NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Vandetanib for treating medullary thyroid cancer [ID1415]

Vandetanib was originally included in the scope for ID56, but as we were unable to release any recommendations for it at the same time as cabozantinib, this was separated out.

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. **Evidence provided by the company** Sanofi

3. **Assessment Group review of evidence**, produced by the School of Health and Related Research (ScHARR)

4. **Response to questions from Dr Mary Lei, clinical expert**

5. **Response to questions from Professor Peter Clark, CDF clinical lead**

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 cabozantinib. NICE recommendations on cabozantinib are published separately in Technology Appraisal 516.

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'.	Please note previously published response in Technology Appraisal (TA) 516. Patient and patient organisation input was fully considered by the NICE appraisal committee, and has been documented in sections 3.1 and 3.10 of the Final Appraisal Document (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'	Please note previously published response in TA516. The committee acknowledged the rarity of the disease in its appraisal of vandetanib (see section 3.23 of the FAD). However, it considered that the ICERs were too high to justify considerable deviation from NICE principles in terms of what is normally considered a cost-effective use of NHS resources.
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	Please note previously published response in TA516. The committee recognised that medullary thyroid cancer is rare. Please see section

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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."	3.23 of the FAD for the committee's 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 3.10 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.
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.	Please note previously published response in TA516. 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 3.4 of the FAD, where the 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	**Inequalities** AMEND believes that it is unacceptable and unethical for the 5th largest economy in the world to not be	Please note previously published response in TA516. Cabozantinib

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		Endocrine Neoplasia Disorders (AMEND)	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	is now recommended as a treatment option.
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.	Please note previously published response in TA516. Cabozantinib is now recommended as a treatment option.
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.	Please note previously published response in TA516. Cabozantinib is now recommended as a treatment option. Comments received from patients and carers during consultation were presented to the appraisal committee. The slides are included in the committee papers for information.
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" "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?"	Please note previously published response in TA516. Cabozantinib is now recommended as a treatment option.
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 previously published response in TA516. Cabozantinib is now recommended as a treatment option. NICE continued discussions with Sanofi and the appraisal committee considered a

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				new submission from the company but was unable to recommend vandetanib because it is not cost-effective.
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.	Please note previously published response in TA516. Please see sections 3.19-3.20 of the FAD for the committee's full considerations with regard to the end of life criteria, and also section 3.23 where the committee's considerations about the rarity of the disease are described. The addendum to NICE's methods guide for appraising life-extending, end-of-life treatments advises committees on the circumstances in which it might be appropriate to recommend treatments where the cost-effectiveness estimates are above the normal threshold range. Cabozantinib is now recommended as a treatment option.
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.	Please note previously published response in TA516. 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.	Please note previously published response in TA516. 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.
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	Please note previously published response in TA516. The committee noted expert advice that patients with progressive and symptomatic

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			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.	disease were likely to have tumour biomarker doubling times of 24 months or less, but that biomarker trends did not form part of the decision to start treatment. The committee also considered it clinically inappropriate to wait for biomarker trends before starting treatment for people with progressive and symptomatic disease. Please see section 3.3 of the FAD.
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.	Please note previously published response in TA516. See section 3.10 of the FAD where this wording has been amended. 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…..'.	Please note previously published response in TA516. Cabozantinib is now recommended as a treatment option. Vandetanib did not meet the criteria for inclusion in the Cancer Drugs Fund. See sections 3.21-3.22 of the FAD.
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 be approved, the remaining treatment options for patients will be limited in both number and effect.	Please note previously published response in TA516. Cabozantinib is now recommended as a treatment option.
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.	Please note previously published response in TA516. Cabozantinib is now recommended as a treatment option.
18	Company	Sanofi	Sanofi Genzyme would like to thank the Appraisal Committee (AC) and the Assessment Group for its	Comments noted. The committee

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			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	recognised the limited treatment options for patients with medullary thyroid cancer but could not recommend vandetanib because of significant uncertainty about the clinical effectiveness of the drug, and cost-effectiveness estimates being much higher than what NICE normally considers to be an acceptable use of NHS resources. The points summarised below were discussed at the NICE appraisal committee meeting on 27th September 2017 (please see the slides presented, available via the NICE website). Please see responses below which separately address each of the points raised.

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			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. • **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:	Comments noted. The committee noted expert advice that patients with progressive and symptomatic disease were likely to have tumour biomarker doubling times of 24 months or less, but that biomarker trends did not form part of the decision to start treatment. The committee also considered it clinically inappropriate to wait for biomarker trends before starting treatment for people with progressive and symptomatic disease. Please see section 3.3 of the FAD. The committee considered if it could recommend vandetanib for use in the Cancer Drugs Fund, but did not consider that data collection would address the uncertainties in the evidence, or that there was a benefit to the NHS from collecting data on patient characteristics. Please see sections 3.21-3.22 of the FAD for the committee's full considerations. As acknowledged, biomarker doubling is "not an explicit criteria used to determine whether treatment should be initiated", and the response to consultation on the Assessment Group's report clarified that "we are not suggesting there *must* be additional criteria for CTN/CEA doubling times . . in practice for patients to be eligible for

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			[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. • **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**	vandetanib." The committee considered all the clinical effectiveness evidence received from the company as per section 3.7 of the guide to the processes of technology appraisal, including the secondary endpoints from the ZETA trial. The additional evidence and revised economic analyses were considered by the committee. See sections 3.6-3.7 of the FAD. The committee acknowledged that patients with symptomatic and

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			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. 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?	progressive disease are also likely to have tumour biomarker doubling times of 24 months or less, but because biomarker trends do not form part of the decision to start treatment it did not consider the restricted EU subgroup to be relevant to clinical practice. Please see section 3.3 of the FAD. The relevant patient population was again discussed at the 2nd and 3rd appraisal committee meetings, and the committee took account of the advice heard from the clinical experts. The EU population included patients with progressive and symptomatic disease, which matched the EXAM trial population which the committee had concluded was relevant to clinical practice, and the criteria for using TKIs. Please see section 3.3 of the FAD.

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			- 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 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).	Comments noted. The committee acknowledged the small numbers of patients covered by the marketing authorisation for vandetanib. 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. The committee recognised the ultra-orphan status of medullary thyroid cancer. It acknowledged the difficulty of appraising drugs for very rare conditions. However, it considered that the ICERs were too high to justify considerable deviation from NICE principles in terms of what is normally considered a cost-effective use of NHS resources. Please see section 3.23 of the FAD.

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			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.	The committee was aware that vandetanib did not meet the criteria for consideration through the Highly Specialised Technologies process because the disease is not chronic, does not require lifelong treatment and is not treated exclusively within a highly specialised service (see section 3.23 of the FAD).

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			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 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.	The committee considered that the crossover-adjusted analysis did not include the patient population relevant to clinical practice and was not sufficiently robust for decision-making (see sections 3.6-3.7 of the FAD), and that EXAM was the most reliable source of survival estimates in the population that reflected clinical practice. See sections 3.19-3.20 of the vandetanib FAD for the committee's full considerations. The committee concluded that vandetanib could be considered to meet the criterion for extension to life. The addendum to NICE's methods guide for appraising life-extending, end-of-life treatments advises committees on the circumstances in which it might be appropriate to recommend treatments where the cost-effectiveness estimates are above the normal threshold range. Please see sections 3.19 and 3.20 for committee's full considerations regarding the end of life criteria.
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"	Comments noted. The committee recognised the crossover design of ZETA, and that the results are more likely to show the effect of immediate vandetanib compared with delayed vandetanib. Please see section 3.5 of the FAD.

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			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.	The committee heard from clinical experts that the decision to start treatment is based on radiological progression and when the disease becomes symptomatic. Please see section 3.3 of the FAD. The committee heard from the clinical experts the importance of balancing the risks and benefits when considering starting treatment with vandetanib. Please see section 3.10 of the FAD where the wording has been amended with regard to reference to the side-effect burden. The committee acknowledged the uncertainty regarding the precise ICER estimate for vandetanib, but considered that the most plausible estimate was significantly higher than £100,000 per QALY gained compared with cabozantinib, and higher than £50,000 per QALY gained compared with best supportive care. Please see sections 3.16 and 3.17 of the FAD. The committee considered that the ICERs were too high to justify considerable deviation from NICE principles. Please see section 3.23

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				of the vandetanib FAD.
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. The committee considered the ultra-orphan status of medullary thyroid cancer. Please see section 3.23 of the FAD for committee's full considerations.
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.	Comment noted. Please see earlier responses.
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. Please see earlier responses regarding the limited treatment options and the budget impact of these treatments.
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.	Comment noted.
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	Comments noted. Please note section 1.2 of the FAD which clarifies that the recommendation is not intended to affect treatment with vandetanib that was started in

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			side-effects. *[References provided but not reproduced here]*	the NHS before the guidance was published.

Summary of comments received from members of the public

Theme	NICE Response
There are no other effective treatments available	Please note previously published response in TA516. The committee recognised the limited treatment options for patients with medullary thyroid cancer. Please note that cabozantinib is now recommended as a treatment option.
TKIs can prolong survival and improve quality of life, and the side effects are tolerable because of this	Please note previously published response in TA516. The committee took into account the patient representative's perspective on the side effects of treatment (please see section 3.10 of the FAD). However, the committee considered that the data presented did not show evidence of prolonged survival. Please see sections 3.5-3.7 of the FAD for the committee's full considerations regarding the clinical effectiveness of vandetanib. Please note that cabozantinib is now recommended as a treatment option.
Not meeting the end of life criteria by 'living too long' is unacceptable	Please note previously published response in TA516. Please see sections 3.19-3.20 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.
Overall survival benefit is difficult to show with trial data because crossover is common	Please note previously published response in TA516. 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.
MTC is a very rare condition; overall cost is low because so few patients need these drugs	Please note previously published response in TA516. The committee acknowledged the rarity of the disease; please see sections 3.1 and 3.23 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.
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	Please note previously published response in TA516. Please note that cabozantinib is now recommended as a treatment option.

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

Department of Health

10 August 2018

Dear Helen,

Re: Vandetanib for the treatment of medullary thyroid cancer [ID1415]

Thank you for the opportunity to provide further information to support the assessment of vandetanib for the treatment of medullary thyroid cancer (MTC).

Since submitting our response on 27 July 2018, the Assessment Group identified a model error and requested responses to four further clarifications questions. We have corrected the error and this response is based on the corrected model results. It also includes responses to the additional clarification questions at the end of the letter.

Fewer than 40 UK patients are treated each year with a TKI for MTC. In the last three years, the TKI products, both vandetanib and carbozantinib have been available on the CDF, the number of patients treated with vandetanib has not varied, peaking between [redacted] (English adult) patients. This is an extremely small, stable patient population.

Twenty five percent of MTC is hereditary. Because of this patients, including families with the third generation to be affected by this disease, made powerful submissions to NICE in response to the negative ACD, seeking continued access to the same treatments options that were available in the CDF. The recommendation for cabozantinib is positive for patients but, as was explicit in the CDF allowing both TKIs to be listed, these drugs are not equivalent or interchangeable and there is a need for both to be available. It is important to note that, unlike cabozantinib, vandetanib has only this indication. It is not licensed for use in any other disease.

In response to the negative ACD and the patient submissions Sanofi has submitted a revised simple patient access scheme (discount of [redacted] off the list price) and continues to strive for a positive NICE recommendation for vandetanib. In line with NICE's Social Value Judgements document, Sanofi is of the opinion that the usual NICE assessment route is not appropriate for such a small patient population due to the inherent uncertainty in data related to such small patient numbers. However, Sanofi has fully engaged with this assessment and continues to do so, providing a significant volume of evidence to support Committee decision making in response to clear patient need.

Sanofi is requesting consideration of vandetanib in a population of MTC patients who are, 'in real need for treatment i.e. with a symptomatic-aggressive course of the disease' [Caprelsa SmPC]. Sanofi has defined this for the purpose of the decision problem as: patients that are symptomatic, progressive (according to radiographic imaging) and have CTN/CEA biomarker doubling time less than 24 months. We are of the view this population is aligned with patients identified by the CHMP/EMA as suitable for treatment with vandetanib and representative of UK-treated patients.

Sanofi acknowledges that the [redacted] crossover from BSC to active treatment and the [redacted] of patients who continued active treatment, after primary endpoint of PFS was met and the study was unblinded, confounds the Overall Survival data. However, throughout this assessment Sanofi has put forward methodological approaches to mitigate both small patient numbers and cross over. Most recently RPSFT modelling has been used to address cross-over. A novel, potential, approach to address post-progression use of vandetanib in the vandetanib arm is also described. The approach adopted in the original Feb 2017 submission, using the full dataset with coefficients for the variables of interest, is a plausible way of addressing small patient numbers, although not able to deal with cross-over.

Sanofi believes the restricted population, as defined in our submission, meets the End of Life criteria based on the most plausible scenarios.

Survival gain > 3 months

The smallest mean survival gain for vandetanib compared with BSC, from the most plausible set of analyses, is [redacted] years ([redacted] months; no RPSFT model, with baseline covariate adjustment, both OS curves Weibull) the largest mean survival gain is [redacted] years ([redacted] months; with RPSFTM, no baseline covariate adjustment, OS curves for BSC and vandetanib being Weibull and exponential respectively). We feel this range should give the committee confidence that in this population no analyses produced a survival gain less than the 3 months required by the EoL criteria.

Patients with a short life expectancy, normally less than 24 months

The crossed over data are particularly problematic in assessing this EoL criterion: the usual life expectancy of patients in the restricted population, as a reminder, [redacted] of BSC patients received active treatment. Therefore, assessment against this criterion needs to be based on the RPSFT modelling undertaken to describe an uncrossed BSC arm.

Overall Survival estimates for BSC from the economic model range from [redacted] years (BSC, RPSFTM, no baseline adjustment, Weibull) to [redacted] years (BSC, RPSFTM, with baseline adjustment, Weibull). All estimates for the BSC arm with any RPSFT model are under two years.

Therefore, Sanofi believes this medicine meets the End of Life criteria for assessment:

1. The patient population with a CTN/CEA biomarker doubling time have a prognosis of less than 24 months
2. The use of vandetanib extends survival in these patients by more than three months
3. There are currently only [redacted] adult and paediatric patients in the UK and Ireland that represent the prevalent population.

In response to the request from the AG and for clarity regarding the analyses, Sanofi have produced an extensive number of analyses in order to understand the uncertainty associated with a recommendation for this group of patients. We believe these should support both decision making and understanding of the uncertainty associated with this population.

All the analyses that include the RPSFT modelling produce BSC OS estimates and vandetanib survival gain estimates that meet the End of Life criteria.

- Survival estimates for BSC and vandetanib from analyses accounting for cross-over demonstrate vandetanib meets NICE's End of Life criteria.
- All ICER estimates that adjust for cross-over and baseline covariates fall below £50,000/QALY when post progression costs are zero.
- Exploratory analyses that aim to remove the benefit of post-progression use of vandetanib result in ICERs below £40,000/QALY.
- The only ICERs that exceed £50,000/QALY are those that include post-progression vandetanib costs.
- NICE should be reassured that the true ICER falls below £50,000/QALY.
- Finally, in line with criteria for EOL, the restricted population, as defined in our submission, is a distinct subgroup of patients who can be readily identified within the NHS.

The results suggest that even with uncertainty due to small patient numbers, in the restricted population, vandetanib offers the NHS good value for money according to the EoL criteria in the treatment of this extremely rare cancer. Further, Sanofi would suggest that although the trial data are limited ([redacted]) given this 'sample population' is larger than the true population that it is intended to describe, it must be sufficient for decision making purposes.

However, small patient numbers lead to residual uncertainty and Sanofi would like to mitigate against use of vandetanib outside of the restricted population, that may not be considered good value for money in the NHS, by committing to work with the treatment centres to support them to use vandetanib in this patient population only.

Sanofi hopes that this commitment to work with the treatment centres, in addition to a revised simple patient access scheme and the extensive data presented will give the Appraisal Committee confidence that the uncertainty due to small patients numbers is managed as well as it can be.

Given the significant burden of this disease for this patient population, the extremely small number of patients and the convergence of ICERs below the £50,000 threshold regardless of the analytical method used, Sanofi kindly requests that the Committee is pragmatic in its consideration of vandetanib for MTC.

Best wishes

Claire GRANT

Head of Health Outcomes
UK & Ireland

Please note commercial-in-confidence information are highlighted in [redacted]; academic-in-confidence information are highlighted in [redacted]

Contents

Part 1: Rationale for seeking assessment of vandetanib in the 'restricted patient population': UK practice aligns with the SmPC

Sanofi's base case population throughout this appraisal has been the 'restricted label population', that is, MTC patients who meet three criteria: symptomatic, progressed (according to radiographic imaging) and have CTN/CEA biomarker doubling time of less than 24 months. We believe that these patients are those 1) the EMA intended to be treated with vandetanib according to its license wording 2) align with the usual UK treated patient population under CDF 3) with optimal benefit/risk balance for vandetanib treatment 4) with most potential to benefit and therefore whose treatment is a good use of NHS resources.

The indication wording for vandetanib is:

> *Caprelsa is indicated for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease.*

The word 'aggressive' in the label does not have a clinically specific meaning and is therefore open to interpretation. Section 4.4 of the SmPC contains clarifying text that refers explicitly to CTN/CEA biomarker levels (underlining added by Sanofi):

> "4.4 Special warnings and precautions for use
> In view of the associated risks, it is important to limit treatment with vandetanib to patients who are in real need for treatment, i.e. with a symptomatic-aggressive course of the disease. Either symptomatic disease or progressive disease alone is not enough to prompt the need of treatment with vandetanib. Rate of change in biomarker levels such as of calcitonin (CTN) and/or carcinoembryonic antigen (CEA) as well as the rate of change of tumour volume during watchful waiting might <u>help to identify not only patients in need for treatment but also the optimal moment to commence treatment with vandetanib</u>."

The EPAR for vandetanib contains further clarifying information. Note, italics from the original EPAR report, underlining added by Sanofi:

> "Following the SAG's advice, the indication was revised to include aggressive and symptomatic disease. The choice of '*aggressive'* instead of '*progressive'* was justified by the fact that the term of "progressive" remains ambiguous (RECIST progression as in the primary criteria or including clinical, RX and biological criteria) and the term "aggressive" is likely to address patients condition with rapid deterioration, for whom an urgent treatment is required.

EPAR page 49/88

Further on in the EPAR the following is reported [underlining added by SGZ]:

"Additional expert consultation

> The SAG was requested to define the restricted population of patients in whom the absolute benefit in terms of progression prevention would compensate for the overall safety profile of vandetanib and to comment on whether other possible methods as FISH or RNA studies would be more sensitive and specific to determine RET status. In view of the associated risks, the SAG 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. …"

EPAR page 51/88

It is our view that the patients Sanofi has defined as the 'restricted population' for this NICE appraisal is very much in the spirit of the vandetanib license wording and EMA's intention to limit treatment with vandetanib to those in urgent need. Further, we consider assessment in this restricted population to be appropriate for MTC patients as it aligns with current, established UK treatment practice. This was supported by clinical experts during this appraisal who stated that most patients treated with vandetanib demonstrably meet the criteria for symptoms, progression and CTN/CEA doubling <24month [underlining added by Sanofi]:

> "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."
>
> ID56 Committee Papers (page 45/84), Section 3. Clinical Experts ACD response

As at the June 2018, there are [redacted] patients on vandetanib in the UK and Ireland (including paediatric patients and patients from Ireland and the devolved nations). From Sanofi sales data we understand there to have consistently been between [redacted] adult English patients treated with vandetanib since 2015. We believe this is evidence that vandetanib is not used indiscriminately in the NHS but rather clinicians are weighing up risk vs benefit and

select only those in urgent need of treatment. The expert clinician verbalised this in the first committee meeting stating they, 'hold off and hold off and hold off' before treating. This is different to other cancers when treatment may be initiated in response to emerging symptom burden.

Sanofi would like to acknowledge that it could have presented the case for the restricted population more clearly in the original submission. However, given that Sanofi's review of the vandetanib trial data, together with consultation with UK clinical experts who have experience using vandetanib, led to a similar population being put forward for NICE assessment as the EMA identified as the population with the most appropriate benefit risk profile for vandetanib use means we are confident that the right things for patients is to seek assessment in this more sick MTC population.

Sanofi would respectfully ask the Committee to consider the vandetanib submission in the light of this information as pertains to CTN/CEA doubling times.

Part 2: Restricted Population – the data from the ZETA trial

As context to the request to provide the RPSFT adjusted results with the full range of potentially plausible curves fitted we thought it helpful to provide the observed (confounded) trial data for the restricted population.

Baseline characteristics of the restricted population

Patients in this population meet three criteria:

- Symptomatic
    - at least one symptom at ZETA trial baseline, including pain score > 4, ≥10 days of opioid use, diarrhoea, flushing, fatigue, pain, nausea, dysphagia, dysphonia, respiratory symptoms, weight loss
- Progressed
    - documented progression within 12 months prior to enrolment on the ZETA trial
- CTN/CEA doubling <24mo

Within the restricted population two 'adjustments' were made in the analysis that was submitted in response to the ACD. The first was to carryout covariate adjustment for the two baseline characteristics that differed between the two trial arms. The second was to use Rank Preserving Structural Failure Time Modelling (RPSFTM) to adjust for cross-over from the BSC arm to the active treatment arm. In line with the DSU document on dealing with cross-over, the adjustment for differences in baseline characteristics was carried out to support the requirements of RPSFT modelling: that treatment difference is the only non-random difference between the two arms in a trial. Discussed in Question 5 are attempts to undo the impact of continued use of vandetanib post progression.

Table 1 shows the baseline characteristics for the restricted population while Table 2 clarifies how many patients received vandetanib post-progression on both the BSC and vandetanib arms.

Table 1. Demographic and Baseline Characteristics: Restricted label population

Parameter	Statistic	Vandetanib (N=[redacted])	Placebo/BSC (N=[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]

Parameter	Statistic	Vandetanib (N=[redacted])	Placebo/BSC (N=[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]

Table 2. Proportion of patients switching / continuing vandetanib post-progression in Restricted label population

Number of patients switching / continuing	ZETA Restricted label
Vandetanib	[redacted]
Placebo/BSC	[redacted]

During the blinded phase of the ZETA study, patients who had Investigator Assessed progression were allowed to switch to active treatment. However, after the results of the PFS analysis (i.e after primary endpoint had been met) randomization was broken and all remaining placebo and vandetanib patients were offered open label vandetanib. This was based on a protocol amendment which allowed patients to be taken off randomized therapy and continue open label therapy or continue on randomized therapy. Therefore, some patients were taken off randomized therapy without Investigator Assessed progression. This means some patients that were then unblinded and offered vandetanib treatment who had started on the vandetanib arm could have continued with active treatment regardless of the progression status.

Progression Free Survival

The ZETA trial primary endpoint was Progression-free survival (PFS), defined as the time from randomisation to documented progression based on central review or death. Analysis

of the primary endpoint is from the data cut data cut reported in the CSR dated 6 July 2011. Unfortunately, PFS data were not updated after this timepoint.

Median progression free survival time was [redacted] days and [redacted] days for the vandetanib and placebo groups, respectively, see
Figure 1 and Table 3 for the hazard ratio of 0.385 (95% CI: 0.182, 0.813) .

Figure 1. [redacted].

Table 3. Analysis of Progression Free Survival

	Vandetanib (N=[redacted])	Placebo/BSC (N=[redacted])
Failure, n	[redacted]	[redacted]
Median Survival Time (days) (95% CI) [1]	[redacted]	[redacted]
Hazard Ratio (Vandetanib vs. Placebo) (95% CI)	[redacted]	

[1] Based on Kaplan-Meier analysis.

Overall survival

Median overall survival from the Kaplan-Meier analysis was [redacted] days and [redacted] days for vandetanib and placebo groups, see Figure 2 and **Table 5** for the KM curve and the hazard ratios.

Figure 2 [redacted].

[redacted]

Part 3: Summary of the economic analyses undertaken to date

Sanofi has endeavoured to put forward as comprehensive an evidence package as possible to facilitate decision making with a data set that is difficult to work with. We would like to remind the Committee that we have been consistent in putting forward the restricted population as the base case population since the original submission. However, we recognise that these patient numbers are as small as the usual UK TKI-treated MTC patient population and have tried to mitigate against this.

Original submission ICERs

In the Feb 2017 submission, OS and PFS curves for the restricted population were estimated by fitting parametric regressions to the entire study population with coefficients set for SympProg to 100% and BiomarkerChg to 100%. Sanofi consider this to be a reasonable approach. (It is the same approach as the famous Framingham equation that underpins all diabetes economic evaluations). Running this original – *crossed-over* – approach through the economic model with the AC's preferred assumptions applied, with the statistical best fitting curves and the clinician preferred curves, and the revised PAS produces the ICER estimates reported in

Table 4.

Table 4 Original parametric regression approach to estimating PFS and OS in the restricted population: data crossed over, revised [redacted] PAS included

PFS – Van	PFS - BSC	OS - Van	OS - BSC	ICER (per QALY)
LogNormal	Exponential	LogNormal	Gamma	£29,986
Weibull	Weibull	Weibull	Weibull	£29,742

This results in ICERs below the £50,000 *without* adjusting for cross-over.

The AGs preferred analysis 4

In the document: Assessment Group critique of additional analyses submitted by Sanofi Genzyme, dated 25th Sept 2017, the AG reported analysis 4 as its preferred analysis with an ICER of £54,548 at a [redacted] The AG's report states, 'The AG recognises however that this [ICER estimate] is likely to represent an overestimate due to the assumption of ongoing post-progression vandetanib use until death in a proportion of patients'.

Sanofi agrees this is likely to be an over-estimate, and so when the revised PAS is applied to this AG analysis, Sanofi is confident that a) the ICER estimate would be less than £50,000 but also b) this would remain an over-estimate due to the assumption of ongoing post-progression vandetanib use until death in a proportion of patients.

This produces an ICER estimate below £50,000.

The Sanofi revised estimates with and without RPSFTM and without post-progression costs

The Sanofi base case for the restricted population produces ICER estimates that range from £34,780 (Weibull for all curves, RPSFTM, with baseline covariate adjustment) to £35,173 (RPSFTM without baseline covariate adjustment statistical best fit curves). The confounded observed data with and without baseline covariate adjustment result in ICER estimates between £27,205 and £29,986.

ICER estimates are all substantially below the £50,000 threshold and some are below the £30,000 threshold.

The Sanofi revised estimates with and without RPSFTM and with post-progression costs included for vandetanib only

When post-progression costs are estimated for the restricted population (with RPSFTM and baseline covariate adjustment with the application of a cost post-progression for patients in the trial that continued vandetanib after the study was unblinded) the ICER range changes to £47,788 to £57,006. A simplifying assumption is needed to run this scenario: that vandetanib patients receiving vandetanib post study unblinding continue on treatment until

death. In line with the AG's comment in relation to analysis 4, this will over estimate vandetanib post-progression costs.

Given the over-estimation of vandetanib costs in this analysis, it is reasonable that this straddles the £50,000 threshold.

Exploratory analysis using statistical modelling to address post-progression vandetanib use

In response to question 5 we discuss below an approach suggested to us by one of the authors of the DSU Technical Support Document 16. The output of this approach results in an ICER of £39,720 (Restricted, RSPFTM, adjusted for baseline covariates, adjusted for costs and efficacy post-progression), compared with the base case ICER of £36,020. This method effectively removes the post-progression benefit off the vandetanib arm. It also adjusts the BSC arm for crossover and baseline covariate differences. In a simplistic way, this analysis provides cost-effectiveness assuming no crossover occurred.

These estimates are again substantially below the £50,000 threshold.

Summary

On the basis of these ICER estimates it can be seen that Sanofi has worked to address the small patient population numbers and mitigate for cross over. While a range of ICERs are presented, it is notable they converge below the £50,000 EoL threshold, with the exception of one approach known to over-state the vandetanib cost.

Regardless of the method or whether the confounded data are effectively 'uncrossed' the majority of the ICER estimates lie within the £30,000 to £50,000 range with many below £40,000. The weight of evidence would suggest the 'true ICER' is below the £50,000 threshold. Given the small patient numbers we hope that this sufficiency of ICERs can reassure the Committee that for the very few patients and families with MTC providing vandetanib as a treatment option would be a good use of NHS resources.

Part 4: Additional analyses requested by NICE

Question 1 - Curve fitting for the 'restricted population

In the basecase analysis submitted in response to the ACD the trial data were adjusted for baseline covariates and for cross-over using the RPSFT method. The resultant overall survival curves for vandetanib, unadjusted and adjusted placebo are presented in Figure 3, see Table 5 median OS and HR.

Figure 3. [redacted]

Table 5 Analysis of Overall Survival with Crossover Placebo Subjects Adjusted with and without RPSFTM Method (with and without baseline co-variate adjustment)

	Vandetanib (N=[redacted])	RPSFTM Baseline Covariates Adjusted Placebo (N=[redacted])	RPSFTM Non-Baseline Covariates Adjusted Placebo (N=[redacted])
Death, n	[redacted]	[redacted]	[redacted]
Median Survival Time (days)(95% CI) [1]	[redacted]	[redacted]	[redacted]
Hazard Ratio (Vandetanib vs. RPSFTM Baseline Covariates Adjusted Placebo) (95% CI) [2]	[redacted]		
Hazard Ratio (Vandetanib vs. RPSFTM No-Baseline Covariate Adjusted Placebo) (95% CI) [3]	[redacted]		

[1] Based on Kaplan-Meier analysis.

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

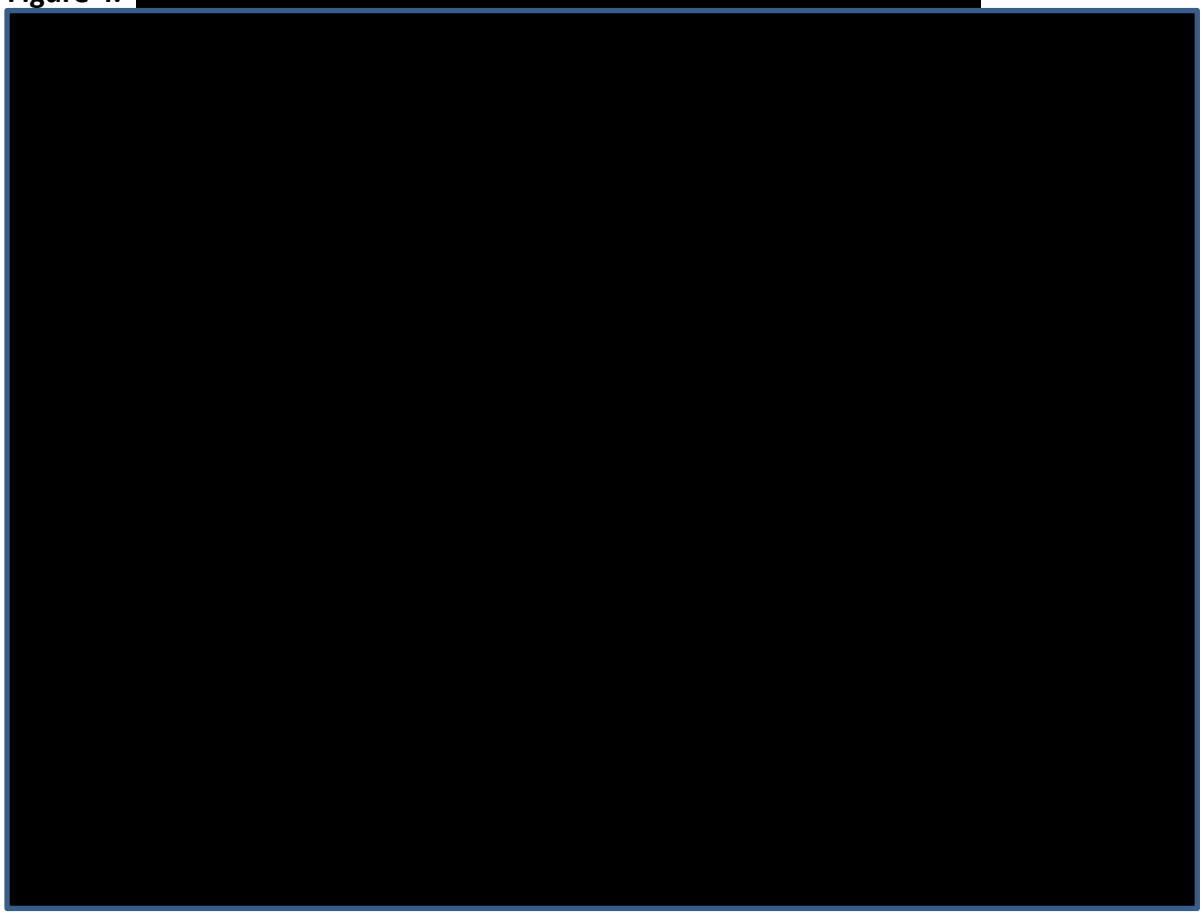
[3] Survival times for the Placebo crossover subjects were adjusted by the RPSFTM method. Results are based on a Cox proportional hazards regression model with term for treatment. The 95% CI is based on the empirical cumulative distribution function of the hazard ratio of 1000 bootstrap iterations.

Based on the AIC and BIC statistics (**Table 6**), we considered all curves to be plausible with the exception of Gompertz for placebo arm, given its outlying AIC/BIC statistics. Gompertz and gamma did not converge for vandetanib nor did gamma for placebo in this analysis therefore these are not considered further. The resultant curves are shown in Figure 4 below.

Table 6. Parametric Survival Analysis with Baseline Covariates Adjustment: Overall Survival with Crossover Placebo Subjects Adjusted with RPSFTM Method (Parameter Estimates)

Analysis	AIC	BIC
Vandetanib		
Weibull	86.989	92.852
Log-normal	84.122	89.985
Log-logistic	84.414	90.276
Exponential	85.970	90.367
Placebo		
Weibull	44.977	48.309
Log-normal	48.254	51.587
Log-logistic	47.645	50.977
Exponential	48.145	50.645
Gompertz	240.269	243.602

Figure 4. [redacted]



Selection of the preferred model according to the DSU methods: visual inspection is difficult in these curves given no curve is an ideal fit and all curves appear to under and over-estimate at different points along the survival curves. In line with the approach discussed in the DSU document, as all possible parametric functions were fitted, we did not construct log-cumulative hazard plots, instead we considered the AIC/BIC statistics.

Based on these, as described above, for gamma data did not converge for either arm, Gompertz did not converge for the vandetanib arm, and Gompertz for placebo was a notable outlier. The remaining curves: exponential, Weibull, LogLogisitc and LogNormal all had similar AIC/BIC statistics. Taking the lowest AIC/BIC statistics indicated LogNormal was the best fit for OS for vandetanib and Weibull was the best fit for OS for placebo. This is therefore what was selected for base case ACD response. A step we omitted in the response to the ACD but have done for these requested analyses is to verify curve clinical plausibility with an experienced clinician. The curves were validated with Dr Jonathan Wadsley MB, BChir, MA, MRCP, FRCR, Consultant Clinical Oncologist, Weston Park Hospital.

We validated the curves with Dr Wadsley by presenting both the curves and also the median survival times estimates from the modelled curves (Table 7) which presents the time range in which 50% and 95% of patients die. For example, Weibull placebo 95%: 0.0501 of the population had died at [redacted] days and 0.0482 of the population had died at [redacted] days. For simplicity we used the range in which 0.05 was reached rather than calculating the exact timepoint from the curve, for ease of understanding the same values are presented as days, months and years.

On review of the curves Dr Wadsley concluded that Weibull was most clinically plausible for both the vandetanib arm and the placebo arm. He noted that Gompertz worked for placebo but isn't available for vandetanib. The other curves underestimate early on and overestimate later on. Dr Wadsley understood the population under discussion was the restricted population. He also noted caution needed to be exercised in interpreting the

curves under consideration given the very small patient numbers. Based on the AIB/BIC statistics Weibull/LogNormal give the best fit (and are in line with the previous submission) therefore these two scenarios are presented. Following the correction to the model error, we checked all the median survival estimates used to in the validation process with Dr Wadsley. In all cases, the new model results do not materially impact the choice of the survival curve because the median survival differ by less than 30 days across all distributions. As the difference is less than 30 days, Weibull continues to be the lower most survival for all analyses performed.

Table 7 Median and 5% survival estimates from the modelled curves: Restricted population, RPSFTM with adjustment for baseline characteristics

		Weibull V	LogNormal V	LogLogistic V	Exponential V	Weibull P	LogNormal P	LogLogistic P	Exponential P	Gompertz P
Days	50%	1350	1250	1200	1200	550	450	500	450	600
		1400	1300	1250	1250	600	500	550	500	650
	95%	4700	6800	6850	5350	1350	1850	1900	3450	1250
		4750	6850	6900	5400	1400	1900	1950	3500	
Months	50%	44.38	41.07	39.43	39.43	18.07	14.78	16.43	14.78	19.71
		46.00	42.71	41.07	41.07	19.71	16.43	18.07	16.43	21.36
	95%	154.52	223.41	225.05	175.77	44.35	60.78	62.42	113.35	41.07
		156.06	225.05	226.69	177.41	46.00	62.42	64.07	114.99	0.00
Years	50%	3.7	3.4	3.3	3.3	1.5	1.2	1.4	1.2	1.6
		3.8	3.6	3.4	3.4	1.6	1.4	1.5	1.4	1.8
	95%	12.9	18.6	18.8	14.6	3.7	5.1	5.2	9.4	3.4
		13.0	18.8	18.9	14.8	3.8	5.2	5.3	9.6	

c) The economic model uses the Appraisal Committee's preferred assumptions: eg, progression free utility of 0.8 and post progression utility of 0.5, annual cost of BSC £2998.21, the total health state costs for patients on vandetanib are [redacted] in the first year and [redacted] in subsequent years. We then applied the preferred parametric models within this economic model. The preferred parametric models run are both:

- vandetanib LogNormal/ BSC Weibull scenario
    - this is consistent with the ACD response and in line with the best fits as indicated by the AIC/BIC statistics
- vandetanib Weibull/BSC Weibull scenario
    - this is the clinicians preferred curve fit

The Sanofi base case preferred parametric models are shown in Table 8. The base also includes adjustment for crossover from placebo arm to active vandetanib treatment using the RPSFT method. The baseline covariate adjustments are made for duration of treatment and prior systemic treatment. All other assumptions for costs and utility include the Appraisal Committee's preferred assumptions.

We present two set of analyses one with £0 post-progression vandetanib costs applied (Sanofi base case) and a scenario with [redacted] of post-progression costs for vandetanib applied. The same pre-progression assumptions are used in these scenarios as in the pre-progression health state in terms of dose received and missed doses. Because of the structure of the model, applying a cost to this health state for post-progression vandetanib treatment results in costs being assumed from entry to this health state until death. These scenarios therefore over-estimate of the costs of vandetanib and result an over-estimated ICER in terms of cost per incremental QALY gained.

Table 8. Sanofi base case preferred parametric models Vandetanib versus BSC – Restricted population

Inputs	Base case	Scenario Analysis
Covariate: Prior Trt and Disease Duration		
PFS distribution BSC	Exponential	Exponential
OS distribution BSC	Weibull	Weibull
PFS distribution vandetanib	LogNormal	LogNormal
OS distribution vandetanib	LogNormal	LogNormal
Population	Restricted	Restricted
Use RPSFT to undo crossover?	Yes	Yes
Post-progression cost (BSC)	Zero	Zero
Post-progression cost (vandetanib)	Zero	44%
PAS discount	[redacted]	[redacted]

Table 9. Sanofi base case Vandetanib versus BSC – Restricted population: Results

Results per Comparator	Placebo	Vandetanib	Difference
Life Years	[redacted]	[redacted]	[redacted]
PFLYs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Treatment Costs, pre-progression (£)	[redacted]	[redacted]	[redacted]
Treatment Costs, post-progression (£)	[redacted]	[redacted]	[redacted]
Monitoring Costs (£)	[redacted]	[redacted]	[redacted]
Adverse Event Costs (£)	[redacted]	[redacted]	[redacted]
Cost of Best Supportive Care (£)	[redacted]	[redacted]	[redacted]
Costs of Palliative care	[redacted]	[redacted]	[redacted]
Total Costs (£)	[redacted]	[redacted]	[redacted]

Health measure	ICER
Life Years	[redacted]
PFLYs	[redacted]
QALYs	£36,020

Table 10. Base case: restricted population, RPSFTM with adjustment for baseline characteristics Sanofi revised base case (revised PAS).

PFS distribution BSC	OS distribution BSC	PFS distribution vandetanib	OS distribution vandetanib	ICER
Exponential	Weibull	LogNormal	LogNormal	£36,020

The equivalent results with an over-estimated cost applied for post-progression vandetanib is shown in Table 11 and Table 12

Table 11. Scenario Analysis Vandetanib versus BSC – Restricted population: Results (with vandetanib post-progression costs included), (revised PAS).

Results per Comparator	Placebo	Vandetanib	Difference
Life Years	[redacted]	[redacted]	[redacted]
PFLYs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Treatment Costs, pre-progression (£)	[redacted]	[redacted]	[redacted]
Treatment Costs, post-progression (£)	[redacted]	[redacted]	[redacted]
Monitoring Costs (£)	[redacted]	[redacted]	[redacted]
Adverse Event Costs (£)	[redacted]	[redacted]	[redacted]
Cost of Best Supportive Care (£)	[redacted]	[redacted]	[redacted]
Costs of Palliative care	[redacted]	[redacted]	[redacted]
Total Costs (£)	[redacted]	[redacted]	[redacted]

Health measure	ICER
Life Years	[redacted]
PFLYs	[redacted]
QALYs	£51,023

Table 12. Scenario analysis: Restricted population, RPSFTM with adjustment for baseline characteristics (revised PAS) with post-progression vandetanib costs applied

PFS distribution BSC	OS distribution BSC	PFS distribution vandetanib	OS distribution vandetanib	ICER
Exponential	Weibull	LogNormal	LogNormal	£51,023

Table 13. Clinical expert preferred distribution Vandetanib versus BSC: Restricted population: no post-progression costs

Results per Comparator	Placebo	Vandetanib	Difference
Life Years	[redacted]	[redacted]	[redacted]
PFLYs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Treatment Costs, pre-progression (£)	[redacted]	[redacted]	[redacted]
Treatment Costs, post-progression (£)	[redacted]	[redacted]	[redacted]
Monitoring Costs (£)	[redacted]	[redacted]	[redacted]
Adverse Event Costs (£)	[redacted]	[redacted]	[redacted]
Cost of Best Supportive Care (£)	[redacted]	[redacted]	[redacted]
Costs of Palliative care	[redacted]	[redacted]	[redacted]
Total Costs (£)	[redacted]	[redacted]	[redacted]

Health measure	
Life Years	[redacted]
PFLYs	[redacted]
QALYs	£34,780

Table 14. Clinical expert preferred distribution: Restricted population, RPSFTM with adjustment for baseline characteristics (revised PAS)

PFS distribution BSC	OS distribution BSC	PFS distribution vandetanib	OS distribution vandetanib	ICER
Weibull	Weibull	Weibull	Weibull	£34,780

The equivalent results with an over-estimated cost applied for post-progression vandetanib is shown in Table 17 and

Table 16.

Table 15. Clinical expert preferred distribution Vandetanib versus BSC: Restricted population: with post-progression costs

Results per Comparator	Placebo	Vandetanib	Difference
Life Years	[redacted]	[redacted]	[redacted]
PFLYs	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
Treatment Costs, pre-progression (£)	[redacted]	[redacted]	[redacted]
Treatment Costs, post-progression (£)	[redacted]	[redacted]	[redacted]
Monitoring Costs (£)	[redacted]	[redacted]	[redacted]
Adverse Event Costs (£)	[redacted]	[redacted]	[redacted]
Cost of Best Supportive Care (£)	[redacted]	[redacted]	[redacted]
Costs of Palliative care	[redacted]	[redacted]	[redacted]
Total Costs (£)	[redacted]	[redacted]	[redacted]

Health measure	
Life Years	[redacted]
PFLYs	[redacted]
QALYs	£54,274

Table 16. Clinical expert preferred distribution: Restricted population, RPSFTM with adjustment for baseline characteristics (revised PAS) with post-progression costs for vandetanib applied

PFS distribution BSC	OS distribution BSC	PFS distribution vandetanib	OS distribution vandetanib	ICER
Weibull	Weibull	Weibull	Weibull	£54,274

d) DSA & PSA results

The sensitivity analyses for the Sanofi base case are provided below.

Figure 5 [redacted]

Figure 6. Sanofi base case Vandetanib versus BSC – Restricted population – probabilistic sensitivity analyses

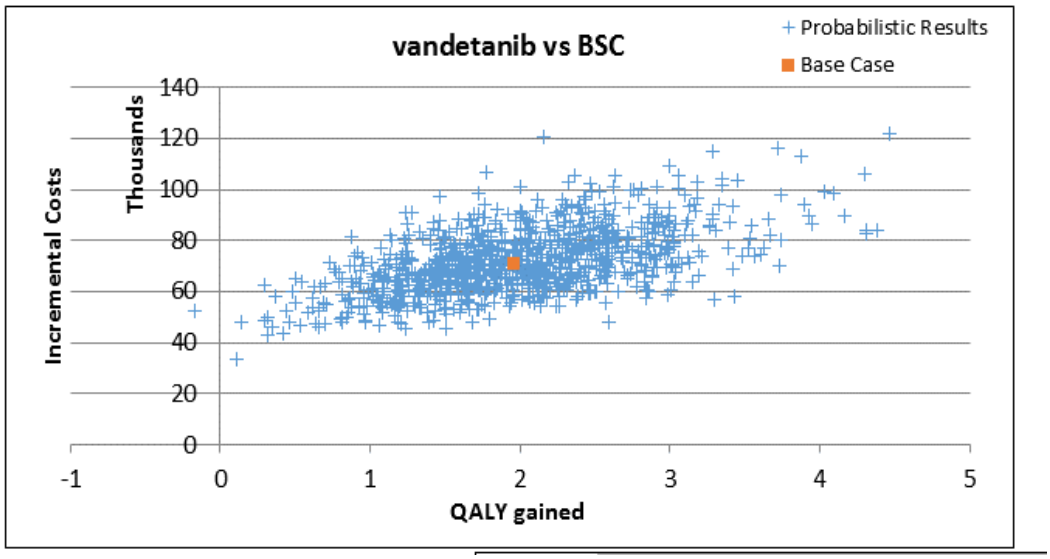


Figure 7. Sanofi base case Vandetanib versus BSC – Restricted population - CEAC

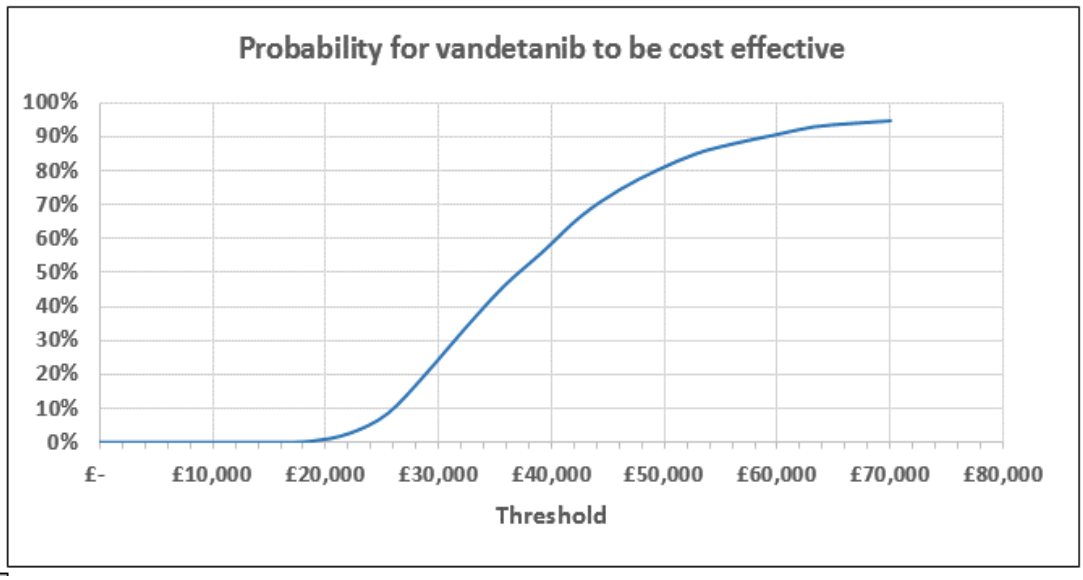


Figure 8 [redacted]

Figure 9. Clinical expert preferred distribution Vandetanib versus BSC: Restricted population – probabilistic sensitivity analysis

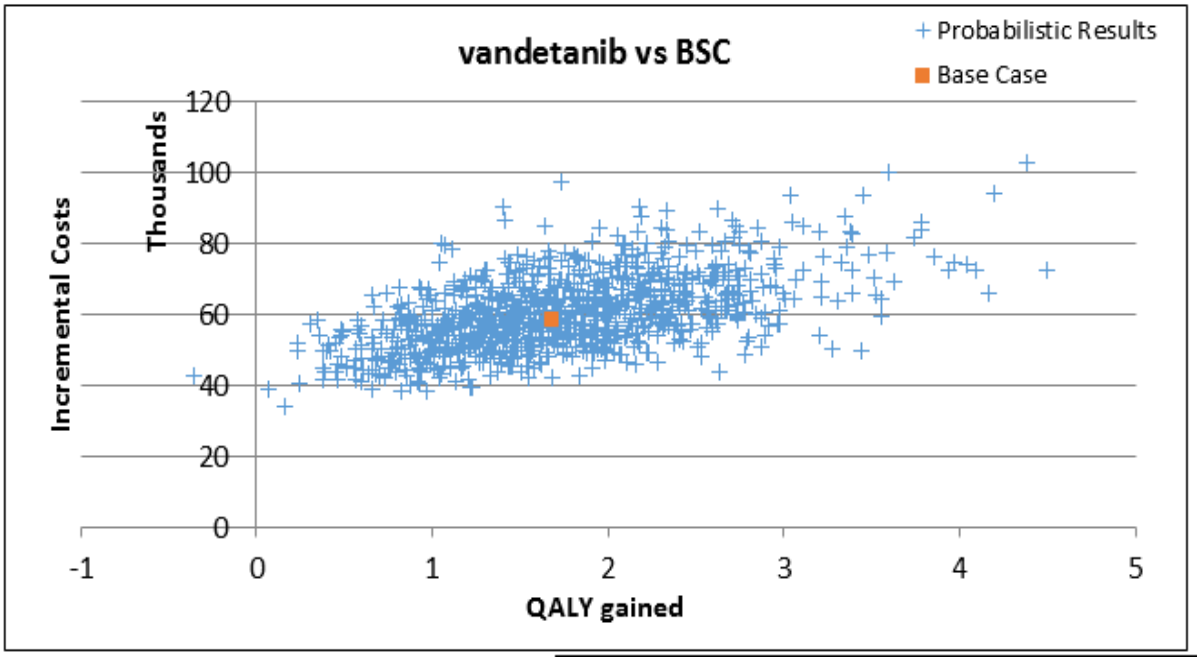
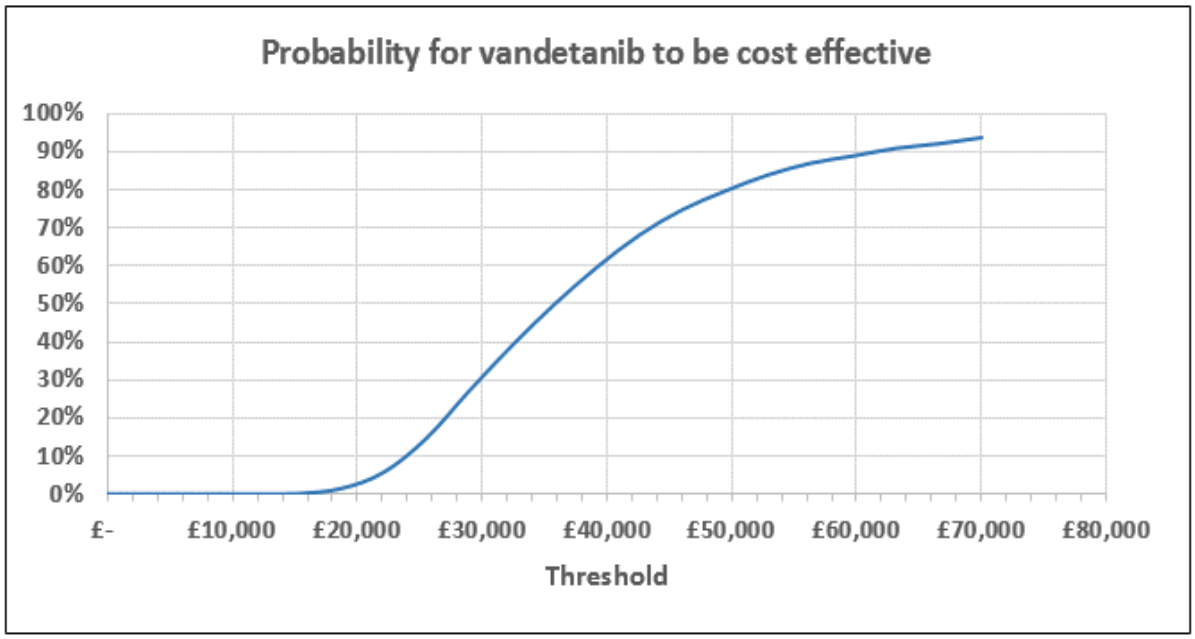


Figure 10. Clinical expert preferred distribution Vandetanib versus BSC: Restricted population – CEAC


Probability for vandetanib to be cost effective
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
£-
£10,000
£20,000
£30,000
£40,000
£50,000
£60,000
£70,000
£80,000
Threshold

Question 2 – no RPSFTM adjustment and with baseline covariate adjustment

An analysis without any RPSFT adjustment (that is, the confounded data) to demonstrate the impact of crossover-adjustment: The above was repeated for the observed data both with and without adjustment for the baseline covariates:

With covariate adjustment

1. Observed trial data with baseline adjustment
2. Median OS and HR
3. AIC and BIC statistics
4. Potential modelled curves
5. Clinical validation of time at which 50% and 5% still alive
6. Cost-effectiveness results

Figure 11 [redacted]

Table 17. [redacted]

	Vandetanib (N=[redacted]) n (%)	Placebo (N=[redacted]) n (%)
Death, n	[redacted]	[redacted]
Median Survival(days)(95% CI)	[redacted]	[redacted]
Hazard Ratio (Vandetanib vs. Placebo) without Baseline Covariates (95% CI)	[redacted]	
Hazard Ratio (Vandetanib vs. Placebo) with Baseline Covariates (95% CI)	[redacted]	

Table 18. Parametric Survival Analysis with Baseline Covariates Adjustment: Overall Survival Based on Trial Data without RPSFTM Adjustment (Parameter Estimates)

Analysis	AIC	BIC
Vandetanib		
Weibull	86.989	92.852
Log-normal	84.122	89.985
Log-logistic	84.414	90.276
Exponential	85.970	90.367
Placebo		
Weibull	53.028	56.361
Log-normal	57.640	60.973
Log-logistic	57.278	60.611
Exponential	52.899	55.398
Gompertz	263.484	266.817

AIC = Akaike Information Criterion; BIC = Bayesian information Criterion; SE = standard error; Vandet = Randomized Vandetanib Treatment; Prior Th. = Prior Systematic Therapy (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 therapy (yes or no). For the by arm analyses, the treatment term was dropped. For placebo, the convergence of the Gamma distribution analysis was questionable and for Vandetanib the analysis resulted in an error message. Similarly, the Gompertz distribution analysis resulted in an error message for Vandetanib. Therefore, the results of these analyses are not shown in the table. The Gompertz model was fitted using SAS Proc NLMIXED, and all other models were fitted using Proc LIFEREG.

Figure 12. [redacted]

Table 19. Observed data *with* covariate adjustment– 50% and 5% survival times

		Weibull V	LogNormal V	LogLogistic V	Exponential V	Weibull P	LogNormal P	LogLogistic P	Exponential P	Gompertz P
Days	50%	1350	1250	1200	1200	1000	800	950	850	1100
		1400	1300	1250	1250	1050	850	1000	900	1150
	95%	4700	6800	6850	5350	2950	4950	5400	3700	2450
		4750	6850	6900	5400	3000	5000	5450	3750	2500
Months	50%	44.35	41.07	39.43	39.43	32.85	26.28	31.21	27.93	36.14
		46.00	42.71	41.07	41.07	34.50	27.93	32.85	29.57	37.78
	95%	154.41	223.41	225.05	175.77	96.92	162.63	177.41	121.56	80.49
		156.06	225.05	226.69	177.41	98.56	164.27	179.06	123.20	82.14
Years	50%	3.7	3.4	3.3	3.3	2.7	2.2	2.6	2.3	3.0
		3.8	3.6	3.4	3.4	2.9	2.3	2.7	2.5	3.1
	95%	12.9	18.6	18.8	14.6	8.1	13.6	14.8	10.1	6.7
		13.0	18.8	18.9	14.8	8.2	13.7	14.9	10.3	6.8

Clinical validation of these curves concluded that Weibull was the most clinically plausible fit for both vandetanib and BSC OS, specifically in terms of late survival. He considered both Weibull and exponential seem reasonable. Based on AIC/BIC statistics exponential/LogNormal were the best fit.

Table 20. Scenario analysis without any RPSFT adjustment with adjustment for baseline characteristics: AIC/BIC best fit statistics

PFS distribution BSC	OS distribution BSC	PFS distribution vandetanib	OS distribution vandetanib	ICER
Exponential	Exponential	LogNormal	LogNormal	£27,205

Table 21. Scenario analysis without any RPSFT adjustment with adjustment for baseline characteristics: clinician preferred curves

PFS distribution BSC	OS distribution BSC	PFS distribution vandetanib	OS distribution vandetanib	ICER
Weibull	Weibull	Weibull	Weibull	£25, 165

Curve fitting for the 'restricted population without RPSFT adjustment and without baseline co-variate

Note this analysis was not requested by NICE however, we have provided for completeness.

1. Observed trial data without baseline adjustment
2. Median OS and HR
3. AIC and BIC statistics
4. Potential modelled curves

5. Clinical validation of time at which 50% and 5% still alive
6. Cost-effectiveness results

Figure 13 [redacted]

Table 22. Median Overall Survival and Hazard ratios Based on Trial Data without RPSFTM Adjustment Restricted population (with and without baseline co-variate adjustment)

	Vandetanib (N[redacted]) n (%)	**Placebo (N[redacted]) n (%)**
Death, n		
Median Survival(days)(95% CI)		
Hazard Ratio (Vandetanib vs. Placebo) without Baseline Covariates (95% CI)		
Hazard Ratio (Vandetanib vs. Placebo) with Baseline Covariates (95% CI)		

Table 23. Parametric Survival Analysis without Baseline Covariates Adjustment: Overall Survival Based on Trial Data without RPSFTM Adjustment (Parameter Estimates)

Analysis	AIC	BIC
Vandetanib		
Weibull	90.329	93.260
Log-normal	88.960	91.892
Log-logistic	89.190	92.121
Exponential	88.401	89.867
Placebo		
Weibull	49.499	51.166
Log-normal	55.242	56.909
Log-logistic	54.750	56.417
Exponential	49.338	50.171
Gamma	48.664	51.164

AIC = Akaike Information Criterion; BIC = Bayesian information Criterion; SE = standard error; Vandet = Randomized Vandetanib Treatment

Note: For the All analyses, the parametric survival analysis was based on a model with a term for treatment. For the by arm analyses, the treatment term was dropped. For Vandetanib, the convergence was questionable for the Gamma distribution analysis, and the Gompertz distribution by arm analysis resulted in error messages for both arms. Therefore, these results are not shown in the table. The Gompertz model was fitted using SAS Proc NLMIXED, and all other models were fitted using Proc LIFEREG.

Figure 14 [redacted]

Table 24. Observed data *without* covariate adjustment– 50% and 5% survival times

		Weibull V	LogNormal V	LogLogistic V	Exponential V	Weibull P	LogNormal P	LogLogistic P	Exponential P
Days	50%	1450	1300	1350	1450	1000	800	1000	850
		1500	1350	1400	1500	1050	850	1050	900
	95%	5950	10400	11300	6300	2950	5450	6100	3750
		6000	10450	11350	6350	3000	5500	6150	3800
Months	50%	47.64	42.71	44.35	47.64	32.85	26.28	32.85	27.93
		49.28	44.35	46.00	49.28	34.50	27.93	34.50	29.57
	95%	195.48	341.68	371.25	206.98	96.92	179.06	200.41	123.20
		197.13	343.33	372.90	208.62	98.56	180.70	202.05	124.85
Years	50%	4.0	3.6	3.7	4.0	2.7	2.2	2.7	2.3
		4.1	3.7	3.8	4.1	2.9	2.3	2.9	2.5
	95%	16.3	28.5	30.9	17.2	8.1	14.9	16.7	10.3
		16.4	28.6	31.1	17.4	8.2	15.1	16.8	10.4

Clinical validation of these curves concluded that Weibull was the most clinically plausible fit for both vandetanib and BSC OS, specifically in terms of late survival. As the AIC/BIC statistics suggest Gamma/LogNormal are the best fit, these are also fitted

Table 25. Scenario analysis without any RPSFT adjustment without adjustment for baseline characteristics: AIC/BIC best fit statistics

PFS BSC distribution	OS distribution BSC	PFS distribution vandetanib	OS distribution vandetanib	ICER
Exponential	Gamma	LogNormal	LogNormal	£29,986

Table 26. Scenario analysis without any RPSFT adjustment without adjustment for baseline characteristics: clinician preferred curves

PFS BSC distribution	OS distribution BSC	PFS distribution vandetanib	OS distribution vandetanib	ICER
Weibull	Weibull	Weibull	Weibull	£29,742

Question 3 – RPSFTM without covariate adjustment for baseline characteristics

The above was repeated for the RPSFT model without adjustment for the baseline covariates:

1. RPSFT modelled OS curves
2. Median OS and HR
3. AIC and BIC statistics
4. Potential modelled curves
5. Clinical validation of time at which 50% and 5% still alive
6. Cost-effectiveness results

Figure 15 [redacted]

Table 27. [redacted]

	Vandetanib (N=[redacted]) n (%)	Placebo (N=[redacted]) n (%)	RPSFT Adjusted Placebo (without Baseline Covariates) (N=[redacted]) n (%)	RPSFT Adjusted Placebo (with Baseline Covariates) (N=[redacted]) n (%)
Death, n				
Median Survival(days)(95% CI)				
Hazard Ratio (Vandetanib vs. Placebo) without Baseline Covariates (95% CI)				
Hazard Ratio (Vandetanib vs. Placebo) with Baseline Covariates (95% CI)				
Hazard Ratio (Vandetanib vs. RPSFT adjusted Placebo) without Baseline Covariates (95% CI*)				
Hazard Ratio (Vandetanib vs. RPSFTM Baseline Covariates Adjusted Placebo) (95% CI) [2]				

Table 28. Parametric Survival Analysis without Baseline Covariates Adjustment: Overall Survival with Crossover Placebo Subjects Adjusted with RPSFTM Method (Parameter Estimates)

Analysis	AIC	BIC
Vandetanib	90.329	
Weibull	88.960	93.260
Log-normal	89.190	91.892
Log-logistic	88.401	92.121

Analysis	AIC	BIC
Exponential		89.867
Placebo	42.497	
Weibull	45.307	44.163
Log-normal	45.323	46.973
Log-logistic	44.769	46.990
Exponential	44.299	45.602
Gamma	235.143	46.799
Gompertz	90.329	236.809

AIC = Akaike Information Criterion; BIC = Bayesian information Criterion; SE = standard error; Vandet = Randomized Vandetanib Treatment

Note: For the All analyses, the parametric survival analysis was based on a model with a term for treatment. For the by arm analyses, the treatment term was dropped. For Vandetanib, the convergence was questionable for the Gamma distribution analysis and the Gompertz distribution resulted in an error message. Therefore, these results are not shown in the table. The Gompertz model was fitted using SAS Proc NLMIXED, and all other models were fitted using Proc LIFEREG.

Figure 16. [redacted]

Table 29. RPSFTM *without* covariate adjustment – 50% and 5% survival times

		Weibull V	LogNormal V	LogLogistic V	Exponential V	Weibull P	LogNormal P	LogLogistic P	Exponential P
Days	50%	1450	1300	1350	1450	450	400	450	350
		1500	1350	1400	1500	500	450	500	400
	95%	5950	10400	11300	6300	1250	1700	1850	1700
		6000	10450	11350	6350	1300	1750	1900	1750
Months	50%	47.64	42.71	44.35	47.64	14.78	13.14	14.78	11.50
		49.28	44.35	46.00	49.28	16.43	14.78	16.43	13.14
	95%	195.48	341.68	371.25	206.98	41.07	55.85	60.78	55.85
		197.13	343.33	372.90	208.62	42.71	57.49	62.42	57.49
Years	50%	4.0	3.6	3.7	4.0	1.2	1.1	1.2	1.0
		4.1	3.7	3.8	4.1	1.4	1.2	1.4	1.1
	95%	16.3	28.5	30.9	17.2	3.4	4.7	5.1	4.7
		16.4	28.6	31.1	17.4	3.6	4.8	5.2	4.8

Clinical validation of these curves concluded that the most clinically plausible fit was Weibull for both vandetanib and BSC OS. Given the AIC/BIC statistics indicated that the best fits were Weibull/exponential these were also fitted.

Table 30. Scenario analysis with RPSFT adjustment without baseline covariate adjustment

PFS distribution BSC	OS distribution BSC	PFS distribution vandetanib	OS distribution vandetanib	ICER
Exponential	Weibull	LogNormal	Exponential	£35,173
Weibull	Weibull	Weibull	Weibull	£31,117

The equivalent results with an over-estimated cost applied for post-progression vandetanib is shown in Table 31

Table 31. Scenario analysis with RPSFT adjustment without baseline covariate adjustment (revised PAS), with post-progression costs for vandetanib applied

PFS distribution BSC	**OS distribution BSC**	**PFS distribution vandetanib**	**OS distribution vandetanib**	**ICER**
Exponential	Weibull	LogNormal	Exponential	£47,788
Weibull	Weibull	Weibull	Weibull	£50,213

Question 4 - Combinations of distributions for PFS and OS

To understand the impact of the different curve fits all combination for PFS and OS, for both arms of the trial, have been fitted. Unlike the AG we took the view that proportional hazard didn't necessarily hold, based on the AIC and BIC statistics and therefore we have fitted the arms to different parametric functions. Note, due to the volume of analyses this would produce have only run this exercise for the base case: restricted population, RPSFTM with adjustment for baseline characteristics with [redacted] applied. All post-progression costs are set £0.

Note in the table below we present the base case ICERs with £0 costs applied to vandetanib post-progression. We also present a selection of ICERs including the lowest and highest ICERs estimates with the over-estimated post-progression vandetanib costs included (these are presented in column post-pgn vand ICER).

Table 32. Combinations of distributions for PFS and OS: restricted population, RPSFTM with adjustment for baseline characteristics, post-progression costs set to £0 including the revised PAS ([redacted] applied)

PFS distribution vandetanib	PFS distribution BSC	OS distribution BSC	OS distribution vandetanib	Base case ICER (per QALY)	Post-pgn Vand ICER
LogNormal	Exponential	Weibull	LogNormal	£36,020	£51,023
LogNormal	Exponential	Weibull	Weibull	£38,318	
LogNormal	Exponential	Lognormal	Lognormal	£36,956	£52,420
LogNormal	Exponential	LogLogistic	Loglogistic	£39,503	
LogNormal	Exponential	Exponential	Exponential	£39,077	
Lognormal	Exponential	Gompertz	LogNormal	£36,080	
Weibull	Weibull	Weibull	Lognormal	£32,530	
Lognormal	Lognormal	Weibull	Lognormal	£36,232	
LogLogistic	LogLogistic	Weibull	Lognormal	£36,483	
Exponential	Exponential	Weibull	Lognormal	£34,571	
Gompertz	Gompertz	Weibull	Lognormal	£33,292	£52,227
Gamma	Exponential	Weibull	Lognormal	£38,365	£49,560

PFS distribution vandetanib	PFS distribution BSC	OS distribution BSC	OS distribution vandetanib	Base case ICER (per QALY)	Post-pgn Vand ICER
Weibull	Weibull	Exponential	Exponential	£35,499	
Weibull	Weibull	Weibull	Weibull	£34,780	£54,274
Weibull	Weibull	Gompertz	LogNormal	£32,602	
Weibull	Weibull	LogNormal	LogNormal	£33,426	
Weibull	Weibull	LogLogistic	LogLogistic	£35,884	£57,006
Exponential	Exponential	Exponential	Exponential	£37,624	
Exponential	Exponential	Weibull	Weibull	£36,882	£53,184
Exponential	Exponential	Gompertz	LogNormal	£36,631	£51,849
Exponential	Exponential	LogNormal	LogNormal	£35,495	
Exponential	Exponential	LogLogistic	LogLogistic	£38,018	
Gompertz	Gompertz	Exponential	Exponential	£36,288	
Gompertz	Gompertz	Weibull	Weibull	£35,560	
Gompertz	Gompertz	Gompertz	LogNormal	£33,365	£52,349
Gompertz	Gompertz	LogNormal	LogNormal	£34,197	
Gompertz	Gompertz	LogLogistic	LogLogistic	£36,674	

PFS distribution vandetanib	PFS distribution BSC	OS distribution BSC	OS distribution vandetanib	Base case ICER (per QALY)	Post-pgn Vand ICER
Gamma	LogLogistic	Exponential	Exponential	£42,037	
Gamma	LogLogistic	Weibull	Weibull	£40,580	
Gamma	LogLogistic	Gompertz	LogNormal	£38,769	£50,086
Gamma	LogLogistic	LogNormal	LogNormal	£40,113	
Gamma	LogLogistic	LogLogistic	LogLogistic	£42,819	£54,127

Table 35 below summarise the ICERs for the 4 different analytical approaches presented above for the clinician preferred curves.

Table 33. Summary table of estimated ICERs using the 4 different methodological approaches: Restricted population, with [redacted] PAS discount, with £0 costs assumed post progression

	PFS distribution BSC	OS distribution BSC	PFS distribution vandetanib	OS distribution vandetanib	ICER
BASECASE - Covariates - RPSFT	Weibull	Weibull	Weibull	Weibull	£34,780
No CoVariates - No RPSFT	Weibull	Weibull	Weibull	Weibull	£29,742
CoVariates - No RPSFT	Weibull	Weibull	Weibull	Weibull	£25,165
No CoVariates - RPSFT	Weibull	Weibull	Weibull	Weibull	£31,117

The results in this table are driven by an interplay of efficacy outcomes (ie, how many life years gained) and the costs of vandetanib treatment both pre- and post-progression. The DSU TSD 16 recommends that adjustment is used to accommodate for baseline differences, which is why this approach is the base case in the RPSFTM submitted. In response to the AG request we ran the analysis without the adjustment for baseline covariates. Without the adjustment for baseline covariates the vandetanib pre-progression costs are higher than with co-variate adjustment a result of the higher pre-progression life years gained for vandetanib. The variables that drive the ICER results can be seen below.

Table 34. Breakdown of key parameters for the four analytical approaches using the clinician preferred curve fittings

		Life Years			PFLYs			QALYS			Pre-Prog Costs	Total Costs		
	ICER	BSC	Vandetanib	Difference	BSC	Vandetanib	Difference	BSC	Vandetanib	Difference	Vandetanib	BSC	Vandetanib	Difference
BASECASE - Covariates - RPSFT	£34,780	1.68	4.31	2.62	0.75	2.01	1.26	[redacted]	[redacted]	[redacted]	[redacted]	£11,330	[redacted]	[redacted]
No CoVariates - No RPSFT	£29,742	3.11	4.77	1.66	0.86	2.10	1.23	[redacted]	[redacted]	[redacted]	[redacted]	£75,716	[redacted]	[redacted]
CoVariates - No RPSFT	£25,165	3.09	4.31	1.22	0.75	2.01	1.26	[redacted]	[redacted]	[redacted]	[redacted]	£78,093	[redacted]	[redacted]
No CoVariates - RPSFT	£31,117	1.50	4.77	3.27	0.86	2.10	1.23	[redacted]	[redacted]	[redacted]	[redacted]	£10,825	[redacted]	[redacted]

Question 5 - Scenario analyses that explore the effect of lower overall survival for vandetanib

As flagged in response to this request, there is no established method to this issue of continuing active treatment post-progression. We reached out for advice to one of the authors of DSU 16. What follows below is based on the advice received from him and his academic colleague. It is important to note that they considered this a possible approach (as opposed to a definitive approach).

The model uses independent survival curves for the vandetanib and BSC and is a cohort model in nature. At time t we know the proportion of patients that are pre- or post-progression. At time t we apply the risk of an event corresponding to the current vandetanib arm survival to the proportion of surviving patients that are pre-progression, and the risk of an event corresponding to the comparator arm to the proportion that are post-progression, to determine the proportion surviving at time t+delta. This would correspond to no ongoing incremental overall survival effect post-progression. This could be relaxed by applying the comparator arm risk to a fraction of the proportion that are post-progression.

As can be seen comparing the results for this analysis to the base case ICER of £39,720 the PFS is the same for both comparators, and OS is the same for BSC. However, OS for vandetanib is lower, as you would expect ([redacted] in base case, [redacted] in this analysis). This increases the ICER from £36,020 in base case to £39,720 in this analysis. What this sensitivity analysis shows is that even if you remove the OS benefit for vandetanib in post-progression state, the ICER remains under £40,000.

Note this analysis was only run with the previous base case. However, as all corresponding estimates that use the clinician preferred parameters result in lower ICERs we would expect to see lower ICERs in this analysis using the clinician preferred curves.

Table 35. Table comparing the results from the base case analysis with the scenario analysis testing the impact of reducing the post-progression survival benefit: restricted population, RPSFTM, with baseline covariate adjust, with revised PAS.

	BASE CASE			Scenario analysis: Base case with post-progression costs included			SENSIVITY ANALYSIS REMOVE POST-PROGRESSION SURVIVAL BENEFIT		
Results per Comparator	Placebo	Vandetanib	Difference	Placebo	Vandetanib	Difference	Placebo	Vandetanib	Difference
Life Years	1.685	4.581	2.896	1.685	4.581	2.896	1.685	4.156	2.471
PFLYs	0.788	2.518	1.730	0.788	2.518	1.730	0.788	2.518	1.730
QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment Costs, pre-progression (£)	£0	[redacted]	[redacted]	£0	[redacted]	[redacted]	£0	[redacted]	[redacted]
Treatment Costs, post-progression (£)	£0	£0	£0	£0	£26,391	£26,391	£0	£0	£0
Monitoring Costs (£)	£0	£7,759	£7,759	£0	£10,838	£10,838	£0	£7,759	£7,759
Adverse Event Costs (£)	£42	£133	£91	£42	£133	£91	£42	£133	£91
Cost of Best Supportive Care (£)	£5,052	£13,736	£8,684	£5,052	£13,736	£8,684	£5,052	£12,461	£7,409
Costs of Palliative care	£6,236	£5,443	-£793	£6,236	£5,443	-£793	£6,236	£5,543	-£693
Total Costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost per QALY gained			**£36,020**			**£51,023**			**£39,720**

Question 6 – comparative plots of observed and RPSFT-adjusted Kaplan-Meier data, and all fitted curves, together with goodness-of-fit statistics.

All of the plots required have been presented above. Please contact us if anything is outstanding.

Question 7 – RPFSFT methodology

During this appraisal there was misunderstanding regarding what Sanofi did and did not do relating to the application of the RPSFT modelling approach to different ZETA trial populations. We accept that Sanofi contributed to that confusion and would here like to set down what was undertaken and when. It is important to note that the text on page 57 of the original submission document that referenced RPSFTM and the restricted population was not accurate.

In the original submission of Feb 2017 we did not complete any RPSFT modelling for any of the ZETA trial populations. We did consider all the approaches in the DSU 16 methodology paper, with RPSFT modelling seeming most likely to be successful. Two issues that were most provoking in the case of vandetanib are the assumptions

1) Assumption of common treatment effect regardless of when treatment is initiated, ie patients that received vandetanib post-progression gain the same benefit from treatment as those that received it pre-progression
2) with the exception of whether active treatment is received or not, there is only random variation between arms due to trial randomization.
    a. It was clear from the data that the arms were not balanced however, in line the advice in the DSU we are now aware that this can be overcome by adjusting for baseline covariates within the RPSFTM

With regards the common treatment effect, the more we have scrutinised the data for the restricted population the less concerned we have become that the common treatment effect assumption is not valid. The DSU document states that the assumption needs to be 'approximately true'. Because of the extent of cross-over ([redacted]), the ZETA trial is essentially a trial of early vs late treatment with vandetanib. The confounded OS data suggest that patients receiving vandetanib 'later' have a notable treatment benefit, if you compare progression free survival with overall survival for the BSC arm and with the vandetanib arm: The median PFS in the BSC arm was [redacted] months (95%CI [redacted]) compared [redacted] months in the vandetanib arm (95%CI [redacted], NR), p=0.12. Median OS in the BSC arm was [redacted] years (95% [redacted]) compared with [redacted] (95%CI [redacted]) in the vandetanib arm. However, we did not have this clarity when we made our Feb 2017 submission.

In advance of the Feb 2017 submission we had undertaken the first step in the RPSFT modelling for what we called in the original submission the EU label population. This is a misnomer, it should have been referred to as the Kreissl analysis. That first step was the production of the η statistic. A negative value represents a beneficial treatment effect while a positive value indicates a detrimental treatment effect. For the EU label population the selected η is 0.04, ie marginally positive, which suggested there was no value in pursuing the RPSFT modelling in this Kreissl analysis. Given the understanding we now have of the data and the CHMP's and SAG's review of the same data set, this is not a surprise as this is not where the data indicate there to be optimal treatment benefit/risk profile. Based on the η statistic for the Kreissl analysis we did not pursue calculate the η statistic for the restricted population. Had we undertaken RPSFT modelling of either population, Sanofi internal research policy would have required us to share it with NICE.

In response to the negative ACD, we sought to explore every avenue open to us to ensure that access to this medicine was maintained, we also had greater clarity on the license and the data set. We sought external academic statistical advice and worked with a health

outcomes consultancy on the RPSFT modelling of the restricted patient population. For information the η statistic associated with the restricted population with adjustment for baseline covariate is [redacted] (as reported in the document submitted as part of the ACD response: Vandetanib additional evidence ACD response 20170918). For information the η statistic associated with the restricted population without adjustment for baseline covariates is [redacted]. Note, a negative η indicates a beneficial treatment effect.

Question 8 - Missing data

If data were missing for CTN or CEA doubling times, then those patients were excluded from the analysis.

The table and figures for the Kreissl analysis patients as requested by NICE are shown below:

a. met the CTN doubling time criterion but had missing data on CEA (N=12)

b. met the CEA doubling time criterion but had missing data on CTN (N=0)

Table 36. ***Missing data status for CEA and CTN doubling time (Kreissl Analysis)***

	Vandetanib 300mg (N=130)	**Placebo (N=60)**	**Total (N=190)**
Patients with both CEA and CTN doubling time <=24 Months	[redacted]	[redacted]	[redacted]
Patients with CTN doubling time <=24 Months but missing CEA doubling time	[redacted]	[redacted]	[redacted]
Patients with CEA doubling time <=24 Months but missing CTN doubling time	0	0	0

Table 37. Baseline Characteristics: Kreissl Analysis Population with CTN Doubling Time <= 24 Months but Missing CEA Data

	Statistic	Vandetanib (N= [redacted]) n (%)	Placebo (N= [redacted]) n (%)
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]

		Vandetanib (N= [redacted])	Placebo (N= [redacted])
	Statistic	n (%)	n (%)
	Median	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]
Sex			
Female	n (%)	[redacted]	[redacted]
Male	n (%)	[redacted]	[redacted]

Table 38. Baseline Characteristics: Kreissl Analysis Population with CTN Doubling Time <= 24 Months but Missing CEA Data

	Statistic	Vandetanib (N=[redacted]) n (%)	Placebo (N=[redacted]) n (%)
Race			
Caucasian	n (%)	[redacted]	[redacted]
RET mutational status			
Unknown	n (%)	[redacted]	[redacted]
Yes	n (%)	[redacted]	[redacted]
Number of sites involved			
3	n (%)	[redacted]	[redacted]
4	n (%)	[redacted]	[redacted]
5	n (%)	[redacted]	[redacted]
6	n (%)	[redacted]	[redacted]

	Statistic	Vandetanib (N=[redacted]) n (%)	Placebo (N=[redacted]) n (%)
8	n (%)	[redacted]	[redacted]
Primary Tumor			
TX	n (%)	[redacted]	[redacted]
T1	n (%)	[redacted]	[redacted]
T3	n (%)	[redacted]	[redacted]
One Stage Classification			
IVC	n (%)	[redacted]	[redacted]
Prior systematic therapy			
None	n (%)	[redacted]	[redacted]
Yes	n (%)	[redacted]	[redacted]

Part 5: Clarification question requested by NICE

Question 1: Please could you explain how this uncertainty has been incorporated into the curve-fitting procedure and demonstrate that the variance-covariance parameters of the fitted parametric models and the associated probabilistic sensitivity analysis reflect this uncertainty?

The survival curves were fit to the estimated patient data using the method of maximum likelihood. The mean and standard deviation for each parameter, the covariance between parameters, and the Cholesky matrix were obtained from the output. For the cost-effectiveness model, the mean parameter values were used for the deterministic base, and for the probabilistic sensitivity analysis, the cholesky decomposition of the covariance matrix of the parameters were used to generate correlated random draws for the parameters of the curves. Please see below the covariance matrix for each individual curve fitting.

Table 39. Parametric Survival Analysis with Baseline Covariates Adjustment: Overall Survival with Crossover Placebo Subjects Adjusted with RPSFTM Method (Covariance Matrix)

Analysis	Variable	Intercept	Scale	Shape	Vandetanib	Prior Th.	Disease Dur.
Vandetanib							
Weibull	Intercept	0.102263	0.009914			-0.052467	-0.005755
Weibull	Scale	0.009914	0.021815			-0.010213	-0.000518
Weibull	Prior Th.	-0.052467	-0.010213			0.142122	-0.001135
Weibull	Disease Dur.	-0.005755	-0.000518			-0.001135	0.000775
Log-normal	Intercept	0.128593	0.010413			-0.070338	-0.007624
Log-normal	Scale	0.010413	0.027244			-0.003515	-0.000168
Log-normal	Prior Th.	-0.070338	-0.003515			0.159846	0.000900
Log-normal	Disease Dur.	-0.007624	-0.000168			0.000900	0.000909
Log-logistic	Intercept	0.115275	0.005227			-0.057438	-0.007959
Log-logistic	Scale	0.005227	0.011601			-0.000876	-0.000126
Log-logistic	Prior Th.	-0.057438	-0.000876			0.154993	0.000158
Log-logistic	Disease Dur.	-0.007959	-0.000126			0.000158	0.001098
Exponential	Intercept	0.143951	0			-0.071988	-0.008171
Exponential	Prior Th.	-0.071988	0			0.196568	-0.001529
Exponential	Disease Dur.	-0.008171	0			-0.001529	0.001101
Placebo							
Weibull	Intercept	0.069233	-0.005536			-0.043358	-0.005911
Weibull	Scale	-0.005536	0.014716			-0.003349	0.000497
Weibull	Prior Th.	-0.043358	-0.003349			0.091680	0.000974
Weibull	Disease Dur.	-0.005911	0.000497			0.000974	0.001195
Log-normal	Intercept	0.120138	-0.001583			-0.068366	-0.010465
Log-normal	Scale	-0.001583	0.020712			0.001971	0.000349
Log-normal	Prior Th.	-0.068366	0.001971			0.158316	-0.000958
Log-normal	Disease Dur.	-0.010465	0.000349			-0.000958	0.002309
Log-logistic	Intercept	0.085745	-0.002156			-0.040259	-0.007413
Log-logistic	Scale	-0.002156	0.008980			0.001028	0.000147

Analysis	Variable	Intercept	Scale	Shape	Vandetanib	Prior Th.	Disease Dur.
Log-logistic	Prior Th.	-0.040259	0.001028			0.140695	-0.002643
Log-logistic	Disease Dur.	-0.007413	0.000147			-0.002643	0.001640
Exponential	Intercept	0.177559	0			-0.108928	-0.015130
Exponential	Prior Th.	-0.108928	0			0.254040	-0.000497
Exponential	Disease Dur.	-0.015130	0			-0.000497	0.003445
Gompertz	Intercept	0.359212		0.000270		-0.158120	-0.012941
Gompertz	Shape	0.000270		0.000000472		-0.000032275	0.000009351
Gompertz	Prior Th.	-0.158120		-0.000032275		0.264863	0.004921
Gompertz	Disease Dur.	-0.012941		0.000009351		0.004921	0.003743
All							
Weibull	Intercept	0.068450	-0.000599		-0.040475	-0.035809	-0.002264
Weibull	Scale	-0.000599	0.010341		0.002487	-0.003232	-0.000041380
Weibull	Vandetanib	-0.040475	0.002487		0.068510	0.016213	-0.000869
Weibull	Prior Th.	-0.035809	-0.003232		0.016213	0.067601	-0.000364
Weibull	Disease Dur	-0.002264	-0.000041380		-0.000869	-0.000364	0.000451
Log-normal	Intercept	0.091053	0.000872		-0.049479	-0.041912	-0.003218
Log-normal	Scale	0.000872	0.013632		0.003189	-0.000520	-0.000007996
Log-normal	Vandetanib	-0.049479	0.003189		0.097662	0.006391	-0.002008
Log-normal	Prior Th.	-0.041912	-0.000520		0.006391	0.087960	0.000223
Log-normal	Disease Dur	-0.003218	-0.000007996		-0.002008	0.000223	0.000653
Log-logistic	Intercept	0.079064	0.000080735		-0.045294	-0.032456	-0.003210
Log-logistic	Scale	0.000080735	0.005824		0.002249	-0.000308	-0.000075735
Log-logistic	Vandetanib	-0.045294	0.002249		0.089833	0.005157	-0.001816
Log-logistic	Prior Th.	-0.032456	-0.000308		0.005157	0.087251	-0.000392
Log-logistic	Disease Dur	-0.003210	-0.000075735		-0.001816	-0.000392	0.000730
Exponential	Intercept	0.118561	0		-0.068228	-0.060703	-0.004102
Exponential	Vandetanib	-0.068228	0		0.118557	0.026063	-0.001596
Exponential	Prior Th.	-0.060703	0		0.026063	0.115965	-0.000654
Exponential	Disease Dur	-0.004102	0		-0.001596	-0.000654	0.000817

Analysis	Variable	Intercept	Scale	Shape	Vandetanib	Prior Th.	Disease Dur.
Gamma	Intercept	0.086328	-0.012269	0.052391	-0.042838	-0.027052	-0.001739
Gamma	Scale	-0.012269	0.033791	-0.093071	-0.001823	-0.022147	-0.001897
Gamma	Shape	0.052391	-0.093071	0.397214	0.021121	0.085056	0.007666
Gamma	Vandetanib	-0.042838	-0.001823	0.021121	0.081749	0.017689	-0.000797
Gamma	Prior Th.	-0.027052	-0.022147	0.085056	0.017689	0.095157	0.001346
Gamma	Disease Dur	-0.001739	-0.001897	0.007666	-0.000797	0.001346	0.000694
Gompertz	Intercept	0.554443		0.000124	-0.247424	-0.053316	-0.006882
Gompertz	Shape	0.000124		6.471321E-8	-0.000040781	-0.000026018	0.000000141
Gompertz	Vandetanib	-0.247424		-0.000040781	0.145846	-0.013473	0.001487
Gompertz	Prior Th.	-0.053316		-0.000026018	-0.013473	0.128132	-0.000762
Gompertz	Disease Dur	-0.006882		0.000000141	0.001487	-0.000762	0.000803

Prior Th.=Prior Systematic Therapy (Yes or No) Disease Dur.=Disease Duration

Table 40. Parametric Survival Analysis with Baseline Covariates Adjustment: Overall Survival Based on Trial Data without RPSFTM Adjustment (Covariance Matrix)

Analysis	Variable	Intercept	Scale	Shape	Vandetanib	Prior Th.	Disease Dur.
Vandetanib							
Weibull	Intercept	0.102263	0.009914			-0.052467	-0.005755
Weibull	Scale	0.009914	0.021815			-0.010213	-0.000518
Weibull	Prior Th.	-0.052467	-0.010213			0.142122	-0.001135
Weibull	Disease Dur.	-0.005755	-0.000518			-0.001135	0.000775
Log-normal	Intercept	0.128593	0.010413			-0.070338	-0.007624
Log-normal	Scale	0.010413	0.027244			-0.003515	-0.000168
Log-normal	Prior Th.	-0.070338	-0.003515			0.159846	0.000900
Log-normal	Disease Dur.	-0.007624	-0.000168			0.000900	0.000909
Log-logistic	Intercept	0.115275	0.005227			-0.057438	-0.007959
Log-logistic	Scale	0.005227	0.011601			-0.000876	-0.000126
Log-logistic	Prior Th.	-0.057438	-0.000876			0.154993	0.000158
Log-logistic	Disease Dur.	-0.007959	-0.000126			0.000158	0.001098
Exponential	Intercept	0.143951	0			-0.071988	-0.008171

Analysis	Variable	Intercept	Scale	Shape	Vandetanib	Prior Th.	Disease Dur.
Exponential	Prior Th.	-0.071988	0			0.196568	-0.001529
Exponential	Disease Dur.	-0.008171	0			-0.001529	0.001101
Placebo							
Weibull	Intercept	0.100066	-0.008827			-0.056126	-0.008855
Weibull	Scale	-0.008827	0.024474			-0.004726	0.000896
Weibull	Prior Th.	-0.056126	-0.004726			0.137422	-0.000598
Weibull	Disease Dur.	-0.008855	0.000896			-0.000598	0.001990
Log-normal	Intercept	0.213940	-0.002773			-0.121529	-0.018593
Log-normal	Scale	-0.002773	0.037079			0.003452	0.000612
Log-normal	Prior Th.	-0.121529	0.003452			0.281852	-0.001796
Log-normal	Disease Dur.	-0.018593	0.000612			-0.001796	0.004102
Log-logistic	Intercept	0.155671	-0.005259			-0.071125	-0.013821
Log-logistic	Scale	-0.005259	0.016381			-0.001163	0.000520
Log-logistic	Prior Th.	-0.071125	-0.001163			0.263485	-0.005210
Log-logistic	Disease Dur.	-0.013821	0.000520			-0.005210	0.003133
Exponential	Intercept	0.174691	0			-0.100917	-0.015273
Exponential	Prior Th.	-0.100917	0			0.255603	-0.002449
Exponential	Disease Dur.	-0.015273	0			-0.002449	0.003669
Gompertz	Intercept	0.357937		0.000140		-0.119758	-0.017734
Gompertz	Shape	0.000140		0.000000121		0.000000572	0.000000303
Gompertz	Prior Th.	-0.119758		0.000000572		0.254996	0.001990
Gompertz	Disease Dur.	-0.017734		0.000000303		0.001990	0.003865
All							
Weibull	Intercept	0.079461	-0.001031		-0.048257	-0.043284	-0.002361
Weibull	Scale	-0.001031	0.012401		0.003699	-0.004121	-0.000034798
Weibull	Vandetanib	-0.048257	0.003699		0.084022	0.022017	-0.001426
Weibull	Prior Th.	-0.043284	-0.004121		0.022017	0.081284	-0.000626
Weibull	Disease Dur	-0.002361	-0.000034798		-0.001426	-0.000626	0.000532
Log-normal	Intercept	0.111861	0.001101		-0.060571	-0.051487	-0.003965

Analysis	Variable	Intercept	Scale	Shape	Vandetanib	Prior Th.	Disease Dur.
Log-normal	Scale	0.001101	0.016646		0.004015	-0.000690	-0.000015148
Log-normal	Vandetanib	-0.060571	0.004015		0.119988	0.007706	-0.002475
Log-normal	Prior Th.	-0.051487	-0.000690		0.007706	0.107973	0.000271
Log-normal	Disease Dur	-0.003965	-0.000015148		-0.002475	0.000271	0.000804
Log-logistic	Intercept	0.095068	-0.000462		-0.055598	-0.034719	-0.003864
Log-logistic	Scale	-0.000462	0.007137		0.003229	-0.000522	-0.000058505
Log-logistic	Vandetanib	-0.055598	0.003229		0.108502	0.000126	-0.001966
Log-logistic	Prior Th.	-0.034719	-0.000522		0.000126	0.105564	-0.000352
Log-logistic	Disease Dur	-0.003864	-0.000058505		-0.001966	-0.000352	0.000835
Exponential	Intercept	0.117336	0		-0.069150	-0.062434	-0.003716
Exponential	Vandetanib	-0.069150	0		0.122183	0.030541	-0.002070
Exponential	Prior Th.	-0.062434	0		0.030541	0.117952	-0.000912
Exponential	Disease Dur	-0.003716	0		-0.002070	-0.000912	0.000816
Gamma	Intercept	0.108745	-0.028778	0.096833	-0.055025	-0.015718	-0.001674
Gamma	Scale	-0.028778	0.051797	-0.131792	0.008471	-0.042872	-0.001652
Gamma	Shape	0.096833	-0.131792	0.456771	-0.013946	0.136251	0.005465
Gamma	Vandetanib	-0.055025	0.008471	-0.013946	0.093040	0.014523	-0.001726
Gamma	Prior Th.	-0.015718	-0.042872	0.136251	0.014523	0.128852	0.001064
Gamma	Disease Dur	-0.001674	-0.001652	0.005465	-0.001726	0.001064	0.000675
Gompertz	Intercept	0.436280		0.000070876	-0.189340	-0.021158	-0.008020
Gompertz	Shape	0.000070876		4.7239904E-8	-0.000007873	-0.000017199	-0.000000134
Gompertz	Vandetanib	-0.189340		-0.000007873	0.126299	-0.032587	0.002157
Gompertz	Prior Th.	-0.021158		-0.000017199	-0.032587	0.126559	-0.000859
Gompertz	Disease Dur	-0.008020		-0.000000134	0.002157	-0.000859	0.000796

Prior Th.=Prior Systematic Therapy (Yes or No) Disease Dur.=Disease Duration

Table 41. Parametric Survival Analysis without Baseline Covariates Adjustment: Overall Survival with Crossover Placebo Subjects Adjusted with RPSFTM Method (Covariance Matrix)

Analysis	Variable	Intercept	Scale	Shape	Vandetanib
Vandetanib					
Weibull	Intercept	0.043439	0.003183		
Weibull	Scale	0.003183	0.030245		
Log-normal	Intercept	0.059342	0.011425		
Log-normal	Scale	0.011425	0.040535		
Log-logistic	Intercept	0.054973	0.003646		
Log-logistic	Scale	0.003646	0.017181		
Exponential	Intercept	0.047619	0		
Placebo					
Weibull	Intercept	0.026774	-0.005383		
Weibull	Scale	-0.005383	0.015931		
Log-normal	Intercept	0.041917	0.001041		
Log-normal	Scale	0.001041	0.022038		
Log-logistic	Intercept	0.038437	-0.001400		
Log-logistic	Scale	-0.001400	0.009919		
Exponential	Intercept	0.062500	0		
Gamma	Intercept	0.091201	-0.044572	0.236799	
Gamma	Scale	-0.044572	0.035384	-0.133969	
Gamma	Shape	0.236799	-0.133969	0.824092	
Gompertz	Intercept	0.211313		0.000275	
Gompertz	Shape	0.000275		0.000000508	
All					
Weibull	Intercept	0.041748	-0.002650		-0.041836
Weibull	Scale	-0.002650	0.012257		0.003055
Weibull	Vandetanib	-0.041836	0.003055		0.073309
Log-normal	Intercept	0.070112	0.000797		-0.069896
Log-normal	Scale	0.000797	0.016775		0.003762

Analysis	Variable	Intercept	Scale	Shape	Vandetanib
Log-normal	Vandetanib	-0.069896	0.003762		0.112947
Log-logistic	Intercept	0.060394	-0.000622		-0.060496
Log-logistic	Scale	-0.000622	0.007202		0.001799
Log-logistic	Vandetanib	-0.060496	0.001799		0.102966
Exponential	Intercept	0.062500	0		-0.062500
Exponential	Vandetanib	-0.062500	0		0.110119
Gamma	Intercept	0.089419	-0.046892	0.151430	-0.024991
Gamma	Scale	-0.046892	0.056320	-0.148485	-0.015830
Gamma	Shape	0.151430	-0.148485	0.506078	0.064246
Gamma	Vandetanib	-0.024991	-0.015830	0.064246	0.084814
Gompertz	Intercept	0.475308		0.000118	-0.246239
Gompertz	Shape	0.000118		6.215225E-8	-0.000046791
Gompertz	Vandetanib	-0.246239		-0.000046791	0.145347

Table 42. Parametric Survival Analysis without Baseline Covariates Adjustment: Overall Survival Based on Trial Data without RPSFTM Adjustment (Covariance Matrix)

Analysis	Variable	Intercept	Scale	Shape	Vandetanib
Vandetanib					
Weibull	Intercept	0.043439	0.003183		
Weibull	Scale	0.003183	0.030245		
Log-normal	Intercept	0.059342	0.011425		
Log-normal	Scale	0.011425	0.040535		
Log-logistic	Intercept	0.054973	0.003646		
Log-logistic	Scale	0.003646	0.017181		
Exponential	Intercept	0.047619	0		
Placebo					
Weibull	Intercept	0.035442	-0.006650		
Weibull	Scale	-0.006650	0.024755		
Log-normal	Intercept	0.077360	0.001906		
Log-normal	Scale	0.001906	0.040865		
Log-logistic	Intercept	0.065312	-0.004870		
Log-logistic	Scale	-0.004870	0.018068		
Exponential	Intercept	0.062500	0		
Gamma	Intercept	0.138063	-0.091724	0.700558	
Gamma	Scale	-0.091724	0.070739	-0.494221	
Gamma	Shape	0.700558	-0.494221	4.009389	
All					
Weibull	Intercept	0.047057	-0.003092		-0.047246
Weibull	Scale	-0.003092	0.014371		0.003972
Weibull	Vandetanib	-0.047246	0.003972		0.082836
Log-normal	Intercept	0.086109	0.000962		-0.085841
Log-normal	Scale	0.000962	0.020565		0.004781
Log-normal	Vandetanib	-0.085841	0.004781		0.138936
Log-logistic	Intercept	0.076460	-0.002094		-0.076864
Log-logistic	Scale	-0.002094	0.008903		0.003813
Log-logistic	Vandetanib	-0.076864	0.003813		0.126576
Exponential	Intercept	0.062500	0		-0.062500
Exponential	Vandetanib	-0.062500	0		0.110119

Analysis	Variable	Intercept	Scale	Shape	Vandetanib
Gamma	Intercept	0.128659	-0.105421	0.454671	-0.016553
Gamma	Scale	-0.105421	0.109105	-0.448510	-0.004770
Gamma	Shape	0.454671	-0.448510	1.990658	0.037170
Gamma	Vandetanib	-0.016553	-0.004770	0.037170	0.051826
Gompertz	Intercept	0.359629		0.000069591	-0.179442
Gompertz	Shape	0.000069591		4.5411169E-8	-0.000014160
Gompertz	Vandetanib	-0.179442		-0.000014160	0.114536

Table 43. Parametric Survival Analysis with Baseline Covariates Adjustment: Progression Free Survival (Covariance Matrix)

Analysis	Variable	Intercept	Scale	Shape	Vandetanib	Prior Trt.	Disease Dur.
Vandetanib							
Weibull	Intercept	0.196392	0.028980			-0.128342	-0.009476
Weibull	Scale	0.028980	0.033616			-0.030924	0.000134
Weibull	Prior Trt.	-0.128342	-0.030924			0.214872	0.000182
Weibull	Disease Dur.	-0.009476	0.000134			0.000182	0.001278
Log-normal	Intercept	0.192171	0.033558			-0.111194	-0.009931
Log-normal	Scale	0.033558	0.049638			-0.023207	0.000117
Log-normal	Prior Trt.	-0.111194	-0.023207			0.226062	0.000627
Log-normal	Disease Dur.	-0.009931	0.000117			0.000627	0.001263
Log-logistic	Intercept	0.193332	0.017490			-0.114762	-0.010842
Log-logistic	Scale	0.017490	0.020420			-0.011978	-0.000075615
Log-logistic	Prior Trt.	-0.114762	-0.011978			0.219462	0.001638
Log-logistic	Disease Dur.	-0.010842	-0.000075615			0.001638	0.001341
Exponential	Intercept	0.247162	0			-0.146470	-0.013870
Exponential	Scale	0	0			0	0
Exponential	Prior Trt.	-0.146470	0			0.267982	0.000480
Exponential	Disease Dur.	-0.013870	0			0.000480	0.001844
Gamma	Intercept	0.465921	-0.042286	0.666702		-0.174181	-0.003947
Gamma	Scale	-0.042286	0.075652	-0.182508		-0.000247	-0.001281
Gamma	Shape	0.666702	-0.182508	1.571842		-0.170878	0.012680
Gamma	Prior Trt.	-0.174181	-0.000247	-0.170878		0.247702	-0.001139
Gamma	Disease Dur.	-0.003947	-0.001281	0.012680		-0.001139	0.001306
Gompertz	Intercept	0.418047		0.000552		-0.181564	-0.014138
Gompertz	Shape	0.000552		0.000001780		-0.000114	-0.000000921

Analysis	Variable	Intercept	Scale	Shape	Vandetanib	Prior Trt.	Disease Dur.
Gompertz	Prior Trt.	-0.181564		-0.000114		0.275230	0.000521
Gompertz	Disease Dur.	-0.014138		-0.000000921		0.000521	0.001844
Placebo							
Weibull	Intercept	0.133007	-0.005701			-0.090397	-0.009642
Weibull	Scale	-0.005701	0.028465			-0.008495	0.000904
Weibull	Prior Trt.	-0.090397	-0.008495			0.173494	-0.000259
Weibull	Disease Dur.	-0.009642	0.000904			-0.000259	0.002277
Log-normal	Intercept	0.176230	0.003257			-0.102966	-0.014250
Log-normal	Scale	0.003257	0.035659			-0.008352	0.000991
Log-normal	Prior Trt.	-0.102966	-0.008352			0.248711	-0.003949
Log-normal	Disease Dur.	-0.014250	0.000991			-0.003949	0.003540
Log-logistic	Intercept	0.187945	0.000549			-0.120167	-0.013780
Log-logistic	Scale	0.000549	0.016140			-0.005612	0.000446
Log-logistic	Prior Trt.	-0.120167	-0.005612			0.251718	-0.001800
Log-logistic	Disease Dur.	-0.013780	0.000446			-0.001800	0.003147
Exponential	Intercept	0.237568	0			-0.165645	-0.016990
Exponential	Scale	0	0			0	0
Exponential	Prior Trt.	-0.165645	0			0.309539	-0.000245
Exponential	Disease Dur.	-0.016990	0			-0.000245	0.004072
Gompertz	Intercept	0.492196		0.000886		-0.344546	-0.009784
Gompertz	Shape	0.000886		0.000003093		-0.000617	0.000024766
Gompertz	Prior Trt.	-0.344546		-0.000617		0.432475	-0.004652
Gompertz	Disease Dur.	-0.009784		0.000024766		-0.004652	0.004175
All							
Weibull	Intercept	0.096033	0.001480		-0.040461	-0.049841	-0.004156
Weibull	Scale	0.001480	0.015609		0.008400	-0.009761	0.000163

Analysis	Variable	Intercept	Scale	Shape	Vandetanib	Prior Trt.	Disease Dur.
Weibull	Vandetanib	-0.040461	0.008400		0.098958	-0.008369	-0.001210
Weibull	Prior Trt.	-0.049841	-0.009761		-0.008369	0.098497	0.000081976
Weibull	Disease Dur	-0.004156	0.000163		-0.001210	0.000081976	0.000809
Log-normal	Intercept	0.121423	0.005300		-0.064716	-0.056833	-0.003980
Log-normal	Scale	0.005300	0.021885		0.007526	-0.007993	0.000180
Log-normal	Vandetanib	-0.064716	0.007526		0.130840	0.004880	-0.002521
Log-normal	Prior Trt.	-0.056833	-0.007993		0.004880	0.117708	-0.000161
Log-normal	Disease Dur	-0.003980	0.000180		-0.002521	-0.000161	0.000874
Log-logistic	Intercept	0.124419	0.001882		-0.066077	-0.061348	-0.004271
Log-logistic	Scale	0.001882	0.009347		0.004779	-0.004299	0.000057751
Log-logistic	Vandetanib	-0.066077	0.004779		0.129816	0.008844	-0.002583
Log-logistic	Prior Trt.	-0.061348	-0.004299		0.008844	0.116454	0.000089299
Log-logistic	Disease Dur	-0.004271	0.000057751		-0.002583	0.000089299	0.000936
Exponential	Intercept	0.150657	0		-0.066046	-0.078472	-0.006352
Exponential	Scale	0	0		0	0	0
Exponential	Vandetanib	-0.066046	0		0.147662	0.000604	-0.002266
Exponential	Prior Trt.	-0.078472	0		0.000604	0.143629	0.000204
Exponential	Disease Dur	-0.006352	0		-0.002266	0.000204	0.001262
Gamma	Intercept	0.179038	-0.037319	0.189089	-0.063392	-0.061762	-0.001199
Gamma	Scale	-0.037319	0.048033	-0.125557	0.010898	-0.004764	-0.001810
Gamma	Shape	0.189089	-0.125557	0.573801	-0.012252	-0.017730	0.008980
Gamma	Vandetanib	-0.063392	0.010898	-0.012252	0.123848	0.002305	-0.002370
Gamma	Prior Trt.	-0.061762	-0.004764	-0.017730	0.002305	0.114308	-0.000325
Gamma	Disease Dur	-0.001199	-0.001810	0.008980	-0.002370	-0.000325	0.001010
Gompertz	Intercept	0.650031		0.000429	-0.261428	-0.132246	-0.009427
Gompertz	Shape	0.000429		0.000001063	-0.000080835	-0.000129	0.000003092

Analysis	Variable	Intercept	Scale	Shape	Vandetanib	Prior Trt.	Disease Dur.
Gompertz	Vandetanib	-0.261428		-0.000080835	0.153346	0.011065	0.001893
Gompertz	Prior Trt.	-0.132246		-0.000129	0.011065	0.159254	-0.000133
Gompertz	Disease Dur	-0.009427		0.000003092	0.001893	-0.000133	0.001267

Table 44. Parametric Survival Analysis without Baseline Covariates Adjustment: Progression Free Survival (Covariance Matrix)

Analysis	Variable	Intercept	Scale	Shape	Vandetanib
Vandetanib					
Weibull	Intercept	0.065289	0.021721		
Weibull	Scale	0.021721	0.042109		
Log-normal	Intercept	0.080428	0.031992		
Log-normal	Scale	0.031992	0.064231		
Log-logistic	Intercept	0.073132	0.014254		
Log-logistic	Scale	0.014254	0.026660		
Exponential	Intercept	0.066667	0		
Exponential	Scale	0	0		
Gamma	Intercept	0.373510	0.070903	0.539848	
Gamma	Scale	0.070903	0.075377	0.056669	
Gamma	Shape	0.539848	0.056669	1.010935	
Gompertz	Intercept	0.198340		0.000484	
Gompertz	Shape	0.000484		0.000001777	
Placebo					
Weibull	Intercept	0.073765	-0.009815		
Weibull	Scale	-0.009815	0.045542		
Log-normal	Intercept	0.081578	0.004725		
Log-normal	Scale	0.004725	0.048955		
Log-logistic	Intercept	0.077791	0.002402		
Log-logistic	Scale	0.002402	0.020862		
Exponential	Intercept	0.076923	0		
Exponential	Scale	0	0		
Gamma	Intercept	0.236105	-0.014530	0.305799	
Gamma	Scale	-0.014530	0.052090	-0.042583	

Analysis	Variable	Intercept	Scale	Shape	Vandetanib
Gamma	Shape	0.305799	-0.042583	0.610143	
Gompertz	Intercept	0.172284		0.000448	
Gompertz	Shape	0.000448		0.000002105	
All					
Weibull	Intercept	0.068316	-0.005132		-0.071015
Weibull	Scale	-0.005132	0.021872		0.016637
Weibull	Vandetanib	-0.071015	0.016637		0.137929
Log-normal	Intercept	0.095334	0.002798		-0.093950
Log-normal	Scale	0.002798	0.028498		0.011293
Log-normal	Vandetanib	-0.093950	0.011293		0.155734
Log-logistic	Intercept	0.090971	0.001306		-0.090309
Log-logistic	Scale	0.001306	0.011992		0.004780
Log-logistic	Vandetanib	-0.090309	0.004780		0.149816
Exponential	Intercept	0.076923	0		-0.076923
Exponential	Scale	0	0		0
Exponential	Vandetanib	-0.076923	0		0.143590
Gamma	Intercept	0.209827	-0.023310	0.235365	-0.088802
Gamma	Scale	-0.023310	0.037396	-0.062974	0.006943
Gamma	Shape	0.235365	-0.062974	0.514193	0.022841
Gamma	Vandetanib	-0.088802	0.006943	0.022841	0.160862
Gompertz	Intercept	0.431013		0.000288	-0.221808
Gompertz	Shape	0.000288		0.000000950	-0.000038072
Gompertz	Vandetanib	-0.221808		-0.000038072	0.145117

Question dated 6th August:

At the PFS endpoint (July 2011), blinding was lifted and vandetanib patients could continue on open-label vandetanib. From this point, PFS was no longer monitored, but OS was still followed up. At this 2011 PFS timepoint, a significant proportion of the vandetanib group were still progression-free or censored and so did not yet have the opportunity to receive post-progression vandetanib (because they had not yet progressed). Our question is: *did the 2011 protocol amendment allow only those patients with progressed disease at the 2011 PFS timepoint to receive post-progression vandetanib, or did it allow for patients who were progression-free at the 2011 PFS timepoint to receive post-progression vandetanib after they later progressed in the future (i.e. could they just continue after they progress)?*

As discussed on page 13, 2011 protocol amendments allowed patients who had Investigator Assessed progression to switch to vandetanib treatment. This meant that (1) patients with progressed disease at the 2011 PFS timepoint could receive post-progression vandetanib (2) patients who did not have documented progression as of July 2011 were also able to continue with vandetanib. PFS data were not collected after this data.

Data from the IPD for the [redacted] patients on vandetanib arm, show that [redacted] patients had open-label vandetanib treatment. Within these [redacted] patients there were 9 patients who had not progressed at the 2011 PFS endpoint, [redacted] patients who had progressed at the 2011 PFS endpoint. In both these subgroups, we can infer there were patients who were treated beyond progression while for some patients the PFS data are not available.

(1) Have the PFS models been fitted based on the biomarker covariates in the whole ZETA population, or using the actual subgroup of patients in the Restricted EU label subgroup (excluding the biomarker covariates)?

(2) Have the OS models been fitted based on the biomarker covariates in the whole ZETA population, or using the actual subgroup of patients in the Restricted EU label subgroup (excluding the biomarker covariates)?

All survival analysis models i.e. PFS and OS were fitted in the Restricted EU label subgroup (patients that are symptomatic, progressive and have CTN/CEA biomarker doubling time less than 24 months) plus adjustment with terms for treatment, disease duration, and prior systematic treatment (yes or no). Only the original submission used the whole ZETA population with biomarker covariates.

References

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2. Kreissl M, Hauch O, Webster A, et al. Efficacy and safety of vandetanib in aggressive and symptomatic medullary thyroid cancer (mtc) – post-hoc analysis from the ZETA trial. *European Thyroid Journal* 2014;3 (suppl 1):73-226.
3. SanofiGenzyme. SPC: Caprelsa 100 mg & 300 mg film coated tablets. 2016

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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21st August 2018

1. Introduction

In February 2018, the National Institute for Health and Care Excellence (NICE) issued a Final Appraisal Determination (FAD) for the use of cabozantinib in treating medullary thyroid cancer (MTC). The FAD makes the following recommendation regarding the use of cabozantinib: *"Cabozantinib is recommended, within its marketing authorisation, as an option for treating progressive medullary thyroid cancer in adults with unresectable, locally advanced or metastatic disease only if the company provides cabozantinib with the discount agreed in the patient access scheme"* (NICE FAD,[1] page 1). The FAD states that at that time, NICE was not in a position to release any recommendations on the use of vandetanib, the other technology included in the scope of this appraisal.[1]

Following the release of the earlier Appraisal Consultation Document (ACD) on cabozantinib and vandetanib in 2017, Sanofi Genzyme submitted additional statistical and health economic analyses relating to the Restricted EU Label subgroup of the ZETA trial.[2] This subgroup relates to patients with symptomatic and progressive disease with carcinoembryonic antigen (CEA) and calcitonin (CTN) doubling times of ≤24 months. Within the company's new analyses, the Rank-Preserving Structural Failure Time (RPSFT) approach was used to adjust for potential confounding of overall survival (OS) outcomes resulting from patients who were initially randomised to the placebo group subsequently switching to vandetanib. The document containing these analyses is hereafter referred to as the "company's 2017 post-ACD response."[3] The company's 2017 post-ACD analyses were critiqued by the Assessment Group (AG);[4] the company's analysis and the AG's critique were discussed at the second Appraisal Committee meeting in September 2017. Subsequently, NICE requested a number of additional analyses and clarifications relating to the Restricted EU Label subgroup of the ZETA trial (see Box 1). The company's response to this request, which is discussed in this addendum, is hereafter referred to as the "company's 2018 post-ACD response."[5]

Box 1: Additional analyses requested by NICE

Base case analysis:

1) For the 'Restricted EU Label' subgroup,
    a. Use the RPSFT adjusted results and fit the full range of potentially plausible models to the data.
    b. Select the preferred model using the criteria from NICE Decision Support Unit Technical Support Document 14.
    c. Apply the preferred parametric models in the economic model, using the Appraisal Committee's preferred assumptions.
    d. Provide deterministic as well as probabilistic results which account for all uncertainty in adjustment procedures.

Scenario analyses:

2) An analysis without any RPSFT adjustment (that is, the confounded data) to demonstrate the impact of crossover-adjustment.
3) An analysis without covariate adjustment in the RPSFT adjusted data to demonstrate the impact of using a covariate adjustment approach.
4) Analyses using all combinations of fitted curves for progression-free survival and overall survival, to explore the impact of different extrapolations on the ICER.
5) Scenario analyses that explore the effect of lower overall survival for vandetanib (to reflect that post-progression treatment would not be given in practice).

Additional information:

6) Provide the comparative plots of observed and RPSFT-adjusted Kaplan-Meier data, and all fitted curves, together with goodness-of-fit statistics.
7) Explain what action was taken that enabled the RPFSFT adjustment to work (when the company's original submission reported that it had not worked)
8) Explain how missing data on biomarkers was handled. Provide baseline characteristics and overall survival plots for 'EU label' patients who:
    a. met the CTN doubling time criterion but had missing data on CEA
    b. met the CEA doubling time criterion but had missing data on CTN.

This addendum provides a critique of the company's 2018 post-ACD response.[5] The AG's critique addresses four main areas of concern: (i) the robustness of the company's RPSFT adjustment; (ii) the definition of the Restricted EU Label subgroup and the means by which missing data have been handled; (iii) issues surrounding the fitting and selection of parametric survivor functions to the available time-to-event data, and (iv) issues and further uncertainties relating to the company's health economic analyses of vandetanib.

2. Critique of the company's additional evidence

2.1 Summary of adjustment for treatment switching in the placebo group of the ZETA trial

2.1.1 Restricted EU Label subgroup

The company's 2018 post-ACD response provides results using two different methods to adjust for treatment switching in the Restricted EU Label subgroup of the ZETA trial: (i) RPSFT adjustment including adjustment of imbalanced baseline covariates for disease duration and prior therapy (company base case, see Figure 1), and (ii) RPSFT adjustment without covariate adjustment (see Figure 2). As discussed within the AG's earlier critique of the company's 2017 post-ACD analyses,[3] the bootstrapping procedure used to produce the 95% confidence interval (CI) was inappropriate and underestimates the uncertainty around the adjusted hazard ratio (HR). Revised CIs were presented within the company's 2018 post-ACD analyses.[5] Without further information on the procedure used, the AG cannot verify that these are correct; however, the wider confidence intervals are more plausible than those presented in the post-ACD analyses.[3]

HRs from Cox proportional hazards (PH) regression models are presented in Table 1. The AG notes that the PH assumption is unlikely to hold as the Kaplan-Meier survivor estimates for the two treatment groups cross. However, the estimated HRs provide some indication of the time-averaged treatment effect (the AG notes that these HRs are not used in the company's health economic analyses).

As shown in Table 1, adjusting for imbalances in the baseline characteristics of disease duration and prior therapy results in a slightly higher HR (less favourable to vandetanib) irrespective of whether RPSFT adjustment is applied, and increases the width of the 95% CIs. Adjusting for treatment switching onto vandetanib following progression in the placebo arm results in a more pronounced HR (favourable to vandetanib), irrespective of whether covariate adjustment is applied, and the 95% CIs are wider, which reflects the uncertainty in the RPSFT adjustment procedure.

Figure 1: Restricted EU Label overall survival curves for vandetanib, unadjusted placebo, and adjusted placebo using RPSFT with covariates for disease duration and prior therapy (company base case, replicated from Sanofi 2018 post-ACD response, Figure 3)

Figure 2: Restricted EU Label overall survival curves for vandetanib, unadjusted placebo, and adjusted placebo using RPSFT without covariates (replicated from Sanofi 2018 post-ACD response, Figure 15)

Table 1: Estimated HRs from Cox proportional hazards model

Data	No covariate adjustment	Adjusted for disease duration (years) and prior therapy (none/yes)
Restricted EU Label subgroup **Observed data (no adjustment for treatment switching)**	[redacted][6]	[redacted]*[3]
Restricted EU Label subgroup **RPSFT-adjusted data (adjusting for cross-over)**	[redacted]	[redacted]
Extended Restricted EU Label subgroup **Reconstructed IPD (no adjustment for treatment switching, described in Section 2.2)†**	[redacted]	Not available

** From Cox proportional hazards model with covariates for disease duration and prior systemic treatment*
† Restricted EU subgroup with additional [redacted] individuals with CTN doubling time ≤24 months. Data reconstructed by AG. See Section 2.2

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

(i) The company's base case uses the RPSFT-adjusted data including adjustment for disease duration and prior therapy. The HR indicates prolonged survival for patients receiving vandetanib compared with placebo; however, the associated 95% CI of [redacted] to [redacted] indicates considerable uncertainty. Based on this analysis, the AG cannot be confident that OS for patients receiving vandetanib is better than that for those receiving placebo. The estimated treatment effects are not statistically significant for any of the four levels of adjustment presented (with/without covariate adjustment and with/without RPSFT).

(ii) RPSFT assumes perfect randomisation - if no treatment was given, equal average survival would be expected in the two groups. This assumption is violated in this case, as the use of a subgroup breaks the original randomisation of the trial. In their most recent evidence submission,[5] the company states that this can be overcome by adjusting for baseline covariates within the RPSFT. The AG considers that, in principle, covariate adjustment is a reasonable approach; however, the small sample size (n=[redacted]) is a limiting factor. The analysis presented by the company includes adjustment for two covariates: (i) disease duration and (ii) prior therapy. Justification for the inclusion of these covariates, and the exclusion of other covariates which may also be imbalanced between the treatment groups e.g. number of sites involved and tumour stage, has not been provided in either the company's 2017 or 2018 post-ACD analyses.[3, 5] As stated in the AG's previous critique,[4] the AG would expect to see a justification for the chosen model, including results for different combinations of covariates.

In addition, the following issues were raised in the AG's critique of the company's 2017 post-ACD response;[4] these issues remain relevant to the company's 2018 post-ACD response:[5]

(i) The RPSFT 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 AG notes that the company has made some attempt to adjust for this continued vandetanib use within their exploratory health economic analyses,[5] although the AG does not consider the proposed method to be robust (see Section 2.4.2 critical appraisal point [iii]).

(ii) Consideration of re-censoring is generally recommended when the RPSFT method is used; this has not been addressed.

(iii) The methodological framework of the RPSFT approach is described briefly on page 10 of the company's 2018 post-ACD response.[5] The statistical model for a general accelerated failure time (AFT) model is given; however, 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).

2.1.2 EU Label subgroup

As discussed in the AG's critique of the company's 2017 post-ACD response,[4] the AG does not agree with the company's justification for not presenting the RPSFT estimates from the broader EU Label subgroup of the ZETA trial. The company's 2017 post-ACD response[3] (page 1) states that the RPSFT-adjusted estimates in the broader EU Label subgroup could not be *"validly used in the model."* Further clarification was provided in the company's 2018 post-ACD response (page 50) which explains that initial RPSFT modelling in the EU Label subgroup suggested a *"detrimental treatment effect"* for patients in the placebo arm switching to vandetanib after progression, which "*suggested there was no value in pursuing the RPSFT modelling in this Kreissl analysis [the EU Label subgroup]*".[5] The AG believes that the possibility of a detrimental treatment effect in the wider EU Label subgroup raises concerns regarding the findings of a beneficial treatment effect in the Restricted EU Label subgroup. The company states that the detrimental finding for the EU Label subgroup is *"not a surprise as this is not where the data indicate there to be optimal treatment benefit/risk profile."* However, the AG believes that although the magnitude of the effect may be different, a beneficial effect would still be expected.

2.2 Concerns regarding the company's handling of missing biomarker data

A key criterion for the definition of the company's Restricted EU Label subgroup is that patients must have both CTN and CEA doubling times of ≤24 months. As described within the company's 2018 post-ACD response (page 7), "*The word 'aggressive' in the label does not have a clinically specific meaning and is therefore open to interpretation*"[5] and the company refers to clarifying text from Section 4.4 of the Summary of Product Characteristics (SmPC) for vandetanib[7] which refers to "*Rate of change in biomarker levels such as of calcitonin (CTN) and/or carcinoembryonic antigen (CEA)*". The company has adopted a strict interpretation which requires that patients must have both CTN and CEA doubling times of ≤24 months. Clinical advice received by the AG suggests that an increase in one biomarker (either CEA or CTN) is indicative of an increase in the other, and that clinicians would treat patients with information from just one of these sources.

The company's 2018 post-ACD response[5] provides additional details relating to missing biomarker data which have not been previously presented. According to the document, [redacted] patients met the CTN doubling time criterion but had missing data on CEA and were thus excluded from the company's

Restricted EU Label subgroup dataset. The company's 2018 post-ACD response also presents Kaplan-Meier OS curves for these patients (see Figure 3).

The AG considers that the company has not justified why these individuals should be excluded from the Restricted EU Label subgroup and notes that the inclusion of these patients would increase the sample size from [redacted] to [redacted] patients (a [redacted] increase).

In order to explore the effect of excluding these individuals from the Restricted EU Label subgroup, the AG reconstructed the individual patient-level data (IPD) using the algorithm reported by Guyot *et al*.[8] Kaplan-Meier survival estimates for this "Extended Restricted EU Label" subgroup constructed by the AG are shown in
Figure 4. Based on the AG's reconstructed analysis, the addition of these [redacted] individuals increases the unadjusted HR from [redacted] to approximately [redacted], see Table 1). Without adjustment for either treatment switching or baseline covariates, this suggests a much less pronounced treatment effect for vandetanib.

Figure 3: EU Label subgroup with CTN doubling time ≤24 months and missing CEA (replicated from Sanofi 2018 post-ACD response, page 58)

Figure 4: Kaplan Meier OS estimate for the Extended Restricted EU Label subgroup based on IPD reconstructed by the AG

2.3 Concerns regarding fitting and selection of parametric functions to model OS

2.3.1 Issues relating to fitting of parametric time-to-event models

The AG has some concerns regarding the company's new survival analyses which are used in the health economic model:

(i) The company were asked to provide analyses using all combinations of fitted curves (see Box 1); however, there appear to have been some issues with the curve fitting process. The company's 2018 post-ACD response (page 19) states that the Gompertz and gamma functions "*did not converge for vandetanib.*"[5] However, the AG has previously fitted these models to the reconstructed IPD (without covariate adjustment).[9] The company's 2018 post-ACD response reports results for the Gompertz model fitted to the placebo group data, albeit with extremely high values of the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) compared with the other fitted models. This indicates a lack of comparability and inconsistency in the model fitting procedure.

(ii) It is not clear how uncertainty due to the RPSFT and baseline covariate adjustment has been represented in the curve fitting procedure. The AG suspects that the company has treated the

adjusted data as if they were observed trial data, rather than as a model-based estimate with associated uncertainty. In analysis request 1d (see Box 1), the company were specifically asked to provide results which account for all uncertainty in adjustment processes. The AG does not believe that this has been done.

2.3.2 Issues relating to selection of parametric time-to-event models

The company's new base case health economic analysis includes the use of a different set of preferred progression-free survival (PFS) and OS functions compared with those selected for use in the economic analyses reported in the original company submission (CS)[6] and the company's 2017 post-ACD response.[3] The parametric curves for PFS and OS selected by the company within the CS, the company's 2017 post-ACD response and the 2018 post-ACD response are summarised in Table 2. Within the company's new base case analyses, PFS and OS curves were selected on the basis of statistical goodness-of-fit only, based on the AIC and BIC. The company also sought expert input from Dr Jon Wadsley (the same clinical expert previously used by the AG and a co-author of the AG report[9]) to select plausible curves for PFS and OS. The company's 2018 post-ACD response includes additional scenario analyses using Dr Wadsley's preferred curves.

Table 2: Parametric curves selected for PFS and OS and basis for justification within the CS, the company's 2017 post-ACD response and the company's 2018 post-ACD response

Analysis	Selection and justification	Vandetanib PFS	BSC PFS	Vandetanib OS	BSC OS
Original submission[6]	Selected curves	Weibull	Weibull	Weibull	Weibull
	Justification	The original CS states *"As there is no clear, clinical expectation for the PFS over the long-term, Weibull was also selected in the base case for consistency"* (CS,[6] page 105)		The CS stated that this function *"matches human mortality better in the long term"* (CS,[6] page 105)	
Company's 2017 post-ACD response[3]	Selected curves	Weibull	Weibull	Log normal	Weibull
	Justification	No justification given for changing preference for vandetanib OS curve to log normal within 2017 post-ACD response submission[3]			
Company's 2018 post-ACD response[5] base case	Selected curves	Log normal	Exponential	Log normal	Weibull
	Justification	Curves selected on the basis of goodness-of-fit statistics (AIC and BIC). No justification is given for changing the curve selection criteria.			
Company's 2018 post-ACD response[5] clinician preferred curves scenario	Selected curves	Weibull	Weibull	Weibull	Weibull
	Justification	Dr Wadsley noted that *"[the] Weibull was most clinically plausible for both the vandetanib arm and the placebo arm. He noted that Gompertz worked for placebo but isn't available for vandetanib. The other curves underestimate early on and overestimate later on."*			

With respect to the company's new curve choices, the AG makes the following observations:

- No justification is given within the company's 2018 post-ACD response with respect to changing the basis for the selection of PFS and OS curves. The AG notes that AIC and BIC concern the relative goodness-of-fit of competing parametric models to the observed data and that these metrics do not take into account the plausibility of the extrapolation. This approach is not advocated in NICE Decision Support Unit Technical Support Document (TSD) 14.[10] Further, the company's 2018 post-ACD response notes that with the exception of the Weibull function and the Gompertz function (for placebo only), Dr Wadsley commented that the other parametric functions either over- or under-estimated OS.[5] As such, the AG does not consider the company's base case curve selections to be appropriate.
- On the basis of the AG's previous curve-fitting exercise (which uses the same data for three of the four curves [OS vandetanib, PFS vandetanib and PFS BSC]) without covariate adjustment, Dr Wadsley preferred the log normal function for PFS and the Gompertz function for OS. As noted in Section 2.3.1, the Gompertz model was not available for vandetanib in the company's new analyses. During subsequent personal correspondence with the AG, Dr Wadsley

emphasised the difficulty associated with selecting plausible curves from the small dataset that comprises the company's Restricted EU Label dataset.

2.4 Further issues and uncertainties relating to the company's health economic analyses in the Restricted EU Label subgroup

2.4.1 Overview of company's new adjusted health economic analyses

As part of their 2018 post-ACD response,[5] the company provided the results of additional health economic analyses within the Restricted EU Label subgroup which explore the impact of:

(i) Including/excluding statistical adjustment of OS outcomes for patients who were randomised to placebo who subsequently received open-label vandetanib (using an RPSFT model).

(ii) Including/excluding statistical adjustment of two covariates which were deemed to be imbalanced at baseline within the Restricted EU Label subgroup of the ZETA trial (disease duration and prior systemic therapy).

(iii) Including/excluding of post-progression vandetanib costs in the vandetanib group.

(iv) Adjusting OS outcomes in the vandetanib group to account for post-progression vandetanib use.

Within all analyses, the parametric survivor functions for PFS and OS were fitted to time-to-event data relating to the full Restricted EU Label subgroup of the ZETA trial (as done by the AG within the AG report,[9] albeit without covariate adjustment), rather than using the ITT ZETA population including biomarkers for symptomatic and progressive disease and CTN/CEA doubling time ≤24 months (as done by the company within the original CS[6]). All analyses also include an updated Patient Access Scheme (PAS) for vandetanib (discount = [redacted]).

The main features of the base case model presented in the company's 2018 post-ACD response[5] are presented in Table 3. As shown in the table, the company's new model is broadly in line with the AG's original analysis. The main exceptions are:

- The company's 2018 post-ACD base case includes parametric models selected on the basis of AIC/BIC without consideration of clinical plausibility of the extrapolation.
- The company's new model includes covariate adjustment (both groups) and treatment switching (placebo group only).
- The costs of pre-progression vandetanib discontinuation is modelled assuming a linear increase up to 1 year; subsequently, all patients are assumed to have discontinued treatment.
- The costs of post-progression vandetanib use in the vandetanib group are excluded.

Table 3: Main features of the company's 2018 model and the original AG model (aspects/features of the company's model which have changed since the original CS are marked with an asterisk*)

Model feature/component	Original AG model[9]	Company's 2018 post-ACD model[5]
Model structure	Partitioned survival model	Partitioned survival model
Method for selecting parametric survivor functions	Clinical plausibility and statistical goodness-of-fit (AIC and BIC)	Statistical goodness-of-fit (AIC and BIC)*
Time-to-event dataset	ZETA subgroup only (without biomarkers)	ZETA subgroup only (without biomarkers)*
OS vandetanib	Gompertz without covariate adjustment	Log normal with covariate adjustment*
OS BSC	Gompertz without covariate adjustment or RPSFT adjustment to account for placebo group patients switching to vandetanib	Weibull with covariate adjustment and RPSFT adjustment to account for placebo group patients switching to vandetanib*
PFS vandetanib	Log normal without covariate adjustment	Log normal with covariate adjustment*
PFS BSC	Log normal without covariate adjustment	Exponential with covariate adjustment*
Health utilities	Based on Fordham *et al*[11] (progression-free=0.80; post-progression=0.50)	Based on Fordham *et al*[11] (progression-free=0.80; post-progression=0.50)*
Health state costs (annual)	Based on clinical advice received by the AG: Vandetanib year 1 cost=£5,152.41 Vandetanib year 2+ cost=£3,408.16 BSC=£2,998.21	Based on clinical advice received by the AG: Vandetanib year 1 cost=£5,152.41* Vandetanib year 2+ cost=£3,408.16* BSC=£2,998.21*
Vandetanib pre-progression discontinuation assumptions	Patients discontinuing vandetanib prior to progression incur 50% of the total PFS cost	Patients discontinuing vandetanib prior to progression discontinue at a linearly increasing rate in the first year and incur no costs thereafter*
Vandetanib post-progression discontinuation assumptions	Patients receiving post-progression vandetanib are treated until death ([redacted] patients in vandetanib group and [redacted] patients in BSC group)	All post-progression costs excluded†
Adjustment of OS curves to remove effect of post-progression vandetanib	None	None†

AG – Assessment Group; ACD – Appraisal Consultation Document; AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion; BSC – best supportive care; RPSFT – Rank-Preserving Structural Failure Time; PFS – progression-free; OS – overall survival

** Model feature/component has changed from the original CS[6]*

† Explored separately in company's new exploratory analyses

2.4.2 Company's new base case results and scenario/sensitivity analysis results

The results of the probabilistic and deterministic versions of the company's base case model are presented in Table 4.

Table 4: Company's new base case results, Restricted EU Label subgroup, including RPSFT adjustment and covariate adjustment, excluding post-progression costs

Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
Probabilistic model					
Vandetanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]*
BSC	[redacted]	[redacted]	-	-	-
Deterministic model					
Vandetanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	-	-	-

Inc. - incremental; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; BSC - best supportive care
** Generated by the AG*

The broad range of analyses presented within the company's 2018 post-ACD response and their corresponding incremental cost-effectiveness ratios (ICERs) are summarised in Table 5; the equivalent ICERs generated by the AG using the company's new model are also shown in the table. The AG notes that there were some minor discrepancies between the results generated by the AG using the company's model and those reported in the company's 2018 post-ACD response document. The AG consider it likely that these discrepancies are a result of minor rounding errors in the model inputs and therefore are not a matter of concern.

Table 5: Summary of all health economic analyses presented within the company's 2018 post-ACD response,[5] deterministic model

Analysis reference	Source of curve selection (company/clinician)	Includes imbalanced covariate adjustment?	Includes RPSFT adjustment for placebo?	Includes post-progression costs for vandetanib?	Includes OS adjustment for post-progression vandetanib?	ICERs Reported in company's 2018 post-ACD response	ICERs generated by AG using 2018 post-ACD model
Tables 9&10, p.25	Company (AIC/BIC)	Yes	Yes	No	No	[redacted]	[redacted]
Tables 11&12, p.26	Company (AIC/BIC)	Yes	Yes	Yes	No	[redacted]	[redacted]
Tables 13&14, p.27	Clinician	Yes	Yes	No	No	[redacted]	[redacted]
Tables 15&16, p.28	Clinician	Yes	Yes	Yes	No	[redacted]	[redacted]
Table 20, p.35	Company (AIC/BIC)	Yes	No	Yes	No	[redacted]	[redacted]
Table 21, p.35	Clinician	Yes	No	Yes	No	[redacted]	[redacted]
Table 25, p.38	Company (AIC/BIC)	No	No	Yes	No	[redacted]	[redacted]
Table 26, p.38	Clinician	No	No	Yes	No	[redacted]	[redacted]
Table 30, p.42	Company (AIC/BIC) and clinician	No	Yes	No	No	[redacted]	[redacted]
Table 31, p.42	Company (AIC/BIC) and clinician	No	Yes	Yes	No	[redacted]	[redacted]
Table 32, p.44-46	All possible	Yes	Yes	No (all) Yes (some)†	No	[redacted]*	[redacted]*
Table 33, p.46	Summarises the 4 possible approaches for clinician's curves				No	[redacted]	[redacted]
Table 35, p.49	Company (AIC/BIC)	Yes	Yes	No	Yes	[redacted]	[redacted]

AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion; RPSFT – rank-preserving structural failure time model; OS – overall survival; ICER – incremental cost-effectiveness ratio; p. - page

** Based on the company's model, the inclusion of post-progression costs appears to be more influential than curve choice*

† Analyses including post-progression costs included for some analyses only

2.4.3 Summary of key ICERs generated using the company's 2018 post-ACD response model

Table 6 summarises the key ICERs generated by the AG using the company's 2018 post-ACD response model. These ICERs have been generated using the company's base case parametric model selections (selected on the basis of AIC and BIC). These analyses indicate the following:

- Covariate adjustment alone reduces the quality-adjusted life year (QALY) gains for vandetanib and BSC compared with the unadjusted values. The effect is more pronounced for vandetanib, hence the incremental QALY gains are smaller when covariate adjustment only is included.
- The inclusion of RPSFT adjustment alone markedly reduces the QALY gains for BSC versus the unadjusted values, hence the incremental QALY gains are increased considerably.
- The inclusion of covariate adjustment and RPSFT adjustment together reduces the QALY gains for both vandetanib and BSC compared with the unadjusted values. The reduction in the estimated number of QALYs is more pronounced in the BSC group, hence the incremental QALYs increase when both RPSFT and covariate adjustments are included.
- The inclusion of post-progression costs results in markedly less favourable ICERs for vandetanib versus BSC.

Table 6: Summary of key ICERs generated by the AG using the company's 2018 post-ACD response model, company's deterministic base case (curves selected on basis of AIC/BIC)

Option	QALYs	Costs	Inc. QALYs	Inc. costs	ICER
(1) RPSFTM, covariate adjustment, no PP vandetanib cost in either group					
Vandetanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	-	`-	-
(2) RPSFTM, no covariate adjustment, no PP vandetanib cost in either group					
Vandetanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	-	`-	-
(3) No RPSFTM, covariate adjustment, no post-progression vandetanib cost in vandetanib group					
Vandetanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	-	`-	-
(4) No RPSFTM, no covariate adjustment, no PP vandetanib cost in vandetanib group					
Vandetanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	-	`-	-
(5) RPSFTM, covariate adjustment, PP vandetanib cost included in vandetanib group					
Vandetanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	-	`-	-
(6) RPSFTM, no covariate adjustment, PP vandetanib cost included in vandetanib group					
Vandetanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	-	`-	-
(7) No RPSFTM, covariate adjustment, PP vandetanib cost included both groups					
Vandetanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	-	`-	-
(8) No RPSFTM, no covariate adjustment, PP vandetanib cost included both groups					
Vandetanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	-	`-	-

QALY – quality-adjusted life year; ICER – incremental cost-effectiveness ratio; RPSFT – Rank-Preserving Structural Failure Time; BSC – best supportive care; PP – post-progression

2.4.2 Critique of company's new adjusted health economic analyses

Notwithstanding the considerable uncertainty relating to the robustness of the results of the company's RPSFT and covariate adjustment and the inappropriate basis for selecting PFS and OS curves, the AG has four further concerns regarding the company's new base case analyses:

(i) Identification of model errors
(ii) Bias associated with excluding the costs associated with post-progression vandetanib use
(iii) Confounding in the company's exploratory analyses to reduce vandetanib post-progression OS benefits
(iv) Uncertainty surrounding pre-progression discontinuation of vandetanib.

As a consequence of these issues, the AG believe that the results of the company's economic analyses should be interpreted with caution.

(i) Identification of model errors

The company's analyses submitted 30th July 2018 were subject to a significant programming error which invalidated all of the results presented within their original 2018 post-ACD response. This error was evident as the company's model suggested PFS sojourn times in both groups which were implausibly low and which deviated significantly from the observed Kaplan-Meier curves for the Restricted EU Label subgroup. The company acknowledged this error and subsequently submitted a corrected model and submission to NICE. Subsequently, the AG identified a further issue in the company's revised model, whereby those patients who discontinue vandetanib prior to progression do not incur BSC costs after vandetanib discontinuation and prior to disease progression. This can be seen by setting the vandetanib drug acquisition and monitoring costs equal to zero and setting the probability of pre-progression vandetanib discontinuation equal to 1.0 – this should increase the BSC costs for vandetanib patients relative to the base case results; however, this is not the case. The AG considers that this reflects a further model error, but notes that its impact is less significant than the covariate adjustment error detailed above. This issue should however be borne in mind when interpreting all ICERs from the company's model. For this reason, additional analyses undertaken by the AG have been implemented within the original AG model (see Table 8).

(ii) Exclusion of the costs associated with post-progression vandetanib use

Within the Restricted EU Label subgroup of the ZETA trial, [redacted] of [redacted] patients ([redacted]) randomised to the vandetanib group received open-label vandetanib. 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 2018 post-ACD base case analysis.[5] The AG notes, however, that the company has presented scenario analyses in which post-progression costs are included (see Table 6). The inclusion of these costs has a significant impact

on the company's base case ICER for vandetanib, leading to an increase from [redacted] per QALY gained (excluding post-progression costs) to [redacted] per QALY gained (including post-progression costs). The company's 2018 post-ACD response notes the point previously made in the AG's earlier critique - that there is uncertainty regarding the duration of post-progression treatment, and 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. Despite this uncertainty, the AG does not consider it appropriate to exclude these costs altogether.

(iii) Company's exploratory analyses to reduce post-progression OS benefit due to continued vandetanib use

The company's 2018 post-ACD response[5] includes an analysis which attempts to adjust for the potential confounding resulting from the continued use of vandetanib after disease progression. The document refers to an analysis whereby the mortality risk for vandetanib is applied to the proportion of vandetanib group patients who are progression-free and the mortality risk for BSC is applied to the proportion of surviving vandetanib group patients in the progressed state. The company notes that this analysis is a "possible" rather than "definitive" approach. Excluding post-progression costs, this approach increases the company's base case ICER for vandetanib from [redacted] per QALY gained to [redacted] per QALY gained. The AG is unclear whether the results of this analysis are meaningful because: (a) the vandetanib OS curve applied to vandetanib group patients who are progression-free will still be subject to potential confounding as a consequence of continued post-progression vandetanib use, and (b) it is unclear whether patients who have discontinued vandetanib will be subject to the same mortality risks as those who have not previously received the drug.

(iv) Assumptions regarding pre-progression discontinuation of vandetanib

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 company's original 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 AG report that they *"agree that it [the modelled reduction in vandetanib costs] was an overestimate."*[12] The company's 2018 post-ACD 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 AG report). This amendment is not described in the company's 2018 post-ACD response[5] and the AG believes that the company's approach is arbitrary.

2.4.3 AG's preferred analysis using the company's model

Based on the company's new analyses, the AG's preferred scenario is detailed in Table 7.

Table 7: AG's preferred scenario including RPSFT and covariate adjustment

Analysis feature	AG justification and additional comments
ICERs based on the AG's original model	An error was identified within the company's new 2018 post-ACD model
Parametric curves selected by the expert clinician	Selecting curves on the basis of AIC/BIC does not consider the plausibility of the extrapolation.
Post-progression vandetanib costs included for patients continuing vandetanib beyond progression	Excluding these costs will underestimate of the ICER, whilst including these costs will overestimate the ICER. The magnitude of the bias is unknown. The bias associated with including these costs may, to some degree, be counterbalanced by the inclusion of potential post-progression OS gains for vandetanib.
Half the cost of vandetanib is included for those who discontinue prior to disease progression	This reflects the AG's original assumption. The amount of drug consumed by these patients is unknown.

The results of the AG's preferred analysis are presented in Table 8, together with two additional exploratory analyses which give some indication of the sensitivity of the model results to the assumptions regarding the probability of pre-progression vandetanib discontinuation and post-progression vandetanib costs. Based on the AG's preferred scenario detailed in Table 7, the AG's preferred analysis suggests an ICER for vandetanib versus BSC of [redacted] per QALY gained. The exclusion of costs accrued by patients who discontinued vandetanib prior to progression, and/or a reduction in the costs of post-progression vandetanib use improve the ICER for vandetanib. Given the AG's concerns regarding the uncertainty surrounding the results of the company's RPSFT analyses, the AG considers that these ICERs should be interpreted with caution.

Table 8: Results for AG's preferred scenario including RPSFT and covariate adjustment and post-progression costs, deterministic model

AG preferred analysis					
Option	**QALYs**	**Costs**	**Inc. QALYs**	**Inc. costs**	**ICER**
Vandetanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	-	-	-
AG exploratory analysis 1 – post-progression drug costs halved					
Option	**QALYs**	**Costs**	**Inc. QALYs**	**Inc. costs**	**ICER**
Vandetanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	-	-	-
AG exploratory analysis 2 – pre-progression discontinuation costs set to zero					
Option	**QALYs**	**Costs**	**Inc. QALYs**	**Inc. costs**	**ICER**
Vandetanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	-	-	-

AG – Assessment Group; QALY – quality-adjusted life year; BSC – best supportive care; ICER – incremental cost-effectiveness ratio

3. Conclusions

Based on the evidence presented by the company, the AG believes that there is considerable uncertainty in the results for the Restricted EU Label subgroup. The key points are summarised below:

- Insufficient justification has been provided for the inclusion criteria for the Restricted EU Label subgroup. In particular, the company did not justify the decision not to include [redacted] individuals who met the CTN doubling time criterion (indicative of aggressive disease) but had missing data on CEA. Inclusion of these individuals would increase the sample size by [redacted]. Initial investigation by the AG suggests that this would result in a much less pronounced treatment effect for vandetanib.
- PFS and OS estimates for the Restricted EU Label subgroup are very uncertain due to the small sample size (n=[redacted]), the high switching proportion ([redacted]) and the breaking of randomisation within the subgroup. The estimated treatment effects are not statistically significant for any of the four levels of adjustment presented (with/without imbalanced covariate adjustment and with/without RPSFT). The company's base case uses the RPSFT-adjusted data including adjustment for disease duration and prior therapy but justification of the adjustment model was not provided. The HR indicates prolonged survival for patients receiving vandetanib compared to placebo, however the associated 95% CI of [redacted] to [redacted] indicates considerable uncertainty.
- The company's initial investigation of the use of the RPSFT to adjust for treatment switching in the broader EU Label subgroup did not suggest a beneficial treatment effect for patients in the placebo arm switching to vandetanib after progression. The AG does not consider that this is a valid reason for not presenting the RPSFT-adjusted estimates in this population. In addition, the AG believes that this raises concerns regarding the finding of a beneficial treatment effect in the smaller Restricted EU Label subgroup.
- Uncertainty does not appear to have been fully accounted for in the company's health economic model. It appears that parametric survival models were fitted to the RPSFT- and covariate-adjusted data without accounting for the considerable uncertainty in the adjustment procedure.
- The credibility of the company's new health economic results are reliant on the robustness of the company's new statistical analyses. Given the uncertainties described above, the AG advises that all economic results presented within the company's 2018 post-ACD response and within this addendum should be interpreted with caution.

4. References

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Ms Kate Moore
Technology Appraisal Project Manager – Committee D
National Institute for Health and Care Excellence
Level 1A / City Tower / Piccadilly Plaza / Manchester M1 4BT

Monday 10 September 2018

Dear Kate

Re: Vandetanib for treating medullary thyroid cancer [ID1415]

Thank you for asking me to answer some questions regarding this technology appraisal. In your letter to me, the following question was asked:

- In the previous submission considered by the committee last year, the company defined the restricted population (that with the biomarker doubling time) as a subset of the EU population. However in its additional evidence (pages 7 – 10), the company explains that the restricted population is actually the EU population and not a subset of it, with references made to the EPAR and SmPC. Could you please comment on the company's assumption that the population with the biomarker doubling time best reflects the EU label for vandetanib?

Thank you for sharing the additional evidence provided by the company.

Regarding the previous submission, the committee noted inconsistencies relating to the definitions of the EU label and the restricted population. In my opinion, the recent additional evidence submitted by the company, clarifies this:

On page 7, the relevant case population was stated to consist of patients with medullary thyroid carcinoma (MTC) who met three criteria: symptomatic, radiological progression and calcitonin/CEA biomarker doubling time of less than 24 months.

The EU label population includes patients with progressive and symptomatic disease. In my opinion, the definition of progressive disease would include patients with objective evidence of progression (worsening radiological changes, or biochemical deterioration with calcitonin/CEA biomarker doubling time of less than 24 months). It would also include symptomatic changes such as worsening breathlessness or worsening cough related to pulmonary infiltration by disease.

Monitoring of the biomarkers calcitonin and CEA is a useful tool to detect progression of disease that may not yet have become clinically apparent. A doubling time of less than 24 months often prompts radiological investigation to assess for progressive disease and would be compared with clinical symptoms. In my experience, and having discussed this patient group with consultant oncologist colleagues specialising in thyroid cancer, the patients with short

doubling time, radiological progression and worsening symptoms often have doubling times that are shorter than 24 months (6-12 month doubling time).

I am aware that another medical expert invited by the NICE committee reported her clinical experience – one of the largest MTC practices in the UK – to the committee. 20 out of 24 patients commenced on vandetanib had calcitonin doubling times significantly shorter than 24 months, with the remaining 4 patients presenting with such symptomatic or demonstrable disease that there was insufficient time to establish a trend in markers. It should be noted also that whilst CEA evaluation is readily available, calcitonin assay results may take longer to become available (weeks in some institutions). These patients would benefit from treatment that offers the potential to delay disease progression and improve symptoms, particularly when the only alternative would be best supportive care.

In summary, in my opinion, the described patient group with a calcitonin/CEA doubling time of less than 24 months, evidence of radiological progression and symptoms would reflect the EU label group with progressive and symptomatic disease.

I am aware that in March 2018, the NICE committee recommended cabozantinib as a treatment option for patients with progressive MTC and unresectable, locally advanced or metastatic disease. In anticipation that the committee may ask: why should vandetanib, another drug, also be recommended for the same indication? – I have provided my opinion below.

No direct comparison for cabozantinib and vandetanib is available but the evidence seems to suggest that they may be similarly effective in delaying progression and improving symptoms.

Both drugs are associated with different toxicity profiles, as acknowledged in the NICE guidance relating to cabozantinib, and toxicities are common with both. Whilst disease extent and symptoms may improve, the side effects may affect quality of life.

When patients require treatment, clinicians assess their current symptoms and history, to recommend which therapeutic agent is likely to be better tolerated. This decision should be made by an oncologist experienced in treating this condition. Even so, due to the extensive toxicity profiles of these agents, some patients may develop unexpectedly severe toxicity and require discontinuation of treatment. These patients would still need treatment for MTC. It would be important to be able to offer them an alternative but similarly effective drug, which might be better tolerated. If an alternative drug were not available, these patients would be likely to deteriorate rapidly with only best supportive care. For this reason, my opinion is that both vandetanib and cabozantinib are needed as treatment options in this indication.

Thank you again for asking me to answer your questions and I hope that this response is useful to the committee.

Kind regards

Mary Lei MBBS MRCP FRCR MD
Consultant clinical oncologist
Guy's Cancer Centre, Guy's and St Thomas' NHS Foundation Trust
London SE1 9RT

From: CLARK, Peter (THE CLATTERBRIDGE CANCER CENTRE NHS FOUNDATION TRUST)
Sent: 10 September 2018 14:09
To: Nwamaka Umeweni
Cc: Jasdeep Hayre
Subject: RE: Tomorrow Comm D Vandetanib

Amaka

1. See section 4.4 of the vandetanib SPC. 'It is important to limit treatment with V to patients who are in real need of treatment ie with a symptomatic-aggressive course of the disease. Either symptomatic disease or progressive disease alone is not enough to prompt the need for treatment with V. Rate of change in biomarker levels such as CTN 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 of treatment but also the optimal moment to commence treatment with V'.
2. The use of the term 'symptomatic-aggressive' and then saying that symptomatic disease alone is not sufficient to prompt the need for treatment is silly without then defining clearly what aggressive means. Everyone one knows what symptomatic means. For the SPC then to go on to talk about rate of change of biomarker/tumour volume which MIGHT be used to start treatment is ducking the issue. These issues of 'aggressive' disease (whatever that is as it will be variably interpreted by clinicians) and biomarker doubling are purely there to rationalise the poor design of the trial in including patients who did not have progressive disease in the first place.
3. So, in practice, if patients are symptomatic, it will be because the disease is progressive and the option of active treatment will be discussed whatever the rate of change of CTN/CEA/tumour volume.
4. In patients with a rapid change in tumour volume in a critical place where the disease may be currently symptomatic but when it becomes symptomatic it could imminently threaten life, treatment will be commenced eg a recurrent neck mass which is growing but now threatening to invade/compress the trachea or a major blood vessel ie when waiting for future symptoms to develop could be hazardous
5. In NHS England's view, there is a very marked difference between the ICERs for the symptomatic and progressive population (based on clinical data of 186 patients) vs the ICER for the symptomatic and progressive population with faster CTN/CEA doubling times (based on only XX patients). This is odd and worrying as to its plausibility when the first group is already based on a subgroup (n=186) and the second on a subgroup of a subgroup (n=XX).
6. There is no data on sequential use of V and C. So if NICE says yes, I would hope that NICE would recognise this and indicate that it V is recommended in patients with symptomatic disease and fast biomarker doubling times in patients who were either prev untreated with any TKI or could not tolerate cabozantinib in the absence of progressive disease on cabozantinib (this is the current position re accessing C from routine commissioning and V from the CDF)
7. The upshot as you say if V is recommended as per the company's wishes then cabozantinib will be used in preference as it is less hassle and clinicians would then be using C for most patients and V for others

I hope this helps
Peter

From: Nwamaka Umeweni
Sent: 10 September 2018 12:18
To: CLARK, Peter (THE CLATTERBRIDGE CANCER CENTRE NHS FOUNDATION TRUST)
Cc: Jasdeep Hayre; Kate Moore
Subject: RE: Tomorrow Comm D Vandetanib

Dear Peter,

Thank you for offering to answer questions by email in advance of the committee meeting tomorrow. We just have a few thoughts about the population to run by you.

The company continue to make the case for the restricted population, that is people with progressive and symptomatic disease and with CTN/CEA doubling time of less than 2 years. They have now stated (pages 7 – 10 of the company's additional evidence) that the biomarker subgroup best reflects the marketing authorisation for vandetanib (which is for aggressive and symptomatic disease) based on supporting information from the SmPC and EPAR. The committee previously heard from clinical experts that although theses biomarkers are regularly monitored in clinical practice and may contribute to a decision to conduct imaging, they are not currently used to initiate treatment.

- If vandetanib were to be recommended, do you foresee any issues/barriers with treatment decisions being made on the basis of the CTN/CEA biomarker doubling times in addition to the disease being progressive and symptomatic?
- Presumably this would mean vandetanib being recommended for a more restricted group than cabozantinib?

Your comment on this would be greatly appreciated.

Thank you.

Regards
Amaka.

Nwamaka Umeweni
Health Technology Assessment Adviser – Technology Appraisals (CHTE)