NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Cabozantinib for treating medullary thyroid cancer [ID56]

The scope for this technology appraisal includes vandetanib. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.

For transparency, we have included the documents considered by the committee for vandetanib, even though we are not releasing any recommendations for this technology at this stage.

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - SanofiGenzyme
   - Ipsen
   - Association for Multiple Endocrine Neoplasia Disorders (AMEND)

   There was a confidential appendix considered with the new value proposition from Ipsen.

   The Department for Health and Social Care submitted a "no comments" response

3. **Comments on the Appraisal Consultation Document from experts:**
   - Joint response from Dr Kate Newbold, clinical expert, nominated by NCRI-ACP-RCP-RCR and Dr Mary Lei, clinical expert, nominated by SanofiGenzyme and endorsed by the Royal College of Physicians

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Additional evidence** submitted by SanofiGenzyme

6. **Assessment Group review of company additional evidence** from School of Health and Related Research (ScHARR)

Any information supplied to NICE which has been marked as confidential, has been

redacted. All personal information has also been redacted.

Cabozantinib and vandetanib for treating medullary thyroid cancer

Multiple Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

The scope for this technology appraisal includes vandetanib. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.
Stakeholder comments received in relation to the evidence for vandetanib only, will be responded to fully upon release of the committee's recommendations on vandetanib.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Patient/professional	Association for Multiple Endocrine Neoplasia Disorders (AMEND)	**Patient Input to the Appraisal Process** Since the patient and patient representative were barely acknowledged at the appraisal consultation meeting (see complaint from [redacted] of Butterfly Thyroid Cancer Trust), we are extremely concerned that patient and patient organisation input to this process has been viewed by the NICE committee as simply a 'tick-box' exercise. We therefore request that all of the following points (some contributed by patients with the cancer who are very unwell) be brought to the attention of the committee at the beginning of the agenda (as recommended by Cancer52 in their 2015 report, 'Speaking up for patients: patient organisation involvement in Health Technology Assessment'). While we may not have strengths in contributing to the clinical or financial data regarding these drugs, we can offer the social and ethical views which are required for consideration as described by the European network for Health Technology Assessment: 'a multidisciplinary process that summarises information about medical, social, economic and ethical issues related to the use of health technology in a systematic, transparent, unbiased and robust manner'.	Comments noted. Patient and patient organisation input was fully considered by the NICE appraisal committee, and has been documented in sections 3.1 and 3.7 of the Final Appraisal Determination (FAD). In addition, comments received from patients and carers during consultation were presented to the appraisal committee. The slides are included in the committee papers for information.
2	Patient/professional	Association for Multiple Endocrine Neoplasia Disorders (AMEND)	**Appraisal Criteria Issues** We are very concerned that these drugs have been appraised using criteria applicable to treatments for more common cancers, but not to rare cancers like medullary thyroid carcinoma. With regard to incomplete data, we feel that the absence of effect does not necessarily imply the effect of absence and that therefore we should be able to offer the chance of therapy despite incomplete data. Since MTC is a very rare cancer, statistics will be scant, data often incomplete and therefore averages wide-ranging and skewed – we don't feel that this should disadvantage these patients. Judging rare cancers using averages and common cancer criteria discriminates against this patient community. Indeed, Cancer52 states in their 2015 report, 'Speaking up for patients: patient organisation involvement in Health Technology Assessment' that 'Patient involvement is particularly important for rare and less common cancers where there may be gaps in the evidence base reflecting small patient numbers. Cancer52 believes that patients can contribute to a fuller understanding of the impact of new medicines'	Comments noted. The committee acknowledged the rarity of the disease but was concerned about the significant uncertainty about the survival benefits of both drugs. Given that cabozantinib has been recommended, the committee did not consider the issue of rarity any further.
3	Patient/professional	Association for Multiple Endocrine Neoplasia	**QALY Calculation Issues** We do not think that the QALY calculations are accurate in this instance. Firstly, with around just 80 patients diagnosed with medullary thyroid carcinoma each year in the UK, this cancer is rare and as such the number of potential patients who may use cabozantinib and vandetanib is much smaller than	Comments noted. The committee recognised that medullary thyroid cancer is rare. Please see section 3.12 of the FAD for the committee's

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		Disorders (AMEND)	may be the case for drugs used for more common cancers. For example, the potential costs in the case of TKIs for MTC is in stark contrast to the hugely expensive breast cancer drug, trastuzumab emtansine (Kadcyla), which received full approval in June this year, and which may be used by around 1,200 patients per year. Secondly, 25% of MTC cases identified in childhood with a hereditary risk of medullary thyroid cancer due to RET gene mutation usually have an improved prognosis when receiving timely prophylactic surgery. Thus, the financial impact of potential TKI prescribing is again reduced in these cases, yet this has not been factored into the QALY calculations since this entire patient community was regarded as unimportant in the Appraisal process. Finally, the common side-effect-reducing dose reductions or drug holidays are not taken into account. To do so would result in an overall lower total cost. An example of a drug holiday was provided to us by this American MEN2b (RET mutation positive) patient: "Prior to being placed on Vandetanib in August 2016, my Calcitonin levels (total thyroidectomy in 1997 at age 13 due to Medullary Thyroid Cancer) had steadily climbed to 20,000. They had reached their "doubling-time" approximately 1 year prior. After being on Vandetanib for 6 months, my Calcitonin levels dropped to under 2,000, and the 5 tumours of MTC that were in my lungs disappeared. My symptoms associated with high Calcitonin levels also disappeared. In March 2017, I was taken off of the Vandetanib and have been closely monitored since. It is now August 2017, and I have been off Vandetanib for 5 months. My Calcitonin levels have remained steady at under 2,000, and the tumours in my lungs have not reappeared. Although the side effects of the Vandetanib were unpleasant, I will not hesitate to be put back on it the next time the MTC requires it. It is my understanding that prior to these pills, once you hit the doubling-time with the Calcitonin, you, at most, have 10-12 years left to live. If I have to feel absolutely [terrible] for a couple of months every so often to lengthen the time I have left on this earth with my son, husband, family, friends, and all of the beautiful things this world offers to brighten my existence, then I will take it in a heartbeat until it is finally time to throw in the towel and let nature take its course."	full considerations. The potential budget impact of the adoption of a new technology does not determine the appraisal committee's decision, as per section 6.2 of the guide to the methods of technology appraisal. Comments from the patient community were fully considered by the NICE appraisal committee, and have been documented in sections 3.1 and 3.7 of the FAD. In addition, comments received from patients and carers during consultation were presented to the appraisal committee. The slides are included in the committee papers for information. Dose interruptions and reductions were included in estimating the cost of the drugs in the Assessment Group's analysis that informed the committee's decisions. Please note that cabozantinib is now recommended as a treatment option. See FAD section 1.1. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.
4	Patient/professional	Association for Multiple Endocrine Neoplasia Disorders (AMEND)	**Exclusion of Patients from Consideration During the Appraisal** The conclusion not to consider RET mutation status is insupportable when germline RET mutation testing is standard practice. To exclude this group of very rare hereditary cancer patients because somatic testing is not routinely done is unfathomable and further disadvantages these rare cancer patients who have no other treatment options beyond timely surgery. Requesting that somatic RET mutation testing becomes standard practice would leave England in a stronger position in terms of research into the disease and future treatments, especially if those new treatments may ultimately be provided at a lower cost.	Comments noted. The committee considered the patient population with medullary thyroid cancer as a whole. It did not consider it appropriate to separate out patients with RET mutation for separate analysis. Please see section 3.3 of the FAD, where the

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				wording has been amended to clarify that the whole population were included in the appraisal, regardless of RET mutation status.
5	Patient/professional	Association for Multiple Endocrine Neoplasia Disorders (AMEND)	**Inequalities** AMEND believes that it is unacceptable and unethical for the 5th largest economy in the world to not be able to offer these patients some form of therapy, particularly for younger patients, when there are absolutely no other therapeutic options at this time. At least 54% of cancer deaths annually are due to rare or uncommon cancers* with the number of deaths continuing to increase. It is therefore time for NICE to step up and increase the treatment options for these patient communities to level the playing field with the 'big four' cancers. *'Rare and Less Common Cancers: Incidence and Mortality in England, 2010 to 2013', Cancer52 and NCIN at PHE report	Comments noted. Cabozantinib is now recommended as a treatment option. See FAD section 1.1. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.
6	Patient/professional	Association for Multiple Endocrine Neoplasia Disorders (AMEND)	**Missed Opportunity** We believe that NICE are over-looking an opportunity to improve outcomes for patients with medullary thyroid carcinoma. This could be achieved by recommending the continuation of funding subject to accurate recording of these patients' treatments to aid current and future research.	Comments noted. Please note that cabozantinib is now recommended as a treatment option. See FAD section 1.1. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.
7	Patient/professional	Association for Multiple Endocrine Neoplasia Disorders (AMEND)	**Progression Free Survival Issues** It is rare to demonstrate an increase in survival these days because of the ways that the trials are set up - but extra months of progression free survival (PFS) are still important. Due to the wide range of responses to the drugs in this small patient community, average PFS times are greatly skewed. Some patients benefit from years of PFS which in some cases enable patients to continue to work and contribute to society. It is widely and internationally acknowledged by experts treating these patients that these drugs offer PFS in metastatic MTC and it is therefore mystifying why this committee does not recognise this.	Comments noted. Please note that cabozantinib is now recommended as a treatment option. See FAD section 1.1. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.
8	Patient/professional	Association for Multiple Endocrine Neoplasia Disorders (AMEND)	**Direct Patient Responses to the Recommendations** These NICE recommendations have caused great upset in this vulnerable UK patient population which is small but well-connected to one another and also with patients overseas where TKIs may be routinely available. Rare cancer patients (like all cancer patients) strive to keep hope in the future and new treatments that this may bring. Their hopes are being dashed since most would never be able to afford to pay for these drugs on private prescription. This is a sample of their responses: "OMG I feel sick. I am not on TKIs yet but that's the point isn't it. Yet. One day I am going to need them what then?" "Oh no! Although my husband is just starting out on his MTC journey we had the knowledge that these drugs would be available as and when" "Shocking decision given the successful use of TKIs in the US"	Comments noted. Please note that cabozantinib is now recommended as a treatment option. See FAD section 1.1. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.

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			"I am on Vandetanib and it has kept me stable for just over a year (I had weeks to live last June as the MTC was taking over my lungs! It is not resectable!) I have been told my MTC will become aggressive if I stop! Terrified!" "Want to cry just can't believe it. Tony on this bus next stop was one of these drugs...wot now? on a bus to nowhere?"	
9	Patient/professional	Association for Multiple Endocrine Neoplasia Disorders (AMEND)	**Pharmaceutical Company Communication** We are concerned that recommendations show that there is no intention to continue to try to negotiate the drug prices with Ipsen and SanofiGenzyme	Please note that cabozantinib is now recommended as a treatment option. See FAD section 1.1. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.
10	Patient/professional	Association for Multiple Endocrine Neoplasia Disorders (AMEND)	**End of Life Issues** We are appalled that your recommendations are based on, among other things, the fact that terminal patients with metastatic MTC patients effectively live too long and/or take too long to die. Again, we feel that these patients are being discriminated against because they have a rare cancer that behaves differently to more common forms of cancer. MTC should not be judged in these terms. In fact, the aim of many cancer treatments now is to ensure that cancer becomes a disease that people live with rather than die from. There is a possibility of achieving this with MTC when combining new therapies with the natural course of disease progression. However, it should be remembered that the disease is not slow growing in all patients.	Comments noted. Please see sections 3.13 and 3.14 of the FAD for the committee's full considerations with regard to the end of life criteria. Please note that cabozantinib is now recommended as a treatment option. See FAD section 1.1. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.
11	Experts	Dr Kate Newbold Dr Mary Lei	As acknowledged by the committee, patients with advanced medullary thyroid cancer have no treatment options other than cabozantinib and vandetanib, which are currently available through the Cancer Drugs Fund in England. It is not a disease that responds to conventional cytotoxics or external beam radiotherapy. We note that the appraisal committee states that these drugs offer the only systemic treatment options for this very small population of patients with progressing, advanced medullary thyroid cancer in that they delay the progression of the disease and in our experience this in turn delays the onset or worsening of disease related symptoms.	Comments noted. Please see section 3.1 of the FAD.
12	Experts	Dr Kate Newbold Dr Mary Lei	We recognize that the data available from the only two randomized controlled trials (ZETA and EXAM) do not allow interpretation of overall survival benefit and this contributes to the uncertainty and cost effectiveness of the drugs. However we would like to emphasise that we initiate these drugs in a carefully selected small group of patients with objective disease progression and disease related symptoms or imminent symptoms in an already rare disease. Therefore the budget impact for the NHS is comparatively low. In addition, with no other treatment options these patients are not incurring costs to the NHS from alternative or additional lines of treatment as we see in the more common advanced, relapsed cancers.	Comments noted. The committee recognised that medullary thyroid cancer is rare. However, the potential budget impact of the adoption of a new technology does not determine the appraisal committee's decision, as per section 6.2 of the guide to the methods of technology appraisal.

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13	Experts	Dr Kate Newbold Dr Mary Lei	Sanofi-Genzyme put forward a model for an EU restricted license (discussed in section 3.4) by suggesting that only patients with tumour marker (calcitonin and CEA) doubling times of 24 months or less would be eligible to start vandetanib. The assessment group felt that this was not valid as tumour marker doubling times are not used by clinicians to determine when to start either vandetanib or cabozantinib. However, as we discussed at the meeting, although we do use radiological evidence of progressive disease (RECIST criteria) and our patients' symptoms, inevitably the tumour marker doubling time will be less than 24 months in this situation. For example, reviewing my own practice I have initiated vandetanib in 24 patients via the cancer drugs fund; twenty had tumour marker doubling times significantly less than 24 months (averaging just over 6 months) and the remaining four started vandetanib at presentation before a trend of markers could be established due to extent of disease and symptoms. Therefore although this has not been a specific selection criterion for initiation of treatment, the group of patients with tumour marker doubling times of 24 months or less is likely to reflect the population that we treat. We would confirm that these drugs are always reserved for this smaller population of patients.	Comments noted. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.
14	Experts	Dr Kate Newbold Dr Mary Lei	We would like to challenge the assumption in section 3.13 '..that when treatment with vandetanib has stopped working, quality of life would actually be improved by stopping treatment because of its associated toxicities.' This is not our experience unfortunately. We find that patients have significant symptoms from progressing disease and particularly a rising calcitonin level which causes diarrhoea, weight loss and fatigue, once they stop vandetanib. Therefore there remains a cost in managing symptoms in patients once disease progression occurs and disease modifying treatments (vandetanib or cabozantinib) are stopped. It is also worth emphasising that we do not continue to prescribe cabozantinib or vandetanib if treatment induced adverse events are not tolerable or manageable, or if the disease is no longer responding. This limits the population of patients on these drugs and the costs incurred in managing adverse events. In reality we do treat a smaller population of patients than a strict interpretation of the marketing authorisation would indicate, and so overall cost may not be of the magnitude that that the ACD assumes.	Comments noted. Please note that cabozantinib is now recommended as a treatment option. See FAD section 1.1. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date. Treatment discontinuation, dose interruptions and reductions were included in estimating the cost of the drugs in the Assessment Group's analysis that informed the committee's decision.
15	Experts	Dr Kate Newbold Dr Mary Lei	As clinicians managing this rare cancer we have significant concerns for our patients if the decision not to recommend either drug is confirmed. We wonder if there is a case for considering a recommendation for funding with prospective data collection to clarify the remaining uncertainties. This would seem to be in line with the Cancer Drugs Fund recommendation category '… where there is plausible potential for a drug to satisfy the criteria for routine commissioning, but there is significant remaining clinical uncertainty which needs more investigation…..'.	Comments noted. Please note that cabozantinib is now recommended as a treatment option. See FAD section 1.1. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.
16	Company	Ipsen	Ipsen are disappointed that NICE has been unable to recommend the use of cabozantinib in medullary thyroid cancer (MTC). Only two systemic treatments are licensed in this advanced setting, each with a distinct safety profile, meaning that they are suitable for different patients. Should neither of these drugs	Comments noted. Please note that cabozantinib is now recommended as a treatment option. See FAD

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			be approved, the remaining treatment options for patients will be limited in both number and effect.	section 1.1.
17	Company	Ipsen	Whilst we understand the background to this appraisal (that is, to ensure a transition from the Cancer Drugs Fund to routine commissioning), we would reiterate our comments from the original scoping exercise that MTC is an extremely rare cancer and, as such, the data are simply not suited to the rigour of a standard NICE technology appraisal. At the time, it was determined that the therapy area did not meet the criteria for Highly Specialised Technology (HST). Nonetheless, we maintain that these medicines would have been better served by an appraisal under that process wherein the framework accommodates not only the limitations of the evidence base but also the wider aspects of the disease and its impacts.	Comments noted. Please note that cabozantinib is now recommended as a treatment option. See FAD section 1.1.
18	Company	Sanofi	Sanofi Genzyme would like to thank the Appraisal Committee (AC) and the Assessment Group for its consideration of the evidence for vandetanib in the treatment of medullary thyroid cancer (MTC). We are disappointed in the draft recommendation not to make this medicine available on the NHS. This decision would leave new adult patients with unresectable, locally advanced or metastatic disease without an active treatment options for MTC, removing it as a care option after one being available via NHS England for almost 3 years. In responding to the ACD we first highlight key areas where we question the conclusions of the AC, and then we respond to the questions posed as part of the consultation process. • This preliminary decision, if ratified, will leave patients with MTC with no active treatment option, after 3 years of provision by NHS England through the Cancer Drugs Fund and despite the positive benefit/risk profile for an Ultra-Orphan as assessed by regulators • Vandetanib treated patients in the UK are most accurately described as; - Symptomatic - Progressive (radiographic imaging) and have - rapid tumour biomarker doubling (CTN/CEA doubling <24months) We request that the NICE AC fully explores the patient population further with clinicians and patients to ensure a fair assessment of clinical benefit and appropriateness of the decision-problem. • Use of standard NICE methodology, despite the rarity of MTC and the small number of treated patients potentially does not take equity considerations fully into account. Vandetanib is used to treat approximately only [redacted] patients each year with a maximum annual budget spend of less than [redacted]. The Highly Specialised Technology (HST) process, and threshold, would be more appropriate methodology to utilise, particularly if cost-effectiveness analysis must be carried out. • We do not consider that there has been appropriate application of the End of Life (EOL) criteria both in terms of mean vs median survival and; criteria for short life expectancy being 'normally less than 24 months' and believe further consideration is required of applicability of EOL • A decision not to recommend this therapy for NHS patients, leaves patients with MTC with no active treatment option, only the option of best supportive care, which has no known anti-cancer benefit We respectfully request that these key issues are discussed at the next AC meeting on 27th September 2017. These points are pivotal to (1) understanding vandetanib use in UK clinical practice; (2) highlighting why treatments for an ultra-orphan disease like MTC cannot be appropriately appraised using the standard NICE processes and should therefore be subject to HST type assessment and finally	Comments noted. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.

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			(3) raising concerns over statements reflected in the ACD that do not appear to reflect the evidence provided. We discuss each of these key points in detail in the attachments below [titled Supporting Evidence]. As you are aware, Sanofi Genzyme have cooperated fully with the MTA process and the significant resource input this entails, despite our consistently stated concern that this topic and these medicines should not be assessed through the Multiple Technology Appraisal process. Given the small number of patients and the manageable and predictable budget, we believe that this process did not represent the most effective use of either NICE, public or indeed our company resources. This draft decision to not recommend an option of care for these rare patients may not reflect the principles that NICE follows in terms of fair (rather than equal) resource allocation which would have applied if the process had been adjusted, as for HST or EOL medicines As a company, we believe it is critical that an active treatment option remains available for this very small population of patients, for whom no other active alternative remains. As such, we are committed to continuing to collaborate with the NICE process and also to working with NHS-England, as the existing providers of this therapy via the Cancer Drugs Fund, to ensure continuity of access to these medicines.	
19	Company	Sanofi	**Understanding vandetanib use in UK clinical practice: The true UK vandetanib-treated population is highly likely to be reflected by the 'Restricted' EU Label population.** Sanofi Genzyme accept that in the UK, and wider clinical practice, biomarker doubling is a prognostic tool and not an explicit criteria used to determine whether treatment should be initiated. However, it is Sanofi Genzyme's view that the Restricted EU label population (symptomatic, aggressive defined as radiographic progression and tumour biomarker [calcitonin (CTN) and carcinoembryonic antigen (CEA) doublings <24months] more closely describes the UK patients routinely treated with vandetanib, rather than the EU label population (symptomatic and aggressive defined as radiographic progression only). At initiation of treatment with vandetanib within its label, most patients will have CTN/CEA doubling <24months. This approach is in line with the intention of clinical practice in the UK selecting patients, within the licensed population, with most urgent need for treatment. The more we understand UK clinical practice, the more clear it becomes that it is very likely most, if not all, patients currently treated have biomarker doubling of <24 months when vandetanib treatment is initiated. Therefore, Sanofi Genzyme believe that the current vandetanib treated population ([redacted]) are highly likely to reflect the 'Restricted' EU label population we presented as our base case. This view can be explored with clinical experts, or retrospective review of NHS existing SACT database rather than formal data-collection. At present CTN/CEA doubling times may not be systematically collected nor documented as part of the data informing the overall decision to treat, but it is a recognised indicator of when disease has changed from indolent to rapid progression and where prognosis has deteriorated. Further, we suggest it would not be difficult to collect these data retrospectively via a case note review or to prospectively collect biomarker data, possibly using the NCRAS system, for patients that clinicians are looking to start on vandetanib. The restricted EU cohort, submitted as our primary case for clinical and cost-effectiveness, demonstrated the greatest clinical benefit in the ZETA trial and highest possibility of being acceptable value to the NHS according to NICE thresholds. The decision to present this subset of the label population as our primary case was based on clinical trends seen in the ZETA ITT population, the European regulators position regarding vandetanib patient selection, published information on impact of rapid tumour biomarker doubling [1,2] and UK clinical practice.	Comments noted. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.

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			• **CTN/CEA doubling in ZETA ITT population** The biomarker inclusion criteria for the ZETA study was CTN ≥500 pg/mL (conventional units) or ≥146.3 pmol/L (international standard units), this is in the low (less severe) range. This is in line with the ZETA trial's broad inclusion criteria and the resulting intention-to-treat patient population that included patients with both indolent and aggressive disease. It was also a secondary endpoint of ZETA, collected to demonstrate an improvement in biochemical response with vandetanib as compared to placebo, as measured by calcitonin (CTN) and carcinoembryonic antigen (CEA).The results in the ITT population demonstrated statistically significant difference between vandetanib and placebo arm for both CTN and CEA response: [redacted] The efficacy of vandetanib at time of progression (ie time to PFS measure) was more marked in comparison with placebo in patients with CTN doubling time ≤ 24 months and CEA doubling time ≤24 months (statistically significant difference versus placebo in these subgroups). The percentage of patients with objective response rates (ORR) was higher in patients with CEA doubling time ≤24 months at baseline compared with CEA doubling time >24 months: [redacted] versus [redacted] respectively. The percentage of patients with ORR was higher in patients with CTN doubling time ≤24 months at baseline compared with CTN doubling time >24 months: [redacted] vs. [redacted] respectively. CEA and CTN doubling times and tumor size have been linked to the rate of objective progression in MTC. For the final OS analysis ([redacted]) [3], the presence of quantitative interactions was assessed by means of an overall global interaction test in a Cox PH model. This was performed for a small, pre-specified group of covariates (including CTN doubling time, CEA doubling time) where there was more biological plausibility that the treatment effect could vary. The most notable treatment-by-covariate interaction in the biomarkers forest plot was for CEA doubling time - CEA doubling time ≤24 months ([redacted]): Within this subgroup, patients randomised to vandetanib strongly benefitted from receiving the treatment from randomisation. The ad hoc Kaplan-Meier curves of final OS by treatment arm and CEA doubling time were separated from the beginning of the study and never crossed (Figure 1 [*provided but not reproduced here*]). - CEA doubling time >24 months ([redacted]): Within this subgroup, a longer survival time was observed in favour of the placebo treatment arm (it should be noted that [redacted] of patients in the placebo arm switched to open-label vandetanib after either disease progression or the primary analysis (ITT population). The Kaplan-Meier curves of final OS by treatment arm and CEA doubling time overlapped during the first 12 to 18 months of the study, and then separated in favour of the placebo arm (Figure 1 [*provided but not reproduced here*]). - This treatment-by-subgroup interaction for CEA doubling time corresponds to the observation of a greater differential benefit in terms of PFS for patients with a CEA doubling time of ≤24 months at baseline, although the HR for the complementary subgroup (CEA doubling time >24 months) did not suggest a lack of benefit.	

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			• **Revised economic analyses post ACD on the Restricted EU label** Post ACD, we have done additional analyses to estimate the 'true' overall survival treatment difference between vandetanib and placebo, as if the placebo patients had not received any vandetanib. The results from the analyses were used to generate additional economic analysis comparing vandetanib to BSC using the same survival partition model that was used for the original submission, but patients on BSC do not crossover to vandetanib at progression. The cost-effectiveness of vandetanib remained consistent and aligned with the data presented in the original submission – these are presented in appendix 1 [*provided but not reproduced here*] • **EMA position, UK clinician position regarding vandetanib use in practice** The European regulators acknowledged the benefit of vandetanib in this subset of patients in the overall ITT population of ZETA study. The EPAR reports the benefit associated with patients with the more rapid doubling biomarkers, noting that CTN doubling time ≤ 24 months and CEA doubling time ≤24 months are known to be markers of poor prognosis and more aggressive disease [5]. This view was supported by clinician feedback at the AC meeting who noted that in the UK clinicians, 'hold off and hold off and hold off' treating patients. Similarly the experts consulted for the AG report state patients with "symptomatic and progressive disease would also likely have CEA/CTN doubling times ≤24 months" (Assessment Group Report, Page 84). • **The 'restricted EU label population' versus 'UK-relevant population' - concerns from the discussion at the first Appraisal committee meeting** Sanofi Genzyme feels the issue of different populations was not well understood in the committee meeting. In hindsight, Sanofi Genzyme's naming of the primary case as 'restricted' group has added to the confusion, and might have been better referred to as 'UK-relevant' population because it was intended to reflect UK practice more clearly. Thus the 'restricted' population in our submission is the same as the UK treated population. It is our view, supported by clinical experts, that it is highly likely that all patients treated with vandetanib will meet criteria for symptoms, progression and rapid tumour biomarker doubling <24month on initiation. This lack of understanding and possible confusion due to the naming of the primary base case, led to the Chair omitting crucial questions to the clinical experts present that would have given more clarity on populations. As such we propose a number of questions that we would like to be asked of the expert clinicians that would address this. In the committee meeting the expert clinicians were asked: 'Do you treat patients who meet the EU label criteria?' The clinicians answered yes. They were asked, 'is biomarker doubling a criteria for prescribing?' The clinician's response was along the lines of: while prescribing decisions are driven by progression as measured by RECIST though imaging and symptom burden, biomarker results may trigger the clinician to request the imaging. The AC have interpreted this as 'No', Sanofi Genzyme interpret this as, 'it is relevant as part of the breadth of parameters clinicians consider when making treatment decisions'. The Chair asked, 'would you treat a patient who was progressed and symptomatic but did not have biomarker doubling?' The clinicians replied 'yes'. The question that was omitted by the Chair is, How often does this happen?/What proportion of patients you have treated are progressed, symptomatic but have doubling >24mo? It should be noted that in this discussion a committee member stated, 'most patients we see have doubling of less than 6 months or less than 12 months'. The expert clinicians concurred.	

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			On this basis Sanofi Genzyme request that the AC specifically ask its clinical experts some key question to explore and understand the different perspectives of treatment. - How many of your patients (%) initiated on vandetanib were symptomatic with progression with biomarker doubling data recorded? - How many of those patients were symptomatic and progressed with biomarker doubling < 24 months? - How many of those patients were symptomatic and progressed with biomarker doubling > 24 months? - Should any of those patients (with biomarker doubling > 24 months) be excluded because they were part of the ZETA trial that had a broad inclusion criteria that included 'indolent' patients? - Is biomarker (i.e. CTN/CEA) information routinely collected in your medical notes? - Is it likely that doubling time data (i.e. < 24months vs > 24 months) will be available to you as part of your routine clinical practice at time you are considering vandetanib initiation? - Is there any clinical reason why biomarker doubling would not apply to cabozantinib within its licensed patient population? Sanofi Genzyme's view is that a discussion around the above questions will highlight that a positive recommendation for this cohort of patients with more aggressive disease will not change clinical practice nor significantly limit the patient population eligible for treatment. Instead, as our base case intended, it more accurately describes existing UK patients treated with vandetanib. Almost 14 years since the ZETA trial was started, the definition of aggressive disease remains open to interpretation and down to individual clinical opinion. It is therefore entirely plausible that patients treated with vandetanib in UK clinical practice have all three criteria present at initiation of systemic treatment. In summary, the restricted EU label population was rejected by the Committee on the basis that the decision to start treatment in clinical practice is based on radiological progression, regardless of the fact the most if not all UK patients are likely to fall within this, rather than the EU, population.	
20	Company	Sanofi	**Ultra-orphan disease such as MTC cannot be appropriated appraised using NICE existing processes** NICE has established and formalised processes for assessment. However, we are concerned that the rigid application of these processes in this assessment is inequitable as it does not reflect the reality of the financial burden on the NHS to pay for these treatments (which is relatively low and predictable) nor the importance of these treatments in a population of fewer than 40 patients per year, take account of 'distributive justice' the concept that 'fair' allocation of resources is not the same as 'equal' allocation of resources. As reported in the paper by Rawlins et al, 'NICE favours an approach based on maximizing benefits per unit cost, but recognizes that this can conflict with the considered moral convictions of many people (including the members o its advisory bodies) Consequently NICE uses a flexible approach that treats decisions on a case-by-case basis'. Sanofi Genzyme requests that the AC uses its decision-making latitude to ensure these [redacted] patients each year have access to an active treatment for their terminal cancer. . • **Use of a standard methodology despite the rarity of the condition under consideration. Vandetanib eligible population is around [redacted] patients/year and estimated annual budget impact of [redacted]** MTC is an ultra-orphan disease with only around 170 patients diagnosed in England each year. For	Comments noted. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.

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			many of these patients surgery is curative meaning only around 30-40 patients per year require systemic therapy. NICE has applied its standard process to this MTA. The reason for this is provided at paragraph 3.21 of the ACD, where the Appraisal Committee states that it "noted the advice from NICE's Social Value Judgements: Principles for the Development of NICE Guidance that NICE should evaluate drugs to treat rare conditions in the same way as any other treatment". The relevant advice, taken from section 4.4 of the second edition of NICE's Social Value Judgements, states: NICE considers that it should evaluate drugs to treat rare conditions, known as 'orphan drugs', in the same way as any other treatment (see Glossary). NICE does not expect to receive referrals from the Secretary of State for Health to evaluate 'ultra-orphan drugs' (drugs used to treat very rare diseases or conditions). This is because the Department of Health currently has other mechanisms to assess the availability of ultra-orphan drugs in the NHS. "Orphan drugs" are defined in NICE's Social Value Judgements as "Drugs indicated for rare conditions or diseases (those that occur in fewer than 1 in 2000 of the population)". "Ultra-orphan drug" is stated to be "A term used by NICE to describe interventions for very rare conditions or diseases that occur in fewer than 1 in 50,000 of the population; it also covers interventions for which there are no other known or possible uses." MTC is an ultra-orphan disease and vandetanib is an ultra-orphan drug according to the definitions used by NICE's Social Value Judgements (SVJ). At the time NICE's Social Value Judgements were formulated, NICE did not expect to appraise ultra-orphan drugs and the advice relied upon by the Appraisal Committee at paragraph 3.21 of the ACD related to orphan drugs but not to ultra-orphans. Therefore the Appraisal Committee should perhaps reconsider its interpretation of NICE's Social Value Judgements as requiring a standard methodology and approach to the appraisal of vandetanib. • **Highly Specialised Treatment** When NICE commenced evaluations of ultra-orphan technologies in 2013, a new procedure was introduced which recognised the fact that the usual methodology could not fairly be applied to these treatments for very rare diseases. NICE's Interim Process and Methods of the Highly Specialised Technologies Programme updated to reflect 2017 changes (the HST Process Guide) states at paragraph 39: "Given the very small numbers of patients living with these very rare conditions a simple utilitarian approach, in which the greatest gain for the greatest number is valued highly, is unlikely to produce guidance which would recognise the particular circumstances of these very rare conditions. These circumstances include the vulnerability of very small patient groups with limited treatment options, the nature and extent of the evidence, and the challenge for companies in making a reasonable return on their research and development investment because of the very small populations treated. Nevertheless, as part of its consideration of the value for money of the technology, the committee must give consideration to the balance between the costs and the benefits". When the HST methodology was introduced, Sir Andrew Dillon explained: "The HST guidance recognises the particular circumstances of these very rare conditions - the vulnerability of very small patient groups with limited treatment options, the nature and extent of the evidence, and the challenge for manufacturers in making a reasonable return on their investment because of the very small populations treated.	

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			In evaluating these drugs, NICE takes into account a greater range of criteria about the benefits and costs of highly specialised technologies than is the case with its appraisals of mainstream drugs and treatments. We do this because applying our standard approach to treatments for very small groups of patients would result in us always recommending against their use. This would be unfair." [italics added] Vandetanib however, is not eligible for assessment under the HST process because it is not expected to have 'life-long use' nor is MTC regarded as a chronic condition (paragraph 28 of the HST Process Guide). However, the circumstance Andrew Dillion describes above exactly applies to this MTA: applying standard methods to this ultra-orphan oncology indication will "result in [NICE] always recommending against their use". We agree this would be unfair. Given the above, the AC should consider the alternative NICE processes it has at its disposal for evaluating novel technologies. Specifically, Sanofi Genzyme believes the new £100,000 HST threshold is the most appropriate of the three available thresholds to apply to this assessment. • **Application of End-of-Life criteria** In addition to the above we cannot agree with the conclusion the committee reached regarding the EOL criteria. The Committee concluded that the end of life criteria do not apply to vandetanib (or cabozantinib) as the life expectancy for patients eligible for treatment but who instead received BSC exceeds the 24 month threshold (which the Committee deems to be a condition to application of the criteria). However, it is worth noting that the actual wording of the criteria (para. 6.2.10 of NICE Guide to Methods of Technology Appraisals) suggests some flexibility in the criteria which is not reflected in the ACD (i.e. "…normally less than 24 months"). Further, although the Committee recognised the median OS in the BSC group in EXAM was less than 24 months, they concluded that the mean estimate was more appropriate for determining applicability of the criteria. Sanofi Genzyme believes patients within the restricted EU population are more likely to have a life expectancy around 24months, with standard of care treatment (in this case BSC). Sanofi Genzyme requests that the AC asks clinicians what average survival they would expect from a patient fitting the restricted population criteria. Indeed, according to NICE process guide detailing criteria for EOL there is no mention that the short life expectancy criteria needs to be described by mean survival [6] and in reality, NICE appraisal committees have accepted median overall survival with respect to EOL criteria [7] in other appraisals (table 2 [*provided but not reproduced here*]). Following the AC meeting and the ACD, SGZ has revised its modelling method for dealing with confounding in the OS analysis caused by crossover and come up with plausible OS estimates for both vandetanib and the 'true' placebo arm, as such we are confident that the discounted mean life years gained predicted by the economic model is 1.6 years. This conclusion remains consistent irrespective of the choice of parametric model used to represent overall survival. The RPSFT model suggests that the median survival in the placebo group of the restricted EU label population is 1.6 years. Therefore, it should be noted that when the OS data for the ZETA subgroup (i.e. restricted EU label population) is adjusted for the open-label vandetanib use, the true survival duration in this population is less than 24 months. The criterion relating to >3 months life extension is likely for vandetanib within the Restricted EU label population (symptomatic and progressive MTC with CEA/CTN doubling time ≤24 months). SGZ accepts there is a degree of uncertainty regarding the precise ICER estimate for vandetanib compared with BSC, however consistent results from the economic model, regardless of whether the	

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			observed (crossed over) trial data were used, whether the uncrossed RPSFT data were used or whether data based on the regression model were used, give a large degree of certainty that the ICER for vandetanib versus BSC is well below the HST £100,000 QALY threshold.	
21	Company	Sanofi	**Concerns over statements reflected in the ACD, despite the evidence provided** At various points in the ACD, it would appear the AC have questioned vandetanib clinical benefit, failed to acknowledge the clinical uncertainty between the label population and the UK treated population and concluded that extension to overall survival is not robust without any recognition of the ZETA trial design. "Clinical trial evidence suggests that cabozantinib and vandetanib are effective in delaying disease progression but may not prolong survival" Vandetanib clinical benefit is clear. According to the European regulators, the superiority of vandetanib over placebo is clinically significant and quite consistent across all pre planned subgroups. The results observed on PFS were supported by results on some secondary endpoints such as ORR ([redacted] for the primary analysis). No statistically significant positive effect of vandetanib over placebo has been demonstrated on OS: HR of [redacted]). But given the level of cross over in this trial ([redacted] on placebo arm crossed to vandetanib), even more mature data did not establish a long term survival benefit, an anticipated outcome for this trial. Because of the proposed cross-over at progression, the OS comparison in fact compares populations that differ mainly by the fact that vandetanib has been proposed early (experimental group) or later on, at progression (placebo arm). In view of the associated risks, the regulators considered that it was important to limit treatment with vandetanib to patients who are in real need for treatment. This can be established based on clinical and biological criteria. From a clinical point of view, this corresponds to patients that can be identified as having a symptomatic-aggressive course of the disease. Either symptomatic disease or progressive disease alone is not enough to prompt the need for treatment with vandetanib. Rate of change in biomarker levels such as of calcitonin and/or CEA as well as the rate of change of tumour volume during watchful waiting might help to identify not only patients in need for treatment but also the optimal moment to commence the treatment. Similarly, imaging data alone is not expected to be useful in identifying patients in need for treatment. "Adverse events are common with both drugs and the decision to use them is based on careful consideration of the risks and benefits" and "The committee acknowledged that although both drugs may work well for some people, for many others there will be a substantial side-effect burden." Sanofi challenges this statement. The incidence of AEs observed in clinical trials, a period during which there's little experience with the tested drugs, would not correspond to the observation in current clinical practice. The post-marketing experience allowed a significant learning towards AEs management (prevention as well as treatment) [8-10]. Since its approval in 2012, clinical experience and information collected on safety demonstrates a good benefit/safety profile on vandetanib. Clinical experts at the AC meeting also confirmed that there are well established protocols for managing AEs related to TKI's in clinical practice. "…neither cabozantinib nor vandetanib can be recommended as a cost-effective use of NHS resources." As noted above, there is a degree of uncertainty regarding the precise ICER estimate for vandetanib compared with BSC. However consistent results from the economic model, regardless of whether the observed (crossed over) trial data were used, whether the uncrossed RPSFT data were used or whether data based on the regression model were used, give a large degree of certainty that the ICER	Comments noted. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.

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			for vandetanib versus BSC is well below the HST £100,000 QALY threshold. This threshold that is more appropriate and fair in assessing therapies for disease areas with such small patients numbers than a standard NICE reference case which has been applied in this case by 'default' or process of elimination of NICE's various value judgements - it as assumed that as vandetanib did not technically meet NICE criteria for HST or EOL, by default the standard reference case an acceptable threshold of £30,000/QALY was applied without discretion in this appraisal. The above statement is therefore should be revised in light of the evidence provided in our submission and in this response.	
22	Company	Sanofi	**Has all of the relevant evidence been taken into account?** The question of whether relevant evidence has been taken into account, assumes that relevant evidence is available. In fact there is limited evidence in this disease area and notable clinical uncertainty. There are no UK/NICE guidelines for treatment of MTC, no clear guidance on identifying and treating patients in practice, despite the drug being funded on CDF since 2014. As highlighted above we believe the right questions were not posed to the clinical experts or patient representatives in the AC meeting. Vandetanib's clinical safety and efficacy has been recognised by the EMA by way of granting it a licence and formal EMA orphan status. The consideration of this as an ultra-orphan disease has not been given adequate consideration in the AC decision making process. There is a lack of guidance from NICE's Decision Support Unit on how adjustments should be made in trials with small patient numbers and where cross-over occurs early on in the trial, at different points in the trial (i.e. before as well as after documented progression) and there is high level of cross over ([redacted] on placebo arm). In UK clinical practice, patients are treated based on urgent need of treatment; very much in line with the intention of the EMA label indication. However the definition of the aggressive patient profile at this point in the treatment pathway is unclear and subject to individual clinical judgement.	Comments noted. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.
23	Company	Sanofi	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** For reasons outlined above, the summaries of the evidence are not reasonable interpretations of the available evidence on vandetanib or systemic treatment of MTC.	Comments noted. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.
24	Company	Sanofi	**Are the recommendations sound and a suitable basis for guidance to the NHS?** The draft recommendations are not suitable for the NHS and final negative decision will mean that treatment which has been available for approximately three years on the NHS, now no longer is an option. Best supportive care, which has no anti-tumour benefit, would be the only option despite the availability of licenced treatment with proven safety and anti-cancer benefit. The financial burden of these products is low for an organisation of the size of the NHS. At the AC meeting it was noted that total spend per year was [redacted] assuming no dose adjustments or treatment discontinuation. Given trial discontinuation rates are [redacted] and dose reductions are [redacted], the true cost to the NHS is likely to be closer to [redacted]. The quote above was based on the price at which vandetanib, and we presume cabozantinib, were sold while on the CDF. Sanofi Genzyme has reduced the price at which we are offering it to the NHS, therefore the cost will be lower than [redacted] per year. The AC draft recommendation is not evidence-based and therefore not suitable for adoption within the NHS.	Comments noted. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.

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25	Company	Sanofi	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** The recommendations would not be unlawful according to the groups listed above.	Comments noted. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.
26	Company	Sanofi	**Conclusion** We urge the AC to recognise the inequities that arise from withdrawing effective treatment options in a very small, stable adult patient population. As it has been available for the last 3 years, vandetanib should continue to be an option for treatment of advanced/metastatic disease in patients whose disease has become aggressive and symptomatic and in whom systemic treatment benefits outweigh risk of side-effects. *[References provided but not reproduced here]*	Comments noted. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.

Summary of comments received from members of the public

Theme	NICE Response
There are no other effective treatments available	Comments noted. The committee recognised the limited treatment options for patients with medullary thyroid cancer. Please note that cabozantinib is now recommended as a treatment option. See FAD section 1.1. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.
TKIs can prolong survival and improve quality of life, and the side effects are tolerable because of this	Comments noted. The committee took into account the patient representative's perspective on the side effects of treatment (please see section 3.7 of the FAD). However, the committee considered that the data presented did not show evidence of prolonged survival. Please see section 3.4 of the FAD for the committee's full considerations regarding the clinical effectiveness of cabozantinib. Please note that cabozantinib is now recommended as a treatment option. See FAD section 1.1. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.
Not meeting the end of life criteria by 'living too long' is unacceptable	Comments noted. Please see sections 3.13 and 3.14 of the FAD for the committee's full considerations with regard to the end of life criteria. Please note that cabozantinib is now recommended as a treatment option. See FAD section 1.1. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.
Overall survival benefit is difficult to show with trial data because crossover is common	Comments noted. There are always likely to be deficiencies in the evidence base available for health technology assessment. Despite such weaknesses in the evidence base, decisions still have to be made about the use of technologies. NICE has to take into account its Social Value Judgements, which state that 'those developing clinical guidelines, technology appraisals or public health guidance must take into account the relative costs and benefits of interventions (their 'cost effectiveness') when deciding whether or not to recommend them.' Please note that cabozantinib is now recommended as a treatment option. See FAD section 1.1. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with

	the committee's recommendations on vandetanib will be released at a later date.
MTC is a very rare condition; overall cost is low because so few patients need these drugs	Comments noted. The committee acknowledged the rarity of the disease; please see sections 3.1 and 3.12 of the FAD for the committee's considerations. The potential budget impact of the adoption of a new technology does not determine the appraisal committee's decision, as per section 6.2 of the guide to the methods of technology appraisal. Please note that cabozantinib is now recommended as a treatment option. See FAD section 1.1. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.
Using the drugs helps future research; not recommending the drugs limits future potential development in this therapy area. Consider interim funding to enable further data to be collected	Comments noted. Please note that cabozantinib is now recommended as a treatment option. See FAD section 1.1. NICE is not currently in a position to release any recommendations on vandetanib. A separate document with the committee's recommendations on vandetanib will be released at a later date.

The following consultees/commentators indicated that they had no comments on the appraisal consultation document:

Department of Health

14th Sept 2017

Dear Kate,

Re: ID56 - Multiple Technology Appraisal: cabozantinib and vandetanib for treating medullary thyroid cancer

Sanofi Genzyme would like to thank the Appraisal Committee (AC) and the Assessment Group for its consideration of the evidence for vandetanib in the treatment of medullary thyroid cancer (MTC). We are disappointed in the draft recommendation not to make this medicine available on the NHS. This decision would leave new adult patients with unresectable, locally advanced or metastatic disease without an active treatment options for MTC, removing it as a care option after one being available via NHS England for almost 3 years.

In responding to the ACD we first highlight key areas where we question the conclusions of the AC, and then we respond to the questions posed as part of the consultation process.

- **This preliminary decision, if ratified, will leave patients with MTC with no active treatment option, after 3 years of provision by NHS England through the Cancer Drugs Fund and despite the positive benefit/risk profile for an Ultra-Orphan as assessed by regulators**
- **Vandetanib treated patients in the UK are most accurately described as;**
    - **Symptomatic**
    - **Progressive (radiographic imaging) and have**
    - **rapid tumour biomarker doubling (CTN/CEA doubling ≤24months)**

  We request that the NICE AC fully explores the patient population further with clinicians and patients to ensure a fair assessment of clinical benefit and appropriateness of the decision-problem.

- **Use of standard NICE methodology, despite the rarity of MTC and the small number of treated patients potentially does not take equity considerations fully into account. Vandetanib is used to treat approximately only [redacted] patients each year with a maximum annual budget spend of less than [redacted]. The Highly Specialised Technology (HST) process, and threshold, would be more appropriate methodology to utilise, particularly if cost-effectiveness analysis must be carried out.**
- **We do not consider that there has been appropriate application of the End of Life (EOL) criteria both in terms of mean vs median survival and; criteria for short life**

expectancy being 'normally less than 24 months' and believe further consideration is required of applicability of EOL

- **A decision not to recommend this therapy for NHS patients, leaves patients with MTC with no active treatment option, only the option of best supportive care, which has no known anti-cancer benefit**

We respectfully request that these key issues are discussed at the next AC meeting on 27th September 2017. These points are pivotal to (1) understanding vandetanib use in UK clinical practice; (2) highlighting why treatments for an ultra-orphan disease like MTC cannot be appropriately appraised using the standard NICE processes and should therefore be subject to HST type assessment and finally (3) raising concerns over statements reflected in the ACD that do not appear to reflect the evidence provided. We discuss each of these key points in detail in the attachments below [titled Supporting Evidence].

As you are aware, Sanofi Genzyme have cooperated fully with the MTA process and the significant resource input this entails, despite our consistently stated concern that this topic and these medicines should not be assessed through the Multiple Technology Appraisal process. Given the small number of patients and the manageable and predictable budget, we believe that this process did not represent the most effective use of either NICE, public or indeed our company resources. This draft decision to not recommend an option of care for these rare patients may not reflect the principles that NICE follows in terms of fair (rather than equal) resource allocation which would have applied if the process had been adjusted, as for HST or EOL medicines

As a company, we believe it is critical that an active treatment option remains available for this very small population of patients, for whom no other active alternative remains. As such, we are committed to continuing to collaborate with the NICE process and also to working with NHS-England, as the existing providers of this therapy via the Cancer Drugs Fund, to ensure continuity of access to these medicines.

Thank you in advance for supporting the NICE Appraisal Committee in their consideration of the value of vandetanib for patients with MTC.

Kind regards

Claire Grant

Head of UK Health Outcomes

Sanofi Genzyme

Supporting evidence

1. **Understanding vandetanib use in UK clinical practice: The true UK vandetanib-treated population is highly likely to be reflected by the 'Restricted' EU Label population.**

Sanofi Genzyme accept that in the UK, and wider clinical practice, biomarker doubling is a prognostic tool and not an explicit criteria used to determine whether treatment should be initiated. However, it is Sanofi Genzyme's view that the Restricted EU label population (symptomatic, aggressive defined as radiographic progression and tumour biomarker [calcitonin (CTN) and carcinoembryonic antigen (CEA) doublings ≤24months] more closely *describes* the UK patients routinely treated with vandetanib, rather than the EU label population (symptomatic and aggressive defined as radiographic progression only). At initiation of treatment with vandetanib within its label, most patients will have CTN/CEA doubling ≤24months.

This approach is in line with the intention of clinical practice in the UK selecting patients, within the licensed population, with most urgent need for treatment. The more we understand UK clinical practice, the more clear it becomes that it is very likely most, if not all, patients currently treated have biomarker doubling of ≤24 months when vandetanib treatment is initiated. Therefore, Sanofi Genzyme believe that the current vandetanib treated population ([redacted]) are highly likely to reflect the 'Restricted' EU label population we presented as our base case. This view can be explored with clinical experts, or retrospective review of NHS existing SACT database rather than formal data-collection.

At present CTN/CEA doubling times may not be systematically collected nor documented as part of the data informing the overall decision to treat, but it is a recognised indicator of when disease has changed from indolent to rapid progression and where prognosis has deteriorated. Further, we suggest it would not be difficult to collect these data retrospectively via a case note review or to prospectively collect biomarker data, possibly using the NCRAS system, for patients that clinicians are looking to start on vandetanib.

The restricted EU cohort, submitted as our primary case for clinical and cost-effectiveness, demonstrated the greatest clinical benefit in the ZETA trial and highest possibility of being acceptable value to the NHS according to NICE thresholds. The decision to present this subset of the label population as our primary case was based on clinical trends seen in the ZETA ITT population, the European regulators position regarding vandetanib patient selection, published information on impact of rapid tumour biomarker doubling [1,2] and UK clinical practice.

➢ ***CTN/CEA doubling in ZETA ITT population***

The biomarker inclusion criteria for the ZETA study was CTN ≥500 pg/mL (conventional units) or ≥146.3 pmol/L (international standard units), this is in the low (less severe) range. This is in line with the ZETA trial's broad inclusion criteria and the resulting intention-to-treat patient population that included patients with both indolent and aggressive disease. It was also a secondary endpoint of ZETA, collected to demonstrate an improvement in biochemical response with vandetanib as compared to placebo, as measured by calcitonin (CTN) and carcinoembryonic antigen (CEA).The results in the ITT population demonstrated statistically significant difference between vandetanib and placebo arm for both CTN and CEA response:

- [redacted]

The efficacy of vandetanib at time of progression (ie time to PFS measure) was more marked in comparison with placebo in patients with CTN doubling time ≤ 24 months and CEA doubling time ≤24 months (statistically significant difference versus placebo in these subgroups).

The percentage of patients with objective response rates (ORR) was higher in patients with CEA doubling time ≤24 months at baseline compared with CEA doubling time >24 months: [redacted] % versus [redacted] % respectively. The percentage of patients with ORR was higher in patients with CTN doubling time ≤24 months at baseline compared with CTN doubling time >24 months: [redacted] respectively. CEA and CTN doubling times and tumor size have been linked to the rate of objective progression in MTC.

For the final OS analysis ([redacted]) [3], the presence of quantitative interactions was assessed by means of an overall global interaction test in a Cox PH model. This was performed for a small, pre-specified group of covariates (including CTN doubling time, CEA doubling time) where there was more biological plausibility that the treatment effect could vary.

The most notable treatment-by-covariate interaction in the biomarkers forest plot was for CEA doubling time

- CEA doubling time ≤24 months ([redacted]): Within this subgroup, patients randomised to vandetanib strongly benefitted from receiving the treatment from randomisation. The ad hoc Kaplan-Meier curves of final OS by treatment arm and CEA doubling time were separated from the beginning of the study and never crossed (
- Figure 1).

- CEA doubling time >24 months ([redacted]): Within this subgroup, a longer survival time was observed in favour of the placebo treatment arm (it should be noted that [redacted] of patients in the placebo arm switched to open-label vandetanib after either disease progression or the primary analysis (ITT population). The Kaplan-Meier curves of final OS by treatment arm and CEA doubling time overlapped during the first 12 to 18 months of the study, and then separated in favour of the placebo arm (
- Figure 1).
- This treatment-by-subgroup interaction for CEA doubling time corresponds to the observation of a greater differential benefit in terms of PFS for patients with a CEA doubling time of ≤24 months at baseline, although the HR for the complementary subgroup (CEA doubling time >24 months) did not suggest a lack of benefit.

Figure 1 ***Kaplan-Meier plot of OS by treatment and CEA doubling time (Full analysis set)***

- ***Revised economic analyses post ACD on the Restricted EU label***

Post ACD, we have done additional analyses to estimate the 'true' overall survival treatment difference between vandetanib and placebo, as if the placebo patients had not received any vandetanib. The results from the analyses were used to generate additional economic analysis comparing vandetanib to BSC using the same survival partition model that was used for the original submission, but patients on BSC do not crossover to vandetanib at progression. The cost-effectiveness of vandetanib remained consistent and aligned with the data presented in the original submission – these are presented in appendix 1

- ***EMA position, UK clinician position regarding vandetanib use in practice***

The European regulators acknowledged the benefit of vandetanib in this subset of patients in the overall ITT population of ZETA study. The EPAR reports the benefit associated with patients with the more rapid doubling biomarkers, noting that CTN doubling time ≤ 24 months and CEA doubling time ≤24 months are known to be markers of poor prognosis and more aggressive disease [5].

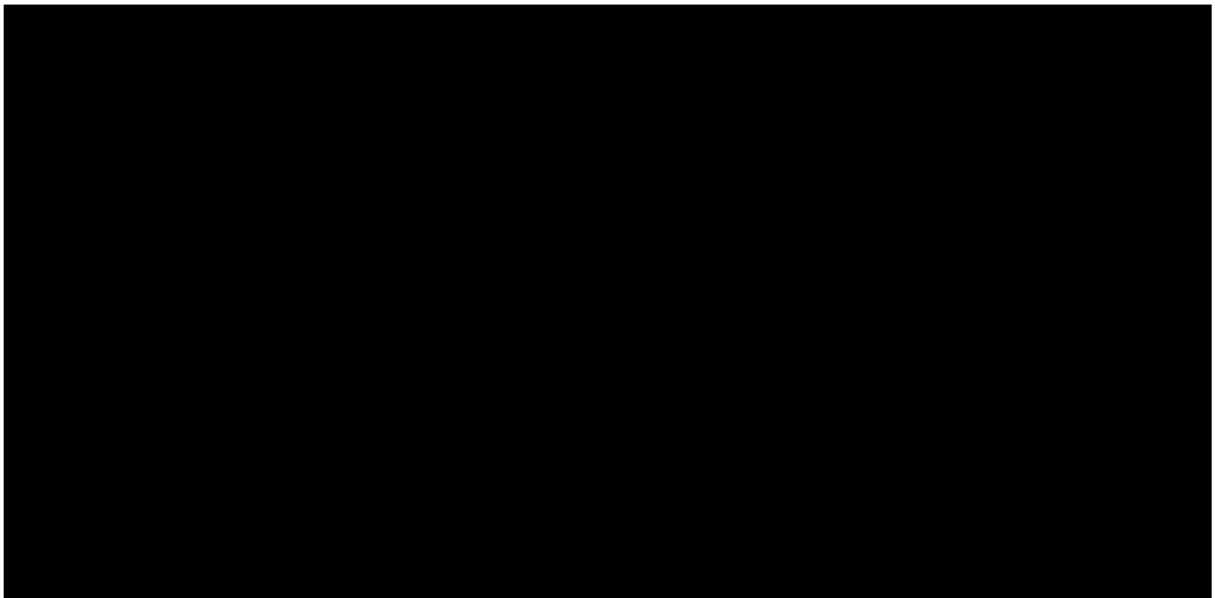
This view was supported by clinician feedback at the AC meeting who noted that in the UK clinicians, 'hold off and hold off and hold off' treating patients. Similarly the experts consulted for the AG report state patients with "symptomatic and progressive disease would also likely have CEA/CTN doubling times ≤24 months" (Assessment Group Report, Page 84).

- ***The 'restricted EU label population' versus 'UK-relevant population' - concerns from the discussion at the first Appraisal committee meeting***

Sanofi Genzyme feels the issue of different populations was not well understood in the committee meeting. In hindsight, Sanofi Genzyme's naming of the primary case as 'restricted' group has added to the confusion, and might have been better referred to as 'UK-relevant' population because it was intended to reflect UK practice more clearly.

Thus the 'restricted' population in our submission is the same as the UK treated population. It is our view, supported by clinical experts, that it is highly likely that all patients treated with vandetanib will meet criteria for symptoms, progression and rapid tumour biomarker doubling ≤24month on initiation.

Figure 2 Vandetanib clinical trial population from ZETA



This lack of understanding and possible confusion due to the naming of the primary base case, led to the Chair omitting crucial questions to the clinical experts present that would have given more clarity on populations. As such we propose a number of questions that we would like to be asked of the expert clinicians that would address this.

In the committee meeting the expert clinicians were asked:

'Do you treat patients who meet the EU label criteria?' The clinicians answered yes. They were asked, 'is biomarker doubling a criteria for prescribing?' The clinician's response was along the lines of: while prescribing decisions are driven by progression as measured by RECIST though imaging and symptom burden, biomarker results may trigger the clinician to request the imaging.

The AC have interpreted this as 'No', Sanofi Genzyme interpret this as, 'it is relevant as part of the breadth of parameters clinicians consider when making treatment decisions'. The Chair asked, 'would you treat a patient who was progressed and symptomatic but did not have biomarker doubling?' The clinicians replied 'yes'. The question that was omitted by the Chair is, How often does this happen?/What proportion of patients you have treated are progressed, symptomatic but have doubling >24mo? It should be noted that in this discussion a committee member stated, 'most patients we see have doubling of less than 6 months or less than 12 months'. The expert clinicians concurred.

On this basis Sanofi Genzyme request that the AC specifically ask its clinical experts some key question to explore and understand the different perspectives of treatment.

- How many of your patients (%) initiated on vandetanib were symptomatic with progression with biomarker doubling data recorded?
- How many of those patients were symptomatic and progressed with biomarker doubling $\leq$ 24 months?
- How many of those patients were symptomatic and progressed with biomarker doubling > 24 months?
- Should any of those patients (with biomarker doubling > 24 months) be excluded because they were part of the ZETA trial that had a broad inclusion criteria that included 'indolent' patients?
- Is biomarker (i.e. CTN/CEA) information routinely collected in your medical notes?
- Is it likely that doubling time data (i.e. $\leq$ 24months vs > 24 months) will be available to you as part of your routine clinical practice at time you are considering vandetanib initiation?

- Is there any clinical reason why biomarker doubling would not apply to cabozantinib within its licensed patient population?

Sanofi Genzyme's view is that a discussion around the above questions will highlight that a positive recommendation for this cohort of patients with more aggressive disease will not change clinical practice nor significantly limit the patient population eligible for treatment. Instead, as our base case intended, it more accurately describes existing UK patients treated with vandetanib.

Almost 14 years since the ZETA trial was started, the definition of aggressive disease remains open to interpretation and down to individual clinical opinion. It is therefore entirely plausible that patients treated with vandetanib in UK clinical practice have all three criteria present at initiation of systemic treatment.

In summary, the restricted EU label population was rejected by the Committee on the basis that the decision to start treatment in clinical practice is based on radiological progression, regardless of the fact the most if not all UK patients are likely to fall within this, rather than the EU, population.

2. **Ultra-orphan disease such as MTC cannot be appropriated appraised using NICE existing processes**

- NICE has established and formalised processes for assessment. However, we are concerned that the rigid application of these processes in this assessment is inequitable as it does not reflect the reality of the financial burden on the NHS to pay for these treatments (which is relatively low and predictable) nor the importance of these treatments in a population of fewer than 40 patients per year, take account of 'distributive justice' the concept that 'fair' allocation of resources is not the same as 'equal' allocation of resources. As reported in the paper by Rawlins et al, 'NICE favours an approach based on maximizing benefits per unit cost, but recognizes that this can conflict with the considered moral convictions of many people (including the members o its advisory bodies) Consequently NICE uses a flexible approach that treats decisions on a case-by-case basis'. Sanofi Genzyme requests that the AC uses its decision-making latitude to ensure these [redacted] patients each year have access to an active treatment for their terminal cancer. .

- ***Use of a standard methodology despite the rarity of the condition under consideration. Vandetanib eligible population is around [redacted] patients/year and estimated annual budget impact of [redacted]***

MTC is an ultra-orphan disease with only around 170 patients diagnosed in England each year. For many of these patients surgery is curative meaning only around 30-40 patients per year require systemic therapy.

NICE has applied its standard process to this MTA. The reason for this is provided at paragraph 3.21 of the ACD, where the Appraisal Committee states that it "noted the advice from NICE's Social Value Judgements: Principles for the Development of NICE Guidance that NICE should evaluate drugs to treat rare conditions in the same way as any other treatment".

The relevant advice, taken from section 4.4 of the second edition of NICE's Social Value Judgements, states:

> NICE considers that it should evaluate drugs to treat rare conditions, known as 'orphan drugs', in the same way as any other treatment (see Glossary).
>
> NICE does not expect to receive referrals from the Secretary of State for Health to evaluate 'ultra-orphan drugs' (drugs used to treat very rare diseases or conditions). This is because the Department of Health currently has other mechanisms to assess the availability of ultra-orphan drugs in the NHS.

"Orphan drugs" are defined in NICE's Social Value Judgements as "Drugs indicated for rare conditions or diseases (those that occur in fewer than 1 in 2000 of the population)".

"Ultra-orphan drug" is stated to be "A term used by NICE to describe interventions for very rare conditions or diseases that occur in fewer than 1 in 50,000 of the population; it also covers interventions for which there are no other known or possible uses."

MTC is an ultra-orphan disease and vandetanib is an ultra-orphan drug according to the definitions used by NICE's Social Value Judgements (SVJ). At the time NICE's Social Value Judgements were formulated, NICE did not expect to appraise ultra-orphan drugs and the advice relied upon by the Appraisal Committee at paragraph 3.21 of the ACD related to orphan drugs but not to ultra-orphans. Therefore the Appraisal Committee should perhaps reconsider its interpretation of NICE's Social Value Judgements as requiring a standard methodology and approach to the appraisal of vandetanib.

- **Highly Specialised Treatment**

When NICE commenced evaluations of ultra-orphan technologies in 2013, a new procedure was introduced which recognised the fact that the usual methodology could not fairly be applied to these treatments for very rare diseases. NICE's Interim Process and Methods of the Highly Specialised Technologies Programme updated to reflect 2017 changes (the HST Process Guide) states at paragraph 39:

> "Given the very small numbers of patients living with these very rare conditions a simple utilitarian approach, in which the greatest gain for the greatest number is valued highly, is unlikely to produce guidance which would recognise the particular circumstances of these very rare conditions. These circumstances include the vulnerability of very small patient groups with limited treatment options, the nature and extent of the evidence, and the challenge for companies in making a reasonable return on their research and development investment because of the very small populations treated. Nevertheless, as part of its consideration of the value for money of the technology, the committee must give consideration to the balance between the costs and the benefits".

When the HST methodology was introduced, Sir Andrew Dillon explained:

> "The HST guidance recognises the particular circumstances of these very rare conditions - the vulnerability of very small patient groups with limited treatment options, the nature and extent of the evidence, and the challenge for manufacturers in making a reasonable return on their investment because of the very small populations treated.
>
> In evaluating these drugs, NICE takes into account a greater range of criteria about the benefits and costs of highly specialised technologies than is the case with its appraisals of mainstream drugs and treatments. *We do this because applying our standard approach to treatments for very small groups of patients would result in us always recommending against their use. This would be unfair*." [italics added]

Vandetanib however, is not eligible for assessment under the HST process because it is not expected to have 'life-long use' nor is MTC regarded as a chronic condition (paragraph 28 of the HST Process Guide). However, the circumstance Andrew Dillion describes above exactly applies to this MTA: applying standard methods to this ultra-orphan oncology indication will "result in [NICE] always recommending against their use". We agree this would be unfair.

Given the above, the AC should consider the alternative NICE processes it has at its disposal for evaluating novel technologies. Specifically, Sanofi Genzyme believes the new £100,000 HST threshold is the most appropriate of the three available thresholds to apply to this assessment.

- **Application of End-of-Life criteria**

In addition to the above we cannot agree with the conclusion the committee reached regarding the EOL criteria. The Committee concluded that the end of life criteria do not apply to vandetanib (or cabozantinib) as the life expectancy for patients eligible for treatment but who instead received BSC exceeds the 24 month threshold (which the Committee deems to be a condition to application of the criteria). However, it is worth noting that the actual wording of the criteria (para. 6.2.10 of NICE Guide to Methods of Technology Appraisals) suggests some flexibility in the criteria which is not reflected in the ACD (i.e. "…*normally* less than 24 months"). Further, although the Committee recognised the median OS in the BSC group in EXAM was less than 24 months, they concluded that the mean estimate was more appropriate for determining applicability of the criteria.

Sanofi Genzyme believes patients within the restricted EU population are more likely to have a life expectancy around 24months, with standard of care treatment (in this case BSC). Sanofi Genzyme requests that the AC asks clinicians what average survival they would expect from a patient fitting the restricted population criteria.

Indeed, according to NICE process guide detailing criteria for EOL there is no mention that the short life expectancy criteria needs to be described by mean survival [6] and in reality, NICE appraisal committees have accepted median overall survival with respect to EOL criteria [7] in other appraisals (table 2).

Table 1 List of NICE technology appraisals were committee used median OS from the control arm of the trials to establish 'normal' life expectancy

TA208: Trastuzumab plus cisplatin and capecitabine or 5- fluorouracil for HER-2 positive metastatic gastric cancer
TA171: Lenalidomide for multiple myeloma
TA 179: Sunitinib for gastrointestinal stromal tumours
TA184: Oral topotecan for small cell lung cancer
TA 185: Trabectedin for soft tissue sarcoma
TA190: Pemetrexed (maintenance treatment) for non-small-cell lung cancer

Following the AC meeting and the ACD, SGZ has revised its modelling method for dealing with confounding in the OS analysis caused by crossover and come up with plausible OS estimates for both vandetanib and the 'true' placebo arm, as such we are confident that the discounted mean life years gained predicted by the economic model is 1.6 years. This conclusion remains consistent irrespective of the choice of parametric model used to represent overall survival. The RPSFT model suggests that the median survival in the placebo group of the restricted EU label population is 1.6 years. Therefore, it should be noted that when the OS data for the ZETA subgroup (i.e. restricted EU label population) is adjusted for the open-label vandetanib use, the true survival duration in this population is less than 24 months. The criterion relating to >3 months life extension is likely for vandetanib within the Restricted EU label population (symptomatic and progressive MTC with CEA/CTN doubling time ≤24 months).

SGZ accepts there is a degree of uncertainty regarding the precise ICER estimate for vandetanib compared with BSC, however consistent results from the economic model, regardless of whether the observed (crossed over) trial data were used, whether the uncrossed RPSFT data were used or whether data based on the regression model were used, give a large degree of certainty that the ICER for vandetanib versus BSC is well below the HST £100,000 QALY threshold.

3. Concerns over statements reflected in the ACD, despite the evidence provided

At various points in the ACD, it would appear the AC have questioned vandetanib clinical benefit, failed to acknowledge the clinical uncertainty between the label population and the UK treated population and concluded that extension to overall survival is not robust without any recognition of the ZETA trial design.

"Clinical trial evidence suggests that cabozantinib and vandetanib are effective in delaying disease progression but may not prolong survival"

Vandetanib clinical benefit is clear. According to the European regulators, the superiority of vandetanib over placebo is clinically significant and quite consistent across all pre planned subgroups. The results observed on PFS were supported by results on some secondary endpoints such as ORR ([redacted] for the primary analysis). No statistically significant positive effect of vandetanib over placebo has been demonstrated on OS: HR of [redacted]. But given the level of cross over in this trial ([redacted] % on placebo arm crossed to vandetanib), even more mature data did not establish a long term survival benefit, an anticipated outcome for this trial. Because of the proposed cross-over at progression, the OS comparison in fact compares populations that differ mainly by the fact that vandetanib has been proposed early (experimental group) or later on, at progression (placebo arm).

In view of the associated risks, the regulators considered that it was important to limit treatment with vandetanib to patients who are in real need for treatment. This can be established based on clinical and biological criteria. From a clinical point of view, this corresponds to patients that can be identified as having a symptomatic-aggressive course of the disease. Either symptomatic disease or progressive disease alone is not enough to prompt the need for treatment with vandetanib. Rate of change in biomarker levels such as of calcitonin and/or CEA as well as the rate of change of tumour volume during watchful waiting might help to identify not only patients in need for treatment but also the optimal moment to commence the treatment. Similarly, imaging data alone is not expected to be useful in identifying patients in need for treatment.

"Adverse events are common with both drugs and the decision to use them is based on careful consideration of the risks and benefits" and "The committee acknowledged that although both drugs may work well for some people, for many others there will be a substantial side-effect burden."

Sanofi challenges this statement. The incidence of AEs observed in clinical trials, a period during which there's little experience with the tested drugs, would not correspond to the observation in current clinical practice. The post-marketing experience allowed a significant learning towards AEs management (prevention as well as treatment) [8-10]. Since its approval in 2012, clinical experience and information collected on safety demonstrates a good benefit/safety profile on vandetanib. Clinical experts at the AC meeting also confirmed that there are well established protocols for managing AEs related to TKI's in clinical practice.

"…neither cabozantinib nor vandetanib can be recommended as a cost-effective use of NHS resources."

As noted above, there is a degree of uncertainty regarding the precise ICER estimate for vandetanib compared with BSC. However consistent results from the economic model, regardless of whether the observed (crossed over) trial data were used, whether the uncrossed RPSFT data were used or whether data based on the regression model were used, give a large degree of certainty that the ICER for vandetanib versus BSC is well below the HST £100,000 QALY threshold. This threshold that is more appropriate and fair in assessing therapies for disease areas with such small patients numbers than a standard NICE reference case which has been applied in this case by 'default' or process of elimination of NICE's various value judgements - it as assumed that as vandetanib did not technically meet NICE criteria for HST or EOL, by default the standard reference case an acceptable threshold of £30,000/QALY was applied without discretion in this appraisal. The above statement is therefore should be revised in light of the evidence provided in our submission and in this response.

Response to questions raised in the ACD

Has all of the relevant evidence been taken into account?

The question of whether relevant evidence has been taken into account, assumes that relevant evidence is available. In fact there is limited evidence in this disease area and notable clinical uncertainty. There are no UK/NICE guidelines for treatment of MTC, no clear guidance on identifying and treating patients in practice, despite the drug being funded on CDF since 2014. As highlighted above we believe the right questions were not posed to the clinical experts or patient representatives in the AC meeting.

Vandetanib's clinical safety and efficacy has been recognised by the EMA by way of granting it a licence and formal EMA orphan status. The consideration of this as an ultra-orphan disease has not been given adequate consideration in the AC decision making process.

There is a lack of guidance from NICE's Decision Support Unit on how adjustments should be made in trials with small patient numbers and where cross-over occurs early on in the trial, at different points in the trial (i.e. before as well as after documented progression) and there is high level of cross over ([redacted] % on placebo arm).

In UK clinical practice, patients are treated based on urgent need of treatment; very much in line with the *intention* of the EMA label indication. However the definition of the aggressive patient profile at this point in the treatment pathway is unclear and subject to individual clinical judgement.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

For reasons outlined above, the summaries of the evidence are not reasonable interpretations of the available evidence on vandetanib or systemic treatment of MTC.

Are the recommendations sound and a suitable basis for guidance to the NHS?

The draft recommendations are not suitable for the NHS and final negative decision will mean that treatment which has been available for approximately three years on the NHS, now no longer is an option. Best supportive care, which has no anti-tumour benefit, would be the only option despite the availability of licenced treatment with proven safety and anti-cancer benefit. The financial burden of these products is low for an organisation of the size of the NHS. At the AC meeting it was noted that total spend per year was £[redacted] million assuming no dose adjustments or treatment discontinuation.

Given trial discontinuation rates are [redacted] and dose reductions are [redacted] the true cost to the NHS is likely to be closer to [redacted]. The quote above was based on the price at which vandetanib, and we presume cabozantinib, were sold while on the CDF. Sanofi Genzyme has reduced the price at which we are offering it to the NHS, therefore the cost will be lower than [redacted] per year.

The AC draft recommendation is not evidence-based and therefore not suitable for adoption within the NHS.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

The recommendations would not be unlawful according to the groups listed above.

Conclusion

We urge the AC to recognise the inequities that arise from withdrawing effective treatment options in a very small, stable adult patient population. As it has been available for the last 3 years, vandetanib should continue to be an option for treatment of advanced/metastatic disease in patients whose disease has become aggressive and symptomatic and in whom systemic treatment benefits outweigh risk of side-effects.

References

1. Barbet J, Campion L, Kraeber-Bodere F, et al. Prognostic impact of serum calcitonin and carcinoembryonic antigen doubling-times in patients with medullary thyroid carcinoma. *J Clin Endocrinol Metab* 2005;90(11):6077-84.
2. Laure Giraudet A, Al Ghulzan A, Auperin A, et al. Progression of medullary thyroid carcinoma: assessment with calcitonin and carcinoembryonic antigen doubling times. *Eur J Endocrinol* 2008;158(2):239-46.
3. Sanofi Genzyme Data on file (2016). An International, Phase III, Randomized, Double-Blinded, Placebo-Controlled, Multi-Center Study to Assess the Efficacy of ZD6474 versus Placebo in Subjects with Unresectable Locally Advanced or Metastatic Medullary Thyroid Cancer CLINICAL STUDY REPORT ADDENDUM
4. Latimer NR et al. Adjusting survival time estimates to account for treatment switching in randomized controlled trials – an economic evaluation context: Methods, limitations, and recommendations. Medical Decision Making 2014; 34: 387–402
5. European Medicines Agency. Assessment report: Caprelsa (vandetanib) 2012. [Available from:

ttp://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d125.
6. National institute for Health and Clinical Excellence Appraising life-extending, end of life treatments. Available on https://www.nice.org.uk/guidance/gid-tag387/resources/appraising-life-extending-end-of-life-treatments-paper2
7. Beyond Cost-effectiveness: Consideration of Innovative and End-of-Life Therapies Workshop on Health Technology Assessment 7 December 2010 Available on file:///C:/Users/E0302739/Downloads/Rinaldi%20Beyond%20Cost-effectiveness_Fiona%20Rinaldi%20ppt%20Compatibility%20Mode.pdf
8. Grande E, Kreissl MC, Filetti S et al. Vandetanib in Advanced Medullary Thyroid Cancer: Review of Adverse Event Management Strategies. Adv Ther (2013) 30:945–966. DOI 10.1007/s12325-013-0069-5
9. Cabinallis M, Hu M, Jimenez C et al. Treating medullary thyroid cancer in the age of targeted therapy. Int. J. Endo. Oncol. (2014) 1(2), 203–216
10. Zamorano JL, Lancellotti P, Mun˜oz DR et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines

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

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 14/09/2017 through NICE Docs or email TACommD@nice.org.uk

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Association for Multiple Endocrine Neoplasia Disorders (AMEND)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments

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

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 14/09/2017 through NICE Docs or email TACommD@nice.org.uk

	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Patient Input to the Appraisal Process** Since the patient and patient representative were barely acknowledged at the appraisal consultation meeting (see complaint from Kate Farnell MBE of Butterfly Thyroid Cancer Trust), we are extremely concerned that patient and patient organisation input to this process has been viewed by the NICE committee as simply a 'tick-box' exercise. We therefore request that all of the following points (some contributed by patients with the cancer who are very unwell) be brought to the attention of the committee at the beginning of the agenda (as recommended by Cancer52 in their 2015 report, 'Speaking up for patients: patient organisation involvement in Health Technology Assessment'). While we may not have strengths in contributing to the clinical or financial data regarding these drugs, we can offer the social and ethical views which are required for consideration as described by the European network for Health Technology Assessment: 'a multidisciplinary process that summarises information about medical, social, economic and ethical issues related to the use of health technology in a systematic, transparent, unbiased and robust manner'.
2	**Appraisal Criteria Issues** We are very concerned that these drugs have been appraised using criteria applicable to treatments for more common cancers, but not to rare cancers like medullary thyroid carcinoma. With regard to incomplete data, we feel that the absence of effect does not necessarily imply the effect of absence and that therefore we should be able to offer the chance of therapy despite incomplete data. Since MTC is a very rare cancer, statistics will be scant, data often incomplete and therefore averages wide-ranging and skewed – we don't feel that this should disadvantage these patients. Judging rare cancers using averages and common cancer criteria discriminates against this patient community. Indeed, Cancer52 states in their 2015 report, 'Speaking up for patients: patient organisation involvement in Health Technology Assessment' that 'Patient involvement is particularly important for rare and less common cancers where there may be gaps in the evidence base reflecting small patient numbers. Cancer52 believes that patients can contribute to a fuller understanding of the impact of new medicines'
3	**QALY Calculation Issues** We do not think that the QALY calculations are accurate in this instance. Firstly, with around just 80 patients diagnosed with medullary thyroid carcinoma each year in the UK, this cancer is rare and as such the number of potential patients who may use cabozantinib and vandetanib is much smaller than may be the case for drugs used for more common cancers. For example, the potential costs in the case of TKIs for MTC is in stark contrast to the hugely expensive breast cancer drug, trastuzumab emtansine (Kadcyla), which received full approval in June this year, and which may be used by around 1,200 patients per year. Secondly, 25% of MTC cases identified in childhood with a hereditary risk of medullary thyroid cancer due to *RET* gene mutation usually have an improved prognosis when receiving timely prophylactic surgery. Thus, the financial impact of potential TKI prescribing is again reduced in these cases, yet this has not been factored into the QALY calculations since this entire patient community was regarded as unimportant in the Appraisal process.

	Finally, the common side-effect-reducing dose reductions or drug holidays are not taken into account. To do so would result in an overall lower total cost. An example of a drug holiday was provided to us by this American MEN2b (*RET* mutation positive) patient: "Prior to being placed on Vandetanib in August 2016, my Calcitonin levels (total thyroidectomy in 1997 at age 13 due to Medullary Thyroid Cancer) had steadily climbed to 20,000. They had reached their "doubling-time" approximately 1 year prior. After being on Vandetanib for 6 months, my Calcitonin levels dropped to under 2,000, and the 5 tumours of MTC that were in my lungs disappeared. My symptoms associated with high Calcitonin levels also disappeared. In March 2017, I was taken off of the Vandetanib and have been closely monitored since. It is now August 2017, and I have been off Vandetanib for 5 months. My Calcitonin levels have remained steady at under 2,000, and the tumours in my lungs have not reappeared. Although the side effects of the Vandetanib were unpleasant, I will not hesitate to be put back on it the next time the MTC requires it. It is my understanding that prior to these pills, once you hit the doubling-time with the Calcitonin, you, at most, have 10-12 years left to live. If I have to feel absolutely [terrible] for a couple of months every so often to lengthen the time I have left on this earth with my son, husband, family, friends, and all of the beautiful things this world offers to brighten my existence, then I will take it in a heartbeat until it is finally time to throw in the towel and let nature take its course."
4	**Exclusion of Patients from Consideration During the Appraisal** The conclusion not to consider *RET* mutation status is insupportable when germline *RET* mutation testing *is* standard practice. To exclude this group of very rare hereditary cancer patients because *somatic* testing is not routinely done is unfathomable and further disadvantages these rare cancer patients who have no other treatment options beyond timely surgery. Requesting that somatic *RET* mutation testing becomes standard practice would leave England in a stronger position in terms of research into the disease and future treatments, especially if those new treatments may ultimately be provided at a lower cost.
5	**Inequalities** AMEND believes that it is unacceptable and unethical for the 5th largest economy in the world to not be able to offer these patients some form of therapy, particularly for younger patients, when there are absolutely no other therapeutic options at this time. At least 54% of cancer deaths annually are due to rare or uncommon cancers* with the number of deaths continuing to increase. It is therefore time for NICE to step up and increase the treatment options for these patient communities to level the playing field with the 'big four' cancers. *'Rare and Less Common Cancers: Incidence and Mortality in England, 2010 to 2013', Cancer52 and NCIN at PHE report
6	**Missed Opportunity** We believe that NICE are over-looking an opportunity to improve outcomes for patients with medullary thyroid carcinoma. This could be achieved by recommending the continuation of funding subject to accurate recording of these patients' treatments to aid current and future research.
7	**Progression Free Survival Issues** It is rare to demonstrate an increase in survival these days because of the ways that the trials are set

	up - but extra months of progression free survival (PFS) are still important. Due to the wide range of responses to the drugs in this small patient community, average PFS times are greatly skewed. Some patients benefit from years of PFS which in some cases enable patients to continue to work and contribute to society. It is widely and internationally acknowledged by experts treating these patients that these drugs offer PFS in metastatic MTC and it is therefore mystifying why this committee does not recognise this.
8	**Direct Patient Responses to the Recommendations** These NICE recommendations have caused great upset in this vulnerable UK patient population which is small but well-connected to one another and also with patients overseas where TKIs may be routinely available. Rare cancer patients (like all cancer patients) strive to keep hope in the future and new treatments that this may bring. Their hopes are being dashed since most would never be able to afford to pay for these drugs on private prescription. This is a sample of their responses: “OMG I feel sick. I am not on TKIs yet but that's the point isn't it. Yet. One day I am going to need them what then?” “Oh no! Although my husband is just starting out on his MTC journey we had the knowledge that these drugs would be available as and when” “Shocking decision given the successful use of TKIs in the US” “I am on Vandetanib and it has kept me stable for just over a year (I had weeks to live last June as the MTC was taking over my lungs! It is not resectable!) I have been told my MTC will become aggressive if I stop! Terrified!” “Want to cry just can't believe it. Tony on this bus next stop was one of these drugs...wot now? on a bus to nowhere?”
9	**Pharmaceutical Company Communication** We are concerned that recommendations show that there is no intention to continue to try to negotiate the drug prices with Ipsen and SanofiGenzyme
10	**End of Life Issues** We are appalled that your recommendations are based on, among other things, the fact that terminal patients with metastatic MTC patients effectively live too long and/or take too long to die. Again, we feel that these patients are being discriminated against because they have a rare cancer that behaves differently to more common forms of cancer. MTC should not be judged in these terms. In fact, the aim of many cancer treatments now is to ensure that cancer becomes a disease that people live with rather than die from. There is a possibility of achieving this with MTC when combining new therapies with the natural course of disease progression. However, it should be remembered that the disease is not slow growing in *all* patients.

Insert extra rows as needed

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

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 14/09/2017 through NICE Docs or email TACommD@nice.org.uk

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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

NICE National Institute for Health and Care Excellence

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Ipsen Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**
Name of commentator person completing form:	**Liz Gray** **Director of Market Access (UK)** **Ipsen Ltd**

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

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 14/09/2017 through NICE Docs or email TACommD@nice.org.uk

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Ipsen are disappointed that NICE has been unable to recommend the use of cabozantinib in medullary thyroid cancer (MTC). Only two systemic treatments are licensed in this advanced setting, each with a distinct safety profile, meaning that they are suitable for different patients. Should neither of these drugs be approved, the remaining treatment options for patients will be limited in both number and effect.
2	Whilst we understand the background to this appraisal (that is, to ensure a transition from the Cancer Drugs Fund to routine commissioning), we would reiterate our comments from the original scoping exercise that MTC is an extremely rare cancer and, as such, the data are simply not suited to the rigour of a standard NICE technology appraisal. At the time, it was determined that the therapy area did not meet the criteria for Highly Specialised Technology (HST). Nonetheless, we maintain that these medicines would have been better served by an appraisal under that process wherein the framework accommodates not only the limitations of the evidence base but also the wider aspects of the disease and its impacts.

Professor Gary McVeigh
Chair, Appraisal Committee D

Tuesday 12th September 2017

Dear Professor McVeigh,

We are grateful for the opportunity to respond to the NICE Appraisal Consultation Document (ACD) reviewing cabozantinib and vandetanib for treating medullary thyroid cancer.

As acknowledged by the committee, patients with advanced medullary thyroid cancer have no treatment options other than cabozantinib and vandetanib, which are currently available through the Cancer Drugs Fund in England. It is not a disease that responds to conventional cytotoxics or external beam radiotherapy. We note that the appraisal committee states that these drugs offer the only systemic treatment options for this very small population of patients with progressing, advanced medullary thyroid cancer in that they delay the progression of the disease and in our experience this in turn delays the onset or worsening of disease related symptoms.

We recognize that the data available from the only two randomized controlled trials (ZETA and EXAM) do not allow interpretation of overall survival benefit and this contributes to the uncertainty and cost effectiveness of the drugs. However we would like to emphasise that we initiate these drugs in a carefully selected small group of patients with objective disease progression and disease related symptoms or imminent symptoms in an already rare disease. Therefore the budget impact for the NHS is comparatively low. In addition, with no other treatment options these patients are not incurring costs to the NHS from alternative or additional lines of treatment as we see in the more common advanced, relapsed cancers.

Sanofi-Genzyme put forward a model for an EU restricted license (discussed in section 3.4) by suggesting that only patients with tumour marker (calcitonin and CEA) doubling times of 24 months or less would be eligible to start vandetanib. The assessment group felt that this was not valid as tumour marker doubling times are not used by clinicians to determine when to start either vandetanib or cabozantinib. However, as we discussed at the meeting, although we do use radiological evidence of progressive disease (RECIST criteria) and our patients' symptoms, inevitably the tumour marker doubling time will be less than 24 months in this situation. For example, reviewing my own practice I have initiated vandetanib in 24 patients via the cancer drugs fund; twenty had tumour marker doubling times significantly less than 24 months (averaging just over 6 months) and the remaining four started vandetanib at presentation before a trend of markers could be established due to extent of disease and symptoms. Therefore although this has not been a specific selection criterion for initiation of treatment,

the group of patients with tumour marker doubling times of 24 months or less is likely to reflect the population that we treat. We would confirm that these drugs are always reserved for this smaller population of patients.

We would like to challenge the assumption in section 3.13 *'..that when treatment with vandetanib has stopped working, quality of life would actually be improved by stopping treatment because of its associated toxicities.*' This is not our experience unfortunately. We find that patients have significant symptoms from progressing disease and particularly a rising calcitonin level which causes diarrhoea, weight loss and fatigue, once they stop vandetanib. Therefore there remains a cost in managing symptoms in patients once disease progression occurs and disease modifying treatments (vandetanib or cabozantinib) are stopped. It is also worth emphasising that we do not continue to prescribe cabozantinib or vandetanib if treatment induced adverse events are not tolerable or manageable, or if the disease is no longer responding. This limits the population of patients on these drugs and the costs incurred in managing adverse events. In reality we do treat a smaller population of patients than a strict interpretation of the marketing authorisation would indicate, and so overall cost may not be of the magnitude that that the ACD assumes.

As clinicians managing this rare cancer we have significant concerns for our patients if the decision not to recommend either drug is confirmed. We wonder if there is a case for considering a recommendation for funding with prospective data collection to clarify the remaining uncertainties. This would seem to be in line with the Cancer Drugs Fund recommendation category '… where there is plausible potential for a drug to satisfy the criteria for routine commissioning, but there is significant remaining clinical uncertainty which needs more investigation…..'.

Thank you for your consideration of this response.

Yours sincerely,

Dr Kate Newbold
Consultant Clinical Oncologist
Chair, NCRI Thyroid Cancer Clinical Studies Group

Dr Mary Lei
Consultant Clinical Oncologist

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

Comments on the ACD Received from the Public through the NICE Website

Name	[redacted]
Role	Patient
Other role	[redacted]
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I am 42 years old. I have MEN2A which was diagnosed after I was underwent surgery for Medullary Thyroid cancer. My [redacted] son also has MEN2A. My Medullary Thyroid Cancer was not completely removed by surgery. My numbers are low but rising and at some point I have always been aware that I would need to go onto TKIs. Many patients have had significant years added to their lives by TKIs and until further breakthroughs are made into what is an extremely rare cancer, TKIs remain our last line of defence. When I read today that NICE is considering withdrawing access to these drugs on the NHS I felt sick with fear. If it is true that NICE's decision is based on the fact that metastic patients live TOO LONG that that is an outrage. These are our lives you are playing with. I have two young boys. I want them to grow old enough to cope without me before I succumb to this incurable disease. I will need TKIs to make that happen. In my case, with my RET mutation and MEN2A, these drugs have been shown to be even more effective. Please don't take away what little help we have available to fight this disease. Many of the standard treatments that are used for other cancers are ineffective for MTC. We can only have so many surgeries before scar tissue makes more impossible. PLEASE don't rob us of our last line of defence.
Date	23 August 2017

Name	[redacted]
Role	Patient
Other role	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I have been suffering from Medullary Thyroid Cancer for 17 years and have had 7 major operations over that time. I have been lucky that it has not spread but I always had the knowledge that there were now medicines that could be used. I

	have friends in the USA who have access to these TKIs. I have now been told that these are no longer going to be offered to new patients on the NHS so I have no future if my MTC spreads and as my blood tests show even after a very big operation last September my calcitonin level is rising showing the cancer is in my body. What future does that give me as my neck is badly damaged with scar tissue after all the operations I have had. We have a very rare cancer but surely we deserve to have some hope. Please reconsider this.
Date	23 August 2017

Name	[redacted]
Role	Patient
Other role	[redacted]
Location	United States
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Prior to being placed on Vandetanib in August 2016, my Calcitonin levels (total thyroidectomy in 1997 at age 13 due to Medullary Thyroid Cancer) had steadily climbed to 20,000. They had reached their "doubling-time" approximately 1 year prior. After being on Vandetanib for 6 months, my Calcitonin levels dropped to under 2,000, and the 5 tumors of MTC that were in my lungs disappeared. My symptoms associated with high Calcitonin levels also disappeared. In March 2017, I was taken off of the Vandetanib and have been closely monitored since. It is now August 2017, and I have been of Vandetanib for 5 months. My Calcitonin levels have remained steady at under 2,000, and the tumors in my lungs have not reappeared. Although the side-effects of the Vandetanib were unpleasant, I will not hesitate to be put back on it the next time the MTC requires it. It is my understanding that prior to these pills, once you hit the doubling-time with the Calcitonin, you, at most, have 10-12 years left to live. If I have to feel like **** for a couple of months every so often to lengthen the time I have left on this earth with my son, husband, family, friends, and all of the beautiful things this world offers to brighten my existence, then I will take it in a heartbeat until it is finally time to throw in the towel and let nature take it's course.
Date	23 August 2017

Name	[redacted]
Role	Patient
Other role	
Location	England
Conflict	N/A
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's	Leaving one chance of cure through surgery is not acceptable

preliminary recommendations)	with this rare form of cancer. Depriving people of the chance to prolong their lives is very short sighted. These drugs should not be withdrawn from the CDF and is totally uncalled for. I have lost faith in the system to have even considered such a notion to treat Medullary Cancer Patients immorally and unfairly! They need to be supported. Thank you
Date	23 August 2017

Name	[redacted]
Role	Patient
Other role	[redacted]
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I am a medically retired Registered Nurse as a result of having metastatic medullary Thyroid cancer. I was diagnosed 22years ago and have had 12 surgeries ranging from minor to life threatening. In June if 2016 my disease progressed to carcinogenic lymphangitis and my breathing was worsening by the day. My tumour markers were rising sharply and there was no potential for surgery. My oncologist suggested Vandetanib which I started as I had no choice(I was literally given a prognosis of weeks). I have now been on Vandetanib for over a year. I had to give up Nursing due to fatigue, but I have a fair quality of life and my cancer has remained stable(no new growth) my tumour markers have come down to the lowest they have ever been in 22years and I am working my way through my 'bucket list'. These drugs are the only possible hope that we have when we have metastatic, unresectable disease. I now have hope and I look to the future. Taking the option of these drugs away is to take away hope for a relatively small number of patients in the grand scheme of things? I am an example of success in Vandetanib and I fully intend to progress into Cabozantanib should Vandetanib stop working? The side effects are a small price to pay for stable disease and 'living'. I urge you to seriously consider your proposals and the hope that you would be shattering by withdrawing these drugs from MTC patients grasp?
Date	23 August 2017

Name	[redacted]
Role	Friend of a cancer patient
Other role	
Location	England
Conflict	
Notes	No
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I know a lovely lady who is receiving this drug and is responding amazingly well to it. She has a young family and deserves every chance of living a full life with the people who

	love her. I would like to know if the people making this decision would be so quick to do so if they had close friends or family members in the same position as those who will be directly affected by it. If this drug is keeping people alive then surely its a no brainer. The lady I know who is receiving this drug is also a registered nurse and has worked hard within the NHS for years helping others which just makes this all the more difficult to comprehend. I am hoping and praying this decision to withdraw treatment does not go ahead
Date	23 August 2017

Name	[redacted]
Role	Patient
Other role	[redacted]
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I have MEN2 which caused my MTC. I was diagnosed at the age of 11 and had a full thyroidectomy within months but it was already a bit late and my postoperative calcitonin levels remained high. They did however remain stable, until about 6 years ago when it started to creep up, indicating that something was growing again. I recently had surgery to remove suspicious tissue from my Thyroid bed, hoping that this would be the source of the high calcitonin. Unfortunately the removed lumps were not cancer and my calcitonin levels have remained high, meaning my MTC has more than likely spread. When I was first told this I will admit I was terrified and I started to do some extra research about possible treatments and found out about Cabozantinib and Vandetanib and as they have been shown to be particularly effective when the tumour has a RET mutation such as occurs in MEN2 I thought, "OK, hopefully we can find my tumour(s) and hopefully they will be operable but even if they aren't at least these drugs will give me, not a cure, but at least a healthier life for longer". I do understand there is not a bottomless pot of money and I know that MTC is a very rare condition but to be told access to these drugs, if I ever needed them, will be denied despite having a known RET mutation, because MTC patients "live too long" is a real slap in the face, especially as there is no other treatment for MTC. Hopefully I will never need this treatment but I might and others definitely will. Please reconsider your decision, people with rare cancers already have a difficult time accessing treatment without removing options from us.
Date	24 August 2017

Name	[redacted]
Role	Carer
Other role	
Location	US
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Please reverse ban on tyrosine kinase inhibitor drugs. My daughter, [redacted], was dxd with MTC at age [redacted]. She has the RET mutation at 98. Her Calcitonin numbers are rising and we don't have any assurances that this time around MTC will be removed from surgery. More pts are living with this due to education and physician awareness. Most died in their cribs from SIDS (I believe). Let's give this growing number of people a real chance at life. My daughter deserves that. Please don't take it away from her!
Date	24 August 2017

Name	[redacted]
Role	Patient
Other role	
Location	US
Conflict	No
Notes	I'm currently in the US, but have family in the U.K. who are affected by this.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I have MTC. I haven't needed these drugs yet, but that time may come. I'm aware that they aren't a cure. But I know many people who have gotten to live long enough to see a child or grandchild finish school, get married, and start a family. I'd hate to think that my life isn't worth saving long enough for that to happen for me.
Date	24 August 2017

Name	[redacted]
Role	Patient
Other role	[redacted]
Location	Other
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	As a 37 year old female who was born and raised in the UK and moved overseas at the age of 27 I was recently diagnosed with MTC. Being told this is an incurable cancer is quite literally the worse news one could ever hear, after much medical research at a time when I am extremely sick i find there are two drugs available that lesson the pain one suffers at the hands of MTC especially when terminally ill and only given a few months to

	live and surgery is not a viable option. I wish to return to the UK to be with my family i need my family i have caner i need my family when doctor tells me there is nothing they can do and i am going to die i need my family when i am in so pain that i literally cannot function as a human being anymore. Taking away these drugs means i die alone overseas with no family i cannot return to my homeland if the medical treatment is not available to me i cannot have a good quality of life for the last few months of my life. Even if these drugs do not have a high success rate one person's quality of life is improved then you have saved a life and given us hope and joy and our families hope and joy. Yes this cancer is slow growing until it isn't until it's aggressive and your life becomes so poor that there is literally nothing you can do; these drugs allow us to carry on when there is literally no other option. Using these drugs also helps study the disease work out what works what does not work and why it the results are the way they are thus setting the way and building a foundation for future cures future drugs that will hopefully one day cure complete and also prevent cancer from ever forming in the first place. so many people with MTC have had symptoms for years and have not been diagnosed or worse misdiagnosed myself included the medical system has already failed us time and time and time again removing these drugs would be yet another failure to a mother, father, daughter, granddaughter, son. we need to help people beat cancer it burdens our society financially and emotionally solving it is the key - only research and continued care for those that are suffering at the hands of cancer will help - it is not only key, it is the only option!
Date	26 August 2017

Name	[redacted]
Role	Patient
Other role	[redacted]
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I have medullary thyroid carcinoma. I was diagnosed at 41 and had a major operation involving the loss of my thyroid, jugular vein, 30 lymph nodes and the paralysis of a vocal chord. I the endured 6 weeks of the most harrowing radiotherapy on both my neck and the metastasis that had appeared on my sacrum. Two years on, although my calcitonin is high (currently 30,000) my scans are clear. I am a very positive person and I'm also not stupid, I know with MTC the chances of reoccurrence are high. My youngest son is [redacted] in my mind, should it come back and it's inoperable I always have the fall back of TKIs when surgery is no longer an option. I want to see him go to prom, to do A levels, to go to university, I want to be a grandma. Without these life extending drugs that may not be possible. I find it inconceivable that you would consider removing them off the drugs fund list. I have had many friends that have lived many

	more years because of these. We are indeed rare, but surely that means fewer of us need the drug. I feel they should be left on the list until the NHS come up with another option? I know there are trials taking place in the USA for immunotherapy but until that becomes a treatment worldwide are you really going to take away the only other thing that can prolong our lives? I find this shortsighted and unethical. I think the NHS is amazing, I have had the most amazing care over the past two years, please please please don't ruin it now. We need these drugs...I want live.
Date	28 August 2017

Name	[redacted]
Role	Carer
Other role	[redacted]
Location	Europe
Conflict	No
Notes	I will raise this with CEO of Thyca US .
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I am based in Dublin, Ireland and am [redacted] group. We have many UK members who are affected by MTC. Personally my sister has MTC and we are based in Dublin, Ireland. We want to support our UK meddie family on this absurd recommendation. My sister is on a tki since Feb (calpresa/vandetnib) and she was only 1.5years diagnosed and whilst MTC is a surgically treated cancer and tki is last resort she is stgae 4 and required tki due to due a number of factors but elevation of liver enzymes was the main one. We liase with MTC experts in MDAnderson and attend Thyca conferences in US. These drugs are crucial to enabling people to survive, yes it is.not a cure but we have many meddies who would have died early in life without these drugs. We have some meddies still on drug from clinical trial back in 2006 onwards and have gone on to marry, have children and survive. In Ireland tki are considered a High drug so my sister receives her freely. I am concerned that outrageous decisions like this in UK could affect or basically to be blunt kill meddies when we should be focusing on helping them to survive any way we can.
Date	28 August 2017

Name	[redacted]
Role	Public
Other role	
Location	Other
Conflict	N/A
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I have a niece with MTC and the drug is making what time she has left to enjoy her time here on earth. It would be a shame for you to stop it

Date	28 August 2017
Name	[redacted]
Role	Patient
Other role	[redacted]
Location	US
Conflict	N/A
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Please do NOT take away these drugs. I myself do not need them and I hope I will remain as I am and not need them As of right now I am stable but I have family in Ireland and one of them NEEDS her Cabo. It is not fair for you to take away these drugs as people will die!!!!
Date	28 August 2017

Name	[redacted]
Role	Carer
Other role	
Location	
Conflict	N/A
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I have dear friends that I feel like are family, to me in Ireland, and am very concerned about this. Why take away something that is hope? Hope for a future that lives depend on? When diagnosed with a life threatening, non-curable cancer, why would anyone feel it is ok, to take away drugs that could potentially help prolong, shrink their tumor burden. Everyone deserves a life to live, to its fullest. These drugs have helped my hubby, to live just a bit longer and I'm so blessed that they were available to him. Please reconsider the removal. Think about yourself, here. What if it were you, depending on hope, for something to prolong your life! Thank you for reading.
Date	28 August 2017

Name	[redacted]
Role	Carer
Other role	[redacted]
Location	Europe
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	To whom it may concern, I am deeply saddened and concerned by the findings of this report, with the proposed cost being extortionate. How can you even consider discriminating against people that cannot afford this treatment?! It's completely unethical! Cancer does not discriminate against poor/working class people. The cost attached to the treatment would cost people their lives! I have a family member with MTC and as difficult as that is and as sad as that is, this is far more worrying and sad. Please, please reconsider. Please stop treating cancer

	treatment as a capitalist business!!! There are real people and real families behind each MTC statistic! Kind regards, [redacted] [redacted]
Date	28 August 2017

Name	[redacted]
Role	Patient
Other role	[redacted]
Location	England
Conflict	No
Notes	My mother died of medullary carcinoma and if the drugs had been available a few years ago she would have carried on working and caring for her family. As it was she died at 46, leaving my youngest brother [redacted] without a mum. A few more years would have made a huge difference.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I have abnormal RET type Multiendocrine Neoplasia (type 2a). I believe all sufferers should receive medication that is proven to slow the progress of medullary tumours when they are present. MEN sufferers contribute to society working and being important parts of their families and communities and if the tumours are slowed this enables them to keep going. Although this form of cancer is rare, there are still a significant number of British families affected and they deserve all the help the can get. MEN people tend to be proactive and self reliant but the nature of the condition precludes it from private medical insurance so out only hope is the NHS, I hope you'll take this into account and keep drugs that help to slow medullary carcinoma down available to NHS paitients.
Date	29 August 2017

Name	[redacted]
Role	Patient
Other role	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I have recently been diagnosed with medullary thyroid cancer. I am booked to have a total thyroidectomy and central lymph node dissection on 20 September. The size of the lump in my neck and my calcitonin levels imply that the cancer has metastasised. It is still undetectable by CT scan. If these drugs are not provided then I will not be able to be treated in future. How do I tell my family that? Please publish some wording that will help me explain that there used to be drugs to treat my illness but there aren't any more.
Date	4 September 2017

Name	[redacted]
Role	Patient
Other role	[redacted]
Location	US
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	As a patient of Medullary Thyroid carcinoma and MENS2, as well as my daughter, I do not want the medications to treat these diseases to be eliminated. We should have a chance to fight and live just as any other disease.
Date	4 September 2017

Name	[redacted]
Role	Public
Other role	[redacted]
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I pay my not inconsiderable taxes knowing that I may, hopefully, never need most of the drugs available. However, I also understand that other people will; this is not a problem to me, I am happy for my taxes to be used to treat others, 'corner cases' if you will. The NHS was founded on the principle of free treatment for all, and that's how it should be. Removing drugs from the few that may need them goes against this principle. I accept that there is only a finite pool of money available, so I would suggest that this pool ought to be increased to ensure that those that need the less common drugs still have free access to them. Without this access, you are effectively condemning many of them to a probable early death. I have a friend who may well need rely on Cabozantinib and vandetanib so I feel particularly strongly about their withdrawal. I would be willing to pay higher taxes, as I imagine most people would, if it meant ensuring the long-term provision of these drugs. Here's a thought - how about improving efficiency in the NHS? Nurses would be able to get better pay and the the people who need these more obscure drugs would be very grateful. [redacted]
Date	6 September 2017

Name	[redacted]
Role	Public
Other role	[redacted]
Location	England

Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	These drugs should not be withdrawn from the Cancer Drugs Fund but should remain available on the NHS. The NHS is not about value for money but about offering the best care possible to all patients regardless of cost. The (relatively) few people who need these drugs have the same rights as all those who have the misfortune to suffer from other perhaps more high profile cancers.
Date	6 September 2017

Name	[redacted]
Role	Public
Other role	[redacted]
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I believe the medication referenced above should me made available on the NHS to provide and extend the quality of life for people diagnosed with MTC. Cost should not be a factor when life and quality of life could be pro-longed. Best regards, Therese Collins
Date	10 September 2017

Name	[redacted]
Role	Public
Other role	
Location	England
Conflict	No
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I understand that the cost is high for these drugs, but it seems that the number of patients who could be treated in this way for MTC would be low. So the overall cost would not be very high, and the practical application of this medication might refine our understanding of its application, its efficacy and the resultant outcomes for those treated.
Date	11 September 2017

Name	[redacted]
Role	
Other role	
Location	Wales
Conflict	No
Notes	I was one of the clinical experts contributing to the clinical discussions with Paul Tappenden
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	Thank you for the opportunity to respond to the report. I developed and continue to run Thyroid Cancer Forum-UK (TCF-UK) which is a multiprofessional forum for consultants involved in the management of patients with thyroid cancer in the UK and overseas. I have been keeping TCF-UK members abreast of the NICE appraisal process and decisions to date and have the support of the following members in relation to this response: [redacted] Consultant Clinical Oncologist, Leeds [redacted], Consultant Clinical Oncologist, Leeds [redacted], Consultant Clinical Oncologist, South Tees [redacted], Consultant Clinical Oncologist, Southampton [redacted], Consultant Clinical Oncologist, Cambridge [redacted], Consultant Clinical Oncologist, Cambridge [redacted], Consultant Endocrinologist, Birmingham [redacted], Consultant Endocrinologist, Edinburgh [redacted], Consultant Clinical Oncologist, Oxford [redacted], Consultant Endocrinologist, Royal Free [redacted], Consultant Clinical Oncologist, Coventry [redacted]. Consultant Endocrinologist, Essen, Germany [redacted], Senior Medical Director, Veracyte, USA [redacted], Consultant Clinical Oncologist, St.Thomas', London [redacted], Consultant Head and Neck Surgeon, Glasgow

	[redacted], Clinical Oncologist, Glasgow [redacted], Consultant Clinical Oncologist, Exeter [redacted], Consultant Clinical Oncologist, Bristol [redacted], Consultant Clinical Oncologist, Guildford I have also had support in principle from [redacted], [redacted] of the EORTC Endocrine Cancer Taskforce and am awaiting written confirmation of support from [redacted] from Harvard Medical School on behalf of the International Thyroid Oncology Group. [redacted], Professor of oncology at the Mayo Clinic has submitted the following for your consideration : Respected Colleagues: This letter is written in the context or providing input pertinent to the NICE proposal to disallow support for provision of vandetanib and cabozantinib to medullary thyroid cancer patients in the United Kingdom. I forward this letter on the behalf of providers and of patients afflicted with metastatic medullary thyroid cancer in support of providing patient access to the regulatory approved drugs vandetanib and cabozantinib. Affordable access to these agents is especially important in this disease wherein no other specifically approved and effective agents exist. By way of introduction, I am a Professor of Oncology at the Mayo Clinic in Rochester, Minnesota USA, and [redacted] the Mayo Clinic Endocrine Malignancies Disease Group and the Endocrine Cancer Care Team (Medical Oncology) within the Mayo Clinic Cancer Center, a major worldwide referral center for the care and treatment of patients with advanced endocrine cancers, including medullary thyroid cancer. Additionally, I serve as a member of the Board of Directors of the International Thyroid Oncology Group (ITOG) and am a member of two American Thyroid Association (ATA) Guidelines Task Forces as well as serve on the ATA Ethics Advisory Committee. I am moreover non-conflicted with regard to any and all pharmaceutical companies, including those that market kinase inhibitors including vandetanib and cabozantinib. Briefly, vandetanib and cabozantinib each have proven clinical efficacy in treating metastatic medullary thyroid cancer; this is substantiated by: 1) high clinical RECIST response rates to both agents, 2) prolonged time to cancer progression compared to placebo in randomized clinical trials â€“ and also 3) emerging evidence of improved overall survival compared to placebo at least in the case of cabozantinib (44.3 vs 18.9 months, cabozantinib vs. placebo respectively, in patients with tumors with the most common RETM918T mutation).

	The later data, indicating a doubling of overall survival, is critical to incorporate into NICE decision-making, as it is my understanding that improved overall survival is a critical determinant of NICE approval criteria. I also note importantly that crossover of patients to other kinase inhibitory therapies is rampant in patient with advanced medullary thyroid cancer patients â€“ meaning that evidence of overall survival benefit is very difficult to develop in the case of thyroid cancer, wherein survival is sufficient to allow frequent therapeutic crossover. I am indebted to you for your kind consideration of additional input related to the approval of vandetanib and cabozantinib for use in metastatic medullary thyroid cancer patients in the United Kingdom. Without this approval, patients in the UK will be significantly disadvantaged relative to corresponding patients in the EU, USA and many other nationsâ€”a situation that I am certain you wish to avoid. [redacted], M.D., Ph.D. Consultant, Division of Medical Oncology and Professor of Oncology Chair, General and Endocrine Cancer Care Teams, Division of Medical Oncology Chair, Endocrine Malignancies Disease Oriented Group, Mayo Clinic Cancer Center Mayo Clinic Rochester, MN 55905

Comments from [redacted] continued	
Section 1 (Appraisal Committee's preliminary recommendations)	I have first-hand experience of treating patients with symptomatic progressive medullary thyroid cancer with both these agents and have witnessed the significant benefits that some patients can reap. I appreciate that anecdotes are not scientific but the following outlines the wide ranging benefits these drugs can have for patients and their families as this is not captured in the ZETA and EXAM papers. I have copied an enlightening first hand insight from one of my own patients below (this will appear in comments 2 and 3) : We understand that a decision has made not to fund the drug Vandetanib via the NHS and subsequently [redacted] has requested we provide the panel with some qualitative information from a patient and family perspective to assist with the deliberations. From both a patient ([redacted]) and a carer/wife ([redacted]) perspective we cannot speak highly enough of the service we have received from the NHS the dedication and commitment of staff to both patient care and research is second

	to none. We are fully aware of the difficult decisions that public bodies have to make in this particularly testing financial climate. Hence we feel privileged that we have been afforded the opportunity to make a contribution to [redacted] submission, by providing some qualitative information to add to the quantitative data you will already have considered When [redacted] was diagnosed 6 years ago we discussed the options available to manage the cancer one of which was the potential of a clinical trial. We agreed that [redacted] would wish to participate in any clinical trial which could inform treatment for the future, for people in similar circumstances. [redacted] was in one way fortunate that due the type of cancer the clinical trial meant everyone got the drug, whilst that didn't indicate success it did meant that various doses were being tested based on previous successful clinical trials to determine the impact on spread of the cancer. When [redacted] commenced the trial he was still in full time employment and it is our view that provision of vandetanib enabled him to continue in his post shaping public services for the future and contributing to services for future generations. The ability to go to work and contribute to society cannot be underestimated in terms of people's well-being. [redacted] was only able to do this as the drug was clearly impacting on his ability to manage his cancer. Improved well-being then flows over into family life enabling [redacted] to achieve milestones and contribute to society in other ways. The impact of the drug on normal every day life cannot be underestimated for both of us the following illustrates some of the impacts it has and continues to have. • In our view it has helped significantly to enable [redacted] to maintain a good quality of life and well-being. • It has undoubtedly extended [redacted] life by a significant number of years and in turn positively impacted on well-being of those around him. • It has provided [redacted] with the opportunity to enjoy a number of significant life events such as grandchildren, new house, family weddings and celebrations he may not have witnessed without it. • It has provided an opportunity for our granddaughter to get to know [redacted] she will now have memories. • It enables [redacted] to maintain an incredibly positive attitude making a significant contribution to his personal mental well-being.

	• It enables [redacted] to keep some of the fear and anxiety associated with cancer at bay for elongated periods of time and to maintain perspective. • It enables Stev[redacted] e to retain mental sharpness and focus to offer help support and help to our family as they have taken up new challenges e.g. attending university and changing careers. • [redacted] is still actively contributing to the development of public services and act as a mentor to new and old colleagues. • It has also allowed [redacted] to provide emotional support and counsel to a number of fellow cancer sufferers striking up some incredibly strong bonds • To conclude we believe the medication has allowed an extended network of family and friends to do a whole heap of things they wouldn't have been able to do with out the drug. • From a carer perspective it has enabled [redacted]to continue to work full time with minimal stress and anxiety, enabling her to continue being a wife. Provision of the drug via a clinical trial has enabled us to do the right thing, to do what matters for fellow medullary thyroid cancer sufferers in the future. We fully acknowledge this form of cancer is fortunately fairly rare thus the decision you make will impact on a relatively small number of people; however the difference it can make is enormous. Please don't deny individuals and their families that opportunity of a good quality of life. [redacted] st September 2017

Comments from [redacted] continued	
Section 1 (Appraisal Committee's preliminary recommendations)	In light of the difficulty interpreting the potential impact of these drugs on overall survival due to the cross over design of the phase 3 studies and the difficulty this then causes in determining cost effectiveness, we would value the opportunity to submit a proposal. Would the NICE appraisal panel consider an interim period of 2-3 years of continued vandetanib and cabozantinib access within the NHS to carefully selected patients on the proviso that such patients are referred to and managed by experienced thyroid oncologists who will collect quantitative and qualitative data on patient outcomes on a national prospective data base? Patients with symptomatic progressive medullary thyroid cancer deemed unsuitable for

	systemic therapy with these agents would also be included on the database. After the pilot phase, data can then be analysed by NICE to ascertain if there is evidence of cost effectiveness and a final appraisal decision would then be given. We feel these drugs show good activity in a clinical area where there is otherwise unmet need but acknowledge the limitations of the available published data. If these drugs are made unavailable at this point in time it will certainly limit the future potential for medullary thyroid cancer patients to participate in clinical trials and for this therapy area to develop. Pharmaceutical companies will be understandably reluctant to invest in this clinical area and we will not be able to join international clinical trials which will be looking at second and third line TKI therapies and combination therapies as we will no longer be in a position to offer what is felt within the clinical community to be the best standard of care.
Date	9 September 2017

Comments from [redacted] continued	
Section 1 (Appraisal Committee's preliminary recommendations)	Dear Sir/ Madam, I submitted comments for the appraisal consultation for cabozantinib and vandetanib in medullary thyroid cancer on 11th September. In this I referenced support from the International Thyroid Oncology Group but I hadn't at that stage received their written letter. It has now arrived and I would be very grateful if it could be added to my submission. I have copied the text below and attached the document. Many thanks for your assistance. Yours faithfully [redacted] [redacted] [redacted] Thyroid Cancer Forum UK (TCF-UK) Consultant Clinical Oncologist Velindre Cancer Centre Cardiff eptember 12, 2017 Dear Dr. Moss, I am glad that you recently reached out to the International Oncology Thyroid Group (ITOG) regarding our consideration of the use of vandetanib and cabozantinib for patients with progressive, metastatic medullary thyroid carcinoma (MTC). Until the ZETA trial, which demonstrated a significant improvement in progression-free survival of approximately 19 months with vandetanib compared to placebo, patients with advanced MTC had no good therapeutic options. (Wells S, et al. J Clin Oncol, 2012) The ZETA trial was considered a major

	breakthrough in the field of thyroid oncology. Similarly, the EXAM trial demonstrated an improvement in progression-free survival of more than 7 months in MTC patients with cabozantinib compared to placebo. (Elisei R, et al. J Clin Oncol, 2013) It was on the basis of both studies that vandetanib and cabozantinib were approved by the FDA in the U.S. and became new established standard of care therapies for patients with progressive, metastatic MTC across the world. Moreover, updated survival analysis presented at the American Thyroid Association meeting in October, 2015 indicated that patients with the RET M918T mutation (the most frequent driver mutation in sporadic medullary thyroid carcinoma) who received cabozantinib had an improved overall survival of **25.4 months**, as compared with the placebo group (HR= 0.60, 95% CI 0.38-0.94; *P*=.026). It is the opinion of ITOG that in the absence of new options for patients with MTC, these patients should continue to have access to these therapies. Without access to vandetanib or cabozantinib, there are no treatment options that have been shown in randomized controlled trials to benefit patients with MTC. We hope that the NICE Appraisal Committee will take this into account in providing guidance to the NHS. I do wish you good luck in advocating for your patients with MTC. Sincerely yours, [redacted] ITOG Associate Professor, Harvard Medical School Director, Head and Neck Cancer Program, Massachusetts General Hospital
Date	15 September 2017

Comments from [redacted] continued	
Section 1 (Appraisal Committee's preliminary recommendations)	Dear Sir/Madam, Here is another letter that I would have liked to include in my online submission but due to the nature of getting multiple European colleagues together in a short space of time it arrived a little later than hoped. I hope this important submission can also be reviewed during the consultation period. Many thanks. Yours faithfully, [redacted] [redacted] Thyroid Cancer Forum UK (TCF-UK) Consultant Clinical Oncologist Velindre Cancer Centre

	Cardiff September 2017 Dear Sir or Madam, We have noticed the recent NICE statement on decline of reimbursement for vandetanib and cabozantinib treatment of medullary thyroid cancer (MTC) in the United Kingdom. On behalf of the European Thyroid Association and of the European Thyroid Association cancer research network (ETA-CRN), we wish to express our sincere concerns about this decision. We agree that the two trials (ZETA and EXAM) leading to approval of both tyrosine kinase inhibitors by the FDA and EMA cannot be compared and that data demonstrating benefit on survival are lacking. However, both trials were not designed to detect survival and since metastatic MTC is a very rare disease, it is highly unlikely that such studies will be done in the future. Both vandetanib and cabozantinib are used in Europe and overseas for more than 5 years and there is substantial and augmenting indication that both drugs may significantly improve quality of life, working ability and survival, when given to the right patients. Thus, while we agree that these drugs should not be administered to every metastatic MTC patient, we are firm that withholding vandetanib or cabozantinib treatment in a patient with aggressive metastastic MTC is not the right decision, but is in fact unethical. Therefore, we would strongly support a joint initiative of the NICE committee and thyroid cancer experts of the British Thyroid Association to re-define criteria for reimbursement of TKI treatment of metastatic MTC, even as part of a registry to enable UK patients to get access to state-of the art treatment of their disease. Yours sincerely, On behalf of ETA [redacted] MD, Spain ([redacted]) [redacted], [redacted] UK (Secretary) On behalf of ETA-CRN [redacted], MD PhD, Germany ([redacted]) [redacted] [redacted] MD, Italy; [redacted], MD, Poland; Thera Links MD, Netherlands; [redacted] MD, Germany; [redacted] PhD, U.K.; [redacted], PhD, Poland
Date	22 September 2017

Appendix 1: Additional analyses on the Restricted EU label in response to the NICE ACD

Following discussion in the Appraisal Committee meeting and receipt of the ACD Sanofi Genzyme re-visited its approach to undoing cross-over and sought external, commercial, expert statistics support. As a result SGZ is updating the following information:

1) Revised the rank preserving structural failure time (RPSFT) model and consequent estimated results for the restricted EU label population
2) Cost effectiveness of vandetanib for each of the below analyses within the restricted population
    a. Cost effectiveness results generated by including the revised vandetanib curve vs RPSFT curve for BSC
    b. Comparison of vandetanib vs BSC using additional costs and utility data as detailed in the assessment report.
    c. Probabilistic sensitivity analyses for each of the above analyses

In the original submission, Sanofi Genzyme identified the RPSFT analysis as the most appropriate statistical approach for this dataset. This methodology can correct for time-dependent treatment changes in survival data whilst respecting the randomization [4]. We attempted to apply RPSFT methodology to the vandetanib restricted EU label population in the original submission, however, we were unable to undo crossover using this RPSFT approach because, patients who crossed over from placebo arm to receive open label vandetanib are patients with progressive disease, and the capacity for a patient to benefit may be different compared to patients with indolent disease and progressive disease. As a result, the common treatment effect assumption may not be clinically plausible.

Thus, it was stated in the submission that RPSFT failed to undo bias as the method looks for the effect sizes needed so that the two survival curves match if they are given the same treatment, if the curves never separate, or don't separate enough because crossover happens too early or before sufficient events occur in placebo (as was the case in ZETA), the curves will match up with effects very close to the null. This was the result obtained in the analyses. Therefore, we submitted as our base case the most conservative approach: the crossed over dataset.

Post ACD, with support from an external expert we re-ran the analyses to confirm its suitability or not in the restricted EU label dataset, looking to estimate the 'true' overall survival treatment difference between vandetanib and placebo, as if the placebo patients had not received any vandetanib, see Figure 2. (Appendix 1 provides further details upon the method used).

Figure A1 – Base Case Overall Survival with modelled overall survival (extrapolation over 20 years)

Additional economic analyses

For the additional economic analyses, Weibull, Log-Normal, and Log-Logistic curves were fit separately to the observed OS curve in the restricted EU label population for vandetanib (rather than fitting to the full EU label population and adjusting via coefficients) and to the uncrossed over (using RPSFT) OS curve for BSC in the restricted EU label population. For the base case analysis, we chose the best fit for each based on the AIC and BIC. The best fits were Log-Normal for vandetanib and Weibull for uncrossed over BSC. However, we used each of the other fits in sensitivity analysis.

The additional economic analysis compares vandetanib to BSC using the same survival partition model that was used for the original submission, but patients on BSC do not crossover to vandetanib at progression. This implies they do not incur a post-progression treatment cost and their survival is estimated using the RPSFT adjustment. By the same token, patients initially on vandetanib discontinue at progression. While this assumption is consistent with the recommended clinical use of vandetanib in the UK, in the ZETA trial there was continued treatment. While the RPSFT analysis provides for estimates of the survival curve without crossover, it does not address continued use of vandetanib post-progression. Thus, the vandetanib OS fitted curve based on the KM curve observed in ZETA may overestimate survival. In addition, the costs may be underestimated because no additional cost of vandetanib is incurred after progression. The impact of this assumption is considered in the sensitivity analysis by allowing continued use post-progression and, thus, accruing additional costs associated with vandetanib.

For comparison with the base case analysis, Table A1 presents the assumptions for the additional analysis, Table A2 presents the revised base case results and Table A3 provides the results of various scenario analyses.

Table A1 –Analysis Assumptions (blank cell means same as Revised Base Case)

Parameter	**Revised Base Case (Post ACD)**	**Base Case (NICE submission)**	**ERG base case**	**Continue Van PD**
Continue vandetanib at prog	0%	[redacted]		44%
Crossover to vandetanib	0%	[redacted]		
PFS distribution BSC	Weibull			
OS distribution BSC	Weibull			
PFS distribution vandetanib	Weibull			
OS distribution vandetanib	LogNormal	Weibull	Weibull	
Use RPSFT	Yes	No	No	
Pre-progression utility	0.87	0.84		
Progressed utility	0.52	0.64		
Discount for Vandetanib	[redacted]	[redacted]		
Oncologist outpt visits/yr	6	36.525		
Cost consultant visit	162.84	0		
Cost nurse visit	99.97	0		
Cost diarrhea	298.41	1102		
Cost hypertension	298.41	982		
Cost prolonged QT interval	298.41	1014		
Cost fatigue	298.41	0		
Cost appetite loss	298.41	1512		
Cost rash	298.41	1078		
Cost asthenia	298.41	0		
Cost dyspnea	298.41	896		
Cost back pain	298.41	1510		
Cost syncope	298.41	1067		

Table A2 – Revised base case results

	Revised base case			Original base case		
Outcome	**BSC**	**Vandetanib**	**Difference**	**BSC**	**Vandetanib**	**Difference**
Life Years	1.685	4.581	2.897	3.100	4.836	1.736
PFLYs	0.759	1.999	1.240	0.759	1.999	1.240
QALYs	1.141	3.078	1.937	2.135	3.491	1.356
Treatment Costs, pre-prog (£)	£0.0	[redacted]	[redacted]	£0.0	[redacted]	[redacted]
Treatment Costs, post-prog (£)	£0.0	£0.0	£0.0	[redacted]	[redacted]	[redacted] 8
Monitoring Costs (£)	£0.0	£3,513.7	£3,513.7	£385.8	£716.9	£331.1
Adverse Event Costs (£)	£41.8	£138.5	£96.7	£136.5	£409.3	£272.8
Cost of Best Supportive Care (£)	£2,514.3	£6,920.5	£4,406.2	£19,521.8	£24,506.4	£4,984.6
Costs of Palliative care	£6,236.0	£5,443.2	-£792.8	£5,916.9	£5,489.9	-£427.0
Total Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER: Life Years	--	--	£24,362	--	--	£25,801
ICER: PFLYs	--	--	£56,908	--	--	£36,116
ICER: QALYs	--	--	[redacted]	--	--	[redacted]

Revised Base Case (Post ACD) =Placebo OS adjusted for crossover and vandetanib OS based on observed OS. Parametric fits: Weibull function for BCS PFS, OS and vandetanib PFS; lognormal function for vandetanib OS. Cost and utility data based on the assessment group's report

Base case (NICE submission) = Evidence and results reported in the company's original submission (includes corrections post NICE clarification response)

Table A3 Scenario analyses

Result	RPSFT Weibull			RPSFT LogNorm			RPSFT LogLog		
	Placebo	Vandetanib	Difference	Placebo	Vandetanib	Difference	Placebo	Vandetanib	Difference
Life Years	1.685	4.309	2.624	1.802	4.581	2.780	1.911	4.405	2.494
PFLYs	0.759	1.999	1.240	0.759	1.999	1.240	0.759	1.999	1.240
QALYs	1.141	2.936	1.796	1.201	3.078	1.876	1.258	2.986	1.728
Treatment Costs, pre-prog (£)	£0.0	[redacted]	[redacted]	£0.0	[redacted]	[redacted]	£0.0	[redacted]	[redacted]
Treatment Costs, post-prog (£)	£0.0	£0.0	£0.0	£0.0	£0.0	£0.0	£0.0	£0.0	£0.0
Monitoring Costs (£)	£0.0	£3,513.7	£3,513.7	£0.0	£3,513.7	£3,513.7	£0.0	£3,513.7	£3,513.7
Adverse Event Costs (£)	£41.8	£138.5	£96.7	£41.8	£138.5	£96.7	£41.8	£138.5	£96.7
Cost of Best Supportive Care (£)	£2,514.3	£6,357.0	£3,842.7	£2,756.4	£6,920.5	£4,164.1	£2,982.9	£6,555.0	£3,572.1
Costs of Palliative care	£6,236.0	£5,628.9	-£607.	£6,207.5	£5,443.2	-£764.	£6,175.9	£5,477.3	-£698.

			1			3			6
Total Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER: Life Years	--	--	£26,745	--	--	£25,310	--	--	£28,002
ICER: PFLYs	--	--	£56,603	--	--	£56,736	--	--	£56,311
ICER: QALYs	--	--	[redacted]	--	--	[redacted]	--	--	[redacted]

Result	Continue Vand PD		
	Placebo	Placebo	Difference
Life Years	1.685	4.581	2.897
PFLYs	0.759	1.999	1.240
QALYs	1.141	3.078	1.937
Treatment Costs, pre-prog (£)	£0.0	[redacted]	[redacted]
Treatment Costs, post-prog (£)	£0.0	[redacted]	[redacted]
Monitoring Costs (£)	£0.0	£5,523	£5,523
Adverse Event Costs (£)	£41.8	£138.5	£96.7
Cost of Best Supportive Care (£)	£2,514.3	£6,920	£4,406
Costs of Palliative care	£6,236	£5,443	-£792
Total Costs (£)	[redacted]	[redacted]	[redacted]
ICER: Life Years	--	--	£41,198
ICER: PFLYs	--	--	£96,236
ICER: QALYs	--	--	[redacted]

RPSFT Weibull = Same as revised base case, but using Weibull function for PFS and OS for and BSC.; RPSFT LogNormal= Using LogNormal function for PFS and OS ; RPSFT LogLog = Using log logistic function
Continue VAD PD= Placebo OS adjusted for crossover and vandetanib OS based on observed OS and allowing continued vandetanib use post-progression ; includes additional costs associated with vandetanib use.

Probabilistic sensitivity analyses for each of the above analyses

The probabilistic sensitivity analysis (PSA) were redone using the survival curve parameters based on the Cholesky decomposition of the covariance matrix. Costs were varied using a log-normal distribution, and utilities were varied using a beta distribution. Figure A2 shows the scatter plot of the PSA results. Out of 1,000 reps, all points but one are in the upper-right quadrant, indicating that vandetanib increased both QALYs and costs. The mean incremental costs were [redacted] and the mean QALYs gained were 1.95. Incremental costs ranged from [redacted] to [redacted], and incremental QALYs ranged from -0.20 to 4.23. Figure A3 shows the cost-effectiveness acceptability curve, with the willingness to pay (WTP) threshold on the horizontal axis and the probability for vandetanib to be cost-effective at that WTP on the vertical axis. Vandetanib reaches a 50% probability of being cost-effective at a WTP of [redacted]. With a WTP of £50,000 per QALY, there is a [redacted] probability that vandetanib is cost-effective.

Figure A2 Scatter plot for PSA results in the base case scenario

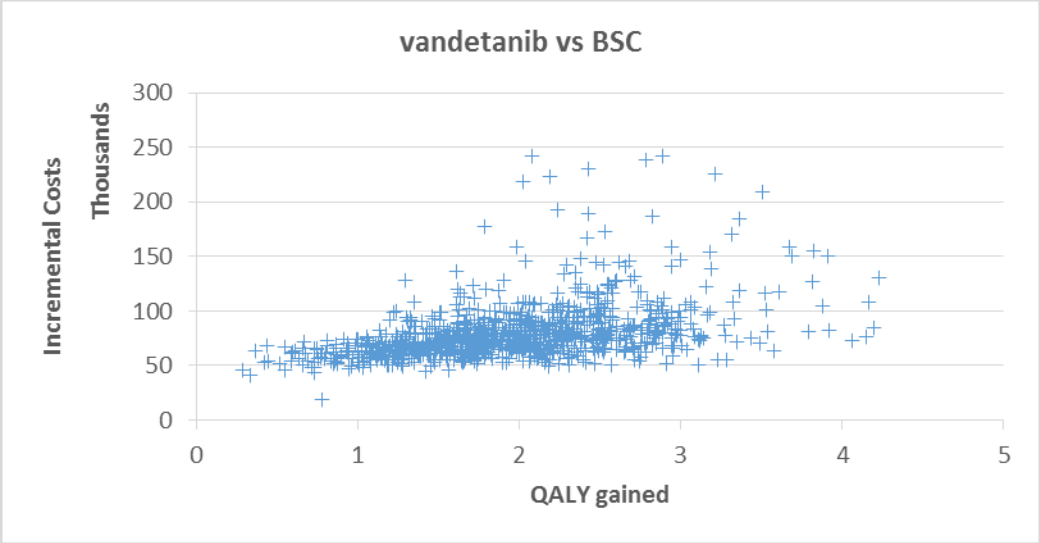
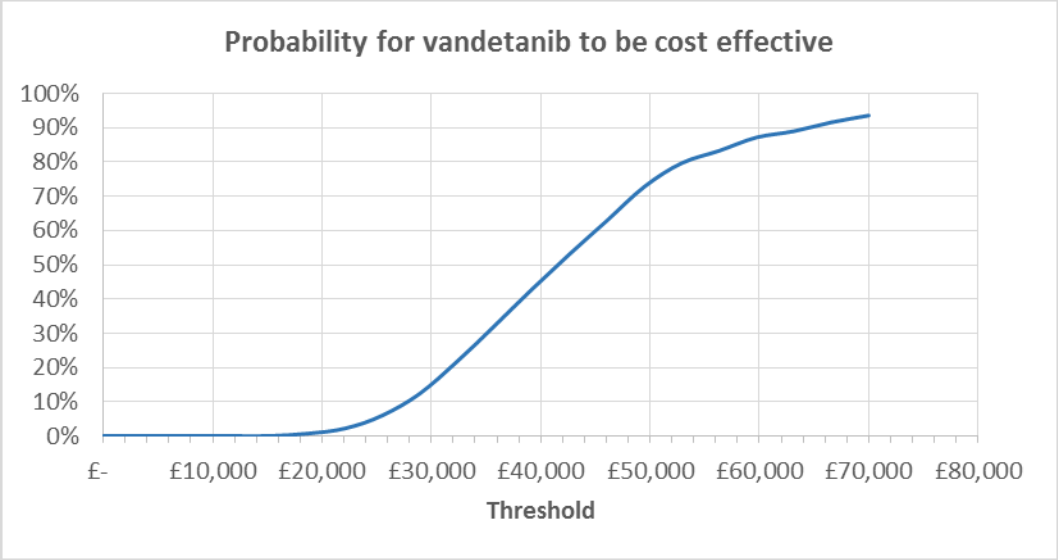


Figure A3 Cost effectiveness acceptability curve for the base case scenario



Conclusion

In concluding on the restricted population analyses, Sanofi Genzyme believe the additional analyses presented support the conclusions of our original submission that vandetanib is both clinically effective and cost-effective for the NHS compared to best supportive care, when used to treat patients in the base case population.

ICERs in the restricted EU population range from [redacted] via the ERG's estimate of [redacted]. This latter being very conservative as it assumes the [redacted] of patients receiving post-progression vandetanib received it for the rest of their lives, which is not likely in the UK setting. All ICERs are deterministic comparing vandetanib with BSC in the restricted EU population.

Sanofi Genzyme Genzyme recognises the concern raised by NICE with regards to the use of the rank preserving structural failure time model (RPSFT) for dealing with confounding due to crossover in the ZETA trial. To address this concern, the technical report below provides a detailed explanation of the application of the RPSFT approach to deriving adjusted overall survival in the restricted EU label population if given best supportive care without crossover.

We trust that in providing the additional analyses the Committee has sufficient reassurance to recommend vandetanib for the treatment of unresectable locally advanced or metastatic medullary thyroid cancer.

Technical report : Detailed explanation of the application of the rank preserving structural failure time approach.

Sanofi Genzyme Genzyme recognises the concern raised by NICE with regards to the use of the rank preserving structural failure time model (RPSFT) for dealing with confounding due to crossover in the ZETA trial. To address this concern, this Appendix provides a detailed explanation of the application of the RPSFT approach to deriving adjusted overall survival in the restricted EU label population if given best supportive care without crossover.

- **Endpoint:**

The analysis endpoint is overall survival (OS) from randomization to death or last date at which the subject was known to be alive, with follow-up through the [redacted] cut-off for the CSR addendum.

- **Study Population:**

The analysis was based on Restricted EU label population, which includes subjects who received randomized treatment and meet the following criteria:

- Progressive (documented progression within 12 months prior to enrollment) and symptomatic (at least one symptom at baseline, including pain score > 4, >=10 days of opioid use, diarrhea, flushing, fatigue, pain, nausea, dysphagia, dysphonia, respiratory symptoms, weight loss)
- Aggressive (CTN and CEA doubling times <=24 months at screening)

- **Demographic and Baseline Characteristics**

Demographic and key baseline characteristics for the Vandetanib and Placebo subjects are summarized in Table 1 below. Examination of the summary statistics for these characteristics revealed moderate differences between the two treatment groups for duration of disease and prior systematic therapy. Consequently, the survival analysis will be adjusted for these variables.

Table A4. Demographic and Baseline Characteristics

Parameter	Statistic	Vandetanib [redacted]	Placebo [redacted]
Age (years)	n	[redacted]	[redacted]
	Mean (Std)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
BMI at Baseline	n	[redacted]	[redacted]
	Mean (Std)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Duration of disease (years)	n	[redacted]	[redacted]
	Mean (Std)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Sex			
Female	n (%)	[redacted]	[redacted]
Male	n (%)	[redacted]	[redacted]
Race			
Oriental	n (%)	[redacted]	[redacted]
Caucasian	n (%)	[redacted]	[redacted]
RET mutational status			
Unknown	n (%)	[redacted]	[redacted]
Yes	n (%)	[redacted]	[redacted]
No	n (%)	[redacted]	[redacted]
Number of sites involved			
2	n (%)	[redacted]	[redacted]
3	n (%)	[redacted]	[redacted]
4	n (%)	[redacted]	[redacted]
5	n (%)	[redacted]	[redacted]
6	n (%)	[redacted]	[redacted]
7	n (%)	[redacted]	[redacted]
Primary Tumor			
TX	n (%)	[redacted]	[redacted]
T1	n (%)	[redacted]	[redacted]
T3	n (%)	[redacted]	[redacted]
T4b	n (%)	[redacted]	[redacted]
One Stage Classification			
IVB	n (%)	[redacted]	[redacted]
IVC	n (%)	[redacted]	[redacted]
Prior systematic therapy			
None	n (%)	[redacted]	[redacted]
Yes	n (%)	[redacted]	[redacted]

- **Time to Open Label Treatment**

Upon disease progression, all subjects (both active and placebo) will be unblinded and given the option to discontinue blinded study treatment and enter follow up and survival, or begin open label Vandetanib 300 mg treatment. Following the approval and implementation of the protocol Amendment 6, investigators will have the option to unblind any subjects remaining on blinded, randomized therapy. A total of [redacted] Placebo subjects crossed over to the open label treatment, and [redacted]. Vandetanib subjects entered into open label treatment. Time to open label treatment for the two treatment groups is summarized in Table A5 below using descriptive statistics.

Table A5. Time to Open Label Treatment

Parameter	**Statistic**	**Vandetanib** [redacted]	**Placebo** [redacted]
Time to Open Label Treatment (Days)	n	[redacted]	[redacted]
	Mean (Std)	[redacted]	[redacted]
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]

The mean time to open label treatment was much shorter for Placebo subjects than for Vandetanib subjects.

- **Analysis of Overall Survival with Unadjusted Data**

The median overall survival times based on Kaplan-Meier analyses, which are presented in Table A6 below, were [redacted] days and [redacted] days for the Vandetanib and Unadjusted Placebo groups, respectively. A Cox proportional hazards regression analysis of the overall survival data with terms for treatment, duration of disease, and prior systematic therapy yielded a hazard ratio of [redacted] (95% CI: [redacted] for Vandetanib vs. Unadjusted Placebo.

Tablele A6. Analysis of Overall Survival with Unadjusted Data

	Vandetanib [redacted]	**Unadjusted Placebo** [redacted]
Death, n	[redacted]	[redacted]
Median Survival Time (days)(95% CI) [1]	[redacted]	[redacted]
Hazard Ratio (Vandetanib vs. Unadjusted Placebo) (95% CI) [2]	[redacted]	

[1] Based on Kaplan-Meier analysis.
[2] Based on a Cox proportional hazards regression model with terms for treatment, disease duration and prior systematic treatment (yes or no).

- **Analysis of Overall Survival with Rank Preserving Structural Failure Time Model**
  The overall survival data for Placebo subjects who crossed over to open-label treatment with Vandetanib 300 mg were adjusted using the Rank Preserving Structural Failure Time Model (RPSFT) method. This method assumes an accelerated failure time model $(T = e^{-\eta} S$, where T is the observed overall survival time, S is the individual's counterfactual, or adjusted, overall survival time, and η is an unknown parameter, which must be estimated. It was done so by a grid search over possible values to find the value of η for which the value of the Wald chi-square statistic for treatment from a Cox proportional hazards regression model of overall survival with terms for treatment, duration of disease, and prior systematic therapy is closest to 0. This resulted in an estimate for η of -[redacted]. (Note that values of η <0 reflect a beneficial treatment effect.) . The list of values for η and the corresponding Wald Chi-Square Statistic for treatment are presented in table below.

Table A7. η Parameter Determination

η	**Wald Chi-Square Statistic for Treatment**
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]

- **Analysis of Overall Survival with Crossover Placebo Subjects Adjusted with RPSFT Method**

A Cox proportional hazards regression analysis of the RPSFT adjusted overall survival data with terms for treatment, duration of disease, and prior systematic therapy yielded a hazard ratio of [redacted] for Vandetanib vs. RPSFT Adjusted Placebo. A bootstrap analysis was performed in order to obtain a confidence interval estimate of the true hazard ratio (Vandetanib vs. RPSFT Adjusted Placebo) based on the RPSFT adjusted overall survival data. One thousand iterations were performed of the Cox proportional hazards regression analysis with terms for treatment, duration of disease, and prior systematic therapy. The 95% confidence interval of ([redacted]) for the true hazard ratio was obtained from the 2.5 and 97.5 percentiles of the resulting hazard ratios. These results are presented in Table 5 below. Kaplan- Meier overall survival curves for Vandetanib, unadjusted Placebo and RPSFT Adjusted Placebo are presented in Figure 1. Baseline covariates adjusted cumulative overall survival probability for Vandetanib vs. RPSFT Adjusted Placebo based on the Cox proportional hazards regression analysis are presented in Figure 2 below.

Table A8. Analysis of Overall Survival with Crossover Placebo Subjects Adjusted with RPSFT Method

	Vandetanib [redacted]	**RPSFT Adjusted Placebo** [redacted]
Death, n	[redacted]	[redacted]
Median Survival Time (days)(95% CI) [1]	[redacted]	[redacted]
Hazard Ratio (Vandetanib vs. RPSFT Adjusted Placebo) (95% CI) [2]	[redacted]	

[1] Based on Kaplan-Meier analysis.
[2] Survival times for the Placebo crossover subjects were adjusted by the RPSFT method. Results are based on a Cox proportional hazards regression model with terms for treatment, disease duration, and prior systematic treatment (yes or no). The 95% CI is based on the empirical cumulative distribution function of the hazard ratio of 1000 bootstrap iterations.

Figure A4. Kaplan-Meier Overall Survival Curves

Figure A5. Baseline Covariates Adjusted Cumulative Overall Survival Probability with Crossover Placebo Subjects Adjusted with RPSFT Method

- Parametric Overall Survival Analysis

Parametric analyses of the RPSFT adjusted overall survival data were performed assuming the following probability distributions using PROC LIFEREG of SAS: Weibull, log-normal, log-logistic, exponential, and gamma (overall analysis only). These analyses were performed by treatment arm and overall. The overall model included terms for treatment, duration of disease, and prior systematic therapy, while the by arm analyses dropped the treatment term. The parameter estimate results of these analyses are shown in Table 6, and the covariance matrices are shown in Table A9.

Table A9 Parametric Survival Analysis with Baseline Covariates Adjustment: Overall Survival with Crossover Placebo Subjects Adjusted with RPSFT Method (Parameter Estimates)

Analysis	Intercept	SE	Scale	SE	Shape	SE	Prior Trt.	Disease Dur.	Vandet	SE	AIC	BIC
Vandetanib												
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]			[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]			[redacted]	[redacted]
Exponential	[redacted]	[redacted]					[redacted]	[redacted]			[redacted]	[redacted]
Placebo	[redacted]											
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]			[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]			[redacted]	[redacted]
Exponential	[redacted]	[redacted]					[redacted]	[redacted]			[redacted]	[redacted]
All												
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exponential	[redacted]	[redacted]	[redacted]				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AIC = Akaike Information Criterion; BIC = Bayesian information Criterion; SE = standard error; Vandet = Randomized Vandetanib Treatment; Prior Trt.=Prior systematic treatment (Yes or No) Disease Dur.=Disease Duration

Note: For the All analyses, the parametric survival analysis was based on a model with terms for treatment, disease duration, and prior systematic treatment (yes or no). For the by arm analyses, the treatment term was dropped. The Gamma distribution model failed to converge for the by arm analysis and thus was not shown in the table.

Table A10 Parametric Survival Analysis with Baseline Covariates Adjustment: Overall Survival with Crossover Placebo Subjects Adjusted with RPSFT Method (Covariance Matrix)

Analysis	Variable	Intercept	Scale	Shape	Vandetanib	Prior Trt.	Disease Dur.
Vandetanib							
Weibull	Intercept	[redacted]	[redacted]			[redacted]	[redacted]
Weibull	Scale	[redacted]	[redacted]			[redacted]	[redacted]
Weibull	Prior Trt.	[redacted]	[redacted]			[redacted]	[redacted]
Weibull	Disease Dur.	[redacted]	[redacted]			[redacted]	[redacted]
Log-normal	Intercept	[redacted]	[redacted]			[redacted]	[redacted]
Log-normal	Scale	[redacted]	[redacted]			[redacted]	[redacted]
Log-normal	Prior Trt.	[redacted]	[redacted]			[redacted]	[redacted]
Log-normal	Disease Dur.	[redacted]	[redacted]			[redacted]	[redacted]
Log-logistic	Intercept	[redacted]	[redacted]			[redacted]	[redacted]
Log-logistic	Scale	[redacted]	[redacted]			[redacted]	[redacted]
Log-logistic	Prior Trt.	[redacted]	[redacted]			[redacted]	[redacted]
Log-logistic	Disease Dur.	[redacted]	[redacted]			[redacted]	[redacted]
Exponential	Intercept	[redacted]	[redacted]			[redacted]	[redacted]
Exponential	Prior Trt.	[redacted]	[redacted]			[redacted]	[redacted]
Exponential	Disease Dur.	[redacted]	[redacted]			[redacted]	[redacted]
Placebo							
Weibull	Intercept	[redacted]	[redacted]			[redacted]	[redacted]
Weibull	Scale	[redacted]	[redacted]			[redacted]	[redacted]
Weibull	Prior Trt.	[redacted]	[redacted]			[redacted]	[redacted]
Weibull	Disease Dur.	[redacted]	[redacted]			[redacted]	[redacted]
Log-normal	Intercept	[redacted]	[redacted]			[redacted]	[redacted]
Log-normal	Scale	[redacted]	[redacted]			[redacted]	[redacted]
Log-normal	Prior Trt.	[redacted]	[redacted]			[redacted]	[redacted]
Log-normal	Disease Dur.	[redacted]	[redacted]			[redacted]	[redacted]
Log-logistic	Intercept	[redacted]	[redacted]			[redacted]	[redacted]

Analysis	Variable	Intercept	Scale	Shape	Vandetanib	Prior Trt.	Disease Dur.
Log-logistic	Scale	[redacted]	[redacted]			[redacted]	[redacted]
Log-logistic	Prior Trt.	[redacted]	[redacted]			[redacted]	[redacted]
Log-logistic	Disease Dur.	[redacted]	[redacted]			[redacted]	[redacted]
Exponential	Intercept	[redacted]	[redacted]			[redacted]	[redacted]
Exponential	Prior Trt.	[redacted]	[redacted]			[redacted]	[redacted]
Exponential	Disease Dur.	[redacted]	[redacted]			[redacted]	[redacted]
All			[redacted]				
Weibull	Intercept	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Weibull	Scale	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Weibull	Vandetanib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Weibull	Prior Trt.	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Weibull	Disease Dur	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Log-normal	Intercept	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Log-normal	Scale	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Log-normal	Vandetanib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Log-normal	Prior Trt.	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Log-normal	Disease Dur	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Log-logistic	Intercept	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Log-logistic	Scale	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Log-logistic	Vandetanib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Log-logistic	Prior Trt.	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Log-logistic	Disease Dur	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Exponential	Intercept	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Exponential	Vandetanib	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Exponential	Prior Trt.	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Exponential	Disease Dur	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Gamma	Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	Scale	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Analysis	Variable	Intercept	Scale	Shape	Vandetanib	Prior Trt.	Disease Dur.
Gamma	Shape	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	Vandetanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	Prior Trt.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	Disease Dur	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Prior Trt.=Prior systematic treatment (Yes or No) Disease Dur.=Disease Duration

Note: For the All analyses, the parametric survival analysis was based on a model with terms for treatment, disease duration, and prior systematic treatment (yes or no). For the by arm analyses, the treatment term was dropped. The Gamma distribution model failed to converge for the by arm analysis and thus was not shown in the table.

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

Assessment Group critique of additional analyses submitted by Sanofi Genzyme

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25th September 2017

1. Introduction

In response to the Appraisal Consultation Document (ACD) for the multiple technology appraisal of cabozantinib and vandetanib for treating unresectable locally advanced or metastatic medullary thyroid cancer,[1] Sanofi Genzyme submitted additional evidence which includes:

- New analyses using the rank preserving structural failure time (RPSFT) approach to adjust for open-label vandetanib use in the placebo group of the Restricted EU label population of the ZETA trial.
- A revised health economic analysis which assesses the cost-effectiveness of vandetanib versus BSC for the Restricted EU label population. This new economic analysis includes: (i) a simple Patient Access Scheme (PAS) discount (now outdated); (ii) the use of the RPSFT-adjusted placebo arm overall survival (OS) curves for the best supportive care (BSC) comparator group and unadjusted curves for the vandetanib group, and (iii) other amendments made to the company's original base case model.[2, 3]

Since submitting this additional evidence, the company has revised their PAS.

This document provides a critique of the company's additional evidence document[3] (Section 2) together with further analyses conducted by applying the company's new survivor functions within the Assessment Group (AG) model, including the company's new PAS (Section 3). The AG's critique addresses four key concerns: (i) the questionable robustness of the company's RPSFT adjustment; (ii) issues surrounding the exploration and selection of parametric survivor functions for OS in the company's new model; (iii) the exclusion of post-progression vandetanib costs from the intervention group in the company's new model; (iv) the introduction of changes to other model parameters which reflect neither the company's original base case model nor the AG model. Other concerns regarding the appraisal process raised within the company's ACD response[2] are not addressed within this critique.

2. Critique of the company's additional evidence

2.1 Adjustment for treatment switching in the placebo group of the ZETA trial

Use of the RPSFT model for the EU label population

The AG does not agree with the company's justification for not presenting the RPSFT estimates from the broader EU label population of the ZETA trial. The company's additional analyses document[3] (page 1) states that the RPSFT-adjusted estimates in the broader EU label population could not be *"validly used in the model"*. The AG believes that the resulting estimates would be valid, but that they probably do not indicate a significant treatment response. However, this cannot be verified by the AG as the results of the analyses have not been presented by the company.

Use of the RPSFT model for the Restricted EU label population

The company provided additional information on the application of the RPSFT method to adjust for cross-over in the Restricted EU label population of the ZETA trial, resulting in an RPSFTM-adjusted hazard ratio (HR) of [redacted] (95% confidence interval [CI] [redacted]). Figure 1 presents the Kaplan-Meier OS curves for the vandetanib arm (red, N=[redacted]), the unadjusted placebo arm (blue, N=[redacted]) and the RPSFTM-adjusted placebo arm (green).

Figure 1: Restricted EU label KM OS curves (reproduced from company's additional analyses document, Figure A4)

The AG considers that the company's adjusted analysis should be interpreted with caution for the following reasons:

- Adjustment for cross-over using RPSFT was considered in the original submission,[4] but the procedure was considered to have *"failed to undo bias"*, providing *"effects very close to the null"*.[5] It is unclear why the company's new results are considerably different.
- The company has raised concerns that the common treatment effect assumption may not be plausible since "*patients who crossed over from [the] placebo arm to receive open label vandetanib are patients with progressive disease, and the capacity for a patient to benefit may be different compared to patients with indolent disease and progressive disease.*"[5]

- RPSFT assumes perfect randomisation (if no treatment was given, equal average survival would be expected in the two groups). The assumption is violated in this case, as the use of a subgroup breaks the original randomisation of the RCT. Although the issue can be addressed by appropriate covariate adjustment, the small sample size (n=[redacted]) is a limiting factor.
- The adjustment procedure corrects for patients from the placebo group who then went on to receive vandetanib. However, no adjustment is made for patients continuing vandetanib treatment after progression. This would be expected to reduce the estimated treatment effect.
- The analysis presented by the company includes adjustment for two covariates - disease duration and prior therapy. The AG considers that covariate adjustment is a reasonable approach; however, justification for the selection of these covariates (and not others, which may also be imbalanced between the treatment groups) was not provided. The AG would expect to see a justification for the chosen model, including results for different combinations of covariates.
- The bootstrapping procedure used to produce the 95% CI was inappropriate and underestimates the uncertainty around the adjusted HR. If implemented correctly, the AG would expect the 95% CI to contain 1.0 (thereby conforming with the 95% CI from the unadjusted analysis).
- Consideration of re-censoring is generally recommended when the RPSFT method is used; this has not been addressed.
- The methodological framework of the RPSFT approach is described briefly on page 10 of the additional analyses document.[3] The statistical model for a general accelerated failure time (AFT) model is given, but the description does not cover aspects that are crucial for the estimation process, such that counterfactual survival time is a sum of observed time spent on treatment and observed time spent off treatment. A more thorough description would be required in order to judge whether the method has been applied appropriately. SAS was used for the analysis, for which there is only user-contributed treatment switching software available. There is therefore a higher chance that the methods may have been incorrectly implemented, compared to if the analyses had been performed in STATA (for which peer-reviewed packages exist).

2.2 Concerns regarding the company's exploration and selection of parametric functions to model PFS and OS

The AG has a number of concerns regarding the company's new survival analyses based on the RPSFT-adjusted placebo group data and the unadjusted vandetanib group data:

- The company selected preferred OS curves for their new base case on the basis of the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC). These statistics provide a measure of the relative goodness-of-fit of competing parametric models, but relate

only to the observed period of the study. No consideration has been given to the clinical plausibility of the competing curves.

- Only a subset of the range of potentially plausible candidate parametric functions can be selected as options within the executable model (the log normal, log logistic and Weibull functions). Table A9 of the company's additional analyses document[3] indicates that exponential and gamma functions were also included in the curve-fitting exercise, however these functions cannot be applied within the executable model.
- The AG's clinical advisor stated a preference for the log normal function for PFS and the Gompertz function for OS (for both treatment groups). This combination of survivor functions cannot be assessed using the company's new model.
- The intercept parameters shown in Table A9 of the company's additional analyses document[3] do not match those used in the new model (vandetanib OS log normal reported intercept=[redacted],[3] vandetanib log normal intercept applied in company's model=[redacted]; placebo Weibull reported intercept=[redacted],[3] placebo Weibull intercept applied in company's model=[redacted]). The AG is unclear whether these discrepancies reflect reporting errors in the company's additional analyses document,[3] or whether incorrect survival function parameters have been applied in the company's new model.
- The company's original model[4] included the selection of the Weibull function for PFS and OS for both the vandetanib and BSC groups. The company's new model[3] applies the log normal model for OS in the vandetanib group. Given that no adjustment has been made to the vandetanib group OS data (see Section 2.1), the justification for selecting a different parametric function to model OS for this group is unclear.

2.3 Exclusion of post-progression vandetanib costs from the intervention group of the company's new model

Within the company's original base case analysis,[4] no adjustment was made to account for treatment switching in the placebo group ([redacted]), or for the continued use of vandetanib following disease progression ([redacted]). As such, the company's original economic analysis included the costs of post-progression vandetanib use in both groups. Clinical advisors to the AG noted that the continued use of vandetanib beyond disease progression does not reflect usual clinical practice in England, hence the survival outcomes observed in the intervention group reflect an atypical treatment pathway. One clinical advisor suggested that if imaging showed a mixed response with the largest or most symptomatic/problematic lesions being stable and some other lesions progressing, vandetanib may still be continued; the advisor did however consider this scenario to be uncommon.[6]

The company's new RPSFT analysis attempts to adjust for the use of open-label vandetanib use in patients who were initially randomised to the placebo group of the ZETA trial. However, as noted in Section 2.1, no attempt has been made to adjust for post-progression vandetanib use in the intervention group. As shown in Table A1 of the company's additional analyses document,[3] the costs of post-progression vandetanib have been set to zero within the company's new base case analysis. These costs are substantial: based on the company's new base case assumptions (as submitted), post-progression vandetanib costs, if included, account for [redacted] of the total cost for the vandetanib group. The AG considers that it is likely that patients who received vandetanib post-progression accrued some benefit from the drug, yet the costs associated with generating these additional health gains have been excluded from the company's new analysis. The AG considers the exclusion of these costs to be inappropriate. The AG also notes however, that the assumption of continued post-progression treatment until death in these patients may lead to some overestimation of the ICER for vandetanib versus BSC.

2.4 Other model parameters which have been altered

The company's ACD response[2] and additional analyses document[3] both state that cost and utility data for the new model are based on the AG report.[6] This statement is inaccurate: the company's new model includes a number of parameters which are different from those used in both the AG model and the company's original model (see
Table **1**):

(1) *Health utilities.* Within the company's new model, the health utility estimates for the progression-free and post-progression states have been set equal to 0.87 and 0.52, respectively. The AG model assumed utility values of 0.80 and 0.50, respectively; these were taken from a time trade-off study reported by Fordham *et al*.[7] The company's original model assumed utility values of 0.84 and 0.64, respectively; the progression-free utility estimate was derived by mapping FACT-G data collected in the ZETA trial to the EQ-5D,[8] whilst the post-progression state value was estimated by applying a disutility sourced from a study of patients with advanced melanoma (Beusterien *et al*[4]). The source of the company's new utility values and the justification for their use are unclear. Applying the AG's utility values increases the ICER for vandetanib.

(2) *BSC costs.* The company's new model applies costs of £788.00 and £2,070.00 for BSC in the progression-free and post-progression states, respectively. In contrast, the AG's model assumed an annual cost for BSC of £2,998.21 in both the progression-free and post-progression states. Applying the AG's BSC costs increases the ICER for vandetanib.

(3) *Monitoring costs.* The company's new model applies a lower cost of vandetanib monitoring (additional to BSC costs) compared with the AG model. Within the company's new model, the additional costs of vandetanib monitoring are estimated to be £2,753.96 in the first year and £1,776.86 in subsequent years. The total health state costs for patients on vandetanib applied in

the AG model are £5,152.41 in the first year and £3,408.16 in subsequent years. Applying the AG's vandetanib monitoring costs increases the ICER for vandetanib.

Table 1: Differences between parameter values used in the company's new model, the company's original model, and the Assessment Group model

Parameter	Assessment Group model[6]	Company's new model[3]	Company's original model[4]
Utility progression-free	0.80	0.87	0.84
Utility post-progression	0.50	0.52	0.64
BSC costs progression-free (annual)	£2,998.21	£788.00	£788.00
BSC costs post- progression (annual)	£2,998.21	£2070.00	£8,083.43
Vandetanib monitoring costs year 1 (annual)	£5,152.41	£2,753.96*	£400.00
Vandetanib monitoring costs year2+ (annual)	£3,408.16	£1,776.86*	£200.00

**additional to BSC costs*

The company's original model included a parameter which reflected reduced costs for patients who discontinued vandetanib prior to disease progression ([redacted]). Whilst these patients could have discontinued treatment at any time, the model assumed that they incur no drug costs (i.e. all patients are assumed to have discontinued at Day 0). The AG believes that this was an unreasonable assumption. Given the absence of evidence to quantify how much vandetanib was received by these patients, the AG model applied half of this total cost. With respect to their original assumption, the company stated in their response to the consultation of the Assessment Report that they *"agree that it was an overestimate."*[9] The company's new model includes additional syntax which appears to apply a linear increase in the proportion of patients who are progression-free and have discontinued vandetanib (as detailed in the company's response to consultation on the Assessment Report[9]). This amendment is not described in the company's additional analysis document[3] and the AG believes that the company's new approach is arbitrary.

3. Additional analysis – application of the company's new PFS and OS survivor functions within the Assessment Group model

Notwithstanding the AG's concerns regarding the robustness of the company's new RPSFT analysis, additional analyses were undertaken by the AG to explore the impact of using the company's new survivor functions on the cost-effectiveness of vandetanib versus BSC (see Table 2). Given the differences between the AG model and the company's model with respect to the approach used to model time-dependent monitoring costs and state dependent BSC costs, it was deemed that the most straightforward means of implementing company's new survivor functions under the AG's preferred assumptions would be to apply these directly within the original AG model.[6] The following amendments were made to the AG model:

1. The Restricted EU label population was selected

2. The new vandetanib PAS was incorporated (discount updated 25th September 2017)
3. The cumulative PFS and OS probabilities in the AG model were replaced with the company's new PFS and OS functions
4. A minor error in the AG model was identified whereby the proportion of patients discontinuing vandetanib prior to progression were still accruing monitoring costs rather than BSC costs. This error, which related only to the analysis of the Restricted EU label analysis, was rectified. Correcting this error has a negligible effect on the ICER for vandetanib.

All other assumptions and data were retained as per the AG's base case analysis.[6]

Table 2: Additional analysis undertaken by the Assessment Group using the company's new survivor functions (note – all results include the company's new PAS dated 25th September)

Analysis	Vandetanib versus BSC		
	Inc. QALYs	Inc. costs	ICER
(1) Company's new base case[3]	1.94	[redacted]	[redacted]
(2) AG model original base case, post-progression vandetanib use in both groups	1.64	[redacted]	[redacted]
(3) AG model with monitoring cost error corrected, post-progression vandetanib use in both groups	1.64	[redacted]	[redacted]
(4) AG model including company's new PFS and OS curves, BSC group post-progression costs set equal to zero, vandetanib group post-progression costs included (preferred analysis)	1.79	[redacted]	[redacted]
(5) AG model including company's new PFS and OS curves, post-progression costs set equal to zero in both groups	1.79	[redacted]	[redacted]
(6) AG model including company's new PFS and OS curves, post-progression costs set equal to zero in both groups, vandetanib pre-progression discontinuation parameter set equal to 1.0	1.79	[redacted]	[redacted]

On the basis of these analyses, the AG's preferred ICER for vandetanib versus BSC using the company's new RPSFT-adjusted OS analyses is [redacted] per QALY gained. The AG recognises however that this is likely to represent an overestimate due to the assumption of ongoing post-progression vandetanib use until death in a proportion of patients. The AG also notes that owing to the questionable reliability of the company's RPSFT analysis, any ICER derived on the basis of the company's new OS functions should be interpreted with caution.

4. References

1. National Institute for Health and Care Excellence. Cabozantinib and vandetanib for treating medullary thyroid cancer - Appraisal Consultation Document. London; 2017.
2. Sanofi-Genzyme. Multiple Technology Appraisal: cabozantinib and vandetanib for treating medullary thyroid cancer - Response to the NICE ACD. Surrey, UK; 2017.
3. Sanofi-Genzyme. Appendix 1: Additional analyses on the Restricted EU label in response to the NICE ACD. Surrey, UK; 2017.
4. Sanofi-Genzyme. Multiple technology appraisal. Vandetanib for treating unresectable locally advanced or metastatic medullary thyroid cancer (ID56). Company's evidence submission. Surrey, UK; 2017.
5. Sanofi-Genzyme. Final clarification questions 29th March 2017. Surrey, UK; 2017.
6. Tappenden P, Carroll C, Hamilton J, Kaltenthaler E, Wong R, Wadsley J*, et al.* Cabozantinib and vandetanib for treating unresectable locally advanced or metastatic medullary thyroid cancer [ID56]. Sheffield, UK; 2017.
7. Fordham BA, Kerr C, de Freitas HM, Lloyd AJ, Johnston K, Pelletier CL*, et al.* Health state utility valuation in radioactive iodine-refractory differentiated thyroid cancer. *Patient Preference & Adherence* 2015;9:1561-72.
8. Beusterien K, Szabo S, Kotapati S, Mukherjee J, Hoos A, Hersey P*, et al.* Societal preference values for advanced melanoma health states in the United Kingdom and Australia. *British Journal of Cancer* 2009;101:387-9.
9. Sanofi-Genzyme. Multiple technology appraisal. Vandetanib for treating unresectable locally advanced or metastatic medullary thyroid cancer (ID56). Company's response to assessment report consultation. Surrey, UK; 2017.