NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Selpercatinib for treating advanced thyroid cancer with RET alterations

1 Recommendations

1.1 Selpercatinib is recommended for use within the Cancer Drugs Fund, as an option for treating:

- advanced RET fusion-positive thyroid cancer in adults who need systemic therapy after sorafenib or lenvatinib
- advanced RET-mutant medullary thyroid cancer in people 12 years and older who need systemic therapy after cabozantinib or vandetanib

It is recommended only if the conditions in the managed access agreement are followed.

1.2 This recommendation is not intended to affect treatment with selpercatinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. This decision should be made jointly by the clinician and the young person and the young person's parents or carers.

Why the committee made these recommendations

People with advanced RET fusion-positive thyroid cancer are usually first offered a partial or full thyroidectomy. This is followed by radioactive iodine and then lenvatinib or sorafenib. People with advanced RET-mutant medullary thyroid cancer are usually offered a partial or full thyroidectomy, followed by cabozantinib.

Clinical trial evidence for selpercatinib is highly uncertain because it is based on an ongoing single arm trial and not all subpopulations represent NHS practice. The results comparing selpercatinib indirectly with with best supportive care are also highly uncertain.

Selpercatinib could be cost effective if more data becomes available from the ongoing trial that shows people live longer with treatment. Data from the trial and NHS practice would also help address the uncertainty about its clinical effectiveness. Selpercatinib is therefore recommended for use in the Cancer Drugs Fund so that more data can be collected.

2 Information about selpercatinib

Marketing authorisation indication

2.1 Selpercatinib (Retsevmo, Eli Lilly) 'as monotherapy is indicated for the treatment of adults with advanced RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and or lenvatinib.'

2.2 Selpercatinib 'as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC) who require systemic therapy following prior treatment with cabozantinib and or vandetanib.'

2.3 The dosage schedule is available in the summary of product characteristics.

Price

2.4 The company-estimated cost of a 28-day cycle of selpercatinib is £8,736.00. The company has a commercial arrangement, which would have applied if the technology had been recommended

3 Committee discussion

The appraisal committee considered evidence submitted by Eli Lilly, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

- cabozantinib is not a relevant comparator for selpercatinib in the RET-mutant medullary thyroid cancer population
- including genetic testing costs in the model is appropriate
- time on treatment for selpercatinib in the economic model should be in line with data from LIBRETTO-001.

It discussed the following issues (issues 2, 3, 4, 5, and 6), which were outstanding after the technical engagement stage. It also discussed the additional issues of whether selpercatinib fulfils the criteria to be considered as a life-extending treatment at the end of life, and the possibility of commissioning selpercatinib through the Cancer Drugs Fund.

The condition and current treatment

Advanced thyroid cancer significantly affects quality of life for patients

3.1 Clinical experts explained that differentiated thyroid cancer and medullary thyroid cancers are rare. Rearranged during transfection (RET)-activating fusions and mutations are important in many cancer types, including different types of thyroid cancer. RET mutations in people with advanced medullary thyroid cancer and RET fusions in people with other thyroid cancers are associated with more aggressive disease and poorer outcomes for patients. The patient experts explained that thyroid cancer can be devastating for people and their families, not only because of the shock of the initial diagnosis, but also because of the relative lack of treatment options that are available. One patient expert described the

distressing effect of being the parent and carer of 2 young children with RET-mutant medullary thyroid cancer. Initial surgical treatment had resulted in extensive post-operative complications. These had permanently affected their child's appearance, had a lasting effect on self-confidence and was a daily reminder of the disease. Further testing of their relatives revealed more people with the hereditary RET gene mutation who required treatment for the disease. Another patient expert described how diagnosis in early adulthood and the lack of treatment options had had a big effect on their mental health. Learning that the only treatments available to slow progression were likely to significantly affect day-to day physical health and might not be tolerable at all because of toxicity contributed to experiences of severe anxiety and depression. The committee concluded that advanced thyroid cancer significantly affects quality of life for patients and carers. A targeted RET inhibitor would offer significant benefit to patients

3.2 The patient and clinical experts explained that there was a significant unmet need for people with RET-mutant medullary thyroid cancer and RET fusion-positive thyroid cancer. For people with medullary thyroid cancer, initial treatment is a partial or full thyroidectomy, or radiotherapy if the disease is inoperable. NICE's technology appraisal guidance on cabozantinib for treating medullary thyroid cancer recommends its use for unresectable, locally advanced or metastatic disease. Best supportive care is the only option for people with medullary thyroid cancer whose disease progresses on cabozantinib or who cannot tolerate it. NICE's technology appraisal guidance on vandetanib for treating medullary thyroid cancer does not recommend it for use. For people with differentiated thyroid cancer, initial treatment is a partial or full thyroidectomy, followed by radioactive iodine. For those whose disease does not respond to radioactive iodine, NICE's technology appraisal guidance on lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine recommends lenvatinib and sorafenib for treating progressive, locally advanced or metastatic disease. Best

supportive care is the only option for people whose disease progresses on lenvatinib or sorafenib or who cannot tolerate them. The patient experts explained that, for people with medullary thyroid cancer, cabozantinib is often very difficult to tolerate because of the side effects. The clinical experts explained that lenvatinib and sorafenib are also associated with significant toxicity, and that a targeted RET inhibitor such as selpercatinib would likely provide clinically meaningful benefit with less toxicity than currently available treatments. The committee understood that patients may choose to have selpercatinib before disease progression because of the poor tolerability of current systemic treatments. The committee agreed that a targeted RET inhibitor would offer significant benefit to patients.

Clinical evidence

The main clinical evidence comes from a single-arm study

3.3 The main clinical evidence for selpercatinib is from LIBRETTO-001, an ongoing single-arm, open-label, multicentre phase 1 to 2 trial in people with advanced solid tumours, with RET activations. The primary outcome of the trial was objective response rate. The company presented 3 analysis sets for people with RET-mutant medullary thyroid cancer:

- Primary analysis set (PAS, n=55): included people who had previously had either cabozantinib, vandetanib, or both
- Supplementary analysis set (SAS1, n=88): included people with RET-mutant medullary thyroid cancer who had not had cabozantinib or vandetanib
- Integrated analysis set (IAS, n=124): included a larger group of patients from the PAS.

For people with RET fusion-positive thyroid cancer, the trial reported results for people whose disease has been previously treated with a systemic therapy (n=19) and those whose disease was untreated (n=8). Results showed that for people with previously treated medullary thyroid cancer, the objective response rate was 69% and median progression-

free survival (PFS) was not estimable. For people with previously treated advanced RET fusion-positive thyroid cancer, the objective response rate was 79%, and median PFS was 20.07 months (95% confidence interval [CI]: 9.4 to not estimable). Median overall survival (OS) in all subgroups for RET fusion-positive thyroid cancer and RET-mutant medullary thyroid cancer were also not estimable. Additional efficacy data from a March 2020 data cut were provided by the company. These data represent a larger sample size and an additional 9.5 months of follow up and show no difference in efficacy compared with the original data cut-off. These data support the original efficacy results but were not used to inform the company's matching-adjusted indirect treatment comparisons (MAIC) and naive indirect treatment comparisons (ITC) for the RET-mutant medullary thyroid cancer and RET fusion-positive thyroid cancer populations respectively. They were not used to inform the base case.

LIBRETTO-001 subpopulations are not all representative of NHS clinical practice

3.4 The ERG explained that in the subset of people with previously treated RET-mutant medullary thyroid cancer over a quarter had had at least 3 previous systemic regimens. The committee noted that the marketing authorisation for selpercatinib for people with RET-mutant medullary thyroid cancer allows its use after cabozantinib or vandetanib. Only cabozantinib is recommended by NICE, therefore the population seen in NHS clinical practice would only have had 1 previous systemic treatment. Of the 55 people in the primary analysis set (disease previously treated with vandetanib, cabozantinib, or both), the median number of previous therapies was 2 (range between 1 and 8); 18 people (33%) had had vandetanib, 13 (24%) had had cabozantinib, and 24 (44%) had had both. Of the 27 people with RET fusion-positive thyroid cancer, 19 people had a previous systemic treatment, and 8 were identified as not having had systemic therapy. The committee noted the very small number of people with RET fusion-positive thyroid cancer in LIBRETTO-001 (n=19), and that this population was also not closely aligned with the population who would

be seen in clinical practice in the NHS, all of whom would have previously had either sorafenib or lenvatinib. Of the 19 that had previously had systemic treatment, 15 had had either lenvatinib or sorafenib and are therefore aligned with the marketing authorisation for RET fusion-positive thyroid cancer. The committee concluded that the results of the single-arm study were based on small numbers and were of limited relevance to the populations specified in the marketing authorisation and people who would be seen in clinical practice in the NHS.

Indirect treatment comparisons

The results of the matching-adjusted indirect comparison for RET-mutant medullary thyroid cancer are uncertain

3.5 For RET-mutant medullary thyroid cancer, the company did an unanchored matching-adjusted indirect comparison (MAIC). The MAIC compared selpercatinib from LIBRETTO-001 with cabozantinib and placebo (a proxy for best supportive care) from the EXAM trial. The EXAM trial compared cabozantinib with placebo in people with progressive medullary thyroid cancer. The committee noted that the LIBRETTO-001 and EXAM trials included both people with untreated and treated disease. In the RET-mutant medullary thyroid cancer subgroup of the EXAM trial, clinical-effectiveness results were not reported separately for people with treated or untreated disease. Therefore the matching-adjusted indirect comparison was done using individual patient-level data from the any-line pooled population from LIBRETTO-001 and summary evidence from the EXAM trial. The committee noted that 79% of people in EXAM had not previously had a multi-kinase inhibitor. Of the people who had had multi-kinase inhibitors, 25% had had 2 or more. The committee understood that the MAIC results now apply to the EXAM population rather than the LIBRETTO-001 population. The committee noted that because this is a mixed population of people with untreated disease and people who had had more than 1 multi-kinase inhibitor, it is not fully representative of either the population stipulated in the marketing authorisation or those

who would be seen in NHS clinical practice (after treatment with cabozantinib only). The committee recalled justification provided in the company submission that the pooled population was preferred over the pre-treated subgroup because it provided a larger patient-level data set, more closely matched the characteristics of the EXAM trial population, and provided more information about the proportion of people with treated or untreated disease, to better adjust for the differences between the trials. The ERG explained that even with this larger population, the results are based on subgroups with small numbers of people, which affects their reliability. The committee noted the ERG's view that there were additional sources of uncertainty in the MAIC. The baseline characteristics of the RET-mutant subgroups were not available for the placebo arm of the EXAM trial, therefore the baseline characteristics of the cabozantinib group were assumed to be similar to those of the placebo arm and were used in the MAIC. The company selected only ECOG performance status and RET-mutation type (RET M918T) as matching variables in the MAIC. The ERG explained that other important prognostic factors may be missing and therefore the MAIC results are likely to be biased because of unobserved confounding. Also, OS data were not available from EXAM for the RET-mutant subgroup so the data were obtained from the unweighted Kaplan–Meier curves from the RET M918T-positive group (45 people having placebo). The committee noted that the results of the MAIC showed that selpercatinib improves PFS and OS compared with best supportive care (the exact results are confidential and cannot be reported here). The company agreed with the ERG's assessment of the limitations of the MAIC, and suggested that it was not possible to resolve these issues. The committee agreed that these issues could not be resolved and that the MAIC was the only source of data available for decision making. The committee concluded that the MAIC contains multiple sources of uncertainty and therefore the results of the MAIC are uncertain.

The results of the ITC for RET fusion-positive thyroid cancer are uncertain

3.6 For RET fusion-positive thyroid cancer, the company did a naive unanchored ITC. The ITC compared single-arm trial data for selpercatinib from LIBRETTO-001 with trial data for placebo (a proxy for best supportive care) from the SELECT trial. The SELECT trial compared lenvatinib with placebo in people with radioiodine-refractory differentiated thyroid cancer. The committee noted that no trial data were identified in people with RET fusion-positive thyroid cancer, but that the prognostic significance of RET fusion in thyroid cancer is unclear. So, it is uncertain if data for people with RET-status thyroid cancer (SELECT) is generalisable to RET fusion-positive thyroid cancer (LIBRETTO-001). The ERG explained that the SELECT trial included predominantly people with untreated disease, with 20.6% having had at least 1 previous therapy, compared with 100% in LIBRETTO-001. However, in SELECT, the treatment effect on PFS in people with treated disease (HR: 0.22; 95% CI: 0.12 to 0.41) was consistent with the overall population (HR: 0.21; 95% CI: 0.16 to 0.28). Also, subgroup data by line of therapy were not reported for OS in SELECT, so it is unclear if the efficacy of best supportive care is generalisable to the population of interest for this submission. In addition, OS was confounded by crossover in SELECT, with most people who had placebo crossing over to lenvatinib. The ERG stressed that the very small numbers of people in LIBRETTO-001 (subgroup of people who had had either sorafenib or lenvatinib, n=15), and with no attempt to balance the 2 patient groups, means that PFS is also likely to be highly uncertain. The committee noted that the results of the ITC show that selpercatinib improves PFS and OS compared with best supportive care (the exact results of the ITC are confidential and cannot be reported here). The company agreed with the ERG's assessment of the limitations of the naive unanchored ITC, and suggested that it was not possible to resolve these issues. The committee agreed that these issues could not be resolved and that the ITC was the only source of data available for

decision making. The committee concluded that the ITC contains multiple sources of uncertainty and therefore the results of the ITC are uncertain.

The company's economic model

The company's model is appropriate for decision making

3.7 The company used a partitioned-survival economic model that included 3 health states: pre-progression, post-progression and death. The committee concluded that the model was generally appropriate and consistent with the models used in other appraisals for thyroid cancer (NICE's technology appraisal guidance on cabozantinib and NICE's technology appraisal guidance on lenvatinib and sorafenib).

Survival extrapolations

Modelled progression-free survival in the RET-mutant medullary thyroid cancer population is highly uncertain

3.8 To estimate PFS for people with RET-mutant medullary thyroid cancer, the company examined a range of stratified and unstratified parametric functions fitted to the weighted Kaplan–Meier data of the any-line population of LIBRETTO-001 (generated in the MAIC) and unweighted, pseudo patient-level Kaplan–Meier data for people with RET-mutant medullary thyroid cancer having placebo in EXAM. Because the statistical fit between the PFS survival functions was so similar, the choice of survival extrapolation was guided by visual fit and clinical plausibility. The company selected the log-logistic for its base case, because it provided a good visual fit to the early Kaplan–Meier data and based on clinical expert opinion. The ERG explained that it agreed with the choice of log-logistic, but that it was unable to verify the clinical justification. It emphasised that the wide spread of the alternative parametric functions suggests a very high degree of uncertainty and was associated with a very wide range of incremental cost-effectiveness ratios (ICERs). The committee noted the agreement between the company and the ERG on the choice of the log-

logistic extrapolation for PFS, but agreed that this choice was uncertain. The committee concluded that the choice of extrapolation for PFS for RET-mutant medullary thyroid cancer was based on very immature survival data and was therefore highly uncertain.

Modelled overall survival in the RET-mutant medullary thyroid cancer population is highly uncertain

3.9 To estimate OS for people with RET-mutant medullary thyroid cancer, the company maintained that the proportional hazards assumption was not violated, and so its preference was for unstratified proportional hazard functions. The company initially selected an extrapolation based on the Weibull function for its base case. The ERG considered that this choice was overly optimistic for selpercatinib OS, predicting too many people alive at 25 years, and instead preferred to explore alternative extrapolations that included stratified functions. The ERG explained its view that the stratified Weibull function provided the best visual fit, best long-term plausibility for best supportive care, and the most reasonable estimate of the benefit of selpercatinib relative to best supportive care given the very limited evidence and immature data available. The company then replaced the Weibull with the stratified gamma in its base case after receiving additional feedback from a clinical expert who suggested it was clinically plausible. The ERG responded that because of the high degree of uncertainty and the importance of clinical judgement, it had no reason to reject this choice of extrapolation for OS. The clinical experts explained that it was very difficult to predict the most appropriate survival extrapolations for the treatments, and in particular selpercatinib. The committee noted the views of the company and ERG and agreed that it was unclear on what basis the clinical expert consulted by the company had preferred the stratified gamma extrapolation for OS, given the extent of the uncertainty expressed by the clinical experts at the meeting. The committee agreed that the choice of extrapolations for OS using either the stratified gamma or stratified Weibull functions in RET-mutant medullary thyroid cancer was plausible but associated with a very wide range of

ICERs. The committee concluded that the choice of extrapolation for OS for RET-mutant medullary thyroid cancer was based on very immature survival data and was therefore highly uncertain.

Modelled progression-free survival in the RET fusion-positive thyroid cancer population is highly uncertain

3.10 To estimate PFS for people with RET fusion-positive thyroid cancer a range of survival functions were fitted to the Kaplan–Meier data for people with previously treated RET fusion-positive thyroid cancer from LIBRETTO-001 and the Kaplan–Meier data of the intention-to-treat population of people having placebo in SELECT. The stratified Weibull extrapolation was selected for PFS based on feedback from clinical experts. The committee noted that the ERG agreed with this choice but recognised the ERG's view that there was no documented justification for the expert's preference. The committee noted that the plausible extrapolations for PFS did not have such a big effect on the ICER range as was the case for RET-mutant medullary thyroid cancer, but concluded that the choice of the stratified Weibull extrapolation for PFS was uncertain.

Modelled overall survival in the RET fusion-positive thyroid cancer population is highly uncertain

3.11 To estimate OS for people with RET fusion-positive thyroid cancer, a range of parametric functions were explored using data from people with previously treated RET fusion-positive thyroid cancer in LIBRETTO-001 and the rank preserving structural failure time-adjusted Kaplan–Meier data from the intention-to-treat population having placebo in SELECT. The company considered the results of the extrapolations using stratified functions as implausible, because of the curves often crossing or converging early along the time horizon. The company explored piecewise exponential functions fitted to the data for 0 to 6 months and for 6 months onwards, which was an approach previously accepted in NICE's technology appraisal guidance on lenvatinib and sorafenib for treating

differentiated thyroid cancer after radioactive iodine. The piecewise exponential model was selected for the company base-case analysis, based on visual fit, external validation with the outcomes seen in LIBRETTO-001 and SELECT and clinical expert opinion. The ERG emphasised that because of the very limited sample size (subgroup of people who had had either sorafenib or lenvatinib, n=15), immaturity of the data and small number of survival events, there was a high degree of uncertainty around the plausible OS estimates for selpercatinib in this population. The ERG agreed with the company that the extrapolations for OS using most of the stratified functions produced implausible results, because of the early crossing or converging of curves that would suggest only marginal benefit of selpercatinib or favourable results for best supportive care. The committee agreed that there is no plausible clinical reason to expect this. The only stratified function for OS which did not result in crossing curves was the stratified gamma, for which the selpercatinib extrapolation was much less optimistic than the base-case piece wise exponential. The committee noted that predicted OS using the stratified gamma function was likely too pessimistic. For OS, the committee considered that the only plausible extrapolation was piecewise exponential. The committee was reminded that the data on which the PFS and OS extrapolations were based was highly uncertain (see section 3.6). The committee concluded that modelled overall survival in the RET fusion-positive thyroid cancer population is highly uncertain.

Utility values in the economic model

The utility values reported by Fordham et al. (2015) are appropriate

3.12 Health-related quality of life (HRQoL) data were collected in LIBRETTO-001 using the EORTC QLQ-C30 questionnaire. No EQ-5D data were available from LIBRETTO-001 and an attempt to map the EORTC QLQ-C30 to EQ-5D utilities resulted in implausible results. The committee noted that the literature review done by the company did not identify any health state utility values specific to people with RET-mutant medullary

thyroid cancer or RET fusion-positive thyroid cancer. The committee recalled the effect of the disease on parents and carers (see section 3.1). It noted that carer utilities had not been captured by the company for inclusion in the economic model for the medullary thyroid cancer population of people aged between 12 and 18, and agreed that this could be an additional benefit not currently captured in the model. The company selected values from a vignette study done by Fordham et al. (2015) to estimate patient utilities in differentiated thyroid cancer for its base case, and these were also accepted in NICE's technology appraisal on cabozantinib for treating medullary thyroid cancer. The value for progression free disease was 0.8 and for progressed disease 0.5. The committee noted that clinical expert opinion suggested that the Fordham utility values were reasonable. The company provided alternative values for progressed disease used in NICE's technology appraisal guidance on lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine from the DECISION study (sorafenib compared with best supportive care) and values accepted by the Scottish Medicines Consortium for cabozantinib and sorafenib. The committee noted that the choice of progressed disease value only had a moderate effect on the ICER. The committee were concerned that the Fordham utility values were based on a vignette study which is not usually accepted by NICE to inform utility values because they are less robust than EQ-5D methods. The committee concluded that, in the absence of more appropriate values collected directly from a relevant population, the utility values reported by Fordham et al. (2015) could be accepted as a plausible estimate of utilities.

End of life

Selpercatinib does not meet the end-of-life criteria for both populations but the data are highly uncertain

3.13 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal.

- For RET-mutant medullary thyroid cancer, in the RET-M918T-positive subpopulation of the EXAM trial, the median OS in the placebo arm was 18.9 months (n=45) and the median OS for the intention-to-treat population treated with placebo was 21.1 months (n=111). The EXAM trial included mainly people who had not previously had multi-kinase inhibitor treatment, whereas people with previously treated RET-mutant disease may have worse prognosis than the intention-to-treat placebo arm of the EXAM trial.
- For RET fusion-positive thyroid cancer, in the intention-to-treat population of the SELECT trial, the company model predicted a median OS of less than 2 years. This population included predominantly (79.4%) people who had not previously had a tyrosine kinase inhibitor, and so may overestimate survival of a pre-treated population.
- For both RET-mutant medullary thyroid cancer and RET fusion-positive thyroid cancer, the company model predicted an extension to life of greater than 3 months compared with current NHS treatment.

The clinical experts agreed with the company that it was plausible that people with previously treated RET-mutant medullary thyroid cancer and RET fusion-positive thyroid cancer had a short life expectancy of less than 24 months, particularly when people's disease progresses on treatment. The ERG explained that the company's predictions rely on evidence from the economic model that is based on results from highly uncertain analyses (see sections 3.5 and 3.6). The ERG also noted that the company's own model for both populations predicts mean life years for

best supportive care of more than 2 years (exact results are confidential). The committee recalled the wording from NICE's guide to the methods of technology appraisal which states that:

- the estimates of the extension to life are sufficiently robust and can be shown or reasonably inferred from either progression-free survival or overall survival and the assumptions used in the reference case economic modelling are plausible, objective and robust.

The committee accepted that for those people whose disease progresses on previous lines of treatment, based on clinical expert opinion, the short life expectancy criteria is likely met. However for those people who cannot tolerate treatment with cabozantinib or sorafenib or lenvatinib the short life expectancy criteria may not be met. This is because people may choose to have selpercatinib before disease progression because of issues with poor tolerability with previous systemic treatment (see section 3.2). The committee agreed that the survival estimates produced by the economic model are highly uncertain (see sections 3.8 to 3.11). The committee was satisfied that selpercatinib likely extends life by at least 3 months. The committee agreed that selpercatinib is unlikely to meet the end-of-life criteria for the whole population specified in the marketing authorisation and for those who would be seen in NHS clinical practice. The committee concluded that selpercatinib does not meet the end-of-life criteria for both populations but the data is highly uncertain.

Results of the cost-effectiveness analysis

Selpercatinib is not recommended for routine use in the NHS

3.14 NICE's guide to the methods of technology appraisal notes that, above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about

recommending a technology if it is less certain about the ICERs presented. NICE's guide to the methods of technology appraisal also states that consideration of the cost effectiveness of a technology is necessary, but not the sole, basis for decision making. The committee considered the rarity of the condition and the lack of effective treatments for people with advanced RET-mutant medullary thyroid cancer and RET fusion-positive thyroid cancer. It also noted the devastating effect of the disease on children and young people with RET-mutant medullary thyroid cancer and that benefits to carers had not been captured in the economic model (see sections 3.1, 3.2 and 3.12). Therefore, it agreed that an acceptable ICER for both populations would be around £30,000 per QALY gained. The committee noted that, when considering the commercial arrangements, selpercatinib was plausibly cost effective in both populations with ICERs around £30,000 per QALY gained (exact ICERs are commercial in confidence and cannot be reported here). The committee recalled that the evidence base was immature and the pivotal trial for selpercatinib was ongoing. It considered that the ICERs are uncertain and could be higher than what NICE normally considers an acceptable use of NHS resources. Therefore, selpercatinib could not be recommended for routine commissioning.

Cancer Drugs Fund

Selpercatinib is recommended for the Cancer Drugs Fund

3.15 Having concluded that selpercatinib could not be recommended for routine use, the committee then considered if it could be recommended for treating advanced thyroid cancer with RET alterations within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum):

- The company expressed an interest in selpercatinib being considered for funding through the Cancer Drugs Fund.

- The company's model is structurally robust for decision making (see section 3.7)
- Data from LIBRETTO-001 are immature. Median PFS and OS in the pre-treated subgroup for RET-mutant medullary thyroid cancer was not estimable, and median OS in the pre-treated subgroup for RET fusion-positive thyroid cancer was not estimable. OS was a key driver of the cost-effectiveness results.
- LIBRETTO-001 is still ongoing and further data could help reduce uncertainties around long-term PFS and OS
- Observational data collection via the Systemic Anti-Cancer Therapy dataset (SACT) could address some of the clinical uncertainty in PFS and OS for selpercatinib.

The committee considered that further data collection in the Cancer Drugs Fund could alleviate some of the uncertainty in the company's estimates. It recognised the rarity of thyroid cancers with RET alterations and that the benefits for carers of children and young people with RET altered thyroid cancers had not been included in the economic model. The committee was satisfied that selpercatinib met the criteria for inclusion in the Cancer Drugs Fund. Therefore, it recommended selpercatinib for use within the Cancer Drugs Fund for treating RET-mutant medullary thyroid cancer and RET fusion-positive thyroid cancer, if the conditions in the managed access agreement are followed. When the guidance is next reviewed, the company should use the committee's preferred assumptions (unless new evidence indicates otherwise), as set out previously.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based

on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh
Chair, appraisal committee
September 2021

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Luke Cowie
Technical lead

Victoria Kelly
Technical adviser

Gavin Kenny
Project manager

ISBN: [to be added at publication]