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List of Abbreviations

Abbreviation or Term	Definition/Explanation
AACR	American Association for Cancer Research
AUC	area under the plasma concentration-time curve
ALK	anaplastic lymphoma kinase gene
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
BID	twice daily
BRAF	B-raf gene
C_{max}	maximum plasma concentration
CHMP	Committee for Medicinal Products for Human Use
COVID-19	coronavirus disease 2019
CRC	colorectal cancer
CTCAE	common terminology criteria for adverse events
CYP3A	cytochrome P450 3A
DDI	drug-drug interaction
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EU	European Union
I	inhibitor concentration
IC_{50}	half maximal inhibitory concentration
ICH	International Council for Harmonisation
KRAS	Kirsten rat sarcoma viral oncogene homolog (protein)
KRAS	Kirsten rat sarcoma viral oncogene homolog (DNA)
KRASG12C	KRAS protein with a G12C amino acid substitution
KRAS p.G12C	KRAS gene with a mutation resulting in a G12C amino acid substitution at the protein level
MATE	multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities

List of Abbreviations

Abbreviation or Term	Definition/Explanation
NCI-ODWG	National Cancer Institute organ dysfunction working group
NSCLC	non-small cell lung cancer
NTRK	neurotrophic tyrosine kinase gene
OATP	organic anion transporter
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD-1	programmed cell death-1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
P-gp	P-glycoprotein
pINN	provisional International Nonproprietary Name
PPI	proton pump inhibitor
QD	once daily
QTc	corrected QT (interval)
QTcF	QT interval corrected for heart rate using Fridericia's formula
RAF	rapidly accelerated fibrosarcoma
RAS	rat sarcoma viral oncogene homolog
RECIST	response evaluation criteria in solid tumors
ROS1	proto-oncogene tyrosine-protein kinase ROS
SD	standard deviation
STK11	serine/threonine kinase 11
t_{max}	time to achieve C_{max}
US	United States
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WHO	World Health Organization

1. Product Development Rationale

This clinical overview summarizes data to support a marketing application for sotorasib (provisional International Nonproprietary Name [pINN]; AMG 510) (oral administration) for the treatment of adult patients with previously treated *KRAS G12C*-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). A justification for Conditional Marketing Authorisation provided in Module 1.5.5.

1.1 *KRAS p.G12C*-Mutated Non-small Cell Lung Cancer

1.1.1 Disease Background

Lung cancer is the leading cause of cancer death, with more than 80% of all lung cancer cases classified as NSCLC. Worldwide, lung cancer (small cell and non-small cell) is the most common cancer occurring in both men and women, with an estimated 2.09 million cases in 2018 (World Health Organization Statistics, 2018). In 2018, more than 250 000, 470 039, and 1 225 000 new cases of lung cancer were reported in North America, Europe, and Asia, respectively. The estimated number of deaths from lung cancer in 2018 was 173 278 in North America, 387 913 in Europe, and 1 068 862 in Asia (Globocan – Lung Cancer, 2018). Advanced NSCLC (stage IIIB and IV) is a serious and life-threatening disease, with a 5-year survival rate of 5.2% (Surveillance, Epidemiology, and End Results [SEER], 2019).

For patients with lung cancer, the most significant symptoms affecting their daily lives have been identified as fatigue, shortness of breath, and chronic pain. Other symptoms include insomnia, anxiety, and depression (US FDA, 2013, Liao et al, 2011; Tishelman et al, 2007; Tishelman et al, 2005; Cooley et al, 2003; Study [redacted]).

1.1.2 Oncogenic *RAS* and *KRAS p.G12C* Mutation

Several proto-oncogene mutations have been implicated in the development of NSCLC. Among these, mutations in the *RAS* family of proto-oncogenes are among the most prevalent. The *RAS* family of proto-oncogenes consists of 3 closely related genes that encode guanosine triphosphatases (GTPases) responsible for regulating cellular proliferation and survival (Simanshu et al, 2017; Barbacid, 1987). Different tumor types are associated with mutations in certain isoforms of *RAS*, with Kirsten rat sarcoma viral oncogene homolog (*KRAS*) being the most frequently mutated isoform in most cancers (Prior et al, 2012).

Of the *KRAS* mutations, an estimated 80% occur at codon 12. The *KRAS p.G12C* mutation in codon 12 is a single guanine to thymine substitution that results in a glycine to cysteine substitution at amino acid position 12. This structural change in the protein

results in a defect in the association of guanosine triphosphatase-activating proteins (GAPs), thereby reducing the hydrolysis of guanosine triphosphate (GTP) by the KRAS protein. The resulting accumulation of active, GTP-bound KRAS leads to proliferative and survival signaling in tumor cells (Jones et al, 2017). It is estimated that the *KRAS p.G12C* mutation is present in approximately 13% of lung adenocarcinoma and has been identified as a putative oncogenic driver in this tumor type (AACR Project GENIE Consortium, 2017; Biernacka et al, 2016; Fernández-Medarde and Santos, 2011).

Based on the estimated incidence of the *KRAS p.G12C* mutation in NSCLC (approximately 13% in Western regions and approximately 3% in Asia [Liu et al, 2020; [Biernacka et al, 2016]) and the estimated number of worldwide lung cancer cases in 2018 (Section 1.1.1), the expected number of new cases diagnosed annually for *KRAS p.*G12C-mutated NSCLC is approximately 33 000 in North America, 61 000 in Europe, and 37 000 in Asia.

The role of *KRAS* mutations in human cancers, including NSCLC, has been known for decades, but no inhibitors specifically targeting *KRAS p.G12C* mutations have been successfully developed until recently (McCormick, 2019). Oncogenic *KRAS* mutations rarely occur concomitantly with other oncogenic mutations such as the epidermal growth factor receptor gene (*EGFR*), anaplastic lymphoma kinase gene (*ALK*), B-raf gene (*BRAF*); proto-oncogene tyrosine-protein kinase ROS (*ROS1*), or neurotrophic tyrosine kinase gene (*NTRK*) (Martorell et al, 2017; Study [redacted] Study [redacted] [data on file]), which is consistent with the findings from a systematic literature search (Study [redacted] conducted by Amgen to identify data on the epidemiology and outcomes among patients with NSCLC driven by $KRAS^{G12C}$ mutations, and with the real word evidence studies as described below.

Natural History of Patients With KRAS p.G12C-mutated NSCLC

To better characterize the natural history of and outcomes to available therapies for patients with *KRAS pG12C*-mutated advanced NSCLC, and therefore the unmet medical need (Section 1.1.3), Amgen conducted 3 real-world evidence studies in the United States:

- Study [redacted] (N = 743), a retrospective cohort study of patients with *KRAS p.G12C*-mutated advanced NSCLC diagnosed between 2011 and 2019 in the Flatiron Health Foundation Medicine Clinico-Genomic Database.

- Study [redacted] (N = 7069), companion study to Study [redacted] a retrospective cohort study of patients with advanced NSCLC (ie, regardless of *KRAS p.G12C* mutation), diagnosed between 2011 and 2019 in the Flatiron Health-Foundation Medicine Clinico-Genomic Database.
- Study [redacted] (N = 416), a retrospective study of patients with *KRAS p.G12C*-mutated metastatic NSCLC diagnosed between 2004 and 2019 (with 99% between 2011 to 2019) in the American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) database.

The patients included in Studies [redacted] and [redacted] were mainly treated at community oncology practices across the United States, while those in Study [redacted] were treated at 3 US comprehensive academic cancer centers (Table 12 in Appendix 1). Patients were followed longitudinally for treatment outcomes. Results from Studies [redacted] and [redacted] showed that patients with *KRAS p.G12C*-mutated advanced NSCLC had similar demographic and clinical characteristics compared with the overall group of patients with advanced NSCLC; however, higher proportions of women, past or present smokers, and non-squamous cell carcinoma histology were observed in the patients with *KRAS p.G12C*-mutated advanced NSCLC.

Consistent with the literature, real-world evidence demonstrated that the *KRAS p.G12C* mutation rarely occurred (≤ 1.2%) with other actionable driver mutations (*EGFR* mutation, *ALK* rearrangement, *ROS1* rearrangement, and *BRAF* mutation), but was observed in the presence of higher serine/threonine kinase 11 (STK11), and higher expression level of programmed death-ligand 1 (PD-L1), and higher tumor mutational burden (Study [redacted] and Study [redacted] . Given that the *KRAS p.G12C* mutation rarely occurs with other actionable driver mutations, currently approved targeted therapies are not an option for most patients with *KRAS p.G12C* mutations.

Treatment patterns were generally similar among patients with *KRAS p.G12C*-mutated advanced NSCLC and the overall group of patients with advanced NSCLC. Platinum-based chemotherapy regimens and regimens including checkpoint inhibitors were the most common regimens in the first- and second-lines of therapy after diagnosis of advanced disease.

Similar proportions of demographic and clinical characteristics were also observed in patients with *KRAS p.G12C* mutations in Study [redacted] The real-world outcomes for these 3 studies are summarized in Table 1 and described below in Section 1.1.3.

1.1.3 Current Treatments and Unmet Medical Need

Current Treatments for Non-small Cell Lung Cancer

Treatment of advanced NSCLC has unequivocally improved since the discovery of immunotherapies (the checkpoint inhibitors) and targeted therapies for a variety of oncogenic mutations. The National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) treatment guidelines call for testing of all patients with NSCLC for oncogenic driver mutations (Ettinger et al, 2019; Planchard et al, 2018). However, 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). Further, oncogenic *KRAS* mutations rarely occur concomitantly with these other actionable oncogenic mutations (Studies [redacted] Scheffler et al, 2019; Martorell et al, 2017; Gainor et al, 2013). Thus, most patients with oncogenic *KRAS* mutations, including the *KRAS p.G12C* mutation, are not candidates for currently approved targeted therapies and consequently are typically treated as patients without targetable mutations (ie, with chemotherapy, immunotherapy, or antiangiogenic agents) (Planchard et al, 2018; Van Cutsem et al, 2014).

In first-line therapy, patients with NSCLC without actionable oncogenic driver mutations are typically treated with checkpoint inhibitors with or without platinum-containing doublets chemotherapy such as cisplatin/pemetrexed. Patients requiring subsequent second-line or later therapy are commonly treated with taxane chemotherapy with or without a vascular endothelial growth factor (VEGF) inhibitor or checkpoint inhibitors/platinum-containing doublet chemotherapy (if not already given in first line). In addition to the chemotherapy regimens above, current second-line treatment options for patients whose tumors are without actionable mutations, including the *KRAS p.G12C* mutation, are summarized in Table 13.

Unmet Medical Need

Checkpoint inhibitors have emerged as the new frontline therapy, and chemotherapy with or without an anti-angiogenic agent is the standard of care for second line or later for patients without actionable mutations (Ettinger et al, 2019; Planchard et al, 2018). Given the low response rates to chemotherapy regimens and poor survival outcomes of patients with NSCLC in second-line or later treatment, new biomarker-driven anticancer therapies are needed in this patient population.

Standard-of-care outcomes for patients with advanced/metastatic NSCLC (who are not candidates for currently approved targeted therapy) in ≥ second-line therapies, who had received first-line platinum-containing chemotherapy doublets (typically cisplatin/pemetrexed), have demonstrated objective response rates (ORRs; objective response = complete response + partial response) between 5.5% to 13% with chemotherapy (typically a taxane) and between 9.7% to 22.5% with chemotherapy plus a vascular endothelial growth factor receptor (VEGFR) inhibitor (Gridelli et al, 2018; Rittmeyer et al, 2017; Herbst et al, 2016; Borghaei et al, 2015; Herbst et al, 2007). These studies have also demonstrated progression-free survival (PFS) and overall survival (OS) of 2.8 to 4.2 months and 6 to 11.4 months, respectively, for chemotherapy alone and 4.8 to 5.4 months and 9.9 to 12.6 months, respectively, for chemotherapy with a VEGFR inhibitor. With these survival outcomes, current treatments remain inadequate.

While checkpoint inhibitors have shown improved efficacy in second line versus docetaxel after platinum-doublet chemotherapy (Vokes et al, 2018; Rittmeyer et al, 2017; Herbst et al, 2016; Borghaei et al, 2015), the treatment landscape has evolved since those studies were completed and checkpoint inhibitors with or without platinum-containing chemotherapy regimens are increasingly being used in first line. There are no large prospective randomized studies currently to inform on the utility of using checkpoint inhibitors in second line if they were used in first-line therapy. Likewise, there are no large randomized clinical trials evaluating the activity of platinum-doublet chemotherapy after initial checkpoint inhibitor monotherapy.

Three real-world evidence natural history studies conducted by Amgen showed that outcomes in second or later lines of therapy for patients with *KRAS p.G12C*-mutated advanced NSCLC were as poor as the overall patient population with advanced NSCLC (Section 1.1.2 and Table 1). These outcomes were consistent in similar patient populations regardless of the line of therapy when treated with current standard of care. In second line of therapy in patients with *KRAS p.G12C*-mutated advanced NSCLC and the overall advanced NSCLC population in Study [redacted] and Study [redacted], the median (95% CI) OS was 9.5 (8.1, 13.1) months and 10.2 (9.5, 11.3) months, respectively. The median (95% CI) real-world PFS was 4.0 (2.8, 5.3) months and 4.0 (3.7, 4.4) months, respectively. Consistent results were observed in Study [redacted]. Overall survival and real-world PFS decreased with each subsequent line of therapy in all 3 studies.

Table 1. Real-world Outcomes for Patients With Advanced Non-small Cell Lung Cancer and *KRAS p.G12C*-mutated Advanced Non-small Cell Lung Cancer by Line of Therapy

	KRAS p.G12C-mutated NSCLC		All NSCLC
Line of Therapy	Study [redacted]	Study [redacted]	Study [redacted]
Median (95% CI) OS (months)			
First	14.9 (12.2, 24.3)	12.0 (9.6, 15.3)	12.9 (11.9, 14.2)
Second	10.1 (7.1, 16.9)	9.5 (8.1, 13.1)	10.2 (9.5, 11.3)
Third	6.5 (5.0, NE)	6.7 (5.9, 10.7)	7.9 (6.6, 8.8)
Fourth	3.0 (2.2, NE)	5.9 (4.3, 12.9)	7.4 (6.4, 8.6)
Median (95% CI) real-world PFS (months)			
First	6.1 (4.4, 9.3)	5.0 (4.4, 5.8)	5.6 (5.3, 5.8)
Second	3.2 (2.1, 5.3)	4.0 (2.8, 5.3)	4.0 (3.7, 4.4)
Third	2.3 (1.4, 4.1)	3.1 (2.4, 4.3)	3.5 (3.1, 3.9)
Fourth	1.8 (1.4, 15.0)	2.6 (2.1, 4.7)	3.0 (2.7, 3.4)

CI = confidence interval; *KRAS p.G12C* = *KRAS* gene with a mutation resulting in a G12C amino acid substitution; NE = not evaluable; OS = overall survival; PFS = progression-free survival

[a] Retrospective Study [redacted] was conducted using the American Association for Cancer Research Project Genomics Evidence Neoplasia Information Exchange database in 416 patients with *KRAS p.G12C*-mutated advanced NSCLC. Retrospective Studies [redacted] and [redacted] were conducted using the United States Flatiron Health - Foundation Medicine Clinico-Genomic Database in 743 patients with *KRAS p.G12C*-mutated advanced NSCLC and 7069 patients with advanced NSCLC (ie, regardless of *KRAS p.G12C* mutation), respectively.

Source: Table 10-9 and Table 10-10 of Study [redacted] Observational Research Study Report (ORSR); Table 10-9 and Table 10-10 of Study [redacted] ORSR; Table 10-9 and Table 10-10 of Study [redacted] ORSR.

The literature is inconclusive with regards to the relative outcomes of patients with *KRAS*-mutated NSCLC, including *KRAS p.G12C*-mutated NSCLC. Data from the French National Cancer Institute indicate that patients with *KRAS*-mutated NSCLC show a lower proportion of responses to cytotoxic chemotherapy and decreased survival compared with the overall population of patients with NSCLC (Barlesi et al, 2016), and this finding has been supported by other data indicating that patients with *KRAS*-mutated NSCLC have a poor prognosis (Wiesweg et al, 2019; Park et al, 2017; Hames et al, 2016; Svaton et al, 2016; Johnson et al, 2013). Similar findings were reported in Chinese patients, with a shorter median OS observed in patients with the *KRAS p.G12C* mutation compared with patients with wildtype tumors (Liu et al, 2020). However, evaluation of patients with *KRAS p.G12C*-mutated NSCLC in Western populations showed that OS was similar with patients with other KRAS mutations (Arbour et al, 2020; Cui et al, 2020a; Cui et al, 2020b) and Japanese patients with the

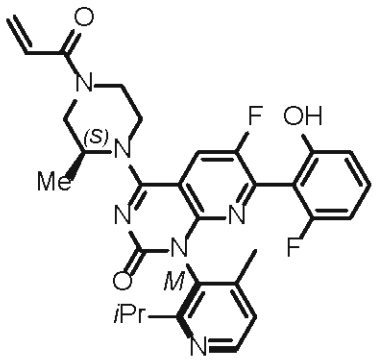
KRAS p.G12C or *p.G12V* mutation had a longer median PFS compared with patients with other *KRAS* mutations (Tamiya et al, 2020).

Overall, the results from the above-referenced real-world evidence studies and published literature show that patients with *KRAS p.G12C*-mutated advanced NSCLC had poor treatment outcomes with existing therapies in second-line or later, and their prognosis was as poor as the overall advanced NSCLC population, highlighting the unmet medical need for this patient population.

1.2 Sotorasib

Sotorasib is a novel, first-in-class, potent, and highly selective small molecule inhibitor that covalently binds to the KRAS protein with a G12C substitution ($KRAS^{G12C}$) and locks it in a guanine diphosphate (GDP)-bound, inactive state. By doing so, sotorasib specifically binds and irreversibly inhibits the $KRAS^{G12C}$ mutant protein. The chemical name of sotorasib is 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1*M*)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]pyrido[2,3-*d*]pyrimidin-2(1*H*)-one. The chemical structure is shown in Figure 1.

Figure 1. Sotorasib Chemical Structure



Sotorasib potently inhibits recombinant $KRAS^{G12C}$ but has minimal effect on wild type KRAS or other mutant versions of KRAS. The covalent, irreversible binding and inhibition of $KRAS^{G12C}$ by sotorasib requires a reactive thiol group adjacent to the sotorasib binding pocket. This thiol is provided by the cysteine at KRAS position 12 (G12C), resulting in a precise interaction that is specific for $KRAS^{G12C}$. The inhibitor contains a thiol-reactive portion that covalently modifies the cysteine residue and locks $KRAS^{G12C}$ in the inactive, GDP-bound conformation. This blocks the interaction of KRAS with effectors such as rapidly accelerated fibrosarcoma (RAF), thereby preventing downstream proliferation and survival signaling, including the phosphorylation of extracellular signal regulated kinase (ERK) (Canon et al, 2019; Simanshu et al, 2017;

Ostrem et al, 2013; Cully and Downward, 2008). 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. At physiologically relevant concentrations, sotorasib targets only the $KRAS^{G12C}$ protein and will affect the signaling and growth of only those tumor cells that have the *KRAS p.G12C* mutation (Section 2 of Module 2.4, Nonclinical Overview). Thus, sotorasib represents an important advance for the treatment of patients with *KRAS p.G12C*-mutated tumors.

1.3 Clinical Development Program

This marketing application provides a clinical evidence package to support the approval of sotorasib monotherapy per oral administration for the treatment of adult patients with previously treated *KRAS G12C*-mutated locally advanced or metastatic NSCLC.

The primary support for the proposed indication is based on efficacy results from the subjects with advanced NSCLC enrolled in the pivotal phase 2 portion of Study [redacted] an ongoing phase 1/2 study evaluating sotorasib for the treatment of *KRAS p.G12C*-mutated advanced NSCLC (hereafter referred to as NSCLC), colorectal cancer (CRC), and other solid tumors. Further efficacy support is provided based on the results from the phase 1 portion assessing sotorasib as monotherapy. This study is being conducted in North America, South America, Australia, Europe, and Asia.

The analysis of the safety profile for sotorasib is primarily based on the pooled monotherapy data from the phase 1 and phase 2 portions of ongoing Study [redacted] (N = 427). In addition to the pooled safety data from Study [redacted] supportive safety data from the following 3 ongoing studies are provided as safety summary reports:

- Study [redacted] is a phase 1 study to assess sotorasib monotherapy in subjects of Chinese descent who have *KRAS p.G12C*-mutated advanced solid tumors.
- Study [redacted] is a phase 1b master protocol study with sotorasib administered in investigational regimens (as monotherapy and in various combination regimens) in subjects with *KRAS p.G12C*-mutated advanced solid tumors.

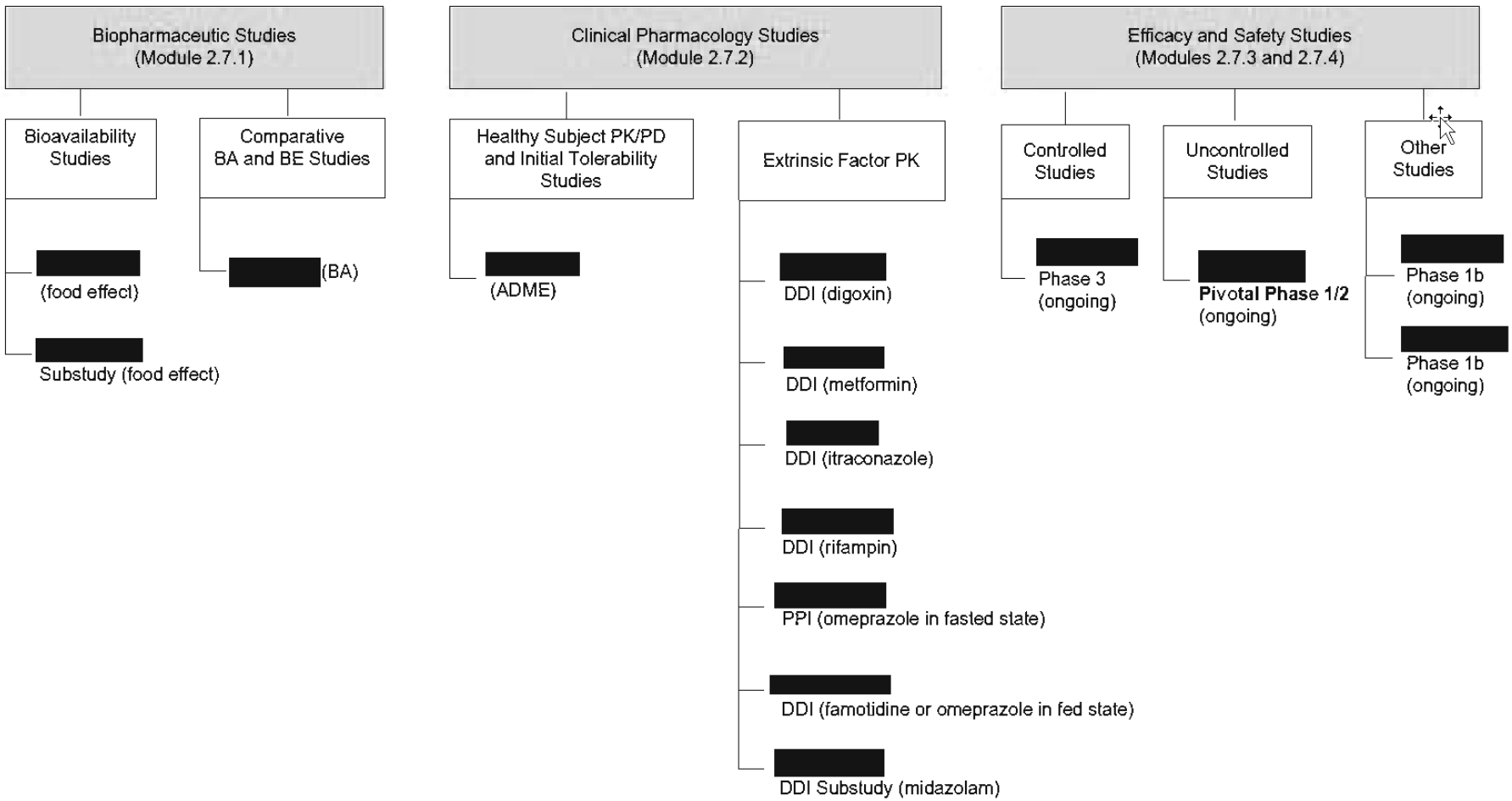
- Study [redacted] is a confirmatory phase 3, multicenter, randomized, open-label, active-controlled study to evaluate efficacy and safety of sotorasib versus docetaxel in previously treated, locally advanced and unresectable or metastatic NSCLC with the *KRAS p.G12C* mutation.

To characterize the initial safety, tolerability, pharmacokinetics, pharmacodynamics, and exposure-response properties of sotorasib, the marketing application also includes 9 clinical pharmacology studies and pharmacokinetic data from the subjects in the pivotal phase 1/2 Study [redacted]

The organization of clinical studies supporting the marketing application is provided in Figure 2. A complete list of completed and ongoing studies, including a summary of the study objectives, design, investigational product, subject enrollment, and duration of study, is provided in the Tabular Listing of All Clinical Studies, Module 5.2. Studies that are not included in this marketing application are listed in Appendix 3.

In addition, as described in Section 1.1, Amgen conducted real-world evidence studies (Study [redacted] Study [redacted], and Study [redacted] characterizing the natural history of patients with *KRAS p G12C*-mutated advanced NSCLC; these reports are included in Module 5. Amgen also conducted a small study from the Syapse Learning Health Network database (Study [redacted]), which showed similar results to the other 3 conducted real-world evidence studies. While the report is included in Module 5 for completeness, due to oversights in following good observational research practices for this study, the results should not be considered as supportive evidence for regulatory discussions.

Figure 2. Organogram of Sotorasib Clinical Studies in This Marketing Application



ADME = absorption, distribution, metabolism, and excretion; BA = bioavailability; BE = bioequivalence; DDI = drug-drug interaction; PPI = proton pump inhibitor
[a] For these ongoing studies, safety data only in the form of a safety summary report(s) to provide narratives for subjects who had serious adverse events and subjects who had treatment-emergent adverse events that led to treatment discontinuation (nonserious and serious).
[b] Phase 2 pivotal study supporting the marketing application (sotorasib monotherapy in subjects with *KRAS p.G12C*-mutated NSCLC).

1.4 Key Regulatory Guidance

The sotorasib clinical program was designed with consideration of the applicable guidelines for clinical study design, assessment of safety and efficacy, selection of endpoints, statistical principles, and report preparation. Clinical studies were conducted under Good Clinical Practices as described in International Council for Harmonisation (ICH) E6 (ICH, 2016), under the principles of the Declaration of Helsinki, and in accordance with local and regional regulations.

Relevant sections of the current European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) guideline on the evaluation of anticancer medicinal products in man, condition specific guidance for NSCLC (EMA, 2016) and of the United States (US) Food and Drug Administration (FDA) guidance on Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics (US FDA, 2015) were considered in development of the sotorasib program.

Key interactions with health authorities regarding the sotorasib development program are summarized in Table 2. Region-specific minutes of meetings with health authorities are provided in Module 1, as applicable.

Table 2. Summary of Relevant Interactions With Health Authorities for the Sotorasib Clinical Program in Non-small Cell Lung Cancer

Regulatory Authority (Region)	Date / Type of Interaction
Center for Drug Evaluation (China)	• [redacted]
European Medicines Agency (European Union)	• [redacted] • 11 September 2020 / EMA Pre-Submission Meeting • 02 November 2020 / CHMP Co-Rapporteur Pre-Submission Meeting • 18 November 2020 / CHMP and PRAC Rapporteur Pre-Submission Meeting
Food and Drug Administration (United States of America)	• [redacted] • 03 April 2020 / Type C Meeting on structure and format of the planned NDA – Clinical • 10 November 2020 / Pre-NDA Meeting – Clinical
Health Canada (Canada)	• [redacted] • 19 November 2020 / Pre-NDS Meeting – Clinical and CMC
Swissmedic (Switzerland)	• [redacted]

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CHMP = Committee for Medicinal Products for Human Use; CMC = Chemistry, Manufacturing, and Control; EMA = European Medicines Agency; HTA = Health Technology Assessment; NDA = New Drug Application; NDS = New Drug Submission; PRAC = Pharmacovigilance Risk Assessment Committee

Amgen sought scientific advice from [redacted] on the sotorasib development plan in NSCLC. Based on the formal interactions, Amgen conducted [redacted]. Additional clinical studies were completed and are included in this submission, [redacted] (Section 3).

Amgen acknowledges the advice related to the pivotal study for this application regarding [redacted] as well as global regulatory agencies, and is discussed further in the justification for Conditional Marketing Authorisation provided in Module 1.5.5.

2. Overview of Biopharmaceutics

The manufacturing processes used during development are presented in Module 2.3, Quality Overall Summary.

Uncoated and film-coated tablets were used in the clinical development program. The film-coated tablet introduced during the phase 2 portion of Study [redacted] o support ongoing phase 1, phase 2, and phase 3 studies is the same as the proposed commercial drug product. All healthy volunteer clinical pharmacology studies were conducted using the film-coated tablet. The comparability of the sotorasib uncoated and film-coated tablets used in the clinical program was demonstrated in vitro (Section 2.4 and Section 3 of Module 2.7.1, Summary of Biopharmaceutics).

Comparability of the uncoated and film-coated tablets that were used during the phase 1 portion and in a subset of subjects from the phase 2 portion of Study [redacted] with the film-coated, proposed commercial formulation, was established through comparable dissolution profiles. The film-coated tablet is formulated using the same ingredients as the uncoated tablets, with a film coating agent applied. The analytical assessments demonstrated the comparability of the uncoated tablet and film-coated tablet. Minor observed differences were not considered significant, and the materials were deemed to be comparable. The non-functional film coating on the tablet provides a consistent aesthetic appearance, which in combination with the shape, debossing marks, and yellow film color provides differentiation from similar products. The film coating could also aid in a patient's ability to swallow the tablets that may also help with patient compliance. Details are provided in Module 2.7.1, Summary of Biopharmaceutics.

In conclusion, the uncoated tablet and the proposed commercial, film-coated tablet were deemed comparable.

Drug Administration and Food Effect

Comparability of sotorasib pharmacokinetics in healthy subjects was assessed following administration as tablets and as tablets pre-dispersed in water in Study [redacted] Systemic exposure of sotorasib was comparable when administered as a tablet or when tablets were dispersed in water (Section 1.3 of Module 2.7.1, Summary of Biopharmaceutics). These data support the administration of film-coated tablets dispersed in water to patients who have difficulty swallowing solids.

In addition, the effect of food was examined in Study [redacted] conducted in healthy subjects and in a subset of subjects with *KRAS p.G12C*-mutated solid tumors within the

phase 1 portion of Study [redacted]. The results of these analyses show that sotorasib can be taken with or without food (Section 3.3.1; Section 2.1 and Section 2.2 of Module 2.7.1, Summary of Biopharmaceutics).

3. Overview of Clinical Pharmacology

The clinical pharmacology program supporting this marketing application was designed to characterize the pharmacokinetic and pharmacodynamic properties of sotorasib and to explore potential drug-drug interactions (DDI) suggested by nonclinical and in vitro studies using pooled human liver microsomes and human hepatocytes (Section 3.1).

The pharmacokinetic and pharmacodynamic data in this marketing application were used to:

- support selection of the dose regimen for the phase 2 study and marketing authorization in the proposed indication
- assess the relationships between dose and exposure, exposure and response, potential effect on renal and hepatic functioning, and QT interval elongation
- determine the effects of sex, body weight, race, and age on pharmacokinetics
- assess the potential for drug-drug interactions and food effect

The clinical pharmacology studies conducted are summarized in Table 25 of Module 2.7.2, Summary of Clinical Pharmacology. In addition, a population pharmacokinetic analysis was conducted using data from subjects in the phase 1/2 Study [redacted] and the sotorasib alone periods of single-dose clinical pharmacology studies.

3.1 Pharmacokinetic Studies Using Human Biomaterials

The in vivo elimination of sotorasib in nonclinical studies suggested oxidative metabolism and non-enzymatic conjugation as the primary routes of elimination, with a potential to cause cytochrome P450 3A (CYP3A)-mediated DDI due to reversible and time-dependent inhibition of CYP3A and induction of CYP3A4 in vitro (Section 1.2 and Section 1.3 of Module 2.7.2, Summary of Clinical Pharmacology). Sotorasib was predicted to have inhibition potential for CYP3A, CYP2C8, and CYP2D6, with CYP3A having the largest estimated R-value (Table 4 of Module 2.6.4, Pharmacokinetics Written Summary). Formation of the main metabolite in nonclinical species, M24, was predominantly catalyzed by CYP3A and was observed at low levels in hepatocytes from nonclinical species and human. As discussed in Section 8.3 of Module 2.6.6, Toxicology Written Summary, no primary pharmacology potency is anticipated from M10 and M24 (nucleotide exchange assay). The metabolites formed by pooled human liver microsomes and hepatocytes were also produced in vitro by liver microsomes and hepatocytes from the rat and dog, the species used in repeat-dose toxicology studies. Additionally, nonclinical studies suggested a potential for sotorasib to cause multidrug

and toxin extrusion (MATE)1, MATE2-K, breast cancer resistance protein (BCRP), and P-glycoprotein (P-gp)-mediated DDI. These results informed the design of the clinical pharmacology DDI program. Details regarding human biomaterial studies are provided in Section 7 of Module 2.6.4, Pharmacokinetic Written Summary.

3.2 Pharmacokinetic and Pharmacodynamic Considerations for Dose Selection

3.2.1 Pharmacokinetics Across a Range of Doses Administered to Subjects With Advanced Solid Tumors

In subjects with *KRAS p.G12C*-mutated advanced solid tumors, increases in sotorasib exposure from 180 to 960 mg once daily (QD) were less than dose proportional based on preliminary data (Table 2 of Module 2.7.2, Summary of Clinical Pharmacology). Sotorasib does not accumulate with multiple oral dosing.

3.2.2 Rationale for Dose Selection

The 960-mg dose was selected as the proposed dose for the intended previously treated patient population based on the totality of evidence available for sotorasib efficacy and safety data (Section 3.1.2 of Module 2.7.2, Summary of Clinical Pharmacology). As summarized in Section 4 and Section 5, the efficacy and safety results from Study [redacted] support the selection of 960 mg QD as an effective and safe dose for reducing tumor burden in subjects with NSCLC. From a clinical efficacy perspective, clinically meaningful response rates were observed at the 960-mg dose in adult subjects with NSCLC, confirming the dose is efficacious. From a clinical safety perspective, 960 mg QD sotorasib monotherapy has shown a tolerable safety profile. Fewer than 18% of subjects with NSCLC receiving 960 mg QD sotorasib had a dose change (ie, a nonzero dose received other than the planned dose), further supporting the 960 mg QD selection (Section 5.1).

From a clinical pharmacology perspective, an exposure-response analysis (Section 3.2.4.2 and Section 3.3.2 of Module 2.7.2, Summary of Clinical Pharmacology) evaluating the relationship between sotorasib dose and select measures of response was conducted in subjects with advanced NSCLC receiving sotorasib in Study [redacted]. Sotorasib 960 mg administered QD was numerically superior for ORR, best tumor size response, PFS, and OS when compared with lower dose groups (180, 360, and 720 mg QD); however, these differences were not statistically significant. Overall, the exposure-response analysis using sotorasib plasma concentrations as a measure of exposure was confounded by the independent effects of baseline disease status on sotorasib pharmacokinetics and efficacy (Section 3.2.4.2).

Exposure-response analysis was also conducted to evaluate the relationship between sotorasib exposure measures and treatment-related adverse events in subjects with advanced solid tumors receiving sotorasib in Study [redacted] (Section 3.2.4.2 and Section 3.3.2 of Module 2.7.2, Summary of Clinical Pharmacology). No significant exposure-response relationships for treatment-related adverse events of interest were identified. A correlation between sotorasib exposure and signs of serious liver injury was not observed.

3.2.3 Absorption, Distribution, Metabolism, and Excretion

In the phase 1/2 study (Study [redacted]), a mean steady-state apparent clearance and steady-state apparent volume of distribution of 32.5 L/hr and 367 L were observed, respectively, with a mean terminal half-life of 5.19 hours in subjects with advanced NSCLC (Table 2 of Module 2.7.2, Summary of Clinical Pharmacology). The time to maximum concentration was observed at 1-hour postdose. In vitro unbound fraction of sotorasib to human plasma proteins was 0.086 to 0.15 at concentrations of 0.25 to 25 µM (Section 5.2.3 of [redacted] Investigator's Brochure).

In the human mass-balance study (Study [redacted] , the geometric mean cumulative recovery over the collection period (0 to 312 hours) was 80.6%. The primary route of excretion was in the feces, accounting for a geometric mean of 74.4% of the administered [^{14}C]-sotorasib, with urine accounting for a geometric mean of 5.81%. On average, 1.47% (geometric mean) of the sotorasib dose was excreted unchanged in the urine, with a geometric mean calculated renal clearance of 0.41 L/hr (Section 2.1.2 of Module 2.7.2, Summary of Clinical Pharmacology).

Metabolite Profiling

M10 and sotorasib were identified as the major components, while M24 was a minor component, comprising of 26.8%, 17.1%, and 7.8% of total radioactivity, respectively, in diluted plasma samples from the human mass-balance study (Study [redacted] . Fecal excretion was the primary route of elimination. Sotorasib was the predominant and only component identified in feces, comprising 53% of the radioactive dose administered. In urine, M10 and sotorasib were identified as 2 of the major components, and neither constituted > 5% of the dose administered. These identified metabolites were also observed and measured in subjects with advanced solid tumors following a single dose and multiple doses (Study [redacted]).

3.2.4 Population Pharmacokinetic-Pharmacodynamic Meta-Analysis of Sotorasib Efficacy and Tolerability Endpoints in Subjects With Advanced Solid Tumors

In accordance with the implementation of ICH and US FDA Guidance for Industry (US FDA, 2003; ICH, 1994; US FDA, 1998), population pharmacokinetic-pharmacodynamic modeling approaches using nonlinear mixed effects were performed to characterize the association between demographic and clinical patient characteristics and plasma concentrations of sotorasib as well as the association of plasma sotorasib exposure with selected measures of efficacy and tolerability in the target adult population.

The primary objectives of the population pharmacokinetic analysis were to characterize sotorasib pharmacokinetics after oral administration and to quantify the interindividual, intraindividual, and residual variability in healthy subjects and subjects with NSCLC, to evaluate effects of subjects' demographic characteristics and other covariates on pharmacokinetic parameters of sotorasib obtained from clinical studies, and to perform simulations to further assess the impact of identified covariates on the sotorasib dosing regimen. Details of the population pharmacokinetic analysis are provided in Section 3 of Module 2.7.2, Summary of Clinical Pharmacology.

3.2.4.1 Population Pharmacokinetic Analysis

Sotorasib pharmacokinetics were characterized using plasma concentration-time data from 500 subjects enrolled in 6 clinical studies (Section 3.3 of Module 2.7.2, Summary of Clinical Pharmacology). Precise and reliable model parameter estimates were obtained with good predictive performance. The final population pharmacokinetic model was a 2-compartment model with first order absorption (characterized using 3 transit compartments) and induction effect on clearance and bioavailability. The estimated relative bioavailability across the 180 to 960 mg range was less-than-dose proportional. Induction after multiple dosing was estimated to reach state-steady in 2 to 3 weeks and associated with a 35% decrease in relative bioavailability and a 91% increase in clearance.

Intrinsic covariates of age, body weight, sex, race, country, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, number of prior anti-cancer therapies, disease stage at screening, mild and moderate renal impairment, and mild hepatic impairment did not show clinically meaningful effects on sotorasib pharmacokinetics, suggesting no dose adjustments were required for these intrinsic factors.

Baseline disease characteristics (patients versus healthy, tumor size, and Eastern Cooperative Oncology Group [ECOG] performance status) and serum albumin were estimated to affect sotorasib pharmacokinetics. This analysis indicated that subjects with lower disease burden or higher albumin have higher clearance and lower sotorasib exposure. However, the effects of differences in disease status (as reflected in effects of baseline albumin, baseline tumor burden, and ECOG status) on sotorasib pharmacokinetics were confounded with the effects of these same covariates on drug response (Section 3.2.4.2 and Section 3.3.2 of Module 2.7.2, Summary of Clinical Pharmacology) and do not warrant dose adjustment.

Administration with a high-fat meal was estimated to increase sotorasib exposure by 38%, however maximal concentrations were unchanged, while co-administration of a proton pump inhibitor (PPI) was estimated to decrease sotorasib exposure and maximal concentrations.

3.2.4.2 Exposure-Response Analysis (Pharmacokinetics and Efficacy)

The analysis dataset for efficacy comprised 248 subjects with NSCLC from phase 1/2 Study [redacted] who had ≥ 1 post-treatment plasma concentration measurement and 1 evaluation of efficacy endpoints (Section 3.3.2 of Module 2.7.2, Summary of Clinical Pharmacology). Subjects who received sotorasib as combination therapy or had other tumor types were excluded from the analysis.

Exposure-response analysis for efficacy was confounded by the independent effects of baseline disease status on sotorasib pharmacokinetics and efficacy. Subjects with lower baseline disease burden exhibited higher clearance and lower sotorasib exposure. The 960 mg dose was numerically superior for ORR, best tumor size response, PFS, and OS when compared to lower dose groups (180, 360, and 720 mg QD), however, these differences were not statistically significant (Figure 37 of Module 2.7.2, Summary of Clinical Pharmacology).

3.2.4.3 Exposure-Response Analysis (Safety)

Effect of Sotorasib on Selected Measures of Hepatic Functioning

The dataset for exposure-response analysis for safety comprised 421 subjects with advanced solid tumors (any tumor type) in the phase 1/2 Study [redacted] who had ≥ 1 post-treatment plasma concentration measurement. No significant exposure-response relationships for treatment-related adverse events of increased ALT, increased AST, and increased total bilirubin were identified. No correlation was

observed between exposure and signs of serious liver injury (defined as ALT or AST > 3 times the upper limit of normal, total bilirubin ≥ 2 times the upper limit of normal, and alkaline phosphatase [ALP] < 2 times the upper limit of normal).

3.3 Extrinsic Factors

The effects of food on the absorption and exposure of a new drug or drug product were conducted as part of marketing applications (US FDA 2002; EMA 2012). A dedicated food-effect study in healthy subjects and a food effect substudy in oncology subjects were conducted.

Studies using human liver microsomes and either chemical inhibitors or CYP-selective inhibitory index compounds support CYP3A enzymes being primarily responsible for oxidative metabolism of sotorasib. Sotorasib was predicted to have inhibition potential for CYP3A and CYP2D6, with CYP3A having the largest estimated R-value (Table 4 of Module 2.6.4, Pharmacokinetics Written Summary). Sotorasib was also predicted to have a clinically relevant induction potential on CYP3A expression. The largest estimated R-value calculated for a panel of transporters were for sotorasib inhibition of MATE1/2K transport. Sotorasib was also predicted to have a clinically relevant inhibition potential of P-gp and breast cancer resistance protein (BCRP) transport, based on either I_{gut}/IC_{50} or I_{total}/IC_{50}. Based on the calculated inhibition/induction potentials of metabolic enzymes and transporters, dedicated drug interaction studies were conducted in healthy subjects. In silico assessments were conducted for evaluating the drug interaction potential CYP2D6 substrates and sotorasib as a perpetrator.

Due to the pH-dependent solubility of sotorasib, dedicated acid-reducing agent studies were conducted in healthy subjects under fasted and fed conditions.

3.3.1 Food

As described in Section 2, sotorasib can be administered with or without food. Based on data from healthy subjects, sotorasib exposure (AUC) increased 1.38-fold and the time to achieve C_{max} (t_{max}) was delayed by 1.25 hours when 360 mg sotorasib was administered with a high-fat meal compared with administration in the fasted state; however, C_{max} was similar in fasted and fed conditions (Study [redacted]). Data from an analysis of subjects who completed the crossover-design food effect substudy of Study [redacted] suggest that administration of sotorasib in the fed state increased steady-state AUC_{0-24} by 1.25-fold, on average (Study [redacted]). Overall, the results of the food effect studies suggest sotorasib exposure increased 25% to 38% when sotorasib was administered with a standardized, high calorie (800 to 1000 kcal)

meal. However, maximal concentrations were similar when administered with or without a high calorie meal.

3.3.2 Drug-drug Interactions

Interactions of sotorasib with digoxin (P-gp substrate), metformin (MATE1 and MATE2-K substrate), itraconazole (CYP3A4 and P-gp inhibitor), rifampin (organic anion transporter [OATP] 1B1/1B3 inhibitors and CYP3A4 inducer), omeprazole (proton pump inhibitor [PPI]), famotidine (histamine-2 receptor antagonist), and midazolam (CYP3A4 substrate) are summarized below in Table 3. Details of the studies are provided in Section 2.3 of Module 2.7.2, Summary of Clinical Pharmacology.

Overall, these results suggest sotorasib may be taken safely with sensitive MATE1/2K substrates, CYP2D6 substrates, strong CYP3A4/P-gp inhibitors, and strong OATP1B1/1B3 inhibitors. However, exposures of P-gp and sensitive CYP3A4 substrates may be altered. Coadministration of PPIs, histamine-2 receptor antagonists, and strong CYP3A4 inducers may lead to decreased sotorasib exposure. Appropriate guidance regarding potential drug-drug interactions is provided in the prescribing information included in Module 1.

Table 3. Summary of Drug-drug Interaction Studies

Study Number	Evaluation	Results
[redacted]	Digoxin DDI (P-gp substrate)	*Sotorasib as perpetrator*: Geometric least squares mean ratio (test/reference) of digoxin AUC_{inf} and C_{max} were 1.214 and 1.914, respectively, when comparing digoxin coadministered with sotorasib (test) and digoxin administered alone (reference). Single doses of 0.5 mg digoxin were safe and well tolerated when administered alone or coadministered with 960 mg sotorasib in healthy subjects. These results suggest that maximal concentrations of P-gp substrates may increase, however, total exposures may not increase following coadministration with sotorasib.
[redacted]	Metformin DDI (MATE1 and MATE2-K substrate)	*Sotorasib as perpetrator*: Geometric least squares mean ratio (test/reference) of metformin AUC_{inf} and C_{max} were 0.985 and 0.996, respectively, when comparing metformin coadministered with sotorasib (test) and metformin administered alone (reference). *Sotorasib as victim*: Geometric least squares mean ratio (test/reference) of sotorasib AUC_{inf} and C_{max} were 0.910 and 0.812, respectively, when comparing sotorasib coadministered with metformin (test) and sotorasib administered alone (reference). Coadministration of 960 mg sotorasib and of 850 mg metformin were safe and well tolerated in healthy subjects. These results indicate that sotorasib and MATE1/2K substrates may be coadministered.
[redacted]	Itraconazole DDI (CYP3A4 and P-gp Inhibitor)	*Sotorasib as victim*: Geometric least squares mean ratio (test/reference) of sotorasib AUC_{inf} and C_{max} were 1.261 and 1.040, respectively, when comparing sotorasib coadministered with itraconazole (test) and sotorasib administered alone (reference). Coadministration of 360 mg sotorasib and 200 mg itraconazole were safe and well tolerated in healthy subjects. These results indicate that sotorasib may be coadministered with strong CYP3A4 and P-gp inhibitors.

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Footnotes are provided on last page of this table.

Table 3. Summary of Drug-drug Interaction Studies

Study Number	Evaluation	Results
[redacted]	Rifampin DDI (OATP inhibitor and CYP3A4 inducer)	*Sotorasib as victim:* Geometric least squares mean ratio (test/reference) of sotorasib AUC_{inf} and C_{max} were 0.766 and 0.840, respectively, when comparing sotorasib coadministered with single-dose rifampin (test) and sotorasib administered as tablets (reference). Geometric least squares mean ratio (test/reference) of sotorasib AUC_{inf} and C_{max} were 0.487 and 0.647, respectively, when comparing sotorasib coadministered with multiple daily dosing of rifampin (test) and sotorasib administered alone (reference). Doses of 960 mg sotorasib were safe and well tolerated when coadministered with a single dose of 600 mg rifampin and following multiple daily dosing of 600 mg rifampin to healthy subjects. These results indicate that sotorasib may be coadministered with OATP1B1/1B3 inhibitors, but coadministration with strong CYP3A4 inducers may decrease sotorasib exposure.
[redacted]	Omeprazole PPI	*Sotorasib as victim:* Geometric least squares mean ratio (test/reference) of sotorasib AUC_{inf} and C_{max} were 0.582 and 0.431, respectively, when comparing sotorasib administered with omeprazole in the fasted condition (test) and sotorasib administered alone in the fasted condition (reference). Single doses of 960 mg sotorasib were safe and well tolerated when coadministered with 40 mg omeprazole or administered alone in healthy subjects. These results suggest coadministration with proton pump inhibitors in the fasted state may decrease sotorasib exposure.
[redacted]	Famotidine or omeprazole in fed state (DDI)	*Sotorasib as victim*: Geometric least-square mean ratios of sotorasib AUC_{inf} and C_{max} were 0.622 and 0.654, respectively when comparing sotorasib coadministered with famotidine (test) and sotorasib alone (reference) in fed conditions. Geometric least-square mean ratios of sotorasib AUC_{inf} and C_{max} were 0.430 and 0.349, respectively when comparing sotorasib coadministered with omeprazole (test) and sotorasib alone (reference) in fed conditions. Doses of 960 mg sotorasib were safe and well tolerated when coadministered with a single dose of 40 mg famotidine and following multiple daily dosing of 40 mg omeprazole under fed conditions to healthy subjects. These results suggest sotorasib exposures may decrease when co-administered with histamine-2 receptor antagonists and proton-pump inhibitors in the fed state.

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Footnotes are provided on last page of this table.

Table 3. Summary of Drug-drug Interaction Studies

Study Number	Evaluation	Results
[redacted] Substudy	Midazolam DDI (CYP 3A4 substrate)	*Sotorasib as inhibitor/inducer of CYP3A4:* Exposure to midazolam decreased when coadministered with sotorasib following multiple daily dosing of sotorasib. Geometric least squares mean ratio (test/reference) of sotorasib AUC_{inf} and C_{max} were 0.47 and 0.52, respectively, when comparing midazolam coadministered with sotorasib (test) and midazolam administered alone (reference). These results suggest that coadministration of sotorasib may decrease the exposure of sensitive CYP3A4 substrates.

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AUC = area under the plasma concentration-time curve; C_{max} = maximum plasma concentration; CYP3A4 = cytochrome P450 3A; DDI = drug-drug interaction; MATE = multidrug and toxin extrusion; OATP = organic anion transporter; P-gp = P-glycoprotein; PPI = proton pump inhibitor
Source: Section 2.3 of Module 2.7.2, Summary of Clinical Pharmacology

3.4 Intrinsic Factors

The influence of demographic and clinical subject characteristic factors on the pharmacokinetics of sotorasib were investigated using population pharmacokinetics (Section 3.3 of Module 2.7.2, Summary of Clinical Pharmacology). Exposure of sotorasib was similar across age, body weight, race categories, between men and women, and no differences were observed between the overall subject population.

Sotorasib pharmacokinetics were not associated with individual markers of renal function, consistent with low radioactive recovery in urine (approximately 6%) in healthy subjects indicating that renal excretion is a minor pathway for sotorasib elimination.

Sotorasib pharmacokinetics were not associated with individual markers of hepatic function or calculated National Cancer Institute organ dysfunction working group (NCI-ODWG) index. The pharmacokinetics of sotorasib in subjects with severe hepatic impairment was not investigated.

3.5 Exposure – Corrected QT Interval Analysis

An extensive assessment of sotorasib's effect on QT interval was made during the Study [redacted], including intensive electrocardiogram (ECG) and sotorasib time-matched plasma concentration collection for all subjects in the phase 1 portion and for a subgroup of 30 subjects in the phase 2 portion and sparse ECG collection for the remaining subjects in the phase 2 portion of the study. The ECGs were sent to a central reader for determination of QRS, QT, corrected QT (QTc), RR, and PR intervals. Overall, ECG data (QRS, QT, QTc, RR, and PR intervals) from approximately 85% of subjects from the phase 1 and phase 2 portions of Study [redacted] were available via

central read and were included in the overall QT analysis (Section 8.9.2 of Study [redacted] Phase 1 and Phase 2). Higher sotorasib concentrations were not associated with QTc prolongation when analyzed using QT interval corrected for heart rate using Fridericia's formula (QTcF) relative to sotorasib time-matched plasma concentrations pooled from phase 1 and phase 2. These data support a conclusion that sotorasib has no direct pharmacological effect on QT interval (Section 5.4.7; Section 4.1 of Module 2.7.2, Summary of Clinical Pharmacology and Study [redacted] clinical study reports in Module 5.3).

4. Overview of Efficacy

For this marketing application, the primary evidence for the efficacy of the proposed indication is based on results from the pivotal phase 2 portion of Study [redacted] in subjects with *KRAS p.G12C*-mutated advanced NSCLC who received 960 mg QD. The study design of Study [redacted] is described in Section 4.1, details on the subject population for the phase 2 NSCLC tumor assessment is provided in Section 4.2, and a summary of the phase 2 efficacy results is provided in Section 4.3.

Efficacy data for NSCLC from the phase 1 portion of Study [redacted] were analyzed separately. The supportive efficacy results from phase 1 are summarized in Section 3.2 of Module 2.7.3, Summary of Clinical Efficacy, with key phase 1 data only discussed herein when relevant for NSCLC. Full efficacy results for phase 1 are provided in the Study [redacted] Phase 1 clinical study report in Module 5.3.5.2.

4.1 Key Design Aspects

4.1.1 Study Design

Study [redacted] is an ongoing phase 1/2, open-label, single-group study evaluating sotorasib in the treatment of subjects with *KRAS p.G12C*-mutated solid tumors.

The primary objectives of the phase 1 portion of the study were to evaluate the safety and tolerability of sotorasib and to estimate the maximum tolerated dose and/or a recommended phase 2 dose of sotorasib. For the phase 2 portion of the study, the primary objective was to evaluate the objective response rate (ORR) for sotorasib as monotherapy in subjects with *KRAS p.G12C*-mutated advanced solid tumors. Secondary objectives for both portions of the study included other measures of sotorasib efficacy (endpoints of duration of response, disease control rate, time to response, progression-free survival [PFS], and overall survival [OS]), safety, and pharmacokinetics.

Subjects in phase 1 were treated with sotorasib monotherapy at 180, 360, 720, or 960 mg once daily (QD). Subjects in phase 2 were treated with sotorasib monotherapy at 960 mg QD, the recommended phase 2 dose identified in phase 1. Subjects were to continue sotorasib treatment until disease progression (unless the subject is eligible for continued treatment), treatment intolerance, withdrawal of consent, death, or other protocol-defined reasons. The primary analysis was to occur approximately 8.5 months after at least 105 subjects with NSCLC or 60 with CRC had enrolled in the phase 2 portion of the study.

Eligible subjects were men or women ≥ 18 years of age, with *KRAS p.G12C*-mutated advanced NSCLC, colorectal cancer, or other solid tumors that were previously documented (phase 1) or identified prospectively using local assessments and confirmed with central laboratory testing for the mutation before enrollment in the study (phase 2). Central laboratory testing was performed using the Qiagen *therascreen*® KRAS RGQ polymerase chain reaction (PCR) In Vitro Diagnostic assay, which has CE (certification) Marking in Europe.

While the *therascreen*® KRAS RGQ PCR Kit that was used to confirm patient status at the central laboratory was labeled according to US regulatory requirements, the kit is currently CE-Marked in the EU. A detailed description, including a summary of the analytical and clinical performance characteristics, is provided in the instructions for use of the *therascreen*® KRAS RGQ PCR kit (QIAGEN 2020).

Approved diagnostics for testing *KRAS pG12C* mutational status are available in other regions. In addition, subjects must have received prior therapy (phase 1, except for the previously untreated metastatic NSCLC cohort) or progressed after receiving prior therapy (phase 2).

4.1.2 Appropriateness of Efficacy Endpoints

The primary endpoint in the phase 2 portion of Study [redacted] to support marketing approval is the objective response rate (ORR; ORR = complete response + partial response), which is reasonably likely to predict clinical benefit and has been used as a an endpoint in support of marketing approval in uncontrolled, single-group studies in advanced solid tumors (Hierro et al, 2019; US FDA, 2018a; US FDA, 2018b; US FDA, 2015; Drilon et al, 2018; Oxnard et al, 2016; Pignatti et al, 2015).

Since the clinical significance of ORR is generally assessed by both its magnitude and duration, duration of response was evaluated as a key secondary endpoint. Other supportive secondary efficacy endpoints include time to response, disease control rate, progression-free survival, and overall survival.

To avoid the introduction of bias in this single-group study, tumor response assessments were conducted by an independent, external radiologic central laboratory using Response Evaluation Criteria in Solid Tumors 1.1 criteria (US FDA 2015; Eisenhauer et al, 2009). The independent central laboratory performing the blinded central review was not subject to input from Amgen, its designees, or any study center involved in the clinical trial. The data received by the external reading radiologist were limited to only

those that were relevant to an independent assessment of tumor response and disease progression. The reading radiologist was blinded to all other data.

For most tumors, spontaneous regression in the absence of treatment is a rare phenomenon; thus, ORR is a convincing measure of antitumor activity showing the proportion of subjects with a response (EMA, 2017). While OS remains the gold standard in clinical studies, analyses to explore the association between ORR and survival have demonstrated patient-level and study-level associations between ORR, PFS, and OS (Blumenthal et al, 2015; Clarke et al, 2015). Studies have also demonstrated that disease control rate (percentage of patients with complete response, partial response or stable disease) can be a strong predictor of clinical benefit since not all patients with advanced NSCLC have tumor shrinkage after cancer therapies (Claret et al, 2013; Lara et al, 2008).

4.1.3 Statistical Methodology

To avoid potential bias due to differences in subject characteristics or other aspects of treatment between phase 1 and phase 2 of the study, the efficacy analysis was conducted separately for data from phase 1 and phase 2. All efficacy data reported for this marketing application are based on cutoff dates of 06 July 2020 (phase 1 interim analysis) and 01 September 2020 (phase 2 primary analysis for NSCLC).

The primary and secondary efficacy endpoints for phase 2 and the corresponding statistical methods of analysis are summarized in Table 4.

The phase 2 primary analysis was to occur approximately 8.5 months after 105 subjects with NSCLC or 60 with CRC, whichever had occurred first, had enrolled in the phase 2 portion of the study. The other tumor types with insufficient follow-up time were analyzed with appropriate interim analysis sets. The primary analysis data cutoff date was selected to ensure that all responders were followed for at least 6 months from the onset of the response and the assumption that most responders had achieved responses by the first or second scan (ie, 1.5 to 3 months from the start of treatment). This assumption was based on the time to response observed in the phase 1 portion of the study. To maintain data integrity, the study team was blinded to phase 2 efficacy data before database lock for the phase 2 primary analysis.

The phase 2 portion of the study targeted an ORR with the lower limit of its 95% confidence interval (CI) to exclude a pre-specified benchmark rate for each tumor type (NSCLC or CRC). For subjects with NSCLC, a large phase 3 study [redacted] for

second-line treatment after disease progression on platinum-based therapy showed that an ORR of 23% (95% CI: 20, 26) was observed with ramucirumab plus docetaxel (Garon et al, 2014; Cyramza® Prescribing Information). Thus, the benchmark ORR to exclude was selected as 23% for NSCLC. A sample size of 105 subjects with NSCLC would provide approximately a 90% probability that the lower limit of the ORR 95% CI exceeds 23% assuming the true ORR improvement is 15%. The minimum observed ORRs that would exclude the benchmark ORR with 105 subjects with NSCLC is 32%. The [redacted]L study population is generally similar to the NSCLC population eligible for the phase 2 portion of Study [redacted]; however, subjects in the [redacted] study were only in second-line treatment, whereas subjects in Study [redacted] are in second to fourth line of treatment. Since the subject population in Study [redacted] had received more previous lines of treatment than those in the [redacted] study, using the benchmark of ORR 23% would demonstrate a clinically meaningful improvement over current standard of care. Since the current standard of care for patients with NSCLC without an actionable driver mutation is to be treated with a checkpoint inhibitor with or without platinum-based chemotherapy in the first-line setting, the most optimal relevant benchmark in the previously-treated patient population is the taxane chemotherapy with VEGFR inhibitor.

The primary analyses for response-related efficacy endpoints in phase 2 were conducted using the full analysis set, which included all subjects who were enrolled in the phase 2 portion of the study, had received ≥ 1 dose of sotorasib, and had ≥ 1 measurable lesion at baseline as assessed by a blinded independent central review per response evaluation criteria in solid tumors (RECIST) version 1.1. Analyses for overall survival were conducted using the safety analysis set, which included all subjects enrolled in phase 2 who received ≥ 1 dose of sotorasib.

Table 4. Efficacy Endpoints and Statistical Methods

Efficacy Endpoints[a]	Definition	Analysis Method
Primary		
Objective Response Rate (ORR)	complete response + partial response as assessed by RECIST 1.1[b]	percentage of subjects with an objective response summarized with Clopper-Pearson exact 95% CI[c]
Secondary		
• Duration of Response (DOR)	time from first evidence of partial response or complete to disease progression or death due to any cause	Kaplan-Meier estimates and corresponding 2-sided 95% CIs for the median and quartiles (based on subjects with a response [responders])
• Disease Control Rate (DCR)	complete response + partial response + stable disease ≥ 5 weeks	summarized as for ORR
• Time to Response (TTR)	time from first dose of sotorasib until the first evidence of partial response or complete response	summarized by the non-missing sample size (n), mean, standard deviation, median, minimum, and maximum for responders
• Progression-free Survival (PFS) • 6-month PFS and 12-month PFS	time from first dose of sotorasib until disease progression or death from any cause	summarized with Kaplan-Meier curves, quartiles, and rates for selected timepoints
• Overall Survival (OS) • 12-month OS	time from first dose of sotorasib until death from any cause	summarized as for PFS

CI = confidence interval; CT = computed tomography; MRI = magnetic resonance imaging; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = response evaluation criteria in solid tumors

[a] The primary and secondary endpoints listed are those from the phase-2 portion of the study. These methods were also used in phase 1 for cohorts with these efficacy endpoints.

[b] Tumor response was evaluated by contrast-enhanced MRI or CT imaging according to RECIST 1.1 (Eisenhauer et al, 2009) and was assessed by blinded independent central review and by the local investigator. Radiographic response (complete response, partial response) required confirmation by a repeat scan ≥ 4 weeks after the first documentation of response.

[c] Clopper and Pearson, 1934

Source: Section 8.8 of Study [redacted] Phase 2

Changes in Study Conduct and Statistical Methods

Amgen has been closely monitoring the evolving Coronavirus Disease 2019 (COVID-19) situation across the globe and has, therefore, taken proactive steps to maintain the safety of study participants and support staff, including Amgen representatives, at all Study [redacted] clinical study centers, and to maintain study data integrity while maintaining compliance with Good Clinical Practices (GCP). Before database lock, Amgen assessed the effect of COVID-19 on Study [redacted], including the effect of changes implemented to ensure subject safety and continuity of the study. The temporary changes implemented in study procedures were documented as protocol deviations as recommended by health authorities. The assessment of the observed deviations due to COVID-19 concluded that the effect on the characterization and inference making on the primary and secondary efficacy endpoints (ORR and DOR) and safety assessments was low (Section 8.9.2 of Study [redacted] Phase 1 and Section 8.9.2 of Study [redacted] Phase 2).

4.2 Demographic and Baseline Characteristics

Phase 2

A total of 126 subjects with *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC (hereinafter referred to as NSCLC) were enrolled in the phase 2 portion of Study [redacted] and had received ≥ 1 dose of sotorasib monotherapy (Table 14b-1.1 of Study [redacted] Phase 2). Of these, 123 subjects received ≥ 1 dose of sotorasib and had ≥ 1 measurable lesion (based on central review) at baseline and were included in the full analysis set for efficacy assessments. As of the data cutoff date of 01 September 2020, 69 of the 126 subjects (54.8%) with NSCLC were continuing participation in the study. Of the 57 subjects (45.2%) who discontinued the study, 47 subjects (37.3%) died and 10 subjects (7.9%) withdrew consent. Eighty-nine subjects (70.6%) had discontinued sotorasib treatment; the most common reasons for discontinuation were disease progression (70 subjects [55.6%]) and adverse event (11 subjects [8.7%]). Median duration (range) of treatment with sotorasib was 24.1 (1.0, 52.1) weeks, with 47.6% and 28.6% of subjects receiving ≥ 6 and ≥ 9 months of treatment, respectively (Table 14b-5.1 of Study [redacted] Phase 2). The median relative dose intensity was 100%.

Of the 126 enrolled subjects with NSCLC, 81.7% were white and 50% were men (Table 14b-2.1 of Study [redacted] Phase 2). The median (range) age was

63.5 (37, 80) years. Most subjects had non-squamous NSCLC (99.2%) and stage IV disease at screening (96.0%) (Table 14n-2.2 of Study [redacted] Phase 2). Per protocol eligibility criteria, subjects had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (38 subjects [30.2%] and 88 subjects [69.8%], respectively). Subjects had received a median of 2 prior lines of anticancer therapy: 54 subjects (42.9%) received 1 prior line, 44 (34.9%) received 2 prior lines, 28 (22.2%) received 3 prior lines, and no subject received 4 or more. A total of 113 subjects (89.7%) received prior platinum-based chemotherapy and 115 subjects (91.3%) received prior anti-PD-1/PD-L1 immunotherapy therapy. A total of 102 subjects (81.0%) had received and progressed on treatment with both checkpoint inhibitors and platinum-based therapy. Most subjects were former smokers (102 subjects, 81.0%) or current smokers (15 subjects, 11.9%). Overall, 7.1% had received and progressed on targeted small molecule therapies (none were approved therapies/combinations for actionable mutations). Based on available data reported by the study centers and consistent with the literature and real-world evidence described in Section 1.1.3, a low number of subjects had co-mutations (10.3% of subjects for *TP53*, 5.6% for *STK11*, 2.4% for *EGFR*, and < 1.6% for all other co-mutations; no subjects had co-mutations in *ALK* or *ROS*) (Table 14n-2.2 of Study [redacted] Phase 2). The exploratory biomarker analysis using central testing for identifying co-mutations is ongoing for phase 2; the report will be submitted separately as a supplemental clinical study report. Overall, 96.8% of subjects had metastatic disease. Per protocol eligibility criteria, while subjects with treated and stable brain metastases could enroll in the study, subjects with active brain metastases were excluded. This is in keeping with the standard of treating active brain metastases with surgery or radiation before initiating pharmacotherapy.

Phase 1

A summary of baseline demographics for the 124 subjects with NSCLC in phase 1 of Study [redacted] is provided in Section 3.1.3.2 of Module 2.7.3, Summary of Clinical Efficacy. As of the data cutoff date of 06 July 2020, 69 of the 124 subjects (55.6%) were continuing participation in the study. Of the 55 subjects (44.4%) who discontinued the study, 44 subjects (35.5%) died and 11 subjects (8.9%) withdrew consent. Seventy-five subjects (60.5%) discontinued sotorasib treatment; the most common reasons for treatment discontinuation were disease progression (53 subjects [42.7%]) and adverse event (12 subjects [9.7%]). Baseline demographic characteristics were

generally similar across the 7 monotherapy dose cohorts. Most subjects were white (81.5%) and women (62.9%); median (range) age was 68.0 (49 to 86) years. Baseline disease characteristics and prior treatments for these subjects are provided in Table 8 of Module 2.7.3, Summary of Clinical Efficacy.

Based on available data reported by the study centers, a low number of subjects had co-mutations (15.3% of subjects for *TP53*, 12.1% for *STK11*, 1.6% for *EGFR*, and ≤ 4% all other co-mutations; no subjects had co-mutations in *ROS*) (Table 14j-2.2 of Study [redacted] Phase 1). Among the 35 subjects with NSCLC included in the exploratory biomarker analysis based on central testing, there were no actionable co-mutations detected and no discernable pattern suggesting mechanisms of resistance in this preliminary dataset (Section 16.1.13.4 of Study [redacted] Phase 1).

Overall, the subjects with NSCLC enrolled across all cohorts in both phase 1 and phase 2 of Study [redacted] had baseline characteristics indicative of subjects with locally-advanced or metastatic NSCLC. Thus, the patient population evaluated in Study [redacted] is considered representative of the overall population of patients with *KRAS p.G12C*-mutated advanced NSCLC and supportive of the proposed indication.

4.3 Efficacy Results

The key efficacy results for tumor response in subjects with NSCLC from the phase 2 portion of Study [redacted] (full analysis set) are provided in Table 5.

Based on blinded independent central review using RECIST 1.1, the ORR among subjects with NSCLC in the phase 2 portion of Study [redacted] was 37.4% (95% CI: 28.8, 46.6) with 46 of the 123 evaluable subjects achieving a complete or a partial response, including 2 subjects (1.6%) with a complete response and 44 subjects (35.8%) with a partial response (Table 5, Figure 3, and Section 3.2.1 in Module 2.7.3, Summary of Clinical Efficacy). The lower limit of the 95% CI excluded the prespecified benchmark ORR of 23% (Section 4.1.3). Among the 46 responders in the phase 2 NSCLC group, the median time to response was 1.35 months (range: 1.2 to 6.1) (Table 5). Median duration of response (DOR) was 8.4 months (95% CI: 6.9, 8.4) (Table 5 and Figure 4). As of the data cutoff date, among the 46 responders, 24 subjects (52.2%) were still receiving treatment with ongoing response; the median follow-up time for DOR was 6.9 months (range: 1.3 to 8.4+) (Section 3.2.2.1 in Module 2.7.3, Summary of Clinical Efficacy).

Among the 99 subjects who had prior treatment with both platinum-based chemotherapy and anti-PD-1 or anti-PD-L1, ORR was 32.3% (95% CI: 23.3, 42.5) and median duration of response was not estimable (95% CI: 6.9 months, not estimable). This subset of subjects had received the most effective available therapies in NSCLC, hence satisfactory treatment options are limited.

Thus, the observed ORR, which is rapid and durable, represents a clinically meaningful benefit when considering the intended patient population with life-threatening disease and limited available therapies (Section 6).

Table 5. Summary of Objective Response Based on Blinded Independent Central Review in Study [redacted] (Phase 2 NSCLC – Full Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 123)
Best overall response - n (%)	
Complete response (CR)	2 (1.6)
Partial response (PR)	44 (35.8)
Stable disease (SD)	53 (43.1)
Progressive disease (PD)	20 (16.3)
Not evaluable (NE)	2 (1.6)
Not done	2 (1.6)
Objective response rate (ORR)	
Number of overall responders - N1 (%)	46 (37.4)
95% CI[a]	(28.84, 46.58)
Disease control rate (DCR) - n (%)	99 (80.5)
95% CIa	(72.37, 87.08)
Duration of objective response (DOR)[b]	
Observed duration ≥ 3 months - n (%)	35 (76.1)
Observed duration ≥ 6 months - n (%)	23 (50.0)
Subject status - n (%)	
Events	14 (30.4)
Progressive disease	13 (28.3)
Death	1 (2.2)
Related to COVID-19	0 (0.0)
Censored	32 (69.6)
On study without disease progression	28 (60.9)
No evaluable post-baseline disease assessment	0 (0.0)
Missed more than 1 consecutive assessments	0 (0.0)
Related to COVID-19	0 (0.0)
Started new anti-cancer therapy	3 (6.5)
Withdrew consent	1 (2.2)
Related to COVID-19	0 (0.0)
Off study due to sponsor decision	0 (0.0)
Related to COVID-19	0 (0.0)
Lost to follow-up	0 (0.0)
Related to COVID-19	0 (0.0)

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Footnotes are provided on last page of table.

Table 5. Summary of Objective Response Based on Blinded Independent Central Review in Study [redacted] (Phase 2 NSCLC – Full Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 123)
Duration of response (KM) (months)	
25th percentile (95% CI)	6.8 (3.5, 7.1)
Median (95% CI)	8.4 (6.9, 8.4)
75th percentile (95% CI)	8.4 (NE, NE)
Min, Max (+ for censored)	1.3+, 8.4
Kaplan-Meier estimate (95% CI)[c]	
At 3 months	89.9 (75.3, 96.1)
At 6 months	76.2 (59.1, 86.9)
At 9 months	0.0 (NE, NE)
At 12 months	0.0 (NE, NE)
Follow-up time for DOR[d] (KM) (months)	
25th percentile (95% CI)	5.5 (2.8, 6.7)
Median (95% CI)	6.9 (5.6, 7.0)
75th percentile (95% CI)	7.1 (7.0, 8.1)
Min, Max (+ for censored)	1.3, 8.4+
Time to objective response (months)[b]	
Number of subjects with objective response	46
Mean (SD)	1.95 (1.23)
Median	1.35
Q1, Q3	1.25, 2.69
Min, Max	1.2, 6.1

Phase 2 data cut-off date 01SEP2020. As of the data cutoff date, a total of 69 of 126 subjects (54.8%) were continuing participation in the study (Section 4.2).

CI = confidence interval; KM = Kaplan-Meier; N = number of subjects in the analysis set; n = number of subjects with observed data; NE = not estimable; NSCLC = non-small cell lung cancer; QD = once daily; RECIST 1.1 = response evaluation criteria in solid tumors;

Months are derived as days x (12/365.25).

Best Overall Response for a subject is the best observed disease response per RECIST1.1 based on central review.

ORR is defined as the proportion of subjects with complete response or partial response and confirmation after at least 4 weeks.

DCR is defined as the proportion of subjects with complete response or partial response with confirmation or stable disease ≥ 5 weeks.

DOR is defined as time from first evidence of complete response or partial response to disease progression or death due to any cause, among responders.

Time to response is defined as time from the first dose of sotorasib until the first evidence of complete response or partial response, among responders.

[a] Exact 95% CI was calculated using the Clopper Pearson method

[b] Time to response and duration of response are calculated among confirmed responders N1.

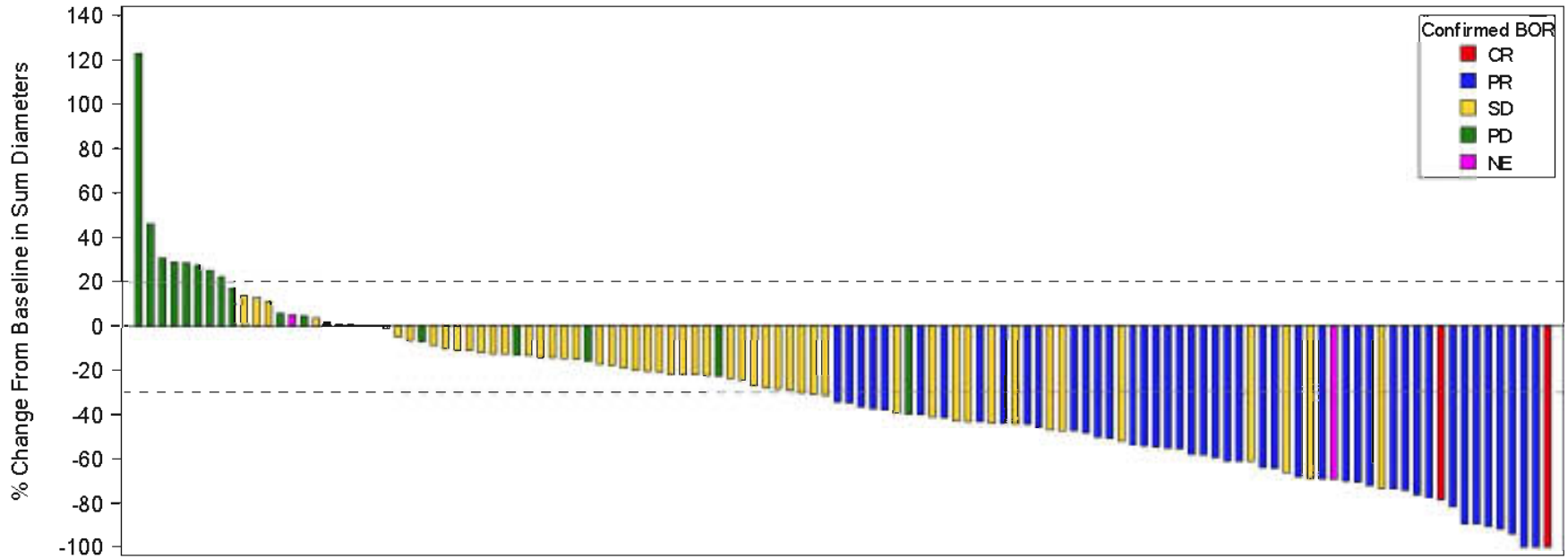
[c] 95% CIs are based on estimated variance for log-log transformation of the KM survival estimate.

[d] Follow-up time is measured by reversing the status indicator for censored and events.

Events marked "Related to COVID-19" were identified from available information collected on the case report form (CRF) and protocol deviation data.

Source: Table 14n-4.1.1 of Study [redacted] CSR Phase 2

Figure 3. Waterfall Plot of Best Tumor Shrinkage by Central Review (Phase 2 NSCLC Full Analysis Set)

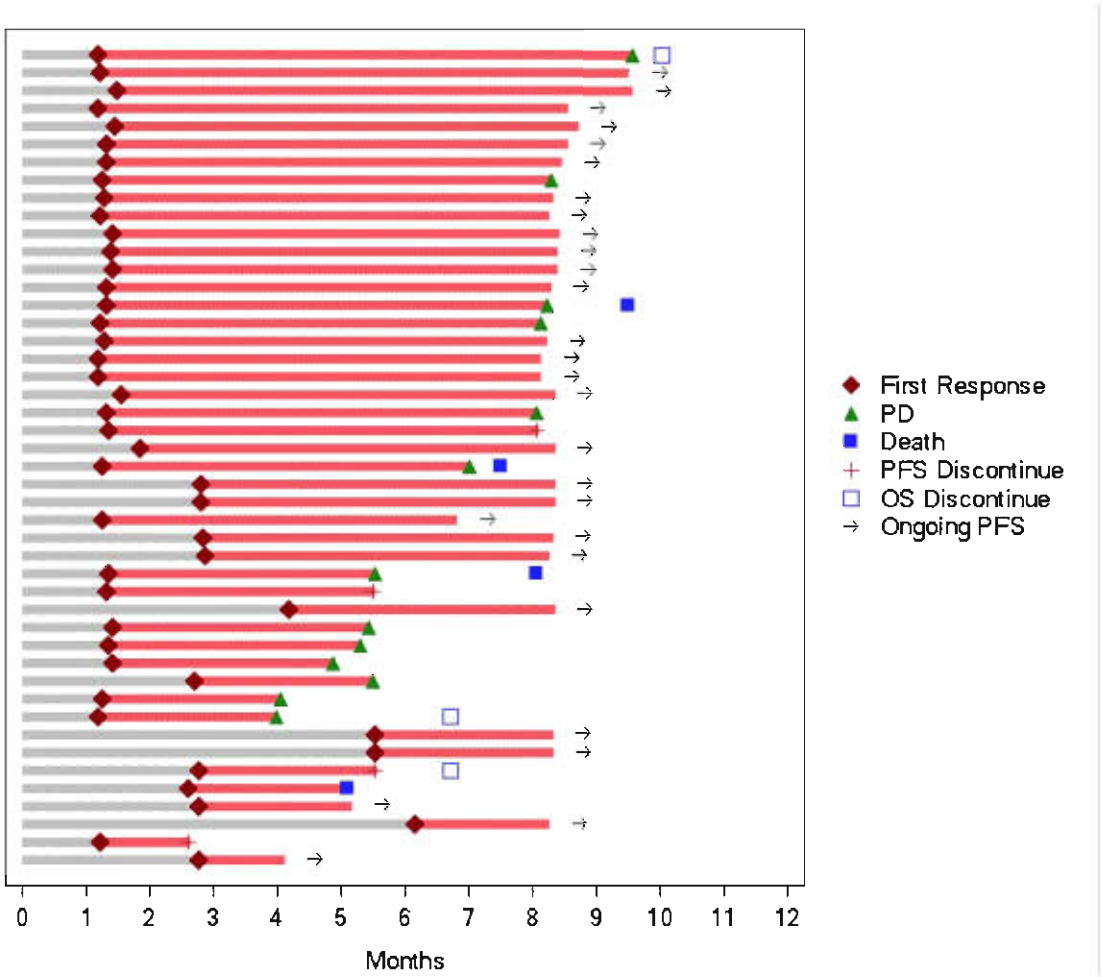


Phase 2 data cut-off date 01SEP2020.
Percent change from baseline in sum of diameters only considers tumor assessments prior to and include the 1st assessment where timepoint response is progressive disease, and prior to start of next anti-cancer therapy.
Three subjects without baseline target lesions and 3 subjects without post-baseline percent changes are not shown.
One CR whose reduction <100% is because target lesions are in lymph nodes.

[redacted]

BOR = best overall response; CR = complete response; PD = progressive disease; PR = partial response; NE = not evaluable; NSCLC = non-small cell lung cancer; SD = stable disease

Figure 4. Duration of Response Based on Blinded Independent Central Review in Study [redacted] (Phase 2 NSCLC – Responders in Full Analysis Set)



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

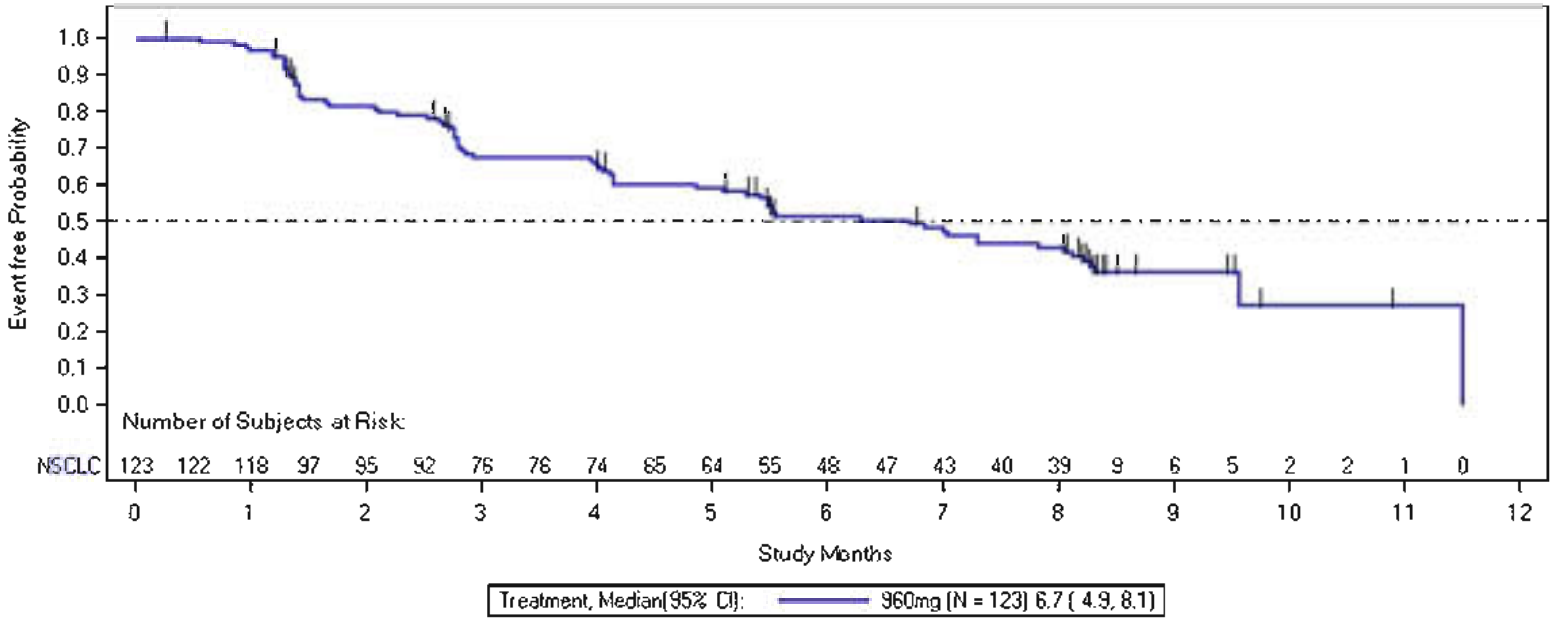
Phase 2 data cutoff date of 01 September 2020. The grey bar represents the time to first response (complete response or partial response) among confirmed responders; the pink bar represents the duration of response. "PFS Discontinue" indicates PFS censor due to no post-baseline assessment, consent withdrawn, start of new anticancer therapy, subject missed ≥ 2 consecutive tumor assessments, removal from study due to sponsor decision, or lost to follow-up. "OS Discontinue" indicates OS censor due to consent withdrawn, completed study, or removal from study due to sponsor decision, or lost to follow up.

Source: Figure 14n-4.1.2 of Study [redacted] Phase 2

The PFS and OS results provide additional evidence of the efficacy of sotorasib. The median follow-up time for PFS was 8.3 months (range: 0.3 to 11.5+). Median PFS based on central review was 6.7 months (95% CI: 4.9, 8.1); the Kaplan-Meier estimate for PFS at 6 months was 51.5% and 36.2% at 9 months (Figure 5; Table 10-2 and Table 10-3 of Study [redacted] Phase 2; Section 3.2.2 of Module 2.7.3, Summary of Clinical Efficacy). Median follow-up time for OS was 9.3 months (range: 1.1 to 12.2). Median OS was 12.0 months (95% CI: 9.5, not estimable); the Kaplan-Meier estimate

for OS at 6 months was 75.5% and 63.4% at 9 months (Figure 6). As of the data cutoff date (01 September 2020), 69 of the 126 subjects (54.8%) were alive at last follow-up visit, 9 (7.1%) had withdrawn consent, and 48 (38.1%) had died.

Figure 5. Kaplan-Meier Plot of Progression-free Survival Based on Blinded Independent Central Review in Study [redacted] (Phase 2 NSCLC – Full Analysis Set)

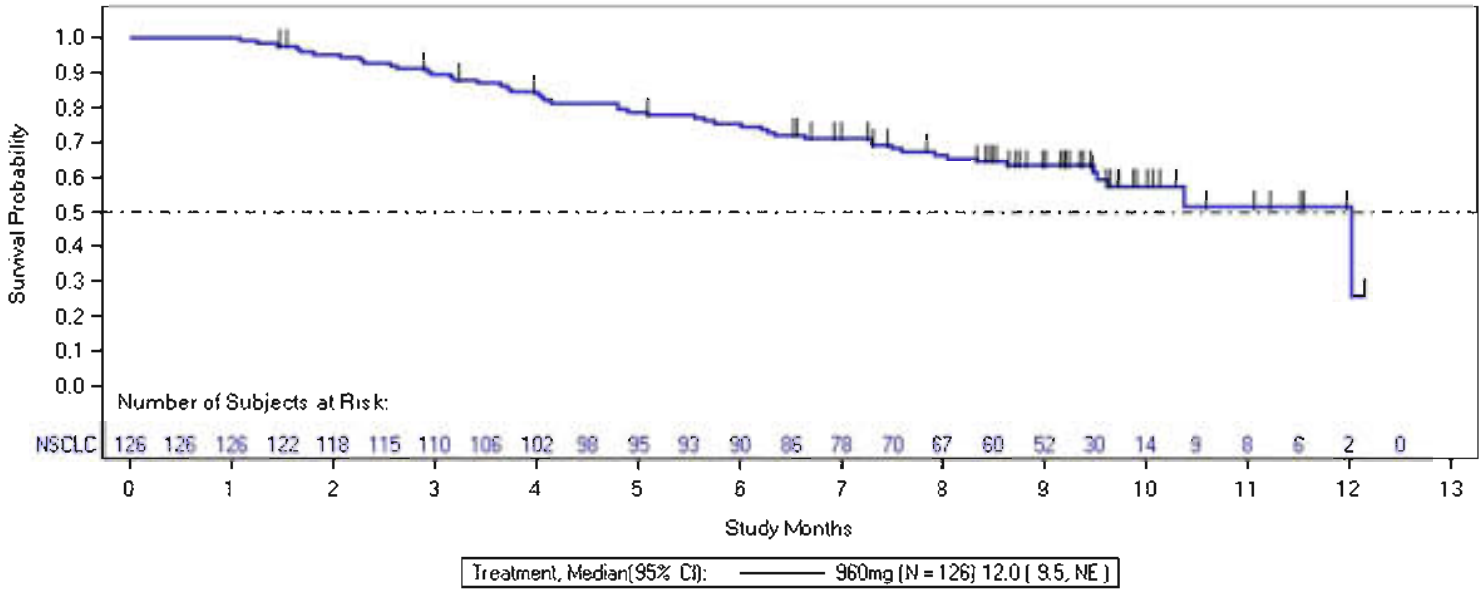


Phase 1 data cut-off date 06JUL2020 Phase 2 data cut-off date 01SEP2020.
Censor indicated by vertical bar |
NE = Not Estimable.
Radiological Progression or Death (whichever occurs earlier) is an event.

[redacted]

NSCLC = non-small cell lung cancer

Figure 6. Kaplan-Meier Plot of Overall Survival in Study [redacted] (Phase 2 NSCLC – Safety Analysis Set)



Phase 1 data cut-off date 06JUL2020. Phase 2 data cut-off date 01SEP2020.
Censor indicated by vertical bar |
NE = Not Estimable.
Death is an event.

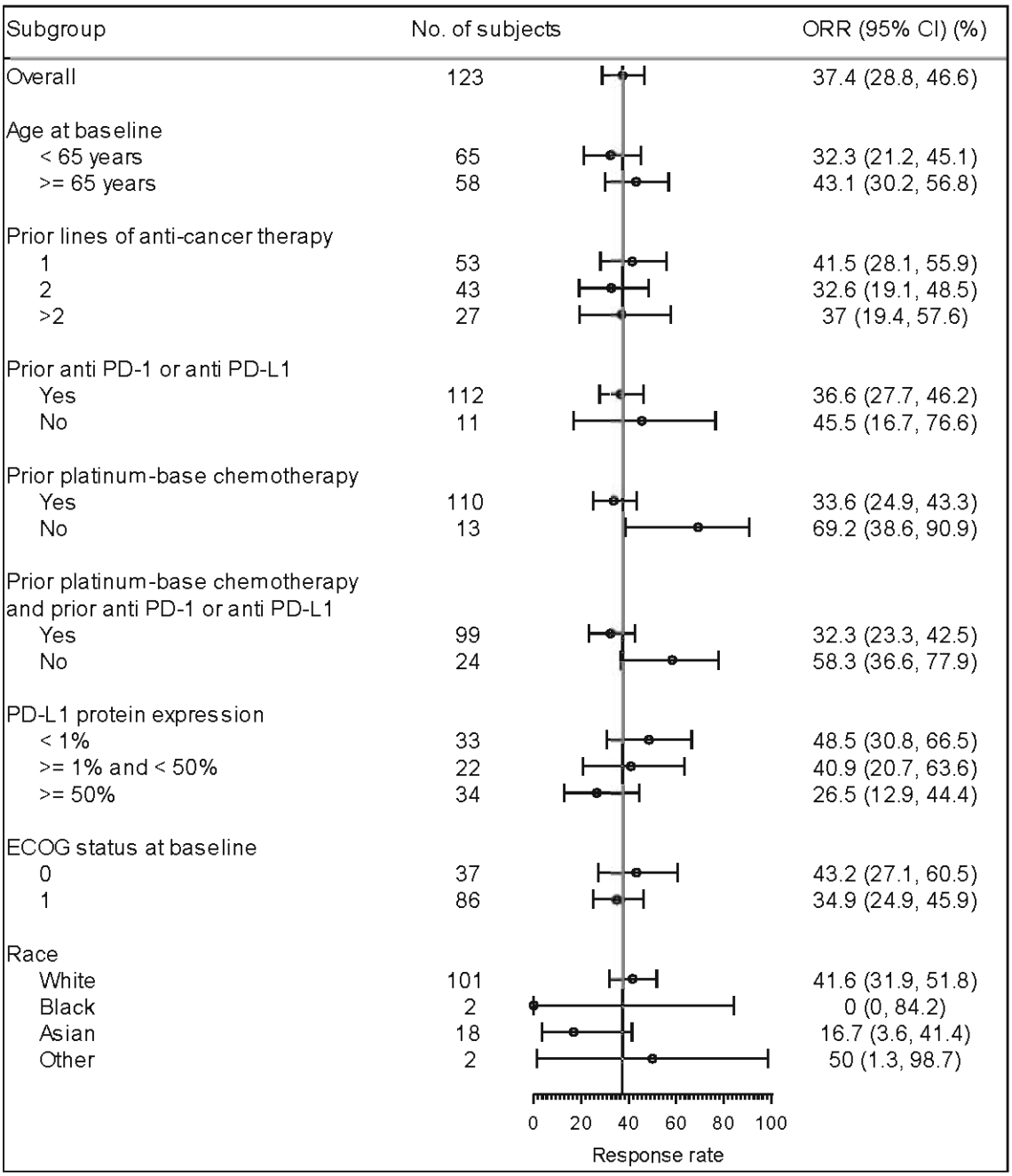
[redacted]

NSCLC = non-small cell lung cancer

Analyses were conducted to explore the consistency of sotorasib treatment effect across subgroups (age, race, prior lines of anticancer therapy, prior immunotherapy treatment, ECOG status, histopathology type, disease status, presence of liver or brain metastasis, smoking history, region, best response on last prior therapy) among subjects with NSCLC in phase 2 (Figure 7). No notable treatment-by-subgroup effects were observed, with the exception of prior platinum-based chemotherapy and presence of brain metastases (Figure 7 and Table 14n-4.1.2 of Study [redacted] Phase 2). The ORR was higher for subjects who had not received prior platinum-based chemotherapy compared with those who had received it and with the overall subject population (69.2% [9 of 13 subjects] vs 33.6% [37 of 110 subjects] and 37.4% [46 of 123 subjects], respectively). The ORR was higher for subjects without brain metastasis than those with brain metastasis (43.3% [42 of 97 subjects versus 15.4% [4 of 26 subjects]). However, subgroup analysis interpretation may be limited because of the small sample size of each subgroup. No notable treatment-by-subgroup effects were observed in subgroup analyses of PFS (Table 14n-4.1.2 of Study [redacted] Phase 2).

Sensitivity analyses were conducted using the assessments reported by the investigator. The concordance rate between investigator and blinded independent radiological central laboratory assessments was 82.9% for ORR, 78.0% for progressive disease status, and 65.0% for progressive disease status and the timing of the progression (Section 3.2.1 of Module 2.7.3, Summary of Clinical Efficacy).

Figure 7. Objective Response Rate Based on Central Review by Subgroup in Study [redacted] (Phase 2 NSCLC – Full Analysis Set)

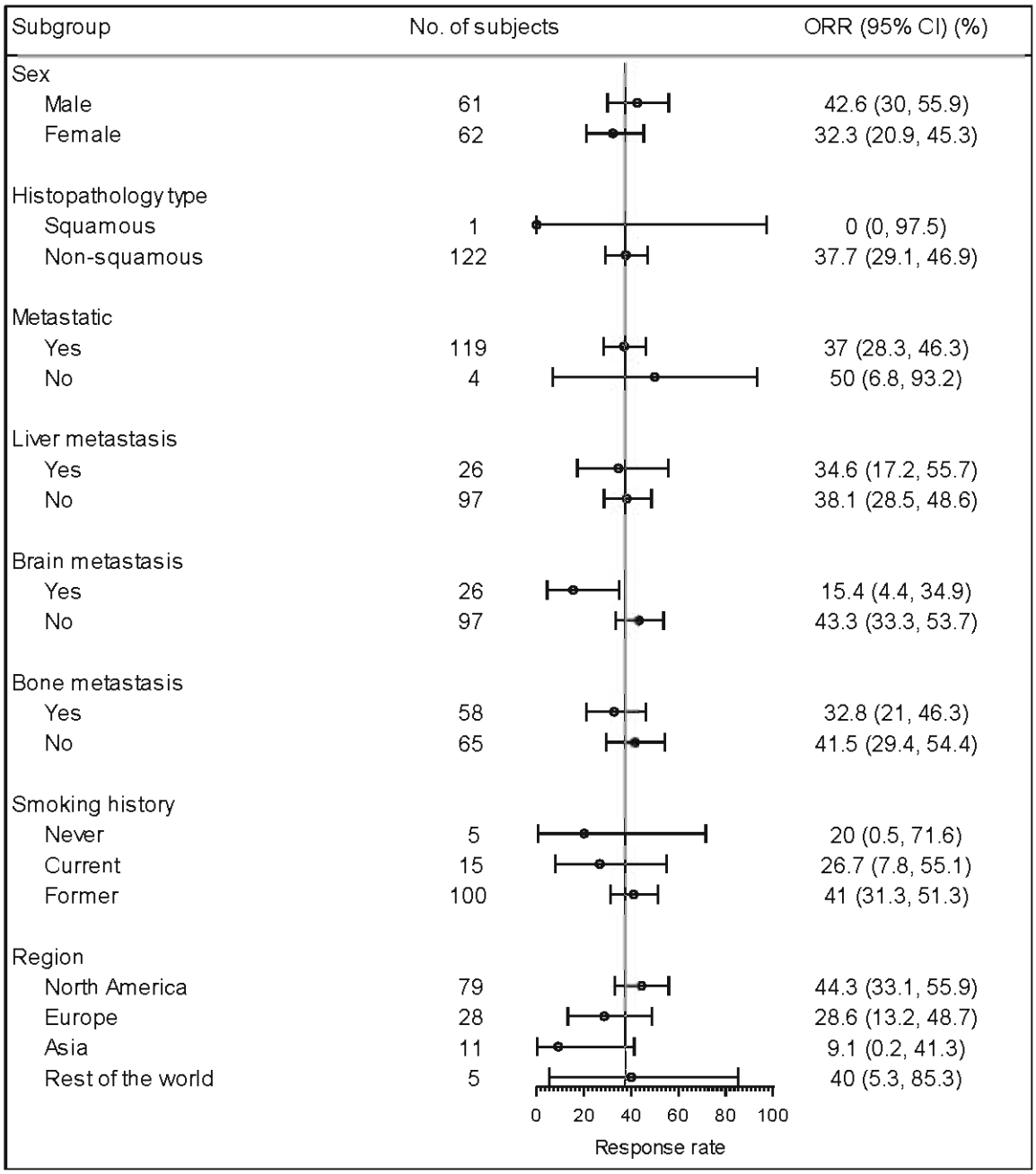


ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small cell lung cancer; PD-1 = programmed cell death-1; PD-L1 = programmed death-ligand 1

Phase 1 data cutoff date 06JUL2020; phase 2 data cutoff date 01SEP2020.

Source: Figure 14n-4.5.1 of Study [redacted] Phase 2

Figure 7. Objective Response Rate Based on Central Review by Subgroup in Study [redacted] Phase 2 NSCLC – Full Analysis Set)



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ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small cell lung cancer; PD-1 = programmed cell death-1; PD-L1 = programmed death-ligand 1

Phase 1 data cutoff date 06JUL2020; phase 2 data cutoff date 01SEP2020.

Source: Figure 14n-4.5.1 of Study [redacted] Phase 2

These efficacy results from phase 2 were consistent with that observed for subjects with NSCLC in the phase 1 portion of Study [redacted] Among the 34 subjects in the ORR analysis set (ie, subjects who received ≥ 1 dose of sotorasib, had ≥ 1 measurable lesion at baseline, and the opportunity to be followed for ≥ 7 weeks starting from day 1) for phase 1 NSCLC 960 mg QD sotorasib monotherapy (fasted) dose cohort, 16 subjects had confirmed partial response (based on central review using RECIST 1.1), for an ORR of 47.1% (95% CI: 29.78, 64.87). The median follow-up time for DOR was 9.0 months; median DOR was not reached. The phase 1 results across dose cohorts are summarized in Section 3.2.3 of Module 2.7.3, Summary of Clinical Efficacy; full results are provided in the Study [redacted] Phase 1 clinical study report. Given that the phase 1 subject population is similar to that in phase 2, the phase 1 efficacy results are supportive of the primary efficacy analysis results from phase 2.

An exploratory objective of the phase 2 portion of Study [redacted] was to investigate the subject experience with sotorasib treatment using patient-reported outcome instruments. Although exploratory, a trend toward improvement or stabilization was observed in the severity of key lung cancer symptoms of cough, dyspnea, and chest pain when compared with baseline (Section 2 of Module 2.7.3, Summary of Clinical Efficacy). Few subjects reported bother due to treatment-related side effects associated with sotorasib. Among those who reported symptom bother, most subjects described their symptoms as mild.

5. Overview of Safety

A schematic representation of studies contributing to the safety in this marketing application is provided in Figure 1 of Module 2.7.4, Summary of Clinical Safety. Studies supporting the safety of sotorasib, but not included in the integrated analyses, are provided as safety summary reports located in Module 5.3.5.4. Safety in healthy volunteers enrolled in the clinical pharmacology studies is provided in full in the individual clinical study reports in Module 5.3.3 and relevant safety data are discussed in Module 2.7.4, Summary of Clinical Safety.

5.1 Exposure to Sotorasib

As of the time of this marketing application, the number of subjects with *KRAS p.G12C*-mutated solid tumors who have been exposed to ≥ 1 dose of sotorasib is provided in Table 6. In addition, more than 100 healthy subjects received ≥ 1 dose of sotorasib in clinical pharmacology/biopharmaceutic studies (Table 1 of Module 2.7.2, Summary of Clinical Pharmacology).

Table 6. Exposure to Sotorasib

Study Number	Number of Subjects who Received Investigational Product
Integrated Analysis	
[redacted] (monotherapy cohorts)[a]	427 sotorasib
Supportive Analyses[b]	
[redacted]	21 sotorasib or docetaxel[c] 3 sotorasib
Sotorasib Combination Studies	
[redacted] (cohort with pembrolizumab)[d]	11
Subprotocol A (with trametinib)	35
Subprotocol C (with RMC-4630)	3
Subprotocol D (with afatinib)	5
Subprotocol E (with atezolizumab)	6
Subprotocol H (with panitumumab)	4

As of 01 September 2020.

[a] Total monotherapy population, ie, any dose, any tumor type, including 339 subjects treated with sotorasib dose of 960 mg QD for all tumor types; of whom, 190 subjects had *KRAS p.G12C*-mutated non-small cell lung cancer. Data cutoff dates are 06 July 2020 (phase 1) and 01 September 2020 (phase 2).

[b] Supportive analyses are provided as safety reports including disposition and demographic data and safety narratives for all studies except for Study [redacted] (cohort with pembrolizumab).

[c] Data from the randomized study are blinded. Subjects are randomized 1:1 to receive sotorasib or docetaxel.

[d] Supportive analyses are provided in Study [redacted] Phase 1 clinical study report and discussed in Module 2.74, Summary of Clinical Safety, as applicable.

Sources: ISS Table 14a-5.1 and ISS Table 14b-5.1; [redacted] Safety Report; [redacted] Safety Report; Table 14p-1.1 of Study [redacted] Phase 1; Study [redacted] Safety Reports for Subprotocols A, C, D, E, and H.

Integrated Analysis (Phase 1 and Phase 2 in Study [redacted]

As of the data cutoff dates for the pooled safety data from Study [redacted], a total of 427 subjects were treated with sotorasib monotherapy across all doses (fed/fasted state) and tumor types (Section 1.5 of Module 2.7.4, Summary of Clinical Safety). This includes 339 subjects who were treated with the intended sotorasib dose of 960 mg QD for all tumor types; of whom, 190 subjects had *KRAS p.G12C*-mutated NSCLC.

Compared with subjects with NSCLC treated with 960 mg QD sotorasib, exposure was lower among subjects treated with 960 mg QD sotorasib for all tumor types and the total combined monotherapy population (any dose/ any tumor type) (21.3 weeks versus 18.0 and 16.9 weeks, respectively) (Table 4 of Module 2.7.4, Summary of Clinical Safety).

Overall, for the 339 subjects with *KRAS p.G12C*-mutated solid tumors (all tumor types) treated with 960 mg QD sotorasib monotherapy, the median duration of treatment was 18.0 weeks, with 100 subjects (29.5%) receiving treatment for ≥ 6 months, 52 subjects (15.3%) for ≥ 9 months, and 11 subjects (3.2%) for ≥ 12 months. The median (Q1, Q3) number of doses received was 123 (62, 201) (range: 2 to 454 doses) (Table 4 of Module 2.7.4, Summary of Clinical Safety). Of these 339 subjects, 241 (71.1%) had discontinued sotorasib treatment; the most frequently reported (subject incidence ≥ 10%) reason for treatment discontinuation was disease progression (58.4%) (Section 1.3 of Module 2.7.4, Summary of Clinical Safety).

Among the 190 subjects with NSCLC treated with 960 mg QD sotorasib monotherapy, median duration of treatment was 21.3 weeks, with 78 subjects (41.1%) treated for ≥ 6 months, 45 subjects (23.7%) for ≥ 9 months, and 6 subjects (3.2%) for ≥ 12 months. The median (Q1, Q3) number of doses received was 143.5 (68, 252) (range: 7 to 454 doses) Table 4 of Module 2.7.4, Summary of Clinical Safety). Of these 190 subjects, 127 subjects (66.8%) had discontinued treatment; the most frequently reported reason (subject incidence ≥ 10%) for treatment discontinuation was disease progression (51.1%) (Section 1.3 of Module 2.7.4, Summary of Clinical Safety).

Regardless of tumor type, the median average daily dose administered was 960 mg and the median relative dose intensity of sotorasib was 100%.

Dose changes (ie, a nonzero dose received other than the planned dose) were reported for 17.9% of subjects with NSCLC treated with 960 mg QD sotorasib monotherapy, with

a median (range) of 0 (0, 441) dose changes (Table 5 of Module 2.7.4, Summary of Clinical Safety). The most frequently reported reason for dose change was adverse event (15.8%) (Section 5.4.6.1). The sotorasib dose was withheld for 49.5% of subjects with NSCLC treated with 960 mg QD sotorasib monotherapy, with a median (range) of 0 (0, 193) doses withheld. Adverse event (33.7%) and 'other' (10.0%) were most frequently reported reasons for the dose being withheld.

Compared with subjects with NSCLC treated with 960 mg QD sotorasib, the sotorasib dose was changed or withheld at a lower subject incidence among subjects treated with 960 mg QD sotorasib for all tumor types (13.6% and 43.4%, respectively) and the total combined monotherapy population (any dose/ any tumor type) (13.3% and 43.8%).

5.2 Assessment of Safety

The primary support for the safety for the proposed indication is based on the integrated safety analyses of pooled data from subjects with NSCLC who were treated with sotorasib monotherapy at 960 mg QD (ie, the intended dose) across phase 1 and phase 2 portions of Study [redacted] (data cutoffs of 09 July 2020 and 01 September 2020, respectively). Safety data of sotorasib monotherapy in this population are compared with subjects who received the intended dose for all tumor types and with the total monotherapy population (any dose/any tumor type).

Safety data from subjects with CRC and other tumor types are provided in Module 2.7.4 (Summary of Clinical Safety); however, notable results are discussed below as needed to fully capture the safety profile of sotorasib.

Data were pooled for the phase 1 and phase 2 portions of Study [redacted] by planned dose levels, treatment (monotherapy), tumor type (NSCLC, CRC, and other tumor types) and total (any dose/any tumor type) (Integrated Summary of Safety in Module 5.3.5.3). Adverse events, exposure, and any other safety assessments were summarized using the safety analysis set, which included subjects enrolled in the sotorasib monotherapy cohorts in phase 1 and phase 2 of Study [redacted] and had received ≥ 1 dose of sotorasib.

According to regulatory guidance, the appropriate size of a safety database depends on the novelty of the drug, the availability of alternative therapies and the relative safety of those alternatives, the intended patient population, and the duration of use (EMA, 2017; US FDA, 2005). With a safety database of 339 subjects who received the intended dose

of 960 mg QD (any tumor type), the chance of observing at least 1 adverse event with an incidence rate of 1% is approximately 97%.

Throughout the sotorasib clinical development program, safety was evaluated by Amgen through routine signal detection activities such as review of all serious adverse events across all the clinical studies.

Two adverse events of interest were analyzed for sotorasib: hepatotoxicity (ie, increased liver function tests), which was based on ongoing clinical trial data, and renal toxicity, which was based on nonclinical studies (Section 1.2.1 of Module 2.7.4, Summary of Clinical Safety; Section 5.4.6). Nonclinical studies showed renal toxicity with repeated dosing in the rat; no analogous renal adverse events have been reported in Study [redacted] (Section 5 of Module 2.4, Nonclinical Overview). Events of hepatotoxicity and renal toxicity are designated as events of interests and are clinically monitored through protocol designated reporting of clinical signs and symptoms, as well as scheduled assessments of laboratory tests.

5.3 Demographic and Baseline Characteristics

Analysis of disposition, demographic, and baseline characteristics was conducted using the integrated safety analysis set, which included all subjects enrolled in phase 1 and phase 2 of Study [redacted] and who had received sotorasib as monotherapy.

The demographics and baseline disease characteristics of subjects in the integrated safety analysis set are provided in Table 7 and Table 8. Most subjects had *KRAS p.G12C*-mutated NSCLC (190 subjects [44.5%]) or CRC (87 subjects [20.4%]). Sex, race, and median age of subjects in the integrated safety analysis set were similar to those in the phase 2 NSCLC safety analysis set.

Table 7. Baseline Demographics (Integrated Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg PO QD Fasted				Total
	NSCLC (N = 190)	CRC (N = 87)	Other Tumor Types (N = 62)	Any Tumor Type (N = 339)	Any Tumor Type / Any Dose (N = 427)
Sex - n (%)					
Men	88 (46.3)	43 (49.4)	38 (61.3)	169 (49.9)	200 (46.8)
Women	102 (53.7)	44 (50.6)	24 (38.7)	170 (50.1)	227 (53.2)
Ethnicity - n (%)					
Hispanic or Latino	3 (1.6)	6 (6.9)	1 (1.6)	10 (2.9)	13 (3.0)
Not Hispanic or Latino	177 (93.2)	79 (90.8)	57 (91.9)	313 (92.3)	392 (91.8)
Missing	10 (5.3)	2 (2.3)	4 (6.5)	16 (4.7)	22 (5.2)
Race - n (%)					
Asian	30 (15.8)	23 (26.4)	12 (19.4)	65 (19.2)	67 (15.7)
Black or African American	4 (2.1)	1 (1.1)	3 (4.8)	8 (2.4)	12 (2.8)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.3)	1 (0.2)
White	152 (80.0)	59 (67.8)	45 (72.6)	256 (75.5)	332 (77.8)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Other	4 (2.1)	3 (3.4)	2 (3.2)	9 (2.7)	13 (3.0)
Age (years)					
Mean	64.5	57.0	61.2	61.9	62.4
SD	9.3	11.4	10.6	10.6	10.6
Median	66.0	58.0	61.0	63.0	63.0
Q1, Q3	57.0, 72.0	50.0, 65.0	56.0, 70.0	55.0, 70.0	56.0, 71.0
Min, Max	37, 83	31, 85	33, 82	31, 85	31, 86
Age group (years) - n (%)					
18 - 64	87 (45.8)	65 (74.7)	37 (59.7)	189 (55.8)	230 (53.9)
65 - 74	82 (43.2)	16 (18.4)	20 (32.3)	118 (34.8)	150 (35.1)
75 - 84	21 (11.1)	5 (5.7)	5 (8.1)	31 (9.1)	45 (10.5)
≥ 85	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.3)	2 (0.5)

Phase 1 data cut-off date 06 July 2020. Phase 2 data cut-off date 01 September 2020.
CRC = colorectal cancer; ECOG = Eastern Cooperative Oncology Group; N = number of subjects in the analysis set, n = number of subjects with observed data, NSCLC = non-small cell lung cancer; PO = oral administration; SD = standard deviation, Q1 = first quartile, Q3 = third quartile; QD = once daily
Source: ISS Table 14a-2.1 and ISS Table 14b-2.1

Table 8. Baseline Disease Characteristics (Integrated Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg PO QD Fasted				Total
	NSCLC (N = 190)	CRC (N = 87)	Other Tumor Types (N = 62)	Any Tumor Type (N = 339)	Any Tumor Type / Any Dose (N = 427)
Region - n (%)					
North America	136 (71.6)	47 (54.0)	34 (54.8)	217 (64.0)	291 (68.1)
Europe	31 (16.3)	13 (14.9)	14 (22.6)	58 (17.1)	59 (13.8)
Asia	17 (8.9)	21 (24.1)	12 (19.4)	50 (14.7)	51 (11.9)
Rest of the world	6 (3.2)	6 (6.9)	2 (3.2)	14 (4.1)	26 (6.1)
ECOG status at baseline - n (%)					
0	55 (28.9)	46 (52.9)	17 (27.4)	118 (34.8)	137 (32.1)
1	133 (70.0)	41 (47.1)	40 (64.5)	214 (63.1)	279 (65.3)
≥ 2	2 (1.1)	0 (0.0)	5 (8.1)	7 (2.1)	11 (2.6)
Number of prior lines of anti-cancer therapy - n (%)					
0	28 (14.7)	0 (0.0)	0 (0.0)	28 (8.3)	28 (6.6)
1	67 (35.3)	4 (4.6)	17 (27.4)	88 (26.0)	113 (26.5)
2	55 (28.9)	25 (28.7)	17 (27.4)	97 (28.6)	116 (27.2)
3	33 (17.4)	26 (29.9)	13 (21.0)	72 (21.2)	91 (21.3)
≥ 4	7 (3.7)	32 (36.8)	15 (24.2)	54 (15.9)	79 (18.5)
Median	1.5	3.0	2.0	2.0	2.0
Type of prior anti-cancer therapy[a] - n (%)					
Chemotherapy	158 (83.2)	87 (100.0)	62 (100.0)	307 (90.6)	394 (92.3)
Immunotherapy	148 (77.9)	7 (8.0)	17 (27.4)	172 (50.7)	238 (55.7)
Targeted biologics	38 (20.0)	78 (89.7)	14 (22.6)	130 (38.3)	168 (39.3)
Targeted small molecules	18 (9.5)	22 (25.3)	7 (11.3)	47 (13.9)	65 (15.2)
Other	2 (1.1)	29 (33.3)	14 (22.6)	45 (13.3)	62 (14.5)
Unknown	21 (11.1)	0 (0.0)	0 (0.0)	21 (6.2)	21 (4.9)
Metastatic - n (%)					
Yes	184 (96.8)	87 (100.0)	61 (98.4)	332 (97.9)	419 (98.1)
No	6 (3.2)	0 (0.0)	1 (1.6)	7 (2.1)	8 (1.9)
Smoking history - n (%)					
Never	12 (6.3)	47 (54.0)	32 (51.6)	91 (26.8)	111 (26.0)
Current	18 (9.5)	7 (8.0)	7 (11.3)	32 (9.4)	41 (9.6)
Former	157 (82.6)	30 (34.5)	22 (35.5)	209 (61.7)	268 (62.8)
Missing	3 (1.6)	3 (3.4)	1 (1.6)	7 (2.1)	7 (1.6)

Phase 1 data cut-off date 06 July 2020. Phase 2 data cut-off date 01 September 2020.
CRC = colorectal cancer; ECOG = Eastern Cooperative Oncology Group; N = number of subjects in the analysis set, n = number of subjects with observed data, NSCLC = non-small cell lung cancer; PO = oral administration; SD = standard deviation, Q1 = first quartile, Q3 = third quartile; QD = once daily
[a] Each subject may have multiple prior therapies. Types of prior anti-cancer therapies were adjudicated and included therapies given in any treatment setting.
Source: ISS Table 14a-2.2 and ISS Table 14b-2.2

5.4 Safety Results

Unless otherwise specified, all adverse events referred to in this section are treatment-emergent adverse events (defined as occurring after the first dose of sotorasib through 30 days after the last dose of sotorasib).

5.4.1 Overall Adverse Events

Most subjects with NSCLC who received 960 mg QD sotorasib monotherapy (187 of 190 subjects [98.4%]) had ≥ 1 adverse event during the study (Table 9). Of these, 114 subjects (60%) had adverse events ≥ grade 3 in severity. Serious adverse events were reported for 99 subjects (52.1%). Adverse events leading to reduction/interruption or discontinuation of sotorasib monotherapy were reported for 67 subjects (35.5%) and 18 subjects (9.5%), respectively (Section 5.4.6.1). Thirty-one subjects (16.3%) had fatal adverse events; none of the deaths were considered by the investigator as related to sotorasib treatment.

The types of adverse events reported for subjects with NSCLC treated with 960 mg QD sotorasib were generally similar to those reported for subjects treated with 960 mg QD for all tumor types and the total monotherapy population (any dose/ any tumor type) (Section 2.1 of Module 2.7.4, Summary of Clinical Safety). While the subject incidence of adverse events was slightly higher for subjects with NSCLC treated with 960 mg QD compared with these 2 groups, this difference is largely attributable to the lower incidence of adverse events for subjects with CRC treated with 960 mg QD (Table 9). .

Table 9. Summary of Treatment-emergent Adverse Events (Integrated Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg PO QD Fasted				Total
	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Any Tumor Type/ Any Dose (N = 427) n (%)
All treatment-emergent adverse events	187 (98.4)	83 (95.4)	55 (88.7)	325 (95.9)	409 (95.8)
Grade ≥ 2	163 (85.8)	56 (64.4)	46 (74.2)	265 (78.2)	336 (78.7)
Grade ≥ 3	114 (60.0)	29 (33.3)	33 (53.2)	176 (51.9)	223 (52.2)
Grade ≥ 4	39 (20.5)	3 (3.4)	16 (25.8)	58 (17.1)	75 (17.6)
Serious adverse events	99 (52.1)	22 (25.3)	32 (51.6)	153 (45.1)	187 (43.8)
Leading to discontinuation of investigational product	18 (9.5)	1 (1.1)	3 (4.8)	22 (6.5)	27 (6.3)
Serious	12 (6.3)	0 (0.0)	3 (4.8)	15 (4.4)	17 (4.0)
Nonserious	7 (3.7)	1 (1.1)	0 (0.0)	8 (2.4)	11 (2.6)
Fatal adverse events	31 (16.3)	2 (2.3)	16 (25.8)	49 (14.5)	62 (14.5)
Treatment-related adverse events	128 (67.4)	44 (50.6)	23 (37.1)	195 (57.5)	251 (58.8)
Grade ≥ 2	73 (38.4)	18 (20.7)	10 (16.1)	101 (29.8)	133 (31.1)
Grade ≥ 3	40 (21.1)	7 (8.0)	3 (4.8)	50 (14.7)	64 (15.0)
Grade ≥ 4	3 (1.6)	1 (1.1)	0 (0.0)	4 (1.2)	7 (1.6)
Serious adverse events	14 (7.4)	1 (1.1)	2 (3.2)	17 (5.0)	22 (5.2)
Leading to discontinuation of investigational product	12 (6.3)	1 (1.1)	0 (0.0)	13 (3.8)	17 (4.0)
Serious	5 (2.6)	0 (0.0)	0 (0.0)	5 (1.5)	6 (1.4)
Nonserious	7 (3.7)	1 (1.1)	0 (0.0)	8 (2.4)	11 (2.6)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

CRC = colorectal cancer; MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer; QD = once daily

Safety analysis set is defined as all enrolled subjects in Study [redacted] who received ≥ 1 dose of sotorasib as monotherapy. Treatment-related adverse events are treatment-emergent adverse events considered related to investigational product by the investigator.

Adverse events coded using MedDRA version 23.0. Severity graded using Common Terminology Criteria for Adverse Events version 5.0.

Source: ISS Table 14a-6.1.1 and ISS Table 14b-6.1.1

5.4.2 Common Adverse Events

In the integrated NSCLC monotherapy 960-mg sotorasib safety dataset, adverse events were reported for 187 of 190 subjects (98.4%) with NSCLC. Of these, the most frequently reported adverse events (subject incidence ≥ 15%) were diarrhea (43.2%), nausea (27.4%), fatigue (23.2%), increased AST (21.1%), increased ALT (20.0%), back pain (18.4%), constipation (16.8%), dyspnea (16.8%), and vomiting (16.8%) (Table 7 of Module 2.7.4, Summary of Clinical Safety). The system organ class with the highest

subject incidence of adverse events was gastrointestinal disorders (136 of 190 subjects [71.6%]) (ISS Table 14b-6.3.1).

The types of adverse events reported for subjects with NSCLC treated with 960 mg QD sotorasib were generally similar to those reported for subjects treated with 960 mg QD for all tumor types and the total monotherapy population (any dose/ any tumor type) (Section 2.1.1 of Module 2.7.4, Summary of Clinical Safety).

5.4.3 Grade 3 or Higher Adverse Events

Grade ≥ 3 adverse events were reported for 114 of 190 subjects (60.0%) with NSCLC treated with 960 mg QD (Table 8 of Module 2.7.4, Summary of Clinical Safety). The most frequently reported grade ≥ 3 adverse events (subject incidence ≥ 5%) for subjects with NSCLC treated with 960 mg QD were increased ALT (7.9%), increased AST (6.8%), pneumonia (6.8%), diarrhea (5.3%), and pleural effusion (5.3%). The system organ class with the highest subject incidence of grade ≥ 3 adverse events was respiratory, thoracic and mediastinal disorders (32 of 190 subjects [16.8%]) (ISS Table 14b 6.3.31).

The types of grade ≥ 3 adverse events reported for subjects with NSCLC treated with 960 mg QD sotorasib were generally similar to those reported for subjects treated with 960 mg QD for all tumor types and the total monotherapy population (any dose/ any tumor type) (Section 2.1.2 of Module 2.7.4, Summary of Clinical Safety).

5.4.4 Serious Adverse Events

Serious adverse events were reported for 99 of 190 subjects with NSCLC (52.1%) treated with 960 mg QD sotorasib (Table 10 of Module 2.7.4, Summary of Clinical Safety). The most frequently reported serious adverse events (subject incidence ≥ 2%) for subjects with NSCLC treated with 960 mg QD sotorasib were pneumonia (7.4%), NSCLC (4.7%), pleural effusion (4.7%), respiratory failure (3.7%), back pain (2.6%), and metastatic lung cancer (2.1%). The system organ class with the highest subject incidence of serious adverse events was respiratory, thoracic and mediastinal disorders (28 of 190 subjects [14.7%]) (ISS Table 14b 6.3.31).

The types of serious adverse events reported for subjects with NSCLC treated with 960 mg QD sotorasib were generally similar to those reported for subjects treated with 960 mg QD for all tumor types and the total monotherapy population (any dose/ any tumor type) (Section 2.1.4 of Module 2.7.4, Summary of Clinical Safety).

5.4.5 Deaths

Fatal adverse events were reported for 31 of 190 subjects with NSCLC (16.3%) who were treated with 960 mg QD sotorasib (Table 9 of Module 2.7.4, Summary of Clinical Safety). Fatal adverse events reported for ≥ 1 subject were NSCLC (8 subjects [4.2%]), metastatic lung cancer (4 subjects [2.1%]), respiratory failure (4 subjects [2.1%]), cardiac arrest (2 subjects [1.1%]), and malignant lung neoplasm (2 subjects [1.1%]).

Most of the causes of death were consistent with disease progression and/or adverse events expected with the underlying disease (Section 2.1.3 of Module 2.7.4, Summary of Clinical Safety). No treatment-related fatal adverse events have been reported as of the respective data cutoff dates in the integrated analysis set nor in any study in the sotorasib clinical development program. Review of fatal adverse events across the sotorasib clinical development program as of the data cutoff dates did not identify any meaningful trends suggesting a causal association between sotorasib use and fatalities.

5.4.6 Other Significant Adverse Events

5.4.6.1 Adverse Events Leading to Dose Reduction/Interruption or Discontinuation of Sotorasib

Dose Reduction or Interruption

Sixty-seven of 190 subjects with NSCLC (35.3%) who were treated with 960 mg QD sotorasib had adverse events leading to sotorasib treatment interruption or a dose reduction (Section 2.1.5.1 of Module 2.7.4, Summary of Clinical Safety). The most frequently reported (subject incidence ≥ 2%) adverse events leading to dose reduction or interruption of sotorasib for subjects with NSCLC treated with 960 mg QD sotorasib were diarrhea (8.4%), increased ALT (8.4%), increased AST (8.4%), increased blood ALP (3.7%), nausea (3.2%), and pneumonia (2.6%). The system organ class with the highest subject incidence of adverse events leading to sotorasib treatment interruption or dose reduction was investigations (24 of 190 subjects [12.6%]).

Treatment Discontinuation

Compared with adverse events leading to dose reduction or interruption, a lower incidence of subjects had adverse events leading to discontinuation of sotorasib.

Eighteen of 190 subjects with NSCLC (9.5%) who were treated with 960 mg QD sotorasib had adverse events leading to sotorasib treatment discontinuation (Section 2.1.5.2 of Module 2.7.4, Summary of Clinical Safety). The most frequently reported (subject incidence ≥ 1%) adverse events leading to sotorasib treatment

discontinuation for subjects with NSCLC treated with 960 mg QD sotorasib were drug-induced liver injury (1.6%), increased ALT (1.6%), increased AST (1.6%), increased blood ALP (1.1%), pneumonitis (1.1%), and increased transaminases (1.1%). Review of the 3 cases of drug-induced liver injury did not meet Hy's law criteria (Section 5.4.7). The system organ class with the highest subject incidence of adverse events leading to sotorasib treatment discontinuation was investigations (6 subjects [3.2%]).

Overall, the types of adverse events leading to both sotorasib treatment interruption/dose reduction or discontinuation reported for subjects with NSCLC treated at the 960 mg QD dose level were generally similar to those reported for subjects treated with 960 mg QD sotorasib for all tumor types and for the total combined monotherapy population (any dose/ any tumor type).

While adverse events leading to sotorasib treatment interruption/dose reduction and to discontinuation were similar in type, the lower subject incidence for the adverse events leading to permanent discontinuation of sotorasib (9.5% versus 35.3% for interruption/dose reduction) supports the proposed prescribing information regarding dose modification guidelines and adverse reactions with sotorasib use.

5.4.6.2 Adverse Events of Interest

5.4.6.2.1 Hepatotoxicity

Hepatotoxicity was identified as an event of interest (Section 5.2). Adverse events of hepatotoxicity are provided in Table 10. Fifty-seven of 190 subjects with NSCLC (30.0%) who were treated with 960 mg QD sotorasib had hepatotoxicity adverse events. The most frequently reported hepatotoxicity adverse events (subject incidence $\geq$ 5%) of any grade among subjects with NSCLC treated with 960 mg QD sotorasib were increased AST (21.1%), increased ALT (20.0%), and increased blood ALP (13.7%) (Section 2.1.5.3.1 of Module 2.7.4, Summary of Clinical Safety). Grade $\geq$ 3 events reported for $\geq$ 2% of subjects were increased ALT (7.9%), increased AST (6.8%), increased blood ALP (4.2%), and increased gamma glutamyl transferase (2.6%). Among the 9 subjects (4.7%) who had serious hepatoxicity adverse events, events reported for $\geq$ 2 subjects were increased ALT and drug-induced liver injury (each in 2 subjects [1.1%]). Events leading to interruption or discontinuation of sotorasib were reported for 24 subjects (12.6%) and 9 subjects (4.7%), respectively. No fatal hepatotoxicity adverse events of interest were reported.

The median (minimum, maximum) time to first onset of hepatotoxicity events was 43.0 (1, 295) days, with a median duration of 45.0 days (Section 2.1.5.3.1.1 of Module 2.7.4, Summary of Clinical Safety). For subjects with grade ≥ 3 events of hepatotoxicity, median (minimum, maximum) time to first onset was 63.5 (16, 139) days, with a median duration of 31.5 days. Most hepatotoxicity adverse events of interest resolved (resolved versus unresolved: 247 vs 43 events for any grade and 62 versus 12 events for grade ≥ 3).

Results were generally consistent with those reported for subjects treated with 960 mg QD sotorasib for all tumor types and the total monotherapy population (any dose/ any tumor type). No subject met Hy's Law criteria (Section 5.4.7).

Increased Alanine Aminotransferase

The median (minimum, maximum) time to first onset of increased ALT events was 54.5 (8, 295) days, with a median duration of 42.0 days. For subjects with grade ≥ 3 events of increased ALT, median (minimum, maximum) time to first onset was 64.0 (22, 13.1) days, with a median duration of 26.0 days. Most adverse events of increased ALT resolved (resolved versus unresolved: 83 versus 10 events for any grade and 23 versus 2 events for grade ≥ 3).

The median time to first onset for an event of increased ALT (any grade) was longer for subjects with NSCLC treated with 960 mg QD sotorasib (54.5 days) and subjects treated with 960 mg QD sotorasib for all tumor types (62.0 days) compared with the total combined monotherapy population (43.5 days).

Increased Aspartate Aminotransferase

The median (minimum, maximum) time to first onset of increased AST events was 62.0 (2, 295) days, with a median duration of 42.0 days. For subjects with grade ≥ 3 events of increased AST, median (minimum, maximum) time to first onset was 49.0 (22, 106) days, with a median duration of 28.0 days. Most adverse events of increased AST resolved (resolved versus unresolved: 80 versus 10 events for any grade and 19 versus 2 events for grade ≥ 3).

The median time to first onset of adverse events of increased AST was longer for subjects treated with 960 mg QD sotorasib (62.0 days) compared with subjects treated with 960 mg QD sotorasib for all tumor types (44.0 days) and the total combined monotherapy population (any dose/ any tumor type) (44.0 days). Whereas, median time

to first onset was shorter for grade ≥ 3 events of increased AST for subjects with NSCLC treated with 960 mg QD sotorasib (49.0 versus 63.0 and 61.0 days, respectively). The median duration for adverse events of increased AST (any grade and grade ≥ 3) was longer for subjects with NSCLC with 960 mg QD sotorasib (42.0 and 28.0 days) compared with subjects treated with 960 mg QD sotorasib for all tumor types (30.5 and 21.0 days) and the total combined monotherapy population (30.0 and 13.5 days).

In general, the liver function test elevations were reversed upon interruption of sotorasib treatment and subjects were able to continue treatment after restarting at the same dose or with dose modification as noted in the proposed prescribing information. Most cases were nonserious, and no subject met Hy's Law criteria (Section 5.4.7). Elevation of ALT and AST are considered adverse drug reactions (Section 5.6), with appropriate guidance provided in the proposed prescribing information included in Module 1.

5.4.6.2.2 Renal Toxicity

Renal toxicity was identified as an event of interest (Section 5.2). Nonclinical toxicology results in rats, although not in dogs, suggested the potential for renal toxicity (Section 5.2 and Module 2.4, Nonclinical Overview). In the integrated safety analysis set for Study [redacted] renal toxicity adverse events were reported for 34 of 190 subjects (17.9%) with NSCLC who were treated with 960 mg QD sotorasib monotherapy (Table 10). The most frequently reported renal toxicity adverse event of interest (subject incidence ≥ 5%) was hyponatremia (7.9%) (Section 2.1.5.3.2 of 2.7.4, Summary of Clinical Safety). Six subjects (3.2%) had grade ≥ 3 renal toxicity adverse events; the most frequently reported (subject incidence ≥ 2%) was hyponatremia (2.1%). Events of hyponatremia were reported as serious adverse events for 2 subjects (1.1%).
One subject (0.5%) had a renal toxicity event of interest leading to interruption of sotorasib (hyponatremia); no subjects discontinued sotorasib due to renal toxicity adverse events. No fatal renal toxicity adverse events of interest were reported. A total of 5 subjects in the monotherapy population had acute kidney injury, including 1 of the 190 subjects with NSCLC receiving 960 mg QD sotorasib and 4 of the 339 subjects treated with 960 mg QD sotorasib for all tumor types. Medical review of the 5 events did not suggest causality between sotorasib and the event of acute kidney injury.

The median (minimum, maximum) time to first onset of renal toxicity events was 23.0 (1, 252) days, with a median duration of 19.0 days (Section 2.1.5.3.2.1 of Module 2.7.4, Summary of Clinical Safety). For subjects with grade ≥ 3 events of renal

toxicity, median (minimum, maximum) time to first onset was 61.0 (14, 141) days, with a median duration of 4.0 days. Most renal toxicity adverse events of interest resolved (53 events resolved versus 9 unresolved [any grade]; all 5 of the grade ≥ 3 events resolved).

Overall, the above results were generally consistent with those reported for subjects treated with 960 mg QD sotorasib for all tumor types and the total combined monotherapy population (any dose/ any tumor type). Renal toxicity will continue to be monitored in the postmarketing data as well as future clinical trials with routine pharmacovigilance activities (Section 5.7).

The events of renal toxicity seen in the clinical studies were generally nonserious, mild to moderate events that did not lead to discontinuation of sotorasib and were not consistent with the type of renal toxicity seen in the nonclinical toxicology program. There were no trends to suggest a causal association between renal toxicity and sotorasib use.

Table 10. Summary of Treatment-Emergent Adverse Events of Interest by Category (Integrated Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg PO QD Fasted				Total
Event of Interest Category	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Any Tumor Types/ Any Dose (N = 427) n (%)
Number of subjects reporting treatment-emergent adverse events of interest	70 (36.8)	21 (24.1)	16 (25.8)	107 (31.6)	128 (30.0)
Hepatotoxicity					
Number of subjects reporting EOI	57 (30.0)	17 (19.5)	14 (22.6)	88 (26.0)	104 (24.4)
Leading to interruption of sotorasib	24 (12.6)	6 (6.9)	3 (4.8)	33 (9.7)	42 (9.8)
Leading to discontinuation of sotorasib	9 (4.7)	0 (0.0)	0 (0.0)	9 (2.7)	13 (3.0)
Serious	9 (4.7)	0 (0.0)	4 (6.5)	13 (3.8)	17 (4.0)
Grade ≥ 3	30 (15.8)	4 (4.6)	5 (8.1)	39 (11.5)	47 (11.0)
Grade ≥ 4	3 (1.6)	0 (0.0)	0 (0.0)	3 (0.9)	5 (1.2)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal toxicity					
Number of subjects reporting EOI	34 (17.9)	7 (8.0)	4 (6.5)	45 (13.3)	53 (12.4)
Leading to interruption of sotorasib	1 (0.5)	1 (1.1)	0 (0.0)	2 (0.6)	2 (0.5)
Leading to discontinuation of sotorasib	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious	2 (1.1)	1 (1.1)	0 (0.0)	3 (0.9)	4 (0.9)
Grade ≥ 3	6 (3.2)	2 (2.3)	1 (1.6)	9 (2.7)	10 (2.3)
Grade ≥ 4	3 (1.6)	0 (0.0)	0 (0.0)	3 (0.9)	3 (0.7)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

CRC = colorectal cancer; EOI = event of interest; MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer; QD = once daily; SMQ = standardized MedDRA query, broad scope; N = number of subjects in the analysis set; n = number of subjects with observed data
Phase 1 data cutoff date 06 July 2020; phase 2 data cut-off date 01 September 2020.
Adverse events coded using MedDRA version 23.0. Severity graded using Common Terminology Criteria for Adverse Events version 5.0.
Hepatotoxicity search strategy: Hepatic Disorders SMQ (Broad).
Renal Toxicity search strategy: Acute Renal Failure SMQ (Broad) or Chronic Kidney Disease SMQ (Broad).
Source: ISS Table 14a-6.5 and ISS Table 14b-6.5

5.4.7 Laboratory Assessments, Vital Signs, Physical Findings, and Other Observations Related to Safety

Assessments of laboratory parameters, vital signs, and electrocardiograms are presented in this section. Adverse events associated with laboratory parameters

(including hepatotoxicity and renal toxicity events of interest [Section 5.4.6.2]), vital signs, and electrocardiograms are presented above in Section 5.4.

Sotorasib treatment was associated with changes in liver enzyme levels. For other laboratory parameters, no changes indicative of a treatment effect for sotorasib were observed.

Grade 3 and 4 increases from baseline for subjects with NSCLC receiving 960 mg QD sotorasib monotherapy were reported for ALT (10.0% and 1.6%, respectively), AST (8.9% and 1.1%), total bilirubin (1.6% and 0%), and ALP (2.6% and 0%) (Section 3 of Module 2.7.4, Summary of Clinical Safety). A higher incidence of grade 3 and 4 increases from baseline in ALT and AST was observed for subjects with NSCLC treated with 960 mg QD sotorasib compared with subjects treated with 960 mg QD sotorasib for all tumor types (6.2% and 0.9% for ALT; 5.6% and 0.9 for AST, grade 3 and 4 increases, respectively) and the total combined monotherapy population (4.9% and 0.7%; 6.2% and 0.9%).

One subject with NSCLC treated with 960 mg QD sotorasib had laboratory criteria that were consistent with a potential Hy's Law case (ie, concurrent ALT or AST $>$ 3 times the upper limit of normal and total bilirubin $\geq$ 2 times the upper limit of normal and ALP $<$ 2 times the upper limit of normal in the absence of alternative etiology). The event occurred after the subject had discontinued sotorasib due to disease progression. Medical review determined this subject did not meet Hy's Law criteria based on the time since the final dose of sotorasib, likely alternative cause of the increased enzymes, and the increased ALP value (Section 3 of Module 2.7.4, Summary of Clinical Safety). No other subjects in the total monotherapy population had concurrent (within 7 days) elevations in ALT or AST $>$ 3 times the upper limit of normal, total bilirubin $\geq$ 2 times the upper limit of normal, and ALP $<$ 2 times the upper limit of normal.

Overall, with the exception of increased liver enzyme levels, no meaningful trends were identified in changes from baseline in any other laboratory parameter and no meaningful differences were observed in subjects with NSCLC receiving 960 mg QD sotorasib compared with subjects receiving 960 mg QD sotorasib for all tumor types or the total combined monotherapy population (any dose/ any tumor type).

The assessments of vital signs and electrocardiograms for the integrated safety analysis set are provided in Section 4 of Module 2.7.4, Summary of Clinical Safety.

No clinically relevant changes were observed in body weight, pulse rate, blood pressure, or body temperature.

Overall, ECG data (QRS, QT, QTc, RR, and PR intervals) from approximately 85% of subjects from the phase 1 and phase 2 portions of Study [redacted] were available via central read and were included in the overall QT analysis (Section 4.2 of Module 2.7.4, Summary of Clinical Safety). Results of categorical changes in QT interval corrected for heart rate using Fridericia's formula were generally consistent for subjects treated with 960 mg QD sotorasib monotherapy for NSCLC, for all tumor types, and for the total combined monotherapy population (any dose/ any tumor type). Evaluation of other electrocardiogram parameters did not identify any clinically relevant changes. An exposure-QTc analysis found no clinically relevant effect of sotorasib on QT interval (Section 3.5).

5.5 Safety in Special Populations and Situations

5.5.1 Subgroup Analyses

The subject incidence of adverse events and serious adverse events was evaluated for subgroups of age ($<$ 65 years versus $\geq$ 65 years and $<$ 75 years versus $\geq$ 75 years), sex, race, and region (Section 5.2 of Module 2.7.4, Summary of Clinical Safety). There were no apparent differences in the types of adverse events reported in the subgroups examined; however, small sample sizes in some subgroups limit the ability to draw conclusions. The overall summary of adverse events by age subset is provided in Section 5.1.2 of Module 2.7.4, Summary of Clinical Safety. No notable safety trends according to age were observed.

5.5.2 Use in Pregnancy and Lactation

No clinical studies of sotorasib have been conducted in pregnant or breastfeeding women. As of the respective data cutoff dates, 1 pregnancy exposure was reported in the partner of a male subject receiving sotorasib treatment; no maternal exposure cases were reported. No pregnancy-related adverse events have been reported to date; the birth outcome is unknown (Section 14.6.2 of Study [redacted] Phase 1). No breastfeeding cases were reported with exposure to sotorasib.

In the rat and rabbit embryo-fetal development toxicology studies, oral sotorasib was not teratogenic (Section 6.2 of Module 2.6.6, Toxicology Written Summary). In the rat, there were no effects on embryo-fetal development up to the highest dose tested (3.9 times higher than the exposure at the maximum recommended human dose of 960 mg based on AUC). In the rabbit, lower fetal body weights and a reduction in the number of

ossified metacarpals in fetuses were observed only at the highest dose level tested (2.2 times higher than the exposure at the maximum recommended human dose of 960 mg based on AUC), which was associated with maternal effects such as decreased body weight gain and food consumption during the dosing phase. Reduced ossification, as evidence of growth retardation associated with reduced fetal body weight, was interpreted as a non-specific effect in the presence of significant maternal toxicity.

Patients should be informed of the potential hazards to the fetus if sotorasib is used during pregnancy, or if the patient becomes pregnant while taking sotorasib.

It is not known if sotorasib or its metabolites is present in human milk. Because of the potential risk for sotorasib to cause adverse effects in breastfed children, a decision must be made to discontinue breast feeding or discontinue sotorasib while breast feeding.

The extent to which sotorasib is present in seminal fluid is unknown. There are no clinical studies to evaluate the effect of sotorasib on fertility.

5.5.3 Other Special Populations and Situations

Sotorasib has not been studied in pediatric subjects.

No dose adjustment is recommended for patients with mild hepatic impairment (AST or ALT $<$ 2.5 x upper limit of normal or total bilirubin $<$ 1.5 x upper limit of normal). Sotorasib has not been studied in subjects with moderate or severe hepatic impairment. Based on population pharmacokinetic analysis, no dose adjustment is recommended for patients with mild (creatinine clearance $\geq$ 60 mL/min) renal impairment (Section 3.2.4.2); sotorasib has not been studied in patients with moderate or severe (creatinine clearance $<$ 60 mL/min) renal impairment. Sotorasib pharmacokinetics were not associated with individual markers of renal function, consistent with low radioactive recovery in urine (approximately 6%) in healthy subjects (Section 3.4).

5.6 Adverse Drug Reactions

To provide a robust dataset at the intended dose and to maximize the potential for identifying adverse events that were related to sotorasib use, adverse drug reactions were evaluated based on the 339 subjects with any tumor type who were treated with sotorasib monotherapy at 960 mg QD. Medical review was based on a broad evaluation of all adverse events (including their severity, onset, duration, and outcome), changes in laboratory values, and vital signs.

Adverse reactions were determined to be those events that were reported ≥ 15% in subjects with any tumor type who were treated with sotorasib monotherapy at 960 mg QD. In addition, medical review of all adverse events reported was undertaken, with special attention to common events, grade ≥ 3 and serious adverse events. A review of all the frequently occurring adverse events was performed, with consideration of the events expected to occur at a particular incidence in patients with known underlying diseases to identify an appropriate initial threshold for identifying adverse drug reactions. Based on this review, adverse drug reactions for sotorasib were initially selected by evaluating adverse events that occurred with a ≥ 15% overall incidence rate, grade ≥ 3 adverse events with a ≥ 2% overall incidence rate, or serious adverse events with ≥ 2% overall incidence rate. An assessment was also performed on adverse events not meeting any of these thresholds that could represent potentially serious toxicities (eg, cardiac and neurological events), or those commonly associated with drug use (eg, rash). Additional considerations such as temporal association, biological plausibility, and medical judgment were then applied for a probable causal drug event association to determine the final adverse drug reactions.

This methodology identified serious adverse events and grade ≥ 3 adverse events including, but not limited to, pneumonia, pleural effusion, bowel obstruction, NSCLC (progression of disease), cholangitis, pulmonary embolism, respiratory failure, blood ALP increased, back pain, and anemia. A comprehensive review of these events resulted in none being selected as adverse drug reactions for sotorasib as they represented events expected at the given rates with the underlying patient diseases, alternative etiologies, and/or a lack of strong evidence of causality to sotorasib.

The resulting list of adverse drug reactions for sotorasib are summarized in Table 11.

Table 11. Adverse Drug Reactions with Sotorasib

System Organ Class	Adverse Reaction	Frequency Category[a]	Overall Subject Incidence (N = 339) n (%)
Gastrointestinal disorders			
	Diarrhea	Very common	116 (34.2)
	Nausea	Very common	81 (23.9)
	Vomiting	Very common	59 (17.4)
	Abdominal pain[b]	Very common	59 (17.4)
General disorders and administration site conditions			
	Fatigue	Very common	67 (19.8)
Investigations			
	Aspartate aminotransferase increased	Very common	54 (15.9)
	Alanine aminotransferase increased	Very common	49 (14.5)

Monotherapy 960mg QD sotorasib for subjects with any tumor type are included. Phase 1 data cut-off date 06JUL2020. Phase 2 data cut-off date 01SEP2020.

[a] Very common (≥ 10%), common (≥ 1% to < 10%), uncommon (≥ 0.1% to < 1%), rare (≥ 0.01% to < 0.1%) and very rare (< 0.01%).

[b] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower.

Coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. Graded using Common Terminology Criteria for Adverse Events version 5.0 criteria.

Source: ISS Table 14-6.9.2 and ISS Table 14c-6.2.500

5.7 Pharmacovigilance and Risk Minimization

Risk mitigation strategies used in the sotorasib clinical program, including clinical monitoring and dose modification guidelines, are consistent with those included in the proposed Prescribing Information through the Dosage and Administration and Warnings and Precautions sections. Based on the comprehensive review of the safety data, Amgen considers that the risks associated with sotorasib can be managed through routine pharmacovigilance and risk communication through the proposed prescribing information, labeling, and packaging and no additional risk minimization measures are proposed.

Amgen has a robust pharmacovigilance program to monitor safety in the postmarketing setting. Routine pharmacovigilance activities include the monitoring of adverse events from clinical studies, postmarketing experience, and literature review. Access to various

databases will serve as additional signal detection (ie, the US FDA Adverse Event Reporting System [FAERS] and VigiBase®, the World Health Organization (WHO) Global Individual Case Safety Report database, EudraVigilance). Amgen will review individual and aggregate adverse event data in the frame of the internal signal detection procedure, including structured searches for important identified risks and important potential risks and periodic trend analysis for increased frequency. Any newly identified safety signals will be further evaluated and, if deemed necessary, will be considered for inclusion in labeling and other forms of risk communication (eg, healthcare professional letter). New and updated safety information will be provided to regulatory authorities consistent with regional standards and laws.

6. Benefits and Risks Conclusions

The key benefits and risks of sotorasib are visually depicted in the Value Tree (Appendix 4) and the favorable and unfavorable effects of sotorasib are summarized in the Effects Table (Appendix 5); the Effects Table also summarizes the strengths and uncertainties of the evidence.

6.1 Therapeutic Context

As described in detail in Section 1.1, locally advanced or metastatic *KRAS p.G12C*-mutated NSCLC is a genetically distinct form of lung cancer. Previously treated *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC is a serious life-threatening condition with poor prognosis and survival. These patients have limited treatment options as there is no regulatory-approved targeted therapy specific for this mutation. Treatment outcomes with available therapies are poor; thus, there is a significant unmet medical need for new therapies in this patient population.

6.2 Benefits

The key clinical benefits of sotorasib for patients with previously treated *KRAS p.G12C*-mutated NSCLC include a clinically meaningful and durable objective response, a predictive biomarker to identify the patient population for personalized therapy, and convenient oral administration for patients. These key benefits of sotorasib are described below; relevant supporting data are provided in Appendix 5. A summary of the strengths and limitations of the evidence is provided in Section 6.4.

Durable Objective Response: Sotorasib monotherapy demonstrated a clinically meaningful and durable objective response among subjects with advanced NSCLC in Study [redacted] (ORR of 37.4%, 95% CI: 28.8, 46.6 and median DOR of 8.4 months, 95% CI: 6.9, 8.4 [in the primary analysis for phase 2]) (Section 4.3).

Predictive Biomarker to Identify the Patient Population for Personalized Therapy: A predictive biomarker identified by using validated in vitro diagnostic testing to select patients with the *KRAS p.G12C* mutation who are most likely to benefit from sotorasib therapy and exclude those who would not benefit from treatment.

Convenient and Flexible Oral Administration: Sotorasib can be administered orally with or without food, in tablets or water dispersion, which provide the patient with convenience and flexibility in their daily life (Section 2).

Survival: The median OS was 12.0 months (95% CI: 9.5, not estimable) and median PFS was 6.7 months (95% CI: 4.9, 8.1) from the pivotal, non-randomized phase 2

portion of Study [redacted] (Section 4.3). The observed median PFS and median OS are considered likely to indicate a treatment effect on progression and survival time and will be confirmed in the ongoing phase 3 randomized, active-controlled Study [redacted]

Overall, sotorasib demonstrated a clinically meaningful durable objective response and potential survival benefits of PFS and OS, with convenient and flexible oral administration in subjects with previously treated *KRAS p.G12C*-mutated advanced NSCLC identified by a predictive biomarker.

6.3 Risks

The key risk with sotorasib is increased liver enzymes (Appendix 5).

Sotorasib has been associated with transient elevations of serum transaminases (ALT and AST), including mostly asymptomatic cases in clinical studies. These elevations improved or resolved with interruption of treatment and did not result in cases of Hy's Law (ie, concurrent increase of AST/ALT and bilirubin with normal ALP in the absence of alternative etiology), liver failure, or fatal cases. Increased AST and ALT are considered adverse drug reactions (Section 5.6).

The risk of increased liver enzymes can be successfully managed with more frequent testing, by dose modification, or with temporary interruption until resolution.

Sotorasib was generally safe and well tolerated, with a low number of adverse events leading to treatment discontinuation in pivotal Study [redacted] (9.5% in the NSCLC 960-mg sotorasib monotherapy cohort [fasted]).

Routine risk minimization activities (ie, risk communications through prescribing information or product packaging) are considered adequate to address the safety concerns associated with the use of sotorasib.

6.4 Strengths and Limitations of the Evidence

The supporting data, strengths, and uncertainties of the evidence are provided in Appendix 5. Based on the totality of data from clinical studies in this marketing application, the strength of the evidence for safe and effective use of sotorasib for the proposed indication include the following:

- Objective response rate and DOR are reasonably likely to predict clinical benefit. An effect on ORR of sufficient magnitude and duration is likely to predict a sufficient effect on PFS (Section 4.1.2).
- Tumor response was based on blinded independent central review assessed by RECIST 1.1 criteria, representing unbiased clinically relevant measures of tumor response to therapy, with mostly consistent response across subgroups.

- Sotorasib was well tolerated for the proposed indication, with a low rate of adverse events (9.5%) leading to sotorasib discontinuation.
- In general, the patients with *KRAS p.G12C*-mutated NSCLC who participated in patient perspective Study [redacted] perceived a hypothetical 25% to 35% response rate of sotorasib to be a meaningful benefit despite an unknown survival benefit. Furthermore, most participants in this study sample indicated that they would choose an oral treatment with a benefit-risk profile similar to that of sotorasib over an intravenous treatment with a benefit-risk profile similar to taxane-based chemotherapy.

Limitations of the evidence for safe and effective use of sotorasib for the proposed indication are as follows:

- Study [redacted] is a single-group, non-randomized study. As such, interpretation of the survival outcome is limited. Furthermore, known and unknown patient selection biases may affect the clinical outcomes. Survival and additional clinical benefits will be confirmed in the ongoing phase 3 randomized, active-controlled Study [redacted]
- Study [redacted] had a relatively short follow up time (median follow-up time for DOR was 6.9 months [range: 1.3 to 8.4]) which limits the accuracy of time-based endpoint estimates (DOR, PFS, and OS). From the available follow-up time from Study [redacted], 50% of responders had a DOR of longer than 6 months, with long-term follow-up ongoing.
- The sotorasib once daily oral regimen is convenient and may improve treatment compliance; however, the potential for dosing errors leading to harm due to the number of pills is not yet known in the real-world setting. Dosing errors leading to adverse events were not observed in pivotal Study [redacted]
- Study [redacted] is a single-group, non-randomized study with limited long-term safety data. There is no direct comparison of the sotorasib safety profile with current standard of care therapy (chemotherapy and immunotherapy).

Uncertainties of the evidence for safe and effective use of sotorasib for the proposed indication are as follows:

- A portion of subjects with *KRAS p.G12C*-mutated advanced NSCLC did not respond to sotorasib treatment in Study [redacted] The effect of co-mutation, resistance mechanism, and additional predictive biomarkers are under investigation in ongoing clinical trials.
- Patients with ECOG performance status $\geq$ 2 account for 30% to 40% of all patients with NSCLC; however, these patients were excluded from most NSCLC clinical trials (including pivotal phase 2 Study [redacted]). It is currently not known if the clinical outcome in patients with ECOG performance status 0 to 1 can be extrapolated to patients with ECOG $\geq$ 2 in the real-world setting (Dall'Olio et al, 2020; Passaro et al, 2019).
- Subjects with active brain metastases from non-brain tumors were excluded from Study [redacted] Brain metastases are associated with a poor prognosis and occur in approximately 16% to 22% of patients with NSCLC (Ali et al, 2013).

The patient subpopulations noted above (ECOG 2 and brain metastases) are being investigated in ongoing clinical studies.

- The ability to predict which patients may be at risk for increased liver enzymes is lacking.
- The patient's previous exposure to immunotherapy may confound the causal association with sotorasib due to delayed immune-related events (DIRE) after discontinuation of immunotherapy (Couey et al, 2019).
- No studies have been specifically conducted or completed in subjects with renal impairment, hepatic impairment, pregnant women, or lactating women.

6.5 Benefit-risk Assessment

The assessment presented in this document demonstrate that the benefit-risk profile of sotorasib at 960 mg QD is favorable for the treatment of adult patients with previously-treated, *KRAS G12C*-mutated locally advanced or metastatic NSCLC.

Previously-treated NSCLC is a serious, life-threatening condition with poor prognosis and survival, and has limited treatment options, with no regulatory approved targeted therapy specific for the *KRAS p.G12C* mutation. The outcomes on available therapies are poor; therefore, there is a significant unmet medical need for the intended patient population. Treatment with sotorasib results in clinically meaningful durable objective response and potential survival benefits of PFS and OS. The availability of a predictive biomarker to identify patients with *KRAS p.G12C*-mutated advanced NSCLC who are most likely to benefit from sotorasib therapy, and exclude those who will not benefit from treatment, is a key factor in improving the positive benefit-risk profile for this product.

Sotorasib is well tolerated and risks associated with sotorasib use can be adequately managed through communication in product labeling, routine pharmacovigilance activities, and routine risk minimization activities.

Sotorasib can be administered orally with or without food, in tablets or water dispersion, which provides patients with convenience and flexibility in their daily lives.

In general, patients with *KRAS p.G12C*-mutated NSCLC who participated in the Amgen patient perspective Study [redacted] perceived a hypothetical 25% to 35% response rate of sotorasib treatment to be a meaningful benefit despite an unknown survival benefit.

In conclusion, sotorasib demonstrated a clinically meaningful durable objective response with an acceptable safety profile in subjects with previously treated *KRAS p.G12C*-mutated NSCLC. Survival and additional clinical benefits will be confirmed in the ongoing phase 3 randomized, active-controlled Study [redacted] The overall benefit-risk profile of sotorasib is favorable.

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8. Appendices

Appendix 1. Real-world Evidence Studies

Table 12. Summary of Descriptive Data for Real-world Evidence Study [redacted] Study [redacted] and Study [redacted]

	KRAS p.G12C-mutated NSCLC		All NSCLC
	Study [redacted]	Study [redacted]	Study [redacted]
Study Description			
Sample size	743	416	7069
Study population	Diagnosed with advanced NSCLC between 2011 and 2019	Diagnosed with metastatic NSCLC between 2004 and 2019	Diagnosed with advanced NSCLC between 2011 and 2019
Dataset	Flatiron Health Foundation Medicine Clinico-Genomic Database	AACR-GENIE	Flatiron Health Foundation Medicine Clinico-Genomic Database
Setting	Mainly community oncology practices across the United States of America	3 comprehensive academic centers in the United States of America	Mainly community oncology practices across United States of America
Patient and Clinical Characteristics			
Median age (years) at advanced diagnosis (range)	68 (29, 85)	67 (38, 86)	68 (24, 85)
Female	61%	64%	50%
Ever smokers	97%	97%	82%
Non-squamous	91%	88%[a]	76%
Diagnosed in 2015 or later[b]	82%	65%	82%

AACR = American Association for Cancer Research; *ALK* = anaplastic lymphoma kinase gene; *BRAF* = B-raf gene; *EGFR* = epidermal growth factor receptor gene; GENIE = Genomics Evidence Neoplasia Information; *KRAS p.G12C* = *KRAS* gene with a mutation resulting in a G12C amino acid substitution at the protein level; NSCLC = non-small cell lung cancer; PD-1 = programmed cell death-1; PD-L1 = programmed death-ligand 1; *ROS1* = proto-oncogene tyrosine-protein kinase ROS

[a] Including adenocarcinoma and large cell carcinoma

[b] For the year of advanced diagnosis.

Source: Study [redacted] Study [redacted] and Study [redacted]

Table 12. Summary of Descriptive Data for Real-world Evidence Study [redacted] Study [redacted] and Study [redacted]

	KRAS p.G12C-mutated NSCLC		All NSCLC
	Study [redacted]	Study [redacted]	Study [redacted]
Molecular Characteristics			
EGFR mutation	1.2%	0.2%	13.6%
ALK rearrangement	0.0%	0.0%	2.7%
ROS1 rearrangement	0.3%	0.2%	0.7%
BRAF mutation	0.9%	1.0%	4.2%
PD-L1 expression			
≥ 50%	39%	38%	29%
1-49%	32%	25%	30%
< 1%	29%	37%	41%
Treatment regimens in second line of therapy			
Platinum-based chemotherapy without PD-1/L1 inhibitors	16%	12%	15%
Platinum-based chemotherapy with PD-1/L1 inhibitor	3%	3%	6%
PD-1/L1 inhibitor monotherapy	58%	55%	45%
Other	23%	30%	34%

AACR = American Association for Cancer Research; *ALK* = anaplastic lymphoma kinase gene; *BRAF* = B-raf gene; *EGFR* = epidermal growth factor receptor gene; GENIE = Genomics Evidence Neoplasia Information; *KRAS p.G12C* = *KRAS* gene with a mutation resulting in a G12C amino acid substitution at the protein level; NSCLC = non-small cell lung cancer; PD-1 = programmed cell death-1; PD-L1 = programmed death-ligand 1; *ROS1* = proto-oncogene tyrosine-protein kinase ROS

[a] Including adenocarcinoma and large cell carcinoma

[b] For the year of advanced diagnosis.

Source: Study [redacted] Study [redacted] and Study [redacted]

Appendix 2. Second-line Non-targeted Treatment Options for Non-small Cell Lung Cancer

Table 13. Second-line Non-targeted Treatment Options for Non-small Cell Lung Cancer

Product Name (INN)	Dosing / Administration	Efficacy Information	Important Safety and Tolerability Issues
Afatinib	tablets: 40 mg orally once daily	Study [redacted] • median OS: 7.9 months • median PFS: 2.4 months • ORR: 3%	diarrhea, bullous and exfoliative skin disorders, interstitial lung disease, hepatic toxicity, gastrointestinal perforation, keratitis, and embryo-fetal toxicity
Atezolizumab	injection (IV infusion): 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks	Study [redacted] • median OS: 13.8 months • median PFS: 2.8 months • ORR: 14%	immune-related events (including pneumonitis, hepatitis, colitis, endocrinopathies); infusion related reactions, infections, and embryo-fetal toxicity
Docetaxel	Injection (IV infusion); 75 mg/m^2 every 3 weeks	Study [redacted] • median survival: 7.5 months • time to progression: 12.3 weeks • response rate: 5.5% Study [redacted] • median survival: 5.7 months • time to progression: 8.3 weeks • response rate: 5.7%	second primary malignancies, cutaneous reactions, neurologic reactions, eye disorders, asthenia, embryo-fetal toxicity, alcohol content, and tumor lysis syndrome
Erlotinib	150 mg orally daily	Study [redacted] • median PFS: 2.2 months • median OS: 6.7 months	interstitial lung disease, renal failure, hepatotoxicity, gastrointestinal perforation, bullous and exfoliative skin disorders, ocular disorders, hemorrhage in patients taking warfarin, and embryo-fetal toxicity
Nintedanib / Docetaxel	capsules: 200 mg orally BID on days 2 to 21 of a 21-day docetaxel treatment cycle	Study [redacted] • median OS: 12.6 months • median PFS: 4.2 months	gastrointestinal disorders, neutropenia and sepsis, hepatobiliary disorders including liver enzyme elevations, hyperbilirubinemia and liver injury, renal impairment/failure, hemorrhage, venous thromboembolism

Footnotes are defined on the last page of the table

Table 13. Second-line Non-targeted Treatment Options for Non-small Cell Lung Cancer

Product Name (INN)	Dosing / Administration	Efficacy Information	Important Safety and Tolerability Issues
Nivolumab	injection (IV): 240 mg every 2 weeks or 480 mg every 4 weeks	Study [redacted]) • median OS: 9.2 months • ORR: 20% • median DOR: not reported • median PFS: 3.5 months	immune-mediated reactions (including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin adverse reactions, and encephalitis), infusion-related reactions, complications of allogeneic HSCT, and embryo-fetal toxicity
Pembrolizumab	injection (IV): 200 mg every 3 weeks or 400 mg every 6 weeks	Study [redacted] vs docetaxel TPS ≥ 50% • median OS: 14.9 vs 8.2 months • median DOR: NR v 8.1 months • ORR: 30% vs 8% TPS ≥ 1% • median OS: 10.4 vs 8.5 months • median DOR: NR vs 6.2 months • ORR: 18% vs 9%	immune-mediated reactions (including pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, nephritis, skin adverse reactions, other adverse reactions), infusion related reactions, complications of allogeneic HSCT, and embryo-fetal toxicity
Pemetrexed	injection (IV): 500 mg/m^2 every 3 weeks	Study [redacted] • median OS: 8.3 months • median PFS: 2.9 months • ORR: 8.5%	myelosuppression, renal failure, bullous and exfoliative skin toxicity, interstitial pneumonitis, radiation recall, and embryo-fetal toxicity
Ramucirumab Docetaxel	injection (IV): 10 mg/kg over 60 minutes on day 1 of a 21-day cycle prior to docetaxel infusion	Study [redacted] • median OS: 10.5 months • median PFS: 4.5 months • ORR 23%	hemorrhage, gastrointestinal perforations, impaired wound healing, arterial thromboembolic events, hypertension, infusion-related reactions, worsening of pre-existing hepatic impairment, posterior reversible encephalopathy syndrome, proteinuria including nephrotic syndrome, thyroid dysfunction, and embryo-fetal risk

ALK = anaplastic lymphoma kinase; DOR = duration of response; EGFR = epidermal growth factor receptor; FDA = Food and Drug Administration; HSCT = hematopoietic stem cell transplantation; INN = International Nonproprietary Name; IV = intravenous; NR = not reached; NSCLC = non-small lung cancer; ORR = objective response rate; OS = overall survival; PD-1 = programmed cell death-1; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; QTc = corrected QT (interval); TKI = tyrosine kinase inhibitors; TPS = tumor proportion score

Source: Product prescribing information; some treatment options may not be approved within the region in which this dossier is being submitted.

Appendix 3. Studies Not Included in the Marketing Application

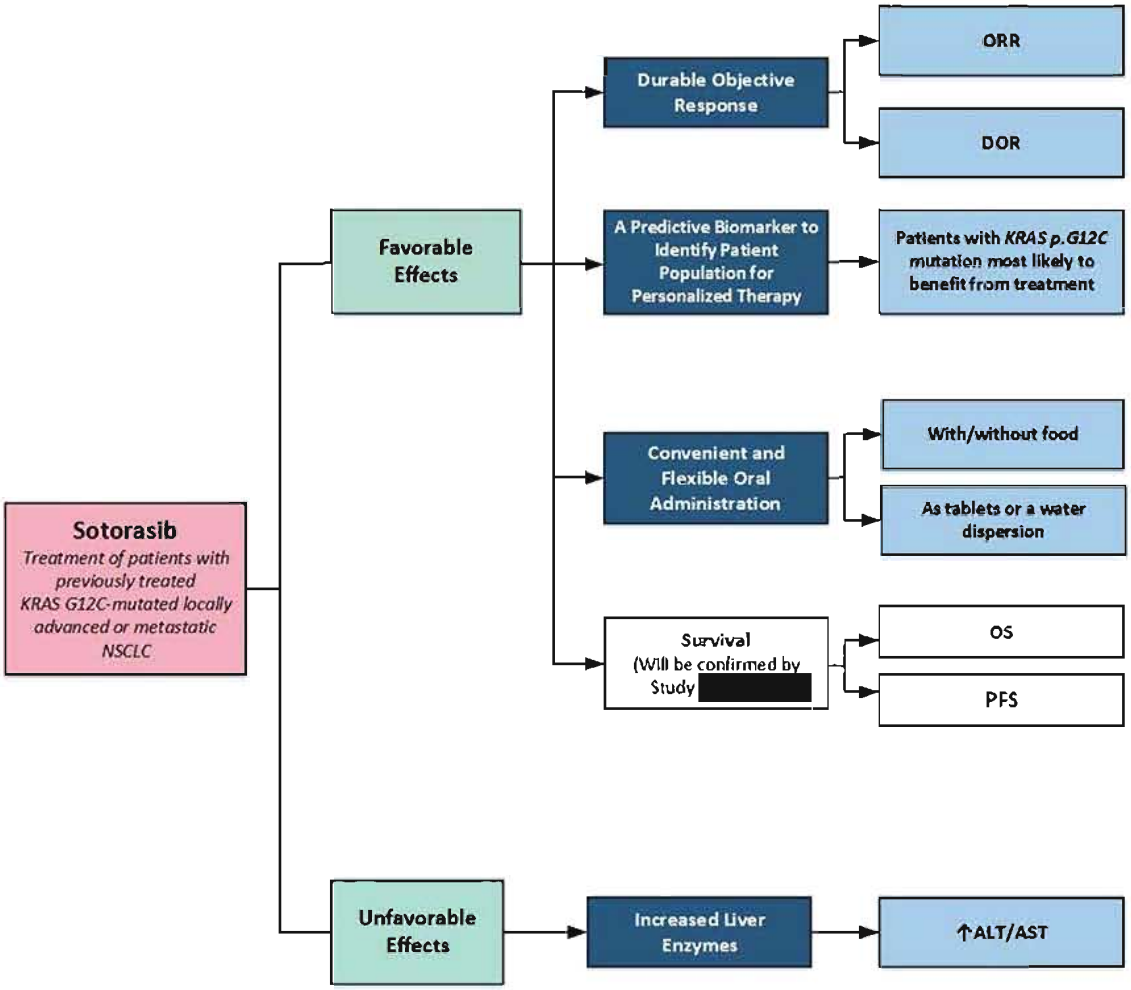
The ongoing clinical studies listed below had not enrolled subjects prior to the data cutoff date of 01 September 2020 and thus are not included in this marketing application.

	Study Title
Study [redacted]	A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 510 (pINN Sotorasib) in Combination With [redacted] n Subjects with Advanced Non-small Cell Lung Cancer (NSCLC) With *KRAS p.G12C* Mutation [redacted]
Study [redacted]	A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of (pINN) Sotorasib (AMG 510) in Combination [redacted] in Subjects With Advanced Non-small Cell Lung Cancer (NSCLC) With *KRAS p.G12C* Mutation [redacted]

Module 5 – Justification for Missing Sections of the eCTD

5.3.1.3 In Vitro – In Vivo Correlation Study Reports
In vitro – in vivo correlation studies were not conducted, as changes to the drug product formulation were not anticipated to affect human exposure
5.3.2.1 Plasma Protein Binding Study Reports
Reports of plasma protein binding studies are provided in Module 4.
5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies
Reports of hepatic metabolism and drug interaction studies are provided in Module 4.
5.3.2.3 Reports of Studies Using Other Human Biomaterials
No in vitro studies using human biomaterials other than plasma protein binding, metabolism or drug interaction studies were performed.
5.3.3.2 Patient PK and Initial Tolerability Study Reports
Reported in Clinical Study Report for [redacted] and summarized in Module 2
5.3.3.3 Intrinsic Factor PK Study Reports
Reported in Population PK Study Report for [redacted] and summarized in Module 2
5.3.4.1 Healthy Subject PD and PK/PD Study Reports
As sotorasib is intended to be indicated for patients with advanced cancer, no PD or PK/PD studies have been conducted in healthy subjects.

Appendix 4. Value Tree for Sotorasib



Up arrow indicates increased.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; B-R = benefit-risk; DOR = duration of response; *KRAS* = Kirsten rat sarcoma viral oncogene homolog; *KRAS p.G12C* = *KRAS* gene with a mutation resulting in a G12C amino acid substitution at the protein level; NSCLC = Non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival

Source: Sotorasib cSBRA v1.0

Appendix 5. Effects Table for Sotorasib Treatment of Patients With Previously Treated *KRAS G12C*-mutated Locally Advanced or Metastatic Non-small Cell Lung Cancer (NSCLC)

Effect		Short Description	Study	Treatment	Statistics	Uncertainties/Strength of Evidence	References
Favorable	Durable Objective Response	Tumor ORR (CR + PR) measured by CT or MRI and assessed by RECIST 1.1 by BICR Percentage of subjects with an ORR summarized with Clopper-Pearson exact 95% CI[a] DOR (calculated only for those subjects with a confirmed CR or PR per RECIST 1.1), defined as the time from first confirmed objective response to confirmed disease progression per RECIST 1.1 or death, whichever was earlier. Summarized with Kaplan-Meier quartiles and rates for selected durations.	[redacted] (phase 2 portion) 123 subjects in the full analysis set (FAS)	Sotorasib monotherapy	ORR: 46/123 subjects (37.4%) (95% CI: 28.8, 46.6) 2/123 subjects (1.6%) achieved CR and 44/123 subjects (35.8%) achieved PR. Median DOR: 8.4 months (95% CI: 6.9, 8.4) among 46 subjects who achieved confirmed response	Strengths • The evidence for the clinical benefit of sotorasib in *KRAS p.G12C*-mutated advanced NSCLC is primarily derived from the pivotal phase 2 portion of Study [redacted] n the biomarker defined population identified by a validated IVD test. • The durable objective response observed in patients with *KRAS p.G12C*-mutated advanced NSCLC is a clear measure of clinical benefit. These were assessed by BICR based on RECIST 1.1 representing unbiased clinically relevant measures of tumor response to therapy with mostly consistent response across subgroups. • The ORR and DOR are acceptable surrogate endpoints which are reasonably likely to predict clinical benefit. An effect on ORR of sufficient magnitude and duration is likely to predict a sufficient effect on PFS (FDA, 2018a; FDA, 2018b; Blumenthal et al, 2015; Clarke et al, 2015; FDA, 2015; Pignatti et al, 2015).	[redacted] (phase 2): Table 10-1

Footnotes and abbreviations are defined on the last page of this table.

Effect		Short Description	Study	Treatment	Statistics	Uncertainties/Strength of Evidence	References
Favorable	Durable Objective Response (continued)					Uncertainties/Limitations • Study [redacted] s a single cohort, non-randomized study. As such, interpretation of the survival outcome in a single-cohort study is limited. Furthermore, known and unknown patient selection biases may affect the clinical outcomes. Survival and additional clinical benefits will be confirmed in the ongoing phase 3 randomized NSCLC Study [redacted] • Study [redacted] had a relatively short follow-up time (median follow-up time for DOR was 6.9 months [range: 1.3 to 8.4]) which limits the accuracy of time-based endpoint estimates (DOR, PFS, and OS). From the available follow-up time from Study [redacted] 50% of responders had a DOR of longer than 6 months, with long-term follow-up ongoing. • A portion of subjects with *KRAS p.G12C*-mutated advanced NSCLC did not respond to sotorasib treatment in Study [redacted] The impact of co-mutation, resistance mechanism, and additional predictive biomarkers are under investigation in ongoing clinical trials. • Patients with ECOG ≥ 2 and patients with active brain metastases from non-brain tumors were excluded from Study [redacted] These subpopulations of patients are being investigated in ongoing clinical studies.	

Footnotes and abbreviations are defined on the last page of this table.

Effect		Short Description	Study	Treatment	Statistics	Uncertainties/Strength of Evidence	References
Favorable	A predictive biomarker to identify patient population for personalized therapy	Patients with *KRAS p.G12C*-mutated advanced NSCLC most likely to benefit from treatment	[redacted]	NA	NA	Strengths: • In vitro diagnostic clinical performance was established in a prospective biomarker selected global population based on a correlation between *KRAS p.G12C* mutation and clinical efficacy. This test identifies those patients who are most likely to benefit from sotorasib therapy and excludes those who would not benefit from treatment. Uncertainties/Limitations: • An IVD test to detect patients with the *KRAS p.G12C* mutation must be performed prior to initiation of sotorasib therapy. The availability and type of test could vary by country.	Reference Country IVD registration or application number (if available)

Footnotes and abbreviations are defined on the last page of this table.

Effect		Short Description	Study	Treatment	Statistics	Uncertainties/Strength of Evidence	References
Favorable	Convenient and Flexible Oral Administration	Evaluate the PK of sotorasib administered in the fasted and fed state in healthy subjects	[redacted]	Sotorasib	NA	Strengths: • Study [redacted] was conducted in a controlled environment, meal timing, strict timing of protocol activities, absence of concomitant medications, and defined healthy population. • Study [redacted] was conducted in tightly controlled conditions (PK sample timing, dose timing, meal timing, all healthy subjects meeting tight inclusion/exclusion criteria). Uncertainties/Limitations: • Study [redacted] had 14 subjects and Study [redacted] had 13 subjects enrolled. • The sotorasib once daily oral regimen is convenient and may improve treatment compliance; however, the potential for dosing errors leading to harm due to the number of pills required is not yet known in the real-world setting. Dosing errors leading to adverse events were not observed in pivotal Study [redacted]	[redacted] Table 14.2.1-3
		Evaluate the PK of sotorasib administered as 8 x 120 mg tablets and as water dispersion in healthy subjects	[redacted]	Sotorasib	NA		[redacted] Table 8

Footnotes and abbreviations are defined on the last page of this table.

Effect		Short Description	Study	Treatment	Statistics	Uncertainties/Strength of Evidence	References
Favorable	Survival	Time from the date of the first dose of sotorasib to the date of disease progression (assessed by BICR per RECIST 1.1) or death on or before the data cutoff date, whichever occurs first. Summarized with Kaplan-Meier curves, quartiles, and rates for selected timepoints	[redacted] (phase 2 portion) 123 subjects in the full analysis set (FAS).	Sotorasib monotherapy	Median KM estimate OS: 12 months (95% CI: 9.5, not estimable) Median KM estimate PFS: 6.7 months (95% CI: 4.9, 8.1)	<u>Strengths</u> • The evidence for the clinical benefit of sotorasib in *KRAS p.G12C*-mutated advanced NSCLC is primarily derived from the pivotal phase 2 portion of Study [redacted] in the biomarker defined population identified by a validated IVD test. <u>Uncertainties/Limitations:</u> • Study [redacted] is a single-cohort, non-randomized study. As such, interpretation of the survival outcome in a single-cohort study is limited. Furthermore, known and unknown patient selection biases may affect the clinical outcomes. Survival and additional clinical benefits will be confirmed in the ongoing phase 3 randomized NSCLC Study [redacted] • Patients with ECOG ≥ 2 and subjects with active brain metastases from non-brain tumors were excluded from Study [redacted] These subpopulations of patients are being investigated in ongoing clinical studies.	[redacted] Table 10-2 Table 10-3

Footnotes and abbreviations are defined on the last page of this table.

Effect		Short Description	Study	Treatment	Statistics	Uncertainties/Strength of Evidence	References
Unfavorable	Increased Liver Enzymes	Subject incidence: increased ALT increased AST	[redacted] (phase 1 and phase 2 portion of the study; all subjects with NSCLC at a dose of 960 mg QD monotherapy)	Sotorasib 960 mg monotherapy NSCLC (fasted)	Integrated safety data Treatment-emergent AEs ALT increased: 38/190 subjects (20.0%); AST increased: 40/190 subjects (21.1%). ≥ Grade 3 treatment-emergent AEs ALT increased: 15/190 subjects (7.9%); AST increased: 13/190 subjects (6.8%). Serious adverse events ALT increased: 2/190 subjects (1.1%) AST increased: 1/190 subjects (0.5%)	Strengths: • Sotorasib was well tolerated for the proposed indication, with a low rate of adverse events (9.5%) and increased AST/ALT events (1.6%) leading to discontinuation. Uncertainties/Limitations: • Study [redacted] is a single-cohort, non-randomized study with limited long-term safety data. In addition, there is no direct comparison of the sotorasib safety profile with current standard of care therapy (chemotherapy and immunotherapy). • The ability to predict which patients may be at risk for increased liver enzymes is lacking. • The patient's previous exposure to immunotherapy may confound the causal association with sotorasib due to DIRE after discontinuation of immunotherapy (Couey et al, 2019).	ISS Safety tables: Table 14b-6.2.1 Table 14b-6.3.31 Table 14b-1.1 Table 14b-6.4.2

Footnotes and abbreviations are defined on the last page of this table.

Effect		Short Description	Study	Treatment	Statistics	Uncertainties/Strength of Evidence	References
Unfavorable	Increased Liver Enzymes (continued)	Subject incidence: increased ALT increased AST	[redacted] (phase 1 and phase 2 portion of the study; all subjects with NSCLC at a dose of 960 mg QD monotherapy)	Sotorasib 960 mg monotherapy NSCLC (fasted)	Integrated safety data (continued) Treatment-emergent AEs leading to discontinuation of sotorasib ALT increased: 3/190 subjects (1.6%) AST increased: 3/190 subjects (1.6%)	Uncertainties/Limitations (continued): • Other key uncertainties of the evidence are that no studies have been specifically conducted or completed to study patients with renal impairment, hepatic impairment, pregnant women, or lactating women.	ISS Safety tables: Table 14b-6.3.33

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BICR = blinded independent central review; CR = complete response; CSR = clinical study report; CT = computerized tomography; DIRE = delayed immune-related events; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; IVD = in vitro diagnostic; KM = Kaplan-Meier; *KRAS* = Kirsten rat sarcoma viral oncogene homolog (DNA); *KRAS p.G12C* = *KRAS* gene with a mutation resulting in a G12C amino acid substitution at the protein level; MRI = magnetic resonance imaging; NA = not applicable; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; QD = once daily; RECIST = Response Evaluation Criteria In Solid Tumors

[a] Clopper and Pearson, 1934.

Source: Sotorasib cSBRA v1.0