

## Health Technology Briefing April 2022

### Selpercatinib for previously untreated medullary thyroid cancer with RET mutation in patients ages 12 and older

Company/Developer

Eli Lilly and Company Ltd

New Active Substance

Significant Licence Extension (SLE)

NIHRIO ID: 31195

NICE ID: 10762

UKPS ID: 662657

#### Licensing and Market Availability Plans

Currently in phase II/III clinical trials.

#### Summary

Selpercatinib is in clinical development for the treatment of medullary thyroid cancer (MTC) with RET mutation in people aged 12 and older. Thyroid cancer is a malignant neoplasm that originates from cells in the thyroid gland located in the front of the neck. MTC is a cancer that forms inside the thyroid in the medulla. The majority of MTC have a mutation in the RET gene which leads to an overactive process that causes the cancer cells to grow uncontrolled. In advanced MTC, the primary treatment is extensive surgical resection with curative intent. Around 10% of these will progress to advanced disease where there are limited first-line systemic options available.

Selpercatinib is an orally administered drug designed to selectively target RET while minimizing its activity against other kinases. It blocks the activity of these abnormal proteins and prevents the growth and spread of cancer cells. If licensed, selpercatinib will offer a treatment option for patients ages 12 and older with advanced and/or metastatic untreated RET-mutant MTC.

## Proposed Indication

Adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer (MTC).<sup>1</sup>

## Technology

### Description

Selpercatinib (LOXO-292, LY3527723) is a novel, ATP-competitive, highly selective small-molecule and is an inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase.<sup>2,3</sup> RET is a type of protein called a kinase, which is involved in various cell processes. RET gene fusions and mutations result in the production of abnormal RET proteins, which spur the growth of cancer cells. Selpercatinib was designed to selectively target RET while minimizing its activity against other kinases.<sup>4</sup> It blocks the activity of these abnormal proteins and prevents the growth and spread of the cancer cells.<sup>5</sup> Selpercatinib inhibits wild-type RET and multiple mutated RET isoforms as well as VEGFR1 and VEGFR3 with IC50 values ranging from 0.92 nM to 67.8 nM. In other enzyme assays, selpercatinib also inhibited FGFR 1, 2, and 3 at higher concentrations that were still clinically achievable.<sup>3</sup>

Selpercatinib is in phase I/II clinical trials (LIBRETTO-001, NCT03157128) for the treatment of patients with advanced RET-altered solid tumours including medullary thyroid cancer (MTC) with RET mutations.<sup>6</sup> It is also currently in phase III clinical development (LIBRETTO-531, NCT04211337) for the treatment of with RET-mutant medullary thyroid cancer (MTC) in first line patients aged 12 and older.<sup>1</sup> The drug is administered orally and patients receive a proposed dose of 160 milligrams (mg) for adults with a body-weight of over 50kg and 120 mg for adults under 50kg twice a day and treatment should be continued until disease progression or unacceptable toxicity.<sup>7,8</sup>

### Key Innovation

Selpercatinib is a first-in-class oral RET inhibitor.<sup>9</sup> Activating RET point mutations account for approximately 60 percent of MTC. RET fusion cancers and RET-mutant MTC are primarily dependent on this single activated kinase for their proliferation and survival. This dependency, often referred to as "oncogene addiction," renders such tumours highly susceptible to small molecule inhibitors targeting RET.<sup>10</sup>

Multikinase inhibitors with RET inhibitor activity have been explored in the clinic for tumours with modest clinical efficacy. As a result of the nonselective nature of these multikinase inhibitors, patients had off-target adverse effects, such as hypertension, rash, and diarrhoea. This resulted in a narrow therapeutic index of these drugs, limiting ability to dose for clinically effective RET inhibition. Therefore, there is a need for highly potent selective RET inhibitors such as selpercatinib that have improved efficacy and a more favourable toxicity profile that effectively alter the landscape of RET-dependent cancers.<sup>11</sup>

### Regulatory & Development Status

Selpercatinib has Marketing Authorisation in the EU/UK for the following indications in adults:<sup>3</sup>

- Advanced RET fusion-positive non-small cell lung cancer (NSCLC) who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy
- Advanced RET fusion-positive thyroid cancer who require systemic therapy following prior treatment with sorafenib and/or lenvatinib

Selpercatinib as monotherapy is also 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.<sup>3</sup>

Selpercatinib is currently in phase III clinical development for Non-Small-Cell Lung Cancer.<sup>12</sup>

## Patient Group

### Disease Area and Clinical Need

MTC is a cancer that forms in the thyroid. The thyroid is a gland located in the front of the neck, just below the Adam's apple. It is responsible for sending out hormones to the body. The inside of the thyroid is called the medulla. The medulla contains special cells called parafollicular C cells that produce and release hormones. MTC develops when the C cells become cancerous and grow out of control.<sup>13</sup> For most people, the cause of MTC is unknown. This is called sporadic medullary thyroid cancer. About 1 in 4 people (25%) who develop MTC have a rare inherited genetic condition called multiple endocrine neoplasia type 2 (MEN2). MEN2A and MEN2B can also cause growths (tumours) in other endocrine glands.<sup>14</sup> Oncogenic RET mutations in patients with MTC is the main feature of tumour growth.<sup>15</sup>

Thyroid cancer is fairly common. There are four different types of thyroid cancers and MTC is the rarest type making up 3% to 4% of all thyroid cancers.<sup>13</sup> Thyroid cancer is the 20<sup>th</sup> most common cancer in the UK, accounting for 1% of all new cancer cases (2016-2018). 72% of thyroid cancer cases in the UK are in females, and 28% are in males.<sup>16</sup> In England (2020-21), there were 6,040 finished consultant episodes (FCEs) and 5,802 admissions regarding malignant neoplasms of the thyroid gland (ICD-10 code C73), which resulted in 1,280 day cases and 11,144 FCE bed days.<sup>17</sup> For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates for stage IV were 77.1% and 64% respectively.<sup>18</sup>

### Recommended Treatment Options

NICE currently recommends Cabozantinib for medullary thyroid cancer in adults.<sup>19</sup>

## Clinical Trial Information

<b>Trial</b>	<b>LIBERTTO-531, <a href="#">NCT04211337</a>, <a href="#">2019-001978-28</a>; A Multicenter, Randomized, Open-label, Phase 3 Trial Comparing Selpercatinib to Physicians Choice of Cabozantinib or Vandetanib in Patients With Progressive, Advanced, Kinase Inhibitor Naïve, RET-Mutant Medullary Thyroid Cancer</b> <b>Phase III: Recruiting</b> <b>Location(s):</b> 9 EU, UK, US, Canada and other countries <b>Primary Completion Date:</b> 20 <sup>th</sup> May 2024
<b>Trial Design</b>	Randomized, parallel assignment, open label
<b>Population</b>	N=400 (estimated), 12 years and older, histologically or cytologically confirmed, unresectable, locally advanced and/or metastatic MTC and no prior history of treatment with kinase inhibitors for advanced/metastatic disease
<b>Intervention(s)</b>	160mg of Selpercatinib given orally twice daily <sup>7</sup>
<b>Comparator(s)</b>	Cabozantinib or vandetanib given orally
<b>Outcome(s)</b>	Primary Outcome: Progression Free Survival (PFS) by BICR [Time frame: Baseline to progressive disease or death from any cause (Estimated at up to 30 Months)]

	See trial record for full list of outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	<p><b>LIBRETTO-001</b>, <a href="#">NCT03157128</a>, <a href="#">2017-000800-59</a>; A Phase 1/2 Study of Oral Selpercatinib (LOXO-292) in Patients With Advanced Solid Tumors, Including RET Fusion-Positive Solid Tumors, Medullary Thyroid Cancer, and Other Tumors With RET Activation (LIBRETTO-001)</p> <p><b>Phase I/II:</b> Recruiting</p> <p><b>Location(s):</b> 5 EU, UK, US, Canada and other countries</p> <p><b>Primary Completion Date:</b> 21<sup>st</sup> November 2022</p>
Trial Design	Single group assignment, open label
Population	N=989 (estimated), 12 years and older, Participants with a locally advanced or metastatic solid tumour that: has progressed on or is intolerant to standard therapy, or for which no standard therapy exists, or in the opinion of the investigator, are not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or decline standard therapy
Intervention(s)	Phase 1 - Multiple doses of LOXO-292 (selpercatinib) Phase 2 - The maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D)
Comparator(s)	N/A
Outcome(s)	<p>Primary Outcome:</p> <ol style="list-style-type: none"> <li>Phase 1: MTD [Time Frame: The first 28 days of treatment (Cycle 1)]</li> <li>Phase 1: RP2D [Time Frame: The first 28 days of treatment (Cycle 1) and every cycle (28 days) for approximately 12 months (or earlier if the participant discontinues from the study)]</li> <li>Phase 2: Objective Response Rate [Time Frame: Approximately every 8 weeks for one year, then every 12 weeks, and 7 days after the last dose (for up to 2 years) in participants who have not progressed.]</li> </ol> <p>See trial record for full list of outcomes</p>
Results (efficacy)	-
Results (safety)	-

<b>Estimated Cost</b>
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Selpercatinib is already marketed in the UK; the 80mg capsule at size 56 costs £4368, at size 60 costs £4680 and size 112 costs £8736. The 40mg capsule at size 56 costs £2184, at size 60 costs £2340 and size 168 costs £6552.<sup>8</sup>

## Relevant Guidance

### NICE Guidance

- NICE technology appraisal. Vandetanib for treating medullary thyroid cancer (TA550). December 2018.
- NICE technology appraisal. Cabozantinib for treating medullary thyroid cancer (TA516). March 2018.

### NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Head and Neck (Adult). B16/S/a.

### Other Guidance

- European Society for Medical Oncology. Clinical practice guidelines – Thyroid cancer. 2019.<sup>20</sup>
- Northern England Strategic Clinical Networks. Head and Neck Cancer Clinical Guidelines. 2017<sup>21</sup>
- American Thyroid Association Management. Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. 2015.<sup>22</sup>
- British Thyroid Association Guidelines for the Management of Thyroid Cancer. 2014.<sup>23</sup>
- London Cancer Alliance. Head and Neck/Thyroid Cancer Clinical Guidelines. 2014.<sup>24</sup>

## Additional Information

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