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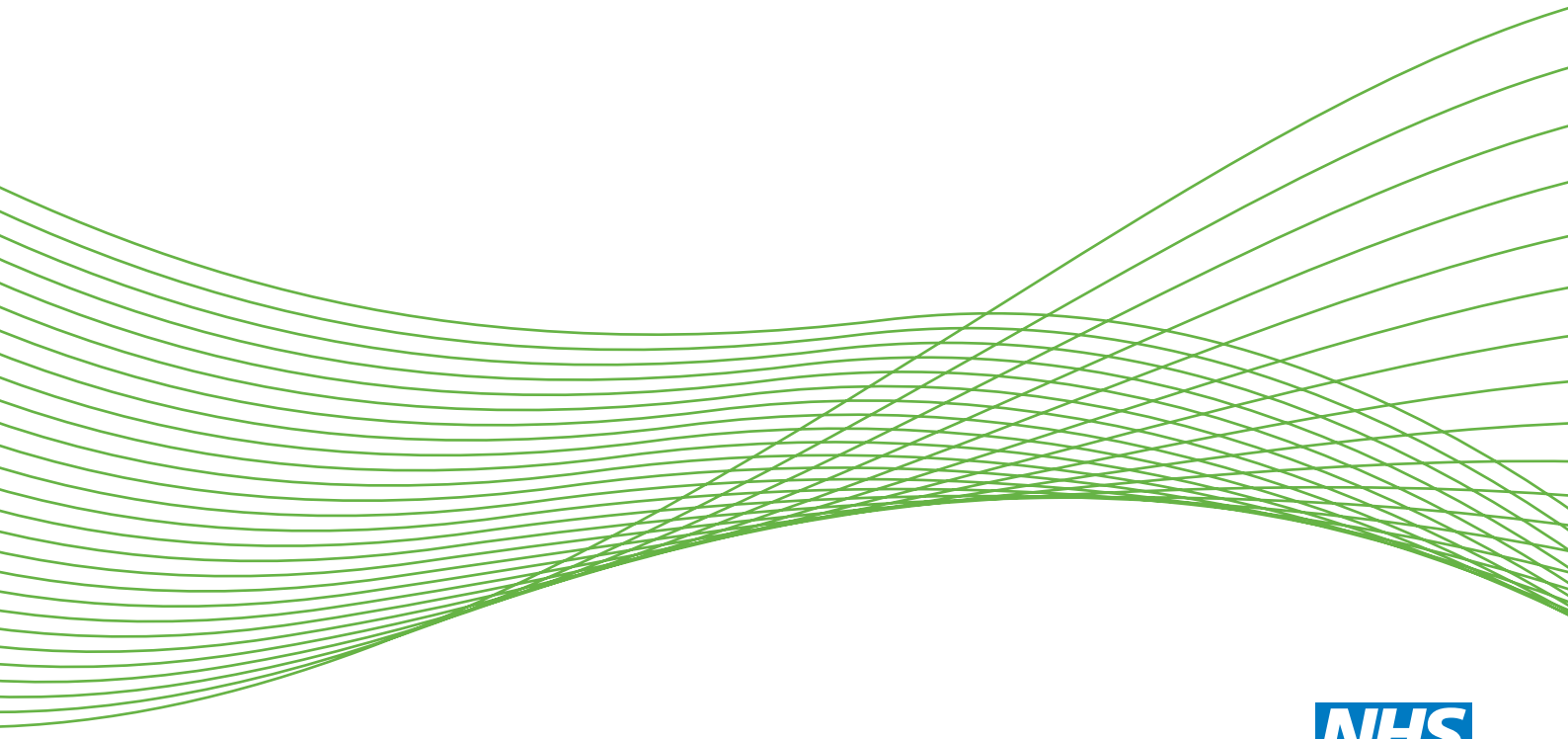

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Paul Tappenden,[1]* Christopher Carroll,[1] Jean Hamilton,[1] Eva Kaltenthaler,[1] Ruth Wong,[1] Jonathan Wadsley,[2] Laura Moss[3] and Sabapathy Balasubramanian[4]

[1]Health Economics and Decision Science, School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK
[2]Weston Park Hospital, Sheffield, UK
[3]Velindre Cancer Centre, Cardiff, UK
[4]Department of Oncology and Metabolism, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

*Corresponding author

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Abstract

Cabozantinib and vandetanib for unresectable locally advanced or metastatic medullary thyroid cancer: a systematic review and economic model

Paul Tappenden,[1]* Christopher Carroll,[1] Jean Hamilton,[1] Eva Kaltenthaler,[1] Ruth Wong,[1] Jonathan Wadsley,[2] Laura Moss[3] and Sabapathy Balasubramanian[4]

[1]Health Economics and Decision Science, School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK
[2]Weston Park Hospital, Sheffield, UK
[3]Velindre Cancer Centre, Cardiff, UK
[4]Department of Oncology and Metabolism, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

*Corresponding author p.tappenden@sheffield.ac.uk

Background: Medullary thyroid cancer (MTC) is a rare form of cancer that affects patients' health-related quality of life (HRQoL) and survival. Cabozantinib (Cometriq®; Ipsen, Paris, France) and vandetanib (Caprelsa®; Sanofi Genzyme, Cambridge, MA, USA) are currently the treatment modality of choice for treating unresectable progressive and symptomatic MTC.

Objectives: (1) To evaluate the clinical effectiveness and safety of cabozantinib and vandetanib. (2) To estimate the incremental cost-effectiveness of cabozantinib and vandetanib versus each other and best supportive care. (3) To identify key areas for primary research. (4) To estimate the overall cost of these treatments in England.

Data sources: Peer-reviewed publications (searched from inception to November 2016), European Public Assessment Reports and manufacturers' submissions.

Review methods: A systematic review [including a network meta-analysis (NMA)] was conducted to evaluate the clinical effectiveness and safety of cabozantinib and vandetanib. The economic analysis included a review of existing analyses and the development of a de novo model.

Results: The systematic review identified two placebo-controlled trials. The Efficacy of XL184 (Cabozantinib) in Advanced Medullary Thyroid Cancer (EXAM) trial evaluated the efficacy and safety of cabozantinib in patients with unresectable locally advanced, metastatic and progressive MTC. The ZETA trial evaluated the efficacy and safety of vandetanib in patients with unresectable locally advanced or metastatic MTC. Both drugs significantly improved progression-free survival (PFS) more than the placebo ($p < 0.001$). The NMA suggested that, within the symptomatic and progressive MTC population, the effects on PFS were similar (vandetanib vs. cabozantinib: hazard ratio 1.14, 95% credible interval 0.41 to 3.09). Neither trial demonstrated a significant overall survival benefit for cabozantinib or vandetanib versus placebo, although data from ZETA were subject to potential confounding. Both cabozantinib and vandetanib demonstrated significantly better objective response rates and calcitonin (CTN) and carcinoembryonic antigen (CEA) response rates than placebo. Both cabozantinib and vandetanib produced frequent adverse events, often leading to dose interruption or reduction. The assessment group model indicates that, within the EU-label population (symptomatic and progressive MTC), the incremental cost-effectiveness ratios (ICERs)

for cabozantinib and vandetanib are > £138,000 per quality-adjusted life-year (QALY) gained. Within the restricted EU-label population (symptomatic and progressive MTC with CEA/CTN doubling times of ≤ 24 months), the ICER for vandetanib is expected to be > £66,000 per QALY gained. The maximum annual budget impact within the symptomatic and progressive population is estimated to be ≈£2.35M for cabozantinib and ≈£5.53M for vandetanib. The costs of vandetanib in the restricted EU-label population are expected to be lower.

Limitations: The intention-to-treat populations of the EXAM and ZETA trials are notably different. The analyses of ZETA subgroups may be subject to confounding as a result of differences in baseline characteristics and open-label vandetanib use. Attempts to statistically adjust for treatment switching were unsuccessful. No HRQoL evidence was identified for the MTC population.

Conclusions: The identified trials suggest that cabozantinib and vandetanib improve PFS more than the placebo; however, significant OS benefits were not demonstrated. The economic analyses indicate that within the EU-label population, the ICERs for cabozantinib and vandetanib are > £138,000 per QALY gained. Within the restricted EU-label population, the ICER for vandetanib is expected to be > £66,000 per QALY gained.

Future research priorities: (1) Primary research assessing the long-term effectiveness of cabozantinib and vandetanib within relevant subgroups. (2) Reanalyses of 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.

Study registration: This study is registered as PROSPERO CRD42016050403.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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Glossary

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.

Extended dominance A situation in which the incremental cost-effectiveness ratio for a given treatment alternative is higher than that of the next most effective (non-dominated) comparator.

Medullary thyroid cancer A rare type of thyroid cancer that originates from the parafollicular cells (also called C cells) of the thyroid.

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.

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.

Simple dominance A situation in which an intervention is less effective and more expensive than its comparator.

List of abbreviations

AE	adverse event
AG	assessment group
AIC	Akaike information criterion
AWMSG	All Wales Medicines Strategy Group
BIC	Bayesian information criterion
BSC	best supportive care
CDF	Cancer Drugs Fund
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	Common Terminology Criteria for Adverse Events
CTN	calcitonin
DICE	discretely integrated condition event
DSA	deterministic sensitivity analysis
ECG	electrocardiography
ECOG	Eastern Cooperative Oncology Group
EGF	epidermal growth factor
EMA	European Medicines Agency
EQ-5D	EuroQol-5 Dimensions
EQ-5D-3L	EuroQoL-5 Dimensions, three-level version
EU	European Union
EXAM	Efficacy of XLI84 (Cabocatinib) in Advanced Medullary Thyroid Cancer
FACT-G	Functional Assessment of Cancer Therapy – General
HFS	hand–foot syndrome
HR	hazard ratio
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IPD	individual patient data
ITT	intention to treat
LYG	life-year gained
MDASI-Thy	MD Anderson Symptom Inventory for thyroid cancer
MEN	multiple endocrine neoplasia
MeSH	medical subject heading
MRI	magnetic resonance imaging
MTC	medullary thyroid cancer
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NR	not reported
OR	odds ratio
ORR	objective response rate
OS	overall survival
PAS	Patient Access Scheme
PD	progressive disease
PFS	progression-free survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services

PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
QTc	corrected QT interval
RAS	RAt Sarcoma
RCT	randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RET	REarranged during Transfection
RPSFT	rank-preserving structural failure time
RTK	receptor tyrosine kinase
SAE	serious adverse event
ScHARR	School of Health and Related Research
SCI	Science Citation Index
SE	standard error
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
TKI	tyrosine kinase inhibitor
TTO	time trade-off
TWP	time to worsening of pain
VEGF	vascular endothelial growth factor
WHO	World Health Organization
WTP	willingness to pay

Note

This monograph is based on the Technology Assessment Report produced for NICE. The full report contained a considerable number of data that were deemed confidential. The full report was used by the Appraisal Committee at NICE in their deliberations. The full report with each piece of confidential data removed and replaced by the statement 'confidential information (or data) removed' is available on the NICE website: www.nice.org.uk.

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences, tables and figures have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all the data considered in the original full NICE report.

Plain English summary

Medullary thyroid carcinoma (MTC) is a rare form of cancer that presents as a mass of tumours in the thyroid gland of the neck. MTC affects both patients' health-related quality of life and survival. Targeted therapies (cabozantinib and vandetanib) are currently used to treat unresectable progressive and symptomatic MTC.

The evidence for the use of cabozantinib and vandetanib in patients with unresectable locally advanced or metastatic MTC was reviewed, and two clinical trials were identified. The trials suggest that both drugs improve progression-free survival. Neither trial demonstrated significant survival benefits for cabozantinib or vandetanib. Both drugs produced frequent adverse events, often leading to dose interruption or reduction.

Whether or not these therapies represent good value for money for the NHS was also assessed. Analyses indicate that the incremental cost-effectiveness ratios (ICERs) (a measure of cost-effectiveness) for cabozantinib and vandetanib versus best supportive care (BSC) in patients with symptomatic and progressive MTC are > £138,000 per quality-adjusted life-year (QALY) gained. Within a subgroup of patients with symptomatic and progressive MTC and carcinoembryonic antigen and/or calcitonin doubling times of $\leq$ 24 months, the ICER for vandetanib versus BSC remains > £66,000 per QALY gained.

Scientific summary

Background

Thyroid cancer is the most common malignant endocrine tumour, but represents only ≈1% of all malignancies. According to Cancer Research UK, 3404 new diagnoses of thyroid cancer were reported in England in 2014: 966 cases (28%) were in men and 2438 cases (72%) were in women [Cancer Research UK. *Thyroid Cancer Statistics*. URL: www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/thyroid-cancer (accessed 27 March 2017)]. There are four main types of thyroid cancer: (1) papillary, (2) follicular, (3) medullary and (4) anaplastic. Medullary thyroid cancer (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: (1) sporadic, (2) multiple endocrine neoplasia (MEN) 2, (3) MEN 3 and (4) familial MTC. Approximately 75% of cases of MTC are sporadic in nature. MTC is very rare and accounts for ≈5% of all thyroid cancers. The estimated annual incidence of MTC in England is ≈170 cases. For patients with regional disease spread, 10-year survival rates are reported to be ≈75%, whereas 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 (Caprelsa®; Cambridge, MA, USA) and cabozantinib (Cometriq®; Ipsen, Paris, France) are the modality of choice for unresectable 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.

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 'European Union (EU)-label population'] and (2) patients with symptomatic and progressive disease with carcinoembryonic antigen (CEA) and calcitonin (CTN) doubling times of $\leq$ 24 months (referred to as the 'restricted EU-label population').

Aims

The aims of the assessment were to:

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

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 included studies 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 with each other, a network meta-analysis (NMA) was performed using data relating to the ZETA trial EU-label and EXAM [Efficacy of XL184 (Cabozantinib) in Advanced Medullary Thyroid Cancer] trial intention-to-treat (ITT) populations.

Cost-effectiveness

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). 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 times of ≤ 24 months) based on a partitioned survival structure implemented using the discretely integrated condition event (DICE) approach. The executable model used to undertake the analysis was also submitted to NICE. The model was scrutinised by the assessment group (AG) 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 AG using a corrected version of the company's model. The manufacturer of cabozantinib did not submit any economic evidence relating to this product.

In the 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 AG developed a de novo health economic model. The AG model used a partitioned survival approach based on three health states: (1) progression free, (2) post progression and (3) 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 Genzyme (Cambridge, MA, USA) and Ipsen (Paris, France) 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 times of ≤ 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 separate confidential appendices to this report.

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 assessed different populations

because the ZETA trial inclusion criteria did not specify 'progressive' disease; therefore, the ITT population in this trial 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 AG confirmed that this group was comparable to the EXAM trial 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 trial ITT population and the ZETA trial EU-label population, PFS was similar for cabozantinib versus placebo [investigator-read hazard ratio (HR) 0.29, 95% confidence interval (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 versus placebo (investigator-read HR 0.33, 95% 0.20 to 0.53; $p = 0.0226$; central review, excluding patients switching treatments, HR 0.47, 95% CI 0.29 to 0.77; $p = 0.0024$ and including open-label populations, HR 0.32 95% CI 0.19 to 0.54; $p < 0.0001$).

The NMA undertaken by the AG suggested that the treatment effects on PFS were broadly similar [vandetanib vs. cabozantinib HR 1.14, 95% credible interval (CrI) 0.41 to 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 to 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 as a result of 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) than placebo, as determined by modified or standard Response Evaluation Criteria in Solid Tumours (RECIST). 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 rate of any serious adverse event (SAE) in the EXAM trial was 42% in the cabozantinib arm compared with 23% in the placebo arm, whereas in the ZETA trial, the incidence rate of SAEs was 31% in the vandetanib arm compared with 13% in the placebo arm.

Cost-effectiveness

The corrected version of the company's (Sanofi Genzyme) 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 times of ≤ 24 months) is approximately £31,546 per quality-adjusted life-year (QALY) gained. However, the AG 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 AG considers it likely that the ICER for vandetanib is considerably higher than the estimates presented within the Sanofi submission to NICE.

Based on the AG'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 AG'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 trial 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 times of ≤ 24 months), the ICER for vandetanib versus BSC is expected to be £66,779 per QALY gained.

Discussion

Two RCTs comparing active treatment with placebo were identified: one of cabozantinib (the EXAM trial) and one of vandetanib (the ZETA trial). The EXAM trial was rated as being at low risk of bias. The ZETA trial was rated as being at moderate or high risk of bias, principally as a consequence of treatment switching that led to the potential confounding of outcome data. There was no direct evidence comparing outcomes for cabozantinib and vandetanib with 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 benefits 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 AG 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, although attempts were made to adjust for this potential confounding in OS using the rank-preserving structural failure time approach, these were not successful. The AG 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 AG undertook fully incremental analyses based principally on the observed outcomes within the EXAM trial. Although these incremental analyses necessarily reflect potentially strong assumptions concerning transferable/equivalent treatment effects between vandetanib and cabozantinib, they are not subject to confounding as a result of 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 > £138,000 per QALY gained. The analyses undertaken in the restricted EU-label population (symptomatic and progressive MTC plus CEA/CTN doubling times of ≤ 24 months) suggest that the ICER for vandetanib versus BSC is expected to be more favourable but still remains > £66,000 per QALY gained; these latter analyses are also subject to potential confounding as a result of open-label vandetanib use.

The AG's economic analysis suggests that NICE's criteria for life-extending therapies given at the end of life are not met for cabozantinib in the symptomatic and progressive MTC population, 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.

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, a 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 trial ITT population and the ZETA trial EU-label population and should be treated with caution because of 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 AG, the ICERs for cabozantinib and vandetanib versus BSC in the EU-label population (symptomatic and progressive MTC) are > £138,000 per QALY gained. The analyses undertaken within the restricted EU-label population (symptomatic and progressive MTC with CEA/CTN doubling times of ≤ 24 months) suggest that the ICER for vandetanib versus BSC is more favourable but remains > £66,000 per QALY gained. The impact of adjusting for open-label vandetanib use on the cost-effectiveness of vandetanib versus BSC is unknown.

Future research priorities include (1) primary research assessing the long-term effectiveness of cabozantinib and vandetanib within relevant subgroups, (2) reanalyses of the ZETA trial to investigate the impact of adjusting for open-label vandetanib use using appropriate statistical methods and (3) studies assessing the impact of MTC on HRQoL.

Study registration

This study is registered as CRD42016050403.

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Chapter 1 Background

Description of the health problem

Incidence and prevalence

Thyroid cancer is the most common malignant endocrine tumour, but represents only ≈1% of all malignancies.[1,2] The disease is more common in women than in men. According to Cancer Research UK, 3404 new diagnoses of thyroid cancer were reported in England in 2014: 966 cases (28%) were in men and 2438 cases (72%) were in women.[1] The age-standardised incidence rate of thyroid cancer is reported to be 7 per 100,000 women and 3 per 100,000 men.[1] The UK incidence rate is the 11th lowest in Europe for men and the 15th lowest in Europe for women. The median age at diagnosis is approximately 50 years.[3,4]

There are four main types of thyroid cancer: (1) papillary, (2) follicular, (3) medullary and (4) anaplastic. Papillary and follicular thyroid cancer are the most common types of thyroid cancer and account for > 90% of all cases.[3] Medullary thyroid cancer (MTC), the disease type considered in this report, 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 ≈5% of all thyroid cancers,[2] although a lower frequency has been quoted by the American Thyroid Association guidelines.[5] Anaplastic cancers, thyroid lymphomas and metastases to thyroid from other primary tumours are rarer than MTC; anaplastic thyroid cancer accounts for ≈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 ≈170 individuals (5% of 3404).

There are four types of MTC: (1) sporadic, (2) multiple endocrine neoplasia (MEN) 2 (formerly MEN 2A), (3) MEN 3 (formerly MEN 2B) and (4) familial MTC. Incidence rates for each type differ by age and sex.[1] Approximately 75% of MTC cases are sporadic in nature, whereas the remaining 25% are genetically determined (MEN 2, MEN 3 and familial MTC).[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 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 MEN 2, MEN 3 and familial MTC have germline *RET* mutation, whereas 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 > 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 either fine-needle aspiration cytology of a thyroid nodule or lymph node or 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 of > 100 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 compartment node dissection, with or without lateral neck dissection).[2,8,9] Patients with MTC may be classified into three groups: (1) patients with localised disease without evidence of metastases, in whom

surgical cure is possible; (2) patients with metastatic disease limited to the neck, in whom surgical cure might be possible but is not always achieved; and (3) patients with distant metastasis, that is the disease has spread outside the neck and in whom surgery is not curative.[3] The only curative treatment for MTC is complete surgical resection, but lymph node or systemic metastases are present at initial diagnosis in around half of MTC cases[5] and resection is sometimes incomplete because of extensive lateral spread.[3,4] Patients with unresectable locally advanced or metastatic MTC were the focus of this review. 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 (see *Impact of health problem* and *Current service provision*).[2,3,5] Therefore, patients with symptomatic and progressive disease, according to the Response Evaluation Criteria in Solid Tumours (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 < 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, that is, 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 ≈75% with regional disease spread[3,14] and range from 21 to 40% for subjects with metastatic disease at diagnosis.[2,3,5] Distant metastases, which can affect multiple organs, most commonly the liver, lungs and bones, 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]

Calcitonin 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[16–20] have indicated that patients with CTN and CEA doubling times of ≤ 24 months have more progressive disease and a reduced survival time compared with patients with CTN and CEA doubling times of > 24 months. A 2005 study[16] reported 5- and 10-year survival rates of 25% and 8%, respectively, in MTC patients with post-operative CTN doubling times of < 6 months, compared with 92% and 37%, respectively, in patients with doubling times of between 6 and 24 months. In the same study,[16] the 10-year survival rate for patients with CTN doubling times of > 24 months was 100%.

Impact of the health problem

Significance for patients

There is little published research concerning the impact of MTC on patients' HRQoL. As noted in the Ipsen (Paris, France) 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. MTC is associated with a number of symptoms that 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 as a result of hormonal excess caused by increased CTN secretion from the parafollicular cells; this may be debilitating and can 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 (e.g. severe diarrhoea) may lead to workplace absence and lost productivity.

Significance for the NHS

Medullary thyroid cancer 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 (Caprelsa®; Cambridge, MA, USA) and cabozantinib (Cometriq®; Ipsen, Paris, France) are also associated with additional monitoring costs. The Summary of Product Characteristics (SmPC) for vandetanib[22] states the following:

> *An ECG [electrocardiography], 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 [corrected QT interval] 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.*
>
> *European Medicines Agency, vandetanib SmPC. © EMA [1995–2018]. Reproduced with permission from the European Medicines Agency*[22]

The SmPC for cabozantinib[23] also recommends close monitoring during the first 8 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).*
>
> *European Medicines Agency, cabozantinib SmPC. © EMA [1995–2018]. Reproduced with permission from the European Medicines Agency*[23]

One of the clinical advisors to the assessment group (AG) noted that although cardiac toxicity is less for cabozantinib than vandetanib, electrocardiographic monitoring may also be required.

Current service provision

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.

Current National Institute for Health and Care Excellence technology appraisal guidance

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

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.[1] Prescribing data from the Cancer Drugs Fund (CDF) indicate that in 2016 (confidential information has been removed) new patients received vandetanib and (confidential information has been removed) new patients received cabozantinib (Professor Peter Clark, Chairperson of CDF, 2017, personal communication). The data from 2015 indicate very similar prescribing

levels, with (confidential information has been removed) new patients starting vandetanib and (confidential information has been removed) patients starting cabozantinib (Professor Peter Clark, personal communication). Based on current prescribing levels, the cost of treating new MTC patients with cabozantinib and vandetanib for 1 year (assuming full dose and excluding any discontinuation) is approximately £1.96M.

Variation in services and uncertainty about best practice

Clinical advisors to the AG noted that although 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 time point 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' (p. 2) (© EMA [1995–2018]. Reproduced with permission from the European Medicines Agency).[22,23] Clinical advisors to the AG 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 from 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. Although 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. In addition, as cabozantinib and vandetanib have multiple targets, although 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.

Current treatment pathway

A summary of the treatment pathway, as developed by the AG, is presented in *Figure 1*. For patients who are ineligible to receive cabozantinib or vandetanib, treatment is likely to comprise 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*.

Description of technology under assessment

Interventions considered in the scope of this report

This assessment includes two interventions: cabozantinib and vandetanib.

Cabozantinib

Cabozantinib has an European Union (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 an individual treatment decision. Cabozantinib is administered orally at a recommended dose of 140 mg once daily, taken as one 80-mg capsule and three 20-mg 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 × 20-mg capsules, (2) 28 × 20-mg capsules and 28 × 80-mg capsules or (3) 84 × 20-mg capsules and 28 × 80-mg capsules. The list price for cabozantinib is £4800 per pack. A confidential Patient Access Scheme (PAS) has been proposed for cabozantinib.

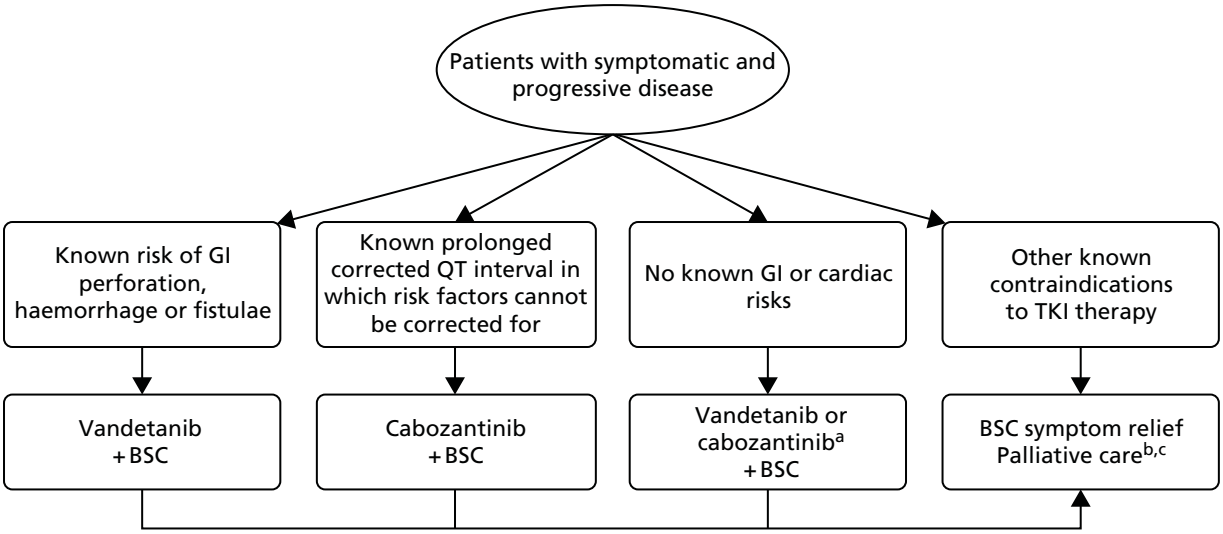

FIGURE 1 Current treatment pathway for adults with symptomatic and progressive MTC. a, Patient may switch to other TKI if intolerant or severe AEs are experienced within 3 months. Note that the vandetanib licence is in aggressive and symptomatic disease, whereas the licence for cabozantinib is for progressive, unresectable locally advanced or metastatic MTC. b, May include palliative surgery, palliative radiotherapy and/or treatments for bone pain. c, Nuclear medicine therapies, such as MIBG/dotatate, may be considered in some patients. AE, adverse event; BSC, best supportive care; GI, gastrointestinal; MIBG, iodine-123 metaiodobenzylguanidine; TKI, tyrosine kinase inhibitor.

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

Cabozantanib and vandetanib are the first-line treatments of MTC when all of the following criteria are met:

- A consultant specialist specifically trained and accredited in the use of systemic anticancer therapy prescribes application and first cycle of systemic anticancer therapy.
- Unresectable, locally advanced or metastatic MTC, confirmed histologically.
- First-line indication.
- Progressive, symptomatic disease.
- For cabozantinib: no history of tyrosine kinase therapy unless intolerant of vandetanib within 3 months of starting it and, on vandetanib, toxicity that cannot be managed by dose delay or dose modification and absence of disease progression.
- For vandetanib: no history of tyrosine kinase therapy unless intolerant of cabozantinib within 3 months of starting it and, on cabozantanib, toxicity that cannot be managed by dose delay or dose modification and absence of disease progression.

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).[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 an individual treatment decision. Vandetanib is administered orally at a recommended dose of 300 mg 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 × 100-mg tablets (cost per pack of £2500) and (2) 30 × 300-mg tablets (cost per pack of £5000). A confidential PAS has also been proposed for vandetanib.

Mode of action

Cabozantinib

Cabozantinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumour growth and angiogenesis, pathological bone remodelling 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 vascular endothelial growth factor (VEGF) 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.[23]

Vandetanib

Vandetanib is a potent inhibitor of VEGF receptor-2 (VEGFR-2) (also known as kinase insert domain-containing receptor), epidermal growth factor receptor (EGFR) and *RET* tyrosine kinases. Vandetanib is also a submicromolar 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 RTK 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]

Current usage in the NHS

As noted in *Current service cost*, 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, (confidential information has been removed) new patients were prescribed cabozantinib or vandetanib through the CDF.

Chapter 2 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, adolescents and children aged ≥ 5 years.[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 an individual treatment decision.[22,23]

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 adolescents and children aged ≥ 5 years;[22] this population is beyond the scope of this appraisal.[26] Clinical advisors to the AG note that the incidence of unresectable locally advanced or metastatic MTC in children and adolescents aged ≥ 5 years is expected to be extremely low.

Interventions

- Cabozantinib (oral).
- Vandetanib (oral).

Relevant comparators

Cabozantinib and vandetanib were compared with:

- each other
- best supportive care (BSC).

Outcomes

The following outcomes are included in this assessment:

- overall survival (OS)
- progression-free survival (PFS)
- response rates
- adverse effects of treatment
- HRQoL.

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

Subgroups

The final NICE scope[26] states that 'If the evidence allows subgroups according to *RET* mutation status will be considered.' Based on the guidance of the clinical advisors to the AG (see *Chapter 1*, *Variation in services and uncertainty about best practice*), *RET* mutation status has not been considered within the health economic analysis presented in this report.

Overall aims and objectives of assessment

The aims of the assessment are to:

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

Chapter 3 Assessment of clinical effectiveness

This section presents a summary and critique of relevant studies on the efficacy and safety of cabozantinib and vandetanib for the treatment of unresectable locally advanced or metastatic MTC. The systematic review was conducted and reported following the general principles outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and checklist[29] and the Centre for Reviews and Dissemination (CRD) guidance.[30] The protocol for this review has been registered with, and is available from, the PROSPERO database (registration number CRD42016050403).[31]

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

Methods for reviewing effectiveness

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

	Criteria	
Element	**Inclusion**	**Exclusion**
Population	Participants with unresectable locally advanced or metastatic MTC, aged ≥ 18 years. 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: • OS • PFS • Response rates • Adverse effects of treatment • HRQoL	
Study design	RCTs are to be included in the clinical effectiveness systematic review. If no relevant RCTs are identified for an intervention, non-randomised comparative studies will be considered for inclusion. Non-randomised comparative studies are also to be included, when necessary, as a source of additional evidence (e.g. regarding AEs related to the interventions)	Pre-clinical or biological 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

N/A, not applicable; RCT, randomised controlled trial.

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 – via Ovid, 1946 to present.
- MEDLINE In-Process & Other Non-Indexed Citations – via Ovid, 1946 to present.
- MEDLINE Epub Ahead of Print – via Ovid, 1946 to present.
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) – via EBSCO*host*, 1982 to present.
- EMBASE – via Ovid, 1980 to present.
- Cochrane Database of Systematic Reviews – via Wiley Online Library, 1996 to present.
- Cochrane Central Register of Controlled Trials (CENTRAL) – via Wiley Online Library, 1995 to present.
- Database of Abstracts of Reviews of Effects – via Wiley Online Library, 1995 to 2015.
- Health Technology Assessment Database (HTA) – via Wiley Online Library, 1995 to present.
- Web of Science [Science Citation Index (SCI)] – via Clarivate Analytics (formerly Thomson Reuters), 1900 to present.
- Conference Proceedings Citation Index (CPCI) – via Clarivate Analytics (formerly Thomson Reuters), 1990 to present.

To identify ongoing or recently completed studies, trial registers were searched using the International Clinical Trials Registry Portal of the World Health Organization (WHO),[32] which regularly compiles and updates data from > 15 clinical trial registers.

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 a RCT or systematic review study design filter. The search strategy was designed to be deliberately broad to capture all intervention studies within the MTC population, that is, 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*.

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] were examined. In addition, company submissions (CSs) 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 AG provided advice on whether or not any relevant studies were missing from the search results.

A comprehensive database of relevant published and unpublished articles was constructed using EndNote version 8 [Clarivate Analytics (formerly Thomson Reuters), Philadelphia, PA, USA] software.

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 that 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 flow chart. 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.

Quality assessment

For the RCT evidence, critical appraisal of included trials was conducted by one reviewer (CC) using the Cochrane Risk of Bias tool;[33] this was checked by a second reviewer (EK) and any discrepancies were resolved through discussion.

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 with vandetanib, a network meta-analysis (NMA) was performed using the ZETA trial EU-label and Efficacy of XL184 (Cabozantinib) in Advanced Medullary Thyroid Cancer (EXAM) trial intention-to-treat (ITT) populations (see *Network meta-analysis*).

Results

Quantity and quality of research available

The details of the study selection process are outlined in the PRISMA flow chart (*Figure 2*). The search identified 1581 references after deduplication, of which 1516 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 ($n = 1$) and a duplicate ($n = 1$). A list of excluded full papers, with reasons, is provided in *Appendix 2*. The excluded studies included

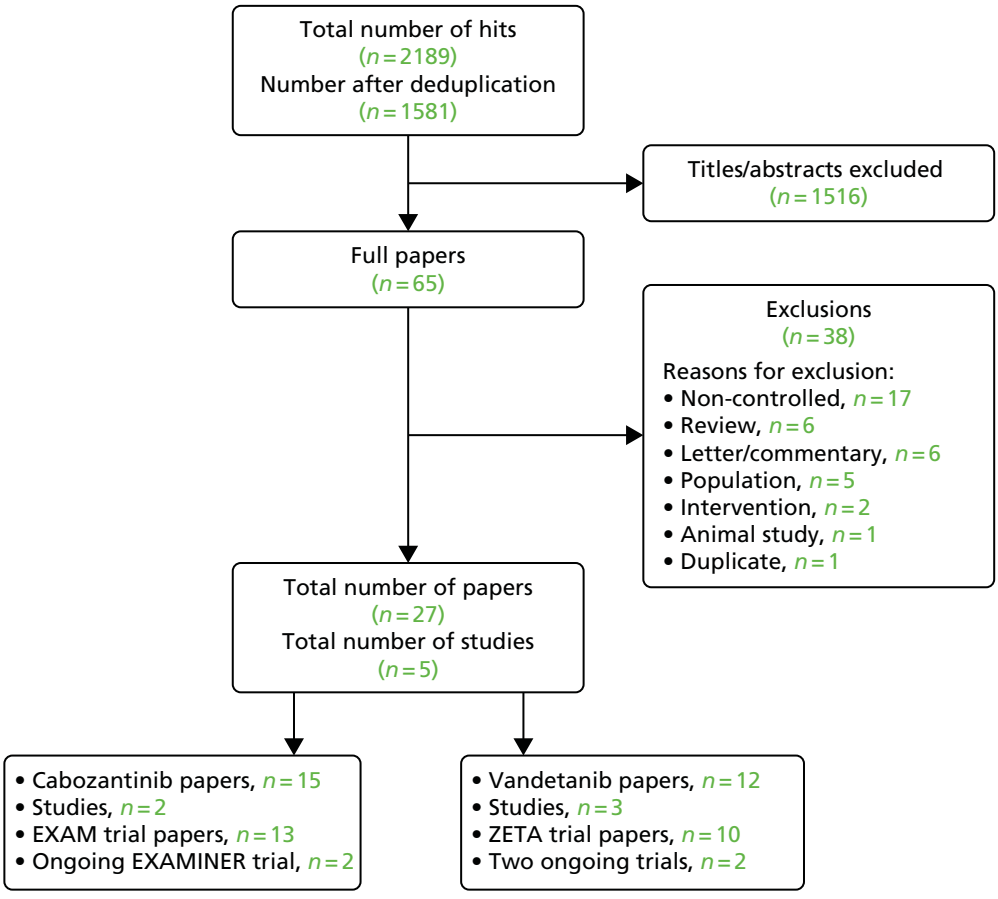

FIGURE 2 PRISMA flow chart.

two single-arm studies of vandetanib in children and adolescents with unresectable locally advanced or metastatic MTC as a result of MEN 2 (one published study[34] and one ongoing study[35]). 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 because of recruitment issues;[36] the remaining four studies[37–40] are ongoing. There is also one published retrospective study[41] comparing MTC patients who received radioactive iodine therapy with those whose did not. As a result, there was no appropriate additional controlled trial evidence of other potential comparators to cabozantinib or vandetanib (e.g. radiotherapy) that could may have been used to inform a NMA.

The final result was 27 publications and protocols relating to five RCTs. For cabozantinib, this included 13 publications[28,42–53] relating to the Phase III EXAM trial,[28,42] which compared 140 mg per day of cabozantinib with placebo, and two publications[54,55] relating to the ongoing EXAMINER trial,[54] which compares 140 mg per day with 60 mg per day of cabozantinib, and seeks to recruit 188 participants (expected completion date: March 2019).[55] For vandetanib, this included 10 publications[18,27,56–63] relating to the Phase III ZETA trial,[27,56] which compares 300 mg per day of vandetanib with placebo, and two publications[64,65] relating to two ongoing vandetanib trials: one trial[64] comparing 300 mg per day with 150 mg per day of vandetanib, and one[65] comparing vandetanib with vandetanib plus bortezomib (Velcade®, Takeda, Osaka, Japan).

No additional relevant papers or studies were identified from the reference lists of included studies or reviews, or from citation searching of the key publications for the EXAM or ZETA trials. The clinical advisors to the AG 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[66] 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,[54] and for vandetanib, the ZETA trial and the ongoing NCT01496313 trial.[64] 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;[67,68] a controlled study to assess the addition of an outreach programme to vandetanib treatment;[69] and two 'real-world', non-controlled, single-arm vandetanib studies.[70–72] All of these studies were identified by the search but were excluded from this review because they did not satisfy the eligibility criteria; either they were 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*).

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 as the percentage of participants with 'aggressive and symptomatic disease' at baseline is reported to be 56% (186/331).[57] 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, objective response rate (ORR), *RET* mutation status, CTN and CEA levels] end points. The cabozantinib trial assessed quality of life using the MD Anderson Symptom Inventory for thyroid cancer (MDASI-Thy), whereas 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)], whereas the FACT-G was not listed in any publication of the ZETA trial, but its results were reported in the Sanofi CS.[66]

TABLE 2 Characteristics of included RCTs

	Trial	
Study	**EXAM[28] (carbozantinib)**	**ZETA[27] (vandetanib)**
Design	International (including Europe), multicentre, Phase III, parallel-group, double-blind RCT	International (including Europe), multicentre, Phase III, parallel-group, double-blind RCT
Follow-up	13.9 months (median); range 3.6–32.5 months	24 months (median)
Population[a]	• Eligible participants were adults with histologically confirmed, unresectable, locally advanced or metastatic MTC • Participants were required to have radiographic disease progression per mRECIST guidelines at screening compared with an image obtained within the previous 14 months. Documentation of PD to establish eligibility was by independent review in 89.4% of patients, and by investigator assessment in the remaining patients	• Eligible participants were adults who had measurable, unresectable locally advanced or metastatic, hereditary or sporadic MTC. Submission of a tumour sample was required except from patients with hereditary MTC who had a documented germline *RET* mutation • Other key inclusion criteria were WHO performance status of 0–2 and a serum CTN level of ≥ 500 pg/ml
	Exclusion criteria: • Included – prior systemic anticancer therapy within 4 weeks or significant cardiac, haematopoietic, hepatic, or renal dysfunction. There was no limit on prior therapy beyond the exclusion criteria	Exclusion criteria: • Included – administration of chemotherapy and/or radiation therapy within 4 weeks before random assignment, or significant cardiac, haematopoietic, hepatic or renal dysfunction
Intervention	140 mg of cabozantinib (free-base equivalent), taken orally once per day until either intolerable toxicity or disease progression as per mRECIST. Dose holds and up to two dose level reductions (to a minimum dose of 60 mg per day) were allowed	300 mg of vandetanib 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, ORR, *RET* mutation status, CTN and CEA levels • AEs measured using 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 CTCAE

CTCAE, Common Terminology Criteria for Adverse Events; mRECIST, modified Response Evaluation Criteria in Solid Tumours; ORR, objective response rate; PD, progressive disease.
a Some additional criteria are detailed in the protocols for cabozantinib[42] and vandetanib.[56]

The definitions of PFS used in the trials were similar (i.e. the time from random assignment to the date of disease progression or death) and both trials employed a central committee to confirm investigator assessments. However, the EXAM trial used the modified RECIST (mRECIST) criteria[10] and employed a blinded independent review committee, whereas the ZETA trial used the standard RECIST criteria, and it is unclear whether or not the central review was blinded.

The EXAM and ZETA trials had 330 and 331 participants, respectively (*Table 3*). 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% in the cabozantinib arm vs. 42% in the placebo arm) and positive *RET* mutation status (46.1% in the cabozantinib arm vs. 52.3% in the placebo arm), indicating that the control group might have had more severe disease.

TABLE 3 Participants' baseline characteristics from the EXAM and ZETA trials

Participant characteristics	Trial			
	EXAM[28] (*N* = 330)		ZETA[27] (*N* = 331)	
	Cabozantinib, 140 mg (*n* = 219)	Placebo (*n* = 111)	Vandetanib, 300 mg (*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[a] (NR)	53[a] (NR)
Disease type, *n* (%)				
Hereditary	12 (6)	8 (7)	28 (12)	5 (5)
Sporadic or unknown	207[b] (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 or 2	95 (43)	55 (50)	77 (33)	42 (42)
Number of organs involved[c]				
0 or 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	NR
Prior anticancer therapy	85 (39)	48 (43)	NR	NR
Prior TKI, *n* (%)				
Yes	44 (20)	24 (22)	NR	NR
No	171 (78)	86 (78)	NR	NR
Unknown	4 (2)	1 (1)	NR	NR

ECOG, Eastern Cooperative Oncology Group; NR, not reported.
a Mean.
b 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]
c Excluding thyroid.
Note
All decimals are rounded up to the nearest whole number.

RET mutation status was unknown in 39% of participants as a result of missing sequence data or the presence of a mutation of unknown significance.[28] The two arms of the vandetanib ZETA trial were 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 the placebo arm vs. 33% for the vandetanib arm) and having involvement of two or more organs (92% for the placebo arm vs. 87% for the vandetanib arm).

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

In both trials, participants discontinued study treatment if there was evidence of disease progression or toxicity. The ZETA trial, however, also permitted treatment continuation or treatment switching post progression.[27] During the randomised phase, if there was disease progression based on investigator assessment, participants discontinued study treatment, but were offered the opportunity to receive vandetanib post progression as unblinded 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 out of 231 (52%) participants discontinued treatment because of progression or toxicity (compared with 55% in the cabozantinib trial[28]), but 44 of these 120 (37%) participants continued to receive vandetanib in the open-label phase. In the placebo arm of the ZETA trial, 71 out of 99 (72%) discontinued 'treatment' because of progression or toxicity (compared with 86% in the cabozantinib trial), and 58 of these 71 (82%) participants then switched to receive vandetanib in the open-label phase. All efficacy and safety data reported subsequently are subject to bias because of treatment switching, unless otherwise stated. This raises issues of confounding for some of the outcome data from the ZETA trial.

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. The Sanofi CS for vandetanib[66] presents PFS and OS outcome data from post hoc analyses on two preplanned subpopulations 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, ≥ 10 mg/day opioid use, diarrhoea, flushing, fatigue, pain, nausea, dysphagia, dysphonia, respiratory symptoms, and weight loss.'[57] This corresponds to the 'EU-label' or 'progressive and symptomatic' population ($n = 186$) referred to in the Sanofi CS.[66] In the post hoc analyses conducted by the company, the data reported by Kreissl *et al.*[57] 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 the Sanofi CS,[66] appendix 6, tables 5 and 7, respectively). Numbers from the published Kreissl *et al.*[57] analyses are used throughout the clinical-effectiveness section, whereas 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 is 'aggressive', that is, with CTN and CEA doubling times of < 24 months from screening. This is the so-called 'restricted EU-label population' [$n =$ (confidential information has been removed)] presented in the Sanofi CS. The Sanofi CS claims that 'This population closely reflects UK clinical practice for TKI treatment' (Sanofi CS,[66] pp. 11 and 54). However, clinical advice received by the AG suggests that CTN and CEA monitoring would not usually inform decisions about whether or not 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)[57] and are reported here because they are used to inform the health economic model developed by the AG. The baseline characteristics of these subgroups are presented in *Table 4*, together with the comparable baseline data for the EXAM trial ITT population. Despite the EXAM trial ITT population being 'progressive' and the EU-label ZETA trial population being 'progressive and symptomatic', clinical advice received by the AG confirmed that these two populations were comparable.

It should also be noted that, among the EU-label population, (confidential information has been removed) of patients in the intervention group continued to receive vandetanib in the open-label phase, whereas (confidential information has been removed) of patients in the placebo arm 'crossed over' to receive open-label vandetanib (see Sanofi clarification response,[73] question 3). In the restricted EU-label population, (confidential information has been removed) of patients in the intervention group continued to receive vandetanib in the open-label phase, whereas (confidential information has been removed) of patients in the placebo arm 'crossed over' to receive open-label vandetanib (Sanofi CS,[66] pp. 17 and 63). All efficacy and safety data reported

TABLE 4 Participants' baseline characteristics in the cabozantinib 'progressive' and the vandetanib EU-label and restricted EU-label populations

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

NR, not reported.
Data from Sanofi CS,[66] tables 17 and 19, and Wells *et al.*[27]

subsequently for this group are subject to bias because of treatment switching, unless otherwise stated. This raises issues of confounding for some of the trial data, including for the restricted EU-label population.

The risk of bias in the EXAM and ZETA trials was assessed using the Cochrane Risk of Bias Tool (*Table 5*). These assessments made use of the protocols (published and unpublished), the trial publications and unpublished CSRs for each trial.

TABLE 5 Risk-of-bias assessment (Cochrane tool) of included RCTs

		Trial	
Risk of bias	**Criteria**	**EXAM (cabozantinib)[28]**	**ZETA (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 CSR55 (section 9.4.3) provide no further details on how randomisation was conducted	Unclear • Participants recruited to this multicentre, Phase III study were randomly assigned in a 2 : 1 ratio to receive oral vandetanib at a starting dose of 300 mg per day or placebo until disease progression • The published protocol (NCT), published CSR, which accompanied the full publication,[27] and an earlier unpublished CSR,[74] provide no further details on how randomisation was conducted. An unpublished CSR (October 2014) clarified that the randomisation was computer-generated. Independent randomisation does not appear to have been conducted
Performance bias	Blinding of participants and personnel	Low • 'Double-blind' was reported but not described in publications, but the 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).[57] There was no evaluation of blinding	Moderate to high • 'Double-blind' was reported but not described. Published CSR and unpublished CSRs state: 'placebo to match vandetanib.' The CSR from October 2014[75] 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 individuals who had switched to open-label (unblinded) treatment (e.g. OS and safety outcomes, as well as post-progression PFS and ORR)

continued

TABLE 5 Risk-of-bias assessment (Cochrane tool) of included RCTs (*continued*)

		Trial	
Risk of bias	**Criteria**	**EXAM (cabozantinib)[28]**	**ZETA (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 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* *Wells* et al.[27] • The majority of trial documents do not state whether or not the confirmatory 'independent central review' was blinded. This is stated only in an unpublished CSR from July 2011,[74] in which the PFS efficacy results are described as being 'based on an independent, blinded central review' (p. 180) (repeated in the Sanofi CS,[66] p. 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[74] 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.' (p. 48) • A number of outcomes are also potentially confounded by the inclusion of individuals who had switched to open-label treatment (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[28] *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 PFS analysis, contributing time-to-event data until the date of censoring*	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.[27] PFS and OS analyses were conducted using the log-rank test (unadjusted model with treatment factor only) in the ITT population. Patients who were progression free or who had died at the time of analysis were censored at the time of their last evaluable RECIST assessment. If a patient was progression-free according to the central read when the patient started to receive open-label treatment, the open-label assessments were included in the derivation of these endpoints

TABLE 5 Risk-of-bias assessment (Cochrane tool) of included RCTs (*continued*)

		Trial	
Risk of bias	**Criteria**	**EXAM (cabozantinib)[28]**	**ZETA (vandetanib)[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. sections 11.4.4.2 and 12.1.6).[76] These are the patient-reported outcome MDASI-Thy 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[75] (data were not reported, only a summary finding). TWP was listed in the protocol, but results only appear in the published and unpublished CSRs
Other bias	Any important concerns about bias not addressed above	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 times are 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 organisational support, collected and managed the data, and performed the statistical analysis* • CTN and CEA doubling times were assessed as confounders[19] (and the Sanofi CS,[66] figure 4, p. 51)

CSP, clinical study protocol; NCT, National Clinical Trial.
Note
All quotations are taken from the full trial publication, except where otherwise specified.

The AG considers the EXAM trial to be of generally good quality, being assessed as having a low risk of performance, detection and attrition bias on account of measures to ensure blinding and the management of dropouts. The EXAM trial 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 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 owing to potential conflicts of interest and the failure to control for the possible treatment effect modifier of CTN and CEA doubling times.

Overall, the AG considers that the ZETA trial was at 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 because of 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 times. In contrast to the EXAM trial, performance bias and detection bias were assessed as being of moderate to high risk because there was a lack of detail on blinding procedures and certain outcomes, and their results were potentially confounded by the inclusion of patients switching to open-label treatment within the analysis.

Assessment of effectiveness

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

Progression-free survival

Both pivotal trials reported PFS as their primary outcome using similar definitions and 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[28,43] (*Table 6*). 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 (confidential information has been removed).

In the post hoc analysis, PFS was also calculated for the EU-label ($n = 186$) and restricted EU-label (confidential information has been removed) populations. For the vandetanib EU-label population, the HR for PFS was reported to be 0.47 (95% CI 0.29 to 0.77; $p = 0.0024$) by central review[66] and 0.33 (95% CI 0.20 to 0.53; $p = 0.0226$) by investigator read.[57] The HR by central review but excluding open-label patients[57] was reported to be 0.32 (95% CI 0.19 to 0.54; $p < 0.001$). According to the Sanofi CS (p. 55),[66] the median PFS for the restricted EU-label group was (confidential information has been removed) in the placebo arm compared with (confidential information has been removed) in the vandetanib arm (confidential information has been removed).

The investigator-read risk of progression, compared with placebo, for the comparable EXAM trial ($n = 331$) and ZETA trial 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 (i.e. Elisei *et al.*)[28] states that 57 out of 219 (26%) participants randomised to cabozantinib had progressed at follow-up compared with 67 out of 111 (60%) participants in the placebo group. The ZETA trial publication[27] reported data on 124 participants who progressed: 73 out of 231 (32%) participants randomised to vandetanib had progressed (previously reported as 37% at 24 months[58]) and 51 out of 100 (51%) participants randomised to placebo had progressed.

In the EXAM trial, the Kaplan–Meier estimates for the proportion of participants alive and progression free at 1 year were reported to be 47.3% for cabozantinib compared with 7.2% for placebo.[28] In the ZETA trial, the proportion of participants in the ITT population alive and progression free at 6 months was reported to be 91% for vandetanib compared with 74% for placebo.[59]

Subgroup analyses according to prespecified 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 considered included sex, performance status, and number of previous anticancer regimens or other TKIs received and response to those therapies.[27,28,43,44,77] The Ipsen CS[21] for cabozantinib reported that PFS was also prolonged in a subgroup of cabozantinib patients ($n = 34$) who had received prior vandetanib (median PFS was 12.8 months for cabozantinib and 2.8 months for placebo, and ORR was 28%, when prior vandetanib use reported). 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]

TABLE 6 The EXAM and ZETA trials' median PFS durations (months)

Assessed by	Trial arm: Cabozantinib ($n = 219$)	Trial arm: Placebo ($n = 111$)	HR (95% CI; p-value)
EXAM trial, (n = 330)[28]			
Central review	11.2	4.0	0.28 (0.19 to 0.40; < 0.001)
Investigator	13.8	3.1	0.29 (0.21 to 0.42; < 0.001)
	Vandetanib ($n = 231$)	**Placebo ($n = 100$)**	
ZETA trial ITT population (n = 331)[27]			
Central review (ITT population)[a]	30.5	19.3[b]	0.46 (0.31 to 0.69; < 0.001)
Central review (excluding open-label)[a]	32.4	16.4[b]	[b]0.28 (0.18 to 0.42; < 0.001[c])
Investigator (all patients, ITT population)	22.3	8.3[b]	0.40 (0.27 to 0.58; < 0.001)
	Vandetanib ($n = 126$)	**Placebo ($n = 60$)**	
ZETA trial EU-label population (n = 186)[57,66]			
Central review (all patients)[a,b]	28.0	16.4	0.47 (0.29 to 0.77; 0.0024)
Central review (excluding open-label)[a,d]	30.1	11.1	0.32 (0.19 to 0.54; < 0.0001)
Investigator[d]	22.1	8.3	0.33 (0.2 to 0.53;[e] 0.0226)
	Vandetanib (confidential information has been removed)	**Placebo (confidential information has been removed)**	
ZETA trial restricted EU-label population (confidential information has been removed)			
(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)

NR, not reported.
a Weibull model-predicted median because median not reached.
b CS only.
c 0.27, 95% CI 0.18 to 0.41; $p < 0.001$.[27]
d Kreissl *et al.*[57]
e Confidence intervals only provided in the Sanofi CS,[66] tables 18 and 22, which also states a p-value of < 0.0001 for this HR.

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 participants in each of these groups within the EXAM trial are presented in *Tables 7* and *8*. The data demonstrate that cabozantinib was associated with a beneficial effect compared with placebo for all subgroups tested (see *Tables 7* and *8*) 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 participants who were also *RAt Sarcoma* (*RAS*) mutation negative.[45,46]

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,[66] section 4.3, p. 45). Subgroup analyses by these criteria were reported in this CS[66] and the unpublished CSR.[74] These found that all subgroups demonstrated

TABLE 7 The *RET*-mutation status in the EXAM trial[28,45] in the post hoc analysis of the EXAM trial (Ipsen CS,[21] Sherman *et al.*[45])

	Patients, *n* (%)		
Mutation status	Total (*N* = 330)	Cabozantinib arm (*N* = 219)	Placebo arm (*N* = 111)
RET *mutation subgroup*			
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)

NR, not reported.

TABLE 8 Progression-free survival by *RET* mutational status in the post hoc analysis of the EXAM trial (Ipsen CS,[21] Sherman *et al.*[45])

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

a beneficial effect on PFS (HR < 1.0), with a statistically significant treatment effect observed between patients with a CTN doubling time of ≤ 24 months and patients with a CEA doubling time of ≤ 24 months (*Figure 3*).

Overall survival

The authors of the EXAM trial paper[28] reported that there was no statistically significant difference between cabozantinib and placebo based on an interim analysis. According to a 2015 abstract,[47] the EXAM trial was designed with 80% power to detect a HR of 0.667 for the secondary end point 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.[47] 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 ($p = 0.241$; *Table 9*).[47]

For the 215 (65%) participants with known positive or negative *RET* mutations in the EXAM trial,[45] 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; $p = 0.240$).[79] For the 126 participants 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

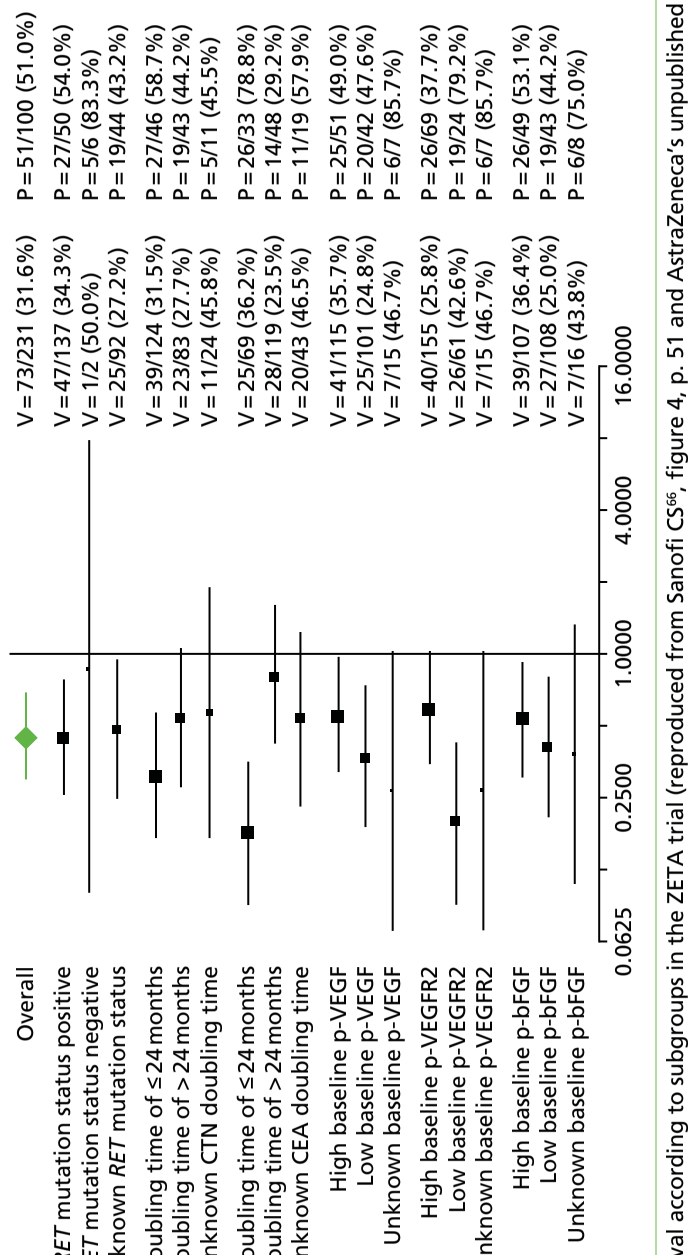

FIGURE 3 Progression-free survival according to subgroups in the ZETA trial (reproduced from Sanofi CS[66], figure 4, p. 51 and AstraZeneca's unpublished CSR dated July 2011[74]).

TABLE 9 Overall survival median duration (months)

Treatment	Placebo	HR (95% CI; *p*-value)
***EXAM trial arm* (N = *330*)[47]**		
Cabozantinib (n = *219*)	*Placebo* (n = *111*)	
26.6	21.1	0.85 (0.64 to 1.12; 0.2409)
***ZETA ITT population* (N = *331*)[27]**		
Vandetanib (n = *231*)	*Placebo* (n = *100*)	
NR	NR	0.99 (0.72 to 1.38; 0.9750)
[a]*EU-label population* (N = *189*)[78]		
Vandetanib (n = *126*)	*Placebo* (n = *60*)	
(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
***Restricted EU-label population (confidential information has been removed)*[a]**		
Vandetanib (confidential information has been removed)	*Placebo (confidential information has been removed)*	
(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)

NR, not reported.
a Survival time was originally reported in years but has been converted to months.

0.38 to 0.94; $p = 0.026$).[47,79] Subgroups of participants lacking *RET* mutations or lacking *RET* M918T showed no increase in OS.[47,79] The secondary end point of improved OS was not met because the difference between arms was not statistically significant in the ITT population.[47]

The data on OS from the ZETA trial were immature: a non-significant interim result was reported (HR 0.89, 95% CI 0.48 to 1.65; *p*-value not reported),[27] as well as the intention to conduct a final analysis when 50% of participants had died. The number of participants who had died at the data cut-off point (31 July 2009) was reported in the published CSR:[27] 32 out of 231 (14%) participants in the vandetanib arm compared with 16 out of 100 (16%) participants in the placebo arm ($p = 0.7115$[27]; and Sanofi CS,[66] p. 49). In the final analysis set (data cut-off point of 7 September 2015), there remained no survival benefit: 50% of participants randomised to vandetanib had died compared with 52% of participants randomised to placebo (HR 0.99, 95% CI 0.72 to 1.38; $p = 0.975$), although the placebo group included participants who had crossed over to vandetanib in the unblinded stage of the trial, thereby potentially confounding these results (Sanofi CS,[66] p. 49).

For the ZETA trial's EU-label population, the estimated median OS was (confidential information has been removed) for vandetanib compared with (confidential information has been removed) for placebo (confidential information has been removed).

According to the Sanofi CS[66] (p. 55 and table 20), the median OS for the restricted EU-label group was (confidential information has been removed) in the placebo arm compared with (confidential information has been removed) in the vandetanib arm (confidential information has been removed).

Response rate

The end point of ORR was reported in both trials, including complete and partial response, and was determined using the stated RECIST criteria[27,28] In the EXAM trial ($n = 312$ for this outcome), no participant had a complete response. Twenty-eight per cent of participants 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.[43,44]

In the full publication of the ZETA trial[27] ($n = 331$ 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. Within an earlier abstract,[60] the odds ratio (OR) was reported to be 5.4 compared with placebo (95% CI 2.99 to 10.79; $p < 0.0001$). It should be noted that 12 out of 13 participants in the placebo group had a response only when they switched to vandetanib in the open-label phase of the trial.[27,58] 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 switching occurred.[57] The Sanofi CS[66] (table 24, p. 67) states that 43.7% of these participants had a response in this vandetanib group ($n = 126$), compared with (confidential information has been removed) in the restricted EU-label vandetanib group (confidential information has been removed). Small numbers of *RET*-negative participants were deemed to render findings from the subgroup analysis of the EU-label group inconclusive, although other analyses did suggest that M918T mutation-positive participants had a better response to vandetanib than M918T mutation-negative patients.[27] The Sanofi CS[66] (p. 51) also stated that higher proportions of participants with a CTN or CEA doubling time of < 24 months (47% and 54%, respectively) achieved ORR than participants with a CTN or CEA doubling time of ≥ 24 months (40% and 37%, respectively).

Calcitonin and carcinoembryonic antigen response

Serum levels of CTN and CEA are recognised indicators of tumour burden and prognosis.[15–17] 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 radiological 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 participants in the cabozantinib group had statistically significantly better responses than those in the placebo group: levels of both biomarkers decreased in the treatment group and increased in the placebo group (*Table 10*).[28,48,49]

In the ZETA trial, higher, statistically significant percentages of participants receiving vandetanib achieved a CTN and CEA response (69% and 52%, respectively) than participants receiving placebo (3% for CTN and 2% for CEA).[27,66]

Lesion size

Lesion size was only measured and reported within the EXAM trial. To be included, participants needed measurable disease at baseline and at least one subsequent assessment.[28] A total of 180 out of 219 cabozantinib participants and 89 out of 111 placebo participants satisfied these criteria. Ninety-four per cent of these cabozantinib participants and 27% of these placebo participants 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.

TABLE 10 The EXAM trial CTN and CEA response rates

Time point	Biomarkers	Trial arm, mean (SD)		*p*-value
		Cabozantinib	Placebo	
Baseline	CTN ($n = 330$), pmol/l	6370 (11,332)	8846 (15,722)	0.27[a]
	CEA ($n = 330$), µg/l	736 (3555)	1108 (5168)	0.58[a]
		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

SD, standard deviation.
a Welsh's *t*-test.

MD Anderson Symptom Inventory – Thyroid

The MDASI-Thy module was the only patient-reported outcome measure used in the EXAM trial and data on this outcome were reported only in the unpublished CSR.[76] Data were also provided by the company at the request of the AG. 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 had been performed, in terms of change from baseline to the data cut-off point, there was no apparent difference between the treatment arms. However, it was stated that there were data for only 75% of participants at week 12, with declining numbers for subsequent assessments.[76]

Functional Assessment of Cancer Therapy – General, and time to worsening of pain

The FACT-G and TWP outcomes were only measured and reported for the ZETA trial; the details and results appear in the published and unpublished CSR,[27,74] although data were also provided by Sanofi at the request of the AG. The CSR[74] states that quality of life was measured using the FACT-G instrument and that, overall, scores between the two arms were similar. TWP was a composite end point, derived from opioid analgesic use and the worst pain item of the Brief Pain Inventory. The ZETA trial reported a significantly longer median TWP for vandetanib (7.85 months) than 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; $p = 0.45$).[66]

Safety outcomes

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

Any adverse event

The EXAM trial safety data were taken from the trial publications or the EXAM Final Analysis Set of August 2014, which was provided in the Ipsen CS[21] for cabozantinib (median follow-up of 10.8 months). The ZETA trial safety data were taken from the final Safety Analysis Set, provided in the Sanofi CS for vandetanib[66] and the unpublished CSR of 2011[74] (median total exposure was 90.1 weeks for vandetanib compared with 39.9 weeks for placebo). Seven participants were missing from the EXAM safety population data; therefore, there were 214 participants for cabozantinib, rather than 219, in the ITT population, and 109 participants for placebo rather than 111.

Adverse events were very common in both trials. Overall, 100% of participants were affected by at least one AE in the cabozantinib arm of the EXAM trial, and 99.6% of participants 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 ≥ 10% and < 20% of participants. Some of these AEs were dry skin, insomnia, abdominal pain, dermatitis acneiform, cough, nasopharyngitis, prolonged ECG QT [as defined by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE[80])], alopecia, pain in extremity, dyspnoea, 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, that is, those affecting ≥ 20% of participants in any trial arm, are presented in *Table 11*. The most common AEs for cabozantinib were diarrhoea (63%), hand–foot syndrome (HFS) (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 HFS.[27,58] Hypertension is a known AE for TKIs.[81,82] The incidence

TABLE 11 Common AEs (any grade) reported for > 20% of participants in any arm of the EXAM or ZETA trials

	Trial (% with event)			
	EXAM		ZETA	
	10.8 months' follow-up (median)[a]		90.1 weeks' follow-up[b]	39.9 weeks' follow-up[b]
AE	Cabozantinib ($n = 214$)	Placebo ($n = 109$)	Vandetanib ($n = 231$)	Placebo ($n = 99$)
Overall	100[a]	95[a]	97[27]	91[27]
Diarrhoea	63	33	56	26
HFS	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

HFS, hand–foot syndrome.
a Ipsen CS[21] from the final analysis of August 2014.
b Median duration of exposure: Sanofi CS,[66] table 33 and CSR 2011,[74] table 40.
Notes
Figures are rounded up to the nearest whole number.
– indicates not reported or < 10%.

of diarrhoea in patients receiving vandetanib treatment for MTC appears to be similar to that reported for patients receiving vandetanib treatment for other cancers,[83] but the rates of any grade or high-grade severity rash and hypertension appear to be higher for vandetanib in MTC patients than in most other cancer patients,[84,85] which might be attributable to longer treatment duration.[85]

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 participants (see *Table 11*), and especially those in the EXAM trial, with radiographic evidence of PD ($n = 330$); for example, percentages of participants with reported symptoms at baseline were pain in 46.1%, diarrhoea in 39.7%, fatigue in 25.8% and dysphonia in 23%.[50] Most symptoms were of grade 1 or 2 severity.

Grade 3 or higher adverse events, and serious adverse events

The adverse events, grade 3 or higher, reported for ≥ 2% of participants are presented in *Table 12*. The most common grade 3 or higher AEs for cabozantinib were diarrhoea (16%), HFS (13%), fatigue (9%), hypertension (8%), asthenia (6%), and decreased weight (5%) and appetite (5%).[28,43] These appear to be consistent with other anti-VEGF TKIs and the open-label cabozantinib studies.[86–89] However, it should be noted that the incidence and severity of HFS reported in the EXAM trial are lower than those reported in other cabozantinib trials for the treatment of other solid malignancies.[90]

TABLE 12 Grade 3 or higher AES reported for ≥ 2% of participants in any arm of the EXAM or ZETA trials

	Trial (% with event)			
	EXAM		ZETA	
	10.8 months' follow-up (median)[a]		90.1 weeks' follow-up[b]	39.9 weeks' follow-up[b]
Adverse event	Cabozantinib ($n = 214$)	Placebo ($n = 109$)	Vandetanib ($n = 231$)	Placebo ($n = 99$)
Overall	69 (78[a])	33	55 (CSR, Langmuir and Yver[19]); 61 (Kreissl *et al.*[57])	24 (CSR and Kreissl *et al.*[57])
Diarrhoea	16	2	11	2
HFS	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

a Ipsen CS,[21] 2017 from final analysis of August 2014.
b Median duration of exposure: Sanofi CS,[66] table 33 and AstraZeneca,[74] table 46.
Notes
Figures are rounded up to the nearest whole number.
– indicates not reported or < 2%.

The most common grade 3 or higher AEs for vandetanib were diarrhoea (11%), hypertension (9%), fatigue (6%) and decreased appetite (4%) as well as rash (4%) and prolonged ECG QT (8%). An exploratory study of a subset of the ZETA trial participants has indicated potential benefits of vandetanib in terms of weight and muscle loss.[61–63] 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 corrected QT interval (QTc) (25%), and cutaneous symptoms (11%).[62] Vandetanib is one of only two TKIs (the other being sunitinib) identified as being associated with prolonged QTc.[91]

Serious adverse events (SAEs), as defined by the National Cancer Institute's CTCAE,[80] affected more participants receiving cabozantinib (42.1%[28] or 53%,[21] depending on the source) than placebo (22.9%[28] or 24%,[21] depending on the source) in the EXAM trial.[21,28] The overall incidence of any SAE in the ZETA trial was 31% in the vandetanib arm and 13% in the placebo arm.[27] SAEs that occurred in ≥ 2% of participants in any arm of the EXAM or ZETA trials were mucosal inflammation, hypocalcaemia, pulmonary embolism, hypertension and diarrhoea.

Grade 5 AEs occurring within 30 days of the last dose were reported in more cabozantinib participants than placebo participants (7.9% and 7.3%, respectively).[28] A number of these grade 5 AEs were specified as being related to cabozantinib: fistula, respiratory failure, haemorrhage, sepsis/multiorgan 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%), and hypertension, dysphagia, dehydration and lung abscess (2.3% each).[92]

Adverse events leading to discontinuation or dose interruption/reduction

Adverse events leading to dose reductions/interruptions and/or discontinuation of treatment were reported for both trials (*Table 13*). There were similar proportions of participants across the two trials who discontinued because of AEs (16% or 23% for cabozantinib and 12% for vandetanib); however, there was a higher percentage of participants 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

TABLE 13 Dose interruption or discontinuation rates in the EXAM and ZETA trials (from the Sanofi CS[66] unless stated)

Trial	Trial arm (%)	
EXAM	***Cabozantinib* (n = *214*)**	***Placebo* (n = *109*)**
Dose interruption because of AE[28]	65	17
Discontinuation because of AE[28]	16 (23[a])	8 (9[a])
Dose interruption or reduction	87	22
Dose reduction[a]	79s	9
ZETA	***Vandetanib* (n = *231*)**	***Placebo* (n = *99*)**
Dose interruption[b]	47	15
Discontinuation because of AEs[27]	12	3
Dose interruption or reduction	49	15
Dose reduction[27]	35	3
EU-label population only (Sanofi CS, table 33)[b]	***Vandetanib* (n = *126*)**	***Placebo* (n = *60*)**
Discontinuation because of AEs	12	2
Dose reduction	33	3

a Data from Sanofi CS,[66] p. 73 only.
b From Sanofi CS,[66] table 33.

dose reduction to manage AEs was performed for 82% of participants treated with cabozantinib,[55] which increased again to 87% in the final analysis.[21] The percentages of participants 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 arm of the 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.[77]

Deaths

In the EXAM trial, at the data cut-off point, 30% of participants (65/214) had died in the cabozantinib arm compared with 28% (30/109) in the placebo arm. Twenty-three per cent (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 and 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 analysis and the final analysis.[21]

During the randomised phase of the ZETA trial, five participants who received vandetanib experienced AEs that led to death. Reasons given were aspiration pneumonia, respiratory arrest, respiratory failure, staphylococcal sepsis, and, in one participant, arrhythmia and acute cardiac failure. Instances of gastroenteritis and gastrointestinal haemorrhage led to death in two participants in the placebo group.[27] The number of deaths reported at the safety follow-up was 10 (4.3%) in the vandetanib group and 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.[74]

Supplementary safety evidence

The Sanofi CS[66] also presented safety data from two additional published studies[69,71] and one ongoing study;[64] 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 300-mg 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.[69] Only the 'real world' study of 68 MTC patients treated with vandetanib in France[71] had a markedly higher incidence of death (42% compared with $\leq$ 12% in the other studies for the 300-mg vandetanib dose) and AE-related discontinuations (27% compared with $\leq$ 15%) than the other study[69] or the ZETA trial. These trials had a similar or shorter duration of follow-up than the ZETA trial, but were not subject to potential confounding because of treatment switching.

Network meta-analysis

Justification for conducting a network meta-analysis

In the absence of head-to-head evidence comparing cabozantinib with vandetanib, an indirect comparison using a NMA was considered. An indirect comparison has previously been published as an abstract[93] and is presented in the Ipsen CS;[21] however, owing 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 participants in the EXAM trial had confirmed disease progression, whereas the ZETA trial recruited a broader population of participants 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 participants ($n = 139$, HR 0.49, 95% CI 0.27 to 0.58) within the Sanofi CS.[66] 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 AG considered a 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 trial: 4.0 months, ZETA trial EU-label population: 16.4 months (by central review)]; however, differences in baseline characteristics of the included studies as a result of differences in study protocols are to be expected and do not invalidate an indirect comparison. For a NMA to be valid, it is important that there is not an imbalance in treatment-effect modifiers. Clinical advisors to the AG 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 trial EU-label population, so balance across the two studies could not be assessed, and there is no clear evidence to demonstrate the balance of this potential treatment-effect modifier. However, subgroup analyses indicated consistent treatment effects according to performance status at baseline for both interventions,[27,28] and clinical advice received by the AG suggested that the ZETA trial EU-label and EXAM trial ITT populations could be considered to be broadly comparable. Therefore, on the basis of clinical advice, and since there was no evidence to invalidate indirect comparison, a NMA was considered to be justified.

Methods for the network meta-analysis

The NMA was conducted by the AG 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; therefore, a NMA was 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 14*. Analyses were conducted using a Bayesian random-effects model, as described by Dias *et al.*[94] Given that there is potential heterogeneity between the trials, a random effects model was considered to be the 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.*[95]), which has a median of 0.08 and 95% range of 0.003 to 2.34 on the untransformed scale.

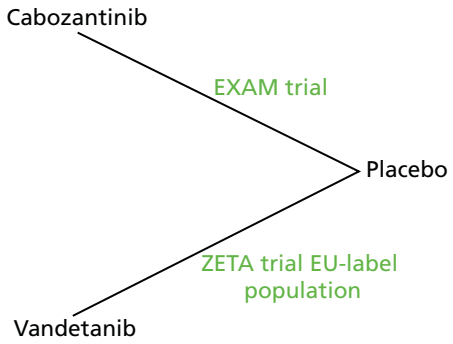

FIGURE 4 Network diagram for the NMA.

TABLE 14 Data for the NMA on PFS

			PFS HR (95% CI)	
Trial	Treatment	Comparator	Investigator read	Central read
EXAM ($n = 330$), Elisei *et al.*[28]	Cabozantinib	Placebo	0.29 (0.21 to 0.42)	0.28 (0.19 to 0.40)
ZETA EU label ($n = 186$), Kreissl *et al.*[57]	Vandetanib	Placebo	0.33 (0.20 to 0.53)	0.47 (0.29 to 0.77)

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 evidence from Speigelhalter *et al.*[96] and Smith *et al.*[97] 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[98] (MRC Biostatistics Unit, Cambridge, UK) and R (The R Foundation for Statistical Computing, Vienna, Austria) using the R2WinBUGS interface package. Convergence to the target posterior distributions was assessed using the Gelman–Rubin statistic, as modified by Brooks and Gelman,[99] for two chains with different initial values. 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 AG (see *Chapter 4*, *Independent assessment group model*). 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 AG'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 *Time to event analysis using individual patient data*), conforming to the recommendation in Guyot *et al.*[100]

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. 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.

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 deemed to be 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). In contrast, the ZETA trial was rated as being at moderate to high risk of bias across a number of domains; in particular, the method of

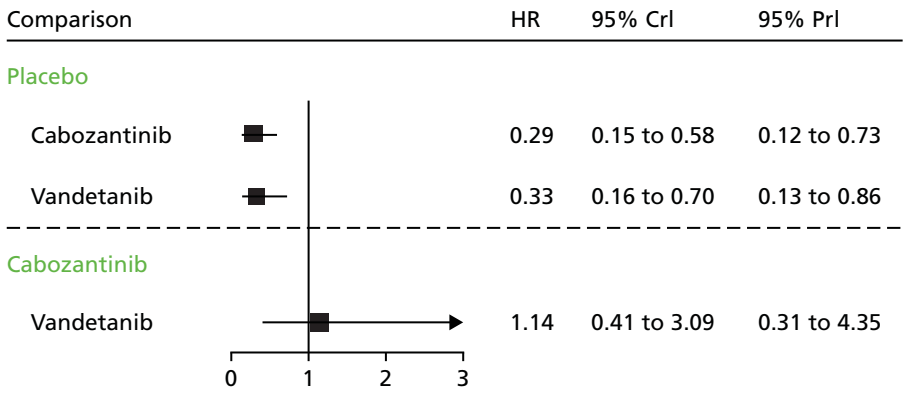

FIGURE 5 Results of the NMA for investigator-read PFS. PrI, prediction interval.

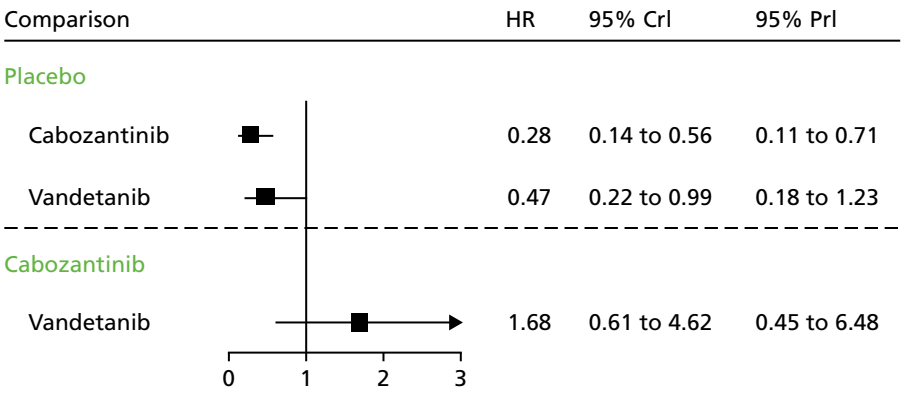

FIGURE 6 Results of the NMA for central-read PFS. PrI, prediction interval.

randomisation was not described and several outcomes were confounded by the inclusion of individuals who had switched to open-label treatment.

The two trials assessed different populations. The EXAM trial ($n = 330$) included only patients with unresectable locally advanced or metastatic and progressive MTC, whereas the ZETA trial inclusion criteria ($n = 331$) did not specify the requirement for patients to have 'progressive' disease; therefore, the ITT population in the ZETA trial generally had less severe disease (there were more participants with potentially indolent disease). The more progressive and severe disease of EXAM trial participants is evidenced by the between-trial baseline differences in performance status (see *Table 3*) and the relatively shorter duration of PFS for the participants in the placebo arm of the EXAM trial. However, a published abstract[57] and the Sanofi CS[66] provided data on a subgroup of the ZETA ITT population, that is, 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 trial EU-label population subgroup), clinical advice received by the AG 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[66] also presented data on a restricted EU-label subgroup from the ZETA trial (confidential information has been removed), which was composed of 'progressive and symptomatic' patients who also had 'aggressive' disease, defined by CTN and CEA doubling times of < 24 months. CTN and CEA doubling times are acknowledged prognostic factors for MTC[15–17] and were not controlled for in the EXAM trial. However, clinical advice received by the AG suggests that these biomarkers are unlikely to be relevant in the presence of other criteria indicating PD (e.g. RECIST criteria and symptoms), and, although they might be used to determine whether or not treatment is still working, they would not be used to inform decisions about whether or not 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 trial ITT population and the ZETA trial EU-label population, PFS was similar for cabozantinib (investigator-read HR 0.29, 95% CI 0.21 to 0.42; $p < 0.001$, central-read 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-read, excluding participants switching treatments, 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 *Progression-free survival*)]. The difference in PFS between vandetanib and placebo was (confidential information has been removed) for the restricted EU-label population (confidential information has been removed).[66] Subgroup analyses demonstrated a favourable treatment effect for all subgroup categories. The publications and CSs also presented data for PFS based on *RET* mutation status, but clinical advice received by the AG 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[66] and the unpublished ZETA trial CSR showed that participants with a CTN or CEA doubling time of

< 24 months had a PFS response to vandetanib that was more pronounced than that of participants with a doubling time of > 24 months and those in whom the doubling time is unknown.[66,74]

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 CrIs 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.[101] The AG 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 *Chapter 4*, *Independent assessment group model*).

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 treatment switching. 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; $p = 0.241$).[47] Within this study, the only significant difference in OS was found for 126 participants 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 participants who had switched to vandetanib in the open-label stage of the trial, thus potentially confounding these results.[66] According to the Sanofi CS,[66] the median OS for the restricted EU-label group was (confidential information has been removed) in the placebo arm compared with (confidential information has been removed) in the vandetanib arm (confidential information has been removed).

Both cabozantinib ($p < 0.001$) and vandetanib (ITT group, $p < 0.001$; EU-label group, $p < 0.0001$) demonstrated significant benefits compared with placebo in terms of ORR, as determined by the 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 conducted exploratory assessments of participants' 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, when assessed, no difference was found between the treatment or placebo arms in either trial; this covers both baseline and follow-ups. Clinical advice received by the AG 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%), HFS (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 HFS. Hypertension is a known AE of TKIs.[81,82] The incidence rates of rash and hypertension appear to be higher for vandetanib in MTC patients than in most other cancer patients,[84,85] which might be attributable to a longer treatment duration.[85]

The most common grade 3 or higher AEs for cabozantinib, as reported from the EXAM trial, were diarrhoea (16%), HFS (13%), fatigue (9%), 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 or higher 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%).[62] Vandetanib is one of only two TKIs (the other being sunitinb) identified as being particularly associated with prolonged QTc interval.[91]

Similar proportions of participants across the two trials discontinued treatment because of AEs (16% for cabozantinib and 12% for vandetanib), but a higher percentage of participants on cabozantinib experienced AEs leading to dose interruption or reduction (65%) than on vandetanib (35%). A later abstract[55] detailing this outcome for the EXAM trial reported that dose reduction to manage AEs was performed for 82% of participants treated with cabozantinib, which increased again to 87% in the final analysis. The percentages of participants 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% 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.[77] The authors of the EXAM trial[28] acknowledged the high rate of dose interruption with 140 mg of cabozantinib: the EXAMINER trial[54] has therefore been developed to assess the efficacy and safety of a lower dose of cabozantinib (60 mg) compared with the current standard dose (140 mg).

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% of participants 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 participant, arrhythmia and acute cardiac failure.[27] Instances of gastroenteritis and gastrointestinal haemorrhage led to deaths in two participants in the placebo group.[27]

Chapter 4 Assessment of cost-effectiveness

This chapter presents a systematic review of existing economic evaluations of treatments for locally advanced or metastatic MTC, and 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 AG.

Systematic review of existing cost-effectiveness evidence

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 HRQoL of patients with locally advanced or metastatic thyroid cancer (including MTC as well as other commoner forms of thyroid cancer). In anticipation of the likely lack of relevant evidence, the AG's search strategy was designed to be intentionally broad.

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

- MEDLINE – via Ovid, 1946 to present
- MEDLINE In-Process & Other Non-Indexed Citations – via Ovid, 1946 to present
- MEDLINE Epub Ahead of Print – via Ovid, 1946 to present
- CINAHL – via EBSCO*host*, 1982 to present
- EMBASE – via Ovid, 1980 to present
- HTA database, 1995 to present
- NHS Economic Evaluation Database (NHS EED), 1995 to 2015
- Web of Science (SCI) – via Clarivate Analytics (formerly Thomson Reuters) 1899 to present
- CPCI – via Clarivate Analytics (formerly Thomson Reuters) 1990 to present.

The search strategy comprised MeSH or Emtree Thesaurus terms and free-text synonyms for 'thyroid cancer'. Searches were translated across databases and were not limited by either 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, when 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 (e.g. 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 (*Box 2*). Although the inclusion criteria for the review of existing economic evaluation studies were 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).

Review of existing economic evaluations: results

Figure 7 presents the study selection results. Before deduplication, the searches yielded 3161 citations (HRQoL search, $n = 1282$ studies; economic evaluation search, $n = 1879$ citations). Following the initial sift, 3057 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

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, for example FNAB (unless the study specifically mentions utilities for advanced/metastatic disease or reports QALYs).
- Partial economic analyses, for example costing studies.
- Editorials.
- Reviews.
- Clinical studies that do not report costs.
- Letters and commentaries.
- Non-English language.

FNAB, fine-needle aspiration biopsy; QALY, quality-adjusted life-year.

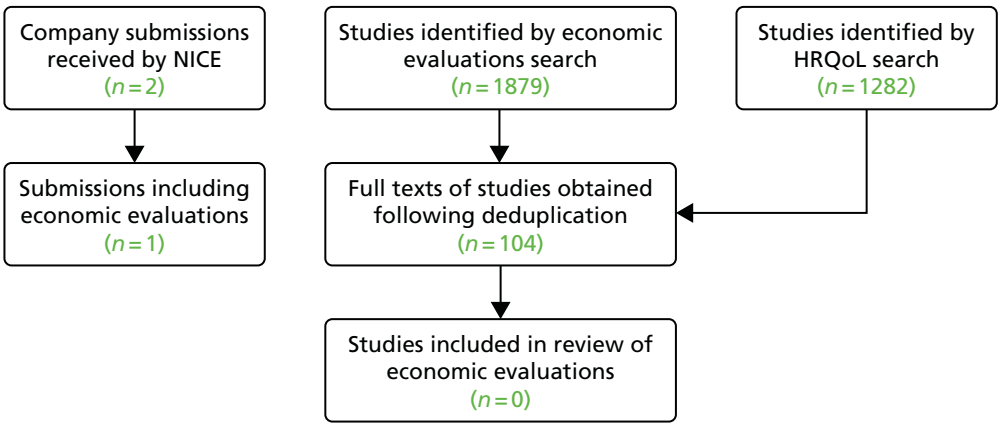

FIGURE 7 Study selection results.

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[102] reported health utilities for patients with radioactive iodine-refractory differentiated thyroid cancer; this study is discussed in further detail in *Independent assessment group model* and *Health-related quality of life*.

Review of models submitted by the companies

The Sanofi submission[66] 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.

Scope of the Sanofi economic evaluation

The Sanofi CS[66] 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 15*. 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, 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 of > 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.[66] The AG noted 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.[66] Costs and health outcomes are discounted at a rate of 3.5% per annum. The company's economic analysis includes a PAS that 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 separate confidential appendix to this report. Costs were valued at 2015/16 prices.

It is important to note from the outset that a substantial proportion of participants (confidential information has been removed) 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 participant following a protocol amendment in January 2010, see the Sanofi clarification response,[73] question A2). In addition, a proportion of participants (confidential information has been removed) in the restricted EU-label population who were allocated to the intervention group continued to receive open-label vandetanib following disease progression. Although the company attempted to adjust for treatment switching using the rank-preserving structural failure time (RPSFT) method, this was not successful (see the Sanofi CS,[66] pp. 98–9); hence, the estimates of

TABLE 15 Sanofi model scope

Model component	Description
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 of > 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	300 mg per day[a] of vandetanib [with post-progression continuation of vandetanib in (confidential information has been removed) of participants]
Comparator	BSC [with switch to 300 mg per day of vandetanib post progression in (confidential information has been removed) 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

a Dose adjustments, treatment interruption and treatment discontinuation are included for participants receiving vandetanib.

OS for both modelled treatment groups are unadjusted and 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 participants post progression, versus BSC with vandetanib use in most participants post progression. The AG 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 AG model (see *Independent assessment group model*).

The AG also notes that two errors were identified within the company's original submitted model, which related to (1) the duration over which QALY losses owing to AEs are applied and (2) inputs relating to the proportion of participants who discontinued vandetanib prior to disease progression (see *Critical appraisal of the economic analysis presented by Sanofi*). All results presented within this report include corrections to these errors.

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[103] (*Figure 8*). The model includes three health states: (1) progression free, (2) post progression and (3) dead. The model operates as follows. At any time t, the probability that a participant allocated to treatment group k is alive is given by $S(t)_{OS}\_k$, whereas the probability that a participant allocated to treatment group k is alive and progression free is given by $S(t)_{PFS}\_k$. The probability that a participant 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) 'BiomarkerChg' (CEA and CTN doubling times of $\leq$ 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: (1) vandetanib drug acquisition costs, (2) monitoring for participants receiving vandetanib, (3) BSC costs, (4) palliative care costs and (5) costs associated with managing AEs.

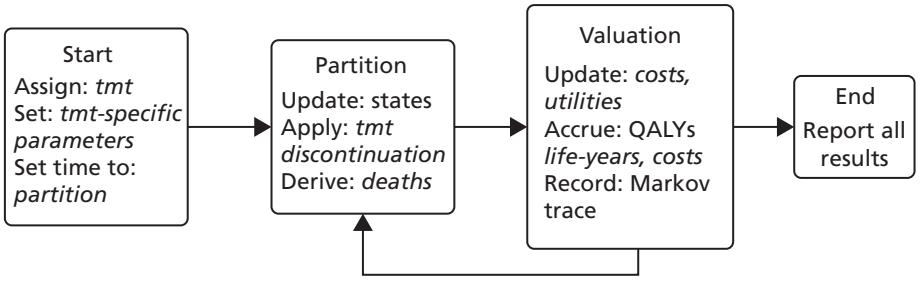

FIGURE 8 Schematic of the Sanofi DICE model (reproduced from the Sanofi CS[66]).

The model employs the following structural assumptions:

- Health-related quality of life is determined according to the presence/absence of disease progression and the incidence of grade 3/4 AEs.
- Progression-free survival 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. when $S(t)_{PFS} > S(t)_{OS}$].
- 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[73]) observed in the ZETA trial.
- Adverse events are assumed to affect both costs and HRQoL. According to the Sanofi CS,[66] 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 *Critical appraisal of the economic analysis presented by Sanofi*) and was corrected by the company in its clarification response[73] (question A18).
- Palliative care costs are assumed to be incurred only during the final month of life.

Evidence used to inform the company's model

Table 16 summarises the evidence used to parameterise the company's model. The derivation of these parameters and their evidence sources are discussed in further detail in the following sections.

Overall survival

Overall survival was defined as the time from randomisation to death or the last date at which the subject was known to be alive.[66] The analyses of OS used individual patient data (IPD) for all participants who received randomised treatment (the safety population) including follow-up to the data cut-off point of 7 September 2015. As noted in *Scope of the Sanofi economic evaluation*, the Sanofi CS[66] states that although attempts were made to adjust for treatment switching using the RPSFT method, these were unsuccessful (Sanofi CS,[66] pp. 98–9). Therefore, the OS data used in the model remain subject to potential confounding as they include data relating to 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,[66] p. 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) 'BiomarkerChg' (CEA and CTN doubling times of $\leq$ 24 months) – using the LIFEREG procedure in SAS® (SAS Institute Inc., Cary, NC, USA. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc. in the USA and other countries. ® indicates USA registration.). 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 was also assessed, although the CS does not provide details about who undertook this assessment or whether or not 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,[73] question A15).

The observed and predicted OS curves are presented in *Figure 17* in *Appendix 3*, based on the comparison presented in both the Sanofi CS[66] and the model. As the CS includes only a comparison of the Weibull function against the empirical Kaplan–Meier data, the AG 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 AG considers this comparison of observed and predicted OS to be inappropriate as the

TABLE 16 The company's model parameters and evidence sources

Parameter group	Evidence source	
PFS	Parametric survival models fitted to ZETA trial ITT population PFS data, and subsequently adjusted by setting the coefficients for covariates 'SympProg' and 'BiomarkerChg' to 100%[66]	
OS	Parametric survival models fitted to ZETA trial safety population OS data, and subsequently adjusted by setting the coefficients for covariates 'SympProg' and 'BiomarkerChg' to 100%	
Health utilities	Progression-free state: the FACT-G scores for the progression-free state observed in the ZETA trial were mapped to the EQ-5D-3L instrument using the algorithm reported by Dobrez *et al.*[104] Post-progression state: calculated using utility multiplier (0.766) for post progression vs. pre progression from SG study of societal preferences for advanced melanoma health states reported by Beusterien *et al.*[105] Disutility due to AEs: disutility for any grade 3/4 AE taken from Beusterien *et al.*'s[105] advanced melanoma SG study	
Time spent receiving vandetanib	Vandetanib group	BSC group
	(a) Pre progression • Percentage of PFS time spent receiving 300 mg/200 mg/100 mg/interrupted dose based on the restricted EU-label population of the ZETA trial[66,78] • An additional constant discontinuation probability (confidential information has been removed) is also assumed[66]	(b) Pre progression • N/A
	(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 while in post-progression state	Based on observed continuation proportion in the vandetanib group of the restricted EU-label population from the ZETA trial (confidential information has been removed)[66]	Based on observed switching proportion in the placebo group of the restricted EU-label population from the ZETA trial (confidential information has been removed)[66]
Vandetanib acquisition cost	Sanofi CS[66]	
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[66,74]	
BSC resource use	Assumption	
AE management costs	*NHS Reference Costs 2015/16*[106]	
BSC costs	*NHS Reference Costs 2015/16*[106]	
Palliative chemotherapy costs	*NHS Reference Costs 2015/16*[106]	
Palliative care costs	Curtis and Burns[107]	

EQ-5D-3L, EuroQol-5-Dimensions, three-level version; N/A, not applicable; SG, standard gamble.

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 *Critical appraisal of the economic analysis presented by Sanofi*). The corresponding AIC/BIC statistics for all five parametric models are presented in *Table 40* in *Appendix 3*.

With respect to the vandetanib group, the AIC and BIC were lowest for the log-normal model, whereas 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,[66] p. 105). The impact of uncertainty surrounding the choice of parametric function for PFS and OS was partially explored in the sensitivity analyses.

Progression-free survival

Progression-free survival was defined as the time from randomisation to documented progression based on central review or death.[66] The Sanofi CS[66] (p. 101) notes that, although the use of central-read PFS is subject to confounding because of treatment switching, using this end point mirrors the per-protocol end points of the ZETA trial. The analyses of PFS used IPD for all randomised participants available at the date of the initial data cut-off point, as reported in the original CSR of 6 July 2011.[74] 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) 'BiomarkerChg' (CEA and CTN doubling times of $\leq$ 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 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,[73] question A15).

The observed and predicted PFS curves are presented in *Figure 18* in *Appendix 3*, 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,[66] p. 56). As the CS includes only a comparison of the Weibull function against the empirical Kaplan–Meier PFS curves, the AG 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 AG notes that the Kaplan–Meier curves used to compare model-predicted with observed PFS within the Sanofi CS and those presented in the company's model differ considerably; the reasons for these differences are unclear. The corresponding AIC/BIC statistics for all five parametric models are presented in *Table 41* in *Appendix 3*.

The AIC and BIC were lowest for the log-normal model for the vandetanib group, whereas 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,[66] p. 105). The impact of uncertainty surrounding the choice of parametric function for PFS and OS was partially explored in the sensitivity analyses.

Health-related quality of life

The health utility values applied in the Sanofi model are summarised in *Table 42* in *Appendix 3*. The ZETA trial assessed HRQoL using the FACT-G instrument;[74] 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 participants who were progression free in the ZETA trial to the EuroQol-5 Dimensions, three-level version (EQ-5D-3L), using a published ordinary least squares algorithm reported by Dobrez *et al.*[104] This mapping exercise produced a mean utility score for the progression-free state of 0.84.

The Sanofi CS[66] notes that in the ZETA trial, post-progression FACT-G data were available for only 62 participants (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 standard gamble study of societal preferences for advanced melanoma states reported by Beusterien *et al.*[105] In 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 × 0.766). The disutility associated with any grade 3/4 AEs was also derived from the Beusterien *et al.*[105] advanced melanoma valuation study (disutility = –0.11). The same disutility was assumed to apply to each type of AE.

Time spent receiving vandetanib

Table 43 in *Appendix 3* 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.[66,78] 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[66] (p. 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 = (confidential information has been removed)]. Although the wording of the CS implies that all participants start treatment on vandetanib and a proportion of participants subsequently discontinue treatment during each cycle, this discontinuation parameter is instead applied as a fixed proportion of participants 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 *Table 43* in *Appendix 3*, is also applied in the post-progression state for the proportions of participants who switch to or continue to receive vandetanib post progression in each treatment group, albeit without the vandetanib discontinuation parameter. As a consequence, participants receive more vandetanib per cycle during the post-progression phase than in the pre-progression phase; it is unclear whether this reflects an error or an unreasonable assumption.

Probability of receiving vandetanib in the post-progression state

Based on the experience of the ZETA trial[66,78] (specifically with respect to the restricted EU-label population), the model assumes that (confidential information has been removed) of participants in the vandetanib group continue to receive vandetanib post progression, whereas (confidential information has been removed) of participants in the BSC group cross over to receive vandetanib post progression. Clinical advisors to the AG 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 44* in *Appendix 3*, based on the current prices listed in the *British National Formulary*.[108]

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*[106] (see *Table 45* in *Appendix 3*). Owing 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 participants who initially receive/continue vandetanib in the intervention group and to the proportion of participants who switch from BSC to vandetanib in the comparator group). Although the monitoring costs are presented in 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 participants continuing or switching to vandetanib post progression (see Sanofi CS,[66] p. 111). The company states that this approach was deemed to be conservative (see Sanofi clarification response,[73] question A20), although the AG notes that the impact on the incremental cost-effectiveness ratio (ICER) is likely to be small.

Adverse event management costs

The company's model includes any grade 3/4 AEs that occurred in ≥ 2% of participants in either treatment group. *Table 46* in *Appendix 3* 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*.[106] In response to a request for clarification from the AG, 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,[73] question A11). The model applies the total AE cost once during the first model cycle. The AG notes that all NHS reference cost codes assume that a participant 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 on the model results.

Palliative care costs

The company's model includes a cost of £5775 for palliative care derived from the Personal Social Services Research Unit (PSSRU)[107] and £827 for palliative chemotherapy given at the end of life, based on *NHS Reference Costs 2015/16*.[106] This cost is applied for the last month before death. As these costs are common to both groups, and because virtually all participants die within the time horizon (> 98.7% of participants), the only differences in these costs between the two treatment groups are as a result of discounting.

Model evaluation methods

The headline results presented in the Sanofi CS[66] 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 1000 Monte Carlo samples. Uncertainty was represented using tornado diagrams, cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs).

Sanofi model results

Sanofi central estimates of cost-effectiveness (excluding Patient Access Scheme, including error corrections)

Table 17 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.

Figure 9 presents the CEACs for vandetanib and BSC, generated by the AG 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.

TABLE 17 Sanofi's base-case estimates of cost-effectiveness (excluding PAS)

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

a Includes post-progression vandetanib costs.
Note
Sanofi probabilistic sensitivity analysis results.

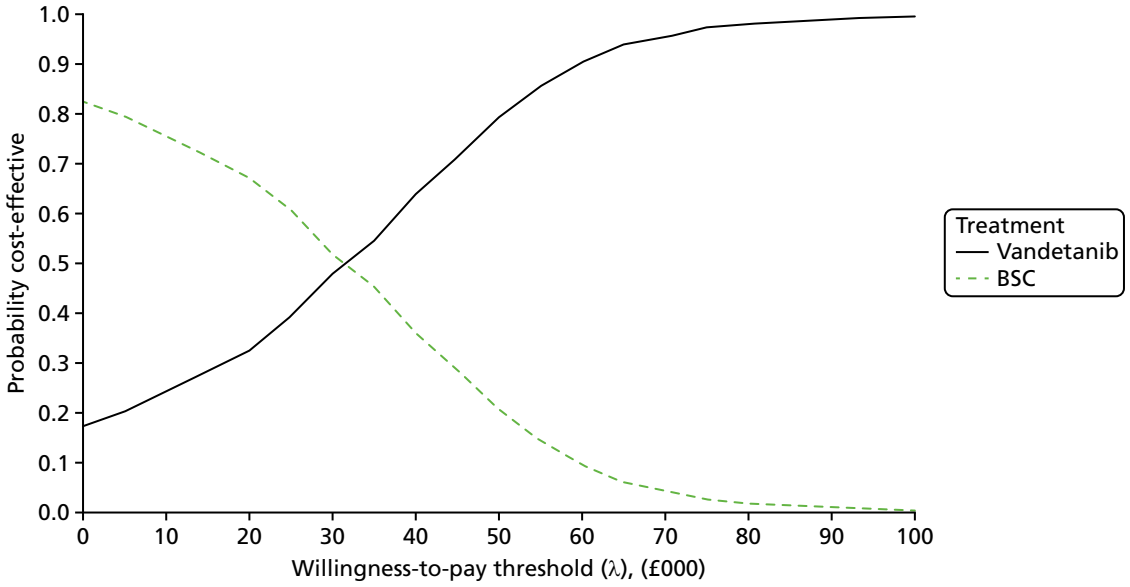

FIGURE 9 Cost-effectiveness acceptability curves generated using the Sanofi model: vandetanib vs. BSC (redrawn by the AG).

Sanofi's deterministic sensitivity analysis results

Figure 10 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 10*) did not have a substantial impact on 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 participants are alive at 20 years (> 8%) using these functions rather than the Weibull model (< 2%).

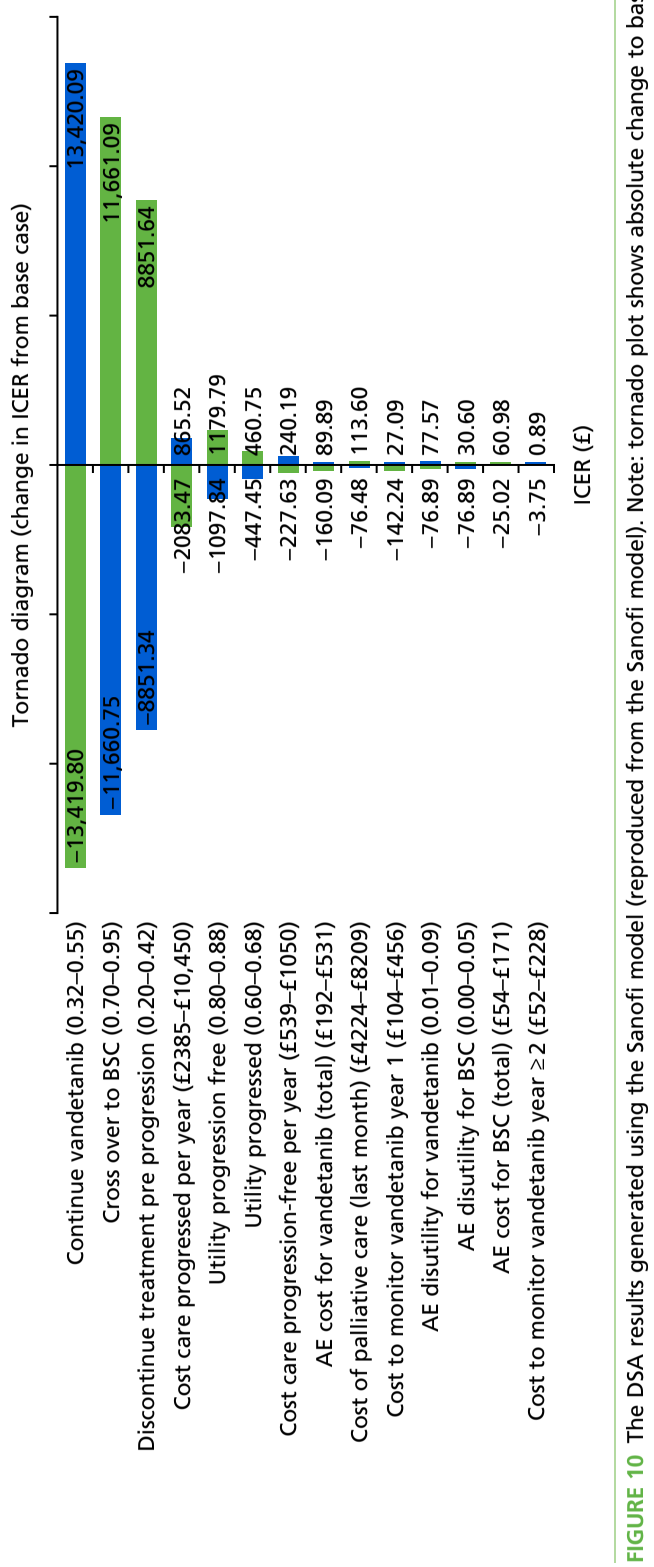

FIGURE 10 The DSA results generated using the Sanofi model (reproduced from the Sanofi model). Note: tornado plot shows absolute change to base-case ICER.

Critical appraisal of the economic analysis presented by Sanofi

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

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

- an assessment of the extent to which the model adheres to the NICE Reference Case[109]
- consideration of key items contained in published economic evaluation and health economic modelling checklists[110,111] to critically appraise the model and associated analysis
- scrutiny of the model and discussion of issues identified among the members of the AG
- 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[66] and the executable model
- replication of the base-case results, PSA and scenario analysis presented within the Sanofi CS[66]
- when possible, checking of the 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 National Institute for Health and Care Excellence Reference Case

Table 18 summarises the extent to which the economic analysis submitted by Sanofi adheres to the NICE Reference Case.[109]

TABLE 18 Adherence of the company's economic analysis to the NICE Reference Case

Element	Reference Case	AG's 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 as follows: 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 of > 4, ≥ 10 days of opioid use, diarrhoea, flushing, fatigue, pain, nausea, dysphagia, dysphonia, respiratory symptoms, weight loss) plus CTN and CEA doubling times of ≤ 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 with 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 are not explicitly considered as comparators

TABLE 18 Adherence of the company's economic analysis to the NICE Reference Case (*continued*)

Element	Reference Case	AG's comments
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The model includes direct health effects
Perspective on costs	NHS and PSS	The Sanofi model adopts a 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 vs. 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 a SG study of societal preferences for advanced melanoma states reported by Beusterien *et al.*[105] A disutility for any grade 3/4 AE is included based on Beusterien *et al.*[105]
Source of data for measurement of HRQoL	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*[106]
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

EQ-5D, EuroQol-5 Dimensions; PSS, Personal Social Services.

The two main deviations from the NICE Reference Case[109] concern the exclusion of cabozantinib as a comparator and the population considered within the economic analysis (the restricted EU-label population). The AG also notes that the clinical evidence and health utilities were not identified using systematic review methods. These issues are discussed further in *Critical appraisal of the economic analysis presented by Sanofi*.

Model verification

The AG reproduced the deterministic version of the company's DICE model using a simple partitioned survival approach implemented in Microsoft Excel® 2016 (Microsoft Corporation, Redmond, WA, USA). *Table 47* in *Appendix 3* compares the results generated by the company's submitted model and the AG's double-programmed model [including corrections detailed in critical appraisal point 6 (see *Box 3*)]. As shown in the table, the results generated by the two models are very similar. The AG is confident that the model has been implemented by the company as intended.

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 in the following sections.

BOX 3 Main issues identified by the AG

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.

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 AG, the company stated that:

> *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. Sanofi Genzyme 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.*
>
> *Reproduced with permission from Sanofi Genzyme, response to clarification questions,[73] question A3*

However, clinical advisors to the AG 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, although CEA and CTN are routinely measured in patients with MTC, these biomarkers are typically used to monitor patients while they are receiving treatment (to assess whether or not treatment is working), rather than to determine whether or not treatment should be initiated. The clinical advisors also noted that patients with symptomatic and progressive disease are also likely to have CEA/CTN doubling times of $\leq$ 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 *Chapter 3*) is clinically appropriate.

Failure to adjust for continued vandetanib use and best supportive care switching to vandetanib post progression

The Sanofi CS states that although 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, the company stated that:

> *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.*
>
> *Reproduced with permission from Sanofi Genzyme, response to clarification questions,[73] question A2*

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 describes the approach as 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, inverse probability-of-censoring weights and two-stage methods); however, these methods were not implemented. Consequently, the OS data for the BSC group remain subject to potential confounding because of treatment switching. Clinical advisors to the AG 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. 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; however, the advisor did note that this scenario is uncommon. Consequently, the AG's notes that the results generated by the company's model may not be meaningful for the purposes of decision-making.

Likely overestimation of costs of vandetanib use in post-progression state

The company's model includes a single progression event that corresponds to the partition between the progression-free and post-progression health states. As a result, 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 be likely to trigger a clinical decision to discontinue vandetanib. This is not reflected in the company's model. The AG accepts that, owing to the failure of the treatment-switching 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 probably 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 in the BSC group than in the intervention group [proportion of patients on treatment post progression: BSC (confidential information has been removed) vs. vandetanib (confidential information has been removed); 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 AG model.

Questionable implementation of the vandetanib discontinuation parameter

Although the company's model includes dose reductions (including treatment interruptions) for participants receiving vandetanib in both groups as per the ZETA trial (see *Table 43* in *Appendix 3*), a further discontinuation parameter is also applied, but only to those participants in the vandetanib group during the progression-free phase. This parameter is applied as a fixed proportion of participants who incur no vandetanib costs (confidential information has been removed) during any model cycle, whilst participants 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 lower than the post-progression vandetanib costs in the BSC group (vandetanib pre-progression drug costs, £75,767; BSC post-progression drug costs, £106,331). This lacks face validity and it is unclear whether or not 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.

Robustness of covariate-adjusted survival modelling to reflect the restricted EU-label population

The Sanofi CS[66] (p. 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 data sets for PFS and OS, respectively, and fitted curves including covariates for symptomatic and progressive disease and for the CEA/CTN biomarker. The AG 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 (confidential

information has been removed), placebo group (confidential information has been removed)] as these are the most relevant data available to estimate PFS and OS in this subgroup. Although the CS explains that the Kaplan–Meier curves feature large steps between events because of 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 AG has further concerns regarding the company's interpretation of their covariate-adjusted survival modelling. Figure 9 of the Sanofi CS[66] presents a comparison of the covariate-adjusted Weibull OS model against the empirical Kaplan–Meier curves from the ZETA trial (see *Figure 17* in *Appendix 3*) and states that:

> *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.*
>
> *Sanofi CS,[66] figure 9 (p. 59)*

However, the comparison of predicted and observed OS probabilities represented in this comparison relates to two different populations: the covariate-adjusted Weibull model relates to the restricted EU-label population, whereas the observed Kaplan–Meier curves relate to the ZETA trial ITT population with CEA and CTN doubling times of ≤ 24 months (excluding the progressive population characteristics). *Figure 19* in *Appendix 3* shows the company's Weibull OS model fitted against the relevant Kaplan–Meier curve for the restricted EU-label subgroup (plotted by the AG). As shown in the figure, the company's Weibull model does not provide a good visual fit to either the vandetanib or the BSC group data.

Technical programming errors

According to the CS[66] (p. 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 that 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 its clarification response[73] (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 (confidential information has been removed) but was later corrected to (confidential information has been removed). Correcting these two errors reduces the company's original deterministic ICER from £40,363 to £31,731 per QALY gained.

The AG also notes that the model does not include any adjustment for logical inconsistency (i.e. when the cumulative survival probability for PFS is greater than that for OS at a given time point). 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 (e.g. 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 48* in *Appendix 3*). This issue could have been resolved by conditioning the PFS survivor function to be equal to or lower than the OS survivor function.

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.*[105] study, which is used to inform the post-progression utility multiplier and the disutility for grade 3/4 AEs, are unclear from the Sanofi CS.[66]

The AG also notes that the Beusterien *et al.*[105] study relates to advanced melanoma health states, hence its relevance to MTC is unclear. Although the Sanofi CS[66] (p. 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 10*).

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. Although 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 *Sanofi model results*). It should also be noted that although 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.

Concerns regarding costings

Clinical advisors to the AG noted several concerns regarding the company's cost assumptions:

1. Monitoring costs. Although the company's model includes the costs associated with ECGs to monitor patients while receiving vandetanib, these costs should also include consultant-/nurse-led outpatient appointments (typically at a frequency of around 12 consultant-led visits and four nurse-led visits per year).
2. Best supportive care costs in post-progression state. The company's assumption of 36.5 outpatient appointments per year (one appointment every 10 days) while patients are receiving BSC is unrealistically high. Clinical advisors to the AG suggested that a more reasonable estimate would be around six appointments per year.
3. Costs of managing AEs. Clinical advisors to the AG 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 *Evidence used to inform the company's model*, 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 probably require the prescription of antihypertensive drugs.

Discussion of existing evidence relating to the cost-effectiveness of cabozantinib and vandetanib for the treatment of locally advanced or metastatic medullary thyroid cancer

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 times of ≤ 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 AG 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 AG considers it probable that the ICER for vandetanib is considerably higher than the estimates presented within the Sanofi CS.

Independent assessment group model

Model scope

The scope of the AG's analysis is summarised in *Table 19*. The AG's analyses are presented across two populations of patients with locally advanced or metastatic MTC: (1) patients with progressive and symptomatic disease (the EU-label population for vandetanib) and (2) 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[66,78] (AG analysis 2). It should be noted that these analyses are limited in that they do not include all relevant treatment options. As the AG 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. 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 trial 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.

TABLE 19 The AG model scope

	Population	
Model scope	**EU-label: symptomatic and progressive MTC**	**Restricted EU-label: symptomatic and progressive MTC with CEA/CTN doubling time of ≤ 24 months**
Intervention(s)	Vandetanib	Vandetanib
	Cabozantinib	
Comparator	BSC	BSC
Outcomes	Incremental cost per QALY gained	Incremental cost per QALY gained
Economic comparisons	AG analysis 1: pairwise economic evaluation of cabozantinib vs. BSC in the EXAM trial ITT population	AG analysis 5: pairwise economic evaluation of vandetanib vs. BSC in the ZETA trial restricted EU-label population
	AG analysis 2: pairwise economic evaluation of vandetanib vs. BSC in the ZETA trial EU-label population	
	AG analysis 3: fully incremental analysis based on EXAM trial ITT population with vandetanib PFS treatment effect applied to EXAM trial placebo baseline; vandetanib OS assumed to be equivalent to cabozantinib OS	
	AG analysis 4: fully incremental analysis based on EXAM trial ITT population assuming PFS and OS are equivalent for vandetanib and cabozantinib	
Perspective	NHS and PSS[a]	NHS and PSS[a]
Time horizon	20 years	20 years
Cycle length	1 month	1 month
Discount rate	3.5% for health outcomes and costs	3.5% for health outcomes and costs

PSS, Personal Social Services.
a PSS costs not explicitly included.

Although 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) that evaluates vandetanib versus BSC within the restricted EU-label population (patients with symptomatic and progressive MTC with CEA/CTN doubling times of $\leq$ 24 months) is also presented as equivalent covariate data were not available from the EXAM trial, 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.[109] Costs were valued at 2016/17 prices.

Model structure

The structure of the AG model is presented in *Figure 11*. As shown in the diagram, the AG model structure is broadly similar to that adopted within the Sanofi model (see *Sanofi model structure*). The AG model adopts a partitioned survival approach, based on three health states: (1) progression free, (2) post progression and (3) dead. For any time, *t*, the probability that a patient is alive and progression free is given by the cumulative survival probability for PFS, whereas 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 at any time *t* is given by the difference between the cumulative survival probabilities for PFS and OS. The model includes an adjustment for logical inconsistency, whereby, if the probability of PFS is greater than that of 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 while receiving cabozantinib and vandetanib [consultant-led outpatient visits, nurse-led outpatient visits, ECG, 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.

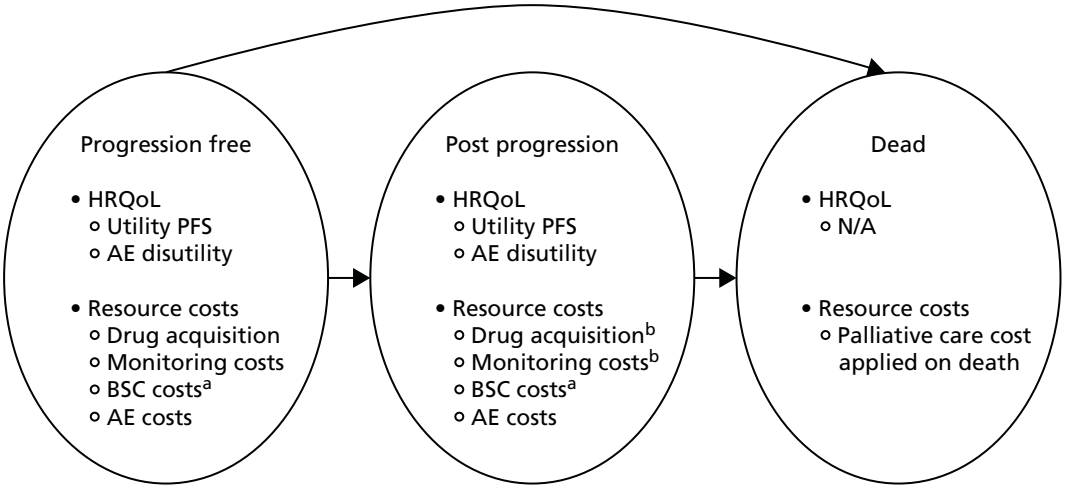

FIGURE 11 The AG model structure. N/A, not applicable. a, Applies only to patients not receiving vandetanib/cabozantinib. b, Applies only to open-label vandetanib costs within pairwise comparisons of vandetanib vs. BSC.

The model employs the following structural assumptions:

- Health-related quality of life 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. when $S(t)_{PFS} > S(t)_{OS}$].
- In the pairwise comparisons of vandetanib versus BSC (see *Table 19*, 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 *Critical appraisal of the economic analysis presented by Sanofi*).
- Grade 3/4 AEs are assumed to affect 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.

Evidence used to inform the model's parameters

Summary of evidence sources used to inform the assessment group model

Table 20 summarises the evidence sources used to inform the AG's health economic model. These evidence sources are discussed in further detail in the subsequent sections.

TABLE 20 Evidence used to inform the AG model

Parameter group	Evidence source
PFS	Pairwise comparisons of TKI vs. BSC (AG analyses 1, 2 and 5) • Parametric PFS functions fitted to IPD from the EXAM and ZETA trials[a] 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
OS	Pairwise comparisons of TKI vs. BSC (AG analyses 1, 2 and 5) • Parametric OS functions fitted to IPD from the EXAM and ZETA trials (includes potential confounding as a result of switching/continuation post progression for vandetanib comparisons)[a] 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

TABLE 20 Evidence used to inform the AG model (*continued*)

Parameter group	Evidence source
Health utilities	Progression-free and post-progression health states • Derived from TTO study utility valuation in radioactive iodine-refractory differentiated thyroid cancer[102] 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[105]
Time spent receiving vandetanib	Based on the proportion of PFS time spent on each dose level (or interrupted treatment) for relevant subgroup in the ZETA trial.[66,73,78] 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 the proportion of PFS time spent on each dose level (or interrupted treatment) within the EXAM trial[28]
Probability of receiving vandetanib while in post-progression state	Treatment switching/continuation proportions observed in relevant subgroups of the ZETA trial.[66,73] Vandetanib dose distribution also applied to post-progression use
Drug acquisition costs	BNF[108]
AE incidence	Derived from EXAM and ZETA trial publications[27,28]
Health state resource use	Personal communication: Dr Jon Wadsley (Weston Park Hospital, Sheffield, 2017) and Dr Laura Moss (Velindre Cancer Centre, Cardiff, 2017)
BSC resource use	Personal communication: Dr Jon Wadsley and Dr Laura Moss
Health state unit costs	*NHS Reference Costs 2015/16*[106]
AE management costs	*NHS Reference Costs 2015/16*.[106] Weighted mean of all non-elective excess bed-days
BSC costs	*NHS Reference Costs 2015/16*[106]
Palliative care and palliative chemotherapy costs	*NHS Reference Costs 2015/16*,[106] and Curtis and Burns[107]

BNF, *British National Formulary*; SG, standard gamble; TTO, time trade-off.
a Data from the ZETA trial were reconstructed IPD rather than raw trial data.

Time-to-event analysis using individual patient data

Table 21 summarises the use of the time-to-event data from the ZETA and EXAM trials within the AG model.

The comparison of cabozantinib with 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.[112]

The comparison of vandetanib with placebo was based on post hoc subgroups of participants enrolled in the ZETA trial: the EU-label population [vandetanib, $n =$ (confidential information has been removed); placebo, $n =$ (confidential information has been removed) for PFS; placebo, $n =$ (confidential information has been removed) for OS] and the restricted EU-label population [vandetanib, $n =$ (confidential information has been removed); placebo, $n =$ (confidential information has been removed)]. Owing to concerns regarding the intellectual property rights of the patient-level data set, 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.[73] The supplied Kaplan–Meier curves were digitised using Engauge Digitizer[113] and IPD were then reconstructed from the digitised curves using the algorithm reported by Guyot *et al.*[114] 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 trial 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

TABLE 21 Summary of time-to-event data used in the AG model

Outcome	Population				
	EU-label: symptomatic and progressive MTC				Restricted EU-label: symptomatic and progressive MTC with CEA/CTN doubling times of ≤ 24 months
	AG analysis 1: cabozantinib vs. BSC (pairwise)	AG analysis 2: vandetanib vs. 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 vs. BSC (pairwise)
PFS					
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
OS					
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

N/A, not applicable.
Note
Data used to inform time-to-event analysis.

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 that can be readily identified from the Kaplan–Meier survival curves, the resulting reconstructed IPD are likely to provide a good approximation of the original data set.

Methods for time-to-event analysis

For each data set, model selection was conducted following the process described in the NICE Decision Support Unit Technical Support Document No. 14.[115,116] Log-cumulative hazard plots were produced to assess the type of hazards observed in the trial 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 the 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 this report (see *Table 23*).

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 *Chapter 3*, *Quantity and quality of research available* and *Justification for conducting a network meta-analysis*, 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 with placebo (either a 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) to approximate the absolute effect for a vandetanib treatment group in the chosen baseline population. The estimated HR from the NMA (see *Chapter 3*, *Network meta-analysis*) was not used as it is generally recommended that estimation of the treatment effects and baseline follows a consistent modelling procedure.[100] Furthermore, the use of HRs would not be appropriate for the accelerated failure time models as these do not make the assumption of proportional hazards.

Curve fitting was conducted in R using the flexsurv package. The muhaz package was used to estimate the empirical hazard function. 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 AG considered that the generalised *F*-distribution model would not be appropriate. The goodness-of-fit information is provided for all considered models.

Cabozantinib versus best supportive care, EXAM trial intention-to-treat population (used in the assessment group's analyses 1, 3 and 4)

Progression-free survival

The analysis of PFS for cabozantinib versus placebo was based on IPD from the full population of the EXAM trial (cabozantinib, $n = 219$; placebo, $n = 111$; see *Figure 20* in *Appendix 4*) provided by Ipsen. Empirical diagnostic plots are provided in *Figure 21* in *Appendix 4*. 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 49* in *Appendix 4*. Plots of the fitted models against the empirical Kaplan–Meier PFS curves are presented in *Figures 22* (cabozantinib) and *23* (placebo) in *Appendix 4*. 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.

Overall survival

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; see *Figure 24* in *Appendix 4*) provided by Ipsen. Log-cumulative hazard plots are provided in *Figure 25, Appendix 4*. 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 49* in *Appendix 4*. Plots of the fitted models against the empirical Kaplan–Meier OS curves are presented in *Figures 26* (cabozantinib) and *Figure 27* (placebo) in *Appendix 4*. 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 based on the AIC (1343.69) and the exponential model provided the best fit based on the BIC (1348.42).

Vandetanib versus best supportive care, ZETA trial EU-label population (used in the assessment group's analysis 2)

Progression-free survival

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* = (confidential information has been removed); placebo, *n* = (confidential information has been removed)]. The Kaplan–Meier curves provided by Sanofi[73] are presented in *Figure 28* in *Appendix 4*. The number of observed events was (confidential information has been removed) in the vandetanib arm and (confidential information has been removed) in the placebo arm (Sanofi CS appendices,[78] table 5, p. 51). The replicated Kaplan–Meier curves appear consistent with the reported data (see *Figure 29* in *Appendix 4*): the replicated median PFS time of (confidential information has been removed) months for placebo is close to the value reported from the observed data (median 16.4, *n* = 60 from Kriessl *et al.*[57]). Median PFS was not reached for the vandetanib arm.

Log cumulative hazard plots are presented in *Figure 30* in *Appendix 4*. 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 50* in *Appendix 4*. Plots of the fitted models against the empirical PFS data are presented in *Figures 31* (vandetanib) and *32* (placebo) in *Appendix 4*. For the placebo arm, the exponential model provided the best fit to the observed data based on both the AIC and the BIC (AIC = 296.49, BIC = 298.58). For the vandetanib arm, the gamma model provided the best fit to the observed data based on 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.

Overall survival

The analysis of OS for vandetanib was based on Kaplan–Meier curves for the EU-label population of the ZETA trial [vandetanib, *n* = (confidential information has been removed); placebo, *n* = (confidential information has been removed)]. The Kaplan–Meier curves provided by the company are shown in *Figure 33* in *Appendix 4*; the number of events observed was (confidential information has been removed) in the vandetanib arm and (confidential information has been removed) in the placebo arm (Sanofi CS appendices,[78] table 7, p. 53). The replicated Kaplan–Meier curves appear consistent with the reported data (see *Figure 34* in *Appendix 4*):

the replicated median OS times of (confidential information has been removed) months for placebo and (confidential information has been removed) months for vandetanib are close to the estimates reported from the observed data (placebo median = (confidential information has been removed); vandetanib median = (confidential information has been removed), from Kreissl *et al.*[57]).

Log-cumulative hazard plots are provided in *Figure 35* in *Appendix 4*. 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 50* in *Appendix 4*. Plots of the fitted models against the empirical Kaplan–Meier OS curves are presented in *Figures 36* (vandetanib) and *37* (placebo) in *Appendix 4*. 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.

Vandetanib versus best supportive care, restricted EU-label population, ZETA trial (used in the assessment group's analysis 5)

Progression-free survival

The analysis of PFS for vandetanib versus placebo was based on Kaplan–Meier curves for the restricted EU-label population of the ZETA trial [vandetanib, *n* = (confidential information has been removed); placebo, *n* = (confidential information has been removed)]. The Kaplan–Meier curves provided by Sanofi are shown in *Figure 38* in *Appendix 4*; the number of progression events observed was (confidential information has been removed) in the vandetanib arm and (confidential information has been removed) in the placebo arm. The replicated Kaplan–Meier curves appear to be consistent with the reported data (see *Figure 39* in *Appendix 4*): the replicated median PFS times of (confidential information has been removed) months for the placebo arm and (confidential information has been removed) months for the vandetanib arm are close to the estimates reported from the observed data [placebo median = (confidential information has been removed) months, vandetanib median = (confidential information has been removed) months (from the Sanofi CS,[78] appendix 6)].

Log-cumulative hazard plots are presented in *Figure 40* in *Appendix 4*. Measures of comparative internal validity are presented in *Table 51* in *Appendix 4*. Plots of the fitted models against the empirical Kaplan–Meier PFS curves are presented in *Figures 41* (vandetanib) and *42* (placebo) in *Appendix 4*. For the placebo arm, the log-logistic model provided the best fit to the observed data based on the AIC (89.55), whereas the exponential model provided the best fit based on the BIC (90.54). For the vandetanib arm, the log-normal model provided the best fit based on the AIC (132.60), whereas the exponential model provided the best fit based on 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.

Overall survival

The analysis of OS for vandetanib was based on Kaplan–Meier curves for the restricted EU-label population within the ZETA trial [vandetanib, *n* = (confidential information has been removed); placebo, *n* = (confidential information has been removed)]. The Kaplan–Meier curves provided by Sanofi are shown in *Figure 43* in *Appendix 4*; the number of progression events observed was (confidential information has been removed) in the vandetanib arm and (confidential information has been removed) in the placebo arm. The replicated Kaplan–Meier curves appear consistent with the reported estimates (see *Figure 44* in *Appendix 4*): the median PFS times of (confidential information has been removed) months for placebo and (confidential information has been removed) months for vandetanib are close to the estimates reported from the observed data (placebo median = (confidential information has been removed) months, vandetanib median = (confidential information has been removed) months, from the Sanofi CS,[78] appendix 6).

Log-cumulative hazard plots are provided in *Figure 45* in *Appendix 4*. Measures of comparative internal validity are presented in *Table 51* in *Appendix 4*. Plots of the fitted models against the empirical Kaplan–Meier OS curves are presented in *Figures 46* (vandetanib) and *47* (placebo) in *Appendix 4*. For the placebo arm, the Gompertz model provided the best fit to the observed data based on 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 based on both the AIC and the BIC (AIC = 212.75, BIC = 214.21).

Combined model used to estimate progression-free survival treatment effect for vandetanib and best supportive care (used in assessment group analysis 3)

The analysis of PFS for vandetanib versus placebo, used to inform AG analysis 3, utilised the Kaplan–Meier curves for the ZETA trial EU-label population [vandetanib, *n* = (confidential information has been removed); placebo, *n* = (confidential information has been removed)]; 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 suggests that the proportional hazards assumption may be considered valid for the observed period, and the use of a single model with a covariate indicating treatment group is therefore appropriate.

Measures of comparative internal validity are presented in *Table 52* in *Appendix 4*. The log-normal model provided the best fit to the observed data based on both the AIC and BIC (AIC = 764.25, BIC = 773.99). *Figure 48* in *Appendix 4* presents plots of the reconstructed survival data for both the placebo and vandetanib groups.

Within the health economic model, the treatment effect covariate (shown in *Table 52* in *Appendix 4*) 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 a 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. These parameters are applied to the survivor function of the baseline proportional hazards/accelerated failure time model as follows.

Proportional hazards models

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

$$S_V(t) = S_P(t)^r. \quad (1)$$

Further detail can be found in Collett.[117]

Accelerated failure time 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:

$$S_V(t) = S_P(\theta t), \quad (2)$$

where $\theta = \exp(-\beta x)$ and β is the coefficient on the analysis scale. Applying the coefficients presented in *Appendix 4*, *Table 52*, we have:

$$S_V(t) = S_P(\exp(-\beta x)t). \quad (3)$$

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 22*. The second clinical advisor felt unable to complete the model selection exercise. The AG's selected base-case survivor functions for each analysis are presented in *Table 23*.

TABLE 22 Clinical advisor's preferred survivor functions

	Advisor number 1 (JW)	
Population	Preferred curve	Justification[a]
EU-label population: symptomatic and progressive MTC		
EXAM trial 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 trial ITT, PFS, placebo	Log-logistic	*Appears to most closely fit observed data*
EXAM trial 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 trial 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 trial EU label, PFS, vandetanib	Log-logistic	*Good fit at early time points and allows for a small proportion of long-term PFS patients*
ZETA trial 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 trial EU label, OS, vandetanib	Log-normal or log-logistic	*Appears to give best fit to early data*
ZETA trial 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 of ≤ 24 months		
ZETA trial 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 trial EU label, PFS, placebo	Log-normal, log-logistic, Gompertz	*Close fit to early data and realistic, small number of longer-term PF survivors*
ZETA trial EU label, OS, vandetanib	Log-logistic, log-normal, Gompertz	*Good fit with early data and realistic number of longer-term survivors*
ZETA trial EU label, OS, placebo	Gompertz	*Closest fit to early data and realistic upper limit of 100 months OS for this poor-prognosis group*

PF, progression free.
a Dr Jon Wadsley, personal communication.

TABLE 23 Survivor functions used in the AG's base-case analysis

Population	Selected curve	Justification
Cabozantinib vs. BSC, EXAM trial ITT population (used in AG analyses 1, 3 and 4)		
EXAM trial 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 trial ITT, PFS, placebo	Log-logistic	Selected based on clinical opinion and on the basis of consistency with the model used for the intervention group. There is a cluster of models that 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 trial 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 based on the BIC)
EXAM trial 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 vs. BSC, ZETA trial, EU-label population (used in AG analysis 2)		
ZETA trial EU label, PFS, vandetanib	Log-logistic	Reflects clinician's choice, justified in terms of the 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 trial 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 was the model selected on basis of consistency with the intervention arm
ZETA trial 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. The log-logistic model was selected for consistency with the comparator arm and is very similar in terms of AIC/BIC
ZETA trial EU label, OS, placebo	Log-logistic	Reflects clinician's choice, justified in terms of the proportion of long-term survivors
Vandetanib vs. BSC, ZETA trial, restricted EU-label population (used in AG analysis 5)		
ZETA trial restricted EU label, PFS, vandetanib	Log-normal	Predicted outcomes are very similar for all three candidate models (log logistic, log normal and Gompertz). The log-normal model was selected because it had the lowest AIC among the competing candidate models
ZETA trial 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 trial restricted EU label, OS, vandetanib	Gompertz	Selected on basis of consistency with comparator arm
ZETA trial restricted EU label, OS, placebo	Gompertz	Models selected on basis of clinical justification (proportion of long-term survivors). Gompertz model has best AIC/BIC

Health-related quality of life

The AG's systematic searches for HRQoL evidence identified only one published study[102] that reports health utilities for states of progression free and post progression in patients with thyroid cancer. In this study, the authors developed vignettes for seven health states based on the results of a previous qualitative study[118] in differentiated thyroid cancer. These states included (1) stable/no response, (2) response (partial and complete), (3) progressive disease, (4) stable/no response with grade 3 diarrhoea, (5) stable/no response with grade 3 fatigue, (6) stable/no response with grade 3 HFS and (7) stable/no response with grades 1 and 2 alopecia. A total of 100 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 24*.

Owing to the lack of published evidence relating to the HRQoL associated with thyroid cancer states, the AG also explored the health utility values considered within previous thyroid cancer drug submissions to the SMC and the AWMSG. *Table 25* summarises the health utilities assumed within these submissions.

The health utilities assumed in the AG's base-case analysis are summarised in *Table 53* in *Appendix 4*. Health utilities associated with the absence/presence of disease progression were based on the study reported by Fordham *et al.*,[102] as this study specifically relates to thyroid cancer states, and health utilities were valued using a preference-based measure (TTO).[102] The disutility associated with grade 3/4 AEs was based on the lower value reported by Beusterien *et al.*[105] (disutility = –0.11). Uncertainty surrounding these parameters was modelled using beta distributions. Alternative utility values based on the cabozantinib[122] and the sorafenib[120] SMC submissions are explored within the sensitivity analyses.

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 54* in *Appendix 4*).[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.

Treatment switching/continuation parameters (assessment group analyses 2 and 5 only)

As noted in *Scope of the Sanofi economic evaluation*, Sanofi applied the RPSFT approach in an attempt to adjust for the high level of treatment switching that occurred within the ZETA trial.[66] However, the company's attempts were reported to have been unsuccessful; hence, the available OS data for vandetanib that 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 AG included the costs associated with treatment switching and vandetanib continuation post progression in the pairwise analyses of vandetanib versus BSC. The number of participants who received vandetanib post progression in each arm of each subgroup of the ZETA trial was provided by Sanofi (see *Table 55* in *Appendix 4*).

TABLE 24 Utility values reported by Fordham *et al.*[102]

Health state	Mean utility (observed, no adjustment)	95% CI
Best state: stable/no response	0.80	0.77 to 0.84
Response to therapy	0.86	0.83 to 0.89
Progressive disease	0.50	0.45 to 0.56
Diarrhoea	0.42	0.36 to 0.48
Fatigue	0.72	0.67 to 0.77
HFS	0.52	0.46 to 0.58
Alopecia	0.75	0.71 to 0.79

TABLE 25 Health utility values applied in other UK thyroid cancer submissions

Body	Drug	Indication	Health utility values
SMC	Lenvatinib[119]	Adult patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine	Derived from Fordham *et al.*[102] 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, HFS, alopecia)
SMC	Sorafenib[120]	Patients with progressive, locally advanced or metastatic, differentiated thyroid carcinoma, refractory to radioactive iodine	Utilities derived from EQ-5D data from the DECISION study[121] Sorafenib, progression free: 0.72 BSC, progression free: 0.80 Post progression (both groups): 0.64
SMC	Cabozantinib[122]	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[123]	Patients with aggressive and symptomatic unresectable locally advanced or metastatic MTC	FACT-G scores collected in the ZETA trial mapped to TTO values. Pre- and post-progression utility values not reported Disutilities for AEs based on Beusterien *et al.*[105] (values of –0.11 and –0.13 assumed)
AWMSG	Cabozantinib[124]	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)

EQ-5D, EuroQol-5 Dimensions; SF-6D, Short Form questionnaire-6 Dimensions.

Resource use and costs

Drug acquisition

Table 56 in *Appendix 4* presents the drug acquisition costs for cabozantinib and vandetanib based on their current list prices.[108] 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 AG's economic analysis including the PAS discounts for vandetanib and cabozantinib are presented in a separate confidential appendix to this report.

Time spent receiving cabozantinib and vandetanib

Table 57 in *Appendix 4* presents the proportion of PFS time spent receiving each dose of cabozantinib within the EXAM trial.[112] *Table 58* in *Appendix 4* presents the proportion of PFS time spent receiving each dose of vandetanib within the ZETA trial subgroups.[66,73] As these data are multinomial in nature, uncertainty was modelled using a Dirichlet distribution with minimally informative priors.

The model also includes a further parameter to reflect those participants who discontinued vandetanib prior to disease progression [(confidential information has been removed) in the restricted EU-label population and 22.31% in the broader EU-label population]. Although these participants 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 *Critical appraisal of the economic analysis presented by Sanofi*, critical appraisal point 4). In contrast to the assumption taken within the Sanofi model, the AG assumed that these participants incur half of the total cost of vandetanib during the progression-free phase (hence the discontinuation parameter was divided by 2). Uncertainty surrounding this parameter was modelled using a beta distribution.

Cost of managing grade 3/4 adverse events

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*[106] (mean cost £298.41). Uncertainty surrounding this parameter was modelled using a normal distribution, assuming that the standard error (SE) was equal to 15% of the mean (SE £44.76).

Best supportive care costs

Resource use for patients receiving cabozantinib, vandetanib and BSC was estimated using expert opinion (Dr Jon Wadsley and Dr Laura Moss, personal communication) (see *Tables 59* and *60* in *Appendix 4*). Clinical advice received by the AG 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, minimum and maximum), which 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:

$$\frac{\text{Lower limit} + \text{mode} + \text{upper limit}}{3}. \quad (4)$$

The numbers of ECGs, CT scans, and blood tests were not associated with uncertain ranges and were thus held as fixed values within the probabilistic analysis.

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,[66] which were, in turn, derived from the *NHS Reference Costs 2015/16*[106] and the PSSRU.[107] A total cost of £6602.52 is applied per patient.

Unit costs

Table 61 in *Appendix 4* summarises the unit costs included in the AG model.

Model evaluation methods

Uncertainty was evaluated using PSA and DSA. PSA was undertaken using simple Monte Carlo sampling methods (2000 samples). The choice of distribution assumed for each parameter group is summarised in *Table 62* in *Appendix 4*. 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.

Model validation

The AG 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*).

Assessment group model results

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

Analysis 1: EU-label population (symptomatic and progressive medullary thyroid cancer), cabozantinib versus best supportive care (pairwise)

Table 26 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 63* in *Appendix 5*. Based on the probabilistic version of the AG 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.

Figure 12 presents 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.

TABLE 26 Analysis 1: EU-label population (symptomatic and progressive MTC), cabozantinib vs. BSC (pairwise), central estimates of cost-effectiveness (PFS = log-logistic, OS = log-logistic for both options)

	Absolute		Incremental		
Option	QALYs	Costs (£)	QALYs	Costs (£)	ICER (£)
Probabilistic model					
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	–	–	–

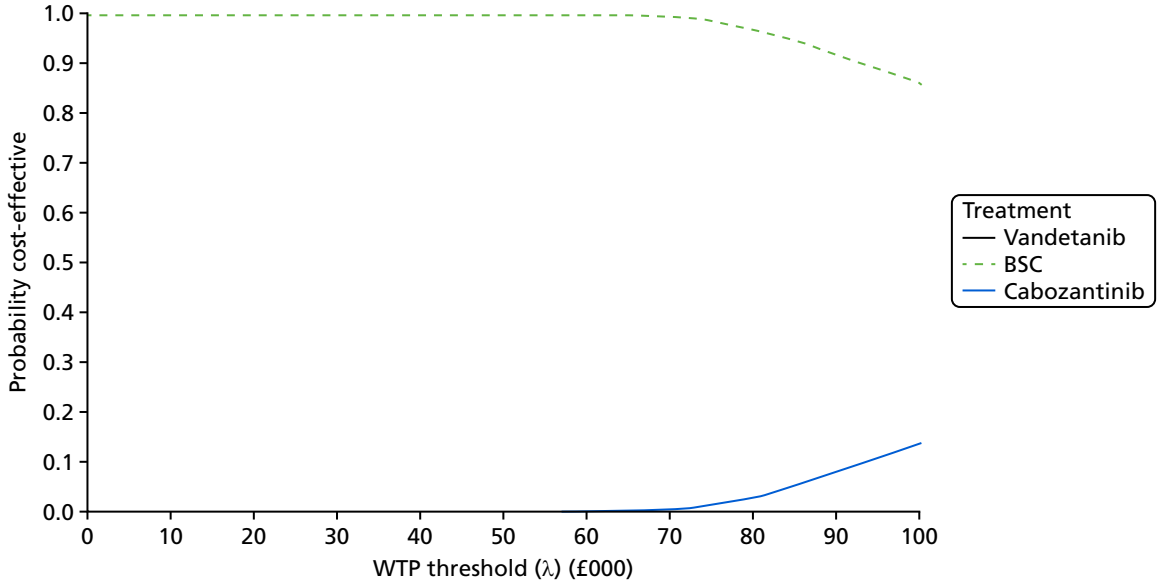

FIGURE 12 Analysis 1: EU-label population (symptomatic and progressive MTC), cabozantinib vs. BSC (pairwise), CEACs (PFS = log-logistic, OS = log-logistic for both options).

Table 27 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 on 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 AG's base-case analysis (PFS = log-logistic, OS = log-logistic) are close to the most favourable scenario.

Analysis 2: EU-label population (symptomatic and progressive MTC), vandetanib versus best supportive care (pairwise)

Table 28 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 as a result of 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 64* in *Appendix 5*. Based on the probabilistic version of the AG 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 than in the vandetanib group: this is likely to be a consequence of confounding as a result of open-label vandetanib use in the placebo group. It is also noteworthy that, based on the selected OS functions, a similar proportion of patients in each group (11–12%) are predicted to still be alive at 20 years as a consequence of the flattening of the tails of the modelled curves; additional analyses undertaken by the AG indicate that the ICER for vandetanib versus BSC remains stable over longer time horizons (the ICER using a 30-year time horizon, excluding any general population mortality constraints, is £345,284 per QALY gained).

Figure 13 presents 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.

TABLE 27 Analysis 1: EU-label population (symptomatic and progressive MTC), cabozantinib vs. BSC (pairwise), DSA results

Scenario	Incremental		
	QALYs	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
PFS – exponential; OS – Weibull	0.42	71,012	170,550
PFS – exponential; OS – Gompertz	0.31	70,525	227,293
PFS – exponential; OS – log-normal	0.47	71,298	150,146
PFS – exponential; OS – log-logistic	0.46	71,251	153,284
PFS – exponential; OS – gamma	0.43	71,061	166,964
PFS – Weibull; OS – exponential	0.38	55,213	147,111
PFS – Weibull; OS – Weibull	0.34	55,035	161,300
PFS – Weibull; OS – Gompertz	0.24	54,530	232,034
PFS – Weibull; OS – log-normal	0.40	55,345	138,424
PFS – Weibull; OS – log-logistic	0.39	55,297	141,864
PFS – Weibull; OS – gamma	0.35	55,093	157,191
PFS – Gompertz; OS – exponential	0.36	52,776	147,369
PFS – Gompertz; OS – Weibull	0.32	52,593	162,336
PFS – Gompertz; OS – Gompertz	0.22	52,105	239,141
PFS – Gompertz; OS – log-normal	0.38	52,879	138,259
PFS – Gompertz; OS – log-logistic	0.37	52,831	141,855
PFS – Gompertz; OS – gamma	0.33	52,642	157,984
PFS – log-normal; OS – exponential	0.46	70,719	152,833
PFS – log-normal; OS – Weibull	0.43	70,551	164,542
PFS – log-normal; OS – Gompertz	0.32	70,024	217,141
PFS – log-normal; OS – log-normal	0.49	70,909	145,511
PFS – log-normal; OS – log-logistic	0.48	70,834	148,443
PFS – log-normal; OS – gamma	0.44	70,617	161,210
PFS – log-logistic; OS – exponential	0.47	72,176	152,470
PFS – log-logistic; OS – Weibull	0.44	72,008	163,867
PFS – log-logistic; OS – Gompertz	0.33	71,481	214,567

TABLE 27 Analysis 1: EU-label population (symptomatic and progressive MTC), cabozantinib vs. BSC (pairwise), DSA results (*continued*)

	Incremental		
Scenario	QALYs	Costs (£)	ICER (£)
PFS – log-logistic; OS – log-normal	0.50	72,342	145,282
PFS – log-logistic; OS – log-logistic[a]	0.49	72,287	148,169
PFS – log-logistic; OS – gamma	0.45	72,070	160,627
PFS – gamma; OS – exponential	0.39	57,437	147,094
PFS – gamma; OS – Weibull	0.36	57,260	160,678
PFS – gamma; OS – Gompertz	0.25	56,743	226,874
PFS – gamma; OS – log-normal	0.42	57,582	138,733
PFS – gamma; OS – log-logistic	0.41	57,535	142,051
PFS – gamma; OS – gamma	0.37	57,318	156,755

a The AG's base-case curve choice.

TABLE 28 Analysis 2: EU-label population (symptomatic and progressive MTC), vandetanib vs. BSC (pairwise), central estimates of cost-effectiveness (PFS = log-logistic, OS = log-logistic for both options)

	Absolute		Incremental		
Option	QALYs	Costs (£)	QALYs	Costs (£)	ICER (£)
Probabilistic model					
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	–	–	–

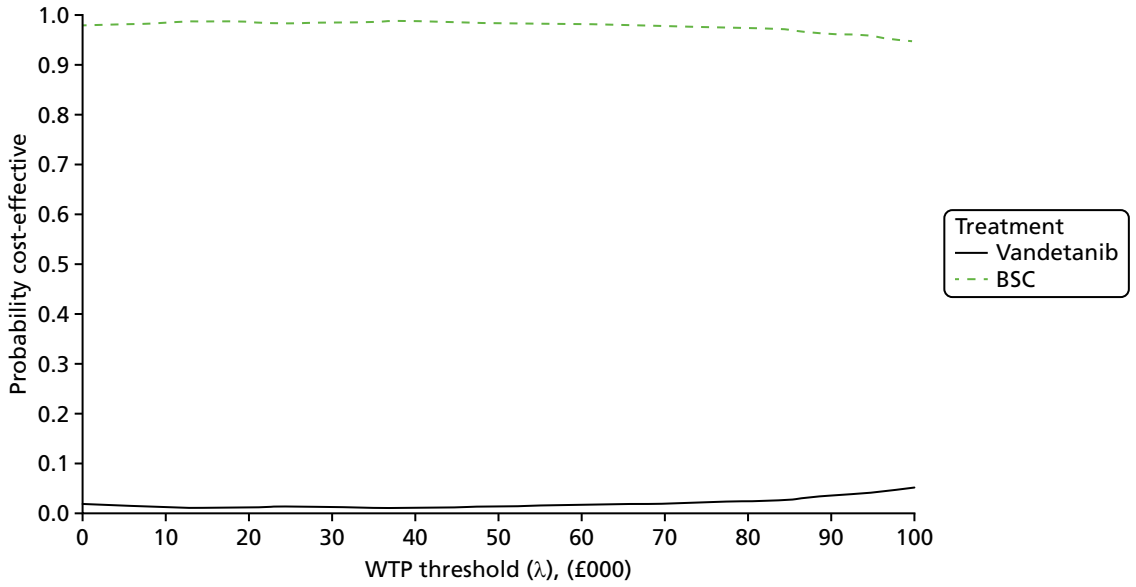

FIGURE 13 Analysis 2: EU-label population (symptomatic and progressive MTC), vandetanib vs. BSC (pairwise), CEACs (PFS = log-logistic, OS = log-logistic for both options).

Table 29 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 produces a considerably more favourable ICER for vandetanib versus BSC than 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 produces ICERs for vandetanib versus BSC ranging from £123,723 per QALY gained to dominated; the parametric survivor functions selected for use in the AG's base case do not represent the most optimistic case for vandetanib, nor do they represent they least favourable.

TABLE 29 Analysis 2: EU-label population (symptomatic and progressive MTC), vandetanib vs. BSC (pairwise), DSA results

	Incremental		
Scenario	QALYs	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
PFS – exponential; OS – Weibull	0.46	62,545	137,196
PFS – exponential; OS – Gompertz	0.59	72,938	123,723
PFS – exponential; OS – log-normal	0.39	49,372	128,083
PFS – exponential; OS – log-logistic	0.37	49,310	134,230
PFS – exponential; OS – gamma	0.43	60,268	139,406
PFS – Weibull; OS – exponential	0.22	37,245	165,924
PFS – Weibull; OS – Weibull	0.22	40,327	179,916

TABLE 29 Analysis 2: EU-label population (symptomatic and progressive MTC), vandetanib vs. BSC (pairwise), DSA results (*continued*)

Scenario	Incremental		
	QALYs	Costs (£)	ICER (£)
PFS – Weibull; OS – Gompertz	0.36	50,707	141,776
PFS – Weibull; OS – log-normal	0.15	27,155	176,631
PFS – Weibull; OS – log-logistic	0.14	27,093	199,768
PFS – Weibull; OS – gamma	0.20	38,051	189,697
PFS – Gompertz; OS – exponential	–0.08	53,486	Dominated
PFS – Gompertz; OS – Weibull	–0.08	56,486	Dominated
PFS – Gompertz; OS – Gompertz	0.07	64,762	969,254
PFS – Gompertz; OS – log-normal	–0.15	43,375	Dominated
PFS – Gompertz; OS – log-logistic	–0.17	43,313	Dominated
PFS – Gompertz; OS – gamma	–0.11	54,271	Dominated
PFS – log-normal; OS – exponential	0.39	97,481	249,691
PFS – log-normal; OS – Weibull	0.39	100,596	257,665
PFS – log-normal; OS – Gompertz	0.53	110,381	209,110
PFS – log-normal; OS – log-normal	0.32	87,433	273,140
PFS – log-normal; OS – log-logistic	0.30	87,371	289,324
PFS – log-normal; OS – gamma	0.37	98,325	267,980
PFS – log-logistic; OS – exponential	0.32	89,180	275,834
PFS – log-logistic; OS – Weibull	0.32	92,278	285,560
PFS – log-logistic; OS – Gompertz	0.46	101,633	218,981
PFS – log-logistic; OS – log-normal	0.25	79,106	312,992
PFS – log-logistic; OS – log-logistic[a]	0.23	79,044	336,896
PFS – log-logistic; OS – gamma	0.30	90,002	300,416
PFS – gamma; OS – exponential	0.28	41,060	147,850
PFS – gamma; OS – Weibull	0.28	44,151	159,114
PFS – gamma; OS – Gompertz	0.41	54,525	132,686
PFS – gamma; OS – log-normal	0.21	30,979	149,603
PFS – gamma; OS – log-logistic	0.19	30,917	163,617
PFS – gamma; OS – gamma	0.25	41,875	164,911

a The AG's base-case curve choice.

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

Table 30 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 the ZETA trial. It should be 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 65* in *Appendix 5*. 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 vs. BSC ICER = £134,817 per QALY gained; cabozantinib vs. 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.

Figure 14 presents 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.

Table 31 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 because of 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 than for 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 because of extended dominance; the ICER for cabozantinib versus BSC is estimated to be £148,169 per QALY gained. The choice of survival curves produces 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 AG's base case do not represent the most optimistic case for either drug, nor are they the least favourable.

TABLE 30 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)

	Absolute		Incremental		
Option	QALYs	Costs (£)	QALYs	Costs (£)	ICER (£)
Probabilistic model					
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	–	–	–

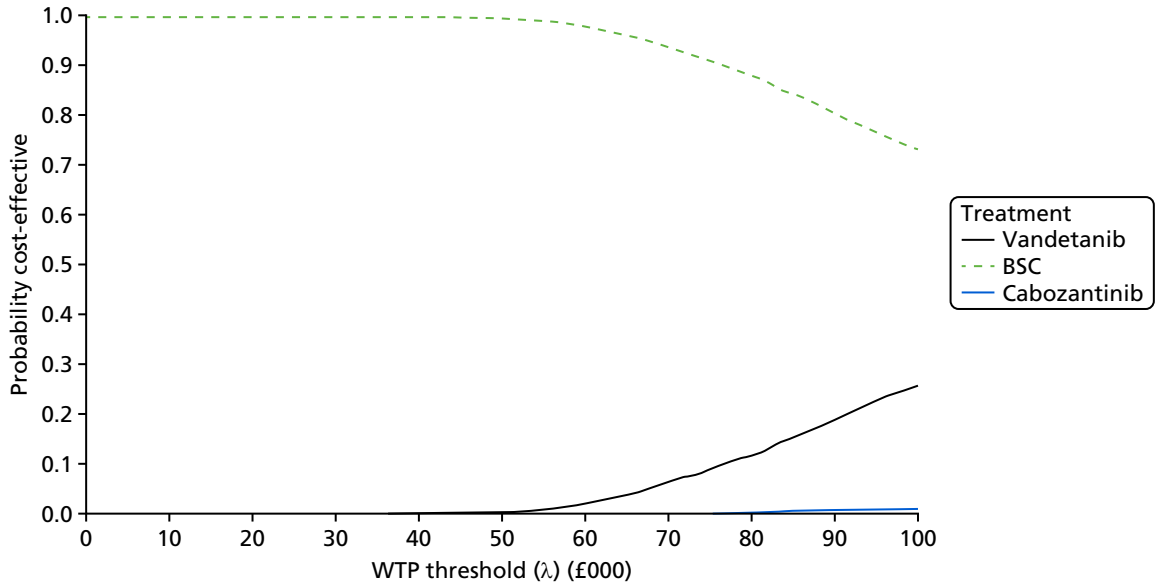

FIGURE 14 Analysis 3: EU-label population (symptomatic and progressive MTC), fully incremental analysis of all options using vandetanib PFS treatment effect from combined model, CEACs (PFS = log-logistic, OS = log-logistic for all options).

TABLE 31 Analysis 3: EU-label population (symptomatic and progressive MTC), fully incremental analysis of all options using vandetanib PFS treatment effect from combined model, DSA results

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

continued

TABLE 31 Analysis 3: EU-label population (symptomatic and progressive MTC), fully incremental analysis of all options using vandetanib PFS treatment effect from combined model, DSA results (*continued*)

	ICER (£) (vs. next-best comparator)	
Scenario	Cabozantinib	Vandetanib
PFS – exponential; OS – gamma	204,220 (vs. vandetanib)	157,880 (vs. BSC)
PFS – Weibull; OS – exponential	197,918 (vs. vandetanib)	133,290 (vs. BSC)
PFS – Weibull; OS – Weibull	197,908 (vs. vandetanib)	150,033 (vs. BSC)
PFS – Weibull; OS – Gompertz	232,034 (vs. BSC)	Extended dominance
PFS – Weibull; OS – log-normal	197,873 (vs. vandetanib)	123,454 (vs. BSC)
PFS – Weibull; OS – log-logistic	197,873 (vs. vandetanib)	127,303 (vs. BSC)
PFS – Weibull; OS – gamma	197,895 (vs. vandetanib)	145,084 (vs. BSC)
PFS – Gompertz; OS – exponential	207,886 (vs. vandetanib)	135,751 (vs. BSC)
PFS – Gompertz; OS – Weibull	207,886 (vs. vandetanib)	152,470 (vs. BSC)
PFS – Gompertz; OS – Gompertz	239,141 (vs. BSC)	Extended dominance
PFS – Gompertz; OS – log-normal	207,886 (vs. vandetanib)	125,894 (vs. BSC)
PFS – Gompertz; OS – log-logistic	207,886 (vs. vandetanib)	129,755 (vs. BSC)
PFS – Gompertz; OS – gamma	207,886 (vs. vandetanib)	147,537 (vs. BSC)
PFS – log-normal; OS – exponential	204,639 (vs. vandetanib)	142,355 (vs. BSC)
PFS – log-normal; OS – Weibull	204,672 (vs. vandetanib)	155,650 (vs. BSC)
PFS – log-normal; OS – Gompertz	217,141 (vs. BSC)	Extended dominance
PFS – log-normal; OS – log-normal	204,981 (vs. vandetanib)	134,340 (vs. BSC)
PFS – log-normal; OS – log-logistic	204,897 (vs. vandetanib)	137,538 (vs. BSC)
PFS – log-normal; OS – gamma	204,722 (vs. vandetanib)	151,833 (vs. BSC)
PFS – log-logistic; OS – exponential	194,919 (vs. vandetanib)	139,808 (vs. BSC)
PFS – log-logistic; OS – Weibull	194,936 (vs. vandetanib)	153,657 (vs. BSC)
PFS – log-logistic; OS – Gompertz	214,567 (vs. BSC)	Extended dominance
PFS – log-logistic; OS – log-normal	195,113 (vs. vandetanib)	131,503 (vs. BSC)
PFS – log-logistic; OS – log-logistic[a]	195,053 (vs. vandetanib)	134,817 (vs. BSC)
PFS – log-logistic; OS – gamma	194,966 (vs. vandetanib)	149,667 (vs. BSC)
PFS – gamma; OS – exponential	180,990 (vs. vandetanib)	97,633 (vs. BSC)
PFS – gamma; OS – Weibull	180,990 (vs. vandetanib)	122,911 (vs. BSC)
PFS – gamma; OS – Gompertz	226,874 (vs. BSC)	Extended dominance
PFS – gamma; OS – log-normal	180,985 (vs. vandetanib)	85,217 (vs. BSC)
PFS – gamma; OS – log-logistic	180,985 (vs. vandetanib)	89,881 (vs. BSC)
PFS – gamma; OS – gamma	180,989 (vs. vandetanib)	114,798 (vs. BSC)

a The AG's base-case curve choice.

Analysis 4: EU-label population (symptomatic and progressive medullary thyroid cancer), cabozantinib and vandetanib assumed equivalent

Table 32 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* in *Appendix 5*. 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 or higher AE profile and the slightly lower total relative dose intensity-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.

Figure 15 presents 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.

TABLE 32 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)

	Absolute		Incremental		
Option	QALYs	Costs (£)	QALYs	Costs (£)	ICER (£)
Probabilistic model					
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	–	–	–

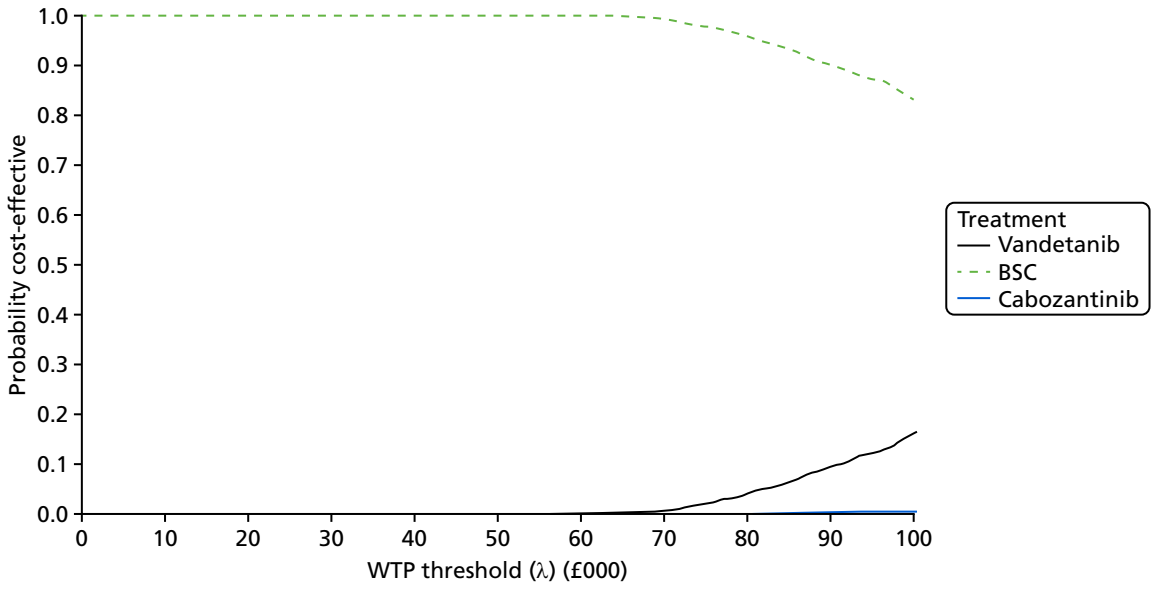

FIGURE 15 Analysis 4: EU-label population (symptomatic and progressive MTC), cabozantinib and vandetanib assumed equivalent, CEACs (PFS = log-logistic, OS = log-logistic for all options).

Table 33 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 outcome data from the EXAM trial. Cabozantinib remains dominated across all scenarios, except for 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 £1.35M per QALY gained. Across the remaining scenarios, the ICER for vandetanib versus BSC remains > £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 of £132,998 to £227,918 per QALY gained; the parametric survivor functions selected for use in the AG's base case are close to the most favourable scenario for vandetanib.

TABLE 33 Analysis 4: EU-label population (symptomatic and progressive MTC), cabozantinib and vandetanib assumed equivalent, DSA results

	ICER (£) (vs. next-best comparator)	
Scenario	Cabozantinib	Vandetanib
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. cabozantinib)
Health state resource use doubled	Extended dominance	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)
PFS – exponential; OS – Weibull	Dominated	163,420 (vs. BSC)
PFS – exponential; OS – Gompertz	Dominated	216,938 (vs. BSC)
PFS – exponential; OS – log-normal	Dominated	144,080 (vs. BSC)
PFS – exponential; OS – log-logistic	Dominated	147,058 (vs. BSC)
PFS – exponential; OS – gamma	Dominated	160,026 (vs. BSC)
PFS – Weibull; OS – exponential	Dominated	141,362 (vs. BSC)
PFS – Weibull; OS – Weibull	Dominated	154,796 (vs. BSC)

TABLE 33 Analysis 4: EU-label population (symptomatic and progressive MTC), cabozantinib and vandetanib assumed equivalent, DSA results (*continued*)

Scenario	ICER (£) (vs. next-best comparator)	
	Cabozantinib	Vandetanib
PFS – Weibull; OS – Gompertz	Dominated	221,301 (vs. BSC)
PFS – Weibull; OS – log-normal	Dominated	133,120 (vs. BSC)
PFS – Weibull; OS – log-logistic	Dominated	136,386 (vs. BSC)
PFS – Weibull; OS – gamma	Dominated	150,910 (vs. BSC)
PFS – Gompertz; OS – exponential	Dominated	141,640 (vs. BSC)
PFS – Gompertz; OS – Weibull	Dominated	155,804 (vs. BSC)
PFS – Gompertz; OS – Gompertz	Dominated	227,918 (vs. BSC)
PFS – Gompertz; OS – log-normal	Dominated	132,998 (vs. BSC)
PFS – Gompertz; OS – log-logistic	Dominated	136,411 (vs. BSC)
PFS – Gompertz; OS – gamma	Dominated	151,689 (vs. BSC)
PFS – log-normal; OS – exponential	Dominated	146,684 (vs. BSC)
PFS – log-normal; OS – Weibull	Dominated	157,787 (vs. BSC)
PFS – log-normal; OS – Gompertz	Dominated	207,458 (vs. BSC)
PFS – log-normal; OS – log-normal	Dominated	139,734 (vs. BSC)
PFS – log-normal; OS – log-logistic	Dominated	142,517 (vs. BSC)
PFS – log-normal; OS – gamma	Dominated	154,630 (vs. BSC)
PFS – log-logistic; OS – exponential	Dominated	146,363 (vs. BSC)
PFS – log-logistic; OS – Weibull	Dominated	157,175 (vs. BSC)
PFS – log-logistic; OS – Gompertz	Dominated	205,085 (vs. BSC)
PFS – log-logistic; OS – log-normal	Dominated	139,536 (vs. BSC)
PFS – log-logistic; OS – log-logistic[a]	Dominated	142,279 (vs. BSC)
PFS – log-logistic; OS – gamma	Dominated	154,103 (vs. BSC)
PFS – gamma; OS – exponential	Dominated	141,316 (vs. BSC)
PFS – gamma; OS – Weibull	Dominated	154,181 (vs. BSC)
PFS – gamma; OS – Gompertz	Dominated	216,482 (vs. BSC)
PFS – gamma; OS – log-normal	Dominated	133,382 (vs. BSC)
PFS – gamma; OS – log-logistic	Dominated	136,532 (vs. BSC)
PFS – gamma; OS – gamma	Dominated	150,469 (vs. BSC)

a The AG's base-case curve choice.

Analysis 5: restricted EU-label population (symptomatic and progressive medullary thyroid cancer with carcinoembryonic antigen/calcitonin doubling times of ≤ 24 months), vandetanib versus best supportive care (pairwise)

Table 34 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 times of ≤ 24 months). Disaggregated LYGs, QALYs and costs are presented in *Table 67* in *Appendix 5*. This analysis closely reflects the economic analysis presented within the Sanofi CS,[66] 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 as a result of the open-label use of vandetanib; hence, post-progression vandetanib costs are included in both treatment groups. Based on the probabilistic version of the AG 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, ≈12% of the vandetanib cohort are still alive at 20 years (indicated by the tail of the modelled curve). Additional analyses undertaken by the AG indicate that the ICER for vandetanib versus BSC is similar over longer time horizons (the ICER using a 30-year time horizon, excluding any general population mortality constraints, is £63,357 per QALY gained). However, the AG considers that the level of survival at 20 years may be an overestimate, and that the true ICER for vandetanib may therefore be > £67,000 per QALY gained. The impact of assuming alternative OS functions is explored within the sensitivity analyses (see *Table 35*).

Figure 16 presents 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.

Table 35 presents the results of the DSAs for the pairwise comparison of vandetanib versus BSC within the restricted EU-label population. As shown in the table, the ICER remains > £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 on 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 of £51,194 to £71,128 per QALY gained; the curves used in the AG's 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 34 Analysis 5: restricted EU-label population (symptomatic and progressive MTC with CEA/CTN doubling times of ≤ 24 months), vandetanib vs. BSC (pairwise), central estimates of cost-effectiveness (PFS = log-normal, OS = Gompertz for both options)

	Absolute		Incremental		
Option	QALYs	Costs (£)	QALYs	Costs (£)	ICER (£)
Probabilistic model					
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	–	–	–

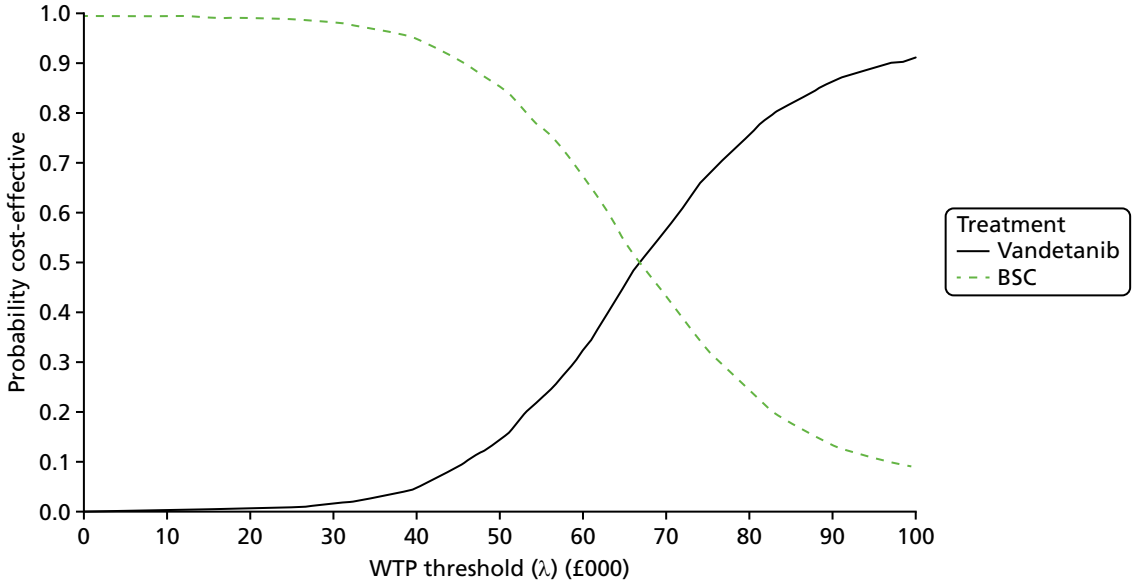

FIGURE 16 Analysis 5: restricted EU-label population (symptomatic and progressive MTC with CEA/CTN doubling times of ≤ 24 months), vandetanib vs. BSC (pairwise), CEACs (PFS = log-normal, OS = Gompertz for both options).

TABLE 35 Analysis 5: restricted EU-label population (symptomatic and progressive MTC with CEA/CTN doubling times of ≤ 24 months), vandetanib vs. BSC (pairwise), DSA results

Scenario	Incremental		
	QALYs	Costs (£)	ICER (£)
Base case	1.64	106,762	65,184
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
PFS – exponential; OS – Weibull	1.30	82,041	63,165
PFS – exponential; OS – Gompertz	1.50	90,264	60,296
PFS – exponential; OS – log-normal	1.28	73,914	57,821

continued

TABLE 35 Analysis 5: restricted EU-label population (symptomatic and progressive MTC with CEA/CTN doubling times of ≤ 24 months), vandetanib vs. BSC (pairwise), DSA results (*continued*)

Scenario	Incremental		
	QALYs	Costs (£)	ICER (£)
PFS – exponential; OS – log-logistic	1.06	56,920	53,857
PFS – exponential; OS – gamma	1.27	80,262	63,172
PFS – Weibull; OS – exponential	1.25	77,205	61,602
PFS – Weibull; OS – Weibull	1.25	77,316	61,765
PFS – Weibull; OS – Gompertz	1.45	85,538	58,993
PFS – Weibull; OS – log-normal	1.23	69,188	56,193
PFS – Weibull; OS – log-logistic	1.01	52,195	51,687
PFS – Weibull; OS – gamma	1.22	75,537	61,739
PFS – Gompertz; OS – exponential	1.40	99,812	71,119
PFS – Gompertz; OS – Weibull	1.41	99,165	70,439
PFS – Gompertz; OS – Gompertz	1.61	106,531	66,060
PFS – Gompertz; OS – log-normal	1.38	91,856	66,516
PFS – Gompertz; OS – log-logistic	1.16	74,863	64,564
PFS – Gompertz; OS – gamma	1.38	97,861	71,128
PFS – log-normal; OS – exponential	1.44	98,830	68,718
PFS – log-normal; OS – Weibull	1.44	98,899	68,821
PFS – log-normal; OS – Gompertz[a]	1.64	106,762	65,184
PFS – log-normal; OS – log-normal	1.42	90,824	64,128
PFS – log-normal; OS – log-logistic	1.19	73,831	61,791
PFS – log-normal; OS – gamma	1.41	97,169	68,989
PFS – log-logistic; OS – exponential	1.44	100,247	69,779
PFS – log-logistic; OS – Weibull	1.44	99,816	69,348
PFS – log-logistic; OS – Gompertz	1.64	107,120	65,132
PFS – log-logistic; OS – log-normal	1.41	92,230	65,198
PFS – log-logistic; OS – log-logistic	1.19	75,237	63,056
PFS – log-logistic; OS – gamma	1.41	98,433	69,923
PFS – gamma; OS – exponential	1.25	76,695	61,206
PFS – gamma; OS – Weibull	1.25	76,806	61,368
PFS – gamma; OS – Gompertz	1.45	85,028	58,651
PFS – gamma; OS – log-normal	1.23	68,678	55,789
PFS – gamma; OS – log-logistic	1.01	51,685	51,194
PFS – gamma; OS – gamma	1.22	75,027	61,334

a The AG's base-case curve choice.

Budget impact analysis

Table 36 presents a budget impact analysis for cabozantinib and vandetanib based on year-on-year drug acquisition costs predicted using the AG 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 (confidential information has been removed) 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 ≈£2.35M. The maximum budget impact for vandetanib within the symptomatic and progressive population is expected to be ≈£5.53M; the costs of vandetanib in the restricted EU-label population are expected to be lower.

Discussion

The AG'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 of ≤ 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 AG 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 AG considers that the ICER for vandetanib is likely to be considerably higher than the estimates presented within the Sanofi CS.[66]

In the light of concerns regarding the economic analysis submitted by Sanofi and the absence of any economic evidence for cabozantinib, the AG developed a de novo health economic model. The AG 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 of ≤ 24 months). Costs and health outcomes were discounted at a rate of 3.5% per annum. Costs were valued at 2016/17 prices. The AG model used a partitioned survival approach based on three health states: (1) progression free, (2) post progression and (3) 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 AG's economic analysis are summarised in *Table 37*.

TABLE 36 Budget impact analysis (£): cabozantinib and vandetanib, EU-label (symptomatic and progressive) MTC population

		Cohort year									
	Cohort year	1	2	3	4	5	6	7	8	9	10
Budget impact – cabozantinib, symptomatic and progressive MTC population (based on EXAM trial ITT PFS population, log-logistic model)											
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 trial EU-label subgroup PFS, log-logistic model)											
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

TABLE 37 Summary of the AG's cost-effectiveness results

Analysis number	Description	Probabilistic ICER (£ per QALY gained)	Probability of being cost-effective at λ = £30,000 per QALY gained	ICER range (£ per QALY gained) from alternative parametric survivor functions
1	Pairwise economic evaluation of cabozantinib vs. BSC in the EXAM trial ITT population	150,874	Cabozantinib: 0.00	138,259–239,141
2	Pairwise economic evaluation of vandetanib vs. BSC in the ZETA trial EU-label population	352,508	Vandetanib: 0.01	123,723 to dominated
3	Fully incremental analysis based on EXAM trial ITT population with vandetanib PFS treatment effect applied to EXAM trial placebo baseline; vandetanib OS assumed to be equivalent to cabozantinib OS	Vandetanib vs. BSC: 138,405	Vandetanib: 0.00	Vandetanib vs. next-best comparator: 85,217 to extendedly dominated
		Cabozantinib vs. vandetanib: 195,593	Cabozantinib: 0.00	Cabozantinib vs. next-best comparator: 180,985–239,141
4	Fully incremental analysis based on EXAM trial ITT population assuming PFS and OS are equivalent for vandetanib and cabozantinib	Cabozantinib = dominated	Cabozantinib: 0.00	Cabozantinib: dominated to dominated
		Vandetanib vs. BSC: 144,841	Vandetanib: 0.00	Vandetanib: 132,998–227,918
5	Pairwise economic evaluation of vandetanib vs. BSC using ZETA trial restricted EU-label population	66,779	Vandetanib: 0.02	51,194–71,128

λ, WTP threshold.
AG analysis 1: EU-label population (symptomatic and progressive MTC), pairwise economic evaluation of cabozantinib vs. BSC.

Assessment group analysis 1: EU-label population (symptomatic and progressive medullary thyroid cancer), pairwise economic evaluation of cabozantinib versus best supportive care

Based on the AG'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 AG's base case is close to the most favourable scenario.

Assessment group analysis 2: EU-label population (symptomatic and progressive medullary thyroid cancer), pairwise economic evaluation of vandetanib versus best supportive care

Based on the probabilistic version of the AG 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 AG's base case does not represent the most optimistic case for vandetanib, nor does it reflect the most pessimistic scenario.

Assessment group analysis 3: EU-label population (symptomatic and progressive medullary thyroid cancer), fully incremental analysis, vandetanib progression-free survival treatment effect applied to EXAM trial placebo baseline, vandetanib overall survival assumed equivalent to cabozantinib overall survival

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 AG's base case represents neither the most favourable nor the least favourable scenario for either drug.

Assessment group analysis 4: EU-label population (symptomatic and progressive medullary thyroid cancer), fully incremental analysis, progression-free and overall survival 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 or higher AE profile and the slightly lower total relative dose intensity-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 AG's base case represents one of the more favourable scenarios for vandetanib.

Assessment group analysis 5: restricted EU-label population (symptomatic and progressive medullary thyroid cancer plus carcinoembryonic antigen/calcitonin doubling times of ≤ 24 months), pairwise economic evaluation of vandetanib versus best supportive care

Based on the probabilistic version of the AG 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 AG's base case represents neither a highly favourable nor a highly unfavourable scenario for vandetanib.

Table 38 highlights the key differences between the AG model and the Sanofi model. Although the two models are very similar in terms of their structure and definition of parameters, the key differences between the analyses relate to (1) the scope of the economic comparisons, (2) the time-to-event data used to inform the analyses (covariate-adjusted ITT/safety data set vs. actual subgroup data), (3) the source of health utility values, (4) assumptions regarding the costs associated with BSC and (5) assumptions regarding the costs of vandetanib in patients who discontinue therapy prior to disease progression.

TABLE 38 Key differences between the Sanofi model and the AG model

Element of economic analysis	Model	
	Sanofi	AG
Comparisons	Vandetanib vs. BSC	Cabozantinib vs. BSC
		Vandetanib vs. BSC
		Full incremental analysis of all options
Trial evidence used to inform time-to-event outcomes	ZETA trial ITT/safety population	EXAM trial ITT, ZETA trial EU label, ZETA trial 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 data set	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.*[105]	Health state utilities derived from Fordham *et al.*[102]
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 the pre-progression vandetanib group	Half of total value applied to all patients receiving vandetanib in progression-free and post-progression states (when applicable)

Chapter 5 Assessment of factors relevant to the NHS and other parties

Additional monitoring requirements

Vandetanib and cabozantinib are associated with additional monitoring requirements, particularly during the first 3 months after initiating treatment (see *Chapter 1*, *Significance for the NHS*) 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.

Current availability of cabozantinib and vandetanib for medullary thyroid cancer

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 TKIs for patients in whom toxicity occurs, provided that (1) switching to the other TKI takes place within 3 months of starting the initial TKI, (2) the toxicity cannot be managed by dose delay or dose modification and (3) 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 AG consider that there is value in having access to both TKIs for this reason.

End-of-life considerations

The end-of-life supplementary advice from NICE[109] 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, usually < 24 months and
- there is sufficient evidence to indicate that the treatment offers an extension to life at least 3 additional months, compared with current NHS treatments.

Table 39 presents the undiscounted LYGs predicted by the AG's base-case model (see *Chapter 4*, *Time to event analysis using individual patient data*). 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 > 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 trial 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 times of ≤ 24 months).

TABLE 39 Undiscounted survival estimates used in the AG model

	Trial population/subgroup					
	EXAM safety population		ZETA symptomatic and progressive		ZETA symptomatic and progressive with CEA/CTN biomarker	
Outcome	Cabozantinib	BSC	Vandetanib	BSC	Vandetanib	BSC
AG 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	

Chapter 6 Discussion

Statement of principal findings

The systematic review of the clinical effectiveness evidence identified two relevant placebo-controlled RCTs: (1) the EXAM trial, which evaluated cabozantinib ($n = 330$), and (2) the ZETA trial, which evaluated vandetanib. The EXAM trial was deemed to be at low risk of bias across most domains, whereas the ZETA trial was deemed to be at 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 the ZETA trial did include a subgroup with 'progressive and symptomatic disease' ($n = 186$), which formed the 'EU-label' population. This group was considered to be comparable to the EXAM ITT population. In terms of efficacy, both cabozantinib and vandetanib significantly improved PFS compared with placebo. In the absence of direct evidence comparing the two interventions, a 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 because of 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 AG suggested that these tools did not necessarily capture symptomatic benefits produced by improved PFS or response to treatment. Both cabozantinib and vandetanib produced frequent AEs, with similar types and rates of grade 3 or higher 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 because of AEs, but a higher percentage of patients experienced AEs leading to dose interruption or reduction on cabozantinib than on vandetanib.

Based on the AG'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 AG'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 times of ≤ 24 months), the ICER for vandetanib versus BSC is expected to be £66,779 per QALY gained.

The AG's economic analysis suggests that NICE's criteria[109] 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 times of ≤ 24 months).

Strengths and limitations of the assessment

The key strengths of this assessment are as follows:

- The AG's economic evaluation includes fully incremental analyses of cabozantinib, vandetanib and BSC within the symptomatic and progressive MTC population.
- The health economic model developed by the AG uses a simple partitioned survival approach that 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 AG'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 AG did not have access to IPD from the ZETA trial; instead, PFS and OS outcomes were replicated using a published algorithm. Although 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 and ZETA trials are notably different. The analyses of the ZETA trial subgroups have been defined post hoc and may be subject to confounding because of 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 AG) may be of limited relevance for decision-making. Conversely, the AG'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.

Uncertainties

The key uncertainties associated with this evaluation are as follows:

- Quality-of-life gains as a result of PFS and related symptom management. These have not been adequately explored in the literature.
- The comparative clinical 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, for example 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.

Other relevant factors

The number of patients who would be eligible for these treatments is very small. In 2016, (confidential information has been removed) patients initiated treatment using cabozantinib [*n* = (confidential information has been removed)] or vandetanib [*n* = (confidential information has been removed)].

Chapter 7 Conclusions

The systematic review of the clinical effectiveness evidence identified two relevant placebo-controlled RCTs: (1) the EXAM trial, which evaluated cabozantinib ($n = 330$); and (2) 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 the ZETA trial did include a subgroup with 'progressive and symptomatic disease' ($n = 186$), which formed the 'EU-label' population. This group was considered to be comparable to the EXAM ITT population. 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 AG'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 AG'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 times of ≤ 24 months), the ICER for vandetanib versus BSC is expected to be £66,779 per QALY gained.

The AG's economic analysis suggests that NICE's criteria[109] 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 times of ≤ 24 months).

The AG's economic analysis suggests that the maximum annual budget impact for cabozantinib within the symptomatic and progressive population is expected to be ≈£2.35M. The maximum budget impact for vandetanib within the symptomatic and progressive population is expected to be ≈£5.53M; the costs of vandetanib in the restricted EU-label population are expected to be lower.

Implications for service provision

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

Suggested research priorities

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

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Contributions of authors

Paul Tappenden (Professor of Health Economic Modelling) acted as the project lead, critiqued the health economic analysis submitted by Sanofi and developed the independent AG model.

Christopher Carroll (Reader in Systematic Review and Evidence Synthesis) undertook the systematic review of clinical effectiveness and safety evidence.

Jean Hamilton (Research Fellow) conducted the statistical analysis.

Eva Kaltenthaler (Professor of Health Technology Assessment) undertook the systematic review of clinical effectiveness and safety evidence.

Ruth Wong (Information Specialist) undertook the electronic searches.

Jonathan Wadsley (Consultant Clinical Oncologist), **Laura Moss** (Consultant Oncologist) and **Sabapathy Balasubramanian** (Consultant Surgeon and Honorary Senior Lecturer) provided clinical advice throughout the appraisal.

All authors were involved in drafting and commenting on the final report.

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Data-sharing statement

Access to the model developed within this study can be requested from the corresponding author. Data that is not in the public domain cannot be shared further owing to the nature of this study. All queries should be submitted to the corresponding author.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Literature search strategies

Clinical effectiveness studies

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Date range searched: 1946 to present.

Date searched: 2 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 Carcinoma, medullary/
9	(medullary or MTC).mp.
10	8 or 9
11	7 and 10
12	Randomized controlled trials as Topic/
13	Randomized controlled trial/
14	Random allocation/
15	randomized controlled trial.pt.
16	Double blind method/
17	Single blind method/
18	Clinical trial/
19	exp Clinical Trials as Topic/
20	controlled clinical trial.pt.
21	clinical trial$.pt.
22	multicenter study.pt.
23	or/12-22
24	(clinic$ adj25 trial$).ti,ab.
25	((singl$ or doubl$ or treb$ or tripl$) adj (blind$ or mask$)).tw.

#	Searches
26	Placebos/
27	Placebo$.tw.
28	(allocated adj2 random).tw.
29	or/24-28
30	23 or 29
31	Case report.tw.
32	Letter/
33	Historical article/
34	31 or 32 or 33
35	exp Animals/
36	Humans/
37	35 not (35 and 36)
38	34 or 37
39	30 not 38
40	meta-analysis/
41	meta-analysis as topic/
42	(meta analy* or metanaly* or metaanaly*).ti,ab.
43	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
44	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
45	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
46	(search* adj4 literature).ab.
47	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or scie nce citation index or bids or cancerlit).ab.
48	cochrane.jw.
49	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
50	or/40-49
51	39 or 50
52	11 and 51

Cost-effectiveness studies

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Date range searched: 1946 to present.

Date searched: 3 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

Date range searched: 1974 to 1 November 2016.

Date searched: 3 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–).

Date searched: 3 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: Wiley Online Library

Health Technology Assessment database: Wiley Online Library.

NHS Economic Evaluation Database: Wiley Online Library.

Date range searched: 1995–2015.

Date searched: 3 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

Cumulative Index to Nursing and Allied Health Literature

Date range searched: 1982 to present.

Date searched: 3 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)

Date range searched: 1946 to present.

Date searched: 3 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.

#	Searches
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

Date range searched: 1974 to 1 November 2016.

Date searched: 3 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.

#	Searches
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–).

Date searched: 3 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: Wiley Online Library

Health Technology Assessment database: Wiley Online Library.

NHS Economic Evaluation Database: Wiley Online Library.

Date range searched: 1995–2015.

Date searched: 3 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	{or #1-#3, #6}

Cumulative Index to Nursing and Allied Health Literature

Date range searched: 1982 to present.

Date searched: 3 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)

#	Searches
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

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Appendix 3 Additional tables and figures relating to the Sanofi model

FIGURE 17 (Confidential information has been removed.)

TABLE 40 The AIC and BIC statistics from Sanofi's covariate-adjusted analysis of the ZETA trial observed OS

	Statistic	
Model	AIC	BIC
Vandetanib		
Weibull	(Confidential information has been removed)	(Confidential information has been removed)
Log-normal	(Confidential information has been removed)	(Confidential information has been removed)
Log-logistic	(Confidential information has been removed)	(Confidential information has been removed)
Exponential[a]	(Confidential information has been removed)	(Confidential information has been removed)
Gamma[a]	(Confidential information has been removed)	(Confidential information has been removed)
Placebo		
Weibull	(Confidential information has been removed)	(Confidential information has been removed)
Log-normal	(Confidential information has been removed)	(Confidential information has been removed)
Log-logistic	(Confidential information has been removed)	(Confidential information has been removed)
Exponential[a]	(Confidential information has been removed)	(Confidential information has been removed)
Gamma[a]	(Confidential information has been removed)	(Confidential information has been removed)

a Not reported in CS; obtained from company's model.

FIGURE 18 (Confidential information has been removed.)

TABLE 41 The AIC and BIC statistics from Sanofi's covariate-adjusted analysis of ZETA trial observed PFS

	Statistic	
Model	AIC	BIC
Vandetanib		
Weibull	(Confidential information has been removed)	(Confidential information has been removed)
Log-normal	(Confidential information has been removed)	(Confidential information has been removed)
Log-logistic	(Confidential information has been removed)	(Confidential information has been removed)
Exponential[a]	(Confidential information has been removed)	(Confidential information has been removed)
Gamma[a]	(Confidential information has been removed)	(Confidential information has been removed)
Placebo		
Weibull	(Confidential information has been removed)	(Confidential information has been removed)
Log-normal	(Confidential information has been removed)	(Confidential information has been removed)
Log-logistic	(Confidential information has been removed)	(Confidential information has been removed)
Exponential[a]	(Confidential information has been removed)	(Confidential information has been removed)
Gamma[a]	(Confidential information has been removed)	(Confidential information has been removed)

a Not reported in CS; obtained from company's model.

TABLE 42 The 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.*[104]
Post progression	0.64	Derived by applying progressive disease to stable disease multiplier from Beusterien *et al.*[105] to pre-progression utility from ZETA trial FACT-G mapping exercise
Disutility any grade 3/4 AE	–0.11	Beusterien *et al.*[105]

TABLE 43 Use of vandetanib during progression-free period

Dose	% of PFS time receiving vandetanib[a]
300 mg (full dose)	66.3
200-mg dose	16.5
100-mg dose	15.5
Interrupted	1.7

a Also applied to post-progression states in both treatment groups.

TABLE 44 Vandetanib acquisition costs according to pack size

	Cost (£)	
Intervention: vandetanib tablets	Per pack (30 tablets)	Annual (assuming full dose)
300 mg	5000.00	60,875.00
100 mg	2500.00	30,437.50

TABLE 45 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 (thyroid-stimulating hormone)	3.00	8	4	24.00	12.00

TABLE 46 Incidence and costs associated with grade 3/4 AEs

AE type	Unit cost (£)	Vandetanib	BSC	*NHS Reference Cost 2015/16*[106] HRG code
Diarrhoea	1102.00	11%	2%	FZ91M: non-malignant gastrointestinal tract disorders without interventions, with a CC score of 0–2
Hypertension	982.00	9%	0%	EB04Z: hypertension
ECG QT prolonged	1014.00	8%	1%	EB07E: arrhythmia or conduction disorders, with a CC score of 0–3
Fatigue	0.00	6%	1%	N/A
Decreased appetite	1512.00	4%	0%	FZ49H: nutritional disorders without interventions, with a CC score of 0 or 1
Rash	1078.00	4%	1%	JD07 K: skin disorders without interventions, with a CC score of 0 or 1
Asthenia	0.00	3%	1%	N/A
Dyspnoea	896.00	1%	3%	DZ19 N: other respiratory disorders without interventions, with a CC score of 0–4
Back pain	1510.00	0%	3%	HC32 K: low back pain without interventions, with a CC score of 0–2
Syncope	1067.00	0%	2%	EB08E: syncope or collapse, with a CC score of 0–3
Weighted AE cost (£)	–	413.42	136.48	–

CC, complexity and comorbidity; HRG, Healthcare Resource Group; N/A, not applicable.

TABLE 47 Comparison of DICE model results and double-programmed AG partitioned survival model

	Model					
	Company			AG's double programmed		
Outcome	Vandetanib	Placebo	Incremental	Vandetanib	Placebo	Incremental
LYGs	4.84	3.10	1.74	4.84	3.10	1.74
PFLYGs[a]	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	4984.56	24,506.45	19,519.65	4986.80
Palliative care costs (£)	5489.93	5916.92	–426.99	5574.17	6004.49	–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

PFLYG, progression-free life-year gained.
a Undiscounted.

FIGURE 19 (Confidential information has been removed.)

TABLE 48 Health state populations by year, PFS (log-normal) and OS (Weibull)

	Group					
	BSC			Vandetanib		
Year	OS	PFS	PPS state population (OS minus PFS)	OS	PFS	PPS state population (OS minus PFS)
0	1.000	1.000	0.000	1.000	1.000	0.000
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	0.170	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	0.030
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**

PPS, post-progression survival.

Note

Bold text indicates logically inconsistent results.

Appendix 4 The Assessment group's model: time-to-event analysis and other model inputs

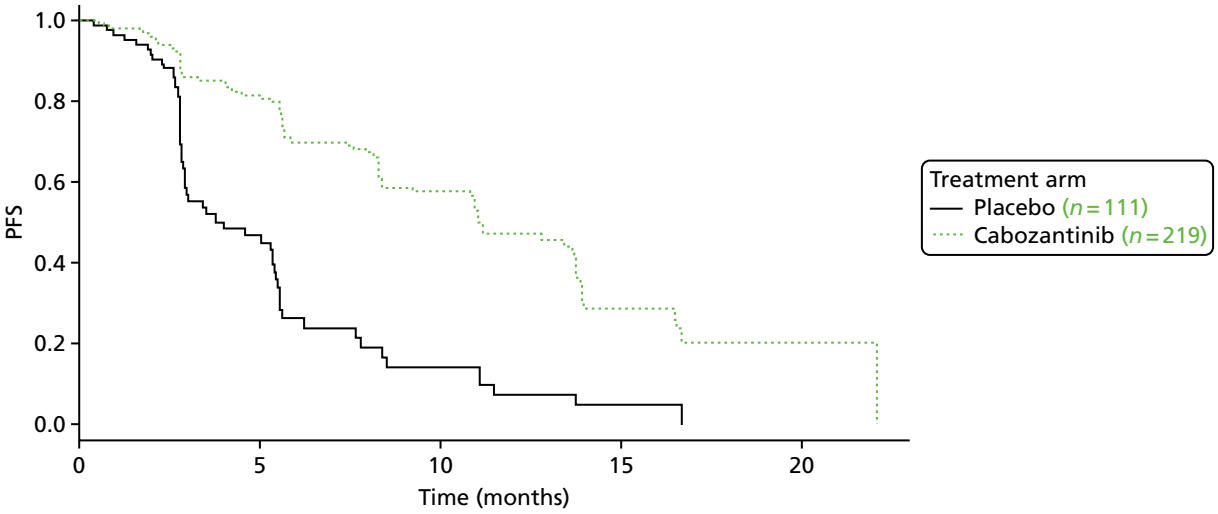

FIGURE 20 EXAM trial ITT population PFS.

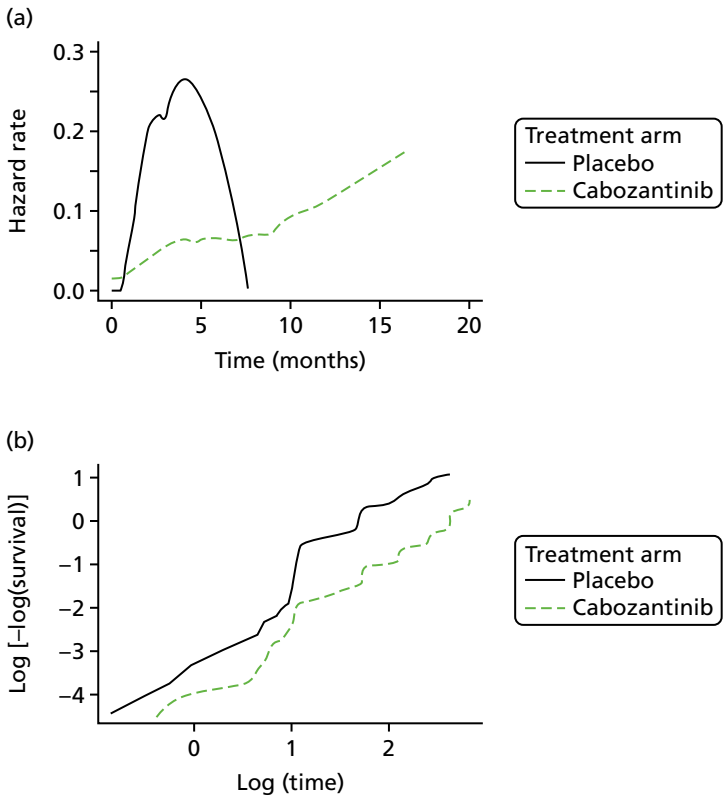

FIGURE 21 ITT EXAM trial standard diagnostic plots for PFS. (a) Empirical hazard function plot; (b) plot for Weibull and exponential; (c) plot for log-logistic; and (d) plot for log-normal. (*continued*)

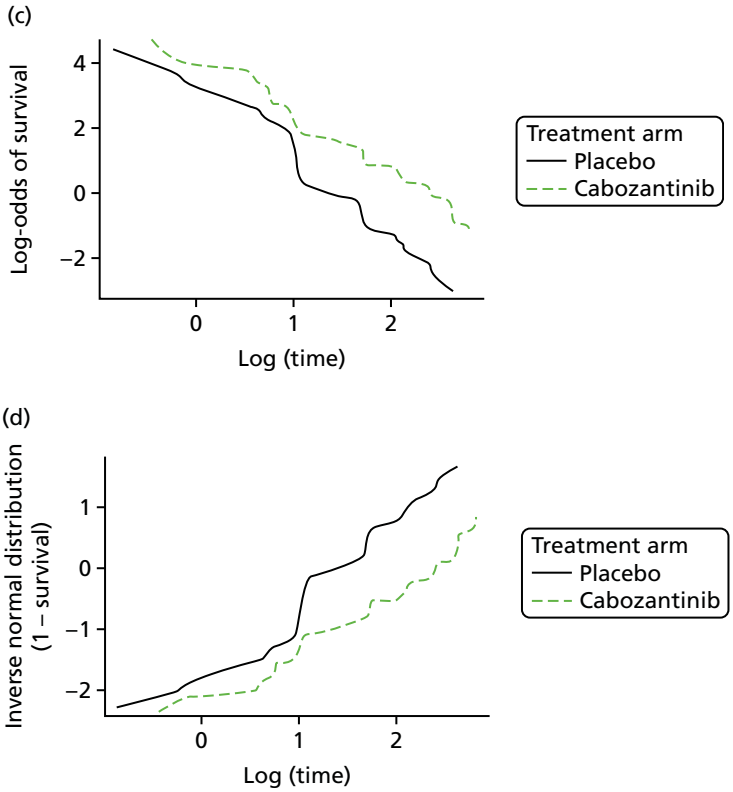

FIGURE 21 ITT EXAM trial standard diagnostic plots for PFS. (a) Empirical hazard function plot; (b) plot for Weibull and exponential; (c) plot for log-logistic; and (d) plot for log-normal.

TABLE 49 Model fit statistics: the EXAM trial's ITT population, individual models for each treatment arm, PFS and OS

	Treatment arm			
	Placebo		Cabozantinib	
Model fit statistic	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	Failed to converge	583.69	597.24
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

TABLE 49 Model fit statistics: the EXAM trial's ITT population, individual models for each treatment arm, PFS and OS (*continued*)

	Treatment arm			
	Placebo		Cabozantinib	
Model fit statistic	AIC	BIC	AIC	BIC
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

Note
Bold indicates the best-fitting model (lowest AIC/BIC).

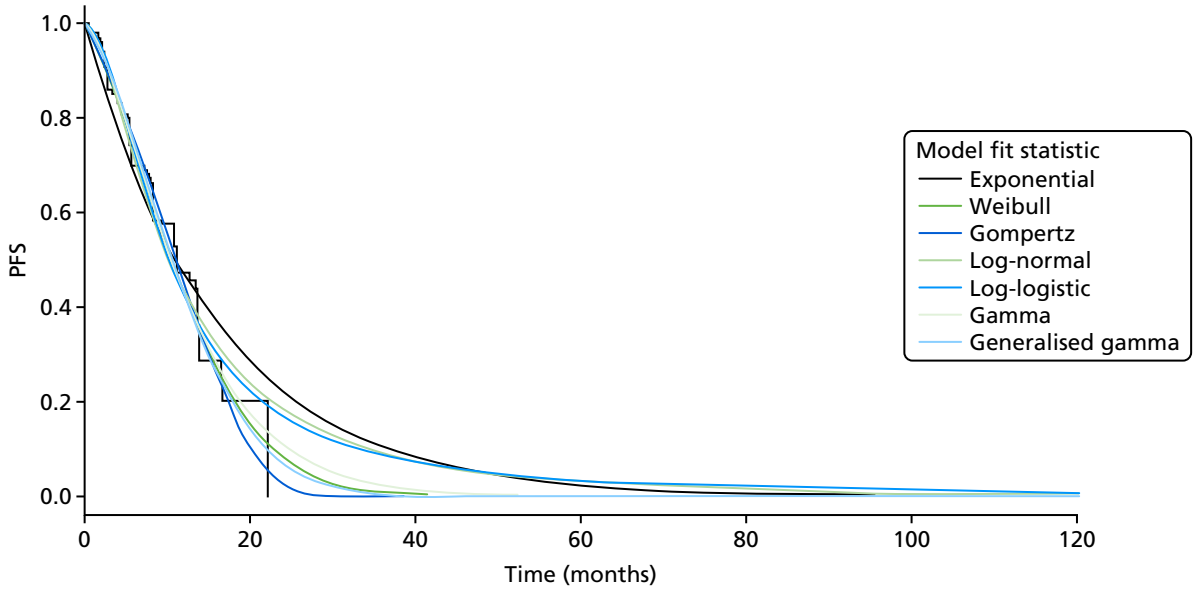

FIGURE 22 EXAM trial ITT population, PFS, cabozantinib group (extrapolation up to 10 years).

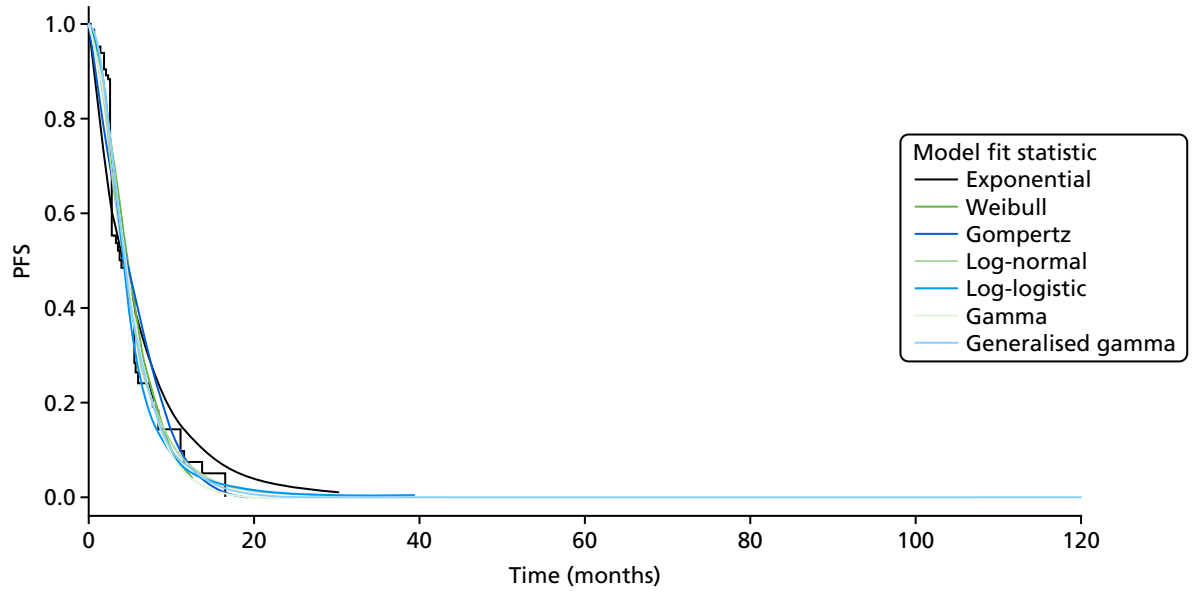

FIGURE 23 EXAM trial ITT population, PFS, placebo group (extrapolation up to 10 years).

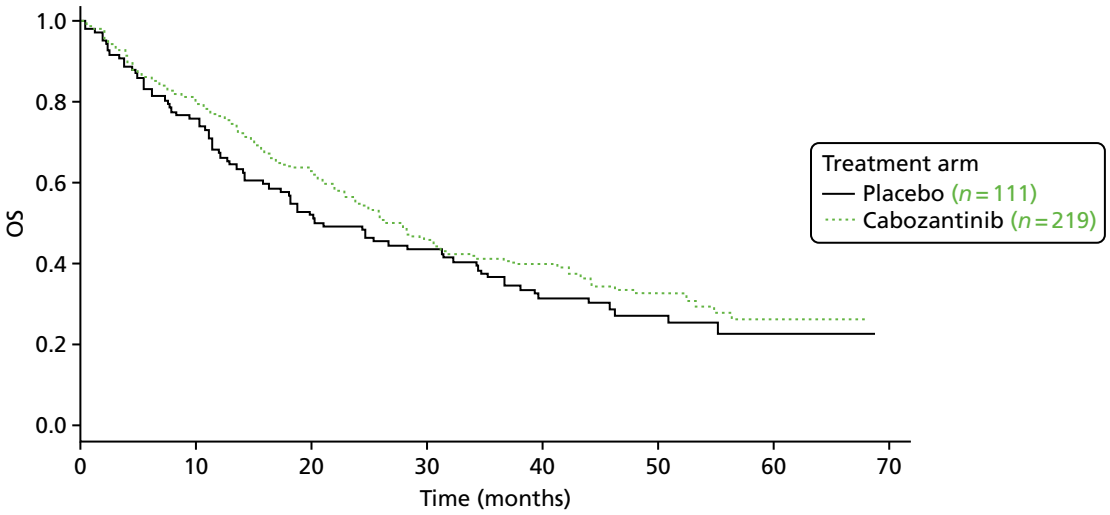

FIGURE 24 EXAM trial ITT population OS.

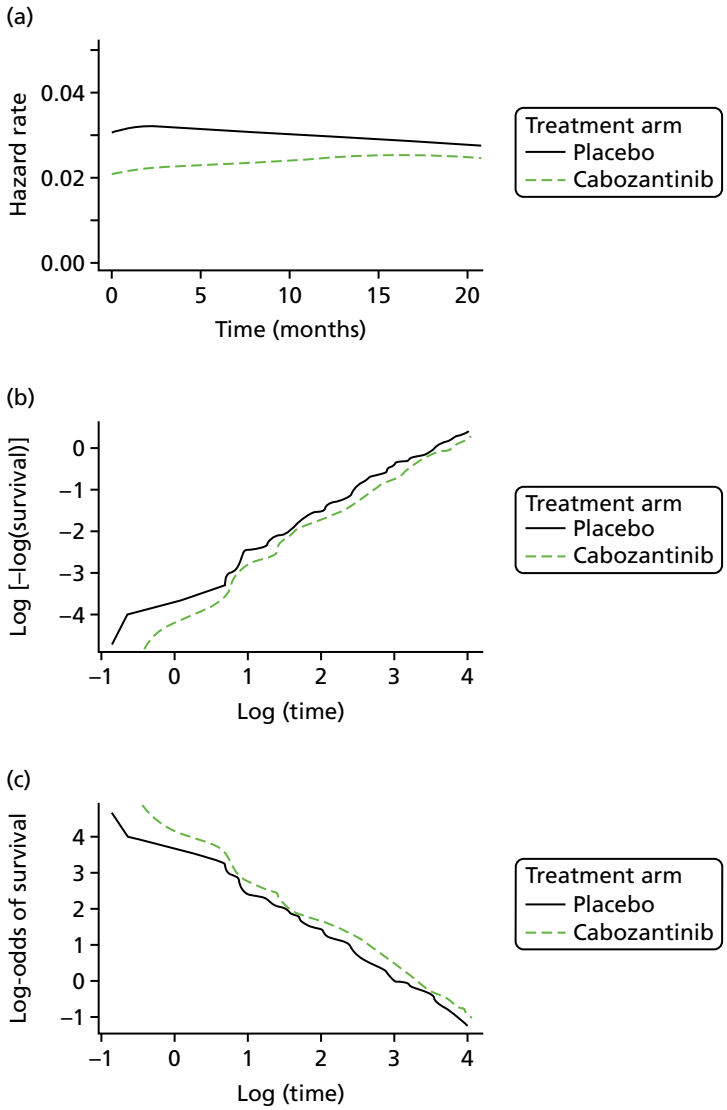

FIGURE 25 EXAM trial ITT population, standard diagnostic plots for OS. (a) Empirical hazard function plot; (b) plot for Weibull and exponential; (c) plot for log-logistic; and (d) plot for log-normal. (*continued*)

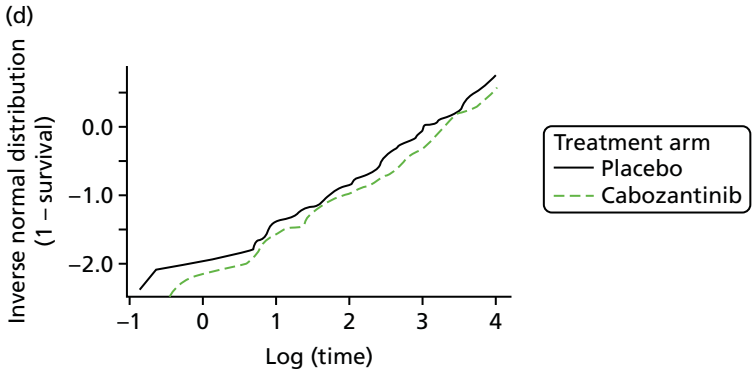

FIGURE 25 EXAM trial ITT population, standard diagnostic plots for OS. (a) Empirical hazard function plot; (b) plot for Weibull and exponential; (c) plot for log-logistic; and (d) plot for log-normal.

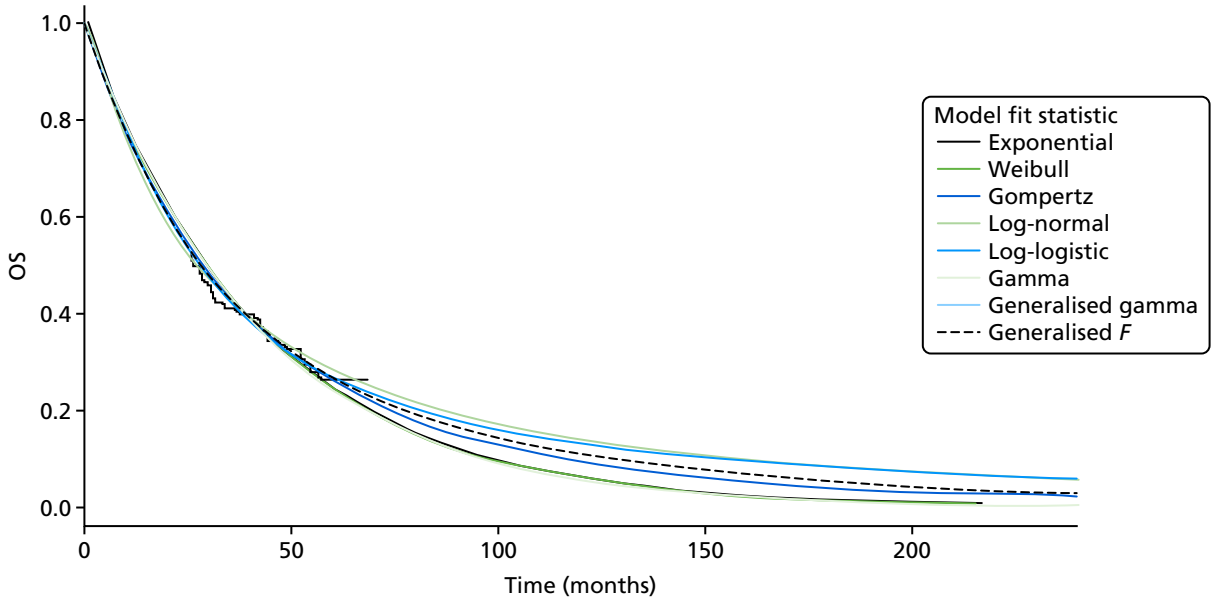

FIGURE 26 EXAM trial ITT population, OS, cabozantinib group (extrapolation up to 20 years).

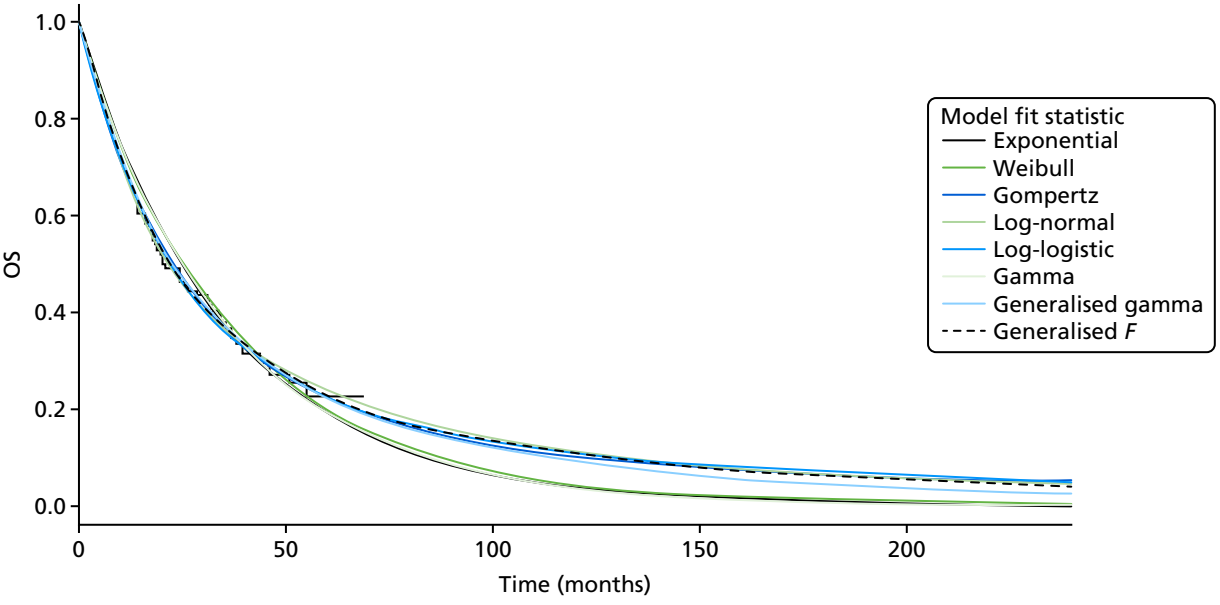

FIGURE 27 EXAM trial ITT population, OS, placebo group (extrapolation up to 20 years).

FIGURE 28 (Confidential information has been removed.)

FIGURE 29 (Confidential information has been removed.)

FIGURE 30 (Confidential information has been removed.)

TABLE 50 Model fit statistics: the ZETA trial's EU-label population, individual models for each treatment, PFS and OS

	Treatment arm			
	Placebo		Vandetanib	
Model fit statistic	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	Failed to converge
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

Note
Bold text indicates the best-fitting model (lowest AIC/BIC).

FIGURE 31 (Confidential information has been removed.)

FIGURE 32 (Confidential information has been removed.)

FIGURE 33 (Confidential information has been removed.)

FIGURE 34 (Confidential information has been removed.)

FIGURE 35 (Confidential information has been removed.)

FIGURE 36 (Confidential information has been removed.)

FIGURE 37 (Confidential information has been removed.)

FIGURE 38 (Confidential information has been removed.)

FIGURE 39 (Confidential information has been removed.)

FIGURE 40 (Confidential information has been removed.)

TABLE 51 Model fit statistics: the ZETA trial's restricted EU-label population, individual models for each treatment, PFS and OS

	Treatment arm			
	Placebo		Vandetanib	
Model fit statistic	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
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

Note
Bold text indicates the best-fitting model (lowest AIC/BIC).

FIGURE 41 (Confidential information has been removed.)

FIGURE 42 (Confidential information has been removed.)

FIGURE 43 (Confidential information has been removed.)

FIGURE 44 (Confidential information has been removed.)

FIGURE 45 (Confidential information has been removed.)

FIGURE 46 (Confidential information has been removed.)

FIGURE 47 (Confidential information has been removed.)

TABLE 52 ZETA trial EU-label model fit statistics and treatment-effect estimates (HR or AFT factor) for single parametric models, PFS

Model fit statistic	PH/AFT	Model fit		Treatment effect		
		AIC	BIC	β	SE (β)	HR/AFT
Exponential	PH	768.38	774.87	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
Weibull	PH	767.30	777.04	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
Gompertz	PH	768.80	778.54	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
Log-normal	AFT	**764.25**	**773.99**	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
Log-logistic	AFT	764.57	774.31	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
Gamma	AFT	766.55	776.29	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
Generalised gamma	AFT	766.09	779.08	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)

AFT, accelerated failure time; PH, proportional hazards.
β, coefficient on analysis scale.
Note
Bold text indicates the best-fitting model (lowest AIC/BIC).

FIGURE 48 (Confidential information has been removed.)

TABLE 53 Health utilities used in the AG model

Health state	Mean (95% CI)	Beta distribution parameters		Source
		α	β	
Progression free	0.80 (0.77 to 0.84)	400.61	100.15	Fordham *et al.*[102]
Post progression	0.50 (0.45 to 0.56)	158.24	158.24	
Disutility AEs	–0.11 (SE 0.02)	26.81	216.94	Beusterien *et al.*[105]

TABLE 54 Grade 3/4 AE rates assumed in the AG model

Treatment arm	Pairwise comparison		Incremental comparisons: all options (AG analyses 3 and 4)
	Cabozantinib vs. BSC (AG analysis 1)	Vandetanib vs. BSC (AG analyses 2 and 5)	
Cabozantinib	0.94	N/A	0.94
Vandetanib	N/A	0.45	0.45
Placebo	0.24	0.14	0.24

N/A, not applicable.

TABLE 55 Proportion of patients who switched to vandetanib or continued vandetanib post progression

Parameter	Population					
	EU-label: symptomatic and progressive MTC			Restricted EU-label: symptomatic and progressive MTC with CEA/CTN doubling time of $\leq$ 24 months		
	Proportion	Continued PP	Not continued PP	Proportion	Continued PP	Not continued PP
Proportion of vandetanib group continuing vandetanib PP	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)
Proportion of BSC group switching to vandetanib PP	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)	(Confidential information has been removed)

PP, post progression.

TABLE 56 Drug acquisition costs: vandetanib and cabozantinib

Item	Cost (£)	
	Per pack	Annual at full dose
Cabozantinib, 84 × 20-mg capsules (two-level dose reduction)	4800.00	62,614.29
Cabozantinib, 28 × 20-mg and 28 × 80-mg capsule combination (one-level dose reduction)	4800.00	62,614.29
Cabozantinib, 84 × 20-mg and 28 × 80-mg capsule combination (full dose)	4800.00	62,614.29
Vandetanib, 30 × 300-mg tablets	5000.00	60,875.00
Vandetanib, 30 × 100-mg tablets	2500.00	30,437.50

TABLE 57 Cabozantinib: proportion of PFS time spent at dose level

Dose	Mean proportion	Dirichlet parameters	
		Days on dose	Total PFS days
Cabozantinib, 140 mg	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Cabozantinib, 100 mg	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Cabozantinib, 60 mg	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed
Cabozantinib, interrupted dose	Confidential information has been removed	Confidential information has been removed	Confidential information has been removed

TABLE 58 Vandetanib: proportion of PFS time spent at dose level

Dose	Mean proportion of PFS time spent on specified dose	Dirichlet parameters	
		Days on dose	Total PFS days
EU-label population: symptomatic and progressive MTC			
Vandetanib, 300 mg	0.73	76,994.70	106,105.13
Vandetanib, 200 mg	0.13	13,806.45	106,105.13
Vandetanib, 100 mg	0.13	13,550.78	106,105.13
Vandetanib, interrupted dose	0.02	1753.20	106,105.13
Restricted EU-label population: symptomatic and progressive MTC with CEA/CTN doubling times of ≤ 24 months			
Vandetanib, 300 mg	0.66	13,769.93	20,746
Vandetanib, 200 mg	0.17	3433.35	20,746
Vandetanib, 100 mg	0.15	3214.20	20,746
Vandetanib, interrupted dose	0.02	328.73	20,746

TABLE 59 Annual BSC resource use included in the AG model

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

a Assumed to reflect monthly intravenous regimen for 5% of patients, also costed to include outpatient visit.

TABLE 60 Total annual health state resource use for cabozantinib and vandetanib included in the AG model

	Treatment			
	Cabozantinib		Vandetanib	
Resource item	Year 1	Subsequent years[a]	Year 1	Subsequent years[a]
Consultant-led outpatient visits	12 (range 4–16)	6 (range 4–12)	12 (range 4–16)	6 (range 4–12)
Nurse-led outpatient visits	4 (range 0–6)	6 (range 0–6)	4 (range 0–6)	6 (range 0–6)
ECG	0	0	12	6
Blood tests	12	6	12	6
CT scan	4	4	4	4

a Assessment group analyses 2 and 5 – subsequent years' costs applied to patients receiving vandetanib in the post-progression state, irrespective of time since model entry.

TABLE 61 Unit costs applied in the AG model

Unit	Cost (£)	SE (£)	Source
Consultant-led outpatient visit (medical oncology)	162.84	6.48	*NHS Reference Costs 2015/16*,[106] 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*,[106] non-consultant-led, non-admitted face-to-face attendance, follow-up, WF01A
CT scan	136.50	7.13	*NHS Reference Costs 2015/16*,[106] outpatient, complex CT scan, RD28Z
MRI scan	161.93	3.68	*NHS Reference Costs 2015/16*,[106] outpatient, MRI scan of two or three areas, without contrast, RD04Z
ECG	207.98	29.16	*NHS Reference Costs 2015/16*,[106] outpatient (medical oncology), ECG monitoring or stress testing, EY51Z
Blood test	3.37	0.26	*NHS Reference Costs 2015/16*,[106] directly accessed pathology, phlebotomy, DAPS08
Palliative care nurse visit	91.83	4.81	*NHS Reference Costs 2015/16*,[106] specialist nursing, palliative/respite care, adult, face to face, N21AF
Palliative radiotherapy (per fraction)	104.77	7.47	*NHS Reference Costs 2015/16*,[106] outpatient, deliver a fraction of treatment on a megavoltage machine, SC22Z
Palliative surgery	3363.82	70.08	*NHS Reference Costs 2015/16*,[106] elective inpatient, thyroid procedures with a CC score of 0 or 1, KA09E
Bisphosphonates for bone metastases (4 mg per 100-ml infusion bags)[a]	150.00	N/A	BNF,[108] Zerlinda 4 mg per 100-ml infusion bags [Actavis UK Ltd (now Accord Healthcare Ltd, Barnstaple, UK)]
Palliative care (last month of life)	5775.52	866.33[b]	PSSRU,[107] palliative care costs (assumes equal weighting between child and adult inpatient and outpatient)

TABLE 61 Unit costs applied in the AG model (*continued*)

Unit	Cost (£)	SE (£)	Source
Palliative chemotherapy (last month of life)	827.00	124.05[b]	Sanofi CS[66] (based on *NHS Reference Costs 2015/16*,[106]) other, procure chemotherapy drugs for regimens in band 1–10, SB01Z–10Z
Cost of managing AEs	298.41	44.76[b]	*NHS Reference Costs 2015/16*,[106] weighted mean of all non-elective excess bed-days, AA22C–YR55Z

CC, complexity and comorbidity; N/A, not applicable.
a Assumed to be given during additional outpatient appointment.
b SE assumed to be 15% of mean.

TABLE 62 Distributions used in PSA

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 trial 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 trial 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)[a]	Triangular	Distribution selected to reflect expert's beliefs
Vandetanib and cabozantinib health state resource use[b]	Triangular	Distribution selected to reflect expert's beliefs
Drug acquisition costs	Fixed	–
Unit costs	Normal	SE derived from interquartile ranges
Palliative care costs	Normal	SE assumed to be 15% of mean
AE costs	Normal	SE assumed to be 15% of mean

a Intravenous bisphosphonates, palliative radiotherapy and palliative surgery held fixed.
b Resources related to monitoring held fixed (ECGs, CT scans and blood tests).

Appendix 5 The Assessment group's model: disaggregated results

TABLE 63 Analysis 1: EU-label population (symptomatic and progressive MTC), cabozantinib vs. BSC (pairwise), disaggregated LYGs, QALYs and costs

	Treatment	
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 (£)	95,307.00	18,063.00
Total cost in progression-free state (£)	79,788.00	1417.00
Total cost in post-progression state (£)	15,519.00	16,647.00
Modelled probability of being alive at 20 years	0.06	0.05

TABLE 64 Analysis 2: EU-label population (symptomatic and progressive MTC), vandetanib vs. BSC (pairwise), disaggregated LYGs, QALYs and costs

	Treatment	
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 (£)	305,003.00	223,755.00
Total cost in progression-free state (£)	216,263.00	8131.00
Total cost in post-progression state (£)	88,740.00	215,624.00
Modelled probability of being alive at 20 years	0.11	0.12

TABLE 65 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

	Treatment		
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 (£)	95,307.00	71,105.00	18,063.00
Total cost in progression-free state (£)	79,788.00	54,284.00	1417.00
Total cost in post-progression state (£)	15,519.00	16,820.00	16,647.00
Modelled probability of being alive at 20 years	0.06	0.06	0.05

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

	Treatment		
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 (£)	95,307.00	92,909.00	18,063.00
Total cost in progression-free state (£)	79,788.00	77,390.00	1417.00
Total cost in post-progression state (£)	15,519.00	15,519.00	16,647.00
Modelled probability of being alive at 20 years	0.06	0.06	0.05

TABLE 67 Analysis 5: restricted EU-label population (symptomatic and progressive MTC with CEA/CTN doubling times of $\leq$ 24 months), vandetanib vs. BSC (pairwise), disaggregated LYGs, QALYs and costs

	Treatment	
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 (£)	245,641.00	108,236.00
Total cost in progression-free state (£)	161,051.00	2956.00
Total cost in post-progression state (£)	84,591.00	105,279.00
Modelled probability of being alive at 20 years	0.12	0.00

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