1. Protocol J2G-GH-B003
A Prospective, Non-Interventional, Post-Marketing Observational Study Evaluating the Effectiveness and Safety of Selpercatinib Capsules in Adults and Pediatric Patients with Advanced or Metastatic *RET* Fusion-Positive Thyroid Cancer

Selpercatinib (LY3527723)

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Observational Study Protocol Electronically Signed and Approved by Lilly: approval date provided below

2. Abstract

Title:

A prospective, non-interventional, post-marketing observational study evaluating the effectiveness and safety of selpercatinib capsules in adults and pediatric patients with advanced or metastatic *RET* fusion-positive thyroid cancer

Rationale and background:

Selpercatinib, a first-in-class highly selective and potent rearranged during transfection (RET) kinase inhibitor, has been approved in multiple countries worldwide for the treatment of advanced/metastatic *RET*-altered thyroid cancers.

In the global Phase 1/2 clinical study (LIBRETTO-001) and in the Chinese Phase 2 clinical study (LIBRETTO-321), selpercatinib demonstrated robust and durable efficacy with a well-tolerated safety profile in patients with *RET* fusion-positive advanced or metastatic thyroid cancer. However, due to the rarity of target patients, only a small group of patients with *RET* fusion-positive thyroid cancer was evaluated in the global and Chinese registration studies. To further describe the effectiveness and safety of selpercatinib in *RET* fusion-positive advanced or metastatic thyroid cancer under real-world clinical practice in China, this prospective non-interventional observational study has been designed to fulfill post-marketing commitment (PMC) on the conditional approval of the thyroid cancer indication.

Objectives and endpoints:

Objectives	Endpoints
Primary	
• To evaluate the effectiveness of selpercatinib by assessing rwORR in Chinese patients with advanced or metastatic *RET* fusion-positive thyroid cancer.	rwORR assessed by investigator
Secondary	
• To evaluate the effectiveness of selpercatinib by assessing rwPFS, rwDoR and rwDCR in Chinese patients with advanced or metastatic *RET* fusion-positive thyroid cancer.	• rwPFS assessed by investigator • rwDoR assessed by investigator • rwDCR assessed by investigator
Exploratory	
• To describe the safety profile of selpercatinib.	Incidence, severity, seriousness, and relatedness of AEs to selpercatinib
• To investigate the treatment patterns of selpercatinib in real-world clinical practice	• Dosing patterns • DoT

Abbreviations: AEs = adverse events; DoT = duration of treatment; rwDCR = real-world disease control rate; rwDoR = real-world duration of response; rwORR = real-world objective response rate; rwPFS = real-world progression-free survival; RET = rearranged in transfection.

Study design: This is a real-world, multi-center, single-arm, prospective, observational study, which aims to evaluate the effectiveness and safety of selpercatinib in patients with advanced or metastatic *RET* fusion-positive thyroid cancer in China.

Population:

Adult and pediatric patients 12 years of age and older with confirmed advanced or metastatic *RET* fusion-positive thyroid cancer who plan to start treatment with selpercatinib or recently initiated the treatment (within 7 days from the time of enrolment) in routine clinical practice setting.

Inclusion Criteria:

1. Patients with advanced or metastatic thyroid cancer confirmed by histology or cytology, such as papillary

thyroid carcinoma (PTC), follicular thyroid cancer (FTC) (including Hurthle cell carcinoma), poorly differentiated thyroid carcinoma (PDTC), ATC (anaplastic thyroid cancer).
2. Patients are radioactive iodine (RAI) therapy refractory or relapsed, or not suitable for RAI therapy.
3. Evidence of a *RET* gene fusion in tumor and/or blood, as confirmed by the site investigator based on the prior medical records or relevant testing results. Prior usage of multikinase inhibitors (MKIs) with anti-*RET* activity are allowed. (Refer to for examples Attachment 2 of MKIs with anti-*RET* activity.)
4. Age ≥12 years at enrollment.
5. Started selpercatinib treatment within 7 days (from the time of enrolment) or plan to receive selpercatinib treatment based on treating physicians' medical judgment following the treatment guidance, approved product label, or other criteria they deem appropriate in China in the routine clinical practice.
6. Willing to participate in this study and informed consent obtained from the patient/legal representative.

Exclusion Criteria:

7. Patients with medullary thyroid cancer (MTC).
8. Prior treatment with selpercatinib (1st dose within 7 days from the time of enrolment can be included in the study), or other selective *RET* inhibitor(s), such as pralsetinib.
9. Are currently enrolled in any other interventional clinical study on drugs. Participation in other observational study is allowed only if the treatment and study procedure described in this protocol won't be impacted.
10. Are contraindicated from the approved label of selpercatinib.

Study Therapies:

Treatment of selpercatinib will be prescribed under a routine medical care based on treating physicians' medical judgment following the treatment guidance, approved product label, or other criteria they deem appropriate.

Planned Duration of Follow-up:

The overall study follow-up duration would be 24 months from the first patient initiating selpercatinib treatment or 6 months after the last patient initiating selpercatinib treatment, whichever comes later. Patients will be followed-up up to 24 months from initiating treatment if still on selpercatinib treatment, or up to 6 months after treatment discontinuation, or the end of overall study follow-up duration, whichever comes first. Treatment discontinuation may be due to progressive disease (PD), unacceptable toxicity, or other reason based on clinicians' judgment and patients' choice.

Variables:

Variables such as demographics, disease and clinical characteristics, medical history, oncology treatment information and selpercatinib treatment pattern, safety information and treatment permanent discontinuation, and effectiveness assessment (real-world objective response rate [rwORR], real-world progression-free survival [rwPFS], real-world duration of response [rwDoR], and real-world disease control rate [rwDCR]), vital sign, European Cooperative Oncology Group Performance Score (ECOG PS) and lab parameters will be collected around time points designated in Attachment 1, if available.

Data sources/Data Collection:

This study is based on primary data collection using electronic data capture (EDC) system. All data reported on electronic case report form (eCRF), or paper documentation will be derived from the source documents (patient medical records, clinical notes, laboratory tests, etc) and compiled by sites.

Study size:

About 15 patients will be enrolled in this study.

The primary endpoint of this study was rwORR. In the previous global clinical trial LIBRETTO-001, the ORR is 82.3% in patients with *RET* fusion-positive thyroid cancer (Sherman et al. 2021); While sorafenib is the first targeted drug approved in the world for the treatment of RAI-refractory, recurrent and metastatic differentiated thyroid cancer, with an objective response rate (ORR) of 12.2% (Brose et al. 2014). This study considered 12 patients with *RET* fusion-positive thyroid cancer who met the effectiveness analysis. If the rwORR observed in this study sample was 41.7% (that is, 5 responders were observed in the 12 analysis patients. The confident level to be equal to or more than 5 responders from 12 patients were 99.98% based on the LIBRETTO-001 results, which is larger than 80%). The two-sided (lower) bound of the 95% confidence interval was 15.2% calculated using the Clopper-Pearson Exact Method, which was higher than the ORR of sorafenib. Assuming 20% drop-out

rate of missing effectiveness evaluation or loss to follow-up in the real-world setting, this study plans to enrol 15 patients with *RET* fusion-positive thyroid cancer.
Data analysis: All enrolled patients receiving at least 1 dose of selpercatinib would be included in the analysis. Descriptive analyses will be conducted to describe the effectiveness and safety of selpercatinib. For effectiveness endpoints, rwORR and rwDCR will be summarized as descriptive statistics in terms of frequencies and percentages, and 95% CIs will be provided. For rwPFS, rwDoR, and duration of treatment (DoT), the medians will be computed together with their 95% CIs using the Kaplan-Meier method. Incidence of safety outcomes (including adverse events [AEs]/ serious adverse events [SAEs]) will be described. Severity and relatedness with selpercatinib treatment will also be summarized.
Milestones: Start of data collection: Estimated Sep 2023. Database lock: Estimated Oct 2025. Final report of study results submission: Estimated Aug 2026.

3. Table of Contents

A Prospective, Non-Interventional, Post-Marketing Observational Study Evaluating the Effectiveness and Safety of Selpercatinib Capsules in Adults and Pediatric Patients with Advanced or Metastatic *RET* Fusion-Positive Thyroid Cancer

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List of Attachments

4. Abbreviations and Definitions

Term	Definition
AE	adverse event
ATC	anaplastic thyroid cancer
CR	complete response
DoT	duration of treatment
eCRF	electronic case report form
ECOG PS	European Cooperative Oncology Group Performance Score
EDC	electronic data capture
ERB	ethical review board
FISH	fluorescence in situ hybridization
FNA	fine needle aspiration
FTC	follicular thyroid cancer
GPP	Good Pharmacoepidemiology Practice
IHC	Immunohistochemistry screening
MedDRA	Medical Dictionary for Regulatory Activities
MKI	multikinase inhibitor
MTC	medullary thyroid cancer
NGS	next-generation sequencing
NSCLC	non-small cell lung cancer
PD	progressive disease
PDTC	poorly differentiated thyroid carcinoma
PR	partial response
PTC	papillary thyroid carcinoma
RAI	radioactive iodine
RECIST	Response Evaluation Criteria in Solid Tumor
RET	rearranged during transfection
RTK	receptor tyrosine kinase
RT-PCR	reverse transcription polymerase chain reaction
rwDCR	real-world disease control rate
rwDoR	real-world duration of response
rwORR	real-world objective response rate
rwPFS	real-world progression-free survival
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
SAS	Statistical Application Software
SD	stable disease
WHO	World Health Organization

5. Background and Rationale

Rearranged during transfection (RET) is a receptor tyrosine kinase (RTK) critical to development of the enteric nervous system and kidney. Postnatally, RET contributes to the maintenance of neural, neuroendocrine, hematopoietic and male germ cell tissues (Mulligan 2014). Genetic alterations in *RET* have been implicated in the pathogenesis of thyroid cancer, non-small cell lung cancer (NSCLC) and several other human cancers.

Thyroid cancer is the most common endocrine malignancy, although it represents less than 1% of all human tumors (Pacini et al. 2012). During the last 20 years, China has experienced significant growth in the number of annual thyroid cancer diagnoses. According to the Dataset Records for National Central Cancer Registry of China, thyroid cancer incidences have steadily increased in China from 2010 to 2014, yet the mortality rate has remained stable during the same period. As of 2015, China accounts for approximately 16% of all new thyroid cancer cases and 14% of thyroid cancer-associated deaths in the world (Huang et al. 2019). There are 2 main histologic subtypes of thyroid cancer based on the cell of origin: follicular and medullary. 1) follicular thyroid cancer, which includes differentiated cancers (papillary thyroid carcinoma [PTC] and follicular thyroid cancer [FTC]), and less differentiated subtypes including poorly differentiated thyroid carcinoma [PDTC] and anaplastic thyroid cancer [ATC]. The thyroid follicle-derived, differentiated cancers (PTC and FTC) are the most common thyroid cancers, accounting for 80% to 85% and 10% to 15% of all thyroid cancer cases, respectively (Aboelnaga and Ahmed 2015). Poorly differentiated subtypes (PDTC and ATC) account for 5% to 10% of thyroid cancers and are characterized by less differentiated histologic features and more aggressive clinical behavior than the differentiated subtypes (Landa et al. 2016). *RET* gene fusions have been identified in approximately 6% to 9% of PTCs and approximately 6% of PDTCs (Fusco et al. 1987; Agrawal et al. 2014; CGARN 2014; Landa et al. 2016; Kato et al. 2017). In China, *RET* gene fusions occurred in 8.5% of PTC patients (CSCO 2021). Neither FTC nor ATC are frequently associated with *RET* gene fusions. Most differentiated thyroid cancers, including PTC, are largely asymptomatic, treatable tumors with an excellent prognosis after surgical resection and radioactive iodine (RAI) therapy (Pacini et al. 2012). However, 10% to 15% of differentiated thyroid cancers exhibit aggressive behavior, and one-third of these patients have tumor recurrences, with about 20% having metastatic disease. These patients are incurable (eg, approximately half of patients with Stage IV PTC die within 5 years [Sturgeon and Angelos 2006; ACS 2019]). Notably, in patients with PTC, *RET* gene fusions are associated with adverse prognostic features (Prasad et al. 2016; Su et al. 2016). 2) Medullary thyroid cancer (MTC), a subtype of thyroid cancer which arises from the parafollicular calcitonin-producing C cells of the thyroid, represents 1% to 2% of thyroid cancers (SEER 2019). Oncogenic *RET* mutations occur in the majority of MTCs, including 90% or more of hereditary MTCs and 50% to 60% sporadic MTC (Donis-Keller et al. 1993; Mulligan et al. 1993; Carlson et al. 1994; Eng et al. 1994; Hofstra et al. 1994; Agrawal et al. 2013; Ji et al. 2015).

Thyroid cancer is rare in young children, with a sharp increase in incidence among adolescents and young adults between 15 and 29 years old (Pole et al. 2017). In comparison to adults, children more often present with aggressive, advanced stage disease. Specifically, PTC, which accounts for approximately 90% of pediatric thyroid cancer, has a high rate of *RET* fusions (approximately 25-30% of sporadic pediatric PTC, and nearly 45% in patients exposed to

radiation.), are associated with more extensive extrathyroidal disease, and offer unique options for targeted medical therapies (Paulson et al. 2019).

Selpercatinib is an oral, highly selective, and ATP-competitive small-molecule inhibitor of RET kinase. Selpercatinib is currently approved in multiple countries for the treatment of advanced or metastatic *RET* fusion-positive NSCLC, and patients ≥12 years with advanced or metastatic *RET*-mutant MTC or *RET* fusion-positive thyroid cancer requiring systemic therapy. FDA also approved selpercatinib as the first and only RET inhibitor for adults with advanced or metastatic solid tumors with a *RET* gene fusion, regardless of type. On September 30, 2022, the National Medical Products Administration (NMPA) granted a conditional approval to selpercatinib in China for the treatment of adult patients with locally advanced or metastatic *RET* fusion-positive NSCLC, adult and pediatric patients 12 years of age and older with advanced or metastatic *RET*-mutant MTC who require systemic therapy, and adult and pediatric patients 12 years of age and older with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate). In the global Phase 1/2 clinical study (LIBRETTO-001), selpercatinib demonstrated robust and durable efficacy with a well-tolerated safety profile in patients across a variety of tumor types in patients with *RET*-driven cancers. Because of the low incidence rate in advanced thyroid cancer and low gene alteration rate, only 42 *RET*-fusion positive advanced/metastatic thyroid cancer patients were enrolled in 16 countries during the nearly 3-year recruitment period (Sherman et al. 2021). The Chinese Phase 2 clinical study (LIBRETTO-321) enrolled only one *RET*-fusion positive advanced/metastatic thyroid cancer patient during the 8-month enrollment period (Zheng et al. 2022).

This study is a post-marketing commitment (PMC) study required by NMPA to provide additional evidence on effectiveness (primary and secondary objectives) and safety (exploratory objective) of selpercatinib in *RET* fusion-positive advanced or metastatic thyroid cancer under real-world clinical practice in China. MTC was not evaluated in this study because it is mainly driven by germline mutations in the *RET* proto-oncogene.

6. Objectives

6.1. Primary Objective

The primary objective of this study is to evaluate the effectiveness of selpercatinib by assessing real-world objective response rate (rwORR) in a routine clinical practice setting during the follow-up period (see details in Section 7.1).

6.2. Secondary Objectives

The secondary objective of this study is to evaluate the effectiveness of selpercatinib by assessing real-world progression free survival (rwPFS), real-world duration of response (rwDoR), and real-world disease control rate (rwDCR) during the follow-up period (see details in Section 7.1).

6.3. Exploratory Objectives

The exploratory objectives of the study include:

- To describe the safety profile of selpercatinib in a routine clinical practice setting, including the incidence, severity, seriousness, and relatedness of adverse events (AEs) to selpercatinib when available during the follow-up period (see details in Section 7.1), and
- To investigate the treatment patterns of selpercatinib in real-world clinical practice, including dosing patterns and duration of treatment (DoT) during the follow-up period (see details in Section 7.1).

7. Research Design

7.1. Summary of Research Design

This is a real-world, multi-center, single-arm, prospective, observational study, which aims at evaluating the effectiveness and safety of selpercatinib in patients with advanced or metastatic *RET* fusion-positive thyroid cancer in China.

Treatment of selpercatinib will be prescribed under a routine medical care based on treating physicians' medical judgment following the treatment guidance, approved product label, or other criteria they deem appropriate. The overall study follow-up duration would be 24 months from the first patient initiating selpercatinib treatment or 6 months after the last patient initiating selpercatinib treatment, whichever comes later. Patients will be followed-up up to 24 months from initiating treatment if still on selpercatinib treatment, or up to 6 months after treatment discontinuation, or the end of the overall study follow-up duration, whichever comes first. Detailed data collection period for effectiveness assessment, safety assessment, and other variables are specified in Attachment 1.

Approximately 15 patients will be enrolled in this study.

7.2. Study Population

This study will include adult and pediatric patients 12 years of age and older with confirmed advanced or metastatic *RET* fusion-positive thyroid cancer who plan to start treatment with selpercatinib or recently initiated the treatment of selpercatinib (within 7 days from the time of enrollment) in routine clinical care setting. The decision to treat is made by the physician and the patient in the routine care of the patient.

All patients presenting during the enrolment period (from site initiation until the targeted number of patients is reached) will be assessed for eligibility according to the defined inclusion/exclusion criteria, and all eligible patients will be offered the opportunity to participate in the study. Each site investigator will keep enrolling patients until the targeted number of patients is reached.

7.2.1. Selection Criteria

Inclusion Criteria:

1. Patients with advanced or metastatic thyroid cancer confirmed by histology or cytology, such as PTC, FTC (including Hurthle cell carcinoma), PDTC, ATC.
2. Patients are RAI therapy refractory or relapsed, or not suitable for RAI therapy.
3. Evidence of a *RET* gene fusion in tumor and/or blood, as confirmed by the site investigator based on the prior medical records or relevant testing results. Prior usage of multikinase inhibitors (MKIs) with anti-*RET* activity are allowed. (Refer to Attachment 2 for examples of MKIs with anti-*RET* activity.)
4. Age ≥12 years at enrollment.
5. Started selpercatinib treatment within 7 days (from the time of enrollment) or plan to receive selpercatinib treatment based on treating physicians' medical judgment following the treatment guidance, approved product label, or other criteria they deem appropriate in China in the routine clinical practice.
6. Willing to participate in this study and informed consent obtained from the patient/legal representative.

Exclusion Criteria:

7. Patients with MTC.
8. Prior treatment with selpercatinib (1st dose within 7 days from the time of enrolment can be included in the study), or other selective *RET* inhibitor(s), such as pralsetinib.
9. Are currently enrolled in any other interventional clinical study on drugs. Participation in other observational study is allowed only if the treatment and study procedure described in this protocol won't be impacted.
10. Are contraindicated from the approved label of selpercatinib.

7.3. Study Therapies

Treatment pattern and treatment initiation or changes will be solely at the discretion of the physician and the patient. There will be no attempt to influence the prescribing patterns of any individual investigator/physician. Selpercatinib will be prescribed in the usual standard of care and will not be provided by the study sponsor. Participation in the study will in no way influence payment or reimbursement for any treatment received by patients during the study.

7.4. Variables/Measures

Variables such as demographics, disease and clinical characteristics, medical history, oncology treatment information and selpercatinib treatment pattern, safety information and treatment permanent discontinuation, and effectiveness assessment (rwORR, rwPFS, rwDoR, and rwDCR), vital sign, European Cooperative Oncology Group Performance Score (ECOG PS), and lab parameters will be collected around time points designated in Attachment 1, if available.

7.4.1. Patient Demographics

- year of birth
- sex (female/male)
- weight, and
- height.

7.4.2. Clinical Characteristics

Oncology diagnosis and medical history

- Primary cancer and metastasis:
    - Histological type: PTC, FTC, ATC, or other
    - Stage at initial diagnosis of thyroid cancer (based on the TNM staging system)
    - Date of initial diagnosis of thyroid cancer
    - Metastatic site(s) if any: bone, brain/spinal cord, liver, lung, lymph nodes, or other
    - Diagnosis of advanced or metastatic cancer, if not the initial diagnosis:
        - Date of diagnosis of advanced stage, and

        - Stage: if not the initial diagnosis, TNM staging system.
- Medical history other than thyroid cancer: disease and year of diagnosis, ongoing status.
- Molecular testing patterns and alterations:
    - Date test requested and date of results
    - Test method used: next-generation sequencing (NGS), reverse transcription polymerase chain reaction (RT-PCR), fluorescence in situ hybridization (FISH), immunohistochemistry screening (IHC), or other
    - Sample used for testing: site of tissue sample (primary tumor, lymph nodes, metastasis, blood, and other) and method for obtaining the sample (surgical tissue, biopsy, punction, fine needle aspiration [FNA], or other)
    - *RET* fusion partners: e.g. CCDC6, NCOA4, and
    - Description of co-alterations identified (irrespective of testing time).

Treatment patterns

- Prior anti-cancer treatment for thyroid cancer: including surgery, RAI, radiotherapy and all the systemic anti-cancer therapies
    - For surgeries: surgical procedure, date of intervention. and intention of the surgical intervention (curative, decrease of tumor burden, palliative, or other)
    - For RAI: treatment start and stop dates, dose administered, treatment with RAI refractory (yes/no/NA)
    - For radiotherapy: type of radiotherapy, start and stop dates, irradiated location, the total dose administered
    - For systemic therapies, will include chemotherapy, immunotherapy, MKIs:
        - Drug class, including specific drug name(s)
        - Treatment start and stop dates
        - Treatment received within the setting of an interventional clinical trial (Yes/No)
        - Best response achieved: response (complete response [CR], partial response [PR]), stable disease (SD), progressive disease (PD), disease not measurable, not evaluated (NE), and
        - Reasons for treatment discontinuation: treatment completed, progression, drug-related toxicity/intolerance, and other.
- Prior medications other than anti-cancer therapy, received within 14 days prior to initiation of selpercatinib

- Selpercatinib administration:
    - Start date
    - Current status:
        - Ongoing,
        - Discontinued, and provide the discontinuation date
    - Dosage and administration details
    - Dose modification (including reason for modification), and
    - Dose interruption and omission.
- Concomitant medications: name, dose, route of administration, start and stop date, indication.

Clinical and laboratory measures:

- Vital signs: blood pressure, heart rate, etc
- ECOG PS (refer to Attachment 4)
- Laboratory Parameters:
    - Haematology profile (such as leukocytes, neutrophils, platelets, and hemoglobin)
    - Serum biochemistry profile (such as alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, direct bilirubin, serum creatinine, and electrolyte), and
    - biochemical markers of remission (thyroglobulin).
- Electrocardiogram.

Clinical effectiveness and safety outcomes

- Response to therapy: tumor response will be assessed by the investigators/treating physicians confirmed radiologically (using criteria such as Response Evaluation Criteria in Solid Tumor [RECIST] guideline [Eisenhauer 2009]; refer to Attachment 3) or confirmed by the physicians based on clinical assessments, as documented in the patient's chart or notes. If available, imaging or report at baseline will be collected for subsequent treatment response evaluation.
    - Response: CR, PR, SD, PD, NE
    - Mode of assessment: radiographic, clinical, both
    - Date of imaging examination, date of assessment (if based on clinical assessment)
    - Type of imaging examination, and
    - Date of death, if occurred.

- Safety: all AEs (including serious adverse events [SAEs]) occurred during the safety evaluation period (see Section 9.1) after administration of selpercatinib will be collected and recorded by investigators using the Adverse Events Collection Form of the electronic case report form (eCRF). The information collected about AEs is as follows, but is not limited to:
    - AE term
    - Whether or not the event met the criteria for SAEs (see Section 9.1)
    - Severity - CTCAE grade if available ([refer to Attachment 5])
    - Event start date and end date
    - Causal relationship with selpercatinib
    - Action taken for selpercatinib, and
    - Event outcome.

7.4.3. Definitions of Outcomes

- **Real-world objective response rate (rwORR)**: proportion of patients with a best response documented as response (CR or PR)
- **Real-world progression-free survival (rwPFS)**: time from selpercatinib treatment initiation to first documented progression or death from any cause, whichever occurred first
- **Real-world disease control rate (rwDCR)**: proportion of patients who have a CR, PR or SD response
- **Real-world duration of response (rwDoR)**: time from the date of first documented response (CR or PR) after selpercatinib treatment initiation to the date of the first documented progression or death from any cause, whichever occurs earlier, during the course of selpercatinib treatment
- **Duration of treatment (DoT)**: time from selpercatinib treatment initiation to the earliest of treatment end date or death, whichever occurs first.
- **Adverse event (AE)**: any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, and
- **Serious AE (SAE)**: refer to Section 9.1.

7.5. Data Sources

This study will be based on primary data collection, and an electronic data capture (EDC) system will be used. To ensure the collection of accurate, complete, and reliable data, the study investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the data to be entered by the site into the provided EDC system for this study. All data reported on the eCRF or paper documentation must be derived from and be consistent with the source documents, or the discrepancies must be explained.

8. Sample Size and Statistical Methods

8.1. Determination of Sample Size

According to Cancer Statistics in China, the annual incidence of thyroid cancer is estimated to be 224,023 for 2022 (Xia et al. 2022) and 95% of those are differentiated thyroid cancers (DTC) (CTA 2020). The majority (96%) of DTC patients were at early stage at diagnose, and thus ~5% of DTC patients would finally progress into advanced or metastatic stage and need systemic treatment including patients had advanced or metastatic thyroid cancer and ineligible for surgery at diagnoses based on marketing research results. The *RET* fusion-positive tumor represents approximately 5.7-7.7% of these patients in China (Wang et al. 2020; Li et al. 2020). Therefore, the annual incidence of *RET* fusion-positive advanced or metastatic thyroid cancer requiring systemic therapy is estimated to be around 600-800 patients per year. As the RE*T* genetic testing rate of metastatic DCT patients was estimated to be 15% in China based on marketing research, and other factors besides the rarity of this disease that would further narrow down the potential patient size, such as patients' affordability and market uptake, the actual use of selpercatinib is expected to be small. The primary endpoint of this study was rwORR and the sample size calculation is based on primary endpoint. In the previous global clinical trial LIBRETTO-001, the ORR was 82.3% (95% CI, 65 to 93%) in patients with *RET* fusion-positive thyroid cancer (Sherman et al. 2021). While sorafenib is the first targeted drug approved in the world for the treatment of RAI-refractory, recurrent and metastatic differentiated thyroid cancer, with an ORR of 12.2% (Brose et al. 2014). Considering the rarity of this disease and other factors that would further narrow down the patient size, such as cost/affordability (no national insurance reimbursement), market uptake, the actual use of selpercatinib is expected to be small.

This study considered 12 patients with *RET* fusion-positive thyroid cancer who met the efficacy analysis. If the rwORR observed in this study sample was 41.7% (that is, 5 responders were observed in the 12 analysis patients. The confident level to be equal to or more than 5 responders from 12 patients were 99.98% based on the LIBRETTO-001 results, which is larger than 80%). The two-sided (lower) bound of the 95% confidence interval was 15.2% calculated using the Clopper-Pearson Exact Method, which was higher than the ORR of sorafenib. Assuming 20% drop-out rate of missing effectiveness evaluation or loss to follow-up in the real-world setting, this study plans to enrol 15[12/(1-20%)=15] patients with *RET* fusion-positive thyroid cancer.

8.2. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Any change to the data analysis methods described in this study protocol will require an amendment ONLY if it changes a principal feature of the study protocol. Any other change to the data analysis methods described in the study protocol and the justification for making the change will be described in the abbreviated study report or equivalent document.

In general, descriptive summary statistics will include:

- For categorical variables: number, number missing, frequency and percentage (with the percentage excluding the number missing in the denominator).

- For continuous variables: number, number missing, mean, median (25th and 75th percentiles), standard deviation, minimum, maximum.

The disposition of all patients who enter the study will be summarized. Patients' demographics and disease characteristics at baseline, will be summarized with descriptive analysis. Concomitant drug therapy will be provided as a listing by patient for all patients, and as a summary.

All medications will be coded to the generic preferred name according to the latest World Health Organization (WHO) drug dictionary. Medical history and AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

All statistical analysis related plans including calculation of study endpoints, presentation format, and content to be included in tables will be described in detail in the statistical analysis plan (SAP).

Additional exploratory analyses will be conducted as deemed appropriate. Analysis will be conducted using Statistical Application Software (SAS), Version 9.4 or a more recent version.

8.3. Limitations of the Research Methods

Small sample size: The relatively small sample size (see Section 8.1) will be a limitation for this study to draw any conclusion based on secondary and exploratory endpoint analysis. Therefore, the study results should be interpreted cautiously and is not proper to be generalizable to the whole patient population. Nevertheless, this observational study would provide an initial insight to increase the knowledge of the effectiveness and safety profile of selpercatinib under the routine clinical practice in China.

Remote visit: Due to impact of COVID-19, patient remote visit may be performed per investigator's decision. However, the outcomes from remote collection and in-person collection can yield disparate results, which will cause the potential bias. Any difference and bias would be discussed in the study report.

Missing data: This is an observational study that patients' treatments and assessment are not intervened and solely depends on the physician's routine clinical practice, it is possible that comparatively higher rate of missing data will be observed than in clinical trials.

8.4. Significance Levels and Multiplicity

Not applicable, due to the descriptive purposes of the study.

8.5. Data Management

8.5.1. Data Collection

A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning, and validation. Patient data are recorded on data forms. Investigators are responsible for the integrity of the data (that is, accuracy, completeness, legibility, and timeliness) reported to Lilly. Datasets and analytic programs will be kept on a secure server and archived according to Lilly's record retention

procedures. All patients who provide consent to release information and who fulfil the study population definition criteria and study entry criteria will be included in the analyses. For those patients who are lost to follow-up, or who drop out of the study, the analyses will include all data up to the point of their last data collection.

The participating physician or site personnel shall make every effort to contact the patients who are lost to follow-up to confirm survival and identify the reason for not being willing to participate within legal and ethical boundaries. Public sources may be searched for vital status information. If vital status is determined, this will be documented, and the patient will not be considered lost to follow-up. All available information in the patient's file through the date of last contact or visit should be entered in the eCRF for the lost to follow-up patients. The SAP will specify the size of patients that will be considered for purposes of endpoint assessment.

8.5.2. File Retention and Archiving

To enable evaluations and/or audits from regulatory authorities or the study sponsor, the investigator agrees to keep records, including the identity of all participating patients, all original signed consent-to-release information, copies of all eCRFs, SAE forms, source documents, and adequate documentation of relevant correspondence. The records should be retained by the physician according to local regulations or as specified in the study specific site contract, whichever is longer.

All patients who provide consent to release information and who fulfil the study population entry criteria will be included in the analyses. For those patients who are lost to follow-up or drop out of the study, the analyses will include all data up to the point of their last data collection.

8.6. Analyses

8.6.1. Primary Objective Analyses

The rwORR will be summarized using descriptive analysis, described in terms of frequencies and percentages, and provide a 95% CI.

8.6.2. Secondary Objective Analyses

Time-to-event analyses (rwPFS and rwDoR) will be performed using Kaplan-Meier estimates to calculate median and 95% CI and estimates at specific time points (e.g. 6 months, 12 months).

Patients who are alive and without documented PD as of a data analysis cut-off date will be right-censored. The censoring date will be determined from the date of last follow-up to the patient without progression.

rwDCR will be summarized using descriptive analysis, described in terms of frequencies and percentages, and provide a 95% CI.

8.6.3. Exploratory Analyses

AEs and SAEs will be summarized using descriptive analysis, described in terms of frequencies and percentages. If applicable, 95% confidence intervals for the proportion of AEs and SAEs will be calculated. The incidence of the AEs and SAEs will also be provided.

In addition, AEs and SAEs will be categorized and summarized by maximum severity and in relation to treatment with selpercatinib. Both AEs and SAEs are summarized by MedDRA system organ class and preferred term.

Selpercatinib treatment will be described including the prescribed dose, dose adjustments, reason for adjustments, using similar descriptive measures listed in Section 8.2. DoT will be analyzed using Kaplan-Meier estimates to calculate median and 95% CI.

8.6.4. Subgroup Analyses

Subgroup analyses may be performed for the effectiveness and safety by demographic and clinical characteristics, and treatment information. For example, the subgroup analysis by age will considered to be conducted: adult (≥18 years); juvenile (≥12 to <18 years).

Further details of subgroup analyses will be described in the SAP.

8.6.5. Interim analyses

The effectiveness and safety may be evaluated periodically according to regulatory request/requirement. Further details will be provided in the SAP.

8.7. Quality Control

Information recorded as part of routine clinical practice will be transcribed to an eCRF. Computerised handling of the data by vendor may generate data queries to which the participating physician is obliged to respond by confirming or modifying the data questioned.

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide written or electronic instructional material to the study sites, as appropriate.
- sponsor start-up training to instruct the physicians and study coordinators on the protocol and completion of the eCRFs.
- make periodic visits to the study site.
- be available for consultation and be in contact with the study site personnel by mail, telephone, and/or fax.
- review and evaluate eCRF data and use standard computer edit checks to detect errors in data collection.
- conduct a quality review of the database.

In addition, data collection and validation procedures will be detailed in appropriate operational documents.

Data quality control will be performed on active sites (that have enrolled at least 1 patient). Quality control will be performed by qualified, designated personnel in each site.

9. Management and Reporting of Adverse Events/Adverse Reactions

9.1. Primary Data Collection Study

The study personnel will collect via electronic data entry all protocol-defined adverse events (AEs), including all associated fatal outcomes, occurring in temporal association with Lilly product that are under evaluation as defined in this protocol. The protocol-defined AEs include All AEs. All AEs arising from the initiation of selpercatinib treatment to 24 months if still on selpercatinib treatment, or 30 days after treatment discontinuation, or the end of overall study follow-up duration, whichever occurs earlier, will be recorded.

Adverse events collected will be summarized in the final study report.

Study personnel are requested to report any suspected adverse reactions (SARs) with Lilly products not under evaluation in this protocol or SARs with non-Lilly products to the appropriate party (for example, regulators or the marketing authorization holder) as they would in normal practice.

Study personnel are not obligated to actively collect AEs or SAEs in patients after completion the safety observational period (from initiation of selpercatinib to 24 months if still on selpercatinib treatment, or 30 days after treatment discontinuation, or the end of overall study follow-up duration, whichever occurs earlier). When patients completed the safety observational period, the AE reporting should follow the normal practice. However, if the study personnel learn of any SAE, including death, at any time after the patient has discontinued from the study and the event is considered reasonably possibly related to the Lilly product under evaluation, the study personnel must promptly notify Lilly.

9.1.1. Serious Adverse Events

The study personnel will report to Lilly or its designee any protocol-defined SAE arising in temporal association with the Lilly product(s) under evaluation within 24 hours of awareness of the event via a sponsor-approved method. Reports issued via telephone are to be immediately followed with official notification on study-specific SAE forms. A protocol-defined SAE is any AE from this study that results in one of the following outcomes:

- Death
- Initial or prolonged inpatient hospitalization
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Or is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above.

9.1.2. Nonserious Adverse Events

The study personnel will record any **nonserious** protocol-defined AE arising in temporal association with the Lilly product under evaluation within 30 days of awareness of the event via EDC system.

9.2. Product Complaints

When a condition related to the selpercatinib necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

Lilly collects product complaints on investigational products, medical devices and drug delivery systems used in medical research studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Complaints related to concomitant drug/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

Researchers are instructed to report product complaints as they would for products in the marketplace.

10. Participant Consent to Release Information, Ethical Review, and Regulatory Considerations

10.1. Participant Consent to Release Information

This is an observational research program and does not impose any form of intervention on the investigator. Hence, the assessment and treatment of the participants is based solely on the investigator's routine or usual practice in the provision of care to participants with advanced or metastatic *RET* fusion-positive thyroid cancer.

As this is an observational study and does not impose any form of intervention, the participant/legal representative will provide authorization for the uses and disclosures of their personal health information as described in the study Consent to Release Information. This consent covers the collection and release of data regarding treatment and its outcomes for the entire period of the study. The process of obtaining consent will be in compliance with all applicable regulations and ICH requirements. The confidential nature of the participant information will be maintained.

10.2. Ethical Review and Regulatory Considerations

Observational studies will be submitted to ethical review boards (ERBs) for approval or waivers sought whenever required by local law. Regulatory authorities will be notified, and approval sought as required by local laws and regulations. Progress reports will be submitted to ERBs and regulatory authorities as required by local laws and regulations.

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Pharmacoepidemiology Practices (GPPs) and applicable laws and regulations of the country or countries where the study is being conducted, as appropriate.

11. Record Keeping, Data Reporting, Data Quality Assurance, and Publications

Participant data are recorded on eCRF. Investigators are responsible for the integrity of the data (that is, accuracy, completeness, legibility, and timeliness) reported to Lilly. The investigator follows local laws and regulations or institutional practices for document retention.

All information about this observational study and individual participant medical information resulting from this study are considered confidential, and disclosure to third parties is prohibited except for regulatory authorities and as applicable by law. Data emerging from this study may be used for submission to the regulatory authorities per the regulatory requirement. Publications may result from this study.

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Attachment 1. Observational Study Protocol Data Collection Schedule

Data Collection Schedule, J2G-GH-B003 Observational Study Protocol

Collect data on the following as indicated:

Data Collection Schedule[a]	Screening & Baseline		During treatment with selpercatinib[b] (Cycle C=28 days)	End of treatment with selpercatinib[c]	
	V1		V2-Vn	Short-term follow-up (V201)	Long-term follow-up (V202)
	Day-28 to C1D1	C1D1 to C1D1 (+7 days)	C1to C24 (±4 weeks)	30±7days	24±4 weeks
Informed Consent[d]	X				
Inclusion/Exclusion Evaluation	X				
Demographics[e]	X				
Diagnosis of *RET* alterations	X[f]				
Medical history and prior anti-cancer treatment	X[f]				
selpercatinib administration[g]		→	→		
Prior therapies[h] and concomitant medications	→	→	→		
Vital signs[i] and ECOG PS	X[j]		X[k]		
Laboratory Test and ECG[l]	X[j]		X[k]		
Tumor Evaluation[m]	X		→	→	→
Survival assessment			→	→	→
Adverse Event		→	→	→	

Abbreviations: C = cycle; D = day; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ECG = electrocardiogram; RET = rearranged in transfection; V = visit.

a. The data collection schedule is specified in the table, but the actual visit time, frequency and examination items will be determined by the investigator according to routine clinical practice. Patient remote visit may be performed per investigator's decision.

b. Recommend conducting the first data collection in 2 months after treatment initiation, and every 3 months in the first year, and then every 6 months in the second year till 24 months during treatment. If the patient does not return to the study center, the post-treatment visit can be conducted by telephone visit.

c. Follow up until death of the patient, withdrawal of informed consent to continue participating in the study, lost to follow-up, or the end of the entire study follow-up period (whichever occurs earlier). The overall study follow-up duration would be up to 24 months from the first patient initiating selpercatinib treatment or up to 6

months after the last patient initiating selpercatinib treatment, whichever comes later. If the patient does not return to the study center, the post-treatment visit can be conducted by telephone visit.

d. Informed consent must be obtained from the patient/legal representative prior to performing any protocol-related procedures. E-Consent may be used per investigators' decision after EC approval obtained.
e. Include year of birth, sex (female/male), weight, height, etc.
f. Include all relevant information (not limited to 28 days prior to C1D1).
g. Include treatment information of selpercatinib: start date, current status (ongoing or discontinued [including discontinuation date]), dosage and administration details, dose modification (including reason for modification), and dose interruption and omission.
h. Collect medication information except for antitumor therapies within 14 days prior to C1D1.
i. Include blood pressure, heart rate, etc.
j. Collect the most recent data before selpercatinib treatment.
k. Collect all the evaluation records within each visit window.
l. Include hematology profile (such as leukocytes, neutrophils, platelets, and hemoglobin), serum biochemical profile (such as alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, direct bilirubin, serum creatinine, and electrolyte), biochemical markers of remission (thyroglobulin), and electrocardiogram.
m. Tumor response should be assessed by the investigators confirmed radiologically (using criteria such as RECIST guideline [Eisenhauer 2009]) or confirmed by the physicians based on clinical assessments, as documented in the patient's chart or notes. Add if available, imaging or report at baseline should be collected for subsequent treatment response evaluation. After the end of selpercatinib treatment, only the tumor assessments of patients who discontinued treatment for reasons other than PD (eg, AE, non-compliance, etc.) will be collected until PD, withdraw informed consent, loss to follow-up, death, or start new anticancer therapy.

Attachment 2. Examples of Multikinase Inhibitors (MKIs) with Anti-RET Activity

Examples of MKIs with Anti-RET Activity but not *RET*-targeted:

Multikinase Inhibitors
Cabozantinib
Vandetanib
Alectinib
Lenvatinib
Ponatinib
Regorafenib
Sunitinib
Sorafenib
Motesanib
sitravatinib (MGCD516)
Anlotinib
Apatinib

Attachment 3. Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) Guidelines for Tumor Response

RECIST Version 1.1

Disease Response Criteria for Target and Non-Target Lesions	
Evaluation of Target Lesions	
Complete Response (CR):	Disappearance of all target lesions. Any pathologic nodes (whether target or non-target lesions) must have a reduction in short axis diameter (SAD) to less than 10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the diameters (SOD) (LD for non-nodal lesions and SAD for nodal lesions) of target lesions, taking as reference the baseline sum LD.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest sum on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5.0 mm. (Note: the appearance of one or more new lesions is also considered progression).
Evaluation of Non-Target Lesions	
Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level.
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Abbreviations: LD = longest diameter.

Source: Available at: https://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf.

Attachment 4. Eastern Cooperative Oncology Group (ECOG) Performance Status

Activity Status	Description
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken et al. 1982.

Attachment 5. NCI-CTCAE version 5.0 criteria

Severity (via CTCAE version 5.0)

Grade 1	• Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	• Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	• Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	• Life-threatening consequences; urgent intervention indicated.
Grade 5	• Death related to AE. • Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

A Semi-colon indicates "or" within the description of the grade.
Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than 5 options for grade selection. ADL (Activities of Daily Living):
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Signature Page for VV-CLIN-074221 v1.0

Approval	Anasofia Afonso Global Patient Safety 22-Dec-2022 16:23:02 GMT+0000

Approval	Hai Dong Chi Medical Director 03-Jan-2023 09:33:50 GMT+0000

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