Summary Table of Study Protocol

Title	Real World Evaluation of Sotorasib among Chinese Non-Small Cell Lung Cancer Patients
Protocol version identifier	20240175, Original Protocol, Version 1.0
Date of last version of the protocol	27 March 2025
EU Post Authorization Study Register No	Not Applicable (NA)
Active Substance	Sotorasib
Medicinal Product	LUMAKRAS® (sotorasib)
Device	Not Applicable (NA)
Product Reference	AMG 510
Procedure Number	Not Applicable (NA)
Joint PASS	No
Research Question and Objectives	Among Chinese patients with *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC, who have received at least 1 prior systemic therapy: • Primary Objective: ○ Characterize the safety profile of sotorasib. • Secondary Objective: ○ Describe real-world overall survival (OS) of sotorasib. • Exploratory Objective: ■ CCI [redacted] ■ [redacted]
Country of Study	China
Authors	PPD [redacted]

Marketing Authorization Holder

Marketing Authorization Holder(s)	Amgen Inc
Marketing Authorization Holder Contact	One Amgen Center Drive Thousand Oaks, CA 91320 USA 1-805-447-1000

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

Confidentiality Notice

If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: United States, 1-800-77-AMGEN. Amgen's general number in the United States (1-805-447-1000).

Investigator's Agreement

I have read the attached protocol entitled Real World Evaluation of Sotorasib among Chinese Non-Small Cell Lung Cancer Patients, dated 27 March 2025, and agree to abide by all provisions set forth therein.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature

Name of Investigator: Date (DD Month YYYY)

Title:

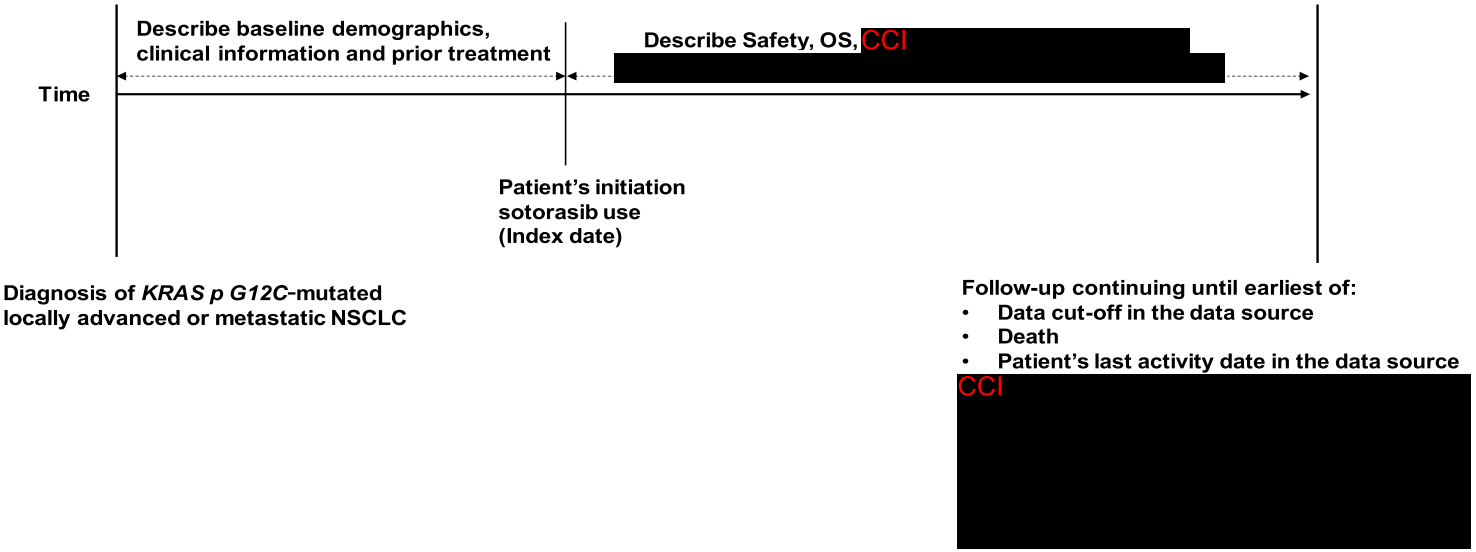
Name of Hospital/Site:

Address/City/State/Country:

Phone Number:

Email:

Study Design Schema



NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival

Note: As the Hong Kong Special Administrative Region (SAR) Clinical Data Analysis and Reporting System (CDARS) database is a closed-loop database with linkage to the regional death registry, patients without evidence of death in the CDARS database by the data cut-off date were considered alive, and their last activity date will be same as the cut-off date.

1. Table of Contents

List of Tables

List of Figures

N/A

List of Appendices

2. List of Abbreviations

AE	Adverse Events
ALK	Anaplastic lymphoma kinase
ALT	alkaline phosphatase
ALP	alanine aminotransferase
AST	aspartate aminotransferase
BMI	Body mass index
CDARS	Clinical Data Analysis and Reporting System
CDMS	Clinical Data management System
CMS	Clinical Management System
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
eDC	Electronic Data Capture (system)
EGFR	epithelial growth factor receptor
EMR	Electronic Medical Records
EPR	Electronic Patient Record
EU	European Union
ICF	Informed Consent Form
ICJME	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IRB	Institutional Review Board
KRAS	Kirsten rat sarcoma viral oncogene homolog (DNA)
MedDRA	Medical Dictionary for Regulatory Activities
NMPA	National Medical Products Administration
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
PASS	Post Authorization Safety Study
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
RAS	Rat sarcoma
SAR	Special Administrative Region
SMQ	Standardized MedDRA query
SOP	Standard Operating Procedure
TEAE	Treatment-emergent adverse event

3. Responsible Parties

Sponsor: Global Development, Amgen Inc

One Amgen Center Drive, Thousand Oaks, CA

The list of investigators is at Amgen and is available upon request.

4. Abstract

Study Title:

Real World Evaluation of Sotorasib among Chinese Non-Small Cell Lung Cancer Patients

- Study Background and Rationale

The United States FDA approved sotorasib in 2021, under accelerated approval based on response rate and duration of response, for the treatment of adult patients with *KRAS p.G12C*-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) who have received at least 1 prior systemic therapy. For this target population within the sotorasib arm of phase III trial (CodeBreak 200): the most common treatment related adverse events of grade 3 or worse were diarrhea (12% patients incidence), alanine aminotransferase (ALT) increase (8% incidence), and aspartate aminotransferase (AST) increase (5% incidence); the median overall survival (OS) was 10.6 months (95% CI 8.9-14.0); and the median progression-free survival (PFS) was 5.6 months (95% CI 4.3-7.8).

Sotorasib is approved for use in over 50 countries and administrative regions; including Hong Kong Special Administrative Region (SAR), Macao SAR, and Taiwan. While sotorasib is being developed in mainland China by participating in a phase III trial (CodeBreak 202), the BOAO Pilot Zone (Hainan Province, China) has permitted its clinical use since August 2021 for the FDA approved indication. This clinical use of sotorasib in regions of China provides an opportunity to add to the totality of evidence for the safety and real-world effectiveness of sotorasib among Chinese patients with NSCLC. RWE guidance documents were used to inform the planning, design and communication of this study (NMPA, 2020; NMPA, 2021; NMPA, 2023a; NMPA, 2023b; ICH, 2024).

- Study Feasibility

Study feasibility within each available data source in China was evaluated in terms of available infrastructure to support execution of a real-world study, accessible data, ethical and security requirements, coverage and accuracy of critical covariates, completeness of follow-up for outcomes, and sample size of the target patient population. Based upon this evaluation, data sources in BOAO Pilot Zone and Hong Kong SAR were selected to be the most relevant to address the study objectives.

- Objectives

Objectives	Endpoints
Primary	
• Characterize the safety profile of sotorasib.	• The patient incidence of adverse events (AE) after sotorasib initiation, including: ○ Treatment-emergent adverse events (TEAE) ○ Adverse event of interest, inclusive of hepatotoxicity, interstitial lung disease/pneumonitis, and renal toxicity ○ Treatment-related AEs ○ Treatment-related AEs of grade 3 or worse ○ Serious treatment-related AEs ○ Treatment-related AEs leading to treatment discontinuation ○ Treatment-related AEs leading to dose reduction ○ Treatment-related AEs leading to death
Secondary	
• Describe real-world OS of sotorasib	• OS from initial date of sotorasib use to date of death
Exploratory	
CCI [redacted]	

Hypothesis

Study objectives are descriptive in nature; no hypothesis will be tested.

- Study Design

The study design is a retrospective cohort followed longitudinally for safety and effectiveness endpoints, based upon review of medical charts.

- Study Population or Data Source

The target population is adult patients with *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC and previously treated with at least 1 prior systemic therapy that have received sotorasib treatment in either location of BOAO Pilot Zone and Hong Kong SAR.

In BOAO Pilot Zone, patients, often residing from across mainland China, need to be physically admitted to one of the several hospitals in BOAO Pilot Zone to receive sotorasib. The first hospitalization includes a complete medical history, radiology scans, tumor biomarker assessment, and liver and renal function tests to inform clinicians' decision to treat. As sotorasib is in the pre-registration program, the government requires close monitoring and reporting of safety events, which are well documented in the established hospital system. Hence, expectation that safety endpoints will be measured adequately in this study. As sotorasib is an oral medication taken daily until disease progression or unacceptable toxicity, patients need to physically return to the BOAO Pilot Zone hospital at least once per month initially, and every 3 months thereafter, to continue therapy. A case report form created for this study will be used to extract the relevant structured and unstructured data from the electronic heath record.

In Hong Kong SAR, the Clinical Data Analysis and Reporting System (CDARS) database will be used to identify patients treated with sotorasib at any public hospital. CDARS is a population-based database covering residents in Hong Kong SAR and can be linked to mortality records. Hence, the expectation that OS will be measured with complete follow-up. While the structure data within CDARS will provide most of the relevant data for study, the unstructured clinical notes within the electronic health record (Electronic Patient Record/Clinical Management System [EPR/CMS]) will also be used to augment information on key covariates.

- Summary of Patient Eligibility Criteria

Inclusion Criteria:

  - Adult (≥ 18 years) as of the index date.
  - *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC
  - Received at least 1 dose of sotorasib.
  - Receipt of at least 1 prior systemic therapy before use of sotorasib
  - Obtained informed consent form (ICF), if required.

Exclusion Criteria:

  - Documentation of being a non-Chinese ethnicity.

- Follow-up

Index date: sotorasib initiation date.

For objective of safety, CCI [redacted] follow-up per patient will continue through earliest date of:

- Last clinical activity in the data source
- Data cut-off in the data source:
  - BOAO Pilot Zone: Ethics Committee (EC) submission date (~ Q2 2025)
  - Hong Kong SAR: Data extraction cut-off date (~ Q3 2025)
- Death
- Last treatment with sotorasib + 30 days

As the Hong Kong SAR CDARS database is a closed-loop database with linkage to the regional deaths registry, patients without evidence of death in the CDARS database by the data cut-off date were considered alive, and their last activity date will be the same as the cut-off date.

For objective of OS, follow-up per patient will continue through earliest date of last clinical activity in the data source, data cut-off in the data source, or death.

CCI [redacted]

- Variables

Outcomes:

- Primary: The patient incidence of AEs after sotorasib initiation.
- Secondary: OS from clinician notes in electronic health record and linkage to mortality records (where available).
- Exploratory: CCI [redacted]
- CCI [redacted]

Exposure:

- Use of sotorasib

Covariates

- Key demographic, clinical characteristics, and pathology covariates including and not limited to age, sex, smoking status, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) performance status, histology, tumor stage, programmed death-ligand 1 (PD-L1) protein expression, presence of tumor mutations or rearrangements, laboratory test, electrocardiogram (ECG) and radiology, prior systemic treatments, brain metastases (if information available), prior lines of systemic therapy, and concomitant medications.

- Study Sample Size

By the time of data cut-off, an estimated about 100 and 15 patients will have been treated with sotorasib and eligible for study inclusion from BOAO Pilot Zone and Hong Kong SAR, respectively. For a sample size of 115 patients and the observation of a proportion of 50% patients with an endpoint the largest level of margin of error (indicating the lowest level of precision) is ± 9.14%.

- Data Analysis

Frequencies will be presented for categorical demographic, clinical, and pathological variables. Descriptive statistics (mean, median, standard deviation, and range) will be presented for continuous variables.

The patient incidence of AEs will be summarized by count and proportions, specifically the proportion of patients experiencing AEs relative to the total number of patients.

Median OS and PFS, along with the corresponding 95% confidence intervals (CIs) will be calculated using Kaplan-Meier estimates. The estimated survival probabilities, along with the corresponding 95% CIs will be presented for patients at 6 and 12 months.

CCI [redacted]

5. Amendments and Updates

None

6. Rationale and Background

6.1 Diseases and Therapeutic Area

Lung cancer is the leading cause of cancer death worldwide (Sung et al, 2021). In 2022, an estimated 1 060 600 new cases of lung cancer and 733 300 people died in China (Han et al, 2024). The 5-year relative survival rate for lung cancer is approximately 19.7% (Zeng et al, 2018).

The RAS proto-oncogene has been identified as an oncogenic driver of tumorigenesis in several cancers, including NSCLC. Different tumor types are associated with mutations in certain isoforms of *RAS*, with KRAS being the most frequently mutated isoform in most cancers (Prior et al, 2012). The *KRAS p.G12C*-mutation is estimated to occur in approximately 13% of lung adenocarcinoma (including NSCLC), 3% of colorectal cancer , and 1% to 2% of numerous other solid tumors (including pancreatic, endometrial, bladder, ovarian, and small cell lung tumors) in the western population (The AACR Project GENIE Consortium, 2017; Biernacka et al, 2016; Neumann et al, 2009). *KRAS p.G12C*-mutation is less prevalent in the Asian population compared to the Western population. It was estimated that the prevalence of *KRAS p.G12C*-mutation ranges from 3% to 4.6% in Chinese NSLSC (Liu SY et al, 2020; Liu Y et al, 2021; Loong et al, 2020; Chen et al, 2022).

Patients with stage VI or advanced stage IIIB/C NSCLC are usually treated in the first line setting with platinum-based doublet therapy and/or checkpoint inhibitors either alone or in combination. Patients whose tumors have actionable mutations or alterations (eg, epithelial growth factor receptor [EGFR], anaplastic lymphoma kinase [ALK], ROS, and BRAF) will receive targeted therapies directed at these specific molecular targets (Ettinger et al, 2022).

In the 2L+ setting for advanced NSCLC in China, patients are typically treated with docetaxel, pemetrexed, or erlotinib (Oncology Society of Chinese Medical Association, 2023). Only 1 *KRAS p.G12C* inhibitor, fulzerasib, received conditional approval by National Medical Products Administration (NMPA) for the treatment of *KRAS p.G12C*-mutated NSCLC in August 2024 in China, although it has not been made commercially available as of September 2024 (NMPA 2024).

6.2 Rationale

In the single-arm phase II trial CodeBreaK 100 for patients with *KRAS p.G12C*–mutated advanced NSCLC previously treated with standard therapies, the median OS was 12.5 months (95% CI, 10.0 to not evaluable), with treatment-related AEs occurring in 69.8% of patients, including grade 3 events in 19.8% of patients (Skoulidis et al, 2021). In the phase III trial CodeBreak 200 comparing sotorasib with docetaxel (first randomized Phase 3 clinical trial of a *KRAS p.G12C* inhibitor) in patients with advanced NSCLC who had progressed after prior platinum-based chemotherapy and a programmed cell death 1 (PD-1) or programmed death-ligand 1(PD-L1) inhibitor,

sotorasib demonstrated good tolerability, with fewer grade 3 or worse events (33% vs. 40%) and fewer serious treatment-related AEs compared to docetaxel (11% vs. 23%), along with better PFS (5.6 months [95% CI 4.3–7.8] vs 4.5 months [3.0-5.7]) and similar OS compared to the docetaxel group (10.6 months [95% CI 8.9-14.0] vs 11.3 months [95% CI 9.0–14.9]). Consistent findings were demonstrated in RWE studies (Thummalapalli R et al, 2023; de Langen AJ et al, 2023), providing valuable context for the results of the current study.

On May 28, 2021, sotorasib was granted accelerated approval in the US by the FDA for adult patients with *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC who have received at least 1 prior systemic therapy (de Langen AJ et al, 2023).

Within the Greater China region, of Chinese population, sotorasib was approved in Hong Kong on April 29, 2022, with indication as monotherapy for the treatment of adult patients with *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC, who have progressed on, or are intolerant to, platinum-based chemotherapy and/or anti-PD-1/LD-L1 immunotherapy. Subsequently, it was approved in Taiwan on June 14, 2022, with indication for the treatment of adult patients with *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC who have received at least 1 prior systemic therapy. Sotorasib has not been approved in mainland China but has been used in BOAO Pilot Zone (Hainan Province, China) since August 2021 through pre-registration program in BOAO Pilot Zone, strictly following FDA approved label. There are no published data on the safety and effectiveness of sotorasib among Chinese patients in real-world and clinical settings. We aim to characterize the safety profile, real-world OS (Lasiter et al, 2022) CCI (Khozin et al, 2019) of sotorasib, CCI [redacted]

6.3 Feasibility (fit-for-purpose evaluation)

Active and accessible data:

As introduced in Section 6.2, sotorasib became available in BOAO Pilot Zone in August 2021 through a pre-registration program. Sotorasib will be continuously available at BOAO Pilot Zone before data cut-off (~Q2 2025). BOAO Pilot Zone is the only place in mainland China with sotorasib access and thus enable a complete capture of all mainland Chinese patients treated with sotorasib in real-world and clinical settings.

Patient-level data in BOAO Pilot Zone will be available and submitted to enable a regulatory authority to reproduce the results.

The Hong Kong SAR Clinical Data Analysis and Reporting System (CDARS) database will be used to extract patients treated with sotorasib in Hong Kong SAR. Clinical Data Analysis and Reporting System is a population-based database with medical records covering residents in Hong Kong SAR who received care from any public hospital. It also contains data on causes of death through its internal linkage to regional deaths registry and have been used in various disease area including lung cancer (Philip et al, 2024). Academic researchers in Hong Kong SAR will be able to apply and access the database. The database is used for efficiency; however, the information is drawn from detailed patient records, ensuring that the analysis is based on comprehensive and accurate medical chart data. Details of data sources are provided in Section 8.4.

Ethical and security requirements

The study will follow requirements of the governance and sites. All data extracted will be anonymized. The study protocol will be reviewed by the IRB of each site in BOAO Pilot Zone and Hong Kong University in Hong Kong SAR. In addition to governance and the IRB, the study will comply with Amgen's global standard operation procedures and technical governance for observational research. The International collaboration Human Genetics Resources Administration of China application will be submitted for BOAO Pilot Zone. Details are provided in Section 9.

Coverage of critical variables

The electronic health record database in BOAO Pilot Zone participating hospitals contain critical data relevant to the research question, for example the exposure of sotorasib, AEs, effectiveness outcomes, and key covariates. The electronic medical record (EMR) system in Hong Kong SAR contains both structured data, including demographic information, diagnosis, prescription records, procedure, hospital stay, discharge information, and unstructured data, including genetic testing results, radiographical and imaging exam results and additional patient information. Critical variables are covered and will be extracted to the extent possible.

Accuracy of the definition of exposure, outcomes, and covariates

Eligible patients need to be physically at BOAO Pilot Zone hospitals to receive treatments, enabling complete sotorasib exposure assessment in electronic health record databases. In addition, as advanced NSCLC is a life-threating disease which

needs close support from physicians specialized in treating NSCLC, it is expected that patients remain at same site in BOAO Pilot Zone for treatment. As sotorasib is used through the pre-registration program, local government authorities require close monitoring and reporting of safety events which were well documented in hospitals by physicians. Besides, physicians were reported to proactively follow-up with patients and document patients' treatment information, follow-up evaluations (both within and outside BOAO Pilot Zone), safety events, treatment outcome and discontinuation in hospital electronic health record database. These real-time data sources will be used to extract comprehensive and accurate outcome and key covariates.

Data will be verified using the data source by the study monitor and reviewed for consistency. All data extracted will be approved by the investigator at the investigational center. Adverse event grades and relationship to sotorasib may be unavailable or unconfirmable for some patients due to limitations in the available information. The level of missingness will be described and results related with grade will be interpreted with caution.

Sample size

The feasibility check indicates that at the data cut-off, approximately 100 sotorasib treated patients in BOAO Pilot Zone, and about 15 patients in Hong Kong SAR, will be eligible for inclusion. Details of sample size calculation are provided in Section 8.5.

Representativeness of the target population

All patients meeting the eligible criteria in BOAO Pilot Zone and in public hospitals in Hong Kong SAR will be included, unless demonstrated operationally unfeasible. This approach will enhance the representativeness of the study's target population across China.

Taiwan was not selected because sotorasib is not reimbursed in Taiwan and individual site chart review of a marketed medication won't capture information outside of that individual site (ie, concern of lost follow up and missing death information).

6.4 Statistical Inference (Estimation)

The objectives of this study are descriptive in nature and will only include estimations, no hypotheses will be tested.

7. Research Question and Objectives

7.1 Primary

To characterize the safety profile of sotorasib in Chinese patients with *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC, who have received at least 1 prior systemic therapy.

7.2 Secondary

To describe real-world OS of sotorasib in Chinese patients with *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC, who have received at least 1 prior systemic therapy.

7.3 Exploratory

CCI [redacted]

8. Research Methods

8.1 Study Design

This is a retrospective medical chart review study of Chinese patients treated with sotorasib in real-world and clinical settings in BOAO Pilot Zone and Hong Kong SAR.

8.2 Setting and Study Population

Two regions will be included in the study, ie, BOAO Pilot Zone and Hong Kong SAR.

Until data cut-off date, approximately 100 sotorasib treated patients in Hainan BOAO Pilot Zone, and about 15 patients in Hong Kong SAR, will be eligible for medical chart review. Details of data sources are provided in Section 8.4.

8.2.1 Study Period

The study eligibility period extends from the patients' index date (ie, the initiation of sotorasib) to the end of study period, defined as the earliest occurrence of patient's last activity date in the data source, data cut-off date or death.

The first available sotorasib use in BOAO Pilot Zone is around August 2021 through a pre-registration program. Specifically, sotorasib was included in the following hospitals'

drug lists and available for prescription: Ruijin Hainan Hospital in July 2022; BOAO Super Hospital in August 2021; BOAO Hengda Hospital in November 2021; and BOAO future Hospital in January 2022. The data cut-off will be the EC submission date (~ Q2 2025).

Sotorasib was approved in Hong Kong on April 29, 2022. The eligible treatment should occur after April 29, 2022. The data cut-off will be the date of data extraction (~ Q3 2025).

8.2.2 Selection and Number of Sites

All four hospitals in BOAO Pilot Zone providing treatment of sotorasib will be included unless demonstrated operationally unfeasible (eg, Ruijin Hainan Hospital, BOAO Super Hospital, BOAO Hengda Hospital, and BOAO Future Hospital).

The Hong Kong SAR CDARS database covering residents in Hong Kong SAR will be used to extract data of sotorasib treated patients. Details of data sources are provided in Section 8.4.

8.2.3 Patient Eligibility

Eligibility criteria will be evaluated during screening and reasons for ineligibility will be extracted in the electronic case report form (eCRF).

8.2.3.1 Inclusion Criteria

- Adult (≥ 18 years) as of the index date
- *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC
- Received at least 1 dose of sotorasib
- Receipt of at least 1 prior systemic therapy before use of sotorasib
- Obtained ICF, if required

8.2.3.2 Exclusion Criteria

Documentation of being a non-Chinese ethnicity.

8.2.4 Matching

Not applicable

8.2.5 Baseline Period

The baseline period is defined as the period starting from diagnosis to the index date. Data ranging from date of diagnosis of advanced NSCLC until the start of index therapy

will be extracted, including baseline demographics, clinical information, and treatments (see details in Section 8.3.3).

8.2.6 Study Follow-up

As the Hong Kong SAR CDARS database is a closed-loop database with linkage to the regional deaths registry, patients without evidence of death in the CDARS database by the data cut-off date were considered alive, and their last activity date will be the same as the cut-off date.

CCI [redacted]

For the objective of OS, follow-up per patient will continue through earliest date of last clinical activity in the data source, data cut-off in the data source, or death.

CCI [redacted]

8.3 Variables

8.3.1 Exposure Assessment

The exposure variable is receipt of sotorasib. Patients will be considered as exposed from time of their initial date of sotorasib administration through treatment discontinuation. If the status of treatment is unclear at the end of the study, the last date of treatment will be considered as either the date of the last prescription in the database plus the corresponding dosing time from that prescription, or the end of the study, whichever occurs earlier. Treatment information of sotorasib will be extracted through follow-up. Detailed sotorasib treatment information to be extracted include:

- Treatment initiation date
- Treatment duration
- Dose and dosing schedule
- Dose reduction and modification, including dates and reasons.
- Treatment interruption, time interval from interruption to re-initiation, and subsequent re-initiation of treatment (if any)

- Treatment discontinuation, including date and reason (if any)

8.3.2 Outcome Assessment

Safety Outcomes

In BOAO Pilot Zone, the AEs recorded in the electronic health record database throughout the study period will be documented and analyzed. Detailed information in medical records including vital signs, concomitant treatments, results of routine laboratory testing, ECG, and radiology will be reviewed to verify these AEs. Severity grade of AEs will be further verified by investigators according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (CTCAE v5.0).

The patient incidence of AE after sotorasib initiation, including:

- TEAE
- Adverse event of interest, inclusive of hepatotoxicity, interstitial lung disease/pneumonitis, and renal toxicity
- Treatment-related AEs
- Treatment-related AEs of grade 3 or worse
- Serious treatment-related AEs
- Treatment-related AEs leading to treatment discontinuation
- Treatment-related AEs leading to dose reduction
- Treatment-related AEs leading to death

In Hong Kong SAR CDARS database, only adverse event of interest, inclusive of hepatotoxicity, interstitial lung disease/pneumonitis, and renal toxicity will be documented and analyzed. Each event of interest is a grouping of individual preferred terms determined using the following standardized MedDRA queries (SMQs): drug-related hepatic disorders – comprehensive search (SMQ narrow) for hepatotoxicity; interstitial lung disease (SMQ narrow) for ILD/pneumonitis; and acute renal failure (SMQ narrow) for renal toxicity. Medical records including diagnosis, vital signs, concomitant treatments, results of routine laboratory testing, ECG, and radiology will be reviewed to identify and verify AE. Detailed testing and exams to review will be further clarified in the statistical analysis plan and eCRF.

OS

- OS: The time from the index date to death from any cause. Patients without evidence of death at data cutoff will be right-censored at their last activity date.

CCI

- [redacted]
- [redacted]

[redacted]

- [redacted]

8.3.3 Covariate Assessment

Covariates are needed to understand the generalizability of study results. Covariates will be assessed during the baseline period. For covariates that can change over time the value at index date will be used; however, if unavailable at index date then the date most proximal to (preceding) index date will be used.

- Demographic and clinical characteristics
  - Age in years at index date
  - Sex (male, female, unknown)
  - Smoking status (current smoker, former smoker, never smoker, unknown/not documented) at index date
  - BMI in kg/m^2 at index date
  - ECOG performance score (0, 1, 2, 3, 4, missing/unknown) at index date
  - PD-L1 tested (yes, no)
  - PD-L1 expression, among tested (percent of positive tumor cells for the sample by PD-L1 staining/testing: $< 1\%$, 1 - $< 50\%$, $\geq 50\%$, or no valid test result)
  - Lab test (ie, blood routine test, urine routine test, blood biochemistry, etc.), ECG, and radiology at baseline

- Prescence of brain metastases (if information is available)
- Prior lines of therapy
- Concomitant medications and comorbidities

- Diagnosis and tumor-related characteristics
  - Time since advanced NSCLC diagnosis
  - Stage at sotorasib initiation (American Joint Committee on Cancer staging; Stage 0, 1, 2, 3, 4, unknown) (further granularity of staging data may be available)
  - Histology (non-squamous cell carcinoma including adenocarcinoma, large-cell carcinoma, others; squamous cell carcinoma; not otherwise specified)
- Tumor specimen-related characteristics
  - Presence of actionable gene alterations: mutations or re-arrangements (eg, ALK, EGFR, ROS proto-oncogene 1, BRAF)
- Treatment-related characteristics
  - Type of regimen sotorasib is used as (eg, monotherapy, combination therapy)
  - Treatment patterns: Available treatment history from site records will be extracted on all patients. Prior treatment history will include systemic anticancer treatments which are generally grouped as chemotherapies, targeted therapies, immunotherapies and others with examples listed below:
    - Chemotherapy
      - Platinum-based chemotherapy
    - Targeted therapy (eg, anti-EGFR, etc.)
    - Immunotherapy
      - PD-1/PD-L1 checkpoint inhibitors
    - Others

8.3.4 Validity and Reliability

In BOAO Pilot Zone, both structured and unstructured data elements will be extracted and validated. Any suspected data abstraction errors will be checked, confirmed or corrected with the clinical investigators responsible for the study operation, by checking the original copy. Unstructured data, which include details not directly captured in a

structured electronic health record field, such as description of AEs in the medical records will require some level of manual abstraction. All abstractors will undergo systematic training before performing data extraction. Besides, key information such as grade of AEs will be verified by investigators.

In Hong Kong SAR, the CDARS database has been used to conduct high quality real-world studies (Chan et al, 2015; Chan et al, 2016; Lau et al, 2017; Man et al, 2017; Wong et al, 2016). Data validation has demonstrated high coding accuracy in CDARS (Chan et al, 2015; Chan et al, 2016; Wong et al, 2016).

8.4 Data Sources

In BOAO Pilot Zone, patients, often residing from across mainland China, need to be physically admitted to one of the several hospitals in BOAO Pilot Zone to receive sotorasib. The first hospitalization includes a complete medical history, radiology scans, tumor biomarker assessment, and liver and renal function tests to inform clinicians' decision to treat. As sotorasib is in the pre-registration program, the government requires close monitoring and reporting of safety events, which are well documented in the established hospital system. Hence, expectation that safety endpoints will be measured adequately in this study. As sotorasib is an oral medication taken daily until disease progression or unacceptable toxicity, patients need to physically return to the BOAO Pilot Zone hospital at least once per month initially, and every 3 months thereafter based on physician's assessment and justification, to continue therapy. Patients seeking refills require recent radiology results, organ function evaluation etc. reassessment. Refills can be initiated with online evaluations and subsequently processed through outpatient clinics at hospitals in Hainan. Reports from Tier A hospitals across China are accepted. A case report form created for this study will be used to extract the relevant structured and unstructured data from the electronic heath record.

In Hong Kong SAR, this study will be using the electronic health records of the CDARS database managed by the Hong Kong Hospital Authority, a statutory body in charge of all public hospitals and their ambulatory clinics in Hong Kong SAR. Anonymized patient data are transferred daily to CDARS for audit purposes from the clinical management system (CMS) of the Hospital Authority, which contains medical records including: demographic information, diagnoses, prescription records, laboratory tests, accident and emergency attendance, outpatient clinics, hospital stay, and discharge information of patients since 1993. It also contains data on causes of death through its internal linkage

to regional deaths registry from the Immigration Department. Hence, expectation that OS will be measured with complete follow-up. A unique reference number is assigned to each patient for identification and data retrieval purposes. The structure data within CDARS will provide most of the relevant data for study, the unstructured clinical notes within the electronic health record (Electronic Patient Record/Clinical Management System [EPR/CMS]) will also be used to augment information on key covariates. Electronic patient record (EPR) consolidates individual patient health records from various sources, including hospitals, clinics, and primary care providers, into a single electronic record, providing a comprehensive view of a patient's medical history.

8.5 Study Sample Size

This is a descriptive study in which patient-level data on safety, OS, CCI [redacted] By the time of data cut-off, there will be approximately 100 sotorasib treated patients in BOAO Pilot Zone assuming all sites are eligible, and about 15 patients in Hong Kong SAR, will be eligible for enrollment.

The estimation precision of parameters is provided based on the preliminary sample count of all patients treated with sotorasib in BOAO Pilot Zone and Hong Kong SAR. The formular, based on the normal approximation to the binomial distribution, for calculating the precision (ie, margin of error, which is represented by one half the desired width of the confidence interval) given a proportion and sample size is as the following:

$$e = \sqrt{\frac{px\,(1-p)x\,(Z_{1-\frac{\alpha}{2}})^2}{n}}$$

Where P is the expected proportion of interest, n is the sample size, and $Z_{1-\frac{\alpha}{2}}$ is the standard normal Z value corresponding to a cumulative probability of $(1-\frac{\alpha}{2})$ （eg, if α= 0.05 then Z=1.96). The following table (Table 1) provides the estimated precision based on the sample size of patients who received sotorasib (N = 115, tentatively) and various proportions of interest.

Table 1. Precision based on the sample size by various proportions

Proportion (1-proportion)	Sample size of patients	The margin of error (absolute precision)
50% (50%)	115	9.14%
40% (60%)	115	8.95%
30% (70%)	115	8.38%
20% (80%)	115	7.31%
10% (90%)	115	5.48%

As the proportion of interest (p) (eg, proportion of treatment-related AEs of grade 3 or worse) in this study is not known in advance, we consider the proportion to be 50% (maximum uncertainty). Such an assumption yields the most conservative, ie, the largest level of margin of error (indicating the lowest level of precision), with is ± 9.14%.

The sample size of patients treated with sotorasib will be confirmed during data cleaning and data analysis phase.

8.6 Data Management

BOAO Pilot Zone

Data relevant for the study will be extracted in the eCRF specifically designed for this study. Electronic case report forms must be completed for each patient enrolled in the study. All data recorded will be anonymized. The data extracted on the eCRFs will be captured in a clinical data management system (CDMS)/electronic data capture (eDC). The CDSM/eDC will be fully validated to ensure that it meets the scientific, regulatory, and logistical requirements for the study before it is used to capture data from this study. Before using the CDMS/eDC, all users will receive training on the system and study-specific training. Data will be extracted at the investigational center by appropriately designated and trained personnel. Data will be verified using the data source by the study monitor and reviewed for consistency by data curation using both automated logical checks and manual review. All data extracted will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

All medical and health related terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Medical and health related terms include AEs, medical procedures, clinical characteristics, clinical diagnosis, names and qualitative results of laboratory tests, etc. All prior and ongoing therapy and medications will be coded according to the Anatomical Therapeutic Chemical Classification System based on generic names. Other social-economic characteristics and geospatial information are complicated according to dictionaries published by the government.

The processes for database curation are consistent across data sources. Data extraction and analysis will be performed according to the applicable practices of data vendor's and Amgen's and will be performed by dedicated personnel trained to work for this study. These personnel will be responsible for data curation, accuracy, quality, completeness, and internal consistency.

Hong Kong SAR

CDARS is created for the delivery of health care. In order to use the data source for research, analytical files must be built that define the study cohort and algorithms are used to identify exposures, outcomes and covariates. Best practices according to China NMPA (China NMPA, 2021) will be used for the reporting of the detailed information behind these operational and design decisions to allow other researchers to reproduce the conduct of study.

8.6.1 Obtaining Data Files

Not applicable

8.6.2 Review and Verification of Data Quality

The accuracy, data quality, and internal consistency of the data from this study will be verified. Data curation is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Data handling, including data quality assurance, will comply with applicable international regulatory guidelines. Data curation and control processes specific to this study, along with all steps and actions taken regarding data curation and data quality assurance, will be confirmed in data curation plan.

Standard operating procedures will be used to guide the conduct of the study. These procedures include internal quality audits of the data, accuracy and consistency of extracted data, validation of coding, rules for secure and confidential data storage, methods to maintain and archive documents, quality country procedure for

programming, standards for writing analysis plans, and requirement for senior scientific review.

eCRFs received will be processed and reviewed for completeness, consistency, and the presence of mandatory values. Applicable terms will be coded according to the coding conventions for this study. Logical checks will be implemented to ensure data quality and accuracy. The eCRF will give immediate feedback if data are missing, out of range, illogical or potentially erroneous. To avoid systematic mistakes when entering data, each site will be asked to document data of 2 patients in the eCRF. Subsequently, the data entry will be checked for consistency and logic. Possible inconsistencies will be discussed and resolved with the site before additional patients are documented by the respective site.

Data will be verified using the data source by the study monitor and reviewed for consistency by data curation using both automated logical checks and manual review. All data extracted will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

Data extraction at each site will be monitored both remotely and in an on-site manner. Written programming will be reviewed independently. The secure storage of data, study programs, log files, output files and back up will be ensured as required by regulatory guidelines. All key study documents, such as the statistical plan and study reports, will undergo quality control and review.

8.7 Data Analysis

8.7.1 Planned Analyses

The analyses of all objectives will be performed using descriptive statistical methods. No hypotheses testing is planned.

8.7.1.1 Interim Analysis/Analyses

The interim analyses will be conducted after completing the data extraction of 30 patients in BOAO Pilot Zone, including analyses to:

- Characterize the safety profile of sotorasib in Chinese patients.
- Describe real-world OS CCI [redacted]

CCI [redacted]

8.7.1.2 Primary Analysis

The primary analyses will be conducted after completing data extractions of all patients from BOAO Pilot Zone and Hong Kong SAR, to:

- Characterize the safety profile of sotorasib in Chinese patients.
- Describe real-world OS CCI [redacted]

CCI [redacted]

8.7.2 Planned Method of Analysis

8.7.2.1 General Considerations

All data analyses will be performed using appropriate software such as SAS statistics software version 9.3 or higher (SAS Institute Inc., Cary, NC). An analysis plan with a detailed description of analyses to be performed will be developed.

All analysis will be conducted separately for patients in BOAO Pilot Zone and Hong Kong SAR CDARS.

8.7.2.2 Missing or Incomplete Data and Lost to Follow-up

This is a retrospective chart review study. Information which is not included in the patient medical charts cannot be reported. Missing data will not be replaced by imputation methods. All analyses will be conducted in patients with available information.

As described in Section 8.4, during the treatment period, physicians proactively follow up with patients in BOAO Pilot Zone. In addition, as advanced NSCLC is a life-threating disease which needs close support from physicians specialized in treating NSCLC, it is expected that patients remain at same site for treatment.

Outcome assessment up to the end of follow-up defined in Section 8.2.6 will be included in the analysis.

8.7.2.3 Descriptive Analysis

8.7.2.3.1 Description of Study Enrollment

Patients will be selected by reviewing the medical charts and enrolling those who meet the eligibility criteria and sign ICF, if required.

8.7.2.3.2 Description of Patient Characteristics

Patients who are 18 years of age or older, have *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC, previously treated with at least 1 prior systemic therapy

and have been treated with at least 1 dose of sotorasib in clinical practice will be included in the study.

8.7.2.4 Analysis of the Primary, Secondary, and Exploratory Endpoint(s)

Frequencies will be presented for categorical demographic (eg, sex, smoking status), clinical (eg, prior treatments, tumor mutations), and pathological (eg, stage, histology) variables. Descriptive statistics (mean, median, standard deviation, and range) will be presented for continuous variables.

The proportion of AEs will be summarized by count and proportions, specifically the proportion of patients experiencing AEs relative to the total number of patients.

Median OS and PFS and the corresponding 95% confidence intervals (CIs) will be calculated using Kaplan-Meier estimates. The estimated survival probabilities, along with corresponding 95% CIs using Kaplan-Meier method will be presented for patients at 6 and 12 months. CCI [redacted]

8.7.2.5 Sensitivity Analysis

8.7.2.5.1 Subgroup Analysis

Subgroups of interest, including but not limited to those defined by characteristics listed below, may be explored, if sufficient numbers are available (eg, n ≥ 10).

Table 2. List of Study Covariates for Subgroup Analyses

Covariate	Characteristics
Sex:	• Male • Female
Calendar year of sotorasib initiation	• Before January 1, 2023 • On/after January 1, 2023
Brain metastasis at sotorasib initiation	• Yes • No
ECOG score at sotorasib initiation	• 0 • 1 • 2 • ≥ 3 • Not available

Number of prior lines of therapy	• 1 • 2 • ≥ 3
Treated with PD-1/PD-L1 inhibitors prior to sotorasib initiation	• Yes • No
Adult patients with other cancer other than NSCLC	• Yes • No

8.7.2.5.2 Stratified Analysis

Not applicable

8.7.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

In the absence of verified death information in BOAO Pilot Zone, such as data from death registries, the reported deaths are utilized for analysis. This may introduce a potential for underestimating survival rates. A sensitivity analysis will be conducted by excluding individuals who were lost to follow-up defined as those whose last activity is earlier than the data cutoff. The characteristics of patients with censoring will be outlined alongside those of patients without censoring, providing insights into their respective profiles.

We will also conduct a sensitivity analysis wherein patients with other actionable mutations (eg, ALK, EGFR) who have received treatment with targeted therapies other than sotorasib will be excluded, as the prognosis among such patient populations could be meaningfully different compared to patients not receiving these targeted therapies.

CCI [redacted] For this analysis, time from treatment initiation to end of follow-up will be calculated as the number of days from treatment initiation to the earliest date of the initiation of other commercial drugs or a clinical study drug, last clinical activity in the data source, data cut-off in the data source, CCI [redacted] or death.

8.7.2.5.4 Other Sensitivity Analysis

Not applicable.

8.7.3 Analysis of Safety Endpoints

All patients participating in the study who meet the eligibility criteria will be included in the safety analysis. All AEs will be coded using MedDRA. For safety outcomes defined in Section 8.3.2, count and proportions will be calculated, respectively.

8.8 Quality Control

At the study level, all aspects of the study from protocol development to the reporting of the results are conducted following Standard Operating Procedures (SOPs) developed by Amgen and/or the vendor.

The investigator, co-investigator(s) and all site staff involved in the study will be trained on the conduct of the study at the time of site initiation. To ensure the integrity of the data, to examine compliance with the protocol and adherence to the data extraction procedures, and to verify that records and documents are being properly maintained for the duration of the study, sites will be monitored both onsite and remotely by the vendor.

Once all data has been entered and all outstanding monitoring issues have been addressed, all sites will be closed out remotely. Monitor contact details for each participating site will be maintained in the Investigator Site File.

All functions, processes, and specifications for data extraction, cleaning and validation will be described in a data curation plan. This plan will be completed prior to the start of data abstraction.

In case data are missing, out of range, illogical or potentially erroneous, the eCRF, that includes automated edit checks, will give immediate feedback and ask for correction.

Thus, high data quality standards will be obtained, and processes and procedures to ensure that the data are as clean and as accurate as possible will be put into practice. A series of programmed data quality checks that automatically detect outages will enhance data quality.

Written programming will be reviewed independently. The secure storage of data, study programs, log files, output files and back up will be ensured as required by regulatory guidelines.

8.9 Limitations of the Research Methods

8.9.1.1 Measurement Errors

As no verified death information is linked (eg, death registry) in BOAO Pilot Zone, the reported death is used. Because of this, it is likely the survival is underestimated. Sensitivity analysis excluding those lost to follow up will be performed.

8.9.1.2 Confounding

Not applicable.

8.9.2 External Validity of Study Design

All Chinese adult patients with *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC who were treated with sotorasib in BOAO Pilot Zone and Hong Kong SAR will be eligible for enrollment. With limited exclusion criteria, this study population well represents Chinese *KRAS p.G12C*-mutated locally advanced or metastatic patients with NSCLC treated in real-world. Patients need to be able to travel to get treatment at BOAO Pilot Zone, indicating better health status and social economic status of the study population.

8.9.3 Analysis Limitations

CCI [redacted] We will perform a sensitivity analysis in which patients who switch to other commercially available drugs or clinical trial medications will be censored for sotorasib treatment.

Estimates of OS are likely to be immature in this study due to the potentially short observation period for some patients. Patients without evidence of death by the data cut-off will be censored at their last confirmed activity date, potentially underestimating the true time at risk. A sensitivity analysis will follow these patients to the end of the study instead of censoring them at their last confirmed activity date.

CCI [redacted]

CCI [redacted]

No further analysis limitations are expected.

8.9.4 Limitations Due to Missing Data and/or Incomplete Data

A limitation of retrospective chart review studies is that only data documented in patient medical records can be transmitted in the eCRF.

We expect that most patients with NSCLC remain at the BOAO Pilot Zone, or same site in Hong Kong SAR for the entire treatment of the disease. To meet the objectives of this study, data will be abstracted which in general are documented in the patient medical records in routine oncology care except for AE grade. Adverse events grade and relationship to sotorasib may not be available for some patients or unable to be confirmed based on the available information. Adverse events grades and relationship to sotorasib will be extracted to the extent possible. Additionally, information on deaths may be incomplete, as the analysis will only use reported deaths. Missingness and incomplete data on the covariates, and potentially others not listed here, may limit the ability to assess certain subgroup of interest. The level of missingness will be described and no attempts at imputation will be made in this study.

Since sotorasib is not widely available in mainland China, the early adopters included in this study may not be fully representative of the broader population that will eventually receive this treatment. For example, as patients are required to travel to BOAO Pilot Zone for therapy, they may generally be healthier than the average patient. Despite this limitation, this study will still provide valuable insights into the safety and effectiveness profile of sotorasib in a real-world context.

During the data abstraction period, manual queries or source data verification will be done. Additionally, missing information in mandatory variables or inconsistent data on these variables in the eCRF will be flagged directly in the eCRF so that it can be added or corrected immediately while entering the data. Furthermore, the monitor will conduct calls with the sites and/or send e-mails to establish progress, address any challenges, and refresh investigators on study responsibilities. In addition to a planned proactive outreach, the data curation will continue to manage investigator-initiated study-related enquiries as needed.

8.10 Other Aspects

Not applicable

9. Protection of Patients

9.1 Informed Consent

Where an informed consent is required per local regulations and sites, an initial sample informed consent form is provided for the investigator or designee to prepare the informed consent document to be used at his or her site. Updates to the sample informed consent form are to be communicated formally in writing from the Amgen Study Manager to the investigator or designee. The informed consent form is to be prepared in the language(s) of the potential patient population.

Where an informed consent is required per local regulations and sites, the investigator or designee will explain to the patient, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study, and answer all questions regarding the study prior to the patient's participation.

The acquisition of informed consent is to be documented in the patient's medical records. The informed consent form is to be signed and personally dated by the patient or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the patient or the patient's legally authorized representative.

If local regulations do not require an informed consent to be signed but mandate that the patient is notified about the study, the investigator or designee should document the notification process in the patient's medical record.

9.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

The study protocol will be reviewed by the EC of each participating study site. In addition, the International collaboration Human Genetics Resources Administration of China application will be submitted for BOAO Pilot Zone.

9.3 Patient Confidentiality

In BOAO Pilot Zone, de-identified patient records will be transferred to Amgen. The investigator must ensure that the patient's confidentiality is maintained for documents submitted to Amgen.

Patient will be assigned a unique identifier. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

In Hong Kong SAR, no patient records or datasets will be transferred to the sponsor. According to local regulation, the data cannot go outside of the academic centre.

For serious AEs reported to Amgen, patients are to be identified by their unique patient identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental regulations, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB, direct access to review the patient's original medical records for verification of data. Direct access includes examining, analysing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the patient to permit such individuals to have access to his/her study-related records, including personal information.

9.4 Patients Decision to Withdraw

Patients have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Withdrawal of consent for a study means that the patient does not wish to or is unable to continue further study participation. Patient data up to withdrawal of consent will be included in the analysis of the study and, where permitted, publicly available data can be included after withdrawal of consent. As per local regulations, upon withdrawal of consent, the patient has the right to request removal of their data that was extracted and not have it further processed. The investigator is to discuss with the patient appropriate steps for withdrawal of their consent from the study.

10. Collection, Recording, and Reporting of Safety Information and Product Complaints

10.1 Definition of Reportable Events

10.1.1 Adverse Events

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product(s) irrespective of a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use

of a product(s), whether or not considered related to the product(s). The definition of an AE includes:

- Worsening of a pre-existing condition or underlying disease
- Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)

10.1.2 Serious Adverse Events

A serious AE is any AE as defined above that meets at least one of the following serious criteria:

- is fatal
- is life threatening (places the patient at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an “other medically important serious event” that does not meet any of the above criteria

A hospitalization meeting the regulatory definition for “serious” is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.
“Other medically important serious events” refer to important medical events 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 in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

10.1.3 Other Safety Findings

Other Safety Findings (regardless of association with an AE) include:

- Medication errors, overdose/underdose, whether accidental or intentional, misuse, addiction, or abuse involving an Amgen product,
- Use of an Amgen product while pregnant and/or breast feeding,
- Transmission of infectious agents,
- Reports of uses outside the terms for authorized use of the product including off-label use,
- Accidental or Occupational exposure,
- Any lack or loss of intended effect of the product(s).

10.1.4 Product Complaints

Product Complaints include any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution to market or clinic. This includes any drug(s), device(s), or combination products provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) or combination product(s) includes investigational product.

10.2 Safety Collection, Recording and Submission to Amgen Requirements

This study is analyzing secondary data from electronic health record databases. The safety outcomes that are listed in Section 8.3.2 will be documented and analyzed in this study. These will be reported in aggregate in the final study report as counts and proportions. See Section 8.3.2 for safety outcomes and definitions. Reportable events suspected to be related to any Amgen medicinal product, combination product or device should be spontaneously reported to Amgen within 1 business day of investigator/vendor awareness. A list of all Amgen medicinal products can be found in the following link: https://wwwext.amgen.com/amgen-worldwide

To spontaneously report a reportable event to Amgen, refer to the following link to locate your Local Amgen contact information by country: https://wwwext.amgen.com/contact-us/product-inquiries

Additional details on what to collect and report to Amgen for the reportable event can be found in the following link: https://wwwext.amgen.com/products/global-patient-safety/adverse-event-reporting. Reportable events suspected to be related to any non–Amgen medicinal product should be reported to the local authority in line with the local country requirements.

11. Administrative and Legal Obligations

11.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. When Amgen amends the protocol and distributes the protocol amendment to the sites, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. The IRB must be informed of all amendments and give approval for all protocol amendments that Amgen provides to the site. The Investigator must send a copy of the approval letter from the IRB to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the contractual agreement. The Investigator is to notify the IRB in writing of the study's completion or early termination and send a copy of the notification to Amgen.

12. Plans for Disseminating and Communicating Study Results

The study will be submitted for publication in a peer-reviewed journal.

12.1 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states:

Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3, and 4.

- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

13. Compensation

If ICF is required by specific site regulation, patients participating in this study will be provided a one-time compensation for the time and effort spent for signing and delivering ICF for this chart review study. Compensation will be in accordance with Amgen's Fair Market Value.

14. References

Biernacka A, Tsongalis PD, Peterson JD, et al. The potential utility of re-mining results of somatic mutation testing: KRAS status in lung adenocarcinoma. *Cancer Genet*. 2016;209(5):195-198.

Chan EW, Lau WC, Leung WK, et al. Prevention of Dabigatran-Related Gastrointestinal Bleeding With Gastroprotective Agents: A Population-Based Study. *Gastroenterology*. 2015;149(3):586-95.e3. doi:10.1053/j.gastro.2015.05.002

Chan EW, Lau WC, Siu CW, et al. Effect of suboptimal anticoagulation treatment with antiplatelet therapy and warfarin on clinical outcomes in patients with nonvalvular atrial fibrillation: A population-wide cohort study. *Heart Rhythm*. 2016;13(8):1581-1588. doi:10.1016/j.hrthm.2016.03.049

Chen H, Huang D, Lin G, et al. The prevalence and real-world therapeutic analysis of Chinese patients with KRAS-Mutant Non-Small Cell lung cancer. *Cancer Med*. 2022;11(19):3581-3592. doi:10.1002/cam4.4739

China National Medicinal Products Administration (NMPA). Guideline on Using Real-World Evidence to Support Drug Research & Development and Evaluation. Available at: https://www.nmpa.gov.cn/directory/web/nmpa/xxgk/ggtg/ypggtg/ypqtggtg/20200107151901190.html. Updated 2020. Accessed September 6, 2024.

China National Medicinal Products Administration (NMPA). Guidelines for Communication of Real-World Evidence to Support Drug Registration Applications. Available at: https://www.cde.org.cn/main/news/viewInfoCommon/8b59a85b13019b5084675edc912004f1. Updated 2023a. Accessed September 6, 2024.

China National Medicinal Products Administration (NMPA). Guidelines for Real-World Data Used to Generate Real-World Evidence. Available at: http://www.hnrws.cn/1004/2485/2494.html. Updated 2021. Accessed September 6, 2024.

China National Medicinal Products Administration (NMPA). The National Medical Products Administration. 21 August 2024. Accessed August 2024. https://www.nmpa.gov.cn/zhuanti/cxylqx/cxypxx/20240821175034132.html

China National Medicinal Products Administration (NMPA). Guidelines on Design and Protocol of Drug Real-world Evidence Study. Available at:

https://www.cde.org.cn/zdyz/domesticinfopage?zdyzIdCODE=684f09aecdd4fb1e3c39134b2c915c4b. Updated 2023b. Accessed September 11, 2024.

Common Terminology Criteria for Adverse Events (CTCAE) Common Terminology Criteria for Adverse Events (CTCAE) V5.0.; 2017. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf#search=%22CTCAE%22

de Langen AJ, Johnson ML, Mazieres J, et al. Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with KRASG12C mutation: a randomised, open-label, phase 3 trial. *The Lancet*. 2023;401(10378). doi:https://doi.org/10.1016/s0140-6736(23)00221-0

Ettinger DS, Wood DE, Aisner DL, et al. Non-Small Cell Lung Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2022;20(5):497-530. doi:10.6004/jnccn.2022.0025.

Han B, Zheng R, Zeng H, et al. Cancer incidence and mortality in China, 2022. *Journal of the National Cancer Center.* 2024;4(1). doi:https://doi.org/10.1016/j.jncc.2024.01.006

International Council for Harmonisation of Technical Requirement for Registration of Pharmaceuticals for Human Use. M14 General Principles on Plan, Design, and Analysis of Pharmacoepidemiological Studies That Utilize Real-World Data for Safety Assessment of Medicines – Draft 21 May 2024. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m14-general-principles-plan-design-and-analysis-pharmacoepidemiological-studies-utilize-real-world. Updated 2024. Accessed September 11, 2024.

Khozin S, Miksad RA, Adami J, et al. Real-world progression, treatment, and survival outcomes during rapid adoption of immunotherapy for advanced non-small cell lung cancer. *Cancer*. 2019;125(22):4019-4032. doi:10.1002/cncr.32383

Lau WCY, Chan EW, Cheung CL, et al. Association Between Dabigatran vs Warfarin and Risk of Osteoporotic Fractures Among Patients With Nonvalvular Atrial Fibrillation. *JAMA*. 2017;317(11):1151-1158. doi:https://doi.org/10.1001/jama.2017.1363

Lasiter L, Tymejczyk O, Garrett-Mayer E, et al. Real-world Overall Survival Using Oncology Electronic Health Record Data: Friends of Cancer Research Pilot. *Clin Pharmacol Ther*. 2022;111(2):444-454. doi:10.1002/cpt.2443

Liu Y, Li H, Zhu J, et al. The Prevalence and Concurrent Pathogenic Mutations of KRASG12C in Northeast Chinese Non-small-cell Lung Cancer Patients. *Cancer Manag Res.* 2021;13:2447-2454. Published 2021 Mar 15. doi:10.2147/CMAR.S282617

Liu SY, Sun H, Zhou JY, et al. Clinical characteristics and prognostic value of the KRAS G12C mutation in Chinese non-small cell lung cancer patients. *Biomark Res*. 2020;8:22. Published 2020 Jun 25. Jun 25;8:22. doi: 10.1186/s40364-020-00199-z

Loong HH, Du N, Cheng C, et al. KRAS G12C mutations in Asia: a landscape analysis of 11,951 Chinese tumor samples. *Transl Lung Cancer Res*. 2020;9(5):1759-1769. doi:10.21037/tlcr-20-455

Man KKC, Ip P, Hsia Y, et al. ADHD Drug Prescribing Trend Is Increasing Among Children and Adolescents in Hong Kong*. Journal of Attention Disorders*. 2017;21(14):1161-1168. doi:https://doi.org/10.1177/1087054714536047

Neumann J, Zeindl-Eberhart E, Kirchner T, Jung A. Frequency and type of KRAS mutations in routine diagnostic analysis of metastatic colorectal cancer. *Pathol Res Pract*. 2009;205(12):858-862.

Oncology Society of Chinese Medical Association; Chinese Medical Association Publishing House. *Zhonghua Zhong Liu Za Zhi*. 2023;45(7):539-574. doi:10.3760/cma.j.cn112152-20230510-00200

Philip CM. Au, Anne WM. Lee, Victor HF, et al. The trends in lung cancer prevalence, incidence, and survival in Hong Kong over the past two decades (2002–2021): a population-based study. *The Lancet regional health Western Pacific.* 2024;45(101030):101030. doi:https://doi.org/10.1016/j.lanwpc.2024.101030

Prior IA, Lewis PD, Mattos C. A comprehensive survey of Ras mutations in cancer. *Cancer Res.* 2012;72(10):2457-2467.

Skoulidis F, Li BT, Dy GK, et al. Sotorasib for Lung Cancers with KRAS p.G12C Mutation. *New England Journal of Medicine*. 2021;384(25):2371-2381. doi:https://doi.org/10.1056/nejmoa2103695

Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021; Online ahead of print.

The AACR Project GENIE Consortium. AACR Project GENIE: Powering Precision Medicine Through An International Consortium. *Cancer Discov*. 2017.

Thummalapalli R, Bernstein E, Herzberg B, et al. Clinical and Genomic Features of Response and Toxicity to Sotorasib in a Real-World Cohort of Patients With Advanced *KRAS G12C*-Mutant Non-Small Cell Lung Cancer. *JCO Precis Oncol*. 2023;7:e2300030. doi:10.1200/PO.23.00030

Wong AYS, Root A, Douglas IJ, et al. Cardiovascular outcomes associated with use of clarithromycin: population based study. *BMJ*. 2016;352:h6926. doi:https://doi.org/10.1136/bmj.h6926

Zeng H, Chen W, Zheng R, et al. Changing cancer survival in China during 2003–15: a pooled analysis of 17 population-based cancer registries. *The Lancet Global Health*. 2018;6(5):e555-e567. doi:https://doi.org/10.1016/S2214-109X(18)30127-X

15. Appendices

Appendix A. List of Stand-alone Documents

None.

Approval Signatures

Document Name: Protocol Original sotorasib 20240175

Document Description: Original Protocol Sotorasib 20240175

Document Number: CLIN-000350012

Approval Date: 28 Mar 2025

Type of Study Protocol: Original

Protocol Amendment No.:

Document Approvals	
Reason for Signing: Functional Area	Name: PPD Date of Signature: 28-Mar-2025 21:48:27 GMT+0000