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

Assessment Report

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

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Contributions of authors

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

About ScHARR

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

The ScHARR Technology Assessment Group (ScHARR-TAG) synthesises research on the clinical effectiveness and cost-effectiveness of healthcare interventions for the NIHR Health Technology Assessment Programme on behalf of a range of policy makers, including the National Institute for Health and Care Excellence (NICE). ScHARR-TAG is part of a wider collaboration of a number of units from other regions including Southampton Health Technology Assessment Centre (SHTAC), University of Southampton; Aberdeen Health Technology Assessment Group (Aberdeen HTA Group), University of Aberdeen; Liverpool Reviews & Implementation Group (LRiG), University of Liverpool; Peninsular Technology Assessment Group (PenTAG), University of Exeter; the NHS Centre for Reviews and Dissemination, University of York; Warwick Evidence, The University of Warwick; the BMJ Group and Kleijnen Systematic Reviews.

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1 DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

DEFINITION OF TERMS

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

Abbreviations

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

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

2 EXECUTIVE SUMMARY

2.1 Background

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

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

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

2.2 Aims

The aims of the assessment are:

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

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

2.3 Methods

Clinical effectiveness

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

Cost-effectiveness

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

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

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

2.4 Results

Clinical effectiveness

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

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

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

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

Cost-effectiveness

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

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

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

2.5 Discussion

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

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

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

2.6 Conclusions

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

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

3 BACKGROUND

3.1 Description of health problem

Incidence and prevalence

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

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

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

Diagnosis and management

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

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

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

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

Prognosis

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

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

3.2 Impact of health problem

3.2.1 Significance for patients

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

3.2.2 Significance for the NHS

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

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

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

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

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

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

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

3.3 Current service provision

3.3.1 Clinical guidelines

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

3.3.2 Current NICE technology appraisal guidance

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

3.3.3 Current service cost

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

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

3.3.4 Variation in services and uncertainty about best practice

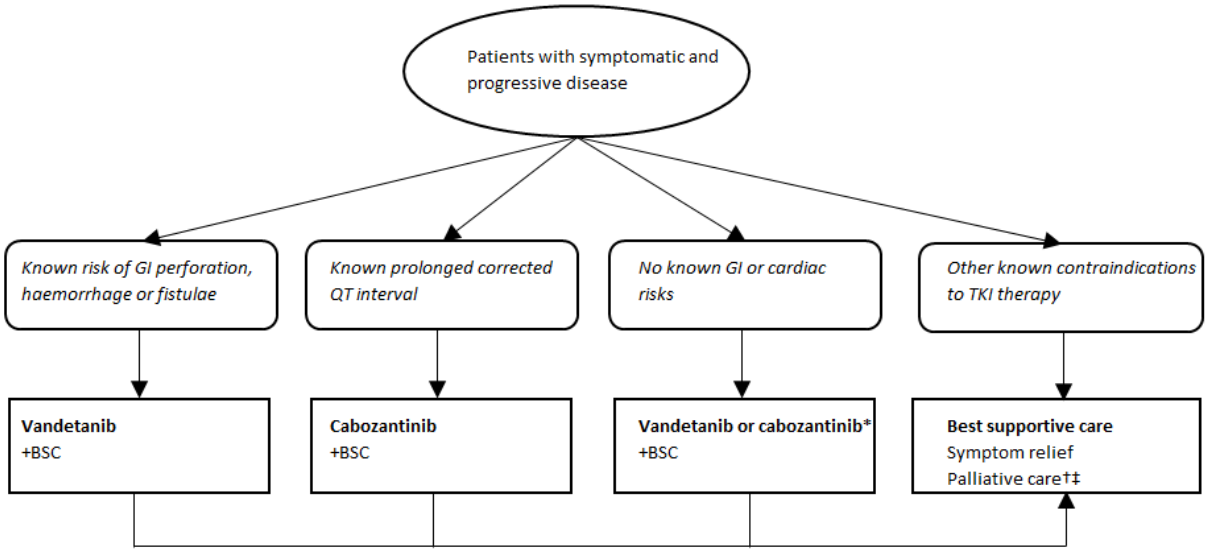
Clinical advisors to the Assessment Group noted that whilst the indications set out in the marketing authorisations for cabozantinib and vandetanib[22, 23] relate to patients with progressive disease, this may be determined on the basis of radiographic evidence or the presence of symptomatic disease.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

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

3.3.5 Current treatment pathway

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

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



*Patient may switch to other TKI if intolerant or severe AEs experienced within 3 months
†may include palliative surgery, palliative radiotherapy and/or treatments for bone pain
‡ nuclear medicine therapies such as MIBG/Dotatate may be considered in some patients

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

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

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

3.4 Description of technology under assessment

3.4.1 Interventions considered in the scope of this report

This assessment includes two interventions: cabozantinib and vandetanib.

Cabozantinib

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

Vandetanib

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

3.4.2 Mode of action

Cabozantinib

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

Vandetanib

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

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

3.4.3 Current usage in the NHS

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

4 DEFINITION OF THE DECISION PROBLEM

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

4.1 Decision problem

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

Population

- Adults with unresectable locally advanced or metastatic MTC.

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

Interventions

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

Relevant comparators

Cabozantinib and vandetanib are compared with:

- Each other
- BSC.

Outcomes

The following outcomes are included in the assessment.

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

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

Subgroups

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

4.2 Overall aims and objectives of assessment

The aims of the assessment are:

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

5. ASSESSMENT OF CLINICAL EFFECTIVENESS

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

5.1 Methods for reviewing effectiveness

5.1.1 Inclusion criteria

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

Table 1: Inclusion and exclusion criteria

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

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

5.1.2 Searches

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

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

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

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

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

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

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

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

5.1.3 Study selection and data extraction

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

5.1.4 Quality assessment

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

5.1.5 Evidence synthesis

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

5.2 Results

5.2.1 Quantity and quality of research available

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

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

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

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

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

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

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

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

Figure 2: **PRISMA flowchart**

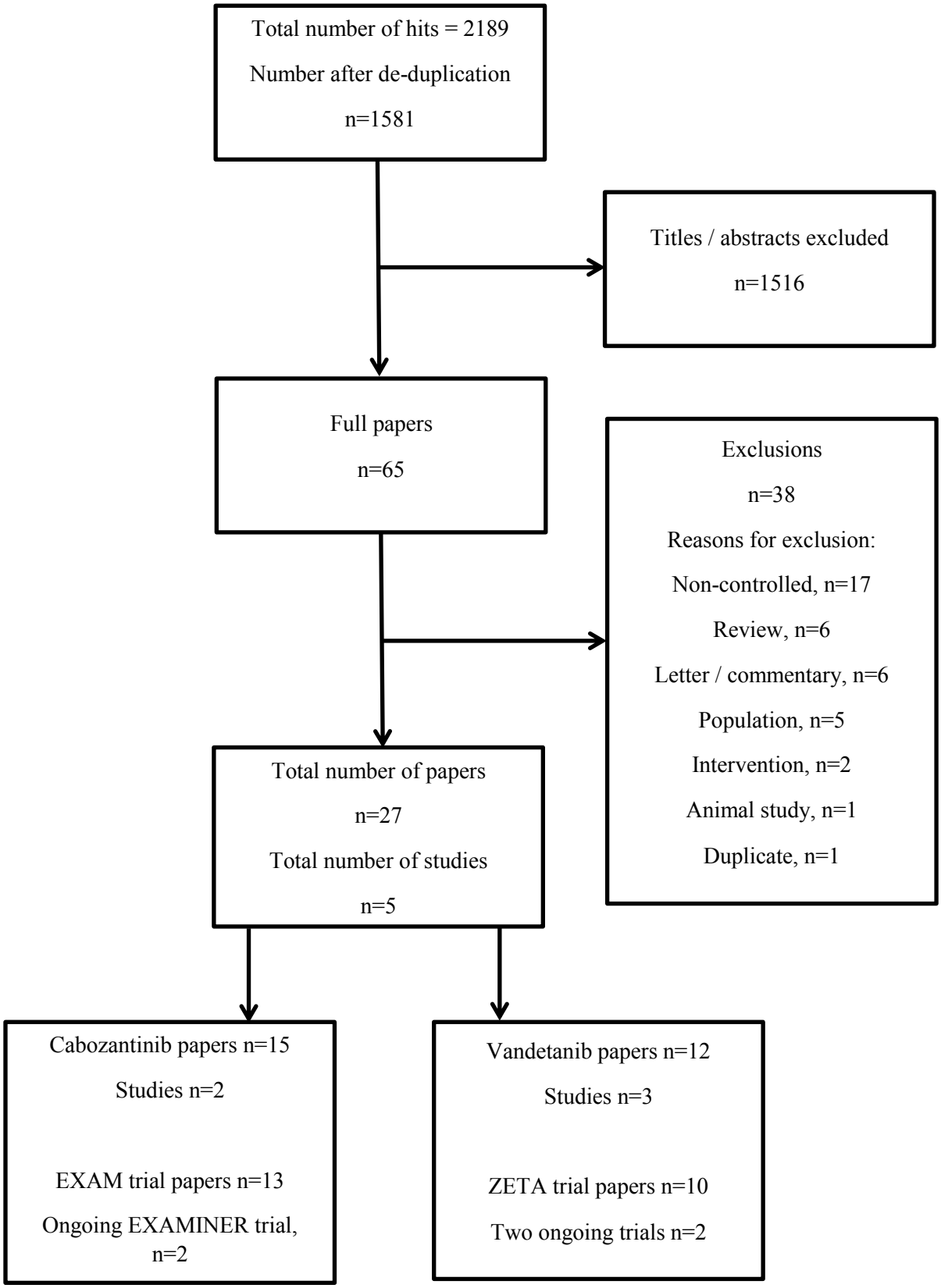


Table 2: **Characteristics of included RCTs**

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

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

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

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

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

Table 3: **Definitions of PFS**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Note: All quotations are taken from the full trial publications

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

5.2.2 Assessment of effectiveness

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

5.2.2.1 Progression-free survival (PFS)

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

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

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

HR – hazard ratio

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

RET – REarranged during Transfection

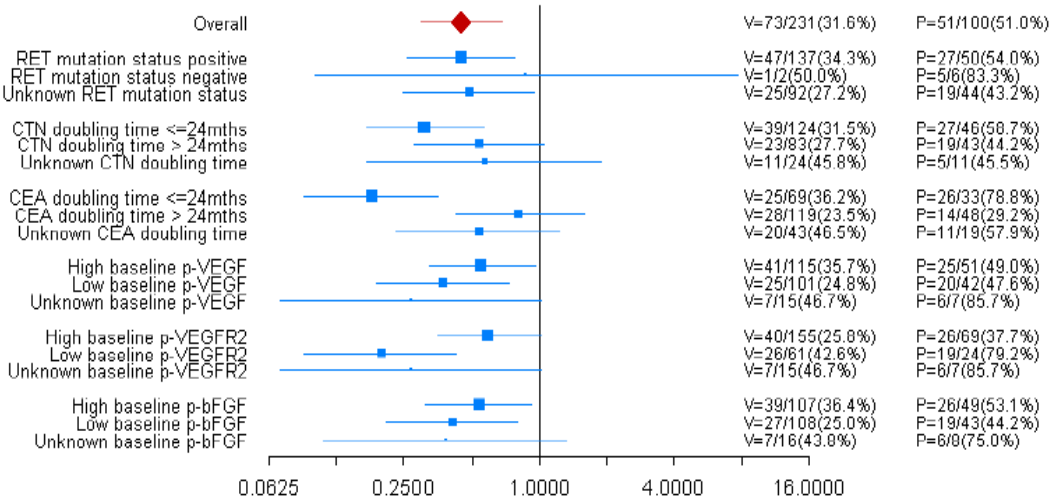
Table 11: **PFS by RET mutational status in *post hoc* analysis of EXAM trial (Ipsen CS,[21] adapted from Sherman *et al*[50])**

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

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

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

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



5.2.2.2 Overall Survival (OS)

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

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

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

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

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

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

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

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

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

5.2.2.3 Response rate

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

Table 13: **Objective response rates**

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

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

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

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

5.2.2.4 CTN and CEA response

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

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

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

**Welsh's t-test*

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

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

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

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

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

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

5.2.2.5 Lesion size

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

5.2.2.6 MD Anderson Symptom Inventory (MDASI-THY)

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

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

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

5.2.3 Safety outcomes

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

5.2.3.1 Any adverse event

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

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

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

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

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

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

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

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

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

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

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

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

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

5.2.3.2 Grade ≥3 and serious adverse events (SAEs)

AEs of Grade 3 or above reported for ≥2% of patients are presented in Table 18. The most common Grade ≥3 AEs for cabozantinib were diarrhoea (16%), hand foot syndrome (HFS, 13%), fatigue (9%) and hypertension (8%), asthenia (6%) and decreased weight (5%) and appetite (5%).[28, 45] These appear to be consistent with other anti-VEGF TKIs and the open-label cabozantinib studies.[65-68] However, it should be noted that the incidence and severity of HFS reported in the EXAM trial is lower than that reported in other cabozantinib trials for the treatment of other solid malignancies.[69]

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

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

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

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

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

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

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

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

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

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

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

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

5.2.3.3 Adverse events leading to discontinuation or dose interruption/reduction

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

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

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

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

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

5.2.3.4 Deaths

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

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

5.2.3.5 Supplementary safety evidence

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

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

5.3 Network meta-analysis

5.3.1 Justification for conducting a network meta-analysis

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

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

5.3.2 Methods for the network meta-analysis

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

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

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

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

Figure 4: **Network diagram for NMA**

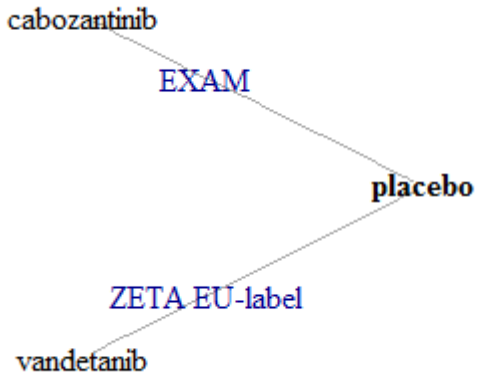


Table 21: **Data for the NMA on PFS**

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

CI – confidence interval

5.3.3 Results of the network meta-analysis

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

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

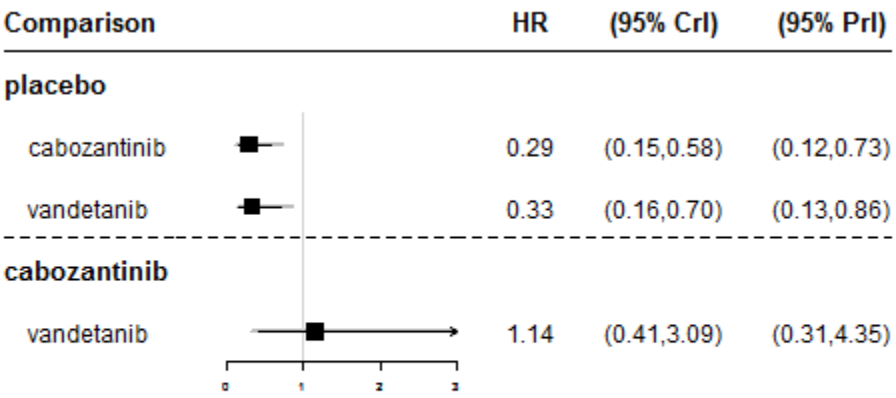
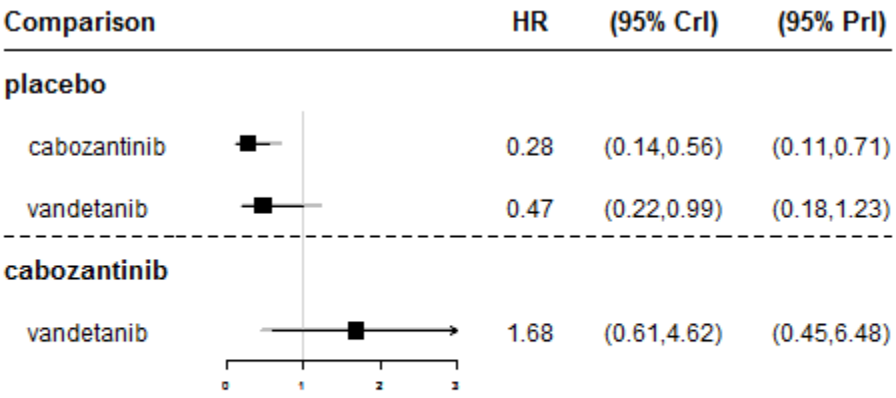


Figure 6: **Results of the NMA for central-read PFS**



5.4 Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6 ASSESSMENT OF COST-EFFECTIVENESS

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

6.1 Systematic review of existing cost-effectiveness evidence

6.1.1 Review of existing economic evaluations - methods

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

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

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

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

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

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

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

Inclusion criteria

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

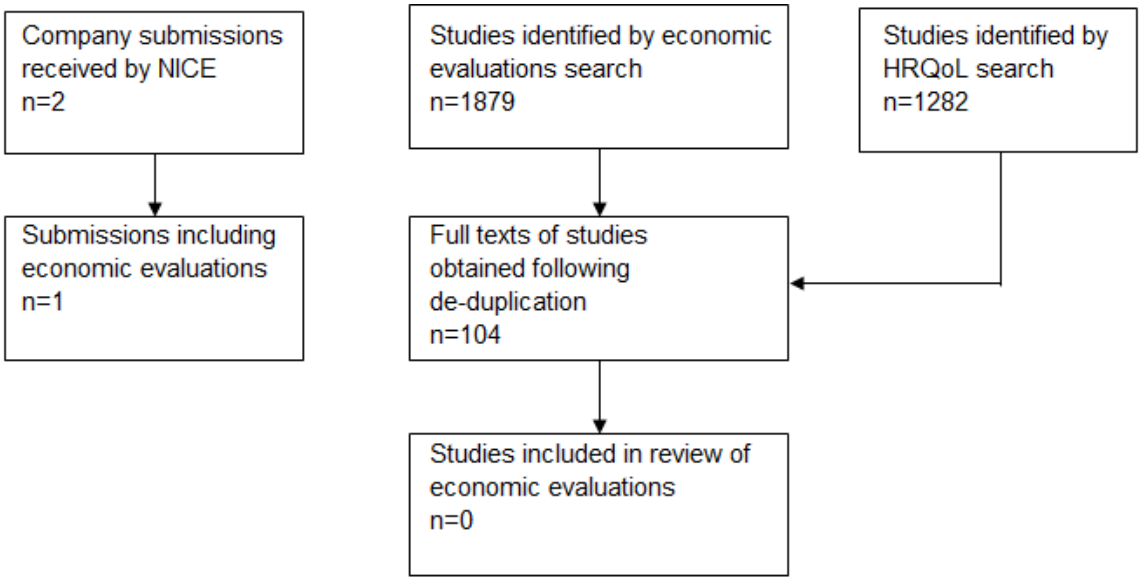
Exclusion criteria

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

6.1.2 Review of existing economic evaluations - results

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

Figure 7: Study selection results



6.1.3 Review of models submitted by the companies

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

6.1.3.1 Scope of the Sanofi economic evaluation

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

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

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

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

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

Table 22: **Sanofi model scope**

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

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

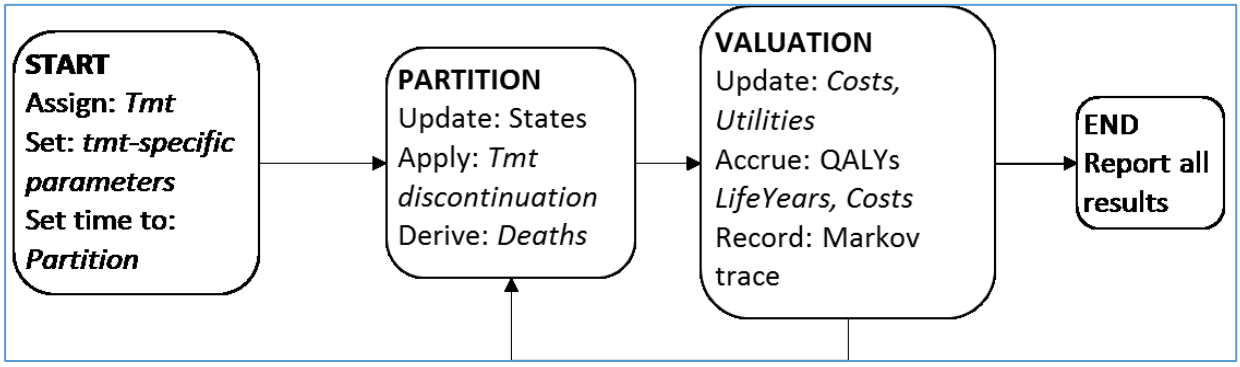
6.1.3.2 Sanofi model structure

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

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

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

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



The model employs the following structural assumptions:

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

6.1.3.3 Evidence used to inform the company's model

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

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

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

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

Overall survival

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

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

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

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

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

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

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

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

Progression-free survival

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

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

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

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

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

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

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

Health-related quality of life

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

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

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

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

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

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

Time spent receiving vandetanib

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

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

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

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

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

Probability of receiving vandetanib in the post-progression state

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

Vandetanib acquisition cost

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

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

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

mg - milligram

Monitoring costs

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

Table 29: Vandetanib monitoring costs assumed in the Sanofi model

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

AE management costs

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

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

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

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

Palliative care costs

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

6.1.3.4 Model evaluation methods

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

6.1.3.5 Sanofi model results

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

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

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

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

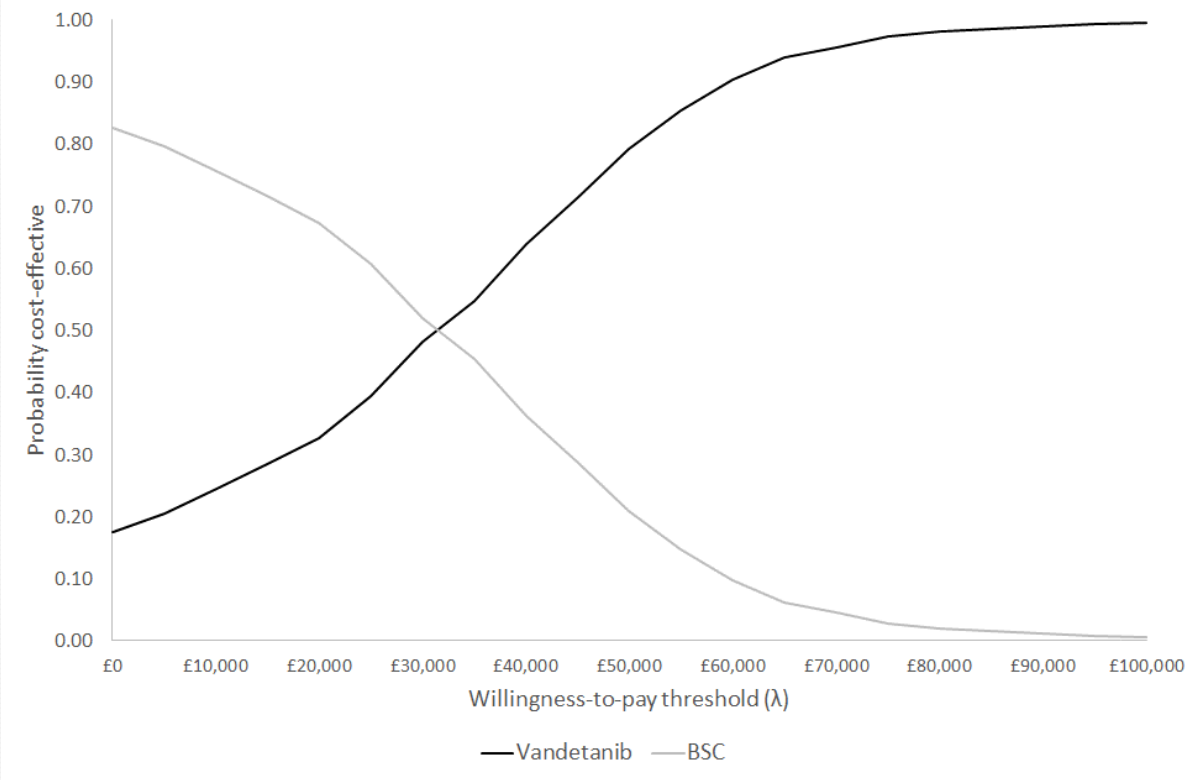
Option	Absolute		Incremental		
	QALYs	Costs	QALYs	Costs	ICER
Probabilistic model					
Vandetanib*	3.53	£181,130	1.34	£42,215	**£31,546**
BSC*	2.19	£138,915	-	-	-
Deterministic model					
Vandetanib*	3.49	£175,316	1.36	£43,024	**£31,731**
BSC*	2.13	£132,292	-	-	-

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

Sanofi probabilistic sensitivity analysis results

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

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

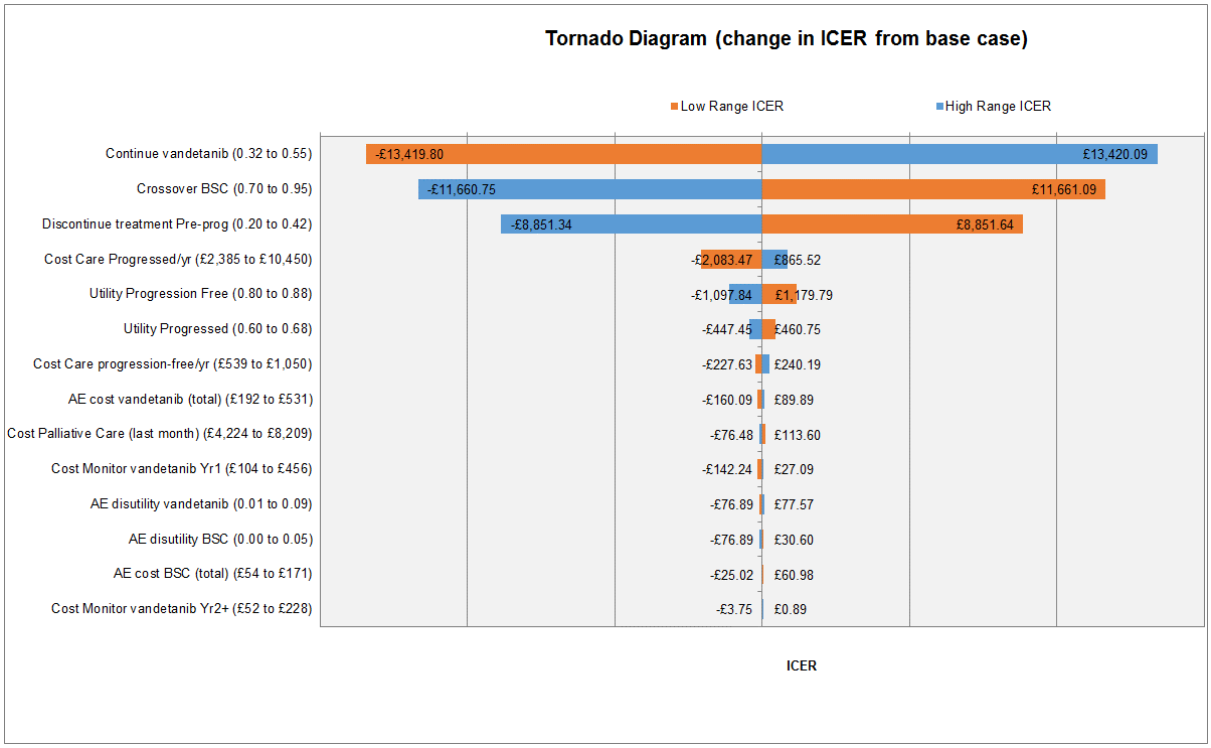


BSC – best supportive care

Sanofi deterministic sensitivity analysis results

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

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



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

6.1.3.6 Critical appraisal of the economic analysis presented by Sanofi

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

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

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

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

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

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

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

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

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

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

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

Model verification

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

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

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

**undiscounted*

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

Summary of main issues identified within the critical appraisal

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

Box 3: Main issues identified by the Assessment Group

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

(1) Relevance of the Restricted EU label population

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

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

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

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

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

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

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

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

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

(4) Questionable implementation of the vandetanib discontinuation parameter

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

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

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

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

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

(6) Technical programming errors

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

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

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

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

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

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

(7) Concerns regarding health utility parameters

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

(8) Limited exploration of uncertainty surrounding survivor functions

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

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

(9) Concerns regarding costings

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

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

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

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

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

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

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

6.2 Independent Assessment Group model

6.2.1 Model scope

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

Table 35: **Assessment Group model scope**

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

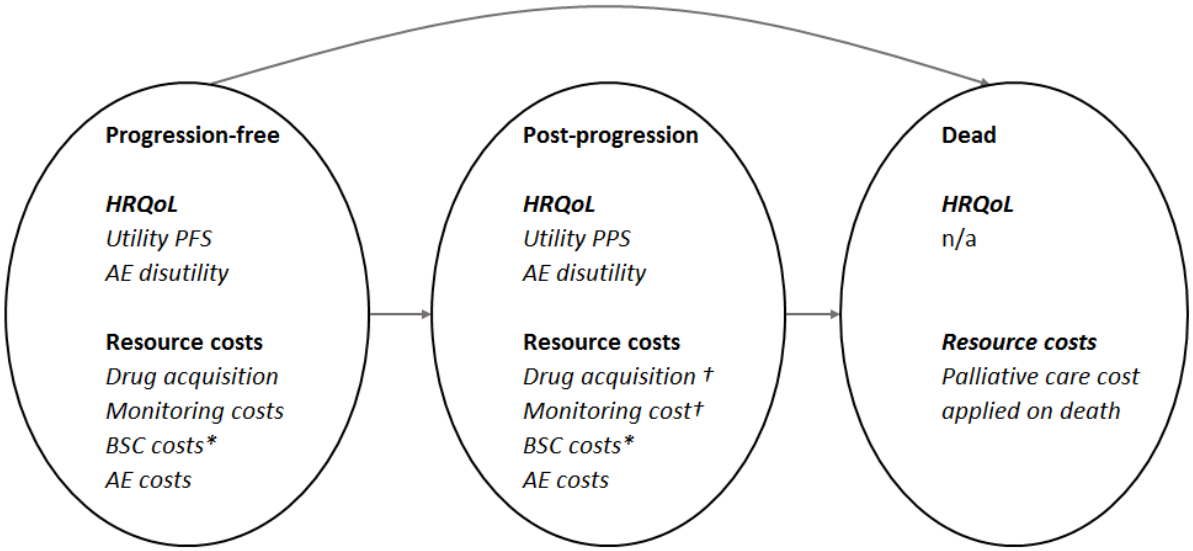
** PSS costs not explicitly included*
CEA – carcinoembryonic antigen; CTN – calcitonin; BSC – best supportive care; QALY – quality-adjusted life year; ITT – intention-to-treat; PFS – progression-free survival; OS – overall survival; NHS – National Health Service; PSS – Personal Social Services

6.2.2 Model structure

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

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

Figure 14: **Assessment Group model structure**



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

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

The model employs the following structural assumptions:

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

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

6.2.3 Evidence used to inform the model's parameters

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

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

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

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

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

6.2.3.2 Time to event analysis using individual patient data

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

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

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

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

Data used to inform time to event analysis

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

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

Methods for time to event analysis

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

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

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

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

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

PFS

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

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

OS

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

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

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

Figure 15: EXAM ITT population PFS

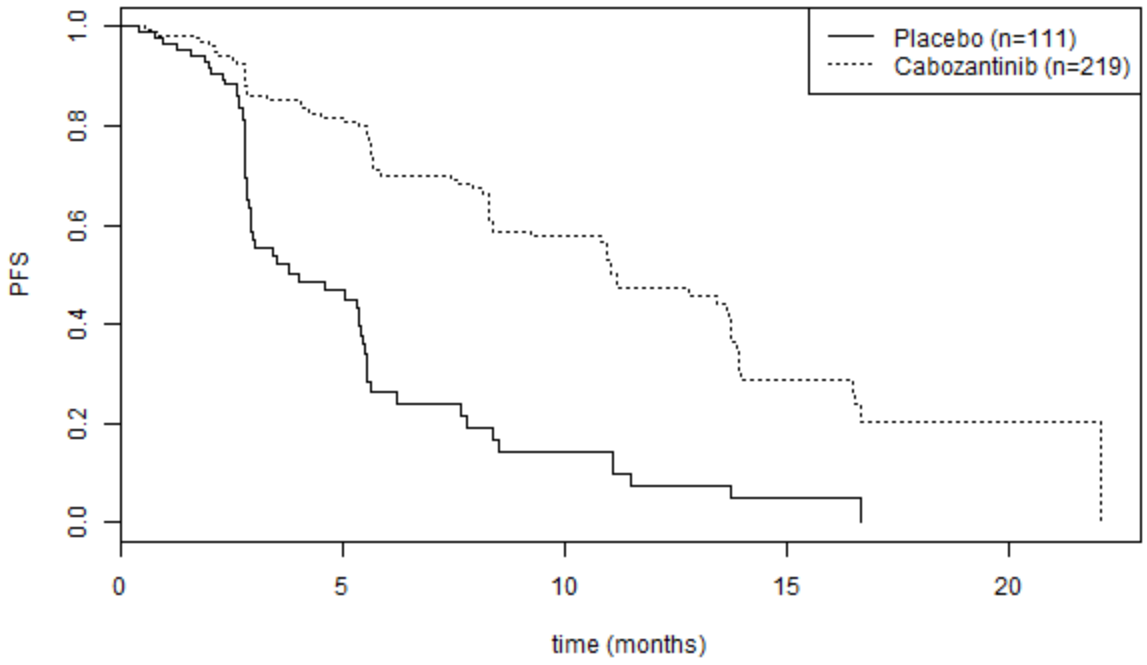


Figure 16: EXAM ITT population OS

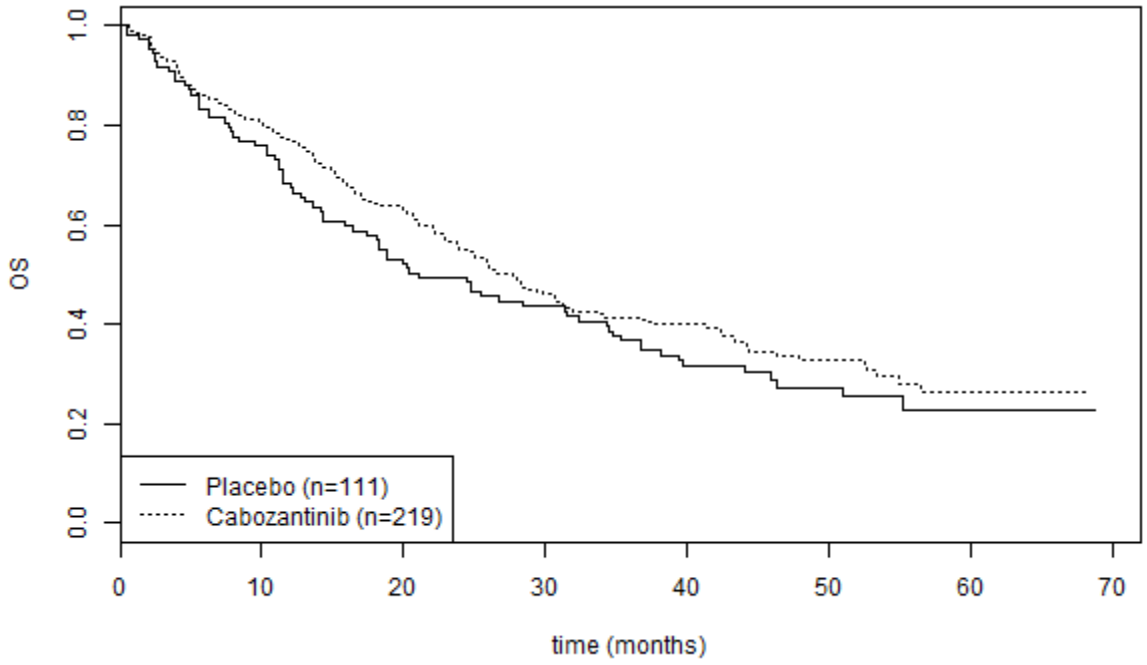


Table 38: Model fit statistics - EXAM ITT population, individual models for each treatment arm, PFS and OS

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

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

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

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

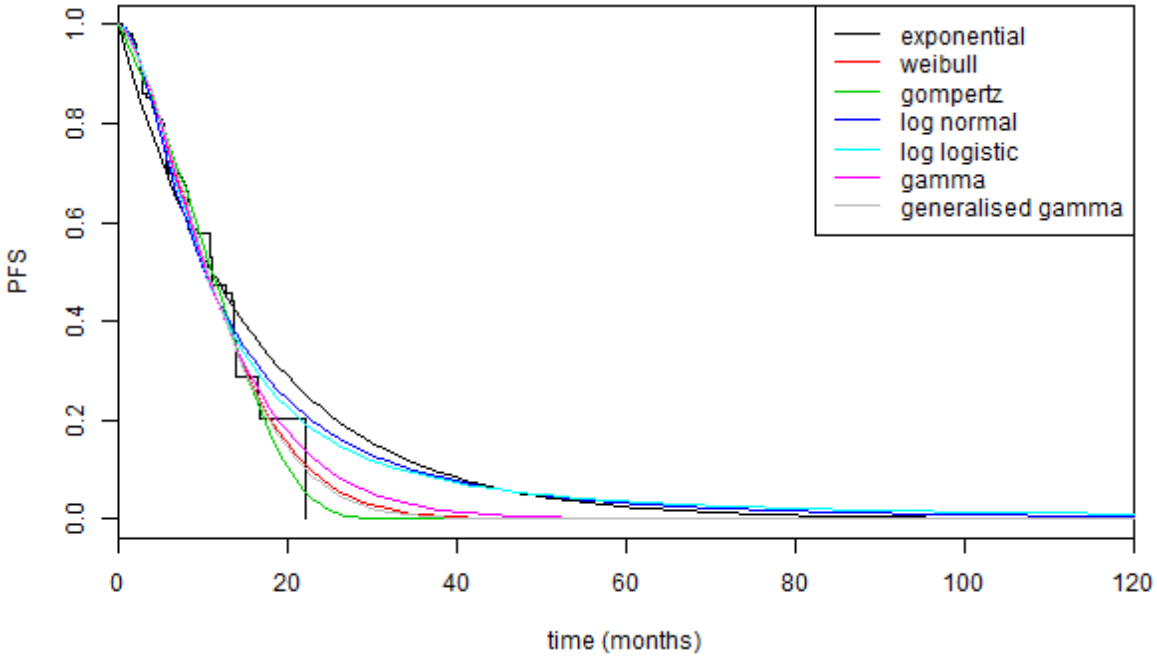


Figure 18: **EXAM ITT population, PFS, placebo group (extrapolation up to 10 years)**

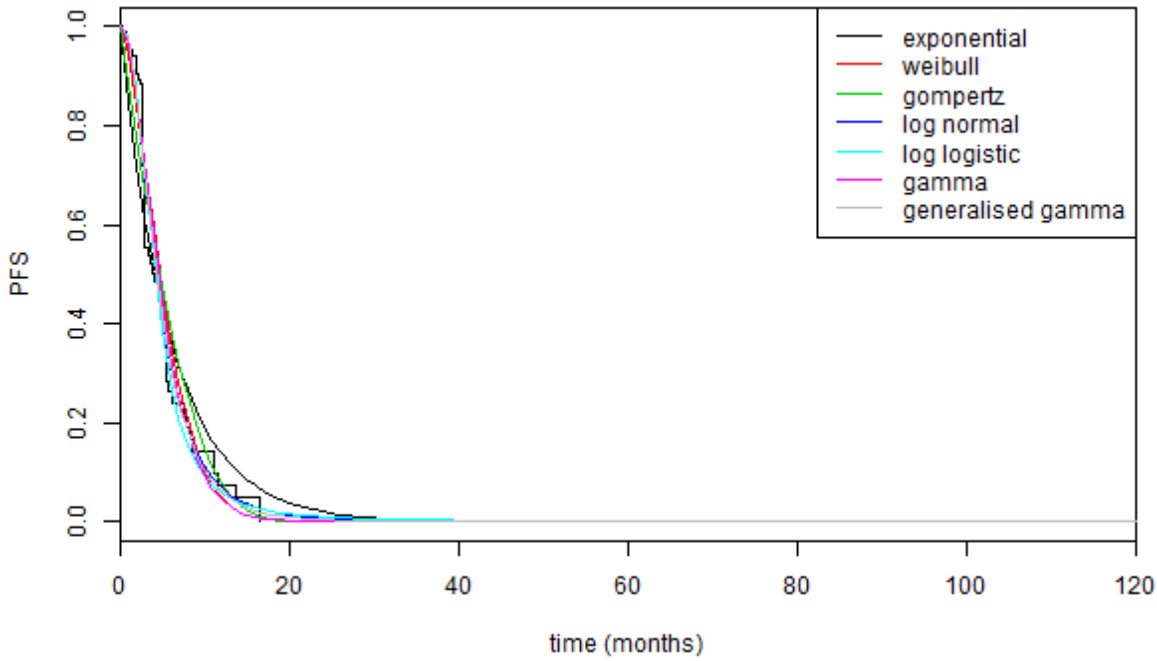


Figure 19: **EXAM ITT population, OS, cabozantinib group (extrapolation up to 20 years)**

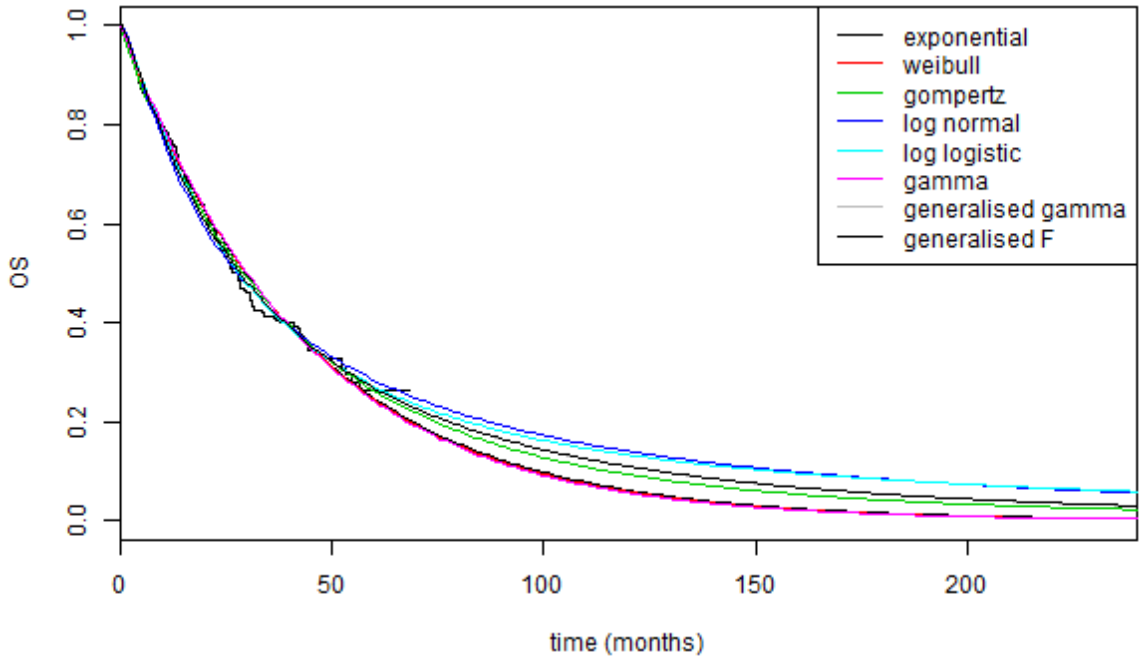
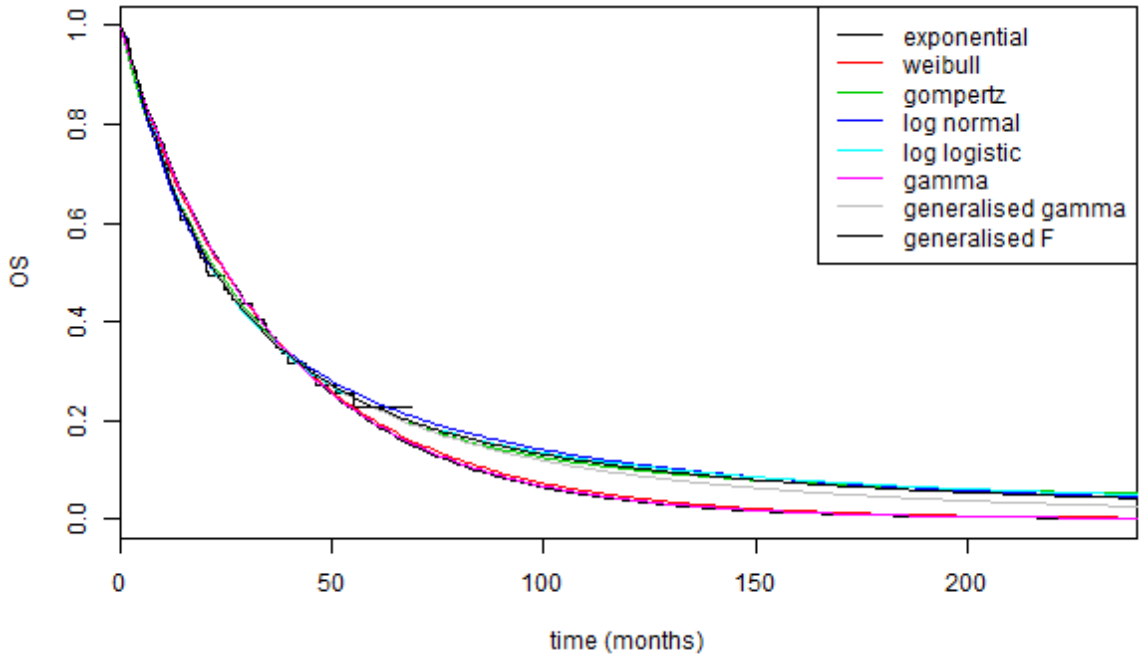


Figure 20: **EXAM ITT population, OS, placebo group (extrapolation up to 20 years)**



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

PFS

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

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

Log cumulative hazard plots are provided in Appendix 3

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

Measures of comparative internal validity are presented in

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

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

Figure 22 (vandetanib) and

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

OS

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

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

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

Log cumulative hazard plots are provided in Appendix 3

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

Measures of comparative internal validity are presented in

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

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

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

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

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

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

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

Figure 24: ZETA EU label population OS

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

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

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

PFS

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

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

Log cumulative hazard plots are presented in Appendix 3,

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

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

OS

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

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

Log cumulative hazard plots are provided in Appendix 3

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

Figure 31 (vandetanib) and

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

PH models

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

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

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

AFT models

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

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

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

Model selection

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

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

Table 43.

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

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

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

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

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

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

6.2.3.3 Health-related quality of life

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

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

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

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

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

Table 45 summarises the health utilities assumed within these submissions.

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

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

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

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

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

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

AE – adverse event

6.2.3.4 Adverse event rates

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

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

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

BSC – best supportive care

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

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

Table 48).

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

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

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

6.2.3.6 Resource use and costs

Drug acquisition

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

Table 49: Drug acquisition costs – vandetanib and cabozantinib

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

mg – milligram

6.2.3.7 Time spent receiving cabozantinib and vandetanib

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

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

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

PFS – progression-free survival; mg – milligram

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

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

PFS – progression-free survival; mg – milligram

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

6.2.3.8 Cost of managing Grade 3/4 AEs

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

6.2.3.9 BSC costs

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

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

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

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

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

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

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

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

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

6.2.3.10 Cost of palliative care

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

6.2.3.11 Unit costs

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

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

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

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

6.2.4 Model evaluation methods

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

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

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

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

6.2.5 Model validation

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

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

6.2.6 Assessment Group model results

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

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

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

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

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

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

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

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

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

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

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

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

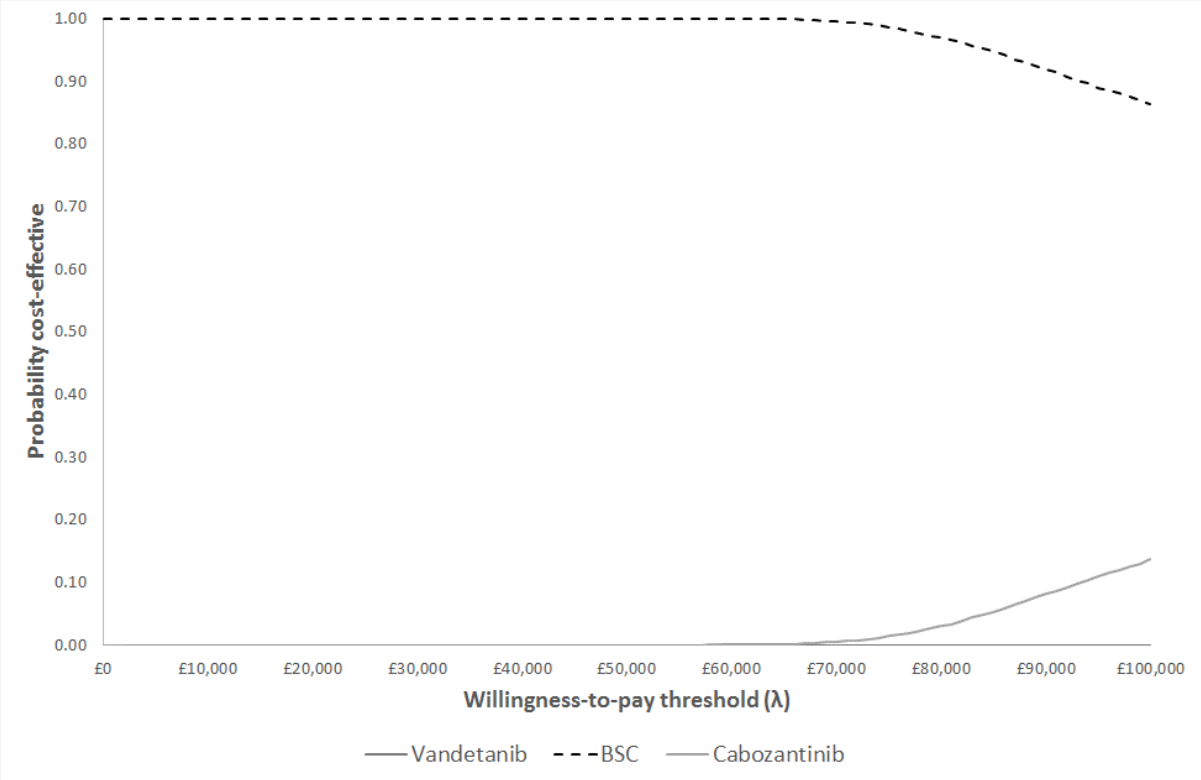


Table 58 presents the results of the DSAs for the pairwise comparison of cabozantinib versus BSC within the EU label (symptomatic and progressive) MTC population. As shown in the table, the ICER remains in excess of £135,000 per QALY gained across all scenarios. The alternative scenarios regarding health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

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

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

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

** Assessment Group base case curve choice*

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

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

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

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

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

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

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

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

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

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

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

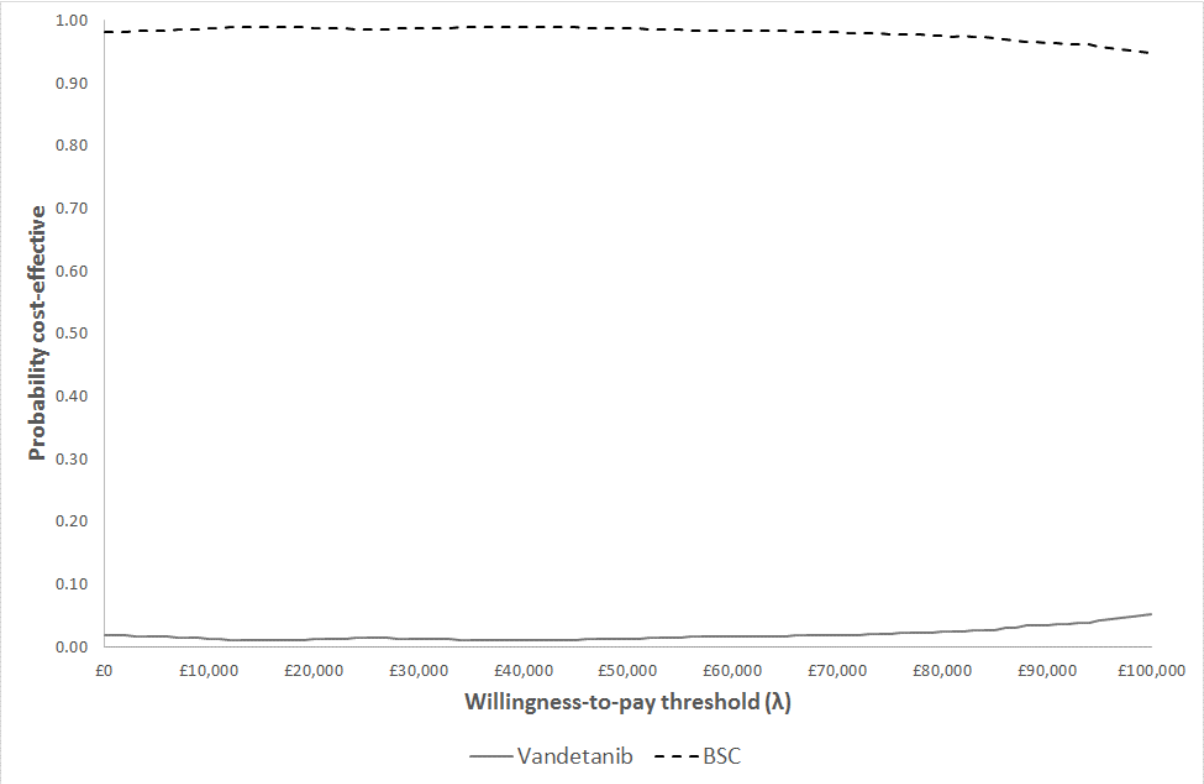


Table 61 presents the results of the DSAs for the pairwise comparison of vandetanib versus BSC within the EU label (symptomatic and progressive) MTC population. Across the range of DSAs considered, the ICERs for vandetanib versus BSC remain above £123,000 per QALY gained. In several scenarios in which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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

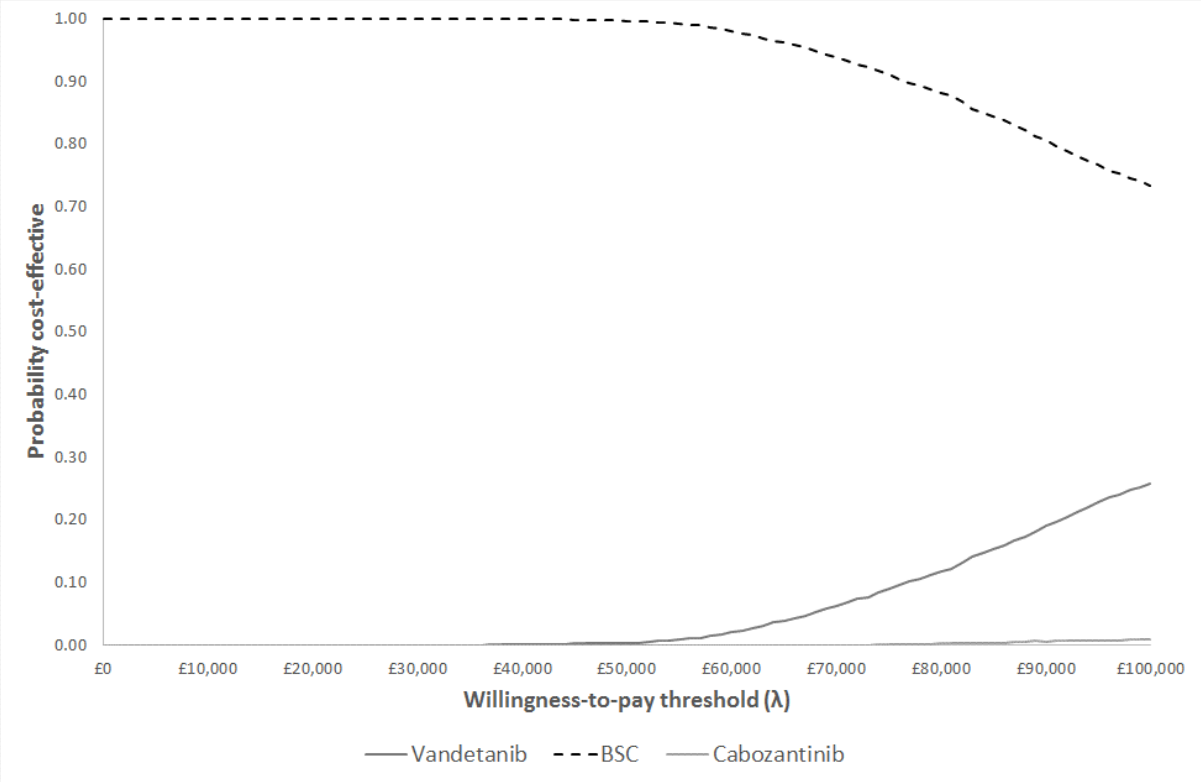


Table 64 presents the results of the DSAs for the fully incremental analyses of cabozantinib, vandetanib and BSC within the EU label (symptomatic and progressive) MTC population, including the PFS treatment effect for vandetanib from the ZETA trial. Across the range of DSAs considered, the ICERs for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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

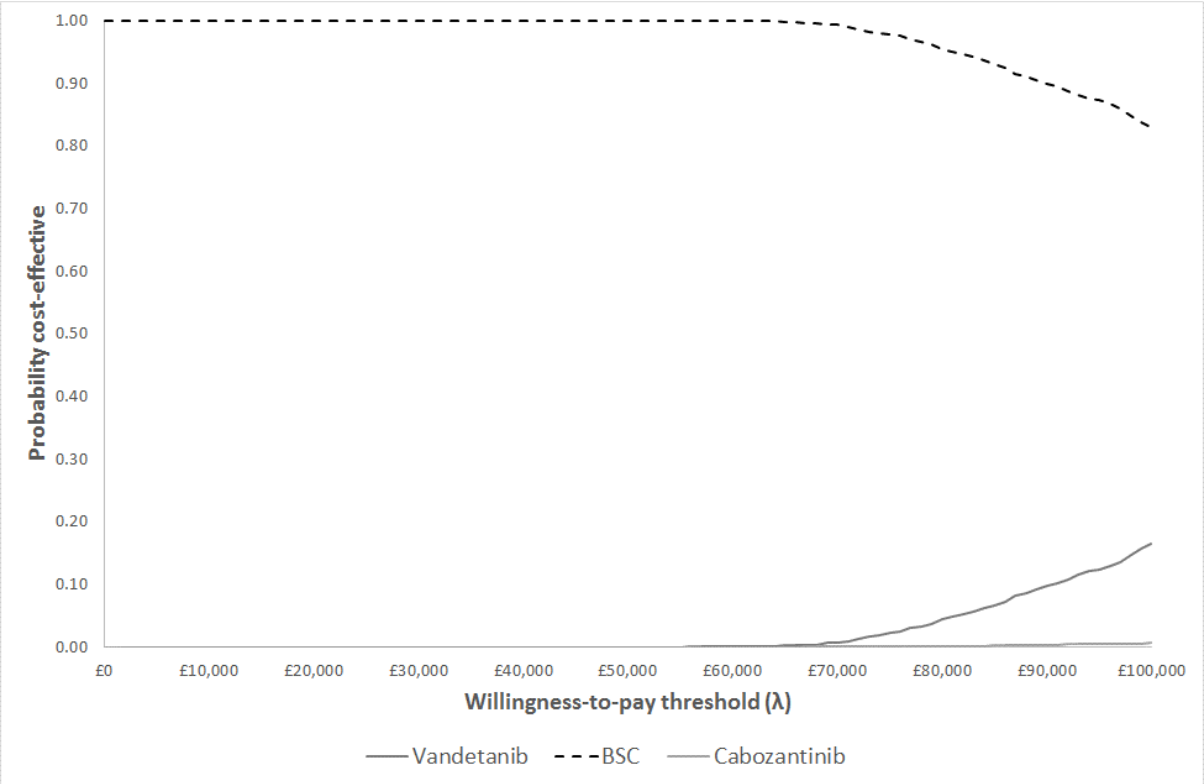


Table 67 presents the results of the DSAs for the fully incremental analysis of all options based on the assumption of equivalent PFS and OS outcomes for cabozantinib and vandetanib, using time-to-event outcomes data from the EXAM trial. Cabozantinib remains dominated across all scenarios, except the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

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

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

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

** Assessment Group base case curve choice*

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

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

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

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

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

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

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

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

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

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

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

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

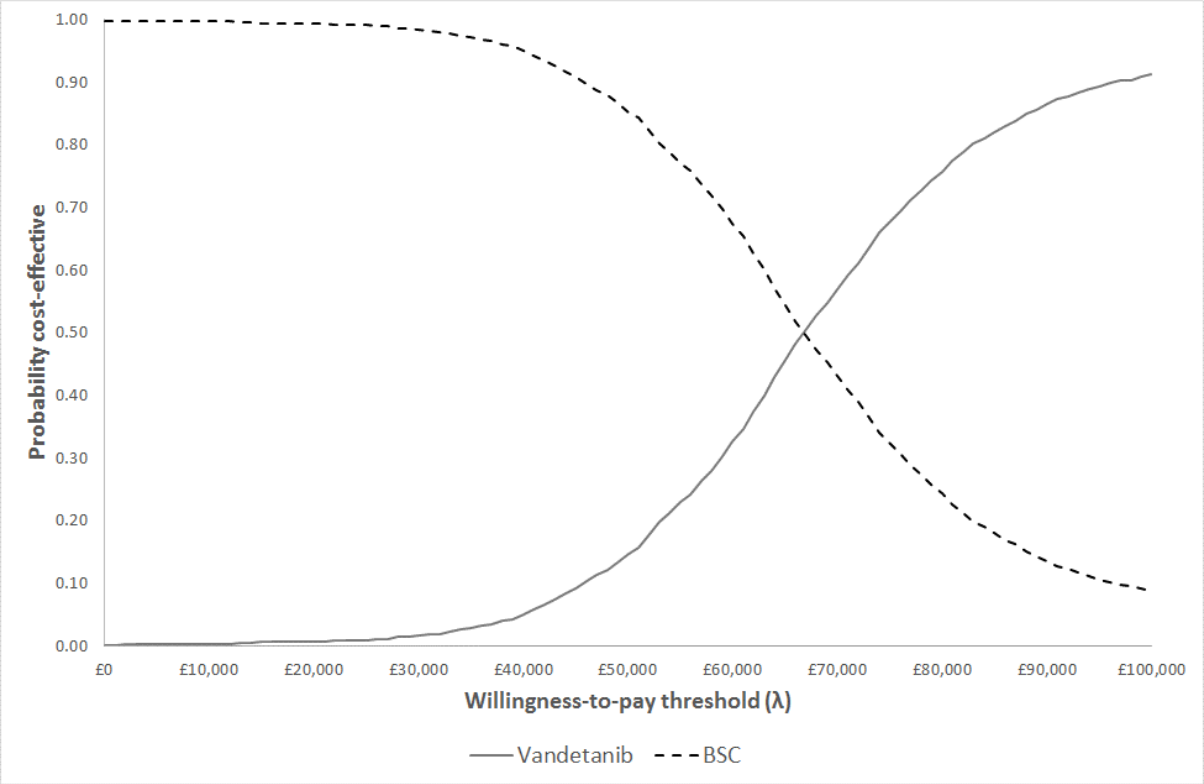


Table 70 presents the results of the DSA for the pairwise comparison of vandetanib versus BSC within the Restricted EU label population. As shown in the table, the ICER remains in excess of £51,000 per QALY gained across all scenarios. The DSAs indicate that the choice of utility values used in the base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

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

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

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

* *Assessment Group base case curve choice*

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

6.3 Budget impact analysis

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

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

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

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

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

6.4 Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7 ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

7.1 Additional monitoring requirements

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

7.2 Current availability of cabozantinib and vandetanib for MTC

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

7.3 End-of-life considerations

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

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

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

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

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

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

8 DISCUSSION

8.1 Statement of principal findings

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

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

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

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

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

8.2 Strengths and limitations of the assessment

The key strengths of this assessment are as follows:

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

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

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

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

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

8.3 Uncertainties

The key uncertainties associated with this evaluation are:

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

8.4 Other relevant factors

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

9 CONCLUSIONS

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

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

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

9.1 Implications for service provision

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

9.2 Suggested research priorities

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

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108. Scottish Medicines Consortium. Cabozantinib 20mg and 80mg hard capsules (Cometriq®) SMC No. (1022/15). SMC: Glasgow; 2015.

109. All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Vandetanib (Caprelsa®) 100 mg and 300 mg film-coated tablets. AWMSG: Vale of Glamorgan; 2014.

110. All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Cabozantinib (Cometriq®) 20 mg and 80 mg hard capsules. AWMSG: Vale of Glamorgan; 2014.

11 APPENDICES

APPENDIX 1: Literature Search Strategies

Cost-effectiveness studies

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

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

Embase 1974 to 2016 November 01
3rd November 2016

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

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

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

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

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

CINAHL 1982 to Present
3rd November 2016

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

Quality of life studies

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

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

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

Embase 1974 to 2016 November 01
3rd November 2016

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

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

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

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

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

CINAHL 1982 to Present
3rd November 2016

#	**Searches**
S1	(MH "Thyroid Neoplasms+")
S2	(thyr?oid* N5 (cancer* or neoplas* or carcinoma* or malignan* or tumor* or tumour* or adenocarcinoma*))
S3	(MH "Thyroid Gland")
S4	(MH "Neoplasms+")
S5	S3 AND S4
S6	S1 OR S2 OR S5
S7	(MH "Quality of Life")
S8	TI (qol or (quality N2 life)) or AB (qol or (quality N2 life))
S9	TI value and TI (money or monetary) or AB value and AB (money or monetary)
S10	(MH "Economic Value of Life")
S11	(MH "Quality-Adjusted Life Years")
S12	TI (qaly* or qald* or qale* or qtime*) or AB (qaly* or qald* or qale* or qtime*)
S13	TI disability adjusted life or AB disability adjusted life
S14	TI daly* or AB daly*
S15	(MH "Health Status Indicators")
S16	TI (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six) or AB (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six)
S17	TI (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six) or AB (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six)
S18	TI quality adjusted life or AB quality adjusted life
S19	TI (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve) or AB (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve)
S20	TI (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen) or AB (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen)
S21	TI (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty) or AB (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty)
S22	TI (euroqol or euro qol or eq5d or eq 5d) or AB (euroqol or euro qol or eq5d or eq 5d)
S23	TI (hql or hqol or h qol or hrqol or hr qol) or AB (hql or hqol or h qol or hrqol or hr qol)
S24	TI (hye or hyes) or AB (hye or hyes)
S25	TI health* year* equivalent* or AB health* year* equivalent*
S26	TI health utilit* or AB health utilit*
S27	TI (hui or hui1 or hui2 or hui3) or AB (hui or hui1 or hui2 or hui3)
S28	TI disutilit* or AB disutilit*
S29	TI rosser or AB rosser
S30	TI quality N2 wellbeing or AB quality N2 wellbeing
S31	TI qwb or AB qwb

S32	TI willingness N2 pay or AB willingness N2 pay
S33	TI standard gamble* or AB standard gamble*
S34	TI time trade off or AB time trade off
S35	TI time tradeoff or AB time tradeoff
S36	TI tto or AB tto
S37	PT letter
S38	PT editorial
S39	PT comment
S40	S37 or S38 or S39
S41	S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36
S42	S41 NOT S40
S43	S6 AND S42

APPENDIX 2: Excluded studies with reasons

Single arm studies:

1. Anagnostou E, Saltiki K, Vasiliou V, et al. Experience from the administration of tyrosine kinase inhibitors (TKI) in patients with metastatic progressive medullary thyroid carcinoma (MTC) in a referral centre in Greece. European Thyroid Journal 2016; 5:75. doi: http://dx.doi.org/10.1159/000447416

2. Chougnet C, Schlumberger M, Isabelle B. Efficacy and toxicity of vandetanib for advanced medullary thyroid cancer treatment, the French experience. European Thyroid Journal 2014; 3: 77-78. doi: 10.1159/000365244

3. Chougnet CN, Borget I, Leboulleux S, et al. Vandetanib for the treatment of advanced medullary thyroid cancer outside a clinical trial: results from a French cohort. Thyroid 2015; 25(4): 386-91. doi: http://dx.doi.org/10.1089/thy.2014.0361

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6. Marquez Fernandez E, Marmesat Rodas B, Quesada Sanz MP, et al. Use of vandetanib in medullary thyroid cancer. International Journal of Clinical Pharmacy 2016; 38 (6):587. doi: http://dx.doi.org/10.1007/s11096-015-0240-y

7. NCT00098345. Efficacy and Tolerability of ZD6474 in Patients With Thyroid Cancer, 2004.

8. NCT00358956. A Study To Assess ZD6474 (ZACTIMA™) Monotherapy In Locally Advanced or Metastatic Hereditary Medullary Thyroid Cancer, 2006.

9. NCT01661179. Evaluate the Safety and Tolerability of Vandetanib in Japanese Patients With Medullary Thyroid Carcinoma, 2012.

10. NCT01683110. Expanded Access of Cabozantinib in Medullary Thyroid Cancer, 2012.

11. NCT01945762. Observational Study to Evaluate Vandetanib in RET -/+ Patients With Metastatic Medullary Thyroid Cancer, 2013.

12. Robinson BG, Paz-Ares L, Krebs A, et al. Vandetanib (100 mg) in patients with locally advanced or metastatic hereditary medullary thyroid cancer. J Clin Endocrinol Metab 2010; 95(6): 2664-71. doi: http://dx.doi.org/10.1210/jc.2009-2461

13. Takahashi S, Tomomatsu J, Okamoto T, et al. Safety and tolerability of vandetanib in japanese patients (PTS) with medullary thyroid cancer (MTC): A phase i/ii open-label study. Thyroid 2015; 25: A273. doi: http://dx.doi.org/10.1089/thy.2015.29004.abstracts

14. Tiedje V, Locati LD, Kroiss M, et al. Cabozantinib therapy in medullary thyroid carcinoma patients outside a clinical trial. Thyroid 2015; 25: A266. doi: http://dx.doi.org/10.1089/thy.2015.29004.abstracts

15. Tiedje V, Ting S, Walter RF, et al. Prognostic markers and response to vandetanib therapy in sporadic medullary thyroid cancer patients. Eur 2016; 175(3): 173-80. doi: http://dx.doi.org/10.1530/EJE-16-0252
16. Wells SA, Jr., Gosnell JE, Gagel RF, et al. Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer. J Clin Oncol 2010; 28(5):767-72. doi: http://dx.doi.org/10.1200/JCO.2009.23.6604
17. Zhang L, Li S, Zhang Y, et al. Pharmacokinetics and tolerability of vandetanib in Chinese patients with solid, malignant tumors: an open-label, phase I, rising multiple-dose study. Clinical Therapeutics 2011;33(3):315-27. doi: http://dx.doi.org/10.1016/j.clinthera.2011.04.005

Reviews:

1. Belum VR, Serna-Tamayo C, Wu S, et al. Incidence and risk of hand-foot skin reaction with cabozantinib, a novel multikinase inhibitor: a meta-analysis. Clin Exp Dermatol 2016; 41(1): 8-15. doi: http://dx.doi.org/10.1111/ced.12694
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4. Rinciog C, Myren KJ, Alden M, et al. An Indirect Treatment Comparison of Cabozantinib Verse Vandetanib in Progressive Medullary Thyroid Cancer (MTC). Value in Health 2014; 17(7): A616-17. doi: http://dx.doi.org/10.1016/j.jval.2014.08.2173
5. Rosen AC, Wu S, Damse A, et al. Risk of rash in cancer patients treated with vandetanib: systematic review and meta-analysis. J Clin Endocrinol Metab 2012; 97(4): 1125-33. doi: http://dx.doi.org/10.1210/jc.2011-2677
6. Thornton K, Kim G, Maher VE, et al. Vandetanib for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease: U.S. Food and Drug Administration drug approval summary. Clin Cancer Res 2012;18(14):3722-30. doi: http://dx.doi.org/10.1158/1078-0432.CCR-12-0411

Letters / commentaries:

1. Anonymous. Vandetanib (Caprelsa) for medullary thyroid cancer. Med Lett Drugs Ther 2012; 54(1381): 3-4.
2. Anonymous. Vandetanib: too dangerous in medullary thyroid cancer. Prescrire International 2012; 21(131): 233.

3. Baudry C, Paepegaey AC, Groussin L. Reversal of Cushing's syndrome by vandetanib in medullary thyroid carcinoma. New England Journal of Medicine 2013; 369(6): 584-86. doi: 10.1056/NEJMc1301428
4. Chatal JF, Kraeber-Bodéré F, Goldenberg DM, et al. Treatment of metastatic medullary thyroid cancer with vandetanib: need to stratify patients on basis of calcitonin doubling time...J Clin Oncol. 2012; 30(2): 134-41. J Clin Oncol 2012;30(17):2165-65.
5. Fuerst M. Medullary Thyroid Cancer: Cabozantinib Extends PFS in Patients with RET or RAS Mutations. Oncology Times 2013: 11-12.
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Population:

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APPENDIX 3: Supplementary information to inform time to event analyses

Figure 39: **ITT EXAM standard diagnostic plots for PFS**

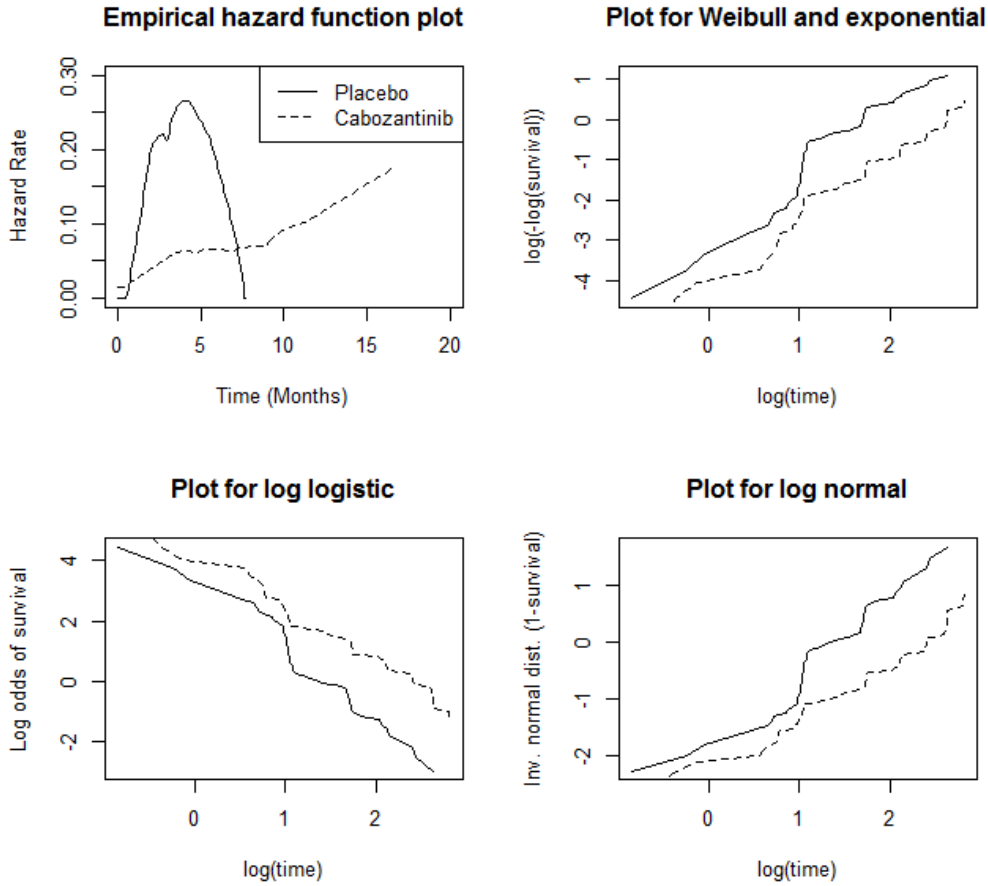

Figure 40: **ITT EXAM standard diagnostic plots for OS**

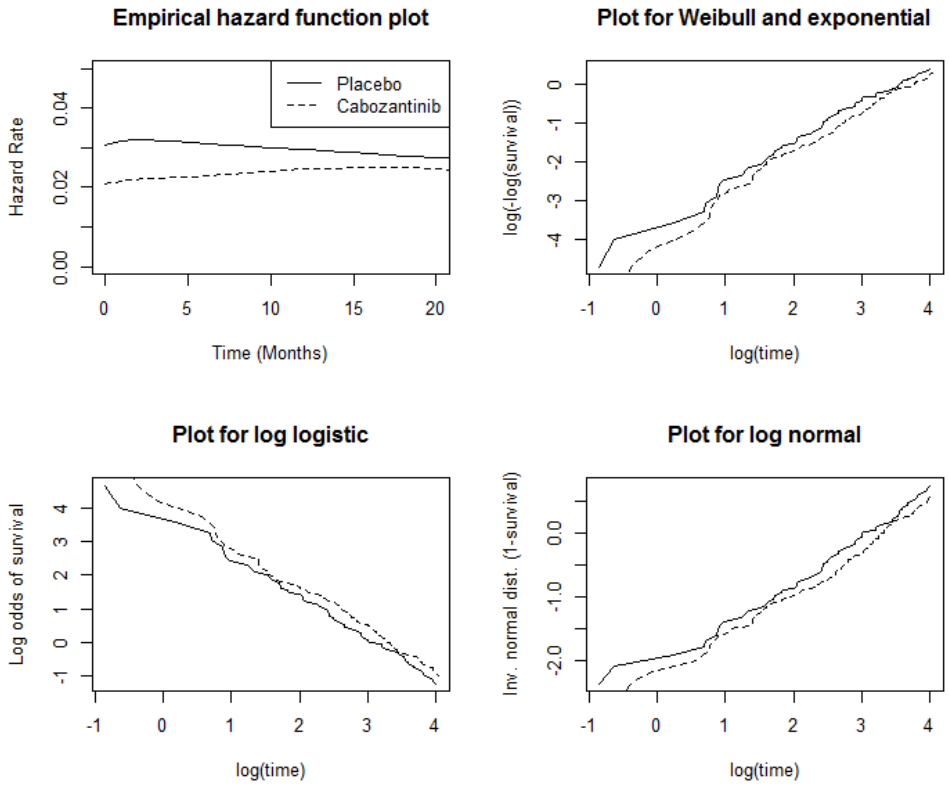

Figure 41: ZETA EU label Kaplan-Meier for PFS from reconstructed IPD

Figure 42: **ZETA EU label Kaplan-Meier for OS from reconstructed IPD**

Figure 43: **ZETA EU label, standard diagnostic plots for PFS**

Figure 44: **ZETA EU label, standard diagnostic plots for OS**

Figure 45: ZETA Restricted EU label Kaplan-Meier for PFS from reconstructed IPD

Figure 46: ZETA Restricted EU label, standard diagnostic plots for PFS

Figure 47: ZETA Restricted EU label Kaplan-Meier for OS from reconstructed IPD

Figure 48: ZETA Restricted EU label, standard diagnostic plots for OS