted to the selected population.

To adjust the intercepts, the calculations must take into account that the subpopulations are subgroups. For each subpopulation and fit, the adjusted intercept is computed as:

$$\text{intercept} + \%\text{SympProg} \times \beta_{\text{SympProg}} + \%\text{BiomarkerChg} \times \beta_{\text{BiomarkerChg}}$$

with the relevant beta coefficients taken from the SAS output in worksheet OS PFS and the appropriate factors for each sub-populations from the ZETA trial (Table 35.).

Table 35. Proportions used to compute intercept for each subpopulation.

Population breakdown	BSC	Vandetanib
Restricted EU label		
% symptomatic & progressive	100%	100%
% with biomarker change	[redacted]	[redacted]
EU label		
% with biomarker change	[redacted]	[redacted]
% symptomatic & progressive	100%	100%

To estimate the OS and PFS curves for the base case subpopulation, the parametric regressions fit to the entire study population were applied by setting the coefficients for SympProg to 100% and BiomarkerChg to [redacted]. This provides the appropriate adjustment for this subpopulation.

The standard error for the intercept is derived from the covariances (*Cov*) of the three factors (Intercept = *I*, BiomarkerChg = *B, SympProg* = *SP*) as:

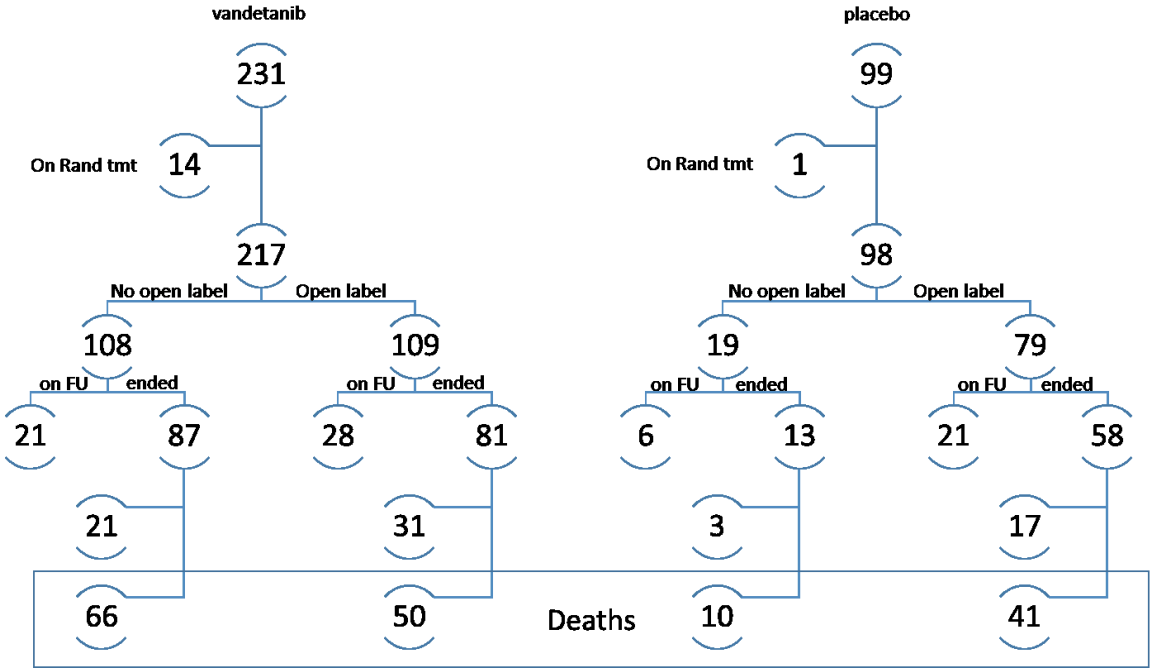
$$\sqrt{(I^2 CovInt + SP^2 CovSP + B^2 CovB) + 2I\ SP\ CovIntSP + 2I\ B\ CovIB + 2SP\ B\ CovSPB}$$

Uncertainty in these parameters was explored in the PSA using Cholesky decompositions.

Crossover

The ZETA trial allowed patients on the placebo arm to receive open-label vandetanib to crossover after a clinical diagnosis of progressive disease and patients who were randomised to vandetanib to continue open-label treatment at that time. The extent of crossover is presented in section 4.10 and Figure 12.

Figure 12. Extent of crossover in the ZETA trial.



In the base-case restricted EU label subpopulation, [redacted] of patients randomized to vandetanib continued open-label treatment while [redacted] of those initially on placebo crossed over to vandetanib.

OS is affected by crossover because the survival observed in the placebo arm reflects the mixed effects of BSC until progression and treatment with vandetanib in the majority of patients afterward. If vandetanib is effective and prolongs survival, crossover will lead to a rapid attenuation of any differences in OS. For this reason, a traditional ITT analysis, in which data are analysed according to the arms to which patients were originally randomised will underestimate vandetanib's effect on OS.

To allow for a proper comparison under the practice conditions in the UK, where it is expected that treatment is stopped at progression, an attempt was made to undo the crossover statistically. Accordingly, methods to adjust for the impact of crossover were considered, including rank-preserving structural failure time (RPSFT) models, inverse probability of censoring weights (IPCW) method, iterative parameter estimation (IPE)

algorithm and two-stage methods. RPSFT was attempted because the technique has been used for crossover adjustment in other recent NICE assessments. This method failed to produce an estimate unconfounded by the extensive crossover to active treatment in the placebo arm early in the trial. Failure to undo crossover statistically means that the base case analysis is a cost-effectiveness analysis of the restricted EU label population within the ZETA trial, extrapolated to account for right censoring (i.e., patients who were alive at the most recent data cut). It is not a perfectly accurate representation of how vandetanib is used or would likely to be used in England and Wales's clinical practice. However, given that crossover is likely to underestimate vandetinib's effectiveness, we likely underestimate the true OS benefit. By including the post-progression active treatment costs, we add in costs not expected in usual English and Welsh clinical practice, however, we strip these out in a sensitivity analysis to understand the impact they have on the ICER results.

AE handling

Vandetanib produces some AEs at a greater frequency than observed with placebo, consistent with its mechanism of action. This was accounted for in the model by applying the observed frequencies of grade 3 or 4 AEs to all patients. As a few patients receiving placebo also experienced grade 3 or 4 AEs, the same was done for the BSC comparator. The cost of managing AEs was derived as the sum of the costs of the specific types of AEs multiplied by their occurrence rate obtained from the ZETA trial. The same was done for the disutility tariff. These items were added to the appropriate output in the first cycle. No discounting was applied as all the AEs occur early during treatment (well before the end of the first year).

Scenarios

A scenario is defined by a set of inputs that identify the population, the context, the assumptions made, the sources of data and any other aspect that may affect the results. In these analyses, multiple scenarios were run:

- Discount rate: 0%, 5%
- Post-progression costs removed
- Utilities source: ZETA unadjusted, Beusterien[54] as reported
- Time horizon: 5, 10 years
- Half-cycle correction: 'off'
- Crossover vandetanib dose: 300 mg

Profiles

A profile is a set of conditions that hold the determinant values that sufficiently characterize a population of interest. As this model is analysed at the cohort level, and no predictors were included in the OS and PFS functions other than the population indicator, the *Profiles* are not in use.

Features of the analysis

The base case for this model is defined by the aspects tabulated in Table 36.

Table 36. Aspects defining the base case.

Factor	Chosen value	Justification
Time horizon	20 years	Patients with unresectable locally advanced or metastatic medullary thyroid cancer have very short life expectancy with only best supportive care. Five-year survival is reported to be 25%[1]; and median overall survival is 2 to 3 years in patients with distant metastatic disease (EPAR). In the EXAM study, placebo patients had OS of 21.1 months.[18] The median survival in the ZETA trial (last cut-off), however, was approximately 6.8 years, and in the restricted population an estimated 0.4% of patients remain alive at 20 years. Thus, a 20-year time horizon was considered sufficient to fully capture the costs and benefits associated with treatment while decreasing the uncertainty of projecting long-term health outcomes.
Cycle length	1 month	The cycle length was chosen to provide reasonable accuracy in deriving the partition proportions.
Half cycle correction	On	Given short cycle, this is not strictly required but implemented per NICE methods guide.
Health effects measured in	QALYs, Life years	OS is the ultimate outcome in late-stage oncology trials. As HRQoL differs depending on the disease status, time spent in each state was adjusted by utility to determine QALYs.
Discount rates	3.5% for costs and QALYs	The discount rate is per the NICE methods guide.
Perspective	NHS	The analysis takes the perspective of the NHS in England and Wales, per the methods guide.
Comparator	Best supportive	In the ZETA trial, vandetanib was compared to best supportive care alone. No comparison is made to

Factor	Chosen value	Justification
	care	carbozantinib due to lack of comparable evidence (see section 4.10)
Population	Restricted	The base case population was chosen to reflect UK practice and be consistent with EU label:[8] • Restricted EU label defined as progressive & symptomatic MTC with rapid biomarker doubling
Source efficacy & safety	ZETA trial	Registration study supporting the vandetanib EU label
OS distribution	Weibull	Similar fit to log-normal and log-logistic but with more plausible long-term survival
PFS distribution	Weibull	Consistency with OS choice
Progression reading	Central	The primary objective of the ZETA study was to demonstrate an improvement in PFS, using centralised, blinded independent review. Although centrally-determined PFS is confounded by crossover, which could happen at site-determined progression, using this endpoint mirrors the per protocol endpoints of the overall study.
Utilities source	Adjusted ZETA	See section 5.4

Intervention technology and comparators

Vandetanib is an orally-administered TKI with activity against RET, VEGFR, EGFR.

Vandetanib is a once daily treatment administered until patients are no longer benefiting from treatment or unacceptable toxicity occurs; in some cases, toxicity can be managed through dose reduction. In the EU, vandetanib is indicated for the treatment of aggressive and symptomatic MTC in patients with unresectable locally advanced or metastatic disease.[8]

Prior to availability of vandetanib, best supportive care (BSC) was the standard management for patients with advanced MTC, and this is still the case in patients where systemic treatment is not suitable. Both vandetanib and carbozantinib are recommended as first line options by the CDF[5]; however, significant clinical differences in the safety profiles of each drug mean that they are not suitable for use in all patients. As such, both options should be available.[5]

Due to difference in the study populations for the ZETA and EXAM trials, lack of access to the individual patient data from EXAM, the inability to adjust statistically for crossover and the clinical need for both treatment options to be available, no formal comparison to cabozantinib has been made. However, a naïve cost minimisation analysis of the two treatments based on the view of the CDF that in cases where a patient can have either treatment, the cheapest should be chosen.[5] This reflects the view that both vandetanib and cabozantinib are considered to have similar efficacy by clinical experts (Appendix). Therefore, in this submission, BSC is the appropriate comparator for vandetanib.

Treatment continuation rules

No continuation or stopping rules were applied to the intervention or comparators in the economic model other than those addressing observed dose reductions, interruptions and discontinuations, described below.

Dose reductions and interruptions

In the ZETA trial, physicians could decrease the dose of blinded treatment to 200 mg per day and further to 100 mg per day if needed. Physicians could also interrupt treatment for a period and then resume. These dose reductions and interruptions were accounted for by calculating a weighted average cost per cycle for vandetanib, which was then applied to patients still on treatment pre-progression. The weights were obtained by taking the pre-progression time spent at each dose and dividing by the total pre-progression time on treatment. The costs for each dose were based on the list prices. As there is no list price for 200 mg, it was assumed that two 100 mg tablets would be taken. The resulting weights are listed in Table 37.

Table 37. Distribution of doses in the base-caseduring progression-free time.

Item	% of PFS time
Full dose	66.3%
200 mg dose	16.5%
100 mg dose	15.5%
Interrupted	1.7%

Patients whose cancer had not yet progressed were allowed, nevertheless, to discontinue treatment. These treatment discontinuations were addressed by applying the relevant proportion to the patients not having progressed in each cycle [redacted].

As the PFS function was derived using data on all patients treated regardless of dose or treatment discontinuation, the dose reductions and interruptions were assumed to only affect the cost of treatment, not its efficacy.

Continuation after progression

The ZETA trial allowed patients to continue on open-label vandetanib at progression, or to cross over if they had been on placebo. This continued use of vandetanib is presumed to have an impact on OS that is reflected in the observed OS functions as noted above.

In the base-case (restricted EU label population), continued treatment is allowed, so ContTmtPD is set to the observed proportion of patients doing so, depending on which treatment they were on prior to progression: 43.7% of patients randomized to vandetanib continued open-label treatment while 82.4% of those initially on placebo crossed over to vandetanib in the base-case subpopulation. This proportion is applied to those in the *Progressed* state, assuming that it remains constant over time. Patients not continuing active treatment are assumed not to go on to any other chemotherapy, receiving only best supportive care; until the last month of life, when palliative chemotherapy is administered.

The patients who crossover to active treatment are assumed to also undergo dose reductions and interruptions and these are incorporated as weights in computing the cost of any continued treatment. As it was not recorded what these dose distributions were in ZETA, it was assumed that the pre-progression dose distribution would apply to those continuing treatment after progression. Although patients crossing over from placebo would initially take a full dose of vandetanib given their tumour load would have increased or stayed the same since starting the trial, the more conservative assumption was made of assigning them the same dose distribution as those continuing vandetanib.

5.3 Clinical parameters and variables

The ZETA study is the principal source of evidence for the economic model, informing key clinical events and outcomes. Patient-level data from the ZETA trial were used to inform overall survival and progression-free survival. AEs were derived from full safety population for ZETA. The analysis modelled all-cause mortality data from the ZETA trial.

Incorporation of clinical data

The ZETA clinical trial did not fully capture the PFS or OS, despite relatively long follow-up (median of 24 months for initial cut-off). At that time, the disease had progressed in only 73 out of 231 patients in the vandetanib arm. At the time of the primary analysis, 48 (14.5%) patients had died, 32 (13.9%) patients in the vandetanib group and 16 (16.0%) in the placebo group. Therefore, 28.9% (48/166) of the final projected number of deaths had occurred at the initial data cut-off (31 July 2009). The results of primary analysis of OS demonstrated that there was no statistically significant difference between patients randomized to vandetanib and those randomized to placebo (HR 0.89, 99.98% CI 0.28, 2.85, p=0.71), largely because of extensive crossover.

The study continued to follow patients for survival and a second data cut-off of 7 September 2015 was implemented for OS (median follow-up of 419 weeks). At that time, a total of 168 deaths representing 50.8% of randomised patients had occurred. Survival remained similar across treatment arms; a total of 116 (50.2%) patients in the vandetanib arm had died compared with 52 (52.0%) patients in the placebo arm. Therefore, extrapolation of PFS and OS data beyond the trial period was necessary.

Individual patient data were obtained from the ZETA trial and analysed using SAS (v 9.4). Validation of results consisted of independent double-programming and comparison with previously-published reports to assure consistency. As it proved impossible to adjust statistically for the confounding caused by cross-over, all results in the cohort model included the crossover effect.

Two endpoints were analysed:

- OS: Time from randomization to death or last date at which the subject was known to be alive. All patients who received randomized treatment (Safety population), with follow-up through the 7 September 2015 cut-off for the CSR addendum were analysed.

- PFS: Time from randomization to documented progression based on central review. Analyses used all randomized patients and data up to the initial data cut-off, as reported in the original CSR of 6 July 2011.

PFS was only analysed through the original study period because date of progression was not recorded consistently after the original study period. PFS based on central review was used because it was readily available for all patients and could be confirmed by comparing results in the full population with published reports from the original study.

To extrapolate results from ZETA, the final cut-off patient-level data were re-analysed and fitted with commonly used distributions (Weibull, log-normal, and log-logistic[55]) using SAS PROC LIFEREG. To allow for differences in OS and PFS among the subpopulations, two indicators were included in the regressions: one for presence of rapid biomarker changes and another for symptomatic, progressive MTC. Goodness of fit was tested using Akaike information criterion (AIC) and Bayesian information criterion (BIC). In addition, the predicted distributions were visually compared to observed Kaplan-Meier (KM) curves, and the long-term projections were assessed for clinical plausibility. Details of the statistical approach are in Appendix 5.

All of the tested distributions fitted the observed OS and PFS KM curves quite well. Indeed, both the AIC and BIC were quite close in all cases. Thus, there was no strong statistical basis for choosing a fit for the base case. The Weibull fit was selected for modelling OS because it matches human mortality better in the long term. As there is no clear, clinical expectation for the PFS over the long-term, Weibull was also selected in the base case for consistency. A visual inspection of the Weibull curves compared with Kaplan-Meier curves suggests this was a conservative parameter to adopt in that it was more likely to underestimated vandetanib efficacy.

Calculation of transition probabilities

As we used a survival partition model, the transition probabilities were not explicitly calculated. Instead, they implicitly lead to the proportions of the cohort who are progression-free, progressed and dead at each cycle. These proportions were read from survival functions that were obtained by fitting the ZETA trial data. Details of the application of the survival functions in the model are provided above, and the statistical methods used for fitting the functions are provided in Appendix 5.

Changes over time

The underlying transition probabilities change over time as specified by the fitted survival functions.

5.4 Measurement and valuation of health effects

No health state utility instrument, such as the EQ-5D, was administered in the ZETA study. In the absence of utility data, the following approach was adopted to estimate utilities for the progression-free and progressed health states.

Derivation of progression-free utility

The ZETA study collected patient-reported outcomes using the FACT-G instrument. This validated cancer-specific instrument is widely used to assess health-related quality of life in patients with any tumour type.[56] An algorithm to convert FACT-G responses to time trade-off (TTO) utilities was published by Dobrez et al[57] (Eq. 7.1). The algorithm is based on directly elicited TTO utilities provided by a large sample of patients with cancer for their health state at the time as well as the patients' responses to the FACT-G. There were 1,433 subjects with one of ten cancer diagnoses: breast (n=250), prostate (n=189), colon (n=170), non-small-cell lung (n=146), head and neck (n=164), non-Hodgkin's lymphoma (n=148), Hodgkin's lymphoma (n=38), small-cell lung (n=35), other known (n=288), and unknown primary cancer type (n=12). The algorithm yielded an equation for utility:

$$
\begin{aligned}
Utility = 1 + & \begin{pmatrix} -0.2222 & \text{if } q1 = [0,1] \\ -0.1137 & \text{if } q1 = [2,3] \end{pmatrix} + \\
& (-0.1537 \quad \text{if } q2 = 0) + \\
& (0.0431 \quad \text{if } q3 = [0,1]) + \\
& \begin{pmatrix} -0.1254 & \text{if } q4 = [0,1] \\ -0.0641 & \text{if } q4 = 2 \\ -0.0345 & \text{if } q4 = 3 \end{pmatrix}
\end{aligned}
$$

where q1 = physical well-being: lack of energy; q2 = physical well-being: feel sick; q3 = functional well-being: able to work; and q4 = functional well-being: able to enjoy life.

Using FACT-G data from the ZETA study, a utility of 0.84 was obtained for progression-free.

Derivation of progressed utility

Although the utility in the progressed state will likely decrease over time as the disease advances, in the economic model a single state is considered and thus, a single constant value is applied.

The FACT-G instrument was administered for a short period after progression, but these data were only available from 62 patients, representing 27% of the 227 who completed it prior to progression. Furthermore, given the proximity of the assessment to the diagnosis of disease progression, it is likely that the scores overestimate HRQoL resulting from the eventual deterioration with progressive disease. Therefore, in the absence of representative utility data for patients with progressing MTC, a utility decrement was applied to the utility for the progression-free state (0.84). This decrement was obtained from a study[54] that employed standard gamble methodology to assess utility scores from members of the UK and Australian general public. Although that study presented health states describing stages in advanced melanoma, the descriptions were universal and not explicitly related to this type of

cancer. Therefore, it was felt that the estimates obtained would be suitable for all advanced and metastatic cancer in the UK, including MTC.

Beusterien and colleagues found the ratio of progressed to progression-free utilities to be 0.766.[54] Applying this ratio to the progression-free utility obtained from ZETA (0.84) resulted in a utility of 0.64 used in the base case for the progressed state.

Given the paucity of utility values for the MTC population and the resulting uncertainty additional deterministic uncertainty analyses were undertaken using the utility estimate (0.83) based on the small sample of FACT-G data obtained after progression in ZETA; and using the estimates exactly as provided by Beusterien (Table 38).[54]

Table 38. Alternative utility values for application to the progressed state.

Source	PFS	PD
ZETA adjusted	0.84	0.64
ZETA	0.84	0.83
Beusterien	0.77	0.59

Utility decrements due to AEs

No studies were found that provided utility estimates for severe AEs (CTCAE grade 3 or 4) experienced by patients with MTC. Therefore, utility decrements were obtained from Beusterien et al.[54] A utility tariff of 0.11 was applied to all AEs. As AEs in the ZETA trial lasted, on average, only a few days and in all cases persisted for less than a month, the tariff for severe AEs, was applied for one month. In addition, as the AEs occurred early in the trial, the tariff is applied during the first cycle.

5.5 Cost and healthcare resource use identification, measurement and valuation

Resource identification, measurement and valuation studies

A systematic review of resource use literature was not performed given the very small number of patients with advanced MTC. There are four categories of resource utilization and cost:

- vandetanib treatment regimen and associated costs (Table 42 and Table 43)

- treatment costs for severe AEs (Table 44)
- cost of BSC (Table 39)
- palliative care costs (Table 40 and Table 41).

Best supportive care

Resource use was estimated for BSC provided during the progression-free state and after progression. In progression-free state, it was assumed that patients would have an outpatient, consultant-led appointment every 3 months. No CT scan was assumed to be performed during progression-free state. In the progressed state, the resource use is based on specialist visits every ten days for progressed disease.[58] It was also assumed that patients in progressed state would have 6 CT scans per year.

NHS reference costs were used for the resources consumed for providing supportive care. The Healthcare Resource Group (HRG) codes used and the unit costs and frequencies of use are described in Table 39. These costs are applied to all patients in each state, regardless of treatment.

Table 39. Costs of best supportive care.

Item	Unit cost	Frequency (/yr)		Total Cost	
		PFS	PD	PFS	PD
WF02A Multi-professional non-admitted face-to-face attendance, follow-up	£ 197.00	4.0	36.5	£ 788.00	£ 7,195.43
RD28Z Complex computerised tomography scan	£ 148.00	0.0	6.0	£ 0.00	£ 888.00

PD: progressed disease; PFS: progression-free state

For uncertainty analyses, interquartile ranges were obtained: £538.92 to £1,050.48 for the cost of care in the progression-free state and £2,384.76 to £10,450.20 for progressive disease state.

Palliative care costs

In addition, the cost of palliative care was based on the average cost of management, including hospitalisation, from the PSSRU 2015–2016. These costs were then applied during the last month of life to all patients. The mean cost was estimated at £189.75 per day (Table 40), amounting to £5,775.52 for the last month of life (given that cycle time is one month). For uncertainty analyses, an interquartile range of £3,819.91 to £7,183.25 was used.

Table 40. Palliative care costs.

	Cost (per day)
Inpatient: specialist palliative care	£397.00
Inpatient: hospital specialist palliative care support	£108.00
Outpatient: medical specialist palliative care attendance	£156.00
Outpatient: non-medical specialist palliative care attendance	£ 98.00
Mean value	£189.75

The cost of palliative chemotherapy was also added in the last month of life. It was computed from the national schedule of reference costs (year 2015–2016) for regimens in band 1 to 10 (Table 41). The mean of £827 was used in the model. An interquartile range of £404 to £1,026 was used in uncertainty analyses.

Table 41. Costs of palliative chemotherapy.

HRG code	**Description**	**Average cost**
SB01Z	Procure chemotherapy drugs for regimens in band 1	£540
SB02Z	Procure chemotherapy drugs for regimens in band 2	£583
SB03Z	Pro Procure chemotherapy drugs for regimens in band 3	£275
SB04Z	Procure chemotherapy drugs for regimens in band 4	£346
SB05Z	Proc Procure chemotherapy drugs for regimens in band 5	£1,255
SB06Z	Procure chemotherapy drugs for regimens in band 6	£234
SB07Z	Procure chemotherapy drugs for regimens in band 7	£746
SB08Z	Procure chemotherapy drugs for regimens in band 8	£1,169
SB09Z	Procure chemotherapy drugs for regimens in band 9	£1,023
SB10Z	Procure chemotherapy drugs for regimens in band 10	£2,103
	Mean value	**£ 827**

Intervention and comparators' costs and resource use

Vandetanib drug costs

Vandetanib is available in both 300 mg and 100 mg tablets. The cost of a 30-tablet pack of vandetanib for each tablet size is taken from the list price in the BNF[21] reduced by [redacted] to take into account the discount currently in place via the CDF (Table 42). This reduced cost is adjusted to an annual value for use in the base case.

Table 42. Costs of vandetanib.

Intervention	Pack (30 tablets)*	Discount	Per year
vandetanib 300 mg tab	£ 5,000	[redacted]	[redacted]
vandetanib 100 mg tab	£ 2,500	[redacted]	[redacted]

*As of January 2017

The recommended licensed dose for oral vandetanib is 300 mg/day. Vandetanib treatment should continue until patients are no longer benefiting from treatment or unacceptable toxicity occurs. In ZETA, as in actual practice, the physician could reduce the dose of vandetanib to manage toxicity, or even interrupt treatment for a period. These dose reductions were assumed to affect only the costs, since the PFS and OS were observed in light of the actual doses used. To take these reductions into account, the amount of the subpopulation's progression-free time spent at each dose was computed: 66.3% at full dose; 16.5% at 200 mg per day; 15.5% at 100 mg per day; and 1.7% interruption.

As patients could continue on vandetanib after progression, or cross over to it if they were on placebo beforehand, the dose distribution during this period was also required. Unfortunately, it was unavailable from ZETA, so it was assumed that the pre-progression distribution applied to patients continuing on vandetanib. Given that those crossing over would be starting vandetanib at full dose and it is unknown what dose reductions would occur, it was assumed that crossover would be at full dose.

Cost of monitoring during vandetanib treatment

After initiating vandetanib, all patients are monitored eight times during the first year, yielding a cost of £400 per year (Table 43).[11] In subsequent years, ECG monitoring should be continued at a rate of four times a year yielding a cost of £200 per year. For uncertainty analyses, an interquartile range of £104 to £456 was used for the first year and £52 to £228 for the subsequent years.

Table 43. Costs of monitoring associated with vandetanib treatment.

Item	Unit cost	Frequency/yr		Total Cost	
		1st yr	Yr 2+	1st yr	Yr 2+
EY51Z Electrocardiogram Monitoring or Stress Testing	£ 40.00	8	4	£ 320.00	£ 160.00
DAPS04 Clinical Biochemistry; DAPS08 Phlebotomy; DAPS05 Haematology	£ 7.00 (1+3+3)	8	4	£ 56.00	£ 28.00
DAPS09 Other (TSH)	£ 3.00	8	4	£ 24.00	£ 12.00

These costs are applied to all patients on vandetanib treatment while progression-free. For those who continue treatment after progression, or crossover, the monitoring costs are also applied, using the value for subsequent years.

Adverse reaction unit costs and resource use

The rates of adverse events were sourced from the primary ZETA publication reporting grade 3 or 4 AEs.[13] These were used in the economic model. The costs of managing these AEs were obtained from the national schedule (year 2015–2016) of reference costs (Table 44) including the HRG codes and descriptions. The total cost of managing AEs was taken as the product of the unit costs and their frequency of occurrence, separately for vandetanib and BSC, yielding £409.32 and £136.48, respectively. A range of £192.05 to £531.00 was used in uncertainty analyses for vandetanib and £54.00 to £170.61 for BSC.

Table 44. Cost of managing AEs in patients receiving vandetanib.

AE type	HRG	Vandetanib	BSC	Unit cost
Diarrhoea	FZ91M Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0–2	11%	2%	£ 1,102
Hypertension	EB04Z Hypertension	9%		£ 982
ECG QT prolonged	EB07E Arrhythmia or Conduction Disorders, with CC Score 0–3	8%	1%	£ 1,014
Fatigue		6%	1%	£-
Decreased appetite	FZ49H Nutritional Disorders without Interventions, with CC Score 0–1	4%		£ 1,512
Rash	JD07K Skin Disorders without Interventions, with CC Score 0–1	4%	1%	£ 1,078
Asthenia		3%	1%	£ -
Dyspnoea	DZ19N Other Respiratory Disorders	1%	3%	£ 896

AE type	HRG	Vandetanib	BSC	Unit cost
	without Interventions, with CC Score 0–4			
Back pain	HC32K Low Back Pain without Interventions, with CC Score 0–2	0%	3%	£ 1,510
Syncope	EB08E Syncope or Collapse, with CC Score 0–3	0%	2%	£ 1,067

5.6 Summary of base-case de novo analysis inputs and assumptions

Summary of base-case de novo analysis inputs

The base-case is defined by a set of context inputs not subject to parameter uncertainty (Table 45). As well as the values of the cost, utility and probability parameters are listed in Table 46. As this is a cohort model and no predictors of survival were fit, patient characteristics such as age are not considered as determinants.

Table 45. Items defining the context of the analyses.

Item	Level	Scenario	Section
Discount rate costs	3.5%	0, 5%	
Discount rate health	3.5%	0, 5%	
Cycle (months)	1	None	5.2
Half-cycle correct?	Yes	No	5.2
Time horizon (years)	20	5, 10	5.2
PFS distribution	Weibull	LogNormal*, Loglogistic	5.3
OS distribution	Weibull	LogNormal,* Loglogistic	5.3
Population	Restricted	Eu Label	5.2

* The fitted curves are available in the economic model. Sheet “Results Report”

Table 46. Cost and utility parameters.

Item	Level	Uncertainty	Section
Utility source	ZETA adjusted	ZETA observed	5.4
Utility progression free	0.84	0.84	5.4

Utility progressed	0.64	0.83	5.4
Cost BSC	£ 0.00	None	
Crossover to vandetanib	82%	69.7–94.3%	5.2
Continue vandetanib post	44%	32.4–55.6%	5.2
Discontinue vandetanib pre-progression	22%	12.2–31.5%	5.2
Cost monitor vandetanib Yr1	£400.00	£104–456	5.5
Cost monitor vandetanib Yr2+	£200.00	£52–228	5.5
Cost care progression-free	£788.00	£538.92–1,050.48	5.5
Cost care progressed	£8.083.43	£2,84.76–10,450.20	5.5
Cost palliative care	£6,602.52	£4,223.91–8,209.25	5.5
AE disutility BSC	0.0154	0.0000–0.0546	5.4
AE cost BSC	£136.48	£54.00–170.61	5.5
AE disutility vandetanib	0.0510	0.0118–0.0902	5.4
AE cost vandetanib	£409.32	£192.05–531.00	5.4

The parameters used to derive the PFS and OS functions are listed for the base case in Table 47. Parameters for the exploratory analysis and other distributions were used in scenario analyses. In addition, the parameters were varied in PSA.

Table 47. Parameters for deriving PFS and OS functions.

PFS & OS parameter	BSC	vandetanib
PFS scale	0.9698	0.6824
PFS scale SE	0.1175	0.0723
PFS intercept	5.65	6.7288
PFS intercept SE	0.237465787	0.299422778
OS scale	0.9096	0.8243
OS scale SE	0.1135	0.0665
OS intercept	7.1532	7.6794

OS intercept SE	0.216025461	0.158354034

Assumptions

Table 48. List of assumptions made in the model and their justification.

Assumption	Justification
Clinical assumptions	
The effect of treatment dose reductions, interruptions and discontinuations is manifest in the observed PFS and OS	Given the relatively small sample size, it is not possible to tease out the effects of treatment variations.
Projections of PFS based on fitting observed ZETA data are accurate reflections of what happens beyond trial follow-up.	The lack of data on progression beyond the data cut-off precludes an alternative.
Subsequent post-progression treatments address symptom palliation rather than extending survival.	Clinical expert opinion
Projections of OS in Restricted population based on the ZETA trial are conservative	Extensive crossover could not be undone statistically
Utility assumptions	
Utilities for progression-free and progressed states are independent of treatment, other than the disutility due to AEs.	There was no significant difference by treatment in ZETA trial.
The relative utility change upon progression observed in Beusterien et al[54] applies to this malignancy.	There are insufficient data available for alternative estimates.
AEs incur a one-time utility decrement at cycle 1.	The AEs occurred early in ZETA and were of short duration.
Cost assumptions	
The resources used for best supportive care in progression-free and progressed states are independent of treatment.	Treatment-specific costs are included in costs of monitoring
AEs were assumed to incur a one-time cost at cycle 1.	As with utility tariffs, the AEs occurred early in the clinical trial and were of short duration.
The dose distribution for patients crossing over from placebo is assumed to be the same as for vandetanib patients	This assumption is conservative and made in absence of further information. It is reasonable to assume that patients

continuing treatment	may switch to 300mg vandetanib due to their tumour load at the point of progression, however we did not have information on length of time placebo patients remain on 300mg.
The effect of treatment dose reductions, interruptions and discontinuations affects only the costs.	Health effects of dose changes are already included in the observed PFS and OS curves.

5.7 Base-case results

Cost consequences

The disaggregated results for the base case (progressive & symptomatic MTC with biomarker change) are presented in

Table 49. Results of the base case analysis confirm unprecedented gains in PFS comparing vandetanib to BSC, an increase of 1.240 years. This translates to an additional 1.736 years of life and a gain of 1.323 QALYs. These results do not adjust for crossover to active treatment in the placebo arm and are, thus, likely to be underestimates of the true benefit of vandetanib.

Table 49. Base case results (restricted EU label population).

Results per Comparator	Placebo	Vandetanib	Difference
Life years	3.100	4.836	1.736
PFLYs	0.759	1.999	1.240
QALYs	2.135	3.491	1.356
Treatment costs, pre-progression (£)	£0.0	[redacted]	[redacted]
Treatment costs, post-progression (£)	[redacted]	[redacted]	[redacted]
Monitoring costs (£)	£386	[redacted]	[redacted]

Adverse event costs (£)	£137	£409	£273
Cost of best supportive care (£)	£19,522	[redacted]	[redacted]
Cost of palliative care (£)	£5,917	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]	[redacted]
ICER			[redacted]

Base-case incremental cost effectiveness analysis results

Given a cost difference of [redacted] and a gain of 1.356 QALYs [redacted], the ICER is estimated to be [redacted] per QALY gained.

Clinical outcomes from the model

The clinical outcomes of the model were compared to those observed in the ZETA trial (Table 50). Given the relatively sparse data in the restricted population, the KM curves from the trial have long "steps" producing inaccurate estimates of the medians. This can be seen in Figure 13 and Figure 14.

Table 50. Clinical outcomes (modelled vs. clinical trial) in the base case restricted EU label population.

Outcome	Clinical trial	Model
Median PFS (yrs)		
BSC	0.46	0.59
Vandetanib	1.61	1.82
Median OS (yrs)		
BSC	3.27	2.55
Vandetanib	4.70	4.42

Figure 13. Comparison of modelled (smooth solid line) with observed (dashed step line) overall survival (OS) in the restricted EU label population.

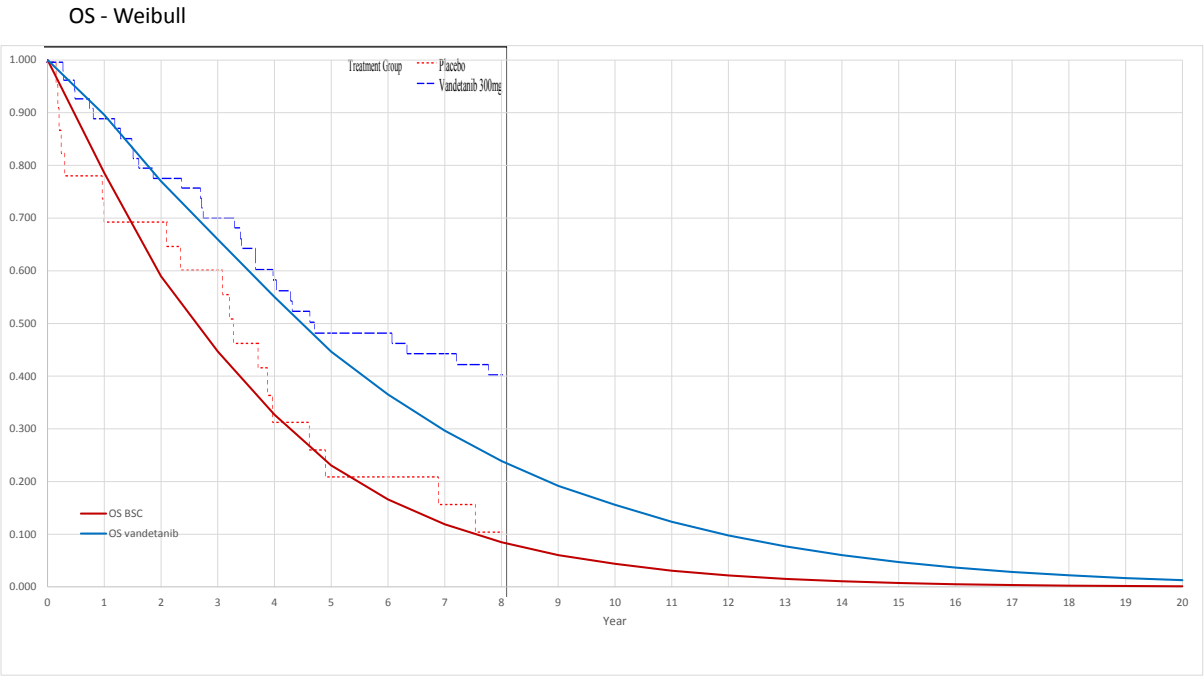
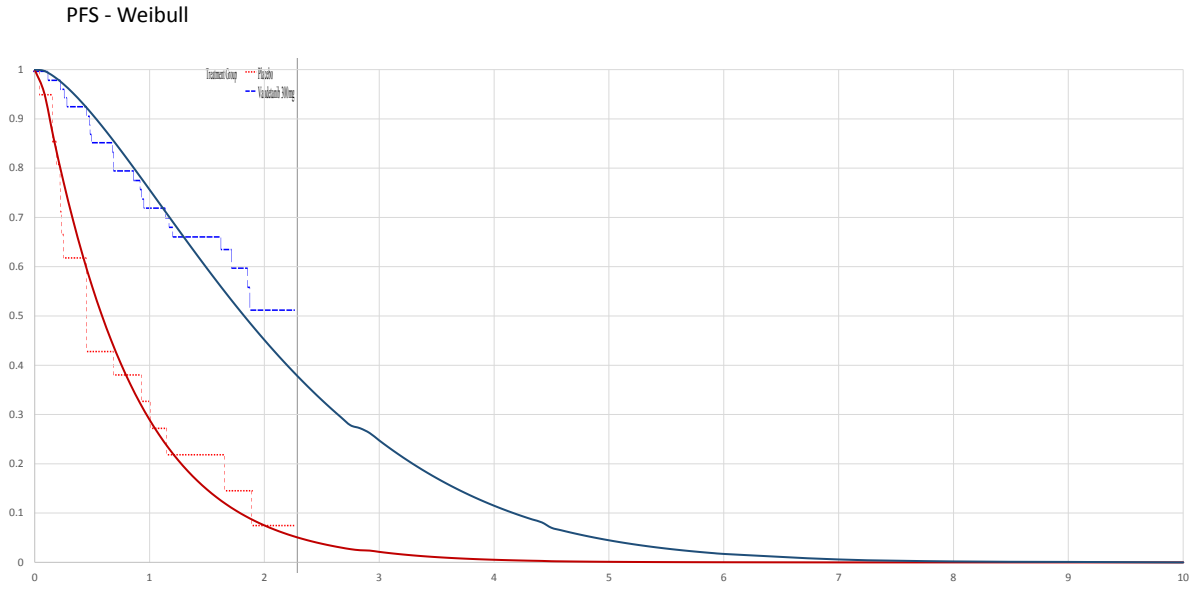


Figure 14. Comparison of modelled (smooth solid line) with observed (dashed step line) progression-free survival (PFS) in the restricted EU label population.



Markov trace

The Markov trace for vandetanib is provided in Figure 15 and for BSC in Figure 16.

Figure 15. Markov trace for vandetanib.

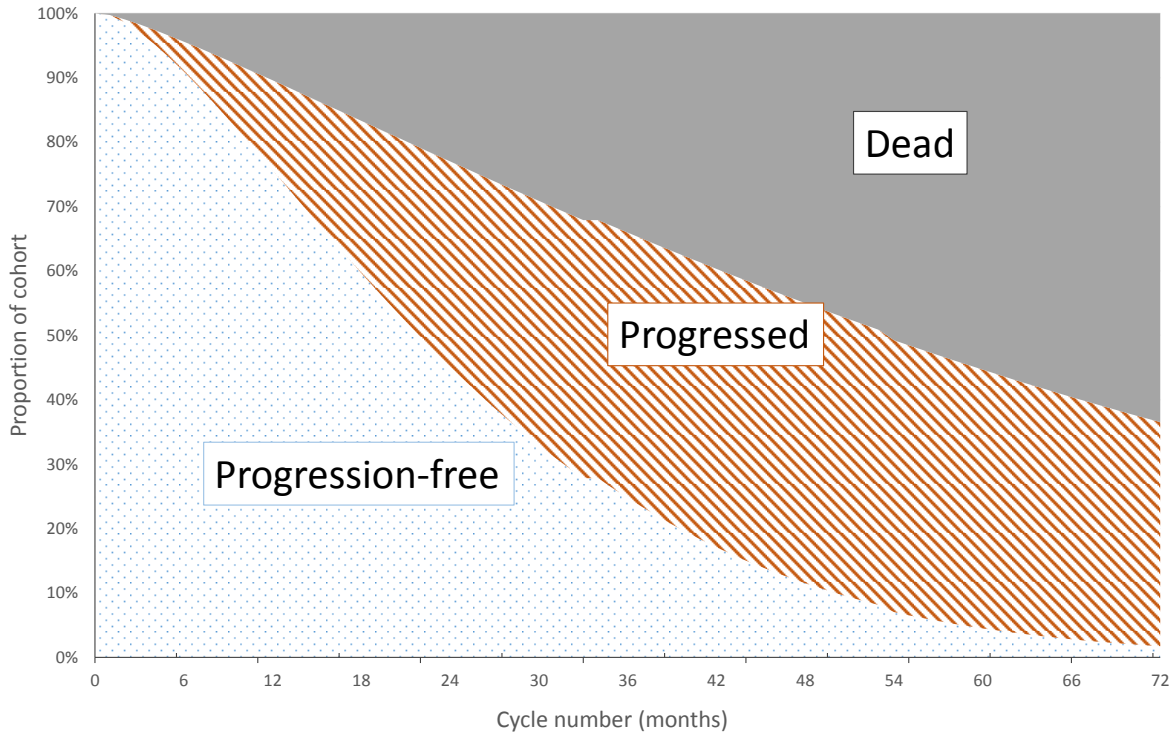
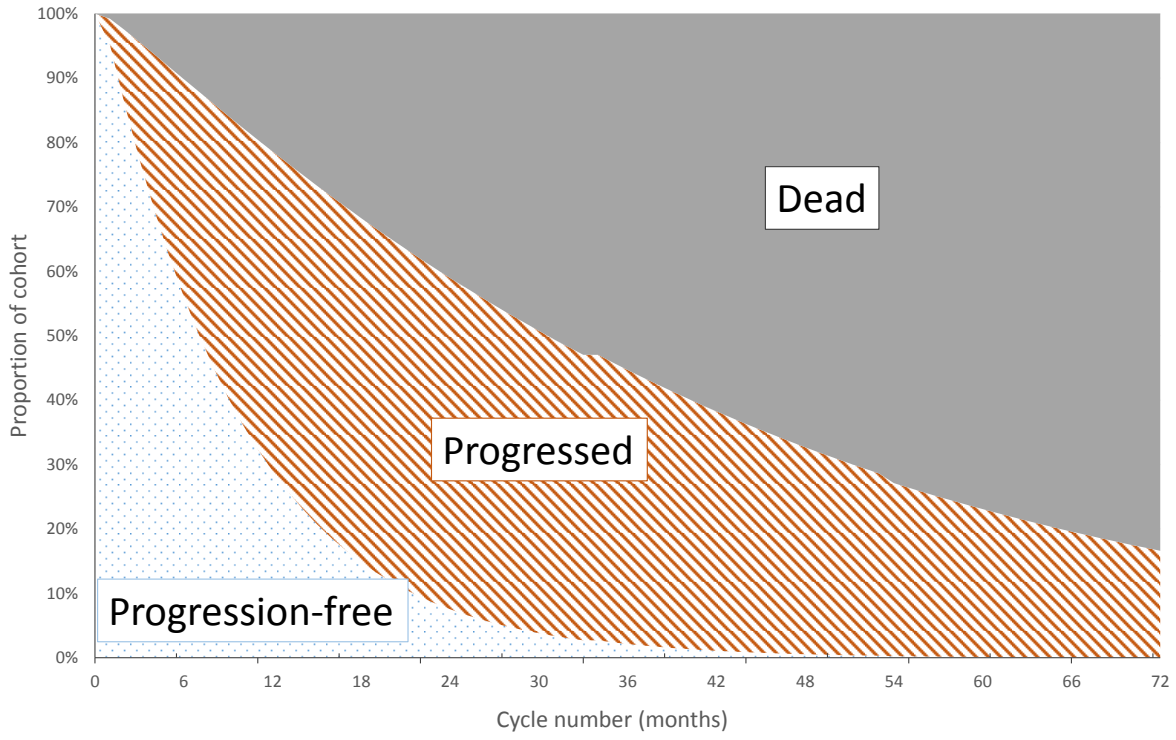


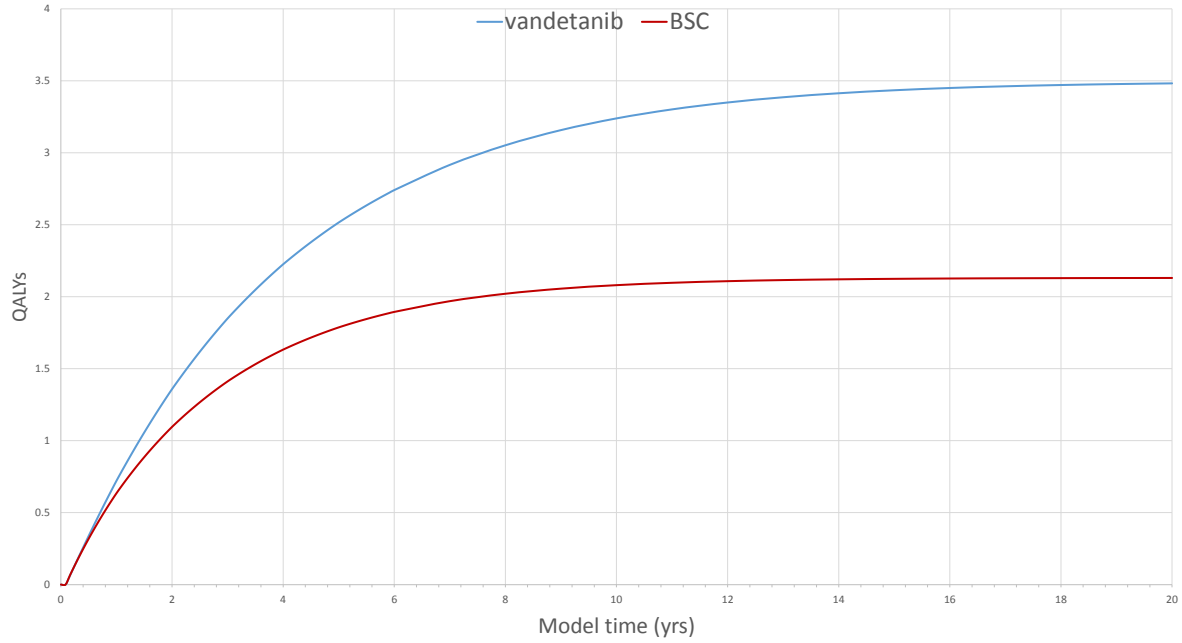
Figure 16. Markov trace for BSC.



QALY accrual over time

The accrual of QALYs over time is shown in Figure 17.

Figure 17. Accrual of QALYs over time.



Disaggregated results of the base case incremental cost effectiveness analysis

The disaggregated results of the base case analysis are presented in

Table 49.

5.8 Sensitivity analyses

Probabilistic sensitivity analysis

In the PSA, the uncertainties around inputs that have parameter uncertainty were estimated, including the intercepts and scales for PFS and OS functions, the utilities, and the non-drug costs. For each parametric PFS and OS function, the Cholesky decomposition of the covariance matrix was used to ensure proper correlation of the function parameters. The same random number was used across all treatment arms when values were drawn for the PSA to ensure consistency.

Distributions

Distributions used in the PSA along with justification are provided in Table 51.

Table 51. Justifications for the distributions used in the PSA.

Parameter	PSA Distribution	Justification
PFS intercept and scale	Normal (Cholesky decomposition)	PFS and OS are projected using parametric functions fitted to the individual trial data. The parametric fittings used maximum-likelihood estimation which assumes the error to be normally distributed. Therefore, a normal distribution was chosen. Cholesky decomposition was used to maintain the correlation between the parameters.
OS intercept and scale		
Monitoring cost	Log normal	This costs were varied using log normal distributions because the interquartile ranges were heavily skewed (as expected for costs). The mean of the log normal was approximated as the midpoint of the interquartile range and the SE was derived from the interval between the logs of the interquartile boundaries.
Care costs	Log normal	
AE costs	Log normal	
AE disutility	Beta	The source for these disutilities provided a standard error from their analyses. This was used to derive the parameters of the beta distribution, which was used because it is bounded by 0 and 1.
Utility for states		
Crossover proportion	Truncated normal	These proportions were estimated (by subpopulation) directly from the trial. Their SE was derived and the 95% confidence interval was used to bound the normal distribution.
Continue vandetanib		
Discontinue treatment		

ICER PSA results

A PSA was run for 1,000 iterations. Figure 18 presents the scatter plot for the incremental costs and QALY gained ICER comparing vandetanib to BSC. The plot indicates a high degree of uncertainty, as expected given the small sample sizes obtained from the ZETA trial. In 98.7% of the model iterations, vandetanib yields more QALYs than BSC (in the other 1.3% it yields fewer QALYs and lower cost). In 11.5% it was dominant (yielded more QALYs and lower cost). In the remainder, vandetanib yielded higher QALYs but at higher cost.

Figure 18. Scatter plot for PSA results in the base case scenario, comparing vandetanib to BSC.

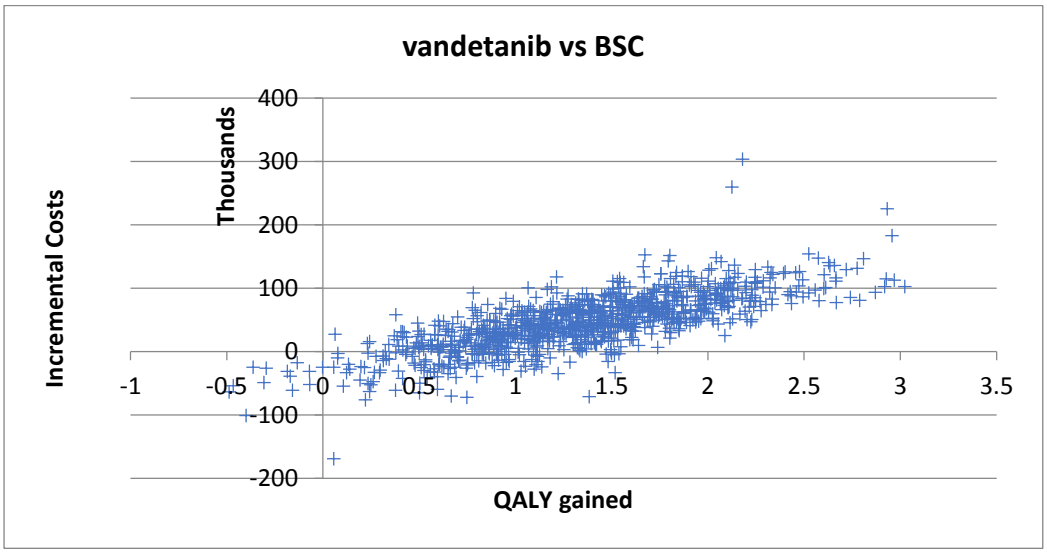
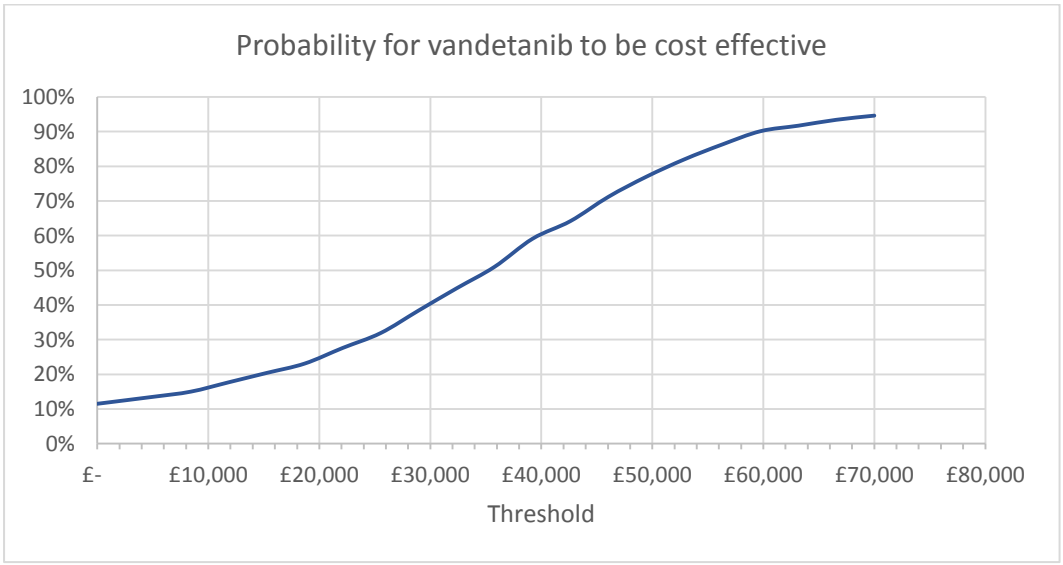


Figure 19 presents the cost-effectiveness acceptability curve. The probability of vandetanib being cost-effective at a willingness-to-pay value of £50,000/QALY is 88% (76% cost-effective plus 12% dominant).

Figure 19. Cost effectiveness acceptability curve for the base case scenario.



Variation from the base case analysis

Deterministic sensitivity analysis

All major model parameters for which values were statistically uncertain were tested in a one-way uncertainty analysis. Minor parameters (e.g. utility decrements for each AE, unit costs and resource use for each resource use item) were incorporated in aggregate form, such as average utility decrement for AEs with each comparator, or care costs for each health state. Where possible, confidence intervals or published ranges were used as alternative values. The parameters were varied as shown in Table 52.

Table 52. Parameter values varied in deterministic uncertainty analyses.

Parameter	Base case	SE	Low	High
Cost of monitoring vandetanib Yr1	£400.00	1.0957	£104.00	£456.00
Cost of monitoring vandetanib Yr2+	£200.00	1.0957	£52.00	£228.00
Cost of care, progression-free/yr	£788.00	0.4948	£538.92	£1,050.48
Cost of care, progressed/yr	£8,083.43	1.0953	£2,384.76	£10,450.20
Cost of palliative care (final month)	£6,602.52	0.4926	£4,223.91	£8,209.25
AE cost of BSC (total)	£136.48	0.8528	£54.00	£170.61
AE cost of vandetanib (total)	£409.32	0.7539	£192.05	£531.00
AE disutility BSC	0.0154	0.0200	0.0000	0.0546
AE disutility for vandetanib	0.051	0.0200	0.0118	0.0902
Utility for progression free	0.84	0.0200	0.8008	0.8792
Utility for progressed	0.64	0.0200	0.6008	0.6792
Crossover BSC	82%	0.1826	69.7%	94.3%
Continue vandetanib	44%	0.1720	32.4%	55.6%
Discontinue treatment Pre-prog	22%	0.1432	12.2%	31.5%

Results of deterministic sensitivity analysis

Results of the one-way sensitivity analysis for vandetanib vs. BSC, in which single parameters were varied one at a time to test impact on model results, are shown in graphical form in Figure 20 and tabulated in Table 53.

Figure 20. Results of deterministic uncertainty analyses for base case scenario.

Table 53. Results of one-way uncertainty analyses for base case scenario.

Parameter	QALYs Low	Cost Low	ICER low	QALYs Hi	Cost Hi	ICER Hi
Cost of monitoring vandetanib Yr1	1.3559	[redacted]	[redacted]	1.3559	[redacted]	[redacted]
Cost of monitoring vandetanib Yr2+	1.3559	[redacted]	[redacted]	1.3233	[redacted]	[redacted]
Cost of care, progression-free/yr	1.3559	[redacted]	[redacted]	1.3233	[redacted]	[redacted]
Cost of care, progressed/yr	1.3559	[redacted]	[redacted]	1.3233	[redacted]	[redacted]
Cost of palliative care (final month)	1.3559	[redacted]	[redacted]	1.3233	[redacted]	[redacted]

AE cost of BSC (total)	1.3559	[redacted]	[redacted]	1.3233	[redacted]	[redacted]
AE cost of vandetanib (total)	1.3559	[redacted]	[redacted]	1.3233	[redacted]	[redacted]
AE disutility BSC	1.3546	[redacted]	[redacted]	1.3625	[redacted]	[redacted]
AE disutility for vandetanib	1.3591	[redacted]	[redacted]	1.2841	[redacted]	[redacted]
Utility for progression free	1.3073	[redacted]	[redacted]	1.3719	[redacted]	[redacted]
Utility for progressed	1.3365	[redacted]	[redacted]	1.3428	[redacted]	[redacted]
Crossover BSC	1.3559	[redacted]	[redacted]	1.3233	[redacted]	[redacted]
Continue vandetanib	1.3559	[redacted]	[redacted]	1.3233	[redacted]	[redacted]
Discontinue treatment Pre-prog	1.3559	[redacted]	[redacted]	1.3233	[redacted]	[redacted]

Scenario analysis

Uncertainty around structural assumptions was examined in scenario analyses and in an exploratory analysis reported below. In these analyses, multiple scenarios were run:

- Discount rate: 0%, 5%
- Post-progression costs removed
- Utilities source: ZETA unadjusted, Beusterien[54] as reported
- Time horizon: 5, 10 years
- Half-cycle correction: off
- Crossover vandetanib dose: 300 mg

Scenario results

The results of the scenario analyses show that there is some variation in the results but the ICERs remain below £50,000 per QALY gained (Table 54).

Table 54. Results of the scenario analysis in the deterministic uncertainty analysis.

Scenario	QALYs		Total costs		ICER (£/QALY)
	Placebo	Vandetanib	Placebo	Vandetanib	

Base Case	2.135	3.491	[redacted]	[redacted]	[redacted]
No Discount	2.312	3.937	[redacted]	[redacted]	[redacted]
Discount 5%	2.070	3.334	[redacted]	[redacted]	[redacted]
Post progression costs removed	2.135	3.491	[redacted]	[redacted]	[redacted]
ZETA utilities	2.580	4.030	[redacted]	[redacted]	[redacted]
Beusterien utilities	1.965	3.209	[redacted]	[redacted]	[redacted]
Crossover at full dose	2.135	3.491	[redacted]	[redacted]	[redacted]
Time Horizon 5 years	1.801	2.542	[redacted]	[redacted]	[redacted]
Time Horizon 10 years	2.086	3.252	[redacted]	[redacted]	[redacted]
LogNormal fits to OS/PFS	2.534	3.905	[redacted]	[redacted]	[redacted]
LogLogistic fits to OS/PFS	2.720	3.860	[redacted]	[redacted]	[redacted]

In all cases, the ICER remained below 50,000 per QALY gained. Only when the rate of continuing vandetanib at progression was set to its upper quartile (56% vs 44% in the trial) did the ICER approach 50,000.

5.9 Exploratory analysis: cost minimisation versus cabozantinib

The comparison below (Table 55) is based on drug acquisition costs for each treatment and does not account for dose reduction, interruption or discontinuations. In rare diseases, such as advanced MTC, efficiency analysis such as cost per QALY may not be the most equitable approach. In clinical practice, vandetanib and cabozantinib are considered by clinicians to be fairly similar in efficacy but with different tolerability issues as well as different evidence bases. For these reasons the CDF panel accepted both products, concluding, 'both drugs could be considered as offering the only systemic therapy for medullary thyroid cancer.'

SanofiGenzyme is concerned that this MTA may lead to one or other of theses TKIs being recommended while the other is not. This simple cost-minimisation analysis based on the assumption of similar efficacy indicates that for whichever TKI comes second a cost-argument may be considered to support the decision-making process in this appraisal.

The cost minimisation used the commercially agreed confidential discount in place for vandetanib compared with list price cabozantinib.

Table 55. Cost minimisation assuming similar efficacy (per patient per year).

	Vandetanib	Cabozantinib[58]	Difference
Drug acquisition cost	[redacted]	£62,571	[redacted]
Monitoring costs	[redacted]	£6	[redacted]
AEs management	[redacted]	£256	[redacted]
Total cost	[redacted]	£62,833	[redacted]

In absence of factors precluding one treatment choice over the other, vandetanib appears to less expensive per patient, per year than cabozantinib. In section 6, it can be seen that vandetanib has limited budget impact based on treatment of around [redacted] patients per year. (section 6)

5.10 Validation

Validation of de novo cost-effectiveness analysis

The structure and programming of the Microsoft Excel® model was validated by two modelling experts not involved in this study and a variety of stress tests were performed to ensure that the model results reflected the inputs entered. For example, both extreme values and equal values across treatment arms were input and actual results compared against expected results. In situations where actual results diverged from expected results, debugging was performed to investigate and remedy discrepancies. Statistical fittings for PFS and OS were validated by comparing observed PFS and OS KM data to the curves derived from the predictions. The PFS and OS extrapolated data matched well against the KM curves from the trial. Predicted OS and PFS survival curves, as well as major model assumptions, were validated by clinical experts practicing in the UK.

5.11 Interpretation and conclusions of economic evidence

The base case population chosen for this appraisal is expected to closely reflect UK clinical practise and is in line with EU recommendation of selecting patients with most the urgent need of treatment and within the ZETA study. The restricted EU label population (defined as progressive and symptomatic MTC with CTN and CEA doubling ≤24months) is a subset of the broader EU label population and has demonstrated significant clinical benefit in the ZETA trial despite substantial crossover in placebo arm.

Methods to adjust for crossover to vandetanib treatment were unsuccessful. The Excel®-based DICE model therefore produced results for a base case population that are an under-

estimate of the treatment benefit of vandetanib over BSC alone. Despite the high level of crossover (in the base-case restricted EU label subpopulation, [redacted] of patients randomized to vandetanib continued open-label treatment while [redacted] of those initially on placebo crossed over to vandetanib), the base case analyses report 1.7 LYG over the time horizon of the model with a cost-effectiveness of [redacted] gained and [redacted]. This result is driven to some extent by the high level of post progression costs due to vandetanib use in the placebo arm.

It should be noted that this subset of patients included only [redacted] patients on vandetanib and [redacted] patients on placebo and has high uncertainty.

Despite this, the overall survival reported with vandetanib in the ZETA trial is remarkable for those patients with advanced disease with distant metastases.

No formal comparison to cabozantinib has been undertaken. Instead a simple cost-comparison of the two treatments, based on assumption of similar efficacy, suggests that vandetanib has a lower cost per patient per year. Further, the overall estimated budget impact of vandetanib in the England and Wales is expected to remain fairly static at [redacted] patients per year, thus costing the NHS [redacted] for next 5 years.

In summary, the issue of crossover in a study conducted in an orphan disease at a time when there were no other active treatments, has highlighted the problem with applying standard cost-effectiveness methodology to very rare diseases with very small patient numbers.

6. Assessment of factors relevant to the NHS and other parties

Estimated number of patients eligible for treatment for advanced MTC

How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

MTC is a type of thyroid cancer. In the UK, 3% of adult thyroid cancers are MTC.[32 33] In the period 2016–2016, an estimated 253 patients were diagnosed with MTC in UK hospitals.[17 34] Vandetanib has a marketing authorisation in the UK for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease.

In order to estimate the number of patients' eligible for treatment with vandetanib in England and Wales, we considered the incidence and prevalence data for thyroid cancer in England and Wales (Table 56 and Table 57). In 2014, there were 3,064 estimated patients with thyroid cancer in England/Wales.[33] The incidence of thyroid cancer is estimated to grow at a rate of 3.55% year-on-year.

Prevalence data for thyroid cancer is less clear. Data from EUCAN estimated a 5-year prevalence of 9471 cases in 2012. Annualising this value gave an average of 1894 cases per year which when applied to England and Wales is 1748. All population estimates for England and Wales were derived from the ONS website.

Mortality rates for thyroid cancer were also applied to the total number of thyroid patients per year. According to Cancer Research UK, the 5-year mortality in patients with advanced disease is estimated at 72% which equated to 14% annually.

Estimating the number of patients with unresectable locally advanced or metastatic disease is more difficult due to lack of published data. According to the SEERs database, nearly half of patients (48%) were diagnosed with localized disease, whereas 35% had tumour extending beyond the thyroid into surrounding tissues or regional lymph node metastases, and 13% had MTC metastatic to distant organs. The EU guidelines state that metastatic disease occurs in between 7% and 23% of patients.[31]

In discussion with UK KOL expert, it would appear that following diagnosis of MTC, patients would be observed periodically to determine whether disease is progressing/or to assess tumour burden. Therefore, patient would only be treated when disease starts to rapidly progress.

In absence of specific data, we assumed that 48% have advanced disease requiring systemic treatment. Of this cohort, and based on current usage of vandetanib in England [redacted] receive vandetanib.

Table 56. The estimated projection of patient numbers over 5 years are based on the increase in total population of England and Wales.

Epidemiology	Value	Notes/reference
Population of UK (2016)	65,504, 320	Based on 2014 UK population (64,596,800) and estimated annual increase of 0.7% up to 2020.
Proportion of England/Wales to UK	89%	2014 population estimates for England/Wales versus UK population were used to estimate this value.
Incidence of thyroid cancer in UK (number of cases)	3400	Published number of new cases in 2014.
Incidence of thyroid cancer in UK (%)	0.01%	Number of new cases of TC/Total UK population (2014)
Incidence of thyroid cancer in England/Wales (number of cases)	3285	2016 estimate
Prevalence of thyroid cancer UK (number of cases, per year)	1968	EUCAN prevalence for the UK over 5 years (9471), annualised.
Prevalence of thyroid cancer - England/Wales (number of cases, per years)	1748	Based on 89% proportion of population.
Mortality in thyroid cancer	0.14	Based on 5-year mortality in stage 4 patients with thyroid cancer
% of thyroid cancer with MTC	3%	Wiltshire et al (2015)[33]
% with advanced disease	48%	Based on SEERS data[31]
% with advanced and symptomatic disease eligible for vandetanib	[redacted]	[redacted]

Table 57. Estimated number of patients with advanced MTC in England and Wales between 2016 and 2020.

	2016	2017	2018	2019	2020
Incidence of TC[1]	3285	3402	3523	3648	3777
Prevalence of TC[2]	1894	1894	1894	1894	1894
	5180	5296	5417	5542	5672
Less mortality[1]	23	23	23	23	24

Total TC population	5157	5273	5394	5519	5648
Number with MTC[3]	254	260	266	272	278
Advanced disease[4]	122	125	127	130	134

1. Based on estimates for incidence and mortality from Cancer research data for 2014 (http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/thyroid-cancer/incidence) and applied to population of England and Wales for the same year (https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationprojections/bulletins/nationalpopulationprojections/2015-10-29#2014-based-principal-population-projections)
2. EUCAN factsheet using prevalence data for 2012 (http://eco.iarc.fr/EUCAN/Cancer.aspx?Cancer=35)
3. Wiltshire 2015
4. Assumption based on SEERS (48%)

It should be noted that eligible population of MTC patients requiring treatment estimated above are similar when HES data are used (Table 58).[34]

Table 58. Eligible population of MTC patients requiring treatment calculated using HES data.

Year	Primary Dx		All Dx			
	Admissions	*3% MTC*	All Dx	*3% MTC*	Main Dx	*3% MTC*
2015–2016	6281	*188*	8423	*253*	6559	*197*
2014–2015	6038	*181*	8107	*243*	6354	*191*
2013–2014	5864	*176*	7634	*229*	6133	*184*
2012–2013	5526	*166*	7268	*218*	5803	*174*

What assumption(s) were made about current treatment options, market share and uptake of technologies?

Current treatment options as listed in the NICE scope are vandetanib and cabozantinib. Both treatments are currently only available via CDF. There are currently have [redacted] patients on commercial vandetanib across the UK (NOT including [redacted]). This equates to an estimated market share of 25%. Should NICE approve vandetanib for use in England/Wales the market share is estimated to [redacted] based on the current patient numbers (Table 59).

In absence of specific market share data on cabozantinib, we have assumed that the same number of patients would be eligible to receive this drug. i.e we have assumed an equal split between the two drugs. The rationale for this assumption is that the two drugs are not interchangeable with the other (see sections 4.10 and 4.13), and will be used based on individual patient circumstances. This view concurs with UK KOL expert opinion.

Table 59. Estimated number of patients on vandetanib between 2016 and 2020.

	2016	2017	2018	2019	2020
Number with MTC (3%)	254	260	266	273	279
Advanced disease	122	125	128	131	134
% on vandetanib or cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number on vandetanib or cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In addition to technology cost, please consider other significant costs associated with the treatment that may be of interest to commissioners

In addition to the cost of treatment (drug acquisition cost), the budget impact analysis has taken into consideration the associated costs with monitoring patients and cost of treatment related adverse events (Table 60).

Over 5 years, given estimated market uptake in eligible patients, the estimated drug costs are highlighted below (Table 61). The drug costs presented is based on full acquisition cost and does not include dose reductions and interruptions; the adverse events and monitoring costs are based on those presented in the economic section. The drug also [redacted].

Table 60. Total costs per patient per year for vandetanib, including drug acquisition, management of adverse events and monitoring.

	Cost/patient/year
Drug	[redacted]
AE	[redacted]
Monitoring	[redacted]
Total * [redacted]	[redacted]

Total budget impact of vandetanib over 5 years

The estimated budget each year is less than [redacted], indicating that vandetanib is an affordable option for the NHS (Table 61).

Table 61. Budget impact of reimbursing vandetanib over 5 years.

	2016	2017	2018	2019	2020
Number on vandetanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs management	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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8. Appendices

Appendix 1: CAPRELSA® Summary of Product Characteristics

Appendix 2: CONFIDENTIAL Key Opinion Leader Feedback

Appendix 3: ZETA and EXAM Safety

Appendix 4: DICE Tables

Appendix 5: Methods for individual-patient-level survival analysis

Appendix 6: CONFIDENTIAL Additional Data for Economic Analyses

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (MTA)

Cabozantinib and vandetanib for treating unresectable locally advanced or metastatic medullary thyroid cancer [ID56]

Thank you for agreeing to give us your views on the treatment(s) being evaluated by NICE in this appraisal and how it/they could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment(s).

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages. If you think your response will be significantly longer than this, please contact the NICE project team to discuss.

When answering the questions from section 3 onwards, please make sure to say which treatment (s) you are commenting on.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Butterfly Thyroid Cancer Trust (BTCT)

Your position in the organisation: [redacted]

Brief description of the organisation: The organisation is the only registered charity in England dedicated to providing information and support to people affected by thyroid cancer, it was set up in response to a paucity of information available when [redacted], [redacted] was diagnosed and treated for thyroid cancer in 2000. There has been a dedicated telephone helpline available from the inception of the charity for over 16 years, over which time we have answered thousands of calls from a vast cross section of people affected by thyroid cancer, to this end we have huge first hand experience of how thyroid cancer affects patients and their loved ones.

The organisation has available a small 'holiday' fund for families requiring respite when in hardship.

We provide up to date patient information via our patient friendly website, leaflets, folders and DVD's, all are free of charge to patients and hospital clinics. Our information is BMA approved.

[redacted] has worked in a voluntary role as 'Thyroid Cancer Patient advisor' within the thyroid cancer team at Freeman Hospital, Newcastle upon Tyne for over 15 years, she has an honorary contract with the Trust and as such is part of the care team. This a unique role /patient/doctor partnership and has led to many awards for the charity.

[redacted] has a vast wealth of experience supporting those patients with non-resectable, advanced, metastatic medullary thyroid cancer (MTC)

[redacted] was lead in the first multi national workshop in 2014 on the use of Tyrosine-Kinase Inhibitors (TKIs) and what this means for patients. There was global representation from leading clinicians, patient organisations and importantly, two terminally ill patients attended to tell their thyroid cancer

journey and what difference access to TKIs such as Vandetanib and Cabozantenib meant to them.

The organisation is funded primarily by individual fundraisers and funds provided by BACIT (Battle against Cancer Investment Trust). Some grants have been made available via pharmaceutical companies designated for annual projects, such as 'Neck Check event 2011', provision of Patient Information DVDs: " Thyroid Cancer Uncovered' and "Living with Advanced Thyroid Cancer" and The First UK Thyroid Cancer Patient/ Doctor Forum in December 2016, Royal Society of Medicine, Wimpole street, London.

The CEO has been invited to present on the patient perspective on Thyroid Cancer across Europe, the USA and Canada and at two World Thyroid Cancer Congress meetings.

BTCT attends all leading Thyroid Cancer Conferences in the UK.

The organisation comprises of one CEO, one administrative assistant, four trustees, two medical advisors, one honorary president and four patrons. There is a panel of 27 patient support contacts available nationally and there are 3000 members. The organisation works closely with a number of specialist thyroid cancer centres in the UK.

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: No

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Medullary Thyroid Cancer is an extremely rare disease with only approx. 100 new cases per year in the UK.

Living with rare cancer is particularly difficult as often the vital support services readily available for the 'common cancers', such as good patient information and dedicated clinical nurse specialists in every unit are not available.

Patients will have often undergone an extensive and protracted treatment journey over a number of years, which include multiple surgeries and radiotherapy. Sadly despite this, the disease progresses, patients know they cannot achieve a cure for their cancer.

They can often have systemic complications including:

Persistent diarrhoea.

Chest and breathing difficulties from lung metastases

Pain

Pathological bone fractures

Swallowing difficulties causing weight loss through poor nutrition.

Anxiety and depression

Inability to continue working has a huge impact on self esteem, and obvious strain on finances leading to stress, anxiety and further strain on personal relationships. Patients often require psychological support and treatment with anti-depressants.

There is a huge issue with respect to knowing which drugs can make a difference to patients and which ones are actually available to patients through the Health Services, this causes massive frustration when patients know that drugs are there that might help them but cannot be accessed.

Quotes from patients:

"I feel so guilty about having to rely on my husband to do so much for me. His whole life now revolves around caring for me and taking me to hospital"

"I'm a mother and I'm terrified I won't live long enough to see my children go through junior school"

"My daughter is pregnant. I need access to a drug that will help me be around to see this baby born"

Patients and loved ones have no hope for the future.

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

The very fact that licenced drugs which can significantly improve patient's quality of life be consistently made available throughout the Health Service, rather than relying on where they are treated.

Specifically, treatment outcomes should be able to achieve a reduction in the progress of the disease, and preferably show that the disease markers have been abated or significantly reduced. For the patient to have confirmation that their disease is not progressing or is abated provides a huge boost to their psychological well being, as well as potentially, improving their symptoms.

Reduction in tumour marker and tumour size results in improvements in existing symptoms such as improved breathing, reduced pain and less probability of fractures or further invasion of tumour into surrounding tissues. Any positive treatment results greatly improves the patient's sense of well being, leading to improved self esteem, reduction in anxiety, improved family relationships, ability to return to work and contribute to society, and less financial pressure. It gives hope!

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these different treatments and which are preferred and why?

Patients who have advanced MTC have no other conventional thyroid cancer treatments other than palliative intervention.

Conventional cancer treatments have no role, chemotherapy is not effective. Radiotherapy may be used only for pain relief, ie palliative. There is no hope of cure, getting better or containing the disease.

What do patients or carers consider to be the advantages of the treatment(s) being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment(s) being appraised.

Improvement in quality of life, contribute to society again, return to work. Patients and families have hope for the future. Live a 'real' life instead of severely impaired by pain and symptoms. Following many requests from patients with advanced TC, my organization has produced the first ever information DVD. It follows a patient's 8 year battle with the disease and how she has been helped physically and emotionally by having access to a TKI. It has enabled her to see two grandchildren being born, something she had previously thought she would not live long enough to see. "My daughter is pregnant. I need access to a drug that will help me be around to see this baby born". I have acted as a patient advocate on a number of occasions to help facilitate access to Vandetanib following progression on Sorafenib, and have seen first hand how this drug has transformed the lives of terminally ill people. One lady had a permanent wheeze and was house bound. She was totally reliant on her husband to care for her and life revolved around hospital appointments. "I feel so guilty about having to rely on my husband to do so much for me. His whole life now revolves around caring for me and taking me to hospital". Two months taking Vandetanib, the wheeze disappeared and she was able to go on holiday

with her family for the first time in two years. Three months after treatment with Vandetanib there were signs of decrease in tumour size and tumour markers were lowered. Another young woman with brain metastases has three young children. She was severely handicapped due to epileptic seizures. Vandetanib has stopped her having seizures and she is able to get out with her children and look after them properly without relying on outside assistance. These patients have been diagnosed with MTC. I hope these examples will demonstrate the life changing impact this medicine can bring.

Please explain any advantages described by patients or carers for the treatment(s) being appraised compared with other NHS treatments in England.

There are no other treatments available

If you know of any differences in opinion between patients or carers about the benefits of the treatment(s) being appraised, please tell us about them.

None

3. What do patients and/or carers consider to be the disadvantages of the treatment(s) being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS

treatments in England.

Patients and carers are frustrated and angry that they are not being offered licenced medicines which are available elsewhere in the UK and also outside of this environ, which have been proven to improve their quality of life. There are cases where, even within England, patients are moving their care centres to be able to access these drugs. Meaning a further significant disruption in their family and working lives due to travel and stay arrangements.

There is also a distinct disparity in drugs being offered depending on the incidence of the disease, where patients with more common malignancies are seen to be given priority on availability of drugs over those with less well known conditions.

Generally, patients do not manage this condition well. Patients with advanced MTC have no treatment options other than palliative interventions. They have no hope of getting better, remission or cure other than the option of clinical trials. This is often sporadic and limited due to the rarity of the disease. Standard cancer treatment such as chemotherapy have no role. Sorafenib was introduced in 2015 but many patients suffered considerable side effects and have since relapsed with disease progression despite taking this drug.

Please list any concerns patients or carers have about the treatment(s) being appraised.

Side effects of Vandetanib and Cabozentanib can include sore hands and feet, hypertension and alopecia. However, all of these can be well managed by the Cancer Care Team. This may lead to an increase in hospital visits for their management, initially.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment(s) being appraised, please tell us about them.

None

4. Patient population

Are there any groups of patients who might benefit more from the treatment(s) than others? If so, please describe them and explain why.

No

Are there any groups of patients who might benefit less from the treatment(s) than others? If so, please describe them and explain why.

No

5. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment(s)?

x Yes ☐ No

ZETA AND EXAM studies

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment(s) as part of their routine NHS care reflects the experiences of patients in the clinical trials.

The patient's experience would be pretty similar although the side effects will be better controlled due to improved understanding of the medicines. There is no evidence that any new side effects have been experienced off study.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in the assessment of the treatment(s) in clinical trials?

Trials have only been able to test progression free survival. Figures on overall survival would be a useful comparison, but won't be available because most patients receive further therapies on progression in a clinical trial. There is also limited data available on QoL and effect on symtpoms.

If already available in the NHS, are there any side effects associated with treatment(s) being appraised that were not apparent in the clinical trials but have emerged during routine NHS care?

No

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐x Yes ☐ No

If yes, please provide references to the relevant studies.

Dr Laura Moss, Velindre Hospital, Cardiff is conducting a QOL study currently.

6. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

None

Are there groups of patients who would have difficulties using the treatment(s) being appraised or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

No

7. Other issues

Do you consider the treatment(s) being appraised to be innovative?

x☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition. (If this applies to more than one treatment

that is being appraised, please give reasons for each one.)

There are no other medicines available

Are there any other issues that you would like the Appraisal Committee to consider?

There are only approx 100 new cases of MTC each year in the UK.

Not all of these patients will go on to require treatment with TKI therapy, indeed many are cured by surgical intervention.

There are very few patients who will require these medicines so the cost implication would not be significant. Currently there are only 33 patients receiving Vandetanib.

8. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Tumour reduction leads to reduction in pain and symptoms
- There is no other effective treatment available for this cancer group
- Improvement in longevity and quality of life
- Patients and family have hope for the future as well as gain in self esteem and confidence, which leads to:
- Improvement in quality of life so able to contribute to society and return to work

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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1. About you and your organisation

Your name: [redacted]

Name of your organisation: Association for multiple endocrine neoplasia disorders (AMEND)

Your position in the organisation: [redacted]

Brief description of the organisation: AMEND is run for patients by patients with the help of an expert medical advisory team. We provide information resources and support services to families affected by multiple endocrine neoplasia (MEN) disorders and associated endocrine conditions. There are several types of MEN syndrome, with MEN type 2 (formerly MEN2a) and MEN type 3 (formerly MEN2b) incorporating medullary thyroid cancer (MTC). AMEND also offers information and support to those affected by sporadic MTC. AMEND is funded through donations, charitable trust grants and unrestricted pharmaceutical company patient group grants. Our membership totals more than 1,100 including more than 800 patients and family members, mainly from the UK.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: none

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Patients with MEN2 and MEN3 often develop MTC in early childhood. The penetrance of MTC in these conditions is almost 100%. In addition, patients with MEN2 and MEN3 often face the challenges of additional medical conditions associated with the MEN syndromes (such as potentially fatal phaeochromocytoma), as well as having to deal with the health of other family members, including children, who have also inherited the condition. The most common RET gene mutations in MEN2 and MEN3 (codons 634 and 918 respectively) predispose the patient to high levels of aggressiveness of disease.

The most common symptoms of metastatic MTC are a rash, flushing and also diarrhoea, which is difficult to control with normal anti-diarrhoeal medications. Fatigue, bone pain and muscle weakness are also reported. The diarrhoea has the greatest negative impact on quality of life and on mental health, with patients reporting that they cannot go out without worrying whether or not there will be a toilet everywhere they go. One patient said, 'My life revolves around going to the toilet which is upsetting and embarrassing because you can't tell people about it'. Not being able to go out, take a day trip or even a holiday impacts negatively not just on the patient but also on their partner and/or family. Any children of a parent with metastatic MTC associated with MEN2/3 may also be negatively impacted emotionally from watching their parent's decline in health, especially if the child has inherited the same condition. Adults with metastatic MTC are often frustrated and suffer compounded mental ill-health at not being able to work.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Like any other cancer patient, the most important treatment outcome is cure of their disease. The Final Scope does not emphasise that appropriate and timely surgery from an experienced surgeon provides the ***only*** possibility for a definitive cure for MTC. Appropriate and timely surgery in MEN usually means surgery in early childhood: within the first year of life in MEN3 and before age 5 in MEN2, preferably before the cancer has developed (prophylactic thyroidectomy). Whilst this is achievable in children with a known family mutation, those diagnosed later in life may need more extensive or multiple surgeries to control the disease. MTC can spread early on in life and therefore the presence if metastatic MTC is relatively common within the patient population. Whilst there is some valuable research in progress into a cure for MTC, this is minimal in comparison with other cancer types. The small patient population also makes meaningful research challenging. Nevertheless, research gives these patients hope for a cure.

Secondly, patients want treatments to extend their life, not just to be with their families or to get their affairs in order, but simply to continue as normal a life as possible, including working. In addition, patients hope to live long enough for another treatment option to be developed and become available to either cure their cancer or to continue to prolong life until a cure is found. The British Thyroid Association guidelines state that, 'Vandetanib and cabozantinib….have shown progression free survival advantage over placebo in prospective randomised controlled trials of 11 and 7 months respectively'.

Finally, the control of the symptoms of metastatic MTC in order to achieve an improved quality of life is extremely important. The Final Scope also does not make it clear that traditional radiotherapy and chemotherapy offer limited utility and are generally only used palliatively to reduce symptoms such as bone pain. The BTA guidelines state that, 'Routine adjuvant external beam radiotherapy (EBTR) has not been shown to improve survival', and that 'Chemotherapy is now rarely used'. Improving the symptoms of metastatic MTC such as diarrhoea and pain improves mental health, quality of life for the whole family, and can result in the patient's continuation of or return to work.

Perros, P et al, BTA guidelines for the management of thyroid cancer. Third edition. British Thyroid Association. July 2014, Clinical Endocrinology, Vol 81, Supp. 1, Chapter 17 'Medullary Thyroid Cancer'

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these different treatments and which are preferred and why?

Metastatic MTC is currently incurable. Radioactive isotope therapy (i.e. MIBG or Octreotide) may offer some symptom relief and progression free survival, but only in those people who show take-up of these agents. Moreover, these treatments require repeat in-patient care and are invasive with potential side effects. Vandetanib and cabozantinib offer a potential period of progression free survival in simpler non-invasive oral form in an outpatient setting. Both treatments show significant progression free survival in RET mutation MTC. In an era of increasingly personalised medicine, both treatments may form the first in a range of tools to treat this condition and extend life until such time as a cure is found.

These agents [vandetanib, cabozantinib] have shown the potential to provide high rates of disease control with durable responses and improved quality of life, and a highly significant improvement of progression-free survival (Schlumberger et al, European Thyroid Association Guidelines for Metastatic MTC, European Thyroid Journal, 2012).

Although cabozantinib does not effect a cure it achieved a statistically significant improvement of progression free survival in clinical trials (Elisei al. 2013).

Targeted therapies are the modality of choice for inoperable progressive and symptomatic disease. Vandetanib and cabozantanib (both tyrosine kinase inhibitors) have shown progression free survival advantage over placebo in prospective randomised controlled trials of 11 and 7 months respectively (Perros et al, BTA Guidelines 2014)

4. What do patients or carers consider to be the advantages of the treatment(s) being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment(s) being appraised.

Benefits of these treatments as described by patients include significant improvements in quality of life due to the tumour growth control and potential

alleviation of symptoms such as diarrhoea, resulting in the ability to more easily leave the house, attend hospital appointments, take a day trip or go on holiday with less worry and embarrassment about frequently needing to find a toilet. The resulting ability to continue working (or return to work) offers improvements in mental health and financial means. These treatments are available in tablet form which means that they are extremely easy to take as an outpatient at home. Dose reductions or 'Drug holidays' are also simpler to implement in the event of serious side effects. Finally, these treatments offer hope to the patient and may help to extend life until such time as other curative or life-extending treatments are developed.

Please explain any advantages described by patients or carers for the treatment(s) being appraised compared with other NHS treatments in England.

Despite no clinical trials into their use in metastatic MTC, radioactive isotope therapy (i.e. MIBG or Octreotide) may currently be used, but only in those people who show take-up of these agents, thus limiting their utility. These treatments require repeat in-patient care, are invasive with slow injection, and have potential side effects. Despite also often causing side-effects such as diarrhoea, rash, nausea, fatigue, hand/foot syndrome and weight-loss (most of which may be managed with other medications), vandetanib and cabozantinib offer a potential period of progression free survival (more so in RET mutation MTC) in simpler non-invasive oral form in an outpatient setting. Simpler, non-invasive and outpatient treatment methods are favoured by patients and carers.

If you know of any differences in opinion between patients or carers about the benefits of the treatment(s) being appraised, please tell us about them.

There are no differences in opinion between patients or carers.

5. What do patients and/or carers consider to be the disadvantages of the treatment(s) being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse

- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Patients' concerns about the current treatments for metastatic MTC in the NHS in England surround the lack of current curative treatments together with the lack of research into MTC compared to other cancer types.

Please list any concerns patients or carers have about the treatment(s) being appraised.

Patients are aware that these treatments do not provide a cure and are concerned at the resistance that they may develop to them over time together with the lack of follow-up treatment options when this happens. They dislike the side-effects but many may be managed with additional medications and patients are often willing to put up with these when they know that the treatment may control further tumour growth. Increased hospital visits for monitoring risk exposure to infection and increases the financial impact on patients. Diarrhoea in some patients may remain or be made worse by these treatments.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment(s) being appraised, please tell us about them.

n/a

6. Patient population

Are there any groups of patients who might benefit more from the treatment(s) than others? If so, please describe them and explain why.

No; all patients with metastatic MTC may benefit from both treatments. However, those with positive RET mutations (including those with MEN2 and MEN3) showed increased benefit.

Are there any groups of patients who might benefit less from the treatment(s) than others? If so, please describe them and explain why.

Those patients with RET negative status may benefit less than those who are RET positive.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment(s)?

☑ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment(s) as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Yes

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in the assessment of the treatment(s) in clinical trials?

Yes, the clinical trials captured outcomes of importance to patients – namely progression free survival. There is a suggestion that those patients on the vandetanib trial were not as sick as those on the cabozantinib trial,however, cabozantinib resulted in a longer progression free survival.

If already available in the NHS, are there any side effects associated with treatment(s) being appraised that were not apparent in the clinical trials but have emerged during routine NHS care?

No

Are you aware of any relevant research on patient or carer views of the

condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☑ No

If yes, please provide references to the relevant studies.

n/a

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

None

Are there groups of patients who would have difficulties using the treatment(s) being appraised or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Patients who are not under the care of an expert multidisciplinary team may not be able to access currently available treatments.

9. Other issues

Do you consider the treatment(s) being appraised to be innovative?

☑ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition. (If this applies to more than one treatment that is being appraised, please give reasons for each one.)

Vandetanib and cabozantinib offer a potential period of progression free survival in simple, non-invasive oral form in an outpatient setting, unlike other treatments. Both treatments show significant progression free survival in RET mutation MTC. They offer the opportunity to extend life until such time as further life-extending treatments are developed or a cure is found.

Are there any other issues that you would like the Appraisal Committee to consider?

n/a

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Patients with metastatic MTC want a cure for their disease, but this is not yet forthcoming
- In the current absence of a cure, they want progression free survival, both of which have been demonstrated using cabozantenib and vandetanib, which may enable them to take advantage of new treatments as they arise
- Some patients experience alleviation of the diarrhoea caused by their MTC from these treatments which improves their quality of life and mental health
- Side-effects from these treatments may be managed with other medications and are seen by many patients as a trade-off against progression free survival and the hope for new treatments
- Both cabozantenib and vandetanib show varying toxicities in different patients, and resistance may eventually develop; therefore the ability to switch between the treatments is needed

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Cabozantinib and vandetanib for treating unresectable locally advanced or metastatic medullary thyroid cancer [ID56]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: NCRI-ACP-RCP-RCR

Are you (tick all that apply):

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: NONE

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Cabozantinib and vandetanib for treating unresectable locally advanced or metastatic medullary thyroid cancer [ID56]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?

Patients with advanced medullary thyroid cancer (MTC) may not require any treatment intervention as the disease may be relatively indolent and remain stable for many years. Currently Vandetanib and Cabozantinib are the only disease modifying drugs licensed in the setting of advanced and progressing MTC. Both are funded for first line treatment in England via the Cancer Drugs Fund (CDF). Cabozantininb is funded in Wales but cabozantinib is not. Neither Vandetanib nor Cabozantinib are recommended by the Scottish Medicines Consortium (SMC); clinicians request these drugs on an individual patient funding basis.

Within England Are there differences of opinion between professionals as to what current practice should be?

No. Within England there is consistency among professionals that targeted therapy with either vandetanib or cabozantinib is the modality of choice in advanced, progressing and symptomatic or imminently symptomatic MTC.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Localised ablative therapies such as surgery and radiotherapy can be useful for controlling a specific symptom caused by a deposit of disease. Supportive measures with analgesia, anti-diarrhoeal agents and bisphosphonates or denosumab can help improve symptoms. None of these interventions are disease modifying but form a best supportive care approach. Radioisotope therapy, for example with lutetium-177 labelled octreotide analogues or Iodine-131 MIBG, is sometimes considered but this treatment lacks phase III data and is not licensed for the treatment of advanced MTC.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?

There continues to be research into the predictive role of the RET mutation. Currently there is not sufficient evidence to exclude treatment for patients without a RET mutation; indeed the trials have shown response to both vandetanib and cabozantinib in RET negative and RET positive tumours.

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Research continues to try to identify subgroups that may benefit more from the technologies. Data is awaited.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?

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These drugs are currently administered within the secondary care setting and we would strongly advocate use within a specialist multidisciplinary thyroid cancer clinic for optimal care.

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Specialist nurses support for patients on these drugs is strongly advised.

If the technology is already available, is there variation in how it is being used in the NHS?

Variation according to availability across the UK as above.

Is it always used within its licensed indications? If not, under what circumstances does this occur?

Our understanding is that clinicians are prescribing according to the licensed indications.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The British Thyroid Association Guidelines on Thyroid Cancer, the American Thyroid Association Guidelines on management of MTC and the European Guidelines on management of metastatic MTC all advise consideration of targeted agents specifically referencing the only two licensed agents vandetanib and cabozantinib for management of advanced MTC.

Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Wells SA Jr1, Asa SL2, Dralle H3, Elisei R4, Evans DB5, Gagel RF6, Lee N7, Machens A3, Moley JF8, Pacini F9, Raue F10, Frank-Raue K10, Robinson B11, Rosenthal MS12, Santoro M13, Schlumberger M14, Shah M15, Waguespack SG6; American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma. Thyroid. 2015 Jun;25(6):567-610.

Guidelines for the management of thyroid cancer.
Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard Ba G, Gilbert J, Harrison B, Johnson SJ, Giles TE, Moss L, Lewington V, Newbold K, Taylor J, Thakker RV, Watkinson J, Williams GR; British Thyroid Association. Clin Endocrinol (Oxf). 2014 Jul;81 Suppl 1:1-122.

2012 European thyroid association guidelines for metastatic medullary thyroid cancer.
Schlumberger M, Bastholt L, Dralle H, Jarzab B, Pacini F, Smit JW; European Thyroid Association Task Force. Eur Thyroid J. 2012 Apr;1(1):5-14.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Cabozantinib and vandetanib for treating unresectable locally advanced or metastatic medullary thyroid cancer [ID56]

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Most clinicians follow the starting and stopping criteria that were defined in the ZETA and EXAM trials, i.e. start once disease has progressed by RECIST criteria within last 12 months and disease is symptomatic or imminently symptomatic; stopping the drug on progression of disease by RECIST.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice.

Yes we feel the trials reflect clinical practice.

Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting?

The trials were investigating the role of new agents in the setting where there were none.

What, in your view, are the most important outcomes, and were they measured in the trials?

Both trials reported benefits in terms of progression free survival compared to placebo (11.2 months versus 4 months for Cabozantinib; 30.5 months versus 19.3 months for vandetanib). For our patients this translates in delay in presentation of symptoms or worsening of symptoms due to progressing disease and may reduce the need for other interventions such as painkillers, palliative radiotherapy or surgery. Unfortunately it is unlikely that we will get data on overall survival benefit from these studies as most patients either 'crossed over' to the active drug from placebo on progression of disease and/or will have subsequently enrolled onto clinical trials for second or third line agents.

If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Cabozantinib and vandetanib for treating unresectable locally advanced or metastatic medullary thyroid cancer [ID56]

The side effects are well recognised toxicities of kinase inhibitors and there is good guidance on how to manage these. Best practice dictates frequent review in first month of starting a drug in order to adjust the dose and/or add in some supportive medications and generally side effects are manageable. Specific side effect of vandetanib is QTc prolongation so ECG monitoring is required and careful attention to concomitant medications that may promote QTc prolongation. Gastrointestinal perforations, fistula development and haemorrhage were noted in patients receiving Cabozantinib and therefore careful assessment of individual patients and their risk of these events due to site of disease is recommended.

In what ways do these affect the management of the condition and the patient's quality of life?

If managed promptly and appropriately these side effects will have minimal effect on quality of life but inevitably both side effects and requirement for hospital visits will have an impact on quality of life. This should therefore be balanced by the likely benefits as assessed by the clinician of slowing progression of disease and possible reduction in disease bulk.

Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Not that we are aware

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

We are not aware of any

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition?

Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

This would not change the availability of the drugs for first line treatment in England. If NICE made any recommendations regarding use in second line then this might increase the numbers being treated but the numbers would be very small and managed by the same teams with expertise.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

We do not foresee any problems regarding this.

NHS England submission to NICE re appraisal of cabozantinib and vandetanib in the treatment of medullary thyroid cancer (MTC)

1. The need for systemic therapy of unresectable locally advanced or metastatic MTC is rare, there being only just over 30 new patients commencing cabozantinib or vandetanib via the CDF each year.
2. Patients with unresectable locally advanced or metastatic MTC generally live for years with their disease which usually progresses slowly. As a consequence, a watch and wait policy is adopted as patients can have active lives for years until they become symptomatic of their advancing disease. It is at this point that systemic drug therapy is indicated as the potential gain of symptomatic benefit then justifies the side-effects of treatment. The 10 year survival rate for unresectable locally advanced/metastatic MTC is 20-40%, an indication of the slow growth rate of MTC.
3. Chemotherapy is not very active at all in MTC and thus it is fair to say that cabozantinib and vandetanib represent the only effective systemic drug treatment options for this disease.
4. Cabozantinib and vandetanib do not have identical modes of action but do share a significant number of common targets involved in tumour growth and angiogenesis.
5. The cabozantinib placebo-controlled RCT only included patients who had documented progressive disease and who were symptomatic whereas the vandetanib placebo-controlled RCT did not specify the need for progressive disease or symptoms. The ITT populations in the two trials therefore are not the same and this is shown by the PFS for the placebo arms: 3.1 mo (investigator) and 4.0 mo (independent) in the cabozantinib trial versus 19.3 mo (independent) in the vandetanib trial. The cabozantinib ITT population of 330 patients thus directly provides evidence as a whole to the marketing authorisation and to the clinical effectiveness of cabozantinib in UK practice. However, a post hoc analysis on 186 patients in the 331 patient vandetanib trial was required to identify the evidence base for the clinical effectiveness of vandetanib in respect of the marketing authorisation and the clinical effectiveness of vandetanib in UK practice. NHS England therefore considers that the pedigree of evidence for cabozantinib is better than for vandetanib as to how these drugs are likely to impact on patients in the clinical setting.
6. Cross over from the placebo arm was formally allowed in the vandetanib RCT and will have informally occurred in the cabozantinib RCT as a consequence of the licensing of both agents and via opportunities for patients to access these or other drugs via clinical trials. It is therefore no surprise that despite a substantial difference in PFS observed in both RCTs, there is no observed difference in overall survival.
7. Because both drugs do not have identical modes of action, they have different side-effects although many of the toxicities are common to both. Cabozantinib causes more hand-foot skin toxicity whereas vandetanib results in more cardiac toxicity.

Dose interruptions or reductions appear higher with cabozantinib at 87% versus 47% for vandetanib but these figures cannot be directly compared because of the different populations of patients in the 2 trials and because of differences in performance status (67% performance status 0 who received vandetanib, 56% who received cabozantnib). Both drugs are subject to additional monitoring by the MHRA on account of their toxicities. What is clear that current licensed doses of both drugs have significant toxicities and patients on these agents require close monitoring (blood tests, ECGs and clinically for a wide variety of side-effects).

8. NHS England notes that an 81 patient randomised phase II trial has completed recruitment which compares current licensed dose of vandetanib (300mg) with half this dose (150mg) with a primary endpoint of response rate. It may be that a lower dose of vandetanib can achieve much of the benefit of treatment as a higher dose but at reduced toxicity. It will be important to know when this study will report and then potentially affect the drug's license.
9. NHS England notes that a 188 patient randomised trial is comparing the current licensed dose of cabozantinib (140mg) with less than half this dose (60mg) with a primary endpoint of progression free survival. It may be that a lower dose of cabozantinib can achieve much of the benefit of treatment as a higher dose but at reduced toxicity. It will be important to know when this study will report and then potentially affect the drug's license.
10. NHS England notes the comments made re RET status by the AG and supports the view that use of such status is not possible in potentially deriving a valid and robust subgroup of potentially greater clinical and cost effectiveness. NHS England observes that the marketing authorisations for both drugs state that patients with unknown/negative RET mutation status for their MTC may derive lower benefit from the two drugs. Such RET mutation status for the disease is best determined at the time of treatment and this is not routine practice in England. Thus the RET status of progressive disease would be a difficult biomarker to implement and in any case requires greater robustness of data to support its use.
11. NHS England notes too the analyses performed on patients with serum marker doubling times for calcitonin and CEA of less than or greater than 24 mo. In English practice, what primarily matters in the clinic and when considering systemic therapy with cabozantinib/vandetanib is whether the patient is symptomatic or not. Such serum marker doubling times are of interest but not used in routine practice.
12. NHS England note that patients in the vandetanib trial could continue on vandetanib after investigator-assessed disease progression (and at least one third of patients did so). In English practice, treatment ceases on disease progression as the treatment is not working and also because quality of life can then be improved by stopping the side-effects of treatment.
13. Vandetanib has 1 marketing authorisation and this is in MTC. Cabozantinib has two marketing authorisations but has two different brand names: cabometyx at a

recommended daily dose of 60mg in renal cancer and cometriq at a recommended dose of 140mg daily in MTC. Such an arrangement with 2 different brand names allows 2 different prices to be set for the same parent drug.

14. The CDF currently has both vandetanib and cabozantinib as options for treating unresectable locally advanced or metastatic MTC. These 2 drugs are as either-or options although patients can swap from one to the other if they cannot tolerate the first drug as long as their disease has not progressed at the time of swapping.
15. The CDF was never presented with any data as to sequential use of these 2 agents. In the cabozantinib phase III trial, 10% of patients had previously received vandetanib. In the vandetanib trial, 40% had received previous systemic therapy but it is not known what these treatments were and how many had received prior cabozantinib. NHS England is not aware of any prospective phase II data as to the sequential use of these 2 drugs and their efficacies and toxicities. Given the substantial overlap in the modes of action of vandetanib and cabozantinib, there is biological plausibility to expect a lesser average benefit with the second drug after disease progression on the first, hence the CDF's current position.
16. Vandetanib and cabozantinib have been in the CDF for over 3 years. NHS England does not regard them as being routinely commissioned: cabozantnib and vandetanib will only be regarded as being routinely commissioned when they are recommended by NICE and thus are funded by the baseline chemotherapy commissioning budget.
17. In summary, MTC is an unusual cancer as patients can often live with their unresectable locally advanced/metastatic disease for years as the disease only progresses slowly. Treatment is only indicated when patients become symptomatic. Both cabozantinib and vandetanib are active drugs in MTC and have a considerable impact on progression free survival but no proof of overall survival improvement. They both have considerable common side-effects although there are some toxicities which apply to one drug versus the other. Dose interruptions and delays are frequently required for both drugs and in practice a significant percentage of patients are unable to tolerate one or the other drug or both. The pedigree of evidence for symptomatic patients in whom systemic therapy is indicated in English practice is better for cabozantinib than it is for vandetanib in view of the design of the cabozantinib RCT. Cabozantinib and vandetanib are the only effective systemic therapy drug options for MTC which explains why they remained in the CDF despite having high individual patient drug costs for treatment.

Prof Peter Clark

NHS England Chemotherapy Lead and National Clinical Lead for the Cancer Drugs Fund

July 2017

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (MTA)

Cabozantinib and vandetanib for treating unresectable locally advanced or metastatic medullary thyroid cancer [ID56]

Thank you for agreeing to give us your views on the treatment(s) being evaluated by NICE in this appraisal and how it/they could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment(s).

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages. If you think your response will be significantly longer than this, please contact the NICE project team to discuss.

When answering the questions from section 3 onwards, please make sure to specify which treatment (s) you are commenting on.

1. About you

Your name: Gareth Bowen
Name of your nominating organisation: Butterfly Thyroid Cancer Trust
Do you know if your nominating organisation has submitted a statement?

☑ Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

☑ Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☑ Yes ☐ No

- a carer of a patient with the condition?

☐ Yes ☑ No

- a patient organisation employee or volunteer?
-

☐ Yes ☑ No

Do you have experience of the treatment (s) being appraised (that is, those included in the title)?

☑ Yes ☐ No

If yes, please tell us which one(s)

Vandetanib

If you wrote the submission from the patient organisation and do not have anything to add, tick here ☐ (If you tick this box, the rest of this form will be deleted after submission.)

2. Living with the condition

What is your experience of living with the condition as a patient or carer?

I was diagnosed with Medullary thyroid cancer in 2005 and had 2 operations to remove the tumours - that last a significant op over 18hrs long followed by many weeks recover (including 2 weeks ITU & HDU). This was followed up 6 months later with 6 weeks of radiotherapy. Following that I have managed to recover reasonably well and the cancer remained static for 4.5yr. As such I was able to return to work, despite still suffering pain from the surgery. Then in 2011 scans showed it had started to metastasise further and there were some tumours in my lungs and liver.

3. Current practice in treating the condition

Which treatment outcomes are important to you? (That is, what would you like treatment to achieve?) Which of these are most important? If possible, please explain why.

Ideally to be cured, but this isnt possible. So I would want that the treatment be able to halt/limit the disease and side effects with a minimal level of its own side-effects. This should allow me to lead a reasonable normal lifestyle.

What is your experience of currently available NHS care and of specific treatments? How acceptable are these treatments – which did you prefer and why?

For someone in my condition/stage, I was told there were no further standard treatments available other than palliative care. It was somewhat of a shock that there was no further treatment possible. However I did manage to get onto the vandetanib drug trial.

4. What do you consider to be the advantages of the treatment(s) being appraised?

Benefits of a treatment might include its effect on:
• the course and/or outcome of the condition

- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that you expect to gain from using the treatment(s) being appraised.

Vandetanib treatment has allowed me to continue my life with minimal complications. The cancer is not increasing and is being held at bay and calcitonin count is descreasing. I am still able to work and perform most normal activities with my family. As a daily tablet treatment it is very convenient. It provides hope where there was none.

Please explain any advantages for the treatment(s) being appraised compared with other NHS treatments in England.

From what I understand there was no other treatments. So the advantage is that this offers a treatment where there was none.

If you know of any differences in opinion between you and other patients or carers about the benefits of the treatment(s) being appraised, please tell us about them.

n/a

5. What do you consider to be the disadvantages of the treatment(s) being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might

be willing to accept or tolerate and which would be difficult to accept or tolerate)

- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns you have about current NHS treatments in England.

As far as I understand there are no conventional treatments available for advanced MTC. It is therefore a concern that a treatment like Vandetanib is currently not generally offered by the NHS.

Please list any concerns you have about the treatment(s) being appraised.

There are some side-effects which impact me –

frequent diarrhoea (reduced by daily loperamide); some tiredness/reduced energy levels; I am frequently cold; acne; a rash on lower legs; raised BP (tablet controlled); I have noticed a slight decrease in mental acuity and concentration, sensitivity to sunlight (can be bad); tender fingertips and tongue at times; reduced healing (particularly noticeable on leg skin) and I have had a slight weight loss. However, I generally do not find these significant issues compared with alternative – eg without this treatment diarrhoea is likely to have been much worse due to the cancer. In addition I need to attend monthly outpatients for tests/monitoring due to some potential dangerous side effects with heart and brain.

Aside from this my main concern is that this drug will stop working or side effect increase in severity. Another concern is that the drug will be taken away due to cost cutting.

If you know of any differences in opinion between you and other patients or carers about the disadvantages of the treatment(s) being appraised, please tell us about them.

n/a

6. Patient population

Do you think some patients might benefit more from the treatment(s) than others? If so, please describe them and explain why.

no

Do you think some patients might benefit less from the treatment(s) than others? If so, please describe them and explain why.

no

7. Research evidence on patient or carer views of the treatment

Are you familiar with the published research literature for the treatment(s)?

☐ Yes ☑ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether your experience of using the treatment(s) as part of routine NHS care reflects the experience of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in the assessment of the treatment(s) in clinical trials?

If already available in the NHS, are there any side effects associated with the treatment(s) being appraised that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity and eliminating discrimination. Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, who they are and why.

n/a

9. Other issues

Do you consider the treatment(s) being appraised to be innovative?

☑ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition. (If this applies to more than one treatment that is being appraised, please give reasons for each one.)

As far as I know there is no alternative to Vandetanib. This has halted all further increase in my cancer for over 5 years. I expect that I would not be alive today if this drug was not available.

Is there anything else that you would like the Appraisal Committee to consider?

no

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- It has successfully halted progression of my cancer for >5yr
- The side effects I experience are manageable
- Tablet based treatment is very convenient
- I am still able to work and contribute
- I have a young family and have been around as they are growing up

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Cabozantinib and vandetanib for treating unresectable locally advanced or metastatic medullary thyroid cancer

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:
Mary Lei

Name of your organisation
Guy's and St Thomas' NHS Foundation Trust

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? YES
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? YES
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? YES – consultant oncologist responsible for proposing and developing local treatment protocols for this condition
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: N/A

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

What is the expected place of the technology in current practice?

Thyroid cancer accounts for 1% of all new cases of cancer in the UK and in 2014, there were 3404 new cases of thyroid cancer diagnosed in the UK (Office for National Statistics data). Medullary thyroid cancer (MTC) is a rare disease, accounting for approximately 3% of all adult thyroid cancers. Approximately 25% of MTCs are hereditary, occurring as part of the multiple endocrine neoplasia (MEN2/3) or familial MTC (FMTC) syndromes. Due to this disease being rare, the British Thyroid Association (BTA) has recommended in the 2014 guidelines that patients are referred for management in a specialist clinical service with support from a regional genetics centre.

For patients with unresectable locally advanced or metastatic MTC, effective treatment strategies are lacking. Traditional treatment approaches for metastatic cancer of other tumour sites include chemotherapy and radiotherapy. In MTC, cytotoxic chemotherapy, for example, doxorubicin, either as single agent or in combination with other drugs, or 5-fluorouracil and dacarbazine, are associated with poor response rates (20-30%) of short duration and are associated with a number of adverse side effects. As a result, chemotherapy is infrequently used. There does not appear to be any significant geographical variation in practice in this respect. The American Thyroid Association (ATA) 2015 guidelines recommend that cytotoxic chemotherapeutic regimens should not be administered as first-line therapy in this setting in view of low response rates and the advent of promising new treatment options.

Palliative radiotherapy is helpful to treat symptomatic masses or painful bone metastases. It is not useful for the treatment of widespread metastatic disease. In general, MTC is not regarded as a highly radiosensitive disease. Other ablative therapies such as surgery, thermoablation or chemoembolization have been considered to treat some sites of metastatic disease on a case-by-case basis.

Treatment with radiolabelled molecules or pretargeted radio-immunotherapy may be considered in selected patients and both the BTA and ATA recommend that this would most ideally be given in the setting of a clinical trial.

The BTA 2014 and ATA 2015 guidelines both recommend treatment with tyrosine kinase inhibitors (TKIs) targeting both rearranged during transfection (RET) and vascular endothelial growth factor receptor (VEGFR) tyrosine kinases as the treatment modality of choice. Both guidelines recommend that vandetanib and cabozantinib, oral TKIs, can be used in this setting, with the ATA guidelines further recommending treatment with vandetanib or cabozantinib as first-line single agent systemic therapy.

Currently, clinical trials are attempting to answer the question as to whether RET mutation status has an impact on the therapeutic benefit of treatment with TKIs. Improvements in progression free survival (PFS) have been observed both in patients with and without a RET mutation.

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Multiple Technology Appraisal (MTA)

My personal perspective is that since the NHS England Cancer Drugs Fund made vandetanib and cabozantinib available as first-line treatment for patients with unresectable, locally advanced or metastatic MTC, providing the disease was progressive or symptomatic, oncologists in England who are specialist in treating this condition have recommended first-line single agent treatment with either vandetanib or cabozantinib in this setting over all other treatment modalities.

Although unresectable, locally advanced or metastatic MTC is associated with a poor prognosis, the natural history of the disease can be very variable with some patients surviving many months to years even in the presence of substantial disease burden. The question regarding when is the optimal time to initiate TKI treatment is an established theme amongst thyroid oncologists. Discussion with my thyroid oncology colleagues has confirmed that oncologists try to delay initiating therapy for as long as is clinically appropriate, before commencing therapy. In the setting of slowly progressive symptomatic disease, balancing the symptoms of disease with well known side effects of TKIs can be challenging and requires the input from an experienced specialist oncologist. Many patients have learned to live with their diagnosis and continue to live active lifestyles or continue to work despite symptomatic progressive disease and may only accept treatment when they feel that their disease-related symptoms have progressed to such a point that they have poor quality of life and are unable to continue with their normal social or professional lives.

My personal opinion is that these treatments should be delivered by an oncologist in the setting of a specialist unit located in a secondary or tertiary centre. This service would be supported by specialist oncology pharmacists and oncology nurses and would ideally be supported during hours by an acute oncology service and out of hours by a 24 hour oncology emergency advice service.

Regarding the toleration of treatment with oral TKIs, it is common for patients to develop side effects that without close and specialist support, may rapidly cause them to feel unwell or experience significant detriment to their quality of life. These side effects are many in number and diverse, ranging from common, less severe effects including mucositis (sore mouth), poor appetite, fatigue, diarrhoea, rash, photosensitivity and hypertension, to rarer but potentially life threatening side effects including ECG changes (QTc interval prolongation) or gastro-intestinal perforation or fistulation. With the support of an experienced oncologist and appropriate specialist oncology infrastructure (nursing/pharmacy/acute oncology support), this treatment can be made as safe as possible. Patient care and safety can be further enhanced by good access to other specialties including cardiology, renal, gastrointestinal physician and dermatology teams.

The Cancer Drugs Fund's criteria on funding these drugs include the requirement that no previous TKI therapy has been given, unless the patient is deemed intolerant to vandetanib and cabozantinib, respectively. I believe that the oncology community observes these criteria. However, there is a widespread impression that this criteria is strict and may prevent appropriate treatment from being delivered. It is expected that patients will develop a number of side effects, with varying and sometimes unpredictable severity according to each patient. Often, it will be several weeks before the optimal tolerated dose has been titrated or before the oncologist deems a patient intolerant to these drugs. With the current criteria, there is a concern that by

the time that it has become clear that a patient is intolerant to their prescribed TKI, they may not be considered eligible to receive the other remaining TKI as an alternative.

The Cancer Drugs Fund provides for either cabozantinib or vandetanib only in the first line setting. There is no provision for the second line setting. Oncologists must choose one of the two drugs and this choice is usually made on their best assessment as to which drug would be best tolerated, as there is no evidence to show superiority in either drug. Whilst both drugs are oral TKIs with demonstrated efficacy, they are different drugs. This is supported by their differing side effect profile. There is a widespread view that it would be beneficial to patients if both drugs could be made available, to be delivered in sequence. The optimal sequence is not known.

Regarding the discontinuation of treatment, this would take place either on disease progression (Cancer Drugs Fund criteria for stopping) or due to excessively high or cumulative side effects. I feel that it would be unlikely for the drug to be continued beyond disease progression, as due to the side effects of the drug combined with symptoms of progressive disease, patients would not be able to and would not choose to continue treatment. Therefore it would be unlikely that this criteria from the Cancer Drugs Fund would be not observed.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Not applicable.

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Multiple Technology Appraisal (MTA)

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Unfortunately not. This is a rare disease and there is a paucity of evidence beyond the two well known phase III studies evaluating vandetanib and cabozantinib (ZETA 2012 and EXAM 2013 studies, respectively) both of which included around 330 patients each.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

My personal recommendation would be for these treatments to be delivered in a specialist oncologist setting supported by an oncology service infrastructure. These oncologists are most likely already treating with these drugs in this setting and it is unlikely that additional resources would be required.