NDA 213246/S-015 and S-016
NDA 218160/S-005 and S-006
Selpercatinib (RETEVMO)

Efficacy Supplement – Clinical and Statistical Review

Application Type (NDA/BLA)	NDA
Application Number(s)/ supplement number	213246/S-015 and S-016 (capsule formulation) 218160/S-005 and S-006 (tablet formulation)
Received Date	S-015: June 18, 2025 S-016: July 22, 2025
PDUFA Goal Date	December 18, 2025
Review Completion Date	*Electronic stamp date*
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Product: **Established Name (Trade name)**	Selpercatinib (RETEVMO)
Pharmacologic Class	Kinase inhibitor
Formulation	Capsule (NDA 213246) Tablet (NDA 218160)
Dosing Regimen	Adult and adolescent patients 12 years of age or older, the recommended dosage is based on weight: • Less than 50 kg: 120 mg orally twice daily • 50 kg or greater: 160 mg orally twice daily Pediatric patients 2 to less than 12 years of age, the recommended dosage is based on body surface area: • 0.33 to 0.65 m^2: 40 mg orally three times daily • 0.66 to 1.08 m^2: 80 mg orally twice daily • 1.09 to 1.52 m^2: 120 mg orally twice daily • ≥1.53 m^2: 160 mg orally twice daily
Applicant	Loxo Oncology Inc., a wholly owned subsidiary of Eli Lilly and Company
Recommended Regulatory Action	Approval

1. Executive Summary:

Selpercatinib (RETEVMO) is a kinase inhibitor approved the following indications:

- Adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a *rearranged during transfection (RET)* gene fusion, as detected by an FDA-approved test;

- Adult and pediatric patients 2 years of age and older with advanced or metastatic medullary thyroid cancer (MTC) with a *RET* mutation, as detected by an FDA-approved test, who require systemic therapy;
- Adult and pediatric patients 2 years of age and older with advanced or metastatic thyroid cancer with a *RET* gene fusion, as detected by an FDA-approved test, who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate);
- Adult and pediatric patients 2 years of age and older with locally advanced or metastatic solid tumors with a *RET* gene fusion, as detected by an FDA-approved test, that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options[1]

[1]This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Efficacy Supplements for selpercatinib were submitted to NDA 213246 (S-015, S-016) and NDA 218160 (S-005, S-006) to update safety and efficacy results in US product labeling. The clinical data to support these supplements was submitted to NDA 213246.

In S-015, the Applicant submitted the final results of study LIBRETTO-121 (J2G-OX-JZJJ; NCT03899792): "A Phase 1/2 Study of the Oral RET Inhibitor LOXO-292 in Pediatric Patients with Advanced *RET*-Altered Solid or Primary Central Nervous System Tumors," to support labeling changes for safety and efficacy in pediatric patients with *RET*-altered solid tumors. In addition, the Applicant submitted a request for Pediatric Exclusivity and submitted the final study reports completed in response to the Written Request issued on June 22, 2023.

In S-016, the Applicant submitted updated safety information regarding the identification of Stevens-Johnson Syndrome as an important new potential risk with proposed changes to *Postmarketing Experience* in Section 6 of product labeling.

The review team determined that revisions to the selpercatinib product labeling were appropriate and considers the Interim Report Submission commitment fulfilled.

2. Background and Regulatory History

Selpercatinib is an oral inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase as well as vascular endothelial growth factor receptors 1 and 3 (VEGFR1 and VEGFR3). Gene mutations and rearrangements (fusions) in RET have the potential to be oncogenic drivers and have been observed in a variety of tumor types, including lung cancer, thyroid cancer, and other solid tumors.

On May 29, 2024, the relevant existing indications for selpercatinib were extended to include pediatric patients 2 years of age and older. As described in the multi-disciplinary review (https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80748745), the

recommendation for accelerated approval was based on results of Study LIBRETTO-121 (J2G-OX-JZJJ; NCT03899792), an international, single-arm, multi-cohort clinical trial of selpercatinib in pediatric and young adult patients with advanced *RET*-altered solid or primary Central Nervous System (CNS) tumors. Patients received selpercatinib 92 mg/m^2 orally twice daily until disease progression, unacceptable toxicity, or other reason for treatment discontinuation. Tumor assessments were performed every 8 weeks for one year, then every 12 weeks; responses were assessed according to RECIST 1.1 per blinded independent review committee (BIRC). Patients were enrolled at sites distributed across multiple geographic regions (North America, Europe, Asia, and Australia), including approximately one-third of patients enrolled in the United States.

The primary efficacy population included 25 patients ages 2 to 20 years of age with locally advanced or metastatic *RET*-activated solid tumors non-responsive to available therapies or with no standard systemic curative therapy available. The recommendation for approval is supported by results from LIBRETTO-001 in adult patients with *RET* fusion-positive NSCLC, thyroid cancer, and other solid tumors, which formed the basis of the prior approvals in these tumor types. Additional supportive information consisted of clinical data from single patient protocols. The Applicant submitted adequate data to support additional dosing regimens for pediatric patients 2 to less than 12 years of age who are able to swallow intact tablets based on body surface area.

In the primary efficacy population (n=25), the confirmed overall response rate (ORR) per RECIST 1.1 as determined by BIRC was 48% (95% Confidence Interval [CI]: 28%, 69%). The median duration of response (DOR) was not reached (95% CI: not evaluable [NE], NE), with 92% of responders remaining in response at 12 months. Durable responses were observed in pediatric and young adult patients with *RET*-mutant MTC (n=14; ORR 43% [95% CI: 18%, 71%]) and *RET* fusion-positive thyroid cancer (n=10; ORR 60% [95% CI: 26%, 88%]). Data in patients with *RET* fusion-positive non-thyroid solid tumors were limited (one patient with a *RET* fusion-positive malignant peripheral nerve sheath tumor who was a non-responder), and the extension of the tissue agnostic indication was supported by data from pediatric patients with *RET* fusion-positive thyroid cancer and adult patients with *RET* fusion-positive solid tumors, BIRC-assessed response data from pediatric patients treated with selpercatinib on single patient protocols, and strong biologic rationale in a very rare genetically defined subgroup of patients.

The overall safety population included 27 pediatric and young adult patients treated with selpercatinib in Study LIBRETTO-121. The evaluation of safety was supported by the safety population characterized in current product labeling, which included 796 predominantly adult patients with solid tumors from Study LIBRETTO-001. Overall, the adverse events observed are generally consistent with the current product labeling. However, an additional warning was added to product labeling for slipped capital femoral epiphysis/slipped upper femoral epiphysis (SCFE/SUFE) in pediatric patients. In the overall safety population (n=27), the most common adverse reactions (≥25%) were musculoskeletal pain, diarrhea, headache, nausea, vomiting, coronavirus infection, abdominal pain, fatigue, pyrexia, and hemorrhage. The most common Grade 3 or 4 laboratory abnormalities (≥5%) were decreased calcium, decreased hemoglobin, and decreased neutrophils.

The Efficacy Supplements submitted to NDA 213246 and 218160 are intended to provide the final results of study LIBRETTO-121 and support a request for Pediatric Exclusivity in response to the Written Request issued on June 22, 2023.

3. Review of Clinical Data

The clinical data to support this supplement was submitted to NDA 213246, supporting document numbers 1057 and 1066.

3.1 Efficacy

The Applicant proposed to include updated efficacy data in labeling from Study LIBRETTO-121 based on a clinical data cutoff date of November 9, 2024, resulting in nearly 2 years of additional follow-up from the original data cutoff date of January 13, 2023.

3.1.1 *RET*-Mutant Medullary Thyroid Cancer (MTC)

Based on the initial data cutoff date of January 13, 2023, the efficacy of selpercatinib was evaluated in **14 patients** with *RET*-mutant MTC who were non-responsive to available therapies or had no standard systemic curative therapy available. The median age was 14 years (range 2 to 20); 64% were male; 71% were White, 14% were Black or African American; and 14% were Hispanic/Latino. Patients had metastatic (71%) or locally advanced (29%) disease; 43% had measurable disease at baseline; 21% had received prior systemic therapy.

Based on the updated data cutoff date of November 9, 2024, no additional patients were enrolled, but additional patients were determined to be responders during the additional follow-up time (Table 1). Two patients ((b) (6) and (b) (6)) who had partial response previously attained complete response. One patient ((b) (6)) with stable disease at the original cutoff demonstrated a complete response, and one patient ((b) (6)) with an unconfirmed complete response at the original cutoff had the response confirmed. The median DOR follow-up time was extended from 25.6 months to 44.2 months.

Table 1: Efficacy Results in LIBRETTO-121: *RET*-Mutant MTC

Efficacy Parameter	**RETEVMO DCO 11/09/24 N = 14***	**RETEVMO DCO 01/13/23 N = 14†**
Overall Response Rate[1], % (95% CI)	57% (29, 82)	43% (18, 71)
Complete response	36%	7%
Partial response	21%	36%
Duration of Response		

Median in months (95% CI)	NR (25, NE)	NR (NE, NE)
% with ≥12 months[2]	88%	100%
% with ≥18 months[2]	88%	67%
% with ≥ 24 months[2]	75%	67%
Range in months	8.3+, 49.7+	13.8+, 30.5+

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

\+ Denotes ongoing response.

DCO = Data Cutoff date; NR = not reached; NE = not estimable.

* Reviewer generated analysis from sNDA 213246, S-015
† Reviewer extracted from the sNDA 213246, S-012 review dated May 28, 2024

3.1.2 *RET* Fusion-Positive Thyroid Cancer

Based on the initial data cutoff date of January 13, 2023, the efficacy of selpercatinib was evaluated in **10 patients** with *RET* fusion-positive thyroid cancer who were non-responsive to available therapies or had no standard systemic curative therapy available. The median age was 13.5 years (range 12 to 20); 60% were male; 40% were White, 50% were Asian; and 30% were Hispanic/Latino. All (100%) patients had metastatic disease and papillary thyroid cancer histology; 40% had measurable disease at baseline; 30% had received prior systemic therapy.

Based on the updated data cutoff date of November 9, 2024, **5 additional patients** were enrolled (total N=15). Updated demographics include median age 12 years (range 6 to 20); 53% were male; 40% were White, 47% were Asian; and 27% were Hispanic/Latino. Patients had metastatic (87%) or locally advanced (13%) disease and papillary thyroid cancer histology; 47% had measurable disease at baseline; 20% had received prior systemic therapy.

With the additional patients and longer duration of follow-up, the confirmed ORR was updated from 60% (95% CI: 26%, 88%) to 53% (95% CI: 27%, 79%) with two responders added as of November 9, 2024. One initially enrolled patient ([(b) (6)]) with stable disease at the original cutoff demonstrated a complete response, and one newly enrolled patient ([(b) (6)]) demonstrated a partial response. The median DOR follow-up time was extended from 17.2 months to 36.6 months.

Table 2: Efficacy Results in LIBRETTO-121: *RET*-Fusion-Positive Thyroid Cancer

Efficacy Parameter	**RETEVMO DCO 11/09/24 N = 15***	**RETEVMO DCO 01/13/23 N = 10†**
Overall Response Rate[1], % (95% CI)	53% (27, 79)	60% (26, 88)

Complete response	27%	30%
Partial response	27%	30%
Duration of Response		
Median in months (95% CI)	NR (NE, NE)	NR (NE, NE)
% with ≥12 months[2]	100%	83%
% with ≥18 months[2]	88%	50%
% with ≥ 24 months[2]	75%	17%
Range in months	12.9+, 44.2+	7.5+, 24.9+

[1] Confirmed overall response rate assessed by BIRC.

[2] Based on observed duration of response.

DCO = Data Cutoff date; NR = not reached; NE = not estimable

\+ Denotes ongoing response.

* Reviewer generated analysis from sNDA 213246, S-015
† Reviewer extracted from the sNDA 213246, S-012 review dated May 28, 2024

3.1.3 Other *RET* Fusion-Positive Solid Tumors

Based on the initial data cutoff date of January 13, 2023, the efficacy of selpercatinib was evaluated in **one patient** with a locally advanced refractory *RET*-fusion positive other type of solid tumor who was unresponsive to available therapies or had no standard systemic curative therapy available. This patient had locally advanced refractory *RET*-fusion positive malignant peripheral nerve sheath tumor and did not respond.

Based on the updated data cutoff date of November 9, 2024, **2 additional patients** were enrolled (total N=3) and had partial responses, as described below:

- Patient (b) (6) was a (b) (6)year-old (b) (6) with locally advanced *RET* fusion-positive (MYH10:RET) congenital infantile fibrosarcoma who had received 2 prior therapies; (b) (6) had a confirmed partial response with DOR of 3.7 months, ongoing on treatment at the time of data cut-off.

- Patient (b) (6) was a (b) (6)-year-old (b) (6) with locally advanced *RET* fusion-positive (MYH10:RET) spindle cell sarcoma who had received 10 prior therapies; (b) (6) had a confirmed partial response with DOR of 3.7 months, ongoing on treatment at the time of data cut-off.

3.2 Safety

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Selpercatinib (RETEVMO)

The Applicant submitted updated safety data from Study LIBRETTO-121, including proposed revisions to Sections 5 and 6 of product labeling, as described in the review below.

The original safety population for LIBRETTO-121 included **27 patients** with a data cutoff date of January 13, 2023. The updated safety population includes **36 patients** with a data cutoff date of November 8, 2024.

Section 5: Warnings & Precautions

As described in the Multidisciplinary Review dated May 28, 2024, slipped capital femoral epiphysis/slipped upper femoral epiphysis (SCFE/SUFE) was added as a Warning in US product labeling. This adverse event is characterized by the posterior and inferior slippage of the proximal femoral epiphysis on the metaphysis (femoral neck), which occurs through the epiphyseal plate (growth plate). SCFE/SUFE occurred in 1 adolescent (**3.7% of 27 patients**) receiving selpercatinib in LIBRETTO-121 and 1 adolescent with *RET*-mutant MTC (0.5% of 193 patients) receiving selpercatinib in LIBRETTO-531. While it was challenging to determine whether selpercatinib contributed to the occurrence of epiphysiolysis in these patients given additional risk factors (e.g., history of epiphysiolysis in contralateral hip, periods of rapid growth, hypothyroidism), a potential relationship could not be excluded. In addition, a high level of suspicion and early diagnosis of this disorder may prevent long-term consequences such as avascular necrosis.

In S-015, the Applicant provided data to update Section 5.11 of product labeling. As of the updated data cutoff, no additional patients had adverse events of epiphysiolysis, which reduced the overall percentage of patients in LIBRETTO-121 who had these events (i.e., 2.8% of 36 patients). US product labeling includes a recommendation to monitor patients for symptoms indicative of SCFE/SUFE and treat as medically and surgically appropriate.

In addition, FDA reviewed the adverse events of fractures which occurred in LIBRETTO-121. These included 5 pediatric patients, 2 of which were classified as serious and both related to a mechanical fall (e.g., fall while operating an electric scooter while on the phone; fall after tripping on a hardwood floor). For the 4 non-serious cases, the contribution of trauma or other external factors was not specified, but there was no evidence of tumor involvement at the fracture sites. Based on the available information and the general background incidence of fractures in children, there did not appear to be a clear association between selpercatinib and the occurrence of fractures.

In the original selpercatinib approval letter, FDA issued a post-marketing requirement (PMR) to assess the risk of long-term adverse effects of selpercatinib on growth and development, including growth plate issues, in patients 2 to < 12 years of age with *RET*-altered solid tumors. The submission of the final report is due by December 2029.

> PMR 4639-4: Conduct comprehensive safety analyses from clinical studies that further characterize the known serious risk of long-term adverse effects of selpercatinib on growth and development, including but not limited to growth

plate abnormalities, in a sufficient number of pediatric patients with *RET*-altered solid tumors ages 2 to < 12 years of age. Monitor patients for growth and development using age-appropriate screening tools. Include evaluations of growth as measured by height, weight, height velocity and height standard deviation scores, age at menarche if applicable (females) and Tanner stage. Monitor patients until discontinuation of study treatment or a minimum of 5 years from start of treatment, whichever occurs first.

Section 6: Adverse Reactions

The Applicant submitted updated datasets for safety (ADSL, ADAE, ADLB) and proposed to update US product labeling for the updated safety population including 36 patients with a data cutoff date of November 8, 2024 (increased from 27 patients with a data cutoff date of January 13, 2023.

The safety population reflects exposure to selpercatinib as a single agent at 92 mg/m^2 orally twice daily evaluated in 36 patients with advanced solid tumors harboring an activating *RET* alteration in LIBRETTO-121. Among the 36 pediatric and adolescent patients who received selpercatinib, 86% were exposed for 6 months or longer and 72% were exposed for greater than one year.

The median age was 13 years (range: 2 to 20 years); 31% were pediatric patients 2 to 12 years of age; 53% were male; and 47% were White, 28% were Asian, and 8% were Black or African American; and 19% were Hispanic/Latino. The most common cancers were MTC (42%), and papillary thyroid cancer (42%).

Serious adverse reactions occurred in 42% of patients who received selpercatinib. Serious adverse reactions occurring in more than 1 patient were vomiting (6%) and fracture (6%).

Dosage interruptions due to an adverse reaction occurred in 42% of patients who received selpercatinib. Adverse reactions requiring dosage interruption in ≥5% of patients included increased ALT (n=3), increased AST (n=3), ascites (n=2), increased bilirubin (n=2), decreased neutrophils (n=2), and pyrexia (n=2).

Dose reductions due to an adverse reaction occurred in 22% of patients who received selpercatinib. Adverse reactions requiring dosage reductions in ≥2% of patients included increased ALT (n=3), decreased neutrophils (n=2), increased weight (n=2), and increased bilirubin (n=1).

The most common adverse reactions (≥25%) were musculoskeletal pain, diarrhea, nausea, hemorrhage, pyrexia, abdominal pain, headache, vomiting, fatigue, cough, rash, coronavirus infection, upper respiratory tract infection, and edema.

The most common Grade 3 or 4 laboratory abnormalities (≥5%) were decreased lymphocytes, decreased calcium, decreased hemoglobin, decreased neutrophils, increased ALT, decreased magnesium, and decreased potassium.

Section 6.2:

In Supplement 16, the Applicant submitted proposed changes to Section 6.2 (Postmarketing Experience). As rationale for this revision, the Applicant stated that as part of routine postmarketing surveillance, Lilly identified Stevens-Johnson Syndrome (SJS) as important new safety information for selpercatinib.

SJS/TEN is a severe cutaneous adverse reaction (SCAR) associated with morbidity and mortality, characterized by epidermal necrolysis with varying degrees of blistering, skin detachment, and sloughing, and usually develops 4 to 28 days after drug exposure.

The Applicant conducted an analysis of the selpercatinib clinical trial database cumulatively through May 8, 2025. No cases were reported for SJS/TEN. A broader SMQ search for SCAR identified a total of 238 TEAEs. Most events were Grade 1 or 2, with <1% of events being Grade 3 (no Grade 4 or 5 events). The majority of these events were stomatitis and mouth ulceration (175 events), which are already included in product labeling.

A broader SMQ search for SCAR identified 92 post-marketing cases of SCAR cumulatively through May 8, 2025. Of these 92 cases, 3 cases of SJS (1 case was duplicated) and 1 case of bullous dermatitis were considered notable and included for further analysis, as follows:

- **JP202504019738**: 50 year-old male with *RET*-mutant MTC concomitantly taking azilsartan; 12 days after starting selpercatinib, he developed widespread erythema and was hospitalized for confluent and palpable atypical target lesions mainly on the trunk and thigh, bloody crusts on the lips, and erosions on the genital mucosa; he was febrile to 39.9°C and laboratory data revealed an inflammatory response with mild liver and renal dysfunction; skin biopsy showed necrosis of epidermal cells and inflammatory cell infiltration extending from the dermis into the epidermis, consistent with the findings of SJS or TEN; since the total skin detachment area was less than 10%, he was diagnosed with SJS; selpercatinib was discontinued and he improved with steroid therapy; this case was published by Tony Y, et al in the Journal of Dermatology, 2025.
- **JP202410018310**: 40-year-old female with *RET* fusion-positive lung adenocarcinoma; 13 days after starting selpercatinib, she experienced Grade 3 SJS and Grade 3 DIC; after improvement, she continued unspecified steroid therapy, and selpercatinib was resumed at small doses (dosage not provided); this case had limited information on medical history, concomitant medications, clinical presentation, and investigations such as skin biopsy, and therefore, other potential risks cannot be ruled out.
- **TW202408011933**: 66-year-old female with *RET*-mutant MTC concomitantly taking vandetanib (for which product labeling includes a warning for SJS); within 1 week of initiation of selpercatinib, she experienced rash all over the body, which was suspected to

be SJS, and the patient was hospitalized; selpercatinib was discontinued, whereas the status of vandetanib therapy was not provided.

- **US202501016771:** 70-year-old male with *RET* fusion-positive lung cancer; 1-2 weeks after starting selpercatinib he developed a Grade 4 maculopapular, purpuric rash, itching, skin peeling off, bleeding, and edema all over his body; this was diagnosed as a bullous rash and the patient was not hospitalized; selpercatinib was interrupted and he was treated with prednisone; after recovery the selpercatinib therapy was resumed and no information was provided on recurrence of events

Given the severity of this rare event and the relatively small post-marketing exposure, the single documented case in the literature, which provides reasonable evidence of a causal association between SJS and selpercatinib, FDA considered it reasonable to add SJS to the warnings section of product labeling.

Given current product labeling already includes a warning for hypersensitivity, the safety information regarding SJS was added to this warning as follows:

(b) (4)

4. Labeling changes

A summary of labeling changes is presented in Table 3.

Table 3: Summary of Labeling Changes (adapted from submission)

Section	Key Updates
Highlights of Prescribing Information	'Recent Major Changes' section updated to reflect the changes made in subsections X; Most common adverse reactions in pediatric patients updated
Dosage and Administration Section 2	Alternative administration instructions added for patients unable to swallow tablets Dosage modification instructions for severe skin reactions including Stevens Johnson Syndrome added.

Warnings and Precautions Section 5	Text revised and added to include updated information related to slipped capital femoral epiphysis in pediatric patients
Adverse Reactions Section 6	Text revised and added to include updated information related to updated safety information for Study LIBRETTO-121. Text added to include safety findings in postmarketing experience
Clinical Studies Section 14	Text revised to include the updated study description and results from Study LIBRETTO-121.
Instructions for Use	Separate Instructions for Use document created to provide detailed instructions for the alternative method of administration for tablets.

The Applicant submitted labeling changes to reflect this approval with this labeling supplement.

5. Recommended Regulatory Action

The clinical review team recommends approval of this labeling supplement as summarized in this review.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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