Public observer slides

Chair's presentation
Cabozantinib and vandetanib for treating medullary thyroid cancer

2nd Appraisal Committee meeting

Committee D

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AG: ScHARR

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Company: Ipsen, Sanofi

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Key issues for discussion

- Do the ACD comments change the Committee's conclusions, specifically on
  - Relevance of the restricted EU population subgroup
  - RET mutation subgroup
  - Approach to appraising these treatments, with regards to rarity of the disease
  - End of life considerations
  - Inclusion in the CDF
- Are the crossover-adjusted results appropriate for decision-making?
- Most appropriate economic analysis for decision-making: Sanofi's or the Assessment Group's? Key differences are:
  - Health utility values
  - Post-progression vandetanib costs
  - Pre-progression vandetanib discontinuation
- Does Sanofi's revised economic analysis change the committee's conclusion that neither drug meets the end of life criterion for short life expectancy?

Interventions

	Cabozantinib (Cometriq, Ipsen)	Vandetanib (Caprelsa, Sanofi)
Action	Tyrosine kinase inhibitor (TKI)	Tyrosine kinase inhibitor (TKI)
Marketing authoris.	Treatment of adults with **progressive**, unresectable locally advanced or metastatic MTC	Treatment of **aggressive and symptomatic** MTC in patients with unresectable locally advanced or metastatic disease
	For patients in whom RET mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision	
Admin.	Oral, capsule	Oral, tablet
Dose	140mg once daily (reduced doses: 100mg, 60mg)	300mg once daily (reduced doses: 200mg, 100mg)
Stopping	Until patient is no longer clinically benefitting from therapy or until unacceptable toxicity occurs	Until disease progression or until the benefits of treatment continuation do no longer outweigh its risk
List price	£4,800 per monthly pack Simple discount PAS agreed	£5,000 per monthly pack Simple discount PAS agreed

ACD: preliminary recommendation

Cabozantinib is not recommended, within its marketing authorisation, for treating progressive medullary thyroid cancer in adults with unresectable, locally advanced or metastatic disease

Vandetanib is not recommended, within its marketing authorisation, for treating aggressive and symptomatic medullary thyroid cancer in adults with unresectable, locally advanced or metastatic disease

Committee's conclusions (1)
Clinical need; relevant trial populations

Clinical need	• Clinical need for active treatment options for MTC • Cabozantinib and vandetanib the only systemic treatment options available (currently via CDF)
Trial evidence	**EXAM (cabozantinib):** • Patients had progressive and symptomatic disease • Relevant to UK clinical practice **ZETA (vandetanib)** 'EU label' (marketing authorisation) subgroup: • Similar to EXAM patients and relevant to clinical practice 'Restricted EU label' subgroup: • 'EU label' with calcitonin [CTN] and carcinoembryonic antigen [CEA] doubling times of <24 months • CTN/CEA doubling times not part of decision to start treatment • Not relevant to appraisal
RET mutation subgroup	• RET mutation testing not done to inform treatment decisions • Not appropriate to consider clinical or cost effectiveness of either drug based on patients' RET mutation status

Committee's conclusions (2)
Clinical effectiveness

Clinical effectiveness	**EXAM:** • PFS benefit for cabozantinib vs. placebo. • OS benefit difficult to establish because results not stat. significant and confounded by subsequent post-progression treatment **ZETA:** • PFS benefit for vandetanib vs. placebo but results uncertain because of potential crossover before progression • OS benefit uncertain because results not stat. significant and confounded by crossover. • Results not suitable for decision-making
Indirect treatment comparison	Cabozantinib and vandetanib likely to be similarly effective

Committee's conclusions (3)
Economic modelling

Model	AG's model preferred because it included relevant patient population
Costs	Preferred AG's cost assumptions relating to: • Application of discontinuation parameter • Monitoring costs
Utilities	Preferred AG's utilities (from a study of differentiated thyroid cancer by Fordham et al.) but values remain uncertain because no direct estimates for MTC available
Relevant analyses	Analyses 1: pairwise cabozantinib vs. BSC Analysis 4: incremental comparison of all treatment options using EXAM trial data, although results uncertain because equal effectiveness assumed for both active treatments *Other analyses disregarded because effectiveness and cost assumptions from ZETA trial were not appropriate for decision-making*

Committee's conclusions (4)
Cost-effectiveness results

ICERs	Most plausible ICER for cabozantinib vs. BSC significantly higher than £30,000 per QALY gained (analyses 1 and 4) Most plausible ICER for vandetanib vs. cabozantinib significantly higher than £100,000 per QALY gained (analysis 4) *Exact ICERs are commercial in confidence and cannot be shown*
End of life criteria	• Both met criterion for extension to life • Neither met criterion for short life expectancy
Cancer Drugs Fund	Neither drug met criteria for inclusion: • Data collection unlikely to address uncertainties in overall survival benefit • Potential for meeting criteria for routine use not considered plausible because of high ICERs
Uncaptured benefit	• Recognised rarity of disease • Noted advice that NICE should evaluate drugs to treat rare conditions in the same way as any other treatment • No health-related benefits not already captured in the analyses

ACD consultation responses

- Consultee comments from:
  - Ipsen
  - Sanofi
  - Association for Multiple Endocrine Neoplasia Disorders (AMEND)

- Commentator comments from:
  - Dr Kate Newbold
  - Dr Mary Lei

- Web comments from:
  - 13 patients
  - 4 carers
  - 4 NHS professionals
  - 6 members of the public

Comments from members of the public, patients, carers, NHS professionals

- No other effective treatments – TKIs are last line of defence
- TKIs add years to life and improve quality of life, enabling people to contribute to society and have time with families
- Side effects of TKIs are worth it for prolonged survival
- People having TKIs reported that cancer had stabilised and they had a decent quality of life
- Not meeting end of life criteria by 'living too long' is unacceptable
- Not considering RET mutation status is insupportable when germline testing is routinely done; somatic testing should also become standard practice
- Using the drugs helps future research; not recommending the drugs limits future potential for MTC patients to join clinical trials, and limits future development in this therapy area
- Overall survival benefit difficult to show with trial data as crossover is common
- Progression-free survival is as important as overall survival
- MTC is a very rare condition; overall cost is low because so few patients need these drugs

MTA inappropriate for rare disease
Comments from Ipsen, Sanofi, experts, patient group

- Standard NICE process discriminates against rare cancers
- Limited evidence available, and clinical effectiveness data likely to be incomplete
- Few patients are treated so budget impact is low; in addition:
  - No costs from additional lines of treatment
  - Discontinuations and dose reductions reduce costs further
  - Financial burden relatively low and predictable
- **Sanofi:** Decision-making latitude warranted by 'distributive justice': fair (rather than equal) allocation of resources
- **Sanofi:** ACD's conclusion on rare conditions does not apply as the Social Value Judgements document refers to **'orphan' drugs**. Vandetanib is an **'ultra-orphan' drug** given that MTC occurs in fewer than 1 in 50,000 people
- **Sanofi:** Unfair not to consider vandetanib via the HST route because it is not life long use and MTC not regarded as a chronic condition

Application of end of life criteria

ACD: It acknowledged that some patients with unresectable, locally advanced or metastatic medullary thyroid cancer live for a long time. This may have skewed the median estimate, and may explain the difference between the median and mean estimates. The committee agreed that the mean estimate was more relevant for end-of-life considerations . . . Neither drug meets the short life expectancy criterion for end of life so the end-of-life criteria do not apply

Comments from AMEND

- Wrong approach for MTC – aim of many cancer treatments now is to make it a disease that people live with rather than die from

Comments from Sanofi

- Criterion of 'normally' less than 24 months implies flexibility that has not been used here
- Median measurements have been used before by NICE Appraisal Committees
- NICE process guide does not stipulate that the mean measurement should be used

Cancer Drugs Fund

Comments from Sanofi

- Relevant population having vandetanib could be clarified by:
  - Retrospective review of SACT data
  - Case note review
  - Prospective collection of biomarker data via National Cancer Registration and analysis service (NCRAS)

Comments from AMEND

- Consider recommending continued funding subject to accurate recording of data to aid current and future research

Comments from experts

- Consider recommending funding with prospective data collection to clarify remaining uncertainties

Comments from NHS Professional

- Consider an interim period of 2-3 years continued access while quantitative and qualitative data on patient outcomes is collected on a national prospective database

Relevant ZETA trial subgroup
Comments from experts

ACD: Clinical experts explained that CTN/CEA biomarkers are regularly monitored, can be prognostic and may contribute to a decision to conduct imaging, but the decision to start treatment itself is based on radiological progression, or when the disease becomes symptomatic, or both . . committee concluded that the MA subgroup was most likely to represent patients seen in practice.

- CTN/CEA doubling times <24 months inevitable with progressive and symptomatic disease
- Patients with CTN/CEA doubling times <24 months likely to reflect patients being treated in clinical practice
- A review of patients currently having vandetanib showed the majority had CTN/CEA doubling times <24 months (the remaining patients started treatment before a marker trend could be established)
- In practice, clinicians treat a smaller population than a strict interpretation of the MA would permit

Relevant ZETA trial subgroup
Comments from Sanofi

- Accept CTN/CEA doubling times are prognostic rather than criteria for starting treatment, but consider they are part of the breadth of parameters clinicians consider when making treatment decisions
- CTN/CEA doubling times <24 months describe patients treated in the UK
- Suggest questions for experts to clarify relevant population
- European regulators recognised treatment should be restricted to those most in need, i.e. with a symptomatic-aggressive course of disease
  - Aggressive disease definition unclear, subjective
- Positive recommendation for these patients would not change clinical practice or limit the patient population eligible for treatment

Sanofi's new analysis
Restricted EU population

- Company's original submission noted that attempts to adjust for crossover were unsuccessful because a common treatment effect assumption may not be clinically plausible (patients crossing over from the placebo arm had progressive disease and so the capacity for treatment benefit may differ from patients with indolent disease)
- Post-ACD, the company sought expert advice and re-ran an adjustment for crossover using the Rank Preserving Structural Failure Time (RPSFT) method, obtaining plausible estimates for the BSC arm
- Revised cost-effectiveness results are presented for the restricted EU population that:
  - Include a revised vandetanib curve vs. RPSFT curve for BSC
  - Include committee's preferred assumptions relating to costs and utilities, as detailed in the AG report.
- **Note**: new PAS approved after submission of additional evidence (not included in company's new cost-effectiveness results; included in AG's cost-effectiveness results only)

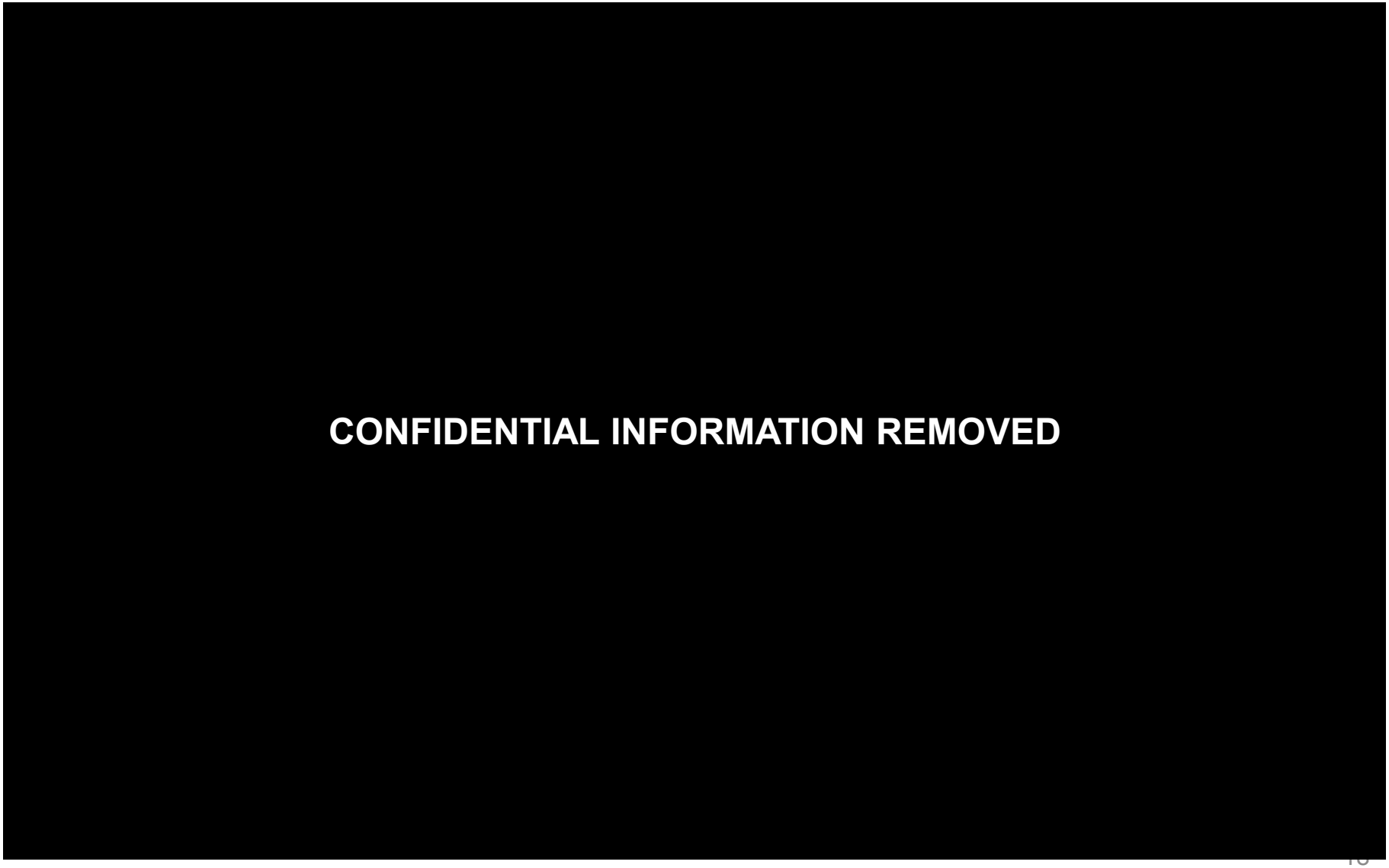
Sanofi's new analysis

Clinical outcomes – crossover adjusted (restricted EU population)

	Vandetanib (n=[redacted])	RPSFT adjusted placebo (n=[redacted])	*Unadjusted placebo (n=[redacted])*
Death, n	[redacted]	[redacted]	
Median survival	[redacted]	[redacted]	[redacted]
Hazard ratio		[redacted]	[redacted]

Note: company reported results of new analysis in days; these have been converted to months (/30)

Sanofi's new analysis
Overall survival



Sanofi's new analysis

Cost-effectiveness results (restricted EU population; old PAS)

Analysis	Incremental QALY	Incremental Cost	ICER
Original base case	1.356	[redacted]	[redacted]
Revised base case	1.937	[redacted]	[redacted]
BSC OS adjusted for crossover; observed vandetanib OS *Cost & utility data based on AG's report* *Weibull curve for BSC PFS, OS and vandetanib PFS; lognormal for vandetanib OS*			
Weibull scenario	2.624	[redacted]	[redacted]
Revised base case with alternative Weibull curve for PFS and OS			
Lognormal scenario	2.780	[redacted]	[redacted]
Revised base case with alternative Lognormal curve for PFS and OS			
LogLog scenario	2.494	[redacted]	[redacted]
Revised base case with alternative LogLog curve for PFS and OS			
Vandetanib post progression scenario	1.937	[redacted]	[redacted]
Revised base case including post-progression vandetanib costs			
End of life	BSC survival (mean, median) is 1.6 years (consistent across scenarios)		

AG's critique of Sanofi's new analysis (1)
Crossover adjustment

- Company stated that RPSFT adjusted estimates for broader EU population could not be 'validly used in the model', therefore the results not reported
  - AG believes results would be valid but likely do not show a significant treatment response
- Adjusted analysis should be interpreted with caution because:
  - RPSFT considered in original submission to have 'failed to undo bias'; it is unclear why the company's new results are substantially different
  - Common treatment effect assumption may not be plausible
  - RPSFT assumes perfect randomisation but use of a subgroup violates this
  - No adjustment made for patients continuing vandetanib treatment after progression (expected to reduce estimated treatment effect)
  - Covariate adjustment reasonable but no justification for the 2 covariates selected (others may also be imbalanced between treatment groups)
  - Method used to estimate 95% CIs inappropriate; underestimates uncertainty
  - Consideration of re-censoring has not been addressed
  - More thorough description of methods needed to judge whether they have been appropriately applied

AG's critique of Sanofi's new analysis (2)
Survival analysis

- Company chose overall survival curves based on AIC/BIC criteria; no consideration of clinical plausibility of competing curves
- Only a subset of potentially plausible parametric functions can be selected within the economic model (log-normal, log-logistic, Weibull)
  - AG's clinical advisor's preferred functions cannot be applied within the model
- Intercept parameters reported do not match those used in model; unclear whether this is reporting error or whether incorrect parameters used in model
- Weibull function selected for vandetanib overall survival in original model; log normal in new model; unclear why when no adjustment has been made for vandetanib group

AG's critique of Sanofi's new analysis (3)
Other model parameters

- Post-progression vandetanib costs excluded for vandetanib group despite no adjustment for post-progression vandetanib use – inappropriate
- Company states other parameters applied as per AG's model, however:
  - Health utilities differ from AG's (Fordham et al); source and justification for company's values unclear
  - Application of vandetanib pre-progression discontinuation parameter differs; company assume a linear increase in proportion of patients discontinuing vandetanib pre-progression; AG apply half the costs of vandetanib to the proportion of patients discontinuing treatment
  - BSC costs and vandetanib monitoring costs differ from AG's
- Using the AG's actual base case assumptions increases the company's revised base case ICER by ~£6k

AG's analysis using adjusted survival functions

Cost-effectiveness results (restricted EU population; new PAS)

Analysis	Incremental QALY	Incremental Cost	ICER
Company's revised base case	1.94	[redacted]	[redacted]
AG's original base case (post-progression vandetanib costs included for both arms)	1.64	[redacted]	[redacted]
AG's model: Post-progression vandetanib costs excluded for both arms	1.79	[redacted]	[redacted]
AG's model: Post-progression vandetanib costs excluded for both arms; pre-progression discontinuation parameter = 1.0	1.79	[redacted]	[redacted]
AG's model – preferred ICER Post-progression vandetanib costs included for vandetanib arm *may overestimate ICER because post-progression vandetanib assumed to continue until death, which is considered unlikely	**1.79**	[redacted]	[redacted]

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