Summary Table of Study Protocol

Title	Post-marketing Surveillance Study for Sotorasib in South Korea
Protocol Version Identifier	20200009
Date of Last Version of the Protocol	02 August 2022
EU Post Authorization Study (PAS) Register No	NA
Active Substance	Sotorasib
Medicinal Product	Sotorasib tablet 120 mg (AMG 510, LUMAKRAS)
Device	NA
Product Reference	NA
Procedure Number	NA
Joint PASS	Yes
Research Question and Objectives	The primary objective is to describe safety of sotorasib in post-marketing clinical practice within the approved indication by estimating the incidence of adverse events, serious adverse events, adverse drug reactions, serious adverse drug reactions, unexpected adverse events, unexpected serious adverse events, unexpected adverse drug reactions, unexpected serious adverse drug reactions, leading to discontinuation of sotorasib, and fatal events; as required by the Ministry of Food and Drug Safety (MFDS). The secondary objective is to describe effectiveness of sotorasib in clinical practice within the approved indication by estimating overall response rate (ORR) and clinical outcome measure by the Investigator.
Country of Study	South Korea
Author	PPD

Marketing Authorization Holder

Marketing authorization holders	Amgen Korea Limited 20th Floor, Ferrum Tower 19 Eulji-ro 5-gil, Jung-gu Seoul 04539 Korea +82-2-3434-4800
MAH Contact	NA

Confidentiality Notice

Investigator's Agreement

I have read the attached protocol entitled "Post-marketing Surveillance Study for Sotorasib in South Korea," dated 02 August 2022, 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:

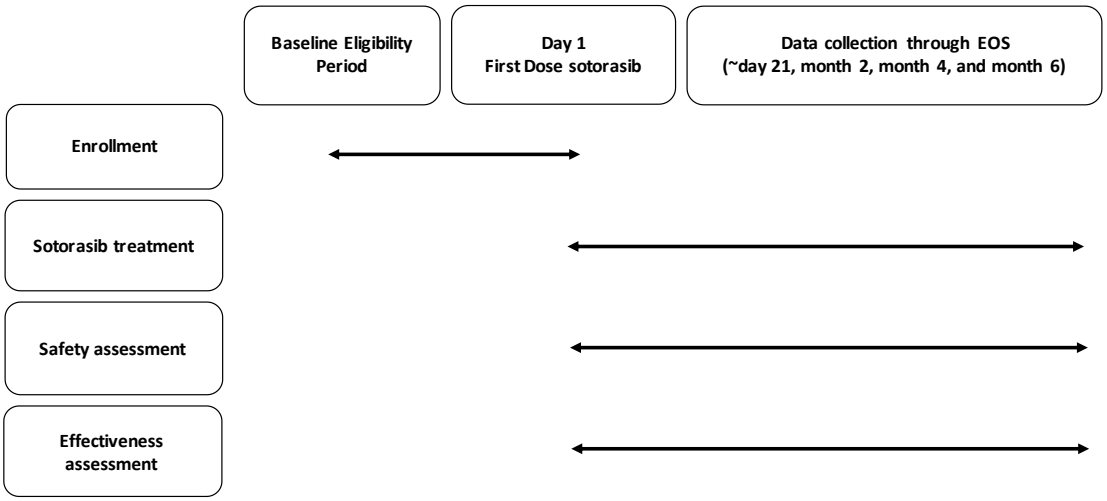
Name of Hospital/Site:

Address/City/State/Country:

Phone Number:

Email:

Figure 1. Study Design Schema



EOS = end of study

Data source - Study data will be collected from the medical records of enrolled patients.

Patient-level characteristics collected:

- demographics, physical measurements, and smoking status (subject number, age, sex, height, weight, smoking history, allergic history, pregnancy, or lactation status)
- clinical and tumor characteristics (date of initial diagnosis, clinical stage, histology, comorbidities [including hepatic impairment and renal impairment], Eastern Cooperative Oncology Group [ECOG] performance score)
- treatment history (prior systemic treatment received in the advanced disease setting, dose, unit and frequency, start and stop dates)
- sotorasib treatment (indication, dose, start date, end date, frequency of sotorasib administration)
- prior and concomitant medications

Investigator Site Information:

- site name, specialty, investigator name, contract date

Safety:

- adverse events
- serious adverse events
- adverse drug reactions
- serious adverse drug reactions
- unexpected adverse events
- unexpected serious adverse events
- unexpected adverse drug reactions
- unexpected serious adverse drug reactions
- adverse events leading to sotorasib discontinuation
- fatal events
- other safety findings
- spontaneously reported product complaints

Clinical outcome:

- Overall Response Rate (ORR)
- clinical outcome measure by the Investigator

1. Table of Contents

List of Tables

List of Figures

List of Appendices

2. List of Abbreviations

Abbreviation or Term	Definition/Explanation
BOR	Best Overall Response
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOS	end of study
ERK	extracellular signal regulated kinase
ICF	informed consent form
IEC	independent ethics committee
IRB	institutional review board
KRAS	Kirsten rat sarcoma viral oncogene homolog (protein)
KRAS	Kirsten rat sarcoma viral oncogene homolog (DNA)
KRAS p.G12C	*KRAS* DNA with a mutation resulting in a G12C mutation at the protein level
$KRAS^{G12C}$	KRAS protein with a G12C mutation at the protein level
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety
NA	not applicable
NE	not evaluable disease
NSCLC	non-small cell lung cancer
ORR	Overall Response Rate
PAS	post authorization study
PD	progressive disease
PR	partial response
PT	Preferred Term
RAF	RAF proto-oncogene serine/threonine-protein kinase
RECIST	response evaluation criteria in solid tumors
RMP	Risk Management Plan
SD	stable disease
SOC	System Organ Class

3. Responsible Parties

The sponsor of the study is Amgen Korea Limited. The list of investigators will be determined by which sites have access to sotorasib. Once the list is compiled, the sponsor or delegate may provide it upon request.

4. Abstract

- **Study Title**

Post-marketing Surveillance Study for Sotorasib in South Korea

- **Study Background and Rationale**

Sotorasib is the first Kirsten rat sarcoma viral oncogene homolog protein (KRAS) with a G12C mutation ($KRAS^{G12C}$) inhibitor to treat *KRAS p.G12C* positive cancer. Sotorasib has clinical trial data (Li et al, 2021; Hong et al, 2020) and has been approved by Ministry of Food and Drug Safety (MFDS). In South Korea, approximately 2% to 4% of patients with non-small cell lung cancer (NSCLC) harbor the *KRAS p.G12C* mutation, and each year approximately 450 to 900 new patients in the South Korea are diagnosed with *KRAS p.G12C*-mutated NSCLC (Korea National Cancer Information Center, 2020; Park et al, 2017; Shin et al, 2017; Sun et al, 2013).

In South Korea, it is mandatory to conduct active pharmacovigilance surveillance as a part of the Risk Management Plan (RMP) to investigate post-marketing safety and effectiveness in patients treated with approved orphan drugs. To comply with this Korean MFDS regulation, Amgen Limited Korea will conduct a post-marketing surveillance study to evaluate the safety and effectiveness of sotorasib in routine clinical practice.

- **Study Feasibility and Futility Considerations**

Not applicable

- **Research Question and Objectives**

Objectives	**Endpoints**
Primary	
• describe safety of sotorasib in post-marketing clinical practice within the approved indication	• incidence of adverse events • incidence of serious adverse events • incidence of adverse drug reactions • incidence of serious adverse drug reactions • incidence of unexpected adverse events • incidence of unexpected serious adverse events • incidence of unexpected adverse drug reactions • incidence of unexpected serious adverse drug reactions • incidence of adverse events leading to sotorasib discontinuation • incidence of fatal events

Secondary	
• describe effectiveness of sotorasib in clinical practice within the approved indication	• Overall Response Rate (ORR) • clinical outcome measure by the Investigator
Exploratory	
• NA	• NA

- **Hypothesis/Estimation**

  No hypothesis will be tested. This study will describe the incidence of adverse events, serious adverse events, adverse drug reactions, serious adverse drug reactions, unexpected adverse events, unexpected serious adverse events, unexpected adverse drug reactions, unexpected serious adverse drug reactions, adverse events leading to sotorasib discontinuation, and fatal events; overall response rate (ORR) after initiation of sotorasib in South Korea.

- **Study Design/Type**

  This is an observational multicenter study in patients who are prescribed sotorasib within the approved indication in a post-marketing setting in South Korea.

- **Study Population or Data Resource**

  Study enrollment will be offered to patients meeting the eligibility criteria at participating medical sites in South Korea. Enrollment will start (estimated fall of 2022) after launch of sotorasib in South Korea and is planned to end 2 years later if enrollment targets are met. A discussion with MFDS will be completed to determine if an extension is required. Patients will be enrolled at participating sites and will be followed for up to 6 months from their first dose of sotorasib, discontinuation of sotorasib plus 30 days, withdrawal of consent, death, or lost to follow-up, whichever occurs first. Investigators are requested to make every effort to enroll all patients in a total surveillance method during the enrollment period.

- **Summary of Subject Eligibility Criteria**

Inclusion Criteria

- subjects prescribed sotorasib in clinical practice according to the approved therapeutic indications, dosage, and administration in South Korea
- subjects or their authorized representative who provide written informed consent to participate in this study

Exclusion Criteria

- Subjects with contraindications as listed on the approved local label
- subjects concurrently participating in another interventional study will not be allowed to participate in this study
- subjects received any prior treatment with sotorasib before day 1 visit

- **Follow-up**

Subjects will be followed from their first dose of sotorasib through the completion of 6 months of sotorasib use, discontinuation of sotorasib plus 30 days, withdrawal of consent, death, or lost to follow-up, whichever occurs first.

Data will be collected from each enrolled subject's medical records.

- **Variables**
  - *Outcome Variables*
    - primary outcome measures: incidence of adverse events, serious adverse events, adverse drug reactions, serious adverse drug reactions, unexpected adverse events, unexpected serious adverse events, unexpected adverse drug reactions, unexpected serious adverse drug reactions, adverse events leading to sotorasib discontinuation, and fatal events
    - secondary outcome measure: ORR and clinical outcome measure by the Investigator
- **Study Sample Size**

Per the most recent MFDS regulatory requirements, the study intends to enroll all eligible subjects in South Korea during the 2 years enrollment period but not less than 25 subjects to collect safety and effectiveness information for the final analysis. Investigators at participating medical sites are requested to make every effort to enroll subjects in a total surveillance method during the enrollment period.

- **Data Analysis**

The data will be summarized descriptively.

The Safety Analysis Set will include all subjects who received at least 1 dose of sotorasib in accordance with the approved therapeutic indications, dosage, and administration in South Korea and completed at least 1 safety follow-up. The incidence of adverse events will be summarized to include all treatment-emergent adverse events recorded from the start of sotorasib on this study or any worsening of medical conditions initially experienced before initiation of this study. All adverse events will be graded using the most recent Common Terminology Criteria for Adverse Events (CTCAE) version. This summary for adverse events will be performed for the following categories:

- all adverse events and adverse drug reactions
- serious adverse events and serious adverse drug reactions
- unexpected adverse events and unexpected adverse drug reactions
- unexpected serious adverse events and unexpected serious adverse drug reactions
- adverse events leading to sotorasib discontinuation
- fatal events

The 6-month cumulative incidence of adverse events will be presented as frequency and percentage.

The Full Effectiveness Analysis Set will include all subjects from the Safety Analysis Set who also have at least 1 follow-up tumor assessment to estimate the ORR after initiation of sotorasib. In addition, the investigators should evaluate the clinical outcome of each subject during the surveillance period.

Subjects will be followed from their first dose of sotorasib through completion of 6 months of sotorasib use, discontinuation of sotorasib plus 30 days, withdrawal of consent, death, or lost to follow-up, whichever occurs first.

The study protocol does not define exact referral dates for follow-up visits.

Follow-up visits occur during routine practice. The investigator documents the date of initial visit and follow-up in the electronic case report form (eCRF) and follows the study procedures pertaining to data collection for the visit.

5. Amendments and Updates

None

6. Rationale and Background

6.1 Diseases and Therapeutic Area

Disease State/Therapeutic Area

Lung cancer is the leading cause of cancer death, with more than 80% of all lung cancer cases classified as NSCLC. In South Korea, lung cancer is the third most common cancer, with 28 651 cases of lung cancer and 20 505 deaths from lung cancer reported in 2020 (Global Cancer Observatory, 2021). Advanced NSCLC (stage IIIB/C and IV) is a serious and life-threatening disease, with a 5-year survival rate of 23.5% in South Korea (National Cancer Statistics, 2020).

Based on the estimated prevalence of the Kirsten rat sarcoma viral oncogene homolog DNA (*KRAS*) *KRAS* DNA with a mutation resulting in a G12C (*KRAS p.G12C*) mutation in NSCLC (approximately 2% to 4% in South Korea [Park et al, 2017; Shin et al, 2017; Sun et al, 2013]) and incidence of lung cancer (Korea National Cancer Information Center, 2020) it is estimated approximately 450 to 900 new patients in the South Korea are diagnosed with *KRAS p.G12C*-mutated NSCLC each year.

Treatment of advanced NSCLC has improved since the clinical practice use of immunotherapies (the checkpoint inhibitors) and targeted therapies for a variety of oncogenic mutations. No anticancer therapies are currently approved for the treatment of patients with NSCLC that specifically target tumors that have the *KRAS p.G12C* mutation (Román et al, 2018; McCormick, 2016).

Amgen Investigational Product Background: Sotorasib

Sotorasib is a small molecule that specifically and irreversibly inhibits the Kirsten rat sarcoma viral oncogene homolog protein (KRAS) with a G12C mutation ($KRAS^{G12C}$) mutant protein (Canon et al, 2019). Sotorasib binds to the P2 pocket of $KRAS^{G12C}$ adjacent to the cysteine at position 12 and the nucleotide-binding pocket. The inhibitor contains a thiol-reactive portion that covalently modifies the cysteine residue and locks $KRAS^{G12C}$ in an inactive, guanosine diphosphate-bound conformation. This blocks the interaction of $KRAS^{G12C}$ with effectors such as RAF proto-oncogene

serine/threonine-protein kinase (RAF), thereby preventing downstream signaling, including the phosphorylation of extracellular signal regulated kinase (ERK) (Canon et al, 2019; Simanshu et al, 2017; Ostrem et al, 2013).

Sotorasib treatment impairs cell growth and induces apoptosis only in tumor cell lines and xenografts that have the *KRAS p.G12C* mutation (Canon et al, 2019). Blockade of $KRAS^{G12C}$ signaling by sotorasib also enhances antigen presentation and inflammatory cytokine production in tumors to inflame the tumor microenvironment and drive permanent anti-tumor immunity.

In advanced NSCLC patients enrolled in the pivotal phase 2 portion of Study 20170543, the confirmed objective response rate is 37.1% (95% CI: 28.6, 46.2). The most common treatment-related adverse events (as determined by the investigator) included: diarrhea (31.0%), nausea (19.0%), increased alanine aminotransferase (15.1%), increased aspartate aminotransferase (15.1%), fatigue (11.1%), and vomiting (7.9%). Treatment-related adverse events led to treatment discontinuation in 7.1% of patients. All fatal adverse events were considered unrelated to sotorasib.

6.2 Rationale

In South Korea, it is mandatory to conduct active pharmacovigilance surveillance as a part of the RMP to investigate post-marketing safety and effectiveness in patients treated with newly approved drugs. To comply with this Korean MFDS regulation, Amgen Limited Korea will conduct a post-marketing surveillance study to evaluate the safety and effectiveness of sotorasib in routine clinical practice. Amgen seeks to enroll all eligible patients in South Korea during the 2-year enrollment period to collect safety and effectiveness information for the final analysis. In addition to meeting the MFDS regulatory requirements, this study also will provide additional safety and effectiveness data beyond that generated in the registrational sotorasib study (Study 20170543).

6.3 Feasibility and Futility Considerations

Not applicable.

6.4 Statistical Inference (Estimation or Hypothesis)

No hypothesis will be tested. Instead, the proposed study will provide descriptive data on use of sotorasib and subject characteristics in the post-marketing setting in South Korea; the incidence of adverse events, serious adverse events, adverse drug reactions, serious adverse drug reactions, unexpected adverse events, unexpected serious adverse events, unexpected adverse drug reactions, unexpected serious adverse drug

reactions, adverse events leading to sotorasib discontinuation, and fatal events; ORR after initiation of sotorasib.

7. Research Question and Objectives

According to local regulation, a post-marketing surveillance study is required for orphan drugs newly approved in South Korea to collect safety and effectiveness data in routine clinical practice. An observational multicenter study design is chosen to meet the local regulations in South Korea.

7.1 Primary

The primary objective of this study is to describe the safety of sotorasib in post-marketing clinical practice within the approved indication by estimating the incidence of adverse events, serious adverse events, adverse drug reactions, serious adverse drug reactions, unexpected adverse events, unexpected serious adverse events, unexpected adverse drug reactions, unexpected serious adverse drug reactions, adverse events leading to sotorasib discontinuation, and fatal events among subjects receiving sotorasib within the approved indication in the post-marketing setting in South Korea as required by the MFDS.

7.2 Secondary

The secondary objective of this study is to describe effectiveness of sotorasib in clinical practice within the approved indication by estimating the ORR and clinical outcome measure by the Investigator.

8. Research Methods

8.1 Study Design

This is an observational multicenter prospective cohort study in subjects who are prescribed sotorasib within the approved indication in a post-marketing setting in South Korea.

Subjects that meet the eligibility criteria (Section 8.2.3) and sign the informed consent will be enrolled. Subjects will be seen by their physician per local standard of care and should receive sotorasib in accordance with the approved therapeutic indication, dosage, and administration in South Korea. Adverse events, serious adverse events, adverse drug reactions, serious adverse drug reactions,adverse events leading to discontinuation of sotorasib, fatal events, other safety findings and spontaneously reported product complaints will be collected for each subject from their first dose of sotorasib on day 1 through the end of study (EOS). Treatment responses will be

collected after day 1 through EOS. Six-month cumulative subject incidence of adverse events will be reported and summarized. Unexpected adverse events, unexpected serious adverse events, unexpected adverse drug reactions, and unexpected serious adverse drug reactions will be analyzed from the collected adverse events/serious adverse events/adverse drug reactions/serious adverse drug reactions as part of a special analysis. Overall response rate is defined as the proportion of patients with a Best Overall Response (BOR) of confirmed complete response (CR) or confirmed partial response (PR) and will also be reported and summarized. The investigators should evaluate the clinical outcome of each subject during the surveillance period and assign one of the following descriptions: improved, not changed, disease progression, or unable to evaluate. End of study is defined as completing 6 months of sotorasib use, discontinuation of sotorasib plus 30 days, withdrawal of consent, death, or lost to follow-up, whichever occurs first. All data collected for the purpose of this study will be entered into the eCRF.

For a full list of data elements, including the timing for each data abstraction, please refer to the schedule of data collection in Table 1.

Table 1. Schedule of Data Collection

	Baseline Eligibility Period[a]	Start of Sotorasib Day 1[a]	Visit(s) Following Day 1 Data will be collected from medical records at each subsequent site visit (expected to occur at ~ day 21, month 2, month 4, and month 6) through EOS
GENERAL ASSESSMENTS			
Eligibility Review	X	X	
Informed Consent	X	X completed before and up to day 1	
DATA COLLECTED (If available in Medical Records)			
Physical measurements • height • weight	X		
Demographic and smoking status data • age • sex • smoking history • allergic history • pregnancy and lactation status	X		
Clinical and tumor characteristics • date of initial diagnosis • clinical stage • histology • comorbidities, including hepatic impairment and renal impairment • ECOG performance score	X		

Footnotes defined on last page of the table

Table 1. Schedule of Data Collection

	Baseline Eligibility Period[a]	Start of sotorasib Day 1[a]	Visit(s) Following Day 1 Data will be collected from the medical records at each subsequent site visit (expected to occur at ~ day 21, month 2, month 4, and month 6) through EOS
DATA COLLECTED (If available in Medical Records)			
Treatment history • prior systemic treatment received in the advanced disease setting • dose, unit and frequency, start and stop dates	X		
Prior and concomitant medications • record history from 1 year before first dose on day 1 through the end of study • dose, unit and frequency, start and stop dates	X		X
Safety events collection* • adverse events • serious adverse events • adverse drug reactions • serious adverse drug reactions • adverse events leading to sotorasib discontinuation • fatal events • other safety findings • spontaneously reported product complaints		X	X Safety events will be entered in the eCRF as data become available Safety events recorded in medical records from the time of first dose on day 1 through EOS will be collected
Effectiveness collection • ORR based on real-world RECIST assessment using RECIST criteria v1.1 or later • clinical outcome measure by the Investigator			X[b]

Footnotes defined on last page of the table

Table 1. Schedule of Data Collection

	Baseline Eligibility Period[a]	Start of sotorasib Day 1[a]	Visit(s) Following Day 1 Data will be collected from the medical records at each subsequent site visit (expected to occur at ~ day 21, month 2, month 4, and month 6) through EOS
DATA COLLECTED (If available in Medical Records)			
Treatment with sotorasib		X	X
• indication			
• dose			
• start date			
• end date			
• frequency of sotorasib administration, drug withdrawal of sotorasib any time from initiation of sotorasib treatment			

ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; ORR = overall response rate; RECIST = response evaluation criteria in solid tumors

Safety events*: Unexpected adverse events, unexpected serious adverse events, unexpected adverse drug reactions, and unexpected serious adverse drug reactions will be analyzed from the collected adverse events/serious adverse events/adverse drug reactions/serious adverse drug reactions as part of a special analysis.

[a] Baseline and day 1 assessments can occur on the same day.

[b] Tumor assessment will not be completed at Day 21

8.2 Setting and Study Population

8.2.1 Study Period

Enrollment is planned to begin after the launch of sotorasib in South Korea and end after 2 years if enrollment targets are met. A discussion with MFDS will be completed to determine if an extension is required. Subjects will be enrolled on a continuous basis at participating sites. Subjects will be followed from their first dose of sotorasib through completion of 6 months of sotorasib use, discontinuation of sotorasib plus 30 days, withdrawal of consent, death, or lost to follow-up, whichever occurs first.

8.2.2 Selection and Number of Sites

Study sites will include approximately 20 sites that have post-market use of sotorasib.We aim to select almost all sites that prescribe sotorasib.

8.2.3 Subject Professional Eligibility

8.2.3.1 Inclusion Criteria

- subjects prescribed sotorasib in clinical practice according to the approved therapeutic indications, dosage, and administration in South Korea
- subjects or their authorized representative who provide written informed consent to participate in this study

8.2.3.2 Exclusion Criteria

- subjects with contraindications as listed on the approved local label
- subjects concurrently participating in another interventional study will not be allowed to participate in this study
- subject has received any prior treatment with sotorasib before day 1 visit

For analysis of subjects used outside of approved indications, see Section 8.7.

8.2.4 Matching

Not applicable.

8.2.5 Baseline Period

Physical measurements, demographics, and clinical and tumor characteristics will be collected from the initial diagnosis to the initiation of sotorasib use. Treatment history, including prior systemic treatment received will be collected from the advanced diagnosis to the initiation of sotorasib use. Prior and concomitant therapies received will be collected from 1 year before first dose on day 1 through the end of study.

8.2.6 Study Follow-up

Patients will be followed from their first dose of sotorasib through completion of 6 months of sotorasib use, discontinuation of sotorasib plus 30 days, withdrawal of consent, death, or lost to follow-up, whichever occurs first.

8.3 Variables

8.3.1 Exposure Assessment

Sotorasib use:

- indication
- dose
- start date
- end date
- frequency of sotorasib administration
- drug withdrawal of sotorasib any time from the initiation of sotorasib treatment

8.3.2 Outcome Assessment

- Primary outcome measure: Incidence of adverse events, serious adverse events, adverse drug reactions, serious adverse drug reactions, unexpected adverse events, unexpected serious adverse events, unexpected adverse drug reactions, unexpected serious adverse drug reactions, adverse events leading to sotorasib discontinuation, and fatal events throughout the treatment/observation period along with their severity, action taken, and causal relationship with sotorasib will be assessed for any subject who has received at least 1 dose of sotorasib according to the approved therapeutic indications, dosage and administration in South Korea and completed at least 1 safety follow-up. Six-month cumulative subject incidence of the adverse events will be reported and summarized. All adverse events will be graded using the most recent CTCAE version.
- Secondary outcome measure: ORR is defined as the proportion of patients with a BOR of confirmed CR or confirmed PR. To assess ORR, a real-world RECIST based response assessment will be utilized since this is standard for clinic practice in South Korea. Subjects will be categorized according to their BOR during the follow-up period using RECIST criteria v1.1 or a more recent version as noted in the subject's medical records. Subjects will be assigned to one of the following best response categories during each assessment:
  - CR or PR
  - SD
  - PD
  - not evaluable disease (NE)

  Each response start date (start date of confirmed PR or better response) or date of disease progression will be assessed at month 2, month 4, and month 6 (EOS visit). Subjects will be followed from their first dose of sotorasib through the completion of 6 months of sotorasib use, discontinuation of sotorasib plus 30 days, withdrawal of consent, death, or lost to follow-up, whichever occurs first.

In addition, investigators should evaluate the clinical outcome of each subject during the surveillance period and assign one of the following descriptions:

- improved
- not changed
- disease progression
- unable to evaluate

8.3.3 Covariate Assessment

- demographics, physical measurements, and smoking status (age, sex, height, weight, smoking history, allergic history, pregnancy, or lactation status)
- clinical and tumor characteristics (date of initial diagnosis, clinical stage, histology, comorbidities [including hepatic impairment and renal impairment], Eastern Cooperative Oncology Group [ECOG] performance score)
- prior systemic treatment received in the advanced disease setting (please refer to the table of data collection)
- sotorasib treatment (please refer to the table of data collection)
- prior and concomitant medications (please refer to the table of data collection)
- adverse events, serious adverse events, adverse drug reactions, serious adverse drug reactions, unexpected adverse events, unexpected serious adverse events, unexpected adverse drug reactions, unexpected serious adverse drug reactions, adverse events leading to sotorasib discontinuation, fatal events, other safety findings, spontaneously reported product complaints.
- treatment response: ORR based on RECIST criteria v1.1, evaluation of investigator (improved, not changed, disease progression, unable to evaluate)

8.3.4 Validity and Reliability

Efforts will be made to collect complete data through the use of clear instructions to investigators regarding the completion of eCRFs. The data collected for this study will be derived from medical records that are kept per routine clinical practice for the documentation and decision-making for a subject's care. The data will be abstracted from the medical records and entered into the eCRF. A detailed data management plan will be implemented to ensure the quality of the collected data.

8.4 Data Sources

The data source for this study is subject medical records. These medical records may include a combination of paper and electronic sources. Study site staff will extract data from the medical records into the study-specific electronic database provided by the sponsor.

8.5 Study Size

Per the most recent MFDS regulatory requirements, the study intends to enroll all eligible subjects in South Korea during the 2 years enrollment period but not less than

25 subjects to collect safety and effectiveness information for the final analysis. Investigators at participating medical sites are requested to make every effort to enroll the subjects in a total surveillance method during the enrollment period.

8.6 Data Management

8.6.1 Obtaining Data Files

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the eCRFs must be maintained and available upon request.
- Updates to eCRFs will be automatically documented through the software's audit trail.

8.6.2 Linking Data Files

Not applicable.

8.6.3 Review and Verification of Data Quality

Automatic checks within the database and further manual review by the sponsor will help to ensure quality and completeness of the data. During this review, subject data is checked for consistency, omissions, and any apparent discrepancies. Data queries will be sent to sites for clarification and resolution of discrepancies.

8.7 Data Analysis

8.7.1 Planned Analyses

8.7.1.1 Interim Analysis/Analyses

According to local regulations, interim analyses will be performed for periodic reporting starting from the initial approval of sotorasib. Periodic reports are submitted to the health authority every 6 months for the first 2 years and every year thereafter until the end of the study period.

8.7.1.2 Final Analysis

The final analysis will be conducted when the last enrolled subject reaches the EOS. A snapshot of the finalized database will be used for analysis. All analyses will be performed using SAS® 9.4 or later versions. Safety and effectiveness data collected at scheduled time points will be used for analysis.

The Safety Analysis Set will include all subjects who received at least 1 dose of sotorasib in accordance with the approved therapeutic indications, dosage, and administration in South Korea and completed at least 1 safety follow-up. The safety analysis will be the analysis conducted using the Safety Analysis Set, and will describe the following assessments:

- adverse events
- serious adverse events
- adverse drug reactions
- serious adverse drug reactions
- unexpected adverse events
- unexpected serious adverse events
- unexpected adverse drug reactions
- unexpected serious adverse drug reactions
- adverse events leading to sotorasib discontinuation
- fatal events

The Full Analysis Set (ie, Effectiveness Analysis Set) will include all subjects from the Safety Analysis Set who have at least 1 follow-up tumor assessment to estimate the ORR after initiation of sotorasib. Subjects will be followed from their first dose of sotorasib through the completion of 6 months of sotorasib use, discontinuation of sotorasib plus 30 days, withdrawal of consent, death, or lost to follow-up, whichever occurs first. In addition, investigators should evaluate the clinical outcome of each subject during the surveillance period and assign one of the following descriptions:

- improved
- not changed
- disease progression
- unable to evaluate

The data of subjects used outside of the approved indication will be analyzed separately.

The study protocol does not define exact referral dates for follow-up visits.

Follow-up visits occur during routine practice. The investigator documents the date of initial visit and follow-up in the eCRF and follows the study procedures pertaining to data collection for the visit.

8.7.2 Planned Method of Analysis

8.7.2.1 General Considerations

The statistical analysis in this post-marketing study will be descriptive in nature, and no hypothesis testing will be performed. Categorical outcomes will be summarized by the number and percentage of subjects in each category. Continuous outcomes will be summarized by the number of non-missing values, mean, standard deviation, median, lower and upper quartiles, and minimum and maximum values. Subject incidence will be summarized for adverse events, serious adverse events, adverse drug reactions,

serious adverse drug reactions, unexpected adverse events, unexpected serious adverse events, unexpected adverse drug reactions, unexpected serious adverse drug reactions. Also, 95% CI will be presented based on exact method for incidence. ORR will be reported with a Clopper-Pearson exact confidence interval.

Difference in safety or effectiveness results by subject's background factor can be analyzed by Chi-square test and to estimate factors that may affect the safety or effectiveness results, multivariate analysis can be conducted.

Additional information will be collected according to the RMP when adverse events related to the Important Safety Specification Requiring Further Evaluation Items in RMP are collected. The special investigation group (elderly, children, hepatic impairment, renal impairment, pregnancy, or lactation) will be analyzed separately.

All adverse events are tabulated in the report using the latest version of Medical Dictionary for Regulatory Activities (MedDRA), using System Organ Class (SOC) and Preferred Term (PT).

8.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Missing safety data will not be imputed as a general rule; analysis will be based on available data.

8.7.2.3 Descriptive Analysis

8.7.2.3.1 Description of Study Enrollment

Physicians will evaluate patients and determine if treatment with sotorasib is appropriate in accordance with local standards and the approved sotorasib indication. The decision to treat the patient with sotorasib should be made independently of, and before, enrollment in the study. Once treatment with sotorasib has been selected, the investigator or an assigned delegate can discuss the details of the study with the prospective subject. Each prospective patient is assessed for eligibility. Once the eligibility conditions are met, which includes signing the consent, the subject will be formally enrolled into the study.

8.7.2.3.2 Description of Subject Characteristics

Baseline characteristics and assessments will be made during the baseline period. Subject characteristics including physical measurements, demographics, smoking status, treatment history as well as clinical and tumor characteristics will be collected during the baseline period by the investigator or a designated representative and will be

summarized using descriptive statistics. Refer to Table 1 for a schedule of data collection.

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

8.7.2.4.1 Analysis of Primary Endpoint

Safety Analysis: The Safety Analysis Set will contain all subjects who have received at least 1 dose of sotorasib in accordance with the approved therapeutic indications, dosage and administration in South Korea and completed at least 1 safety follow-up. The report will include treatment-emergent, treatment-related adverse events and serious adverse events. The reports will use the standard SOC and PT system and will use the most recent CTCAE grading system. Subject listing of all adverse events, serious adverse events, adverse drug reactions, serious adverse drug reactions, unexpected adverse events, unexpected serious adverse events, unexpected adverse drug reactions, unexpected serious adverse drug reactions, adverse events leading to sotorasib discontinuation, and fatal events will also be included. All adverse events and serious adverse events will be summarized using descriptive methods. If an adverse event occurs multiple times in the same subject, the most severe grade of the adverse event will be presented. Frequencies and percentages for discrete variables; mean, standard deviation, median, minimum, and maximum values for continuous variables will be reported.

8.7.2.4.2 Analysis of Secondary Endpoint

Effectiveness Analysis: Investigators will use the RECIST criteria v1.1, or a more recent version if available, to assess the tumors based on magnetic resonance imaging or computed tomography scans beginning at the baseline and succeeding visits as part of routine clinical practice. Based on all the available data and for each time point post-baseline, the site investigator will classify the tumors into one of the categories: CR, PR, SD, PD or NE. The number and percentage of subjects with a BOR of CR, PR, SD, and PD will be presented. The ORR (%) across all timepoints = ([Number of BOR of confirmed CR + Number of BOR of confirmed PR]/Total number treated) x 100. In addition, investigators should evaluate the clinical outcome of each subject during the surveillance period and assign one of the following descriptions:

- improved
- not changed
- disease progression
- unable to evaluate

8.7.2.4.3 Analysis of Exploratory Endpoint

Not applicable.

8.7.2.5 Sensitivity Analysis

8.7.2.5.1 Subgroup Analysis

Subgroups of interest such as males and females, specific age groups, renal and hepatic impairment, and concomitant medications, may be undertaken if enough subjects are available. If the number of subjects is insufficient, it will be replaced by listing table.

8.7.3 Analysis of Safety Endpoint(s)/Outcomes(s)

The safety analysis set will contain all subjects who have received at least 1 dose of sotorasib in accordance with the approved therapeutic indications, dosage, and administration in South Korea and completed at least 1 safety follow-up. Analysis of safety endpoints will be conducted as described in Section 8.7.2.4.1.

The 6-month cumulative incidence of adverse events will be summarized to include all recorded treatment-emergent adverse events from the first dose of sotorasib or any worsening of medical conditions initially experienced before the first dose of sotorasib. This summary for adverse events will be performed for the following categories:

- all adverse events and adverse drug reactions
- serious adverse events and serious adverse drug reactions
- unexpected adverse events and unexpected adverse drug reactions
- unexpected serious adverse events and unexpected serious adverse drug reactions
- adverse events leading to sotorasib discontinuation
- fatal events

8.8 Quality Control

The Amgen representative(s) and regulatory authority inspectors are responsible for inspecting the various records of the study (eg, eCRFs and other pertinent data) provided that subject confidentiality is respected.

Amgen or its designee is responsible for verifying the eCRFs to confirm adherence to the protocol, completeness, accuracy, and consistency of the data and adherence to local regulations on the conduct of surveillance studies.

The investigator agrees to cooperate with Amgen or contract research organization staff to ensure that any problems detected in the course of the study, including delays in completing eCRFs, are resolved.

In accordance with the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Quality, Compliance, and Audit function (or designees).

8.9 Limitations of the Research Methods

The current study plans to adopt rigorous observational data collection methods for the study.

8.9.1 Internal Validity of Study Design

Information bias and missing or incomplete data is a potential risk for information bias and efforts will be made to collect complete data through the use of clear instructions to investigators regarding the completion of eCRFs.

There is no systematic review or systematic method of adverse event collection. Adverse events are collected as part of a regular interaction with the subject as would be in normal practice. Therefore, adverse events collected are subject to reporting bias, but such effect is inherent to real-world surveillance.

8.9.1.1 Measurement Error(s)/Misclassification

As with any surveillance study that relies on data entry from multiple sites, there is the potential for misclassifying adverse events and adverse drug reactions. Misclassifications can impact the validity of outcomes as well as affect overall conclusions.

8.9.1.2 Information Bias

Missing or incomplete data is a potential risk for information bias and efforts will be made to collect complete data through the use of clear instructions to investigators regarding the completion of eCRFs.

There is no systematic review or systematic method of adverse event collection. Adverse events are collected as part of a regular interaction with the subject as would be in normal practice. Therefore, adverse events collected are subject to reporting bias, but such effect is inherent to real-world surveillance.

8.9.1.3 Selection Bias

This study is an observational study in a real-world setting. The inclusion criteria are intended to enroll all patients prescribed sotorasib in clinical practice according to the approved therapeutic indications, dosage, and administration in South Korea. Consecutive enrollment will be performed to potentially reduce selection bias.

8.9.1.4 Confounding

Not applicable.

8.9.2 External Validity of Study Design

The participating medical centers are expected to represent approximately over 80% of the total patients treated with sotorasib in South Korea, so it is expected that the results from current study are generally extendable to the general population of patients treated with sotorasib in South Korea. Also, as with other studies, this study only includes patients who provide consent to participate, and patients that did not participate in this study may be different compared to those who did.

8.9.3 Limitations Due to Missing Data and/or Incomplete Data

Some subjects may discontinue the study, creating missing or incomplete data for the study endpoint assessments. Such discontinuations may be related or informative to the outcomes. Consequently, there is a risk for bias due to missing completed data and lack of robust data to analyze results.

8.10 Other Aspects

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

9. Protection of Human Subjects

9.1 Informed Consent

An initial sample informed consent form (ICF) 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 ICF are to be communicated formally in writing from the Clinical Study Manager to the investigator or designee. The written ICF is to be prepared in the language(s) of the potential patient population.

Before a subject's participation in the study, the investigator or designee will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study, and answer all questions regarding the study.

The acquisition of informed consent is to be documented in the subject's medical records, and the ICF is to be signed and personally dated by the subject or a legally authorized representative and by the person who conducted the informed consent discussion. The original signed ICF is to be retained in accordance with institutional

policy, and a copy of the ICFs must be provided to the subject or the subject's legally authorized representative.

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

9.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed ICF, other written patient information, and any proposed advertising material must be submitted to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for written approval. A copy of the written approval of the protocol and ICF must be received by Amgen before the study can be executed. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB/IEC of deviations from the protocol or serious adverse event(s) occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures. The investigator is responsible for obtaining annual IRB approval and IRB/IEC renewal throughout the duration of the study. Copies of the investigator's reports, where applicable by local regulations and the IRB/IEC continuance of approval must be sent to Amgen.

Any protocol amendments will be submitted to the local IRB for their review and approval. Annual IRB approval/renewal throughout the duration of the study will be obtained and copies of the IRB continuance of approval will be sent to Amgen.

9.3 Patient Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

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

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject 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 ICFs) are to be kept in confidence by the investigator, except as described below.

In compliance with local country regulations, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject'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 subject to permit such individuals to have access to his/her study-related records, including personal information.

9.4 Subjects Decision to Withdraw

Subjects 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 subject does not wish to or is unable to continue further study participation. Subject 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. The investigator is to discuss with the subject 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 adverse event is any untoward medical occurrence in a subject/patient administered a pharmaceutical product(s) irrespective of a causal relationship with this treatment.

An adverse event 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 adverse event 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)

It is the investigator's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen.

An adverse drug reaction is a noxious and unintended response to a pharmaceutical product(s) administration normally. Adverse drug reactions are adverse events

considered related to sotorasib by the investigator, including those with unknown relationship.

Unexpected adverse events or unexpected adverse drug reactions means adverse events or adverse drug reactions not reflected in precautions of approved local label.

10.1.2 Serious Adverse Events

A serious adverse event/serious adverse device effect is any adverse event/adverse device effect as defined above that meets at least one of the following serious criteria:

- is fatal
- is life threatening (places the subject 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 subject 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 adverse event) 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 sotorasib.

10.2 Safety Collection, Recording and Submission to Amgen Requirements

This study is collecting information from healthcare professionals and patient's medical records prospectively.

All reportable events (adverse events, product complaints, and other safety findings) considered to have occurred following subject exposure to sotorasib will be collected from the time of first dose to 30 days after final dose of sotorasib or EOS, whichever occurs first. The investigator is responsible for ensuring that all reportable events they become aware of during the prospective period, are recorded in the subject's study documentation. It is the investigator's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen. If further safety related data is needed to fulfill any regulatory reporting requirements for a reportable event, then additional information may need to be collected from the subject's records after the subject ends the study. All reportable events must be submitted as individual safety reports to Amgen Safety or delegate via the applicable Safety Reporting Form (paper or electronic form) within the timelines stated in Table 2 below.

Table 2. Types of Safety Data to be Collected and Reported in Primary Data Collection Studies Collecting All Reportable Events

Reportable Events/Event Type	Reporting Timeframe
• Serious Adverse Events (related and non-related) • Product Complaints (serious and non-serious) • Other Safety Findings (serious and non-serious) • Pregnancy and/or Lactation Exposure	• Within 1 business day from when Investigator first becomes aware of the event
• Non-serious Adverse Events (related and non-related)	• Within 15 calendar days from when Investigator first becomes aware of the event

Reportable events that are suspected to be related to any Amgen medicinal product, combination product, or device where there is no exposure to state studied/supplied Amgen product(s) 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.

See Appendix C for sample Safety Report Form(s), Appendix D for Additional Safety Reporting Information regarding the adverse event grading scale used in this study, and Appendix E for sample Pregnancy and Lactation Notification Forms. The investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded in the study documentation where safety data may also be recorded.

10.2.1 Collection of Pregnancy and Lactation Information

Female Subjects Who Become Pregnant

Investigator will collect pregnancy information on any female subject who becomes pregnant following exposure to sotorasib through 7 days after the last dose of sotorasib.

Information will be recorded on the Pregnancy Notification Form (see Appendix E). The worksheet must be submitted to Amgen Safety within 1 business day of when investigator first becomes aware of the subject's pregnancy (Note: Investigator is not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

After receipt of the Pregnancy Notification Form, Amgen Safety will provide investigator with a consent form and questionnaire to collect additional information. After obtaining the female subject's signed consent for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant following exposure to sotorasib through 7 days after the last dose of sotorasib. This

information will be forwarded to Amgen Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

Any termination of pregnancy will be reported to Amgen Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is considered another safety finding, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.

If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.

Male Subjects with Partners who Become Pregnant (or Were Pregnant at the Time of Enrollment)

In the event a male subject fathers a child following exposure to sotorasib, and for an additional 7 days after discontinuing sotorasib, the information will be recorded on the Pregnancy Notification Form. The form (see Appendix E) must be submitted to Amgen Safety within 1 business day of when the investigator first becomes aware of the pregnancy. (Note: Investigator is not required to provide any information on the Pregnancy Notification Form that violates the country or regions local privacy laws).

After receipt of the Pregnancy Notification Form, Amgen Safety will provide investigator with a consent form and questionnaire to collect additional information. The investigator will attempt to obtain a signed consent for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.

After obtaining the female partner's signed consent for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Safety.

Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

Any termination of the pregnancy will be reported to Amgen Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

Investigator will collect lactation information on any female subject who breastfeeds while taking sotorasib through 7 days after discontinuing sotorasib.

Information will be recorded on the Lactation Notification Form (see Appendix E) and submitted to Amgen Safety within 1 business day of when the investigator's first becomes aware of the lactation exposure.

With the female subjects signed consent for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking sotorasib through 7 days after discontinuing sotorasib.

10.2.2 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required in accordance with local requirements to regulatory authorities, Investigators/institutions, IRBs/IECs, or other relevant ethical review board(s) in accordance with pharmacovigilance guidelines and in compliance with local regulations. The investigator is to notify the appropriate IRB/IEC or other relevant ethical review board of reportable events in accordance with local procedures and statutes.

11. Administrative and Legal Obligations

11.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the investigator must be obtained where applicable per local governing law and/or regulations. The IRB/IEC must be informed of all amendments and give approval. The investigator **must** send a copy of the approval letter from the IRB/IEC 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/IEC 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 final report will also be provided to the MFDS as part of RMP implementation periodic report.

12.1 Publication Policy

The results of this study will be submitted for publication. Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors 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. References

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14. Appendices

Appendix A. List of Stand-alone Documents

None.

Appendix B. ENCePP Checklist for Study Protocols

Study title:
Post Marketing Surveillance Study for Sotorasib in South Korea

EU PAS Register® number: NA
Study reference number (if applicable): 20200009

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	8.2.1
1.1.2 End of data collection[2]	☒	☐	☐	8.2.1
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☐	☒	☐	
1.1.6 Final report of study results	☐	☒	☐	

EU = European Union; PAS = post authorization study

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6.2
2.1.2 The objective(s) of the study?	☒	☐	☐	7
2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.2.3
2.1.4 Which hypothesis (-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	6.4

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design		Yes	No	N/A	Section Number
3.1	Is the study design described? (eg, cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.1
3.3	Does the protocol specify measures of occurrence? (eg, rate, risk, prevalence)	☒	☐	☐	8.3.2
3.4	Does the protocol specify measure(s) of association? (eg, risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm [NNH])	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg, adverse events that will not be collected in case of primary data collection)	☒	☐	☐	10

Comments:

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.1	Is the source population described?	☒	☐	☐	8.2.3
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	8.2.1
	4.2.2 Age and sex	☐	☒	☐	
	4.2.3 Country of origin	☒	☐	☐	8.2.3.1
	4.2.4 Disease/indication	☒	☐	☐	6.1
	4.2.5 Duration of follow-up	☒	☐	☐	8.2.1
4.3	Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	8.2.3

Comments:

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (eg, operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.3.1

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.2	Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☒	☐	☐	8.9.1.2
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (eg, dose, duration)	☒	☐	☐	8.3.1
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement		Yes	No	N/A	Section Number
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.3.2
6.3	Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	8.9.1.1/ 8.9.1.2/8.8
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (eg, HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

DALYS = disability adjusted life years; HRQoL = health-related quality of life; QALYs = quality adjusted life years

Comments:

Section 7: Bias		Yes	No	N/A	Section Number
7.1	Does the protocol address ways to measure confounding? (eg, confounding by indication)	☐	☐	☒	
7.2	Does the protocol address selection bias? (eg, healthy user/adherer bias)	☒	☐	☐	8.9.1.3

Section 7: Bias	Yes	No	N/A	Section Number
7.3 Does the protocol address information bias? (eg, misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	8.9.1.2

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (eg, collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.1
9.1.2 Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.1
9.1.3 Covariates and other characteristics?	☒	☐	☐	8.1
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.1
9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.1
9.2.3 Covariates and other characteristics? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.1
9.3 Is a coding system described for:				
9.3.1 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical [ATC] Classification System)	☐	☒	☐	
9.3.2 Outcomes? (eg, International Classification of Diseases [ICD], Medical Dictionary for Regulatory Activities [MedDRA])	☒	☐	☐	8.3.2/ Appendix D

Section 9: Data sources	Yes	No	N/A	Section Number
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (eg, based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.7
10.2 Is study size and/or statistical precision estimated?	☐	☒	☐	
10.3 Are descriptive analyses included?	☒	☐	☐	8.7
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	8.7.2.2
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.6
11.2 Are methods of quality assurance described?	☒	☐	☐	8.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	8.9.1.3
12.1.2 Information bias?	☒	☐	☐	8.9.1.3
12.1.3 Residual/unmeasured confounding? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (eg, study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☐	☒	

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/Institutional Review Board been described?	☒	☐	☐	9.2
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	8.8

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12.1

Comments:

Name of the main author of the protocol: PPD

Date: 01/04/2021

Signature: PPD

Appendix C. Sample Safety Reporting Form(s)

Project ID: 20200009	A	Observational Research Safety Reporting Form	Date of Reporter Awareness:
			Date Reported to Amgen:
	Reports to: Amgen Local Office	Email (preferred) avc-aqs-in-kr-pm@amgen.com Fax: 080-908-0982	

1. Initial: ☐ Follow-up: ☐
2. Site Number: Subject Number:
3. Indicate event type: *(Please tick all that apply)* ☐ AE/Other Safety Finding ☐ Product Complaint (PC) ☐ Adverse Device Effect (ADE)

4. Contact Details (Vendor/Investigator) **5. Reporter ID**

Name	Phone	Fax	Name or ID	Phone	Fax
Address			Address		
City	State/Province		City	State/Province	
Postal Code	Country		Postal Code	Country	

6. HCP Contact Details (if other than reporter) **7. Patient**

Name			Initials (optional)	Sex	Age (at time of event)	Was consent obtained to follow-up with HCP?
Country				☐ F ☐ M		☐ Yes ☐ No
Address						
City	State/Province	Postal Code	Weight	Height	Race	Is patient also reporter? ☐ Yes ☐ No
Phone	Fax		☐ lbs ☐ kg	☐ in ☐ cm		

8. Medical History (include primary diagnosis) **9. Suspect Product Information (include dosing details)**

Product/Device: ____ Lumakras (sotorasib)_____

Indication: _____

	Start Date (day month year)	Stop Date (day month year)	Dose	Route	Frequency

Pregnant? ☐ Yes ☐ No Lactating? ☐ Yes ☐ No

Allergy: _____

Prefilled Syringe? ☐ Yes ☐ No

Other Device _____

Lot # _____ ☐ Unknown

Serial # _____ ☐ Unavailable / Unknown

Vial Size

10. AE, Other Safety Finding, or PC/ADE information **HCP ONLY**

Finding (List main event first; one event per line)	Onset Date (day month year)	Resolved Date (If patient died, list date of death) Cause of Death: (provide autopsy report) (day month year)	Hospitalization: Hospitalized? ☐ Yes ☐ No; Prolonged Hospitalization? ☐ Yes ☐ No; Admitting dx; Date Admitted (day month year); Date Discharged (day month year)	Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/Prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly/birth defect; 06 Other significant medical hazard; 07 Non serious	Action Taken: 1=none; 2=dose reduced; 3=dose increased; 4=drug withdrawn; 5=drug rechallenge (state outcome)	Outcome: 01 Recovered/ Resolved; 02 Recovering/ Resolving; 03 Not recovered/not resolved; 04 Recovered/ resolved with sequelae; 05 Fatal; 06 Unknown	Severity 1=mild 2=moderate 3=severe	Relationship to Product/Device Is there a reasonable possibility that the event may have been caused by the Product/Device? Product	Device
								Y N	Y N
								Y N	Y N
								Y N	Y N
								Y N	Y N
								Y N	Y N

									Y N	Y N

11. Concomitant Medications (eg. chemotherapy)

Medication Names	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No	Co-suspect Yes	Continuing No	Continuing Yes	Dose	Route	Frequency	Treatment Meds

12. Relevant Laboratory Values (include dates, allergies, and any relevant prior therapy)

Date Day Month Year	Test / Unit										
	Test										
	Unit										

13. Other Relevant Test (diagnostics and procedures)

Date Day Month Year	Additional Tests	Results	Units

14. Description: Provide chronological summary and details of AE symptoms, PC or ADE that are listed in section 10 (signs, diagnosis, treatment, concomitant medications including those used to treat event).

Appendix D. Additional Safety Reporting Information

Adverse Event Severity Scoring System

The Common Terminology Criteria for Adverse Events (CTCAE) is available at the following location:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Appendix E. Pregnancy and Lactation Notification Forms

AMGEN Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20200009

Study Design: ☐ Interventional ■ Observational (If Observational: ■ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd__/ yyyy_____

Has the pregnant female already delivered? ☐Yes ☐No ☐Unknown ☐N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐Yes ☐No ☐Unknown ☐N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

AMGEN Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20200009

Study Design: ☐ Interventional ■ Observational (If Observational: ■ Prospective ☐ Retrospective)

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Subject ID # ____ **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details: _____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____