Redacted according to Section 41, FOI Act

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List of Abbreviations

Abbreviation or Term	Definition/Explanation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
ISS	Integrated Summary of Safety
KRAS	Kirsten rat sarcoma viral oncogene homolog
$KRAS^{G12C}$	KRAS protein with a G12C amino acid substitution
KRAS p.G12C	*KRAS* gene with a mutation resulting in a G12C amino acid substitution
MedDRA	Medical Dictionary for Regulatory Activities
NSCLC	non-small cell lung cancer
QTcF	QT interval corrected for heart rate using Fridericia's formula
SMQB	standardized MedDRA query, broad scope

1. Exposure to the Drug

1.1 Introduction

Sotorasib (AMG 510) is a small molecule that specifically binds and irreversibly inhibits the Kirsten rat sarcoma viral oncogene homolog protein (KRAS) with the G12C amino acid substitution ($KRAS^{G12C}$). This Summary of Clinical Safety summarizes data to support marketing authorization of sotorasib for the treatment of patients with previously treated *KRAS p.G12C*-mutated (ie, *KRAS* gene with a mutation resulting in a G12C amino acid substitution) locally-advanced or metastatic non-small cell lung cancer (NSCLC).

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). 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). 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. Advanced NSCLC (stage IIIB and IV) is a serious and life-threatening disease, with a 5-year survival of 5.2% (Surveillance, Epidemiology, and End Results Program, 2019).

A number of 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 express guanosine triphosphatases 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 *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, thereby reducing the hydrolysis of guanosine triphosphate by the KRAS protein. The resulting accumulation of active, guanosine triphosphate-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

(Biernacka et al, 2016) and has been identified as a putative oncogenic driver in this tumor type (AACR Project GENIE Consortium, 2017; 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, 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 therapies specifically targeting *KRAS p.G12C* mutations have been successfully developed until recently (McCormick, 2019). Oncogenic *KRAS* mutations rarely (≤ 1.2%) occur concomitantly with other oncogenic mutations in genes such as the epidermal growth factor receptor gene (Martorell et al, 2017). 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). The outcomes for patients with advanced NSCLC with the *KRAS p.G12C* mutation are poor with existing therapies in second-line or later, and their prognosis is as poor as the overall population of patients with advanced NSCLC (Wiesweg et al, 2019; Park et al, 2017; Barlesi et al, 2016; Svaton et al, 2016; Johnson et al, 2013). Therefore, there is a need for additional novel, biomarker driven, anticancer therapies with better efficacy and tolerable safety profiles to address *KRAS p.G12C*-driven tumors.

Sotorasib is a novel small molecule that specifically binds and irreversibly inhibits the $KRAS^{G12C}$ mutant protein. The structure is presented in Figure 1 of Module 2.5, Clinical Overview. Sotorasib binds to the P2 pocket of $KRAS^{G12C}$ adjacent to the cysteine at position 12 and the nucleotide binding pocket. The inhibitor contains a thiol reactive portion that covalently modifies the cysteine residue and locks $KRAS^{G12C}$ in an inactive, guanosine diphosphate-bound conformation. This blocks the interaction of KRAS with effectors such as RAF, thereby preventing downstream signaling, including the phosphorylation of extracellular-signal-regulated kinase (Canon et al, 2019; Simanshu et al, 2017; Ostrem et al, 2013; Cully and Downward, 2008). Inactivation of KRAS by ribonucleic acid interference or small molecule inhibition has previously demonstrated an inhibition of cell growth and induction of apoptosis in tumor cell lines and xenografts that

have *KRAS* mutations, including the *KRAS p.G12C* mutation (Janes et al, 2018; McDonald et al, 2017; Xie et al, 2017; Ostrem and Shokat, 2016; Patricelli et al, 2016). Studies with sotorasib have confirmed these in vitro findings and have likewise demonstrated selective inhibition of cell growth and regression of tumors with *KRAS p.G12C* mutations (Section 2.1 of Module 2.4, Nonclinical Overview). No other wild-type or mutant protein or receptor has been identified that binds sotorasib, nor has any impact been observed in cells without the *KRAS p.G12C* mutation.

The primary evidence of efficacy for this marketing application is provided by subjects with advanced NSCLC enrolled in the pivotal phase 2 portion of the phase 1/2 Study [redacted] with supportive evidence provided by the phase 1 portion assessing sotorasib monotherapy. The sotorasib development program also includes an ongoing confirmatory, active-controlled phase 3 study for the treatment of NSCLC (Study [redacted], as well as an ongoing phase 1 pharmacokinetic study in subjects of Chinese descent (Study [redacted]), and an ongoing 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]). In addition, a full clinical pharmacology program has examined the pharmacokinetics of sotorasib and explored potential drug-drug interactions.

To support the safety of the proposed indication at the indicated dose, the marketing application provides results of an integrated analysis of safety from the overall sotorasib development program. The primary safety analysis of sotorasib is based on the pooled sotorasib monotherapy data from the phase 1 and phase 2 portions of Study [redacted] In addition to the safety data from Study [redacted] supportive safety data from 3 ongoing studies ([redacted]) are provided as safety summary reports, including disposition and demographic data and safety narratives for subjects who had deaths, serious treatment-emergent adverse events, treatment-emergent adverse events (hereafter referred to as adverse events) that led to treatment discontinuation, pregnancies, and adverse events of interest (hepatotoxicity, renal toxicity).

The clinical studies supporting the marketing application are shown in Figure 2 of Module 2.5, Clinical Overview and are listed in Module 5.2, Tabular Listing of All Clinical

Studies. Studies that are not included in this marketing application are listed in Appendix 2 of Module 2.5, Clinical Overview.

1.2 Overall Safety Evaluation Plan and Narratives of Safety Studies

1.2.1 Overall Safety Evaluation Plan

The analysis of the safety profile of sotorasib is primarily based on the pooled monotherapy data from the phase 1 and phase 2 portions of ongoing Study [redacted] (data cutoffs of 06 July 2020 and 01 September 2020, respectively). Study [redacted] is a phase 1/2 study evaluating sotorasib for the treatment of NSCLC, colorectal cancer, and other solid tumors with the *KRAS p.G12C* mutation in North and South America, Australia, Europe, and Asia. The analyses presented in this Summary of Clinical Safety characterize the safety profile of sotorasib to support the proposed indication of the treatment of patients with previously treated *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC.

Additional analysis of the safety profile of sotorasib is provided from the following monotherapy and combination therapy studies:

- sotorasib monotherapy:
  - Study [redacted], a phase 3, randomized, active-controlled study to evaluate the efficacy and safety of sotorasib monotherapy versus docetaxel in subjects with previously treated locally advanced and unresectable or metastatic NSCLC with the *KRAS p.G12C* mutation (data cutoff of 01 September 2020)
  - Study [redacted], a phase 1 study to assess sotorasib monotherapy in Chinese subjects with *KRAS p.G12C*-mutated advanced NSCLC, colorectal cancer, and other solid tumors (data cutoff of 01 September 2020)
- sotorasib combination therapy:
  - Part 1c/2c of Study [redacted], evaluating sotorasib plus pembrolizumab combination therapy in subjects with *KRAS p.G12C*-mutated advanced NSCLC (data cutoff of 06 July 2020)
  - Study [redacted], an ongoing phase 1b master protocol study with sotorasib containing subprotocols evaluating multiple investigational regimens of sotorasib in subjects with advanced solid tumors with the *KRAS p.G12C* mutation
    - Study [redacted] Subprotocol A, evaluating sotorasib in combination with trametinib (data cutoff of 01 September 2020)
    - Study [redacted] Subprotocol C, evaluating sotorasib in combination with RMC-4630, an SHP2 inhibitor (data cutoff of 01 September 2020)
    - Study [redacted] Subprotocol D, evaluating sotorasib in combination with afatinib (data cutoff of 01 September 2020)
    - Study [redacted] Subprotocol E, evaluating sotorasib in combination with atezolizumab (data cutoff of 01 September 2020)

- Study [redacted] Subprotocol H, evaluating sotorasib in combination with panitumumab or in combination with panitumumab and FOLFIRI (data cutoff of 01 September 2020)

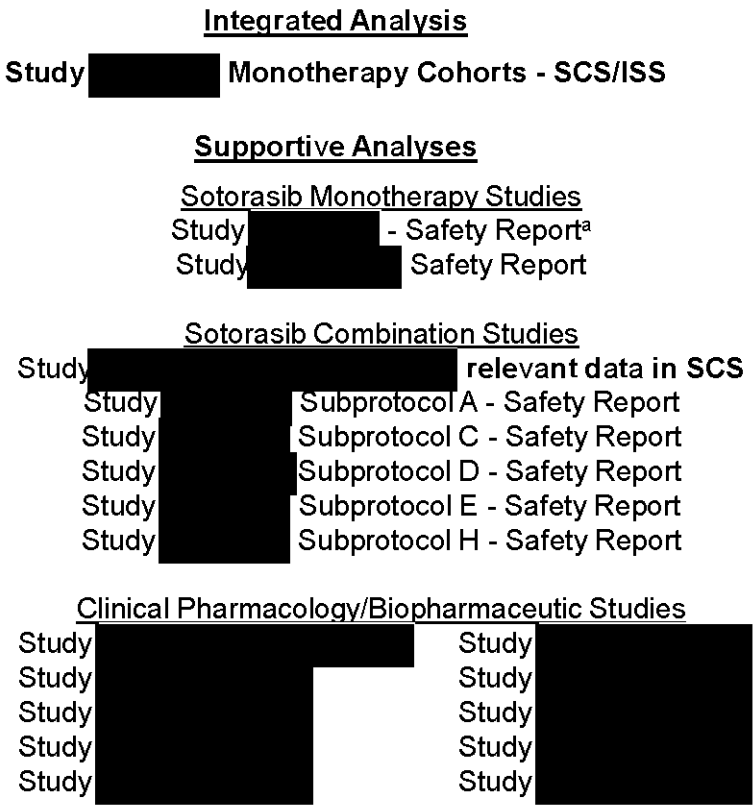
A schematic for the clinical studies which contributed to safety analysis, including a description of the reporting of the safety data for each study, is provided in Figure 1.

An integrated analysis of pooled monotherapy data from the phase 1 and phase 2 portions of Study [redacted] is described in this Summary of Clinical Safety; tables and listings are provided for the integrated summary in the Integrated Summary of Safety (ISS) located in Module 5. Relevant safety data from the sotorasib plus pembrolizumab combination therapy cohorts of Study [redacted] are also discussed within this Summary of Clinical Safety (see Section 2.1.5.3.1).

Safety data from individual cohorts in phase 1 and phase 2 of Study [redacted] are reported in the respective clinical study reports (Study [redacted] Phase 1 and Study [redacted] Phase 2). In addition, safety reports, including disposition and demographic data and safety narratives (see Section 2.2), are provided in Module 5 for the following ongoing sotorasib studies that had enrolled subjects as of the data cutoff date: Study [redacted] Study [redacted] Substudy A, Study [redacted] Substudy C, Study [redacted] Substudy D, Study [redacted] Substudy E, Study [redacted] Substudy H, and Study [redacted]

Finally, 9 clinical pharmacology and biopharmaceutic studies have been conducted in healthy subjects and subjects with *KRAS p.G12C*-mutated advanced solid tumors and are described in Module 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods, and Module 2.7.2, Summary of Clinical Pharmacology. Safety data from these studies are presented in full in the individual clinical study reports.

Thus, within this Summary of Clinical Safety, safety data are presented for an integrated analysis of sotorasib monotherapy in phase 1 and 2 of Study [redacted] Safety data from all other studies are only discussed herein when relevant.



CSR = clinical study report; ISS = Integrated Summary of Safety;
SCS = Summary of Clinical Safety

Safety report includes disposition and demographic data and safety narratives.

[a] Data from the randomized study are blinded.

1.2.1.1 Statistical Analyses and Methods

Within this Summary of Clinical Safety, data are presented side-by-side as follows:

- subjects with *KRAS p.G12C*-mutated NSCLC (hereafter referred to as NSCLC), including both previously treated subjects and treatment naïve subjects, who received at least 1 dose of sotorasib monotherapy at 960 mg once-daily in the fasted state
- subjects with *KRAS p.G12C*-mutated colorectal cancer who received at least 1 dose of sotorasib monotherapy at 960 mg once-daily in the fasted state
- subjects with *KRAS p.G12C*-mutated other tumors (non-NSCLC and non-colorectal cancer) who received at least 1 dose of sotorasib monotherapy at 960 mg once-daily in the fasted state
- subjects treated with sotorasib monotherapy at 960 mg once-daily in the fasted state for all tumor types
- the total monotherapy population (ie, all subjects who received at least 1 dose of sotorasib monotherapy for all tumor types, dose levels/regimens, and fed/fasted state)

The primary analysis of safety for the proposed indication is based on the integrated safety analyses from subjects with NSCLC who were treated with sotorasib monotherapy at 960 mg once-daily (ie, the intended dose) across the phase 1 and phase 2 portions of Study [redacted] 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. Safety data from subjects with colorectal and other tumor types are provided in the in-text tables, but only notable data are discussed as needed to fully capture the safety profile of sotorasib.

No formal hypothesis testing was performed. All analyses are descriptive.

In the ISS (located in Module 5), data are summarized by dose regimen, tumor type, and fed/fasted status as follows:

- different dose regimens of sotorasib monotherapy and the fasted versus fed state (180, 360, 720, and 960 mg once-daily fasted, 960 mg once-daily fed, 480 mg twice-daily fed, and any dose regimen) for subjects with any tumor type
- different tumor types (*KRAS p.G12C*-mutated NSCLC, colorectal cancer, other tumor types, and any tumor type) for sotorasib monotherapy at 960 mg fasted

The planned integrated analysis of the monotherapy cohorts is described in the ISS Supplemental Statistical Analysis Plan.

The impact of COVID-19 on Study [redacted] on the statistical methods are provided in Section 8.10 of Study [redacted] Phase 1 and Section 8.10 of Study [redacted] Phase 2.

1.2.1.1.1 Datasets for Safety Evaluation

The Safety Analysis Set is defined as all subjects who enrolled in the sotorasib monotherapy cohorts in the phase 1 and phase 2 portions of Study [redacted] and received at least 1 dose of sotorasib.

Exposure, adverse events, and other safety assessments were summarized using the Safety Analysis Set.

1.2.1.1.2 Investigational Product Exposure Analysis

Sotorasib exposure was summarized descriptively in terms of number of cycles started, number of doses of investigational product, cumulative dose by unit and average dose delivered per day, and relative dose intensity. Subjects with dose modifications and the reason for modification were summarized.

1.2.1.1.3 Adverse Event Analysis

Treatment-emergent adverse events are defined as adverse events starting on or after the first dose of sotorasib and up to and including 30 days after the last dose of sotorasib or the end of study date, whichever was earlier. Treatment-related adverse events are defined as treatment-emergent adverse events that have a reasonable possibility in the investigator's opinion of being caused by investigational product.

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA; version 23.0) and graded using National Cancer Institute – Common Terminology Criteria for Adverse Events (CTCAE; version 5.0).

Two adverse events of interest were analyzed for sotorasib: hepatotoxicity, which was identified based on ongoing clinical study data, and renal toxicity, which was identified based on nonclinical studies (Module 2.4, Nonclinical Overview). Adverse events of interest were defined by standardized MedDRA query, broad scope (SMQB) terms: hepatotoxicity is based on the hepatic disorders (SMQB) search strategy and renal toxicity is based on the combined incidence of the acute renal failure (SMQB) and chronic kidney disease (SMQB) search strategies.

The subject incidence of adverse events, treatment-related adverse events, and adverse events of interest was summarized for the following categories:

- all adverse events
- adverse events by CTCAE grade
- serious adverse events
- fatal adverse events
- adverse events leading to discontinuation of investigational product

Events of interest were also summarized by time to first onset and duration.

In addition, adverse events were summarized for the following subgroups:

- race (white, black, Asian, others)
- age at baseline (< 65 years, ≥ 65 years, < 75 years, ≥ 75 years)
- sex (men, women)
- region (North America, Europe, Asia, rest of the world)

An analysis of adverse drug reactions for sotorasib is described in Section 5.6 of Module 2.5, Clinical Overview.

1.2.1.1.4 Laboratory Tests, Vital Signs, and Electrocardiograms

Actual values and changes from baseline of selected laboratory parameters were summarized. Shift tables between the worst postbaseline (including unscheduled visits) and baseline grades were produced for select laboratory parameters. Laboratory value changes from baseline of at least 3 CTCAE grades and laboratory value excursions used to identify potential Hy's Law cases were also summarized.

The incidence of subjects with abnormal changes in vital signs, including systolic and diastolic blood pressure, pulse rate, and body temperature, was summarized.

The subject incidence of centrally-read, triplicate electrocardiogram data was summarized as follows:

QT interval corrected for heart rate using Fridericia's formula (QTcF interval):

- maximum postbaseline values ≤ 450, > 450 to 480, > 480 to 500, or > 500 msec
- changes from baseline ≤ 30, > 30 to 60, and > 60 msec

Heart rate:

- > 25% decrease from baseline to < 50 bpm
- > 25% increase from baseline to > 100 bpm

PR interval:

- > 25% increase from baseline to > 200 msec

QRS interval:

- > 25% increase from baseline to > 120 msec

Due to a breach in data security, electrocardiogram 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 are included in the analysis (see Section 8.9.2 of Study [redacted] Phase 1 and Section 8.9.2 of Study [redacted] Phase 2).

1.2.2 Narratives of Studies That are Sources of Clinical Safety Data

A study narrative for Study [redacted] including safety data, is provided in Section 2 of Module 2.7.3, Summary of Clinical Efficacy. Study narratives for Study [redacted] Study [redacted], and Study [redacted] are provided in Appendix 1.

1.3 Subject Disposition

As of the data cutoff dates for the phase 1 and phase 2 portions of Study [redacted], a total of 427 subjects were treated with sotorasib monotherapy across all doses and tumor types (Table 1). This includes 339 subjects who were treated with the intended

sotorasib dose of 960 mg once-daily (fasted) for all tumor types; of whom, 190 subjects had *KRAS p.G12C*-mutated NSCLC.

As of the data cutoff dates, 127 subjects (66.8%) with NSCLC treated at 960 mg once-daily had discontinued treatment; the most frequently reported (≥ 10% of subjects) reason for treatment discontinuation was disease progression (51.1%). Similar findings were observed in subjects treated with 960 mg once-daily for all tumor types and the total monotherapy population (ie, subjects treated with any sotorasib monotherapy dose for all tumor types), respectively, for which 71.1% and 70.0% of subjects discontinued sotorasib; the most frequently reported reason for treatment discontinuation was disease progression (58.4% and 57.1%).

Table 1. Subject Disposition With Discontinuation Reason (All Monotherapy Enrolled Subjects)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Enrolled	190 (100.0)	87 (100.0)	62 (100.0)	339 (100.0)	427 (100.0)
Investigational product accounting					
Subjects who never received sotorasib	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects who received sotorasib	190 (100.0)	87 (100.0)	62 (100.0)	339 (100.0)	427 (100.0)
Subjects who discontinued sotorasib	127 (66.8)	70 (80.5)	44 (71.0)	241 (71.1)	299 (70.0)
Adverse event	18 (9.5)	1 (1.1)	3 (4.8)	22 (6.5)	27 (6.3)
Death	4 (2.1)	0 (0.0)	2 (3.2)	6 (1.8)	8 (1.9)
Subject request	6 (3.2)	5 (5.7)	1 (1.6)	12 (3.5)	17 (4.0)
Noncompliance	1 (0.5)	0 (0.0)	1 (1.6)	2 (0.6)	2 (0.5)
Disease progression	97 (51.1)	64 (73.6)	37 (59.7)	198 (58.4)	244 (57.1)
Requirement for alternative therapy	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
Study completion accounting					
Subjects continuing study	105 (55.3)	55 (63.2)	32 (51.6)	192 (56.6)	237 (55.5)
Subjects who discontinued study	85 (44.7)	32 (36.8)	30 (48.4)	147 (43.4)	190 (44.5)
Lost to follow-up	0 (0.0)	1 (1.1)	1 (1.6)	2 (0.6)	2 (0.5)
Death	72 (37.9)	25 (28.7)	25 (40.3)	122 (36.0)	155 (36.3)
Withdrawal of consent from study	13 (6.8)	6 (6.9)	4 (6.5)	23 (6.8)	33 (7.7)

CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QD = once-daily
Source: ISS Table 14a-1.1 and ISS Table 14b-1.1

1.4 Demographic and Other Characteristics of Study Population

1.4.1 Demographics

The population of subjects with NSCLC treated at 960 mg once-daily had slightly more women (53.7%) and were mostly white (80.0%); the median (range) age was 66.0 (37 to 83) years (Table 2).

Demographics were generally consistent for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population. A smaller proportion of subjects with NSCLC treated at 960 mg once-daily were < 65 years of age compared with subjects treated at 960 mg once-daily for all tumor types or with the total monotherapy population (45.8% versus 55.8% and 53.9%, respectively).

Table 2. Baseline Demographics (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
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 (n [%])					
18 to 64 years	87 (45.8)	65 (74.7)	37 (59.7)	189 (55.8)	230 (53.9)
65 to 74 years	82 (43.2)	16 (18.4)	20 (32.3)	118 (34.8)	150 (35.1)
75 to 84 years	21 (11.1)	5 (5.7)	5 (8.1)	31 (9.1)	45 (10.5)
≥ 85 years	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.3)	2 (0.5)

CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QD = once-daily
Source: ISS Table 14a-2.1 and ISS Table 14b-2.1

1.4.2 Baseline Characteristics

Subjects with NSCLC treated with 960 mg once-daily had a median of 1.5 prior lines of anticancer therapy (Table 3). Twenty-eight subjects (14.7%) had received 0 prior lines of anticancer therapy, 67 subjects (35.3%) had received 1 prior line, 55 subjects (28.9%) had received 2 prior lines, 33 subjects (17.4%) had received 3 prior lines, and 7 subjects (3.7%) had received ≥ 4 prior lines. The most frequently reported (≥ 20% of subjects) prior anticancer therapies included chemotherapy (83.2%), immunotherapy (77.9%), and targeted biologics (20.0%); most subjects (70.5%) received both platinum-based chemotherapy and anti-programmed cell death-1 (anti-PD-1) or programmed death-ligand 1 (anti-PD-L1) therapy. Most subjects had a baseline Eastern Cooperative Oncology Group (ECOG) status of 1 (70.0%), metastatic disease (96.8%), and a history of smoking (82.6%).

Baseline characteristics for subjects with NSCLC were generally consistent with those for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population, with differences mainly attributable to the type of primary cancer (eg, types of prior anticancer therapies and subjects' smoking status).

Subjects with NSCLC treated with 960 mg once-daily were less heavily pretreated compared with subjects treated at 960 mg once-daily for all tumor types or the total monotherapy population. The only subjects in the total monotherapy population who had no prior lines of anticancer therapy were the 28 subjects with NSCLC treated with 960 mg once-daily (26 of whom were enrolled in the treatment naïve cohort in the phase 1 portion of Study [redacted] Only 3.7% of subjects with NSCLC treated with 960 mg once-daily had ≥ 4 prior lines of anticancer therapy compared with 15.9% of subjects treated at 960 mg once-daily for all tumor types and 18.5% of subjects in the total monotherapy population.

Table 3. Baseline Disease Characteristics (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
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)
Eastern Cooperative Oncology Group performance status at baseline					
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 anticancer therapy					
0	28 (14.7)[a]	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 anticancer therapy[b]					
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)
Platinum-based chemotherapy and anti-PD-1 or anti-PD-L1[c]	134 (70.5)	5 (5.7)	14 (22.6)	153 (45.1)	216 (50.6)
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)

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Footnotes are defined on the last page of the table.

Table 3. Baseline Disease Characteristics (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Metastatic disease					
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					
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)

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CRC = colorectal cancer; NSCLC = non-small cell lung cancer; PD-1 = programmed cell death-1; PD-L1 = programmed death-ligand 1; QD = once-daily

[a] Includes 26 subjects enrolled in the treatment naïve cohort in the phase 1 portion of the study.

[b] Each subject may have multiple prior therapies. Types of prior anticancer therapies were adjudicated and include therapies given in any treatment setting.

[c] Platinum-based chemotherapy and anti PD-1 or anti PD-L1 therapy could have been in combination or across different lines.

Source: ISS Table 14a-2.2 and ISS Table 14b-2.2

1.5 Overall Extent of Exposure

Subjects with NSCLC treated with 960 mg once-daily received sotorasib monotherapy for a median of 21.3 weeks, with 41.1% and 3.2% of subjects receiving treatment for ≥ 6 and ≥ 12 months, respectively (Table 4).

Exposure was slightly lower for subjects treated at 960 mg once-daily for all tumor types or the total monotherapy population than for subjects with NSCLC treated at 960 mg once-daily. In these populations, subjects received sotorasib monotherapy for a median of 18.0 and 16.9 weeks, respectively, and 29.5% and 26.9% of subjects received treatment for ≥ 6 months, respectively.

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

Table 4. Summary of Sotorasib Exposure (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Number of cycles started					
Mean	7.6	6.4	5.0	6.8	6.5
SD	5.0	4.2	3.2	4.6	4.7
Median	6.0	6.0	4.0	6.0	5.0
Q1, Q3	4.0, 12.0	4.0, 8.0	2.0, 7.0	3.0, 9.0	3.0, 9.0
Min, Max	1, 25	1, 20	1, 18	1, 25	1, 27
Number of doses per subject					
Mean	159.7	129.7	96.6	140.4	139.8
SD	105.4	86.0	68.7	97.6	99.0
Median	143.5	119.0	84.0	123.0	122.0
Q1, Q3	68.0, 252.0	84.0, 166.0	42.0, 131.0	62.0, 201.0	62.0, 197.0
Min, Max	7, 454	21, 406	2, 385	2, 454	1, 560
Duration on treatment (weeks)					
Mean	24.05	19.09	14.25	20.98	20.18
SD	15.28	12.54	9.79	14.22	14.44
Median	21.29	18.00	12.29	18.00	16.86
Q1, Q3	12.00, 38.00	12.00, 24.00	6.43, 20.57	10.14, 29.14	9.00, 28.00
Min, Max	1.0, 74.1	3.0, 58.0	0.3, 55.0	0.3, 74.1	0.1, 80.7
Number and percentage of subjects with treatment duration					
< 3 months	61 (32.1)	34 (39.1)	34 (54.8)	129 (38.1)	172 (40.3)
≥ 3 months	129 (67.9)	53 (60.9)	28 (45.2)	210 (61.9)	255 (59.7)
≥ 6 months	78 (41.1)	17 (19.5)	5 (8.1)	100 (29.5)	115 (26.9)
≥ 9 months	45 (23.7)	6 (6.9)	1 (1.6)	52 (15.3)	58 (13.6)
≥ 12 months	6 (3.2)	4 (4.6)	1 (1.6)	11 (3.2)	15 (3.5)

Footnotes are defined on the last page of the table.

Table 4. Summary of Sotorasib Exposure (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Average dose delivered (mg) per day[a]					
Mean	868.68	924.11	913.76	891.15	850.37
SD	178.03	88.66	121.32	151.78	197.93
Median	960.00	960.00	960.00	960.00	960.00
Q1, Q3	902.61, 960.00	944.09, 960.00	948.43, 960.00	924.88, 960.00	828.31, 960.00
Min, Max	145.1, 965.3	465.7, 960.0	328.0, 974.1	145.1, 974.1	145.1, 974.1
Relative dose intensity (%)[b]					
Mean	90.49	96.26	95.18	92.83	93.24
SD	18.55	9.24	12.64	15.81	15.16
Median	100.00	100.00	100.00	100.00	100.00
Q1, Q3	94.02, 100.00	98.34, 100.00	98.80, 100.00	96.34, 100.00	96.34, 100.00
Min, Max	15.1, 100.5	48.5, 100.0	34.2, 101.5	15.1, 101.5	15.1, 102.1

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CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QD = once-daily
[a] Average dose delivered is the cumulative dose divided by the number of days on treatment.
[b] Relative dose intensity = actual dose intensity/planned dose intensity*100, where actual (planned) dose intensity is the actual (planned) cumulative dose (mg/kg) divided by the actual (planned) duration of investigational product administration (weeks).
Source: ISS Table 14a-5.1 and ISS Table 14b-5.1

Dose changes (ie, any nonzero dose received other than the planned dose) were reported in 17.9% of subjects with NSCLC treated with sotorasib monotherapy at 960 mg once-daily, with a median (range) of 0 (0, 441) dose changes (Table 5). The most frequently reported reason for dose change was adverse event (15.8%) (see Section 2.1.5.1).

The sotorasib dose was withheld in 49.5% of subjects with NSCLC treated with sotorasib monotherapy at 960 mg once-daily, with a median (range) of 0 (0, 193) doses withheld. The most frequently reported reasons for the dose being withheld were adverse event (33.7%) and other (10.0%).

Compared with subjects with NSCLC treated with sotorasib at 960 mg once-daily, the sotorasib dose was changed or withheld, respectively, for a slightly lower incidence of subjects treated with sotorasib monotherapy at 960 mg once-daily for all tumor types (13.6% and 43.4%) and in the total monotherapy population (13.3% and 43.8%).

Table 5. Summary of Sotorasib Dose Modification (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Number of subjects with any dose change (n [%])	34 (17.9)	6 (6.9)	6 (9.7)	46 (13.6)	57 (13.3)
Primary reason(s) for dose change[a]					
Adverse event	30 (15.8)	4 (4.6)	4 (6.5)	38 (11.2)	46 (10.8)
Noncompliance	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.5)
Dose administration error	2 (1.1)	1 (1.1)	0 (0.0)	3 (0.9)	5 (1.2)
Per protocol	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
PI decision	2 (1.1)	1 (1.1)	0 (0.0)	3 (0.9)	3 (0.7)
Other	5 (2.6)	2 (2.3)	3 (4.8)	10 (2.9)	11 (2.6)
Number of dose change per subject					
Mean	17.6	3.8	2.0	11.2	9.7
SD	59.5	18.8	10.6	46.3	41.8
Median	0.0	0.0	0.0	0.0	0.0
Min, Max	0, 441	0, 139	0, 79	0, 441	0, 441
Number of subjects grouped by number of dose change (n [%])					
0	156 (82.1)	81 (93.1)	56 (90.3)	293 (86.4)	370 (86.7)
1	5 (2.6)	2 (2.3)	2 (3.2)	9 (2.7)	10 (2.3)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
> 3	29 (15.3)	4 (4.6)	4 (6.5)	37 (10.9)	46 (10.8)

Footnotes are defined on the last page of the table.

Table 5. Summary of Sotorasib Dose Modification (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Number of subjects with any dose withheld (n [%])	94 (49.5)	32 (36.8)	21 (33.9)	147 (43.4)	187 (43.8)
Primary reason(s) for dose withheld[a]					
Adverse event	64 (33.7)	22 (25.3)	16 (25.8)	102 (30.1)	129 (30.2)
Noncompliance	18 (9.5)	12 (13.8)	6 (9.7)	36 (10.6)	42 (9.8)
Dose administration error	2 (1.1)	0 (0.0)	0 (0.0)	2 (0.6)	5 (1.2)
Per protocol	12 (6.3)	4 (4.6)	0 (0.0)	16 (4.7)	24 (5.6)
PI decision	10 (5.3)	3 (3.4)	2 (3.2)	15 (4.4)	16 (3.7)
Other	19 (10.0)	4 (4.6)	5 (8.1)	28 (8.3)	37 (8.7)
Number of dose withheld per subject					
Mean	11.4	4.9	5.0	8.5	8.1
SD	23.0	10.5	10.9	18.9	18.0
Median	0.0	0.0	0.0	0.0	0.0
Min, Max	0, 193	0, 59	0, 50	0, 193	0, 193
Number of subjects grouped by number of dose withheld (n [%])					
0	96 (50.5)	55 (63.2)	41 (66.1)	192 (56.6)	240 (56.2)
1	13 (6.8)	5 (5.7)	3 (4.8)	21 (6.2)	26 (6.1)
2	3 (1.6)	2 (2.3)	1 (1.6)	6 (1.8)	11 (2.6)
3	5 (2.6)	3 (3.4)	3 (4.8)	11 (3.2)	13 (3.0)
> 3	73 (38.4)	22 (25.3)	14 (22.6)	109 (32.2)	137 (32.1)

CRC = colorectal cancer; NSCLC = non-small cell lung cancer; PI = principal investigator; QD = once-daily
[a] Subjects may be counted more than once. Multiple modifications with the same reason are counted once per subject.
Source: ISS Table 14a-5.2 and ISS Table 14b-5.2

2. Adverse Events

2.1 Analysis of Adverse Events

The subject incidence of adverse events was slightly higher for subjects with NSCLC treated at 960 mg once-daily compared with subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population (Table 6). This difference is largely attributable to the lower incidence of adverse events in subjects with colorectal cancer treated at 960 mg once-daily.

Non-small Cell Lung Cancer, 960 mg Once-daily

Most subjects (187 of 190 subjects [98.4%]) with NSCLC treated at 960 mg once-daily had at least 1 adverse event (Table 6). Of these, 128 subjects (67.4%) had at least 1 treatment-related adverse event. Grade ≥ 3 and serious adverse events were reported for 114 subjects (60.0%) and 99 subjects (52.1%), respectively; these events were considered treatment related for 40 subjects (21.1%) and 14 subjects (7.4%), respectively. Fatal adverse events were reported for 31 subjects (16.3%); none of the fatal events were considered treatment related. Adverse events leading to sotorasib discontinuation were reported for 18 subjects (9.5%), including 12 subjects (6.3%) with treatment-related events. Adverse events leading to dose reduction or interruption of sotorasib were reported for 67 subjects (35.3%) and were considered treatment related for 41 subjects (21.6%) (ISS Table 14b-6.3.34 and ISS Table 14b-6.1.501).

All Tumor Types, 960 mg Once-daily

Most subjects (325 of 339 subjects [95.9%]) treated at 960 mg once-daily for all tumors had at least 1 adverse event, including 195 subjects (57.5%) with at least 1 treatment-related adverse event (Table 6). Grade ≥ 3 and serious adverse events were reported for 176 subjects (51.9%) and 153 subjects (45.1%), respectively; these events were considered treatment related for 50 subjects (14.7%) and 17 subjects (5.0%), respectively. Fatal adverse events were reported for 49 subjects (14.5%); none of the fatal events were considered treatment related. Adverse events leading to sotorasib discontinuation were reported for 22 subjects (6.5%), including 13 subjects (3.8%) with treatment-related events. Adverse events leading to dose reduction or interruption of sotorasib were reported for 106 subjects (31.3%) and were considered treatment related for 58 subjects (17.1%) (ISS Table 14b-6.3.34 and ISS Table 14b-6.1.501).

All Tumor Types, All Doses

Most subjects (409 of 427 subjects [95.8%]) in the total monotherapy population had at least 1 adverse event (Table 6). Of these, 251 subjects (58.8%) had at least 1 treatment-related adverse event. Grade ≥ 3 and serious adverse events were reported for 223 subjects (52.2%) and 187 subjects (43.8%), respectively; these events were considered treatment related for 64 subjects (15.0%) and 22 subjects (5.2%), respectively. Fatal adverse events were reported for 62 subjects (14.5%); none of the fatal events were considered treatment related. Adverse events leading to sotorasib discontinuation were reported for 27 subjects (6.3%), including 17 subjects (4.0%) with treatment-related events. Adverse events leading to dose reduction or interruption of sotorasib were reported for 134 subjects (31.4%) and were considered treatment related for 73 subjects (17.1%) (ISS Table 14a-6.3.34 and ISS Table 14a-6.1.501).

Table 6. Summary of Treatment-emergent Adverse Events (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total 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 treatment-emergent 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; NSCLC = non-small cell lung cancer; QD = once-daily
Severity was 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

2.1.1 Common Adverse Events

The subject incidence of adverse events that occurred in ≥ 5% of subjects in any group is provided in Table 7. Within each group in Table 7, the most common (≥ 10% of subjects) adverse events are indicated in bold.

The types of adverse events observed in subjects with NSCLC treated at 960 mg once-daily were generally similar to those reported for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population.

Non-small Cell Lung Cancer, 960 mg Once-daily

Adverse events were reported for 187 subjects (98.4%) with NSCLC treated at 960 mg once-daily (Table 7). The most frequently reported (≥ 20% of subjects) adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were gastrointestinal disorders (71.6%); musculoskeletal and connective tissue disorders (49.5%); general disorders and administration site conditions (47.4%); respiratory, thoracic and mediastinal disorders (47.4%); infections and infestations (41.1%); investigations (39.5%); metabolism and nutrition disorders (39.5%); nervous system disorders (28.4%); and skin and subcutaneous tissue disorders (25.3%) (ISS Table 14b-6.3.1).

The most frequently reported (≥ 10% of subjects) adverse events in subjects with NSCLC treated at 960 mg once-daily by preferred term were diarrhea (43.2%), nausea (27.4%), fatigue (23.2%), increased aspartate aminotransferase (AST) (21.1%), increased alanine aminotransferase (ALT) (20.0%), back pain (18.4%), constipation (16.8%), dyspnea (16.8%), vomiting (16.8%), cough (14.2%), increased blood alkaline phosphatase (ALP) (13.7%), arthralgia (12.6%), decreased appetite (12.6%), anemia (12.1%), peripheral edema (12.1%), pneumonia (10.5%), and headache (10.0%) (Table 7).

All Tumor Types, 960 mg Once-daily

Adverse events were reported for 325 subjects (95.9%) treated at 960 mg once-daily for all tumor types (Table 7). The most frequently reported (≥ 20% of subjects) adverse events in subjects treated at 960 mg once-daily for all tumor types by system organ class were gastrointestinal disorders (67.3%); general disorders and administration site conditions (41.6%); musculoskeletal and connective tissue disorders (40.7%); respiratory, thoracic and mediastinal disorders (35.1%); infections and infestations (34.8%); investigations (32.2%); metabolism and nutrition disorders (29.5%); nervous system disorders (24.2%); and skin and subcutaneous tissue disorders (22.1%) (ISS Table 14b-6.3.1).

The most frequently reported (≥ 10% of subjects) adverse events in subjects treated at 960 mg once-daily for all tumor types by preferred term were diarrhea (34.2%), nausea (23.9%), fatigue (19.8%), vomiting (17.4%), increased AST (15.9%), increased ALT (14.5%), back pain (13.0%), constipation (13.0%), abdominal pain (12.4%), anemia (11.5%), cough (11.5%), dyspnea (11.5%), increased blood ALP (10.0%), and pyrexia (10.0%).

All Tumor Types, All Doses

Adverse events were reported for 409 subjects (95.8%) in the total monotherapy population (Table 7). The most frequently reported (≥ 20% of subjects) adverse events in the total monotherapy population by system organ class were gastrointestinal disorders (66.3%); musculoskeletal and connective tissue disorders (41.2%); general disorders and administration site conditions (40.5%); respiratory, thoracic and mediastinal disorders (34.4%); infections and infestations (34.2%); investigations (33.0%); metabolism and nutrition disorders (30.7%); nervous system disorders (27.6%); and skin and subcutaneous tissue disorders (21.1%) (ISS Table 14a-6.3.1).

The most frequently reported (≥ 10% of subjects) adverse events in the total monotherapy population by preferred term were diarrhea (34.4%), nausea (24.1%), fatigue (20.1%), vomiting (16.6%), increased AST (15.7%), increased ALT (14.5%), abdominal pain (12.9%), back pain (12.6%), constipation (12.6%), dyspnea (11.7%), anemia (11.5%), cough (11.5%), decreased appetite (10.8%), and headache (10.1%).

Table 7. Summary of Treatment-emergent Adverse Events by Preferred Term (Occurring in at Least 5% of Subjects in Any Group) (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
Preferred Term	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Number of subjects with treatment-emergent adverse events	187 (98.4)	83 (95.4)	55 (88.7)	325 (95.9)	409 (95.8)
Diarrhoea	**82 (43.2)**	**25 (28.7)**	**9 (14.5)**	**116 (34.2)**	**147 (34.4)**
Nausea	**52 (27.4)**	**20 (23.0)**	**9 (14.5)**	**81 (23.9)**	**103 (24.1)**
Fatigue	**44 (23.2)**	**13 (14.9)**	**10 (16.1)**	**67 (19.8)**	**86 (20.1)**
Aspartate aminotransferase increased	**40 (21.1)**	**9 (10.3)**	5 (8.1)	**54 (15.9)**	**67 (15.7)**
Alanine aminotransferase increased	**38 (20.0)**	7 (8.0)	4 (6.5)	**49 (14.5)**	**62 (14.5)**
Back pain	**35 (18.4)**	5 (5.7)	4 (6.5)	**44 (13.0)**	**54 (12.6)**
Constipation	**32 (16.8)**	8 (9.2)	4 (6.5)	**44 (13.0)**	**54 (12.6)**
Dyspnoea	**32 (16.8)**	5 (5.7)	2 (3.2)	**39 (11.5)**	**50 (11.7)**
Vomiting	**32 (16.8)**	**16 (18.4)**	**11 (17.7)**	**59 (17.4)**	**71 (16.6)**
Cough	**27 (14.2)**	7 (8.0)	5 (8.1)	**39 (11.5)**	**49 (11.5)**
Blood alkaline phosphatase increased	**26 (13.7)**	5 (5.7)	3 (4.8)	**34 (10.0)**	41 (9.6)
Arthralgia	**24 (12.6)**	4 (4.6)	2 (3.2)	30 (8.8)	42 (9.8)
Decreased appetite	**24 (12.6)**	5 (5.7)	2 (3.2)	31 (9.1)	**46 (10.8)**
Anaemia	**23 (12.1)**	**10 (11.5)**	6 (9.7)	**39 (11.5)**	**49 (11.5)**
Oedema peripheral	**23 (12.1)**	4 (4.6)	5 (8.1)	32 (9.4)	40 (9.4)
Pneumonia	**20 (10.5)**	1 (1.1)	4 (6.5)	25 (7.4)	31 (7.3)
Headache	**19 (10.0)**	**11 (12.6)**	2 (3.2)	32 (9.4)	**43 (10.1)**
Abdominal pain	18 (9.5)	**11 (12.6)**	**13 (21.0)**	**42 (12.4)**	**55 (12.9)**
Pyrexia	18 (9.5)	**11 (12.6)**	5 (8.1)	**34 (10.0)**	40 (9.4)
Pruritus	17 (8.9)	5 (5.7)	1 (1.6)	23 (6.8)	29 (6.8)
Hypokalaemia	16 (8.4)	2 (2.3)	2 (3.2)	20 (5.9)	23 (5.4)
Insomnia	16 (8.4)	5 (5.7)	1 (1.6)	22 (6.5)	31 (7.3)
Pleural effusion	16 (8.4)	3 (3.4)	2 (3.2)	21 (6.2)	24 (5.6)

Footnotes are defined on the last page of the table.

Table 7. Summary of Treatment-emergent Adverse Events by Preferred Term (Occurring in at Least 5% of Subjects in Any Group) (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
Preferred Term	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Productive cough	16 (8.4)	0 (0.0)	1 (1.6)	17 (5.0)	22 (5.2)
Hyponatraemia	15 (7.9)	0 (0.0)	2 (3.2)	17 (5.0)	20 (4.7)
Dizziness	14 (7.4)	5 (5.7)	2 (3.2)	21 (6.2)	34 (8.0)
Anxiety	13 (6.8)	4 (4.6)	2 (3.2)	19 (5.6)	21 (4.9)
Myalgia	13 (6.8)	7 (8.0)	2 (3.2)	22 (6.5)	28 (6.6)
Pain	13 (6.8)	0 (0.0)	2 (3.2)	15 (4.4)	16 (3.7)
Hypertension	12 (6.3)	2 (2.3)	3 (4.8)	17 (5.0)	19 (4.4)
Lymphocyte count decreased	12 (6.3)	1 (1.1)	0 (0.0)	13 (3.8)	18 (4.2)
Pain in extremity	12 (6.3)	8 (9.2)	0 (0.0)	20 (5.9)	27 (6.3)
Rash maculo-papular	12 (6.3)	2 (2.3)	2 (3.2)	16 (4.7)	17 (4.0)
Weight decreased	12 (6.3)	3 (3.4)	1 (1.6)	16 (4.7)	19 (4.4)
Fall	11 (5.8)	3 (3.4)	1 (1.6)	15 (4.4)	18 (4.2)
Musculoskeletal pain	11 (5.8)	5 (5.7)	2 (3.2)	18 (5.3)	26 (6.1)
Upper respiratory tract infection	10 (5.3)	6 (6.9)	2 (3.2)	18 (5.3)	27 (6.3)
Urinary tract infection	10 (5.3)	5 (5.7)	6 (9.7)	21 (6.2)	27 (6.3)
Gastrooesophageal reflux disease	3 (1.6)	3 (3.4)	5 (8.1)	11 (3.2)	12 (2.8)
Ascites	1 (0.5)	1 (1.1)	5 (8.1)	7 (2.1)	7 (1.6)
Tumour pain	1 (0.5)	0 (0.0)	4 (6.5)	5 (1.5)	6 (1.4)
Cholangitis	0 (0.0)	3 (3.4)	4 (6.5)	7 (2.1)	7 (1.6)
Pancreatic carcinoma	0 (0.0)	0 (0.0)	4 (6.5)	4 (1.2)	4 (0.9)
Pancreatic carcinoma metastatic	0 (0.0)	0 (0.0)	4 (6.5)	4 (1.2)	4 (0.9)
Small intestinal obstruction	0 (0.0)	5 (5.7)	3 (4.8)	8 (2.4)	10 (2.3)

CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QD = once-daily
Adverse events were coded using Medical Dictionary for Regulatory Activities version 23.0.
Bold text identifies adverse events with a ≥ 10% subject incidence in any group.
Source: ISS Table 14a-6.2.1 and ISS Table 14b-6.2.1

2.1.1.1 Treatment-related Adverse Events

The types of treatment-related adverse events observed in subjects with NSCLC treated at 960 mg once-daily were generally similar to those reported for subjects treated at 960 mg once-daily for all tumor types and the total monotherapy population.

Non-small Cell Lung Cancer, 960 mg Once-daily

Treatment-related adverse events were reported for 128 subjects (67.4%) with NSCLC treated at 960 mg once-daily (Table 6).

The most frequently reported (≥ 20% of subjects) treatment-related adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were gastrointestinal disorders (40.5%) and investigations (23.7%) (ISS Table 14b-6.3.35).

The most frequently reported (≥ 10% of subjects) treatment-related adverse events in subjects with NSCLC treated at 960 mg once-daily by preferred term were diarrhea (27.9%), nausea (16.3%), increased ALT (16.3%), increased AST (16.3%), and fatigue (11.1%) (ISS Table 14b-6.3.35).

All Tumor Types, 960 mg Once-daily

Treatment-related adverse events were reported for 195 subjects (57.5%) treated at 960 mg once-daily for all tumor types (Table 6).

The most frequently reported (≥ 20% of subjects) treatment-related adverse event by system organ class for subjects treated at 960 mg once-daily for all tumor types was gastrointestinal disorders (33.3%) (ISS Table 14b-6.3.35).

The most frequently reported (≥ 10% of subjects) treatment-related adverse events in subjects treated at 960 mg once-daily for all tumor types by preferred term were diarrhea (22.1%), nausea (12.4%), increased AST (11.2%), and increased ALT (10.9%) (ISS Table 14a-6.3.35).

All Tumor Types, All Doses

Treatment-related adverse events were reported for 251 subjects (58.8%) in the total monotherapy population (Table 6).

The most frequently reported (≥ 20% of subjects) treatment-related adverse event by system organ class for the total monotherapy population was gastrointestinal disorders (34.2%) (ISS Table 14a-6.3.35).

The most frequently reported (≥ 10% of subjects) treatment-related adverse events in the total monotherapy population by preferred term were diarrhea (23.0%), nausea (11.9%), increased AST (11.5%), and increased ALT (11.2%).

2.1.2 Grade 3 or Higher Adverse Events

The subject incidence of grade ≥ 3 adverse events that occurred in ≥ 2% of subjects in any group is provided in Table 8. Within each group in Table 8, the most commonly reported (≥ 5% of subjects) grade ≥ 3 adverse events are indicated in bold.

The types of grade ≥ 3 adverse events observed in subjects with NSCLC treated at 960 mg once-daily were generally similar to those reported for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population.

Non-small Cell Lung Cancer, 960 mg Once-daily

Grade ≥ 3 adverse events were reported for 114 subjects (60.0%) with NSCLC treated at 960 mg once-daily (Table 8).

The most frequently reported (≥ 10% of subjects) grade ≥ 3 adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were respiratory, thoracic and mediastinal disorders (16.8%); investigations (15.8%); benign, malignant and unspecified neoplasms (incl cysts and polyps) (12.1%); infections and infestations (12.1%); gastrointestinal disorders (11.1%); and musculoskeletal and connective tissue disorders (10.0%) (ISS Table 14b-6.3.31).

The most frequently reported (≥ 5% of subjects) grade ≥ 3 adverse events in subjects with NSCLC treated at 960 mg once-daily by preferred term were increased ALT (7.9%), increased AST (6.8%), pneumonia (6.8%), diarrhea (5.3%), and pleural effusion (5.3%) (Table 8).

All Tumor Types, 960 mg Once-daily

Grade ≥ 3 adverse events were reported for 176 subjects (51.9%) treated at 960 mg once-daily for all tumor types (Table 8).

The most frequently reported (≥ 10% of subjects) grade ≥ 3 adverse events by system organ class for subjects treated at 960 mg once-daily for all tumor types were gastrointestinal disorders (14.7%); benign, malignant and unspecified neoplasms (incl cysts and polyps) (11.8%); respiratory, thoracic and mediastinal disorders (11.5%); investigations (10.9%); and infections and infestations (10.3%) (ISS Table 14b-6.3.31).

The most frequently reported (≥ 5% of subjects) grade ≥ 3 adverse event in subjects treated at 960 mg once-daily for all tumor types by preferred term was pneumonia (5.3%) (Table 8).

All Tumor Types, All Doses

Grade ≥ 3 adverse events were reported for 223 subjects (52.2%) in the total monotherapy population (Table 8).

The most frequently reported (≥ 10% of subjects) grade ≥ 3 adverse events by system organ class for the total monotherapy population were gastrointestinal disorders (14.3%); benign, malignant and unspecified neoplasms (incl cysts and polyps) (11.9%); investigations (11.7%); and respiratory, thoracic and mediastinal disorders (10.8%) (ISS Table 14a-6.3.31).

The most frequently reported (≥ 5% of subjects) grade ≥ 3 adverse events in the total monotherapy population by preferred term were pneumonia (5.4%) and increased ALT (5.2%) (Table 8).

Table 8. Summary of Grade ≥ 3 Adverse Events by Preferred Term (Occurring in at Least 2% of Subjects in Any Group) (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
Preferred Term	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Number of subjects with grade ≥ 3 adverse events	114 (60.0)	29 (33.3)	33 (53.2)	176 (51.9)	223 (52.2)
Alanine aminotransferase increased	**15 (7.9)**	1 (1.1)	0 (0.0)	16 (4.7)	**22 (5.2)**
Aspartate aminotransferase increased	**13 (6.8)**	2 (2.3)	0 (0.0)	15 (4.4)	21 (4.9)
Pneumonia	**13 (6.8)**	1 (1.1)	**4 (6.5)**	**18 (5.3)**	**23 (5.4)**
Diarrhoea	**10 (5.3)**	2 (2.3)	2 (3.2)	14 (4.1)	18 (4.2)
Pleural effusion	**10 (5.3)**	2 (2.3)	2 (3.2)	14 (4.1)	15 (3.5)
Non-small cell lung cancer	9 (4.7)	0 (0.0)	0 (0.0)	9 (2.7)	11 (2.6)
Back pain	8 (4.2)	1 (1.1)	0 (0.0)	9 (2.7)	10 (2.3)
Blood alkaline phosphatase increased	8 (4.2)	1 (1.1)	1 (1.6)	10 (2.9)	13 (3.0)
Respiratory failure	7 (3.7)	0 (0.0)	0 (0.0)	7 (2.1)	7 (1.6)
Dyspnoea	6 (3.2)	0 (0.0)	0 (0.0)	6 (1.8)	10 (2.3)
Gamma-glutamyltransferase increased	5 (2.6)	1 (1.1)	0 (0.0)	6 (1.8)	7 (1.6)
Pulmonary embolism	5 (2.6)	1 (1.1)	1 (1.6)	7 (2.1)	7 (1.6)
Hypokalaemia	4 (2.1)	0 (0.0)	0 (0.0)	4 (1.2)	5 (1.2)
Hyponatraemia	4 (2.1)	0 (0.0)	0 (0.0)	4 (1.2)	4 (0.9)
Lung cancer metastatic	4 (2.1)	0 (0.0)	0 (0.0)	4 (1.2)	7 (1.6)
Lymphocyte count decreased	4 (2.1)	0 (0.0)	0 (0.0)	4 (1.2)	6 (1.4)
Anaemia	3 (1.6)	**5 (5.7)**	0 (0.0)	8 (2.4)	13 (3.0)
Vomiting	3 (1.6)	1 (1.1)	**4 (6.5)**	8 (2.4)	8 (1.9)
Abdominal pain	2 (1.1)	1 (1.1)	**4 (6.5)**	7 (2.1)	10 (2.3)
Fatigue	2 (1.1)	1 (1.1)	2 (3.2)	5 (1.5)	7 (1.6)
Nausea	2 (1.1)	0 (0.0)	2 (3.2)	4 (1.2)	4 (0.9)
Acute kidney injury	1 (0.5)	2 (2.3)	1 (1.6)	4 (1.2)	5 (1.2)
Ascites	1 (0.5)	0 (0.0)	3 (4.8)	4 (1.2)	4 (0.9)

Footnotes are defined on the last page of the table.

Table 8. Summary of Grade ≥ 3 Adverse Events by Preferred Term (Occurring in at Least 2% of Subjects in Any Group) (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
Preferred Term	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Blood creatine phosphokinase increased	1 (0.5)	2 (2.3)	0 (0.0)	3 (0.9)	5 (1.2)
Large intestinal obstruction	1 (0.5)	2 (2.3)	0 (0.0)	3 (0.9)	3 (0.7)
Cholangiocarcinoma	0 (0.0)	0 (0.0)	2 (3.2)	2 (0.6)	2 (0.5)
Cholangitis	0 (0.0)	3 (3.4)	**4 (6.5)**	7 (2.1)	7 (1.6)
Duodenal obstruction	0 (0.0)	0 (0.0)	2 (3.2)	2 (0.6)	2 (0.5)
Hydronephrosis	0 (0.0)	2 (2.3)	0 (0.0)	2 (0.6)	2 (0.5)
Hypertension	4 (2.1)	0 (0.0)	2 (3.2)	6 (1.8)	6 (1.4)
Pancreatic carcinoma	0 (0.0)	0 (0.0)	**4 (6.5)**	4 (1.2)	4 (0.9)
Pancreatic carcinoma metastatic	0 (0.0)	0 (0.0)	**4 (6.5)**	4 (1.2)	4 (0.9)
Small intestinal obstruction	0 (0.0)	4 (4.6)	3 (4.8)	7 (2.1)	9 (2.1)
Tumour pain	0 (0.0)	0 (0.0)	2 (3.2)	2 (0.6)	3 (0.7)
Urinary tract infection	0 (0.0)	0 (0.0)	2 (3.2)	2 (0.6)	2 (0.5)

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CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QD = once-daily
Adverse events were coded using Medical Dictionary for Regulatory Activities version 23.0. Severity was graded using Common Terminology Criteria for Adverse Events version 5.0.
Bold text identifies adverse events with a ≥ 5% subject incidence in any group.
Source: ISS Table 14a-6.3.31 and ISS Table 14b-6.3.31

2.1.2.1 Treatment-related Grade 3 or Higher Adverse Events

The types of treatment-related grade ≥ 3 adverse events observed in subjects with NSCLC treated at 960 mg once-daily were generally similar to those reported for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population.

Non-small Cell Lung Cancer, 960 mg Once-daily

Treatment-related grade ≥ 3 adverse events were reported for 40 subjects (21.1%) with NSCLC treated at 960 mg once-daily (Table 6).

The most frequently reported (≥ 5% of subjects) treatment-related grade ≥ 3 adverse event in subjects with NSCLC treated at 960 mg once-daily by system organ class was investigations (11.6%) (ISS Table 14b-6.3.37).

The most frequently reported (≥ 2% of subjects) treatment-related grade ≥ 3 adverse events in subjects with NSCLC treated at 960 mg once-daily by preferred term were increased ALT (7.4%), increased AST (5.8%), and diarrhea (4.2%).

All Tumor Types, 960 mg Once-daily

Treatment-related grade ≥ 3 adverse events were reported for 50 subjects (14.7%) treated at 960 mg once-daily for all tumor types (Table 6).

The most frequently reported (≥ 5% of subjects) treatment-related grade ≥ 3 adverse event by system organ class for subjects treated at 960 mg once-daily for all tumor types was investigations (7.4%) (ISS Table 14b-6.3.37).

The most frequently reported (≥ 2% of subjects) treatment-related grade ≥ 3 adverse events in subjects treated at 960 mg once-daily for all tumor types by preferred term were increased ALT (4.4%), diarrhea (3.5%), and increased AST (3.5%).

All Tumor Types, All Doses

Treatment-related grade ≥ 3 adverse events were reported for 64 subjects (15.0%) in the total monotherapy population (Table 6).

The most frequently reported (≥ 5% of subjects) treatment-related grade ≥ 3 adverse event by system organ class for the total monotherapy population was investigations (7.7%) (ISS Table 14a-6.3.37).

The most frequently reported (≥ 2% of subjects) treatment-related grade ≥ 3 adverse events in the total monotherapy population by preferred term were increased ALT (4.9%), increased AST (4.0%), and diarrhea (3.5%).

2.1.3 Deaths

The subject incidence of fatal adverse events is provided in Table 9. Within each group in Table 9, the most common (≥ 2 subjects) fatal adverse events are indicated in bold.

The types of fatal adverse events observed in subjects with NSCLC treated at 960 mg once-daily were generally similar to those reported for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population.

Non-small Cell Lung Cancer, 960 mg Once-daily

Fatal adverse events were reported for 31 subjects (16.3%) with NSCLC treated at 960 mg once-daily (Table 9). Fatal adverse events reported for more than 1 subject included 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%]).

A medical review of the fatal adverse events of respiratory failure and cardiac arrest found all subjects had medical history, disease-related pathology, and/or disease progression at the time of fatality.

All Tumor Types, 960 mg Once-daily

For subjects treated at 960 mg once-daily for all tumor types, fatal adverse events were reported for 49 subjects (14.5%). Fatal adverse events reported for more than 1 subject included NSCLC (8 subjects [2.4%]), metastatic lung cancer (4 subjects [1.2%]), metastatic pancreatic carcinoma (4 subjects [1.2%]), pancreatic carcinoma (4 subjects [1.2%]), respiratory failure (4 subjects [1.2%]), cardiac arrest (2 subjects [0.6%]), cholangiocarcinoma (2 subjects [0.6%]), and malignant lung neoplasm (2 subjects [0.6%]). Of note, the fatal adverse events were consistent with subjects' cancer type (see also Section 9.3 of Study [redacted] Phase 1 and Section 9.3 of Study [redacted] Phase 2).

All Tumor Types, All Doses

For the total monotherapy population, fatal adverse events were reported for 62 subjects (14.5%). Fatal adverse events reported for more than 1 subject in the total monotherapy population included NSCLC (10 subjects [2.3%]), metastatic lung cancer (6 subjects [1.4%]), metastatic colorectal cancer (4 subjects [0.9%]), metastatic pancreatic carcinoma (4 subjects [0.9%]), pancreatic carcinoma (4 subjects [0.9%]), respiratory failure (4 subjects [0.9%]), lung adenocarcinoma (3 subjects [0.7%]), cardiac arrest (2 subjects [0.5%]), cholangiocarcinoma (2 subjects [0.5%]), malignant lung neoplasm (2 subjects [0.5%]), metastatic NSCLC (2 subjects [0.5%]), and small intestinal obstruction (2 subjects [0.5%]).

A medical review of the fatal adverse events of small intestinal obstruction found both subjects had medical history, disease-related pathology, and/or disease progression at the time of fatality.

Table 9. Fatal Adverse Events by Preferred Term (Safety Analysis Set)

Preferred Term	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Number of subjects with fatal adverse events	31 (16.3)	2 (2.3)	16 (25.8)	49 (14.5)	62 (14.5)
Non-small cell lung cancer	**8 (4.2)**	0 (0.0)	0 (0.0)	**8 (2.4)**	**10 (2.3)**
Lung cancer metastatic	**4 (2.1)**	0 (0.0)	0 (0.0)	**4 (1.2)**	**6 (1.4)**
Respiratory failure	**4 (2.1)**	0 (0.0)	0 (0.0)	**4 (1.2)**	**4 (0.9)**
Cardiac arrest	**2 (1.1)**	0 (0.0)	0 (0.0)	**2 (0.6)**	**2 (0.5)**
Lung neoplasm malignant	**2 (1.1)**	0 (0.0)	0 (0.0)	**2 (0.6)**	**2 (0.5)**
Adenocarcinoma	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
Cardiac failure	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
Gastric ulcer	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
Haemorrhage intracranial	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
Hypovolaemic shock	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
Large intestinal obstruction	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
Lung adenocarcinoma	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	**3 (0.7)**
Non-small cell lung cancer metastatic	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	**2 (0.5)**
Non-small cell lung cancer stage IV	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
Pneumonia	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
Systemic inflammatory response syndrome	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
Adenocarcinoma pancreas	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.3)	1 (0.2)
Aspiration	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.3)	1 (0.2)
Cholangiocarcinoma	0 (0.0)	0 (0.0)	**2 (3.2)**	**2 (0.6)**	**2 (0.5)**
Cholangitis	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.3)	1 (0.2)
Colon cancer	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.3)	1 (0.2)
Colorectal cancer metastatic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**4 (0.9)**
Dyspnoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Endometrial adenocarcinoma	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.3)	1 (0.2)

Footnotes are defined on the last page of the table.

Table 9. Fatal Adverse Events by Preferred Term (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
Preferred Term	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Large cell lung cancer	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.3)	1 (0.2)
Malignant neoplasm of unknown primary site	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.3)	1 (0.2)
Pancreatic carcinoma	0 (0.0)	0 (0.0)	**4 (6.5)**	**4 (1.2)**	**4 (0.9)**
Pancreatic carcinoma metastatic	0 (0.0)	0 (0.0)	**4 (6.5)**	**4 (1.2)**	**4 (0.9)**
Small intestinal obstruction	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.3)	**2 (0.5)**

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CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QD = once-daily
Adverse events were coded using Medical Dictionary for Regulatory Activities version 23.0.
Bold text identifies adverse events with ≥ 2 subjects in any group.
Source: ISS Table 14a-6.3.32 and ISS Table 14b-6.3.32

Review of fatal adverse events across the sotorasib clinical development program as of the respective data cutoff dates did not identify any meaningful findings.

2.1.3.1 Treatment-related Fatal Adverse Events

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.

2.1.4 Serious Adverse Events

The subject incidence of serious adverse events that occurred in ≥ 2% of subjects in any group is provided in Table 10. Within each group in Table 10, the most commonly reported (≥ 2% of subjects) serious adverse events are indicated in bold.

The types of serious adverse events observed in subjects with NSCLC treated at 960 mg once-daily were generally similar to those reported for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population.

Non-small Cell Lung Cancer, 960 mg Once-daily

Serious adverse events were reported for 99 subjects (52.1%) with NSCLC treated at 960 mg once-daily (Table 10).

The most frequently reported (≥ 5% of subjects) serious adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were respiratory, thoracic and mediastinal disorders (14.7%); infections and infestations (12.1%); benign, malignant and unspecified neoplasms (incl cysts and polyps) (11.1%); gastrointestinal disorders (9.5%); and musculoskeletal and connective tissue disorders (6.3%) (ISS Table 14b-6.3.16).

The most frequently reported (≥ 2% of subjects) serious adverse events in subjects with NSCLC treated at 960 mg once-daily by preferred term 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%) (Table 10).

All Tumor Types, 960 mg Once-daily

Serious adverse events were reported for 153 subjects (45.1%) treated at 960 mg once-daily for all tumor types (Table 10).

The most frequently reported serious adverse events (≥ 5% of subjects) by system organ class for subjects treated at 960 mg once-daily for all tumor types were gastrointestinal disorders (12.4%); benign, malignant and unspecified neoplasms (incl cysts and polyps) (11.2%); infections and infestations (9.7%); respiratory, thoracic and mediastinal disorders (9.7%); and hepatobiliary disorders (5.6%) (ISS Table 14b-6.3.16).

The most frequently reported (≥ 2% of subjects) serious adverse events in subjects treated at 960 mg once-daily for all tumor types by preferred term were pneumonia (5.6%), pleural effusion (3.8%), NSCLC (2.7%), small intestinal obstruction (2.4%), respiratory failure (2.1%), and cholangitis (2.1%) (Table 10).

All Tumor Types, All Doses

Serious adverse events were reported for 187 subjects (43.8%) in the total monotherapy population (Table 10).

The most frequently reported serious adverse events (≥ 5% of subjects) by system organ class for the total monotherapy population were benign, malignant and unspecified neoplasms (incl cysts and polyps) (11.5%); gastrointestinal disorders (11.2%); respiratory, thoracic and mediastinal disorders (9.4%); and infections and infestations (8.9%) (ISS Table 14a-6.3.16).

The most frequently reported (≥ 2% of subjects) serious adverse events in the total monotherapy population by preferred term were pneumonia (5.6%), pleural effusion (3.5%), NSCLC (2.6%), and small intestinal obstruction (2.3%) (Table 10).

Table 10. Summary of Serious Adverse Events by Preferred Term (Occurring in at Least 2% of Subjects in Any Group) (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
Preferred Term	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Number of subjects with serious adverse events	99 (52.1)	22 (25.3)	32 (51.6)	153 (45.1)	187 (43.8)
Pneumonia	**14 (7.4)**	1 (1.1)	**4 (6.5)**	**19 (5.6)**	**24 (5.6)**
Non-small cell lung cancer	**9 (4.7)**	0 (0.0)	0 (0.0)	**9 (2.7)**	**11 (2.6)**
Pleural effusion	**9 (4.7)**	**2 (2.3)**	**2 (3.2)**	**13 (3.8)**	**15 (3.5)**
Respiratory failure	**7 (3.7)**	0 (0.0)	0 (0.0)	**7 (2.1)**	7 (1.6)
Back pain	**5 (2.6)**	1 (1.1)	0 (0.0)	6 (1.8)	6 (1.4)
Lung cancer metastatic	**4 (2.1)**	0 (0.0)	0 (0.0)	4 (1.2)	7 (1.6)
Abdominal pain	2 (1.1)	0 (0.0)	**3 (4.8)**	5 (1.5)	6 (1.4)
Vomiting	2 (1.1)	0 (0.0)	**2 (3.2)**	4 (1.2)	4 (0.9)
Ascites	1 (0.5)	0 (0.0)	**2 (3.2)**	3 (0.9)	3 (0.7)
Large intestinal obstruction	1 (0.5)	**2 (2.3)**	0 (0.0)	3 (0.9)	3 (0.7)
Cholangiocarcinoma	0 (0.0)	0 (0.0)	**2 (3.2)**	2 (0.6)	2 (0.5)
Cholangitis	0 (0.0)	**3 (3.4)**	**4 (6.5)**	**7 (2.1)**	7 (1.6)
Duodenal obstruction	0 (0.0)	0 (0.0)	**2 (3.2)**	2 (0.6)	2 (0.5)
Pancreatic carcinoma	0 (0.0)	0 (0.0)	**4 (6.5)**	4 (1.2)	4 (0.9)
Pancreatic carcinoma metastatic	0 (0.0)	0 (0.0)	**4 (6.5)**	4 (1.2)	4 (0.9)
Small intestinal obstruction	0 (0.0)	**5 (5.7)**	**3 (4.8)**	**8 (2.4)**	**10 (2.3)**
Tumour pain	0 (0.0)	0 (0.0)	**2 (3.2)**	2 (0.6)	3 (0.7)

CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QD = once-daily
Adverse events were coded using Medical Dictionary for Regulatory Activities version 23.0.
Bold text identifies adverse events with a ≥ 2% subject incidence in any group.
Source: ISS Table 14a-6.3.16 and ISS Table 14b-6.3.16

2.1.4.1 Treatment-related Serious Adverse Events

The types of the treatment-related serious adverse events observed in subjects with NSCLC treated at 960 mg once-daily were generally similar to those reported for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population.

Non-small Cell Lung Cancer, 960 mg Once-daily

Treatment-related serious adverse events were reported for 14 subjects (7.4%) with NSCLC treated at 960 mg once-daily (Table 6).

The most frequently reported (≥ 2% of subjects) treatment-related serious adverse event in subjects with NSCLC treated at 960 mg once-daily by system organ class was investigations (2.6%) (ISS Table 14b-6.3.36).

The most frequently reported (≥ 1% of subjects) treatment-related serious adverse events in subjects with NSCLC treated at 960 mg once-daily by preferred term were increased ALT, nausea, and pneumonitis (each 1.1%).

A comprehensive medical review was performed for the events of pneumonitis from the entire dataset, including the 2 events of serious treatment-related pneumonitis and 1 additional event of serious pneumonitis. Each event had confounders and/or alternative etiology to explain the pneumonitis (eg, progression of disease, radiotherapy) and do not suggest a causal relationship with sotorasib use.

All Tumor Types, 960 mg Once-daily

Treatment-related serious adverse events were reported for 17 subjects (5.0%) treated at 960 mg once-daily for all tumor types (Table 6).

For subjects treated at 960 mg once-daily for all tumor types, no treatment-related serious adverse events were reported by system organ class for ≥ 2% of subjects or by preferred term for ≥ 1% of for subjects (ISS Table 14b-6.3.36).

All Tumor Types, All Doses

Treatment-related serious adverse events were reported for 22 subjects (5.2%) in the total monotherapy population (Table 6).

The most frequently reported treatment-related serious adverse events (≥ 2% of subjects) by system organ class for the total monotherapy population was investigations (2.1%) (ISS Table 14a-6.3.36).

The most frequently reported (≥ 1% of subjects) treatment-related serious adverse events in the total monotherapy population by preferred term were increased ALT (1.4%) and increased AST (1.2%).

2.1.5 Other Significant Adverse Events

2.1.5.1 Adverse Events Leading to Dose Reduction or Interruption of Sotorasib

The types of adverse events leading to dose reduction or interruption of sotorasib observed in subjects with NSCLC treated at 960 mg once-daily were generally similar to those reported for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population.

Non-small Cell Lung Cancer, 960 mg Once-daily

Adverse events leading to dose reduction or interruption of sotorasib were reported for 67 subjects (35.3%) with NSCLC treated at 960 mg once-daily (ISS Table 14b-6.3.34).

The most frequently reported (≥ 5% of subjects) adverse events leading to dose reduction or interruption of sotorasib in subjects with NSCLC treated at 960 mg once-daily by system organ class were investigations (12.6%); gastrointestinal disorders (10.5%); and respiratory, thoracic and mediastinal disorders (5.3%).

The most frequently reported (≥ 2% of subjects) adverse events leading to dose reduction or interruption of sotorasib in subjects with NSCLC treated at 960 mg once-daily by preferred term were diarrhea (8.4%), increased ALT (8.4%), increased AST (8.4%), increased blood ALP (3.7%), nausea (3.2%), and pneumonia (2.6%).

All Tumor Types, 960 mg Once-daily

Adverse events leading to dose reduction or interruption of sotorasib were reported for 106 subjects (31.3%) treated at 960 mg once-daily for all tumor types (ISS Table 14b-6.3.34).

The most frequently reported (≥ 5% of subjects) adverse events leading to dose reduction or interruption of sotorasib by system organ class for subjects treated at 960 mg once-daily for all tumor types were gastrointestinal disorders (12.1%) and investigations (9.7%).

The most frequently reported (≥ 2% of subjects) adverse events leading to dose reduction or interruption of sotorasib in subjects treated at 960 mg once-daily for all

tumor types by preferred term were diarrhea (6.8%), increased ALT (6.5%), increased AST (6.5%), nausea (3.5%), increased blood ALP (2.9%), and vomiting (2.1%).

All Tumor Types, All Doses

Adverse events leading to dose reduction or interruption of sotorasib were reported for 134 subjects (31.4%) in the total monotherapy population (ISS Table 14a-6.3.34).

The most frequently reported (≥ 5% of subjects) adverse events leading to dose reduction or interruption of sotorasib by system organ class for the total monotherapy population were gastrointestinal disorders (11.7%) and investigations (10.3%).

The most frequently reported (≥ 2% of subjects) adverse events leading to dose reduction or interruption of sotorasib in the total monotherapy population by preferred term were increased ALT (7.3%), increased AST (7.0%), diarrhea (6.6%), nausea (3.0%), and increased blood ALP (2.8%).

2.1.5.1.1 Treatment-related Adverse Events Leading to Dose Reduction or Interruption of Sotorasib

The types of treatment-related adverse events leading to dose reduction or interruption of sotorasib observed in subjects with NSCLC treated at 960 mg once-daily were generally similar to those reported for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population.

Non-small Cell Lung Cancer, 960 mg Once-daily

Treatment-related adverse events leading to dose reduction or interruption of sotorasib were reported for 41 subjects (21.6%) with NSCLC treated at 960 mg once-daily (ISS Table 14b-6.1.501).

The most frequently reported (≥ 2% of subjects) treatment-related adverse events leading to dose reduction or interruption of sotorasib in subjects with NSCLC treated at 960 mg once-daily by system organ class were investigations (11.1%); gastrointestinal disorders (8.9%); and hepatobiliary disorders (2.1%).

The most frequently reported (≥ 1% of subjects) treatment-related adverse events leading to dose reduction or interruption of sotorasib in subjects with NSCLC treated at 960 mg once-daily by preferred term were diarrhea (7.9%), increased AST (7.9%), increased ALT (7.4%), nausea (3.2%), increased blood ALP (2.6%), abnormal hepatic function (1.1%), and vomiting (1.1%).

All Tumor Types, 960 mg Once-daily

Treatment-related adverse events leading to dose reduction or interruption of sotorasib were reported for 58 subjects (17.1%) treated at 960 mg once-daily for all tumor types (ISS Table 14b-6.1.501).

The most frequently reported (≥ 2% of subjects) treatment-related adverse events leading to dose reduction or interruption of sotorasib by system organ class for subjects treated at 960 mg once-daily for all tumor types were investigations (8.0%) and gastrointestinal disorders (7.4%).

The most frequently reported (≥ 1% of subjects) treatment-related adverse events leading to dose reduction or interruption of sotorasib in subjects treated at 960 mg once-daily for all tumor types by preferred term were diarrhea (5.9%), increased AST (5.9%), increased ALT (5.6%), nausea (2.7%), and increased blood ALP (2.4%).

All Tumor Types, All Doses

Treatment-related adverse events leading to dose reduction or interruption of sotorasib were reported for 73 subjects (17.1%) in the total monotherapy population (ISS Table 14a-6.1.501).

The most frequently reported (≥ 2% of subjects) treatment-related adverse events leading to dose reduction or interruption of sotorasib by system organ class for the total monotherapy population were investigations (8.4%) and gastrointestinal disorders (7.0%).

The most frequently reported (≥ 1% of subjects) treatment-related adverse events leading to dose reduction or interruption of sotorasib in the total monotherapy population by preferred term were increased AST (6.6%), increased ALT (6.3%), diarrhea (5.6%), nausea (2.3%), and increased blood ALP (2.1%).

2.1.5.2 Adverse Events Leading to 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.

The subject incidence of adverse events leading to discontinuation of sotorasib that occurred in ≥ 2 subjects in any group is provided in Table 11. Within each group in Table 11, the most commonly reported (≥ 2 subjects) adverse events are indicated in bold.

The types of adverse events leading to discontinuation of sotorasib observed in subjects with NSCLC treated at 960 mg once-daily were generally similar to those reported for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population.

Non-small Cell Lung Cancer, 960 mg Once-daily

Adverse events leading to the discontinuation of sotorasib were reported for 18 subjects (9.5%) with NSCLC treated at 960 mg once-daily (Table 11).

The most frequently reported (≥ 2% of subjects) adverse event leading to the discontinuation of sotorasib in subjects with NSCLC treated at 960 mg once-daily by system organ class was investigations (3.2%) (ISS Table 14b-6.3.33).

The most frequently reported (≥ 1% of subjects) adverse events leading to the discontinuation of sotorasib in subjects with NSCLC treated at 960 mg once-daily by preferred term 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%) (Table 11).

Review of the 3 cases of drug-induced liver injury did not meet Hy's Law criteria (see Section 2.1.5.3.1).

All Tumor Types, 960 mg Once-daily

Adverse events leading to discontinuation of sotorasib were reported for 22 subjects (6.5%) treated at 960 mg once-daily for all tumor types (Table 11).

No adverse event led to the discontinuation of sotorasib by system organ class for ≥ 2% of subjects or by preferred term for ≥ 1% of subjects treated at 960 mg once-daily for all tumor types (ISS Table 14b-6.3.33).

All Tumor Types, All Doses

Adverse events leading to discontinuation of sotorasib were reported for 27 subjects (6.3%) in the total monotherapy population (Table 11).

The most frequently reported (≥ 2% of subjects) adverse event leading to the discontinuation of sotorasib by system organ class for the total monotherapy population was investigations (2.3%) (ISS Table 14a-6.3.33).

The most frequently reported (≥ 1% of subjects) adverse events leading to the discontinuation of sotorasib in the total monotherapy population by preferred term were increased ALT and increased AST (each 1.4%) (Table 11).

Table 11. Summary of Adverse Events Leading to Withdrawal of Sotorasib by Preferred Term (Occurring in at Least 2 Subjects in Any Group) (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
Preferred Term	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Number of subjects with adverse events leading to withdrawal of investigational product	18 (9.5)	1 (1.1)	3 (4.8)	22 (6.5)	27 (6.3)
Alanine aminotransferase increased	**3 (1.6)**	0 (0.0)	0 (0.0)	**3 (0.9)**	**6 (1.4)**
Aspartate aminotransferase increased	**3 (1.6)**	0 (0.0)	0 (0.0)	**3 (0.9)**	**6 (1.4)**
Drug-induced liver injury	**3 (1.6)**	0 (0.0)	0 (0.0)	**3 (0.9)**	**3 (0.7)**
Blood alkaline phosphatase increased	**2 (1.1)**	0 (0.0)	0 (0.0)	**2 (0.6)**	**3 (0.7)**
Pneumonitis	**2 (1.1)**	0 (0.0)	0 (0.0)	**2 (0.6)**	**2 (0.5)**
Transaminases increased	**2 (1.1)**	0 (0.0)	0 (0.0)	**2 (0.6)**	**2 (0.5)**
Pneumonia	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	**2 (0.5)**

CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QD = once-daily
Adverse events were coded using Medical Dictionary for Regulatory Activities version 23.0.
Bold text identifies adverse events with ≥ 2 subjects in any group.
Source: ISS Table 14a-6.3.33 and ISS Table 14b-6.3.33

2.1.5.2.1 Treatment-related Adverse Events Leading to Treatment Discontinuation

The types of treatment-related adverse events leading to discontinuation of sotorasib observed in subjects with NSCLC treated at 960 mg once-daily were generally similar to those reported for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population.

Non-small Cell Lung Cancer, 960 mg Once-daily

Treatment-related adverse events leading to the discontinuation of sotorasib were reported for 12 subjects (6.3%) with NSCLC treated at 960 mg once-daily (Table 6).

The most frequently reported (≥ 2% of subjects) treatment-related adverse event leading to the discontinuation of sotorasib in subjects with NSCLC treated at 960 mg once-daily by system organ class was investigations (3.2%) (ISS Table 14b-6.1.500).

The most frequently reported (≥ 1% of subjects) treatment-related adverse events leading to the discontinuation of sotorasib in subjects with NSCLC treated at 960 mg once-daily by preferred term were drug-induced liver injury (1.6%), increased ALT (1.6%), increased AST (1.6%), increased blood ALP (1.1%), increased transaminases (1.1%), and pneumonitis (1.1%).

All Tumor Types, 960 mg Once-daily

Treatment-related adverse events leading to discontinuation of sotorasib were reported for 13 subjects (3.8%) treated at 960 mg once-daily for all tumor types (Table 6).

No treatment-related adverse event led to the discontinuation of sotorasib by system organ class for ≥ 2% of subjects or by preferred term for ≥ 1% of subjects treated at 960 mg once-daily for all tumor types (ISS Table 14b-6.1.500).

All Tumor Types, All Doses

Treatment-related adverse events leading to discontinuation of sotorasib were reported for 17 subjects (4.0%) in the total monotherapy population (Table 6).

The most frequently reported (≥ 2% of subjects) treatment-related adverse event leading to the discontinuation of sotorasib by system organ class for the total monotherapy population was investigations (2.3%) (ISS Table 14a-6.1.500).

The most frequently reported (≥ 1% of subjects) treatment-related adverse events leading to the discontinuation of sotorasib in the total monotherapy population by preferred term were increased ALT and increased AST (each 1.4%).

2.1.5.3 Adverse Events of Interest

As described in Section 1.2.1.1.3, hepatotoxicity and renal toxicity were prespecified as adverse events of interest. The subject incidence of events of interest are described in the sections that follow. Changes in hepatic and renal laboratory parameters while on study treatment are discussed in Section 3.

2.1.5.3.1 Hepatotoxicity

The types of hepatotoxicity adverse events observed in subjects with NSCLC treated at 960 mg once-daily were generally similar to those reported for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population.

None of the cases of hepatotoxicity adverse events in any subjects had laboratory values consistent with Hy's Law (see also Section 3).

Non-small Cell Lung Cancer, 960 mg Once-daily

In subjects with NSCLC treated at 960 mg once-daily, hepatotoxicity adverse events of interest were reported for 57 subjects (30.0%) (Table 12). The most frequently reported (≥ 5% of subjects) hepatotoxicity adverse events of any grade were increased AST (21.1%), increased ALT (20.0%), and increased blood ALP (13.7%) (Table 13).

Grade ≥ 3 hepatotoxicity adverse events of interest were reported for 30 subjects (15.8%) with NSCLC treated at 960 mg once-daily (Table 12). The most frequently reported (≥ 2% of subjects) grade ≥ 3 hepatotoxicity adverse events were increased ALT (7.9%), increased AST (6.8%), increased blood ALP (4.2%), and increased gamma-glutamyltransferase (2.6%) (ISS Table 14b-6.6.3).

Serious hepatotoxicity adverse events of interest were reported for 9 subjects (4.7%) with NSCLC treated at 960 mg once-daily (Table 12). The most frequently reported (≥ 1% of subjects) serious hepatotoxicity adverse events were increased ALT (1.1%) and drug-induced liver injury (1.1%) (ISS Table 14b-6.6.2).

Most subjects with NSCLC treated at 960 mg once-daily were able to continue treatment; 24 subjects (12.6%) and 9 subjects (4.7%) had events of interest leading to interruption or discontinuation of sotorasib, respectively (Table 12). The most frequently reported (≥ 1% of subjects) hepatotoxicity adverse events leading to dose modification of sotorasib were increased ALT (3.2%), increased AST (2.6%), and increased blood ALP (1.1%) (ISS Table 14b-6.6.5). The most frequently reported (≥ 1% of subjects) hepatotoxicity adverse events leading to discontinuation of sotorasib were increased ALT (1.6%), increased AST (1.6%), drug-induced liver injury (1.6%), increased blood ALP (1.1%), and increased transaminases (1.1%) (ISS Table 14b-6.6.4).

No fatal hepatotoxicity adverse events of interest were reported (Table 12).

All Tumor Types, 960 mg Once-daily

In subjects treated at 960 mg once-daily for all tumor types, hepatotoxicity adverse events of interest were reported for 88 subjects (26.0%) (Table 12). The most frequently reported (≥ 5% of subjects) hepatotoxicity adverse events of any grade were increased AST (15.9%), increased ALT (14.5%), and increased blood ALP (10.0%) (Table 13).

Grade ≥ 3 hepatotoxicity adverse events of interest were reported for 39 subjects (11.5%) treated at 960 mg once-daily for all tumor types (Table 12). The most frequently reported (≥ 2% of subjects) grade ≥ 3 hepatotoxicity adverse events were increased ALT (4.7%), increased AST (4.4%), and increased blood ALP (2.9%) (ISS Table 14b-6.6.3).

Serious hepatotoxicity adverse events of interest were reported for 13 subjects (3.8%) treated at 960 mg once-daily for all tumor types (Table 12). No serious hepatotoxicity adverse events were reported for ≥ 1% of subjects (ISS Table 14b-6.6.2).

Hepatotoxicity events of interest leading to interruption or discontinuation of sotorasib were reported for 33 subjects (9.7%) and 9 subjects (2.7%) treated at 960 mg once-daily for all tumor types, respectively (Table 12). The most frequently reported (≥ 1% of subjects) hepatotoxicity adverse events leading to dose modification of sotorasib were increased ALT (1.8%) and increased AST (1.5%) (ISS Table 14b-6.6.5). No hepatotoxicity adverse events led to discontinuation of sotorasib for ≥ 1% of subjects treated at 960 mg once-daily for all tumor types (ISS Table 14b-6.6.4).

No fatal hepatotoxicity adverse events of interest were reported (Table 12).

All Tumor Types, All Doses

In the total monotherapy population, hepatotoxicity adverse events of interest were reported for 104 subjects (24.4%) (Table 12). The most frequently reported (≥ 5% of subjects) hepatotoxicity adverse events of any grade were increased AST (15.7%), increased ALT (14.5%), and increased blood ALP (9.6%) (Table 13).

A total of 5 subjects (1.2%) had adverse events of drug-induced liver injury. None of the cases met Hy's Law criteria; the events were generally consistent with other cases of increased liver enzymes reported with sotorasib monotherapy.

Grade ≥ 3 hepatotoxicity adverse events of interest were reported for 47 subjects (11.0%) in the total monotherapy population (Table 12). The most frequently reported

(≥ 2% of subjects) grade ≥ 3 hepatotoxicity adverse events were increased ALT (5.2%), increased AST (4.9%), and increased blood ALP (3.0%) (ISS Table 14a-6.6.3).

Serious hepatotoxicity adverse events of interest were reported for 17 subjects (4.0%) in the total monotherapy population (Table 12). The most frequently reported (≥ 1% of subjects) serious hepatotoxicity adverse events were increased ALT (1.4%) and increased AST (1.2%) (ISS Table 14a-6.6.2).

Hepatotoxicity events of interest leading to interruption or discontinuation of sotorasib were reported for 42 subjects (9.8%) and 13 subjects (3.0%) in the total monotherapy population, respectively (Table 12). The most frequently reported (≥ 1% of subjects) hepatotoxicity adverse events leading to dose modification of sotorasib were increased ALT and increased AST (each 1.4%) (ISS Table 14a-6.6.5). The most frequently reported (≥ 1% of subjects) hepatotoxicity adverse events leading to discontinuation of sotorasib were increased ALT and increased AST (each 1.4%) (ISS Table 14a-6.6.4).

No fatal hepatotoxicity adverse events of interest were reported (Table 12).

Table 12. Summary of Hepatotoxicity Treatment-emergent Adverse Events of Interest (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
Hepatotoxicity	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Treatment-emergent adverse events	57 (30.0)	17 (19.5)	14 (22.6)	88 (26.0)	104 (24.4)
Leading to interruption of investigational product	24 (12.6)	6 (6.9)	3 (4.8)	33 (9.7)	42 (9.8)
Leading to discontinuation of investigational product	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)

CRC = colorectal cancer; MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer; QD = once-daily; SMQB = standardized MedDRA query, broad scope
Adverse events were coded using MedDRA version 23.0. Severity was graded using Common Terminology Criteria for Adverse Events version 5.0.
Hepatotoxicity is based on the hepatic disorders (SMQB) search strategy.
Source: ISS Table 14a-6.5 and ISS Table 14b-6.5

Table 13. Treatment-emergent Hepatotoxicity Events of Interest (Occurring in at Least 2 Subjects in Any Group) (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
Preferred Term	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Subjects with hepatoxicity treatment-emergent adverse events of interest	57 (30.0)	17 (19.5)	14 (22.6)	88 (26.0)	104 (24.4)
Aspartate aminotransferase increased	**40 (21.1)**	**9 (10.3)**	**5 (8.1)**	**54 (15.9)**	**67 (15.7)**
Alanine aminotransferase increased	**38 (20.0)**	**7 (8.0)**	**4 (6.5)**	**49 (14.5)**	**62 (14.5)**
Blood alkaline phosphatase increased	**26 (13.7)**	**5 (5.7)**	**3 (4.8)**	**34 (10.0)**	**41 (9.6)**
Blood bilirubin increased	**7 (3.7)**	**4 (4.6)**	**2 (3.2)**	**13 (3.8)**	**15 (3.5)**
Gamma-glutamyltransferase increased	**7 (3.7)**	**2 (2.3)**	**3 (4.8)**	**12 (3.5)**	**13 (3.0)**
Hypoalbuminaemia	**7 (3.7)**	1 (1.1)	1 (1.6)	**9 (2.7)**	**9 (2.1)**
Drug-induced liver injury	**4 (2.1)**	0 (0.0)	1 (1.6)	**5 (1.5)**	**5 (1.2)**
Liver function test abnormal	**3 (1.6)**	0 (0.0)	0 (0.0)	**3 (0.9)**	**3 (0.7)**
Transaminases increased	**3 (1.6)**	1 (1.1)	1 (1.6)	**5 (1.5)**	**5 (1.2)**
Hepatic function abnormal	**2 (1.1)**	1 (1.1)	1 (1.6)	**4 (1.2)**	**4 (0.9)**
International normalised ratio increased	**2 (1.1)**	0 (0.0)	0 (0.0)	**2 (0.6)**	**2 (0.5)**
Liver function test increased	**2 (1.1)**	0 (0.0)	0 (0.0)	**2 (0.6)**	**2 (0.5)**
Ascites	1 (0.5)	1 (1.1)	**5 (8.1)**	**7 (2.1)**	**7 (1.6)**
Jaundice	1 (0.5)	**2 (2.3)**	0 (0.0)	**3 (0.9)**	**3 (0.7)**

CRC = colorectal cancer; MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer; QD = once-daily
Adverse events were coded using MedDRA version 23.0.
Hepatotoxicity is based on the hepatic disorders (standardized MedDRA query, broad scope) search strategy.
Bold text identifies adverse events with ≥ 2 subjects in any group.
Source: ISS Table 14a-6.6.1 and ISS Table 14b-6.6.1

Sotorasib Plus Pembrolizumab Combination Therapy

Combination therapy with sotorasib plus pembrolizumab in the phase 1 portion of Study [redacted] showed a higher incidence of hepatotoxicity when compared with sotorasib monotherapy. Of the 11 subjects treated with this combination therapy,

7 subjects (63.6%) had hepatotoxicity adverse events of interest, including increased ALT (63.6%), increased AST (63.6%), increased blood ALP (18.2%), and autoimmune hepatitis (9.1%) (Table 14p-6.14.1 of Study [redacted] Phase 1). Grade ≥ 3 hepatotoxicity adverse events included increased ALT (54.5%), increased AST (54.5%), and autoimmune hepatitis (9.1%) (Table 14p-6.16.1 of Study [redacted] Phase 1). The events for 6 subjects (54.5%) were managed by temporarily withholding sotorasib and pembrolizumab.

2.1.5.3.1.1 Hepatotoxicity Time to Onset and Resolution

The subject incidence of adverse events of interest are described in the sections that follow. Changes in hepatic laboratory parameters while on study treatment are discussed in Section 3.

Hepatotoxicity Events of Interest

The median (range) time to first onset for any grade and grade ≥ 3 hepatotoxicity adverse events of interest in subjects with NSCLC treated at 960 mg once-daily was 43.0 (1, 295) and 63.5 (16, 139) days, respectively (ISS Table 14b-6.7.1).

Most hepatotoxicity adverse events of interest resolved for both any grade events (247 resolved events versus 43 unresolved events) and grade ≥ 3 events (62 resolved events versus 12 unresolved events) (ISS Table 14b-6.8.1). The median (range) duration for any grade and grade ≥ 3 hepatotoxicity adverse events of interest that resolved was 45.0 (4, 250) days and 31.5 (2, 148) days, respectively.

Results were generally consistent with those in subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population (ISS Table 14a-6.7.1 and ISS Table 14a-6.8.1).

Increased ALT Events of Interest

The median (range) time to first onset for any grade and grade ≥ 3 adverse events of increased ALT in subjects with NSCLC treated at 960 mg once-daily was 54.5 (8, 295) and 64.0 (22, 13.1) days, respectively (ISS Table 14b-6.7.4).

Most of the adverse events of increased ALT resolved for both any grade events (83 resolved events versus 10 unresolved events) and grade ≥ 3 events (23 resolved events versus 2 unresolved events) (ISS Table 14b-6.8.4). The median (range) duration for any grade and grade ≥ 3 adverse events of increased ALT that resolved was 42.0 (3, 189) days and 26.0 (3, 54) days, respectively.

Results were generally consistent with those in subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population (ISS Table 14a-6.7.4 and ISS Table 14a-6.8.4). However, the median time to first onset for any grade adverse event of increased ALT was longer for subjects with NSCLC treated at 960 mg once-daily (54.5 days) and subjects treated at 960 mg once-daily for all tumor types (62.0 days) compared with the total monotherapy population (43.5 days).

Increased AST Events of Interest

The median (range) time to first onset for any grade and grade ≥ 3 adverse events of increased AST in subjects with NSCLC treated at 960 mg once-daily was 62.0 (2, 295) and 49.0 (22, 106) days, respectively (ISS Table 14b-6.7.3).

Most of the adverse events of increased AST resolved for both any grade events (80 resolved events versus 10 unresolved events) and grade ≥ 3 events (19 resolved events versus 2 unresolved events) (ISS Table 14b-6.8.3). The median (range) duration for any grade and grade ≥ 3 adverse events of increased AST that resolved was 42.0 (3, 250) and 28.0 (3, 64) days, respectively.

The median time to first onset for any grade adverse event of increased AST was longer for subjects with NSCLC treated at 960 mg once-daily (62.0 days) compared with subjects treated at 960 mg once-daily for all tumor types (44.0 days) and the total monotherapy population (44.0 days). The median time to first onset for grade ≥ 3 adverse event of increased AST was shorter for subjects with NSCLC treated at 960 mg once-daily (49.0 versus 63.0 and 61.0 days, respectively) (ISS Table 14a-6.7.3 and ISS Table 14b-6.7.3).

The median (range) duration for any grade and grade ≥ 3 adverse events of increased AST that resolved, respectively, was longer for subjects with NSCLC treated at 960 mg once-daily (42.0 and 28.0 days) compared with subjects treated at 960 mg once-daily for all tumor types (30.5 and 21.0 days) and the total monotherapy population (30.0 and 13.5 days) (ISS Table 14a-6.8.3 and ISS Table 14b-6.8.3).

2.1.5.3.2 Renal Toxicity

The types of renal toxicity adverse events observed in subjects with NSCLC treated at 960 mg once-daily were generally similar to those reported for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population.

Non-small Cell Lung Cancer, 960 mg Once-daily

In subjects with NSCLC treated at 960 mg once-daily, renal toxicity adverse events of interest were reported for 34 subjects (17.9%) (Table 14). The most frequently reported (≥ 5% of subjects) renal toxicity adverse event of any grade was hyponatremia (7.9%) (Table 15).

Grade ≥ 3 renal toxicity adverse events of interest were reported for 6 subjects (3.2%) with NSCLC treated at 960 mg once-daily (Table 14). The most frequently reported (≥ 2% of subjects) grade ≥ 3 renal toxicity adverse event was hyponatremia (2.1%) (ISS Table 14b-6.6.3).

Serious renal toxicity adverse events of interest were reported for 2 subjects (1.1%) with NSCLC treated at 960 mg once-daily (Table 14). The most frequently reported (≥ 1% of subjects) serious renal toxicity adverse event was hyponatremia (1.1%) (ISS Table 14b-6.6.2).

Most subjects with NSCLC treated at 960 mg once-daily were able to continue treatment. Only 1 subject (0.5%) had renal toxicity events of interest leading to interruption of sotorasib and no subjects discontinued sotorasib due to renal toxicity adverse events (Table 14).

No fatal renal toxicity adverse events of interest were reported (Table 14).

All Tumor Types, 960 mg Once-daily

In subjects treated at 960 mg once-daily for all tumor types, renal toxicity adverse events of interest were reported for 45 subjects (13.3%) (Table 14). The most frequently reported (≥ 5% of subjects) renal toxicity adverse event of any grade was hyponatremia (5.0%) (Table 15).

Grade ≥ 3 renal toxicity adverse events of interest were reported for 9 subjects (2.7%) treated at 960 mg once-daily for all tumor types (Table 14). No grade ≥ 3 renal toxicity adverse events were reported for ≥ 2% of subjects (ISS Table 14b-6.6.3).

Serious renal toxicity adverse events of interest were reported for 3 subjects (0.9%) treated at 960 mg once-daily for all tumor types (Table 14). No serious renal toxicity adverse events were reported for ≥ 1% of subjects (ISS Table 14b-6.6.2).

Two subjects (0.6%) had renal toxicity events of interest leading to interruption of sotorasib; no subjects discontinued sotorasib due to renal toxicity adverse events (Table 14).

No fatal renal toxicity adverse events of interest were reported (Table 14).

All Tumor Types, All Doses

In the total monotherapy population, renal toxicity adverse events of interest were reported for 53 subjects (12.4%) (Table 14). No renal toxicity adverse events were reported for ≥ 5% of subjects in the total monotherapy population (Table 15).

Grade ≥ 3 renal toxicity adverse events of interest were reported for 10 subjects (2.3%) in the total monotherapy population (Table 14). No grade ≥ 3 renal toxicity adverse events were reported for ≥ 2% of subjects (ISS Table 14a-6.6.3).

Serious renal toxicity adverse events of interest were reported for 4 subjects (0.9%) in the total monotherapy population (Table 14).

Two subjects (0.5%) had renal toxicity events of interest leading to interruption of sotorasib; no subjects discontinued sotorasib due to renal toxicity adverse events (Table 14).

No fatal renal toxicity adverse events of interest were reported (Table 14).

Table 14. Summary of Renal Toxicity Treatment-emergent Adverse Events of Interest (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
Renal Toxicity	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Treatment-emergent adverse events	34 (17.9)	7 (8.0)	4 (6.5)	45 (13.3)	53 (12.4)
Leading to interruption of investigational product	1 (0.5)	1 (1.1)	0 (0.0)	2 (0.6)	2 (0.5)
Leading to discontinuation of investigational product	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; MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer; QD = once-daily; SMQB = standardized MedDRA query, broad scope
Adverse events were coded using MedDRA version 23.0. Severity was graded using Common Terminology Criteria for Adverse Events version 5.0.
Renal toxicity is based on the combined incidence of the acute renal failure (SMQB) and chronic kidney disease (SMQB) search strategies.
Source: ISS Table 14a-6.5 and ISS Table 14b-6.5

Table 15. Treatment-emergent Renal Toxicity Events of Interest (Occurring in at Least 2 Subjects in Any Group) (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
Preferred Term	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Subjects with renal toxicity treatment-emergent adverse events of interest	34 (17.9)	7 (8.0)	4 (6.5)	45 (13.3)	53 (12.4)
Hyponatraemia	**15 (7.9)**	0 (0.0)	**2 (3.2)**	**17 (5.0)**	**20 (4.7)**
Hypoalbuminaemia	**7 (3.7)**	1 (1.1)	1 (1.6)	**9 (2.7)**	**9 (2.1)**
Blood creatinine increased	**6 (3.2)**	**2 (2.3)**	0 (0.0)	**8 (2.4)**	**9 (2.1)**
Hyperkalaemia	**6 (3.2)**	1 (1.1)	0 (0.0)	**7 (2.1)**	**9 (2.1)**
Hypocalcaemia	**4 (2.1)**	1 (1.1)	0 (0.0)	**5 (1.5)**	**6 (1.4)**
Hyperphosphataemia	**3 (1.6)**	1 (1.1)	0 (0.0)	**4 (1.2)**	**4 (0.9)**
Acute kidney injury	1 (0.5)	**2 (2.3)**	1 (1.6)	**4 (1.2)**	**5 (1.2)**
Proteinuria	1 (0.5)	0 (0.0)	1 (1.6)	**2 (0.6)**	**3 (0.7)**

CRC = colorectal cancer; MedDRA = Medical Dictionary for Regulatory Activities; NSCLC = non-small cell lung cancer; QD = once-daily; SMQB = standardized MedDRA query, broad scope
Adverse events were coded using MedDRA version 23.0.
Renal toxicity is based on the combined incidence of the acute renal failure (SMQB) and chronic kidney disease (SMQB) search strategies.
Bold text identifies adverse events with ≥ 2 subjects in any group.
Source: ISS Table 14a-6.6.1 and ISS Table 14b-6.6.1

A total of 5 subjects in the total monotherapy population had acute kidney injury, including 1 subject with NSCLC treated at 960 mg once-daily and 4 subjects treated at 960 mg once-daily for all tumor types (Table 15). All 5 events of acute kidney injury occurred in the context of other clinical events (eg, diarrhea). Four of the events were reported as resolved and of these, 3 had negative rechallenge; the fourth had permanently discontinued investigational product before the event of acute kidney injury. A medical review of all 5 events did not suggest causality between sotorasib and the event of acute kidney injury.

2.1.5.3.2.1 Renal Toxicity Time to Onset and Resolution

The median (range) time to first onset for any grade and grade ≥ 3 renal toxicity adverse events of interest in subjects with NSCLC treated at 960 mg once-daily were 23.0 (1, 252) days and 61.0 (14, 141) days, respectively (ISS Table 14b-6.7.2).

Most renal toxicity adverse events of interest of any grade resolved (53 resolved events versus 9 unresolved events) and all 5 grade ≥ 3 events resolved (ISS Table 14b-6.8.2). The median (range) duration for any grade and grade ≥ 3 renal toxicity adverse events of interest were 19.0 (1, 114) and 4.0 (1, 113) days, respectively.

Results were generally consistent with subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population; however, the median time to onset for any grade renal toxicity was longer for the total monotherapy population (31.0 days) and the median times to onset for grade ≥ 3 renal toxicity adverse events of interest were longer for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population (99.0 and 97.0 days, respectively) (ISS Table 14a-6.7.2).

2.1.6 Analysis of Adverse Events by Organ System or Syndrome

Treatment-emergent adverse events in the system organ class of gastrointestinal disorders were the most frequently observed in the integrated analysis (ISS Table 14a-6.3.1 and ISS Table 14b-6.3.1) and are discussed in Section 2.1.1.

2.2 Subject Narratives

Subject narratives of deaths, serious adverse events, adverse events that led to discontinuation of investigational product, selected adverse events of interest (hepatotoxicity, renal toxicity), and pregnancies are provided as follows:

- Section 14.6.2 of Study [redacted] Phase 1
- Section 14.6.2 of Study [redacted] Phase 2
- Section 7 through Section 10 of Study [redacted]
- Section 7 through Section 10 of Study [redacted] Substudy A
- Section 7 through Section 10 of Study [redacted] Substudy C
- Section 7 through Section 10 of Study [redacted] Substudy D
- Section 7 through Section 10 of Study [redacted] Substudy E
- Section 7 through Section 10 of Study [redacted] Substudy H
- Section 7 through Section 10 of Study [redacted]

3. Clinical Laboratory Evaluations

Assessment of clinical laboratory parameters is presented in this section. Adverse events associated with laboratory parameters, including hepatotoxicity and renal toxicity, are presented in Section 2.1.

Hepatotoxicity

Increased ALT and increased AST are known adverse drug reactions for sotorasib. Hepatotoxicity adverse events of interest are discussed in Section 2.1.5.3.1. The time to onset for hepatotoxicity adverse events, including increased ALT and AST, along with the time to resolution is provided in Section 2.1.5.3.1.1.

For subjects with NSCLC treated at 960 mg once-daily, increases from baseline of 3 and 4 CTCAE grades, respectively, were reported for ALT in 10.0% and 1.6% of subjects, AST in 8.9% and 1.1% of subjects, total bilirubin in 1.6% and 0% of subjects, and ALP in 2.6% and 0% of subjects (ISS Table 14b-7.2.2, ISS Table 14b-7.2.4, ISS Table 14b-7.2.18, and ISS Table 14b-7.2.19).

Increases in ALT or AST $>$ 3 times the upper limit of normal were reported for 38 subjects (20.1%) with NSCLC treated at 960 mg once-daily (ISS Table 14b-7.3). Increases in total bilirubin $>$ 2 times the upper limit of normal were reported for 5 subjects (2.6%).

A slightly higher incidence of elevations from baseline in ALT and AST was observed for subjects with NSCLC treated at 960 mg once-daily compared with subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population (ISS Table 14a-7.2.18, ISS Table 14a-7.2.19, ISS Table 14a-7.3, ISS Table 14b-7.2.18, ISS Table 14b-7.2.19, and ISS Table 14b-7.3).

One subject with NSCLC treated at 960 mg once-daily had laboratory criteria that were consistent with a potential Hy's Law case (ie, 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 within a 7-day window) (ISS Table 14b-7.3). This subject had normal liver enzymes while on sotorasib treatment. Two weeks after discontinuation of sotorasib due to disease progression, the subject had worsening of previously diagnosed heart failure leading to cardiac arrest. At this time, the subject had abnormal liver enzymes which were numerically consistent with 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, this subject did not meet Hy's Law criteria.

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 (ISS Table 14a-7.3).

Renal Toxicity

Renal toxicity adverse events of interest are discussed in Section 2.1.5.3.2.

No meaningful trends were identified in changes from baseline in renal parameters and no meaningful differences were observed in subjects with NSCLC treated at 960 mg once-daily compared with subjects treated at 960 mg once-daily for all tumor types or the total monotherapy population (ISS Table 14a-7.1.1, ISS Table 14a-7.1.4, ISS Table 14b-7.1.1, and ISS Table 14b-7.1.4).

The only renal laboratory parameter with a $\geq$ 3 CTCAE grade change from baseline reported for $\geq$ 1% of subjects with NSCLC treated at 960 mg once-daily was a 3 grade increase in urine protein (4.2%) (Table 16).

Other Laboratory Parameters

The remaining laboratory parameter with a $\geq$ 3 CTCAE grade change from baseline reported for $\geq$ 1% of subjects with NSCLC treated at 960 mg once-daily was a 3 grade decrease in potassium (4.7%) (Table 16).

No meaningful trends were identified in changes from baseline in any other laboratory parameter and no meaningful differences were observed in subjects with NSCLC treated at 960 mg once-daily compared with subjects treated at 960 mg once-daily for all tumor types or the total monotherapy population (ISS Table 14a-7.1.1, ISS Table 14a-7.1.2, ISS Table 14a-7.1.3, ISS Table 14a-7.1.4, ISS Table 14b-7.1.1, ISS Table 14b-7.1.2, ISS Table 14b-7.1.3,and ISS Table 14b-7.1.4).

Table 16. Summary of Worst Toxicity ≥ 3 Grade Increase From Baseline in Laboratory Parameters (Safety Analysis Set)

			Sotorasib Monotherapy				
			960 mg QD Fasted				Any Dose
Panel Laboratory Parameter	Direction of Toxicity	Change in Grade From Baseline	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Chemistry							
Alanine aminotransferase	Increase	3	19 (10.0)	2 (2.3)	0 (0.0)	21 (6.2)	24 (5.6)
	Increase	4	3 (1.6)	0 (0.0)	0 (0.0)	3 (0.9)	4 (0.9)
Albumin	Decrease	3	1 (0.5)	0 (0.0)	1 (1.6)	2 (0.6)	2 (0.5)
Alkaline phosphatase	Increase	3	5 (2.6)	0 (0.0)	0 (0.0)	5 (1.5)	8 (1.9)
Aspartate aminotransferase	Increase	3	17 (8.9)	2 (2.3)	0 (0.0)	19 (5.6)	21 (4.9)
	Increase	4	2 (1.1)	0 (0.0)	0 (0.0)	2 (0.6)	3 (0.7)
Calcium (corrected)	Increase	3	0 (0.0)	0 (0.0)	2 (3.2)	2 (0.6)	2 (0.5)
	Increase	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Creatine kinase 2	Increase	3	1 (0.5)	2 (2.3)	0 (0.0)	3 (0.9)	4 (0.9)
	Increase	4	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.3)	2 (0.5)
Creatinine	Increase	3	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.3)	2 (0.5)
	Increase	4	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.3)	1 (0.2)
Fibrogen	Decrease	3	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
	Decrease	4	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)

Footnotes are defined on the last page of the table.

Table 16. Summary of Worst Toxicity ≥ 3 Grade Increase From Baseline in Laboratory Parameters (Safety Analysis Set)

			Sotorasib Monotherapy				
			960 mg QD Fasted				Any Dose
Panel Laboratory Parameter	Direction of Toxicity	Change in Grade From Baseline	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Chemistry (continued)							
Magnesium	Increase	3	1 (0.5)	2 (2.3)	0 (0.0)	3 (0.9)	3 (0.7)
Potassium	Decrease	3	9 (4.7)	0 (0.0)	1 (1.6)	10 (2.9)	11 (2.6)
Sodium	Decrease	3	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
	Decrease	4	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
Total bilirubin	Increase	3	3 (1.6)	3 (1.6)	3 (1.6)	3 (0.9)	4 (0.9)
Coagulation							
Activated partial thromboplastin time	Increase	3	3 (1.6)	0 (0.0)	0 (0.0)	3 (0.9)	3 (0.7)
Hematology							
Hemoglobin	Increase	3	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
	Decrease	3	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
Lymphocytes	Increase	3	2 (1.1)	0 (0.0)	0 (0.0)	2 (0.6)	2 (0.5)
	Decrease	3	3 (1.6)	4 (4.6)	0 (0.0)	7 (2.1)	11 (2.6)
	Decrease	4	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.3)	1 (0.2)
Platelets	Decrease	4	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.3)	1 (0.2)

Footnotes are defined on the last page of the table.

Table 16. Summary of Worst Toxicity ≥ 3 Grade Increase From Baseline in Laboratory Parameters (Safety Analysis Set)

			Sotorasib Monotherapy				
			960 mg QD Fasted				Any Dose
Panel Laboratory Parameter	Direction of Toxicity	Change in Grade From Baseline	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Hematology (continued)							
Total neutrophils	Decrease	3	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
	Decrease	4	0 (0.0)	1 (1.1)	1 (1.6)	2 (0.6)	4 (0.9)
White blood cells	Decrease	3	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.3)	2 (0.5)
	Decrease	4	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.3)	1 (0.2)
Urinalysis							
Urine protein	Increase	3	8 (4.2)	1 (1.1)	1 (1.6)	10 (2.9)	14 (3.3)

CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QD = once-daily
Laboratory abnormalities were graded using Common Terminology Criteria for Adverse Events version 5.0.
Source: ISS Table 14a-7.2.2, ISS Table 14a-7.2.4, ISS Table 14a-7.2.18, ISS Table 14a-7.2.19, ISS Table 14a-7.4, ISS Table 14b-7.2.2, ISS Table 14b-7.2.4, ISS Table 14b-7.2.18, ISS Table 14b-7.2.19, and ISS Table 14b-7.4

4. Vital Signs, Physical Findings, and Other Observations Related to Safety

Assessments of vital signs and electrocardiograms are presented in this section. Adverse events associated with vital signs and electrocardiograms are presented in Section 2.1.

4.1 Vital Signs

For subjects with NSCLC treated at 960 mg once-daily, no meaningful trends were identified in changes from baseline in vital sign parameters (ISS Table 14b-8.2.1, ISS Table 14b-8.2.2, ISS Table 14b-8.2.3, ISS Table 14b-8.2.4, ISS Table 14b-8.2.5, and ISS Table 14b-8.2.6). Likewise, no meaningful trends were identified for subjects treated at 960 mg once-daily for all tumor types or for the total monotherapy population (ISS Table 14a-8.2.1, ISS Table 14a-8.2.2, ISS Table 14a-8.2.3, ISS Table 14a-8.2.4, ISS Table 14a-8.2.5, and ISS Table 14a-8.2.6).

Abnormal changes in vital sign parameters reported for ≥ 5% of subjects with NSCLC treated at 960 mg once-daily included systolic blood pressure ≥ 160 mmHg (17.9%), weight increase ≥ 10% from baseline (12.1%), diastolic blood pressure ≤ 50 mmHg (9.5%), systolic blood pressure ≤ 90 mmHg (7.4%), and weight decrease ≥ 10% from baseline (5.3%) (Table 17).

Findings were generally similar for subjects treated at 960 mg once-daily for all tumor types or for the total monotherapy population. Abnormal changes in vital sign parameters reported for ≥ 5% of subjects treated at 960 mg once-daily for all tumor types included systolic blood pressure ≥ 160 mmHg (16.2%), weight increase ≥ 10% from baseline (9.4%), diastolic blood pressure ≤ 50 mmHg (7.7%), systolic blood pressure ≤ 90 mmHg (6.5%), and weight decrease ≥ 10% from baseline (6.2%).

Abnormal changes in vital sign parameters reported for ≥ 5% of subjects in the total monotherapy population included systolic blood pressure ≥ 160 mmHg (15.2%), weight increase ≥ 10% from baseline (9.6%), diastolic blood pressure ≤ 50 mmHg (8.0%), systolic blood pressure ≤ 90 mmHg (8.0%), weight decrease ≥ 10% from baseline (6.8%), and pulse rate > 120 bpm (6.1%).

Table 17. Abnormal Changes in Vital Signs (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Pulse rate					
> 120 bpm	9 (4.7)	3 (3.4)	1 (1.6)	13 (3.8)	26 (6.1)
< 50 bpm	3 (1.6)	2 (2.3)	7 (11.3)	12 (3.5)	15 (3.5)
Systolic blood pressure					
≥ 160 mmHg	34 (17.9)	9 (10.3)	12 (19.4)	55 (16.2)	65 (15.2)
≤ 90 mmHg	14 (7.4)	2 (2.3)	6 (9.7)	22 (6.5)	34 (8.0)
Diastolic blood pressure					
≥ 105 mmHg	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
≤ 50 mmHg	18 (9.5)	4 (4.6)	4 (6.5)	26 (7.7)	34 (8.0)
Weight					
Decease ≥ 10% from baseline	10 (5.3)	4 (4.6)	7 (11.3)	21 (6.2)	29 (6.8)
Increase ≥ 10% from baseline	23 (12.1)	6 (6.9)	3 (4.8)	32 (9.4)	41 (9.6)
Body temperature					
> 39°C	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.5)

CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QD = once-daily
Source: ISS Table 14a-8.1 and ISS Table 14b-8.1

4.2 Electrocardiograms

In subjects with NSCLC treated at 960 mg once-daily and available data (see Section 1.2.1.1.4), elevated postbaseline QTcF intervals were reported infrequently, with maximum postbaseline QTcF intervals > 450 to 480 msec or > 480 to 500 msec reported for 5.8% and 0.5%, respectively; no subjects with NSCLC treated at 960 mg once-daily had a postbaseline QTcF interval > 500 msec (Table 18).

Few subjects with NSCLC treated at 960 mg once-daily had changes from baseline in QTcF interval > 30 to 60 msec (7.4%) and no subjects had changes from baseline in QTcF interval > 60 msec.

Results of categorical changes in QTcF interval were generally consistent for subjects treated at 960 mg once-daily for all tumor types or for the total monotherapy population.

In subjects treated at 960 mg once-daily for all tumor types, elevated postbaseline QTcF intervals were reported infrequently, with maximum postbaseline QTcF intervals > 450 to 480 msec or > 480 to 500 msec reported for 5.9% and 0.3%, respectively; no subjects treated at 960 mg once-daily for all tumor types had a postbaseline QTcF interval > 500 msec.

Changes from baseline in QTcF interval > 30 to 60 msec were reported for 7.7% of subjects treated at 960 mg once-daily for all tumor types; no subjects had changes from baseline in QTcF interval > 60 msec.

In the total monotherapy population, elevated postbaseline QTcF intervals were reported infrequently, with maximum postbaseline QTcF intervals > 450 to 480 msec or > 480 to 500 msec reported for 7.3% and 0.2%, respectively; 1 subject (0.2%) in the total monotherapy population had a postbaseline QTcF interval > 500 msec.

The subject with a postbaseline QTcF interval > 500 msec had a baseline QTcF of 481 msec. This subject did not have any adverse events at the time of the increased QTcF values nor did the subject have any adverse events at any time on study from the system organ classes of cardiac disorders or nervous system disorders, or other potential clinical correlations.

Changes from baseline in QTcF interval > 30 to 60 msec were reported for 8.7% of subjects in the total monotherapy population; no subjects had changes from baseline in QTcF interval > 60 msec.

Table 18. Summary of Electrocardiogram Parameter Categories (Safety Analysis Set)

Parameter	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
QTcF interval					
Baseline					
≤ 450 msec	144 (75.8)	70 (80.5)	57 (91.9)	271 (79.9)	342 (80.1)
> 450 to 480 msec	5 (2.6)	1 (1.1)	1 (1.6)	7 (2.1)	11 (2.6)
> 480 to 500 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
> 500 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	41 (21.6)	16 (18.4)	4 (6.5)	61 (18.0)	73 (17.1)
Maximum postbaseline					
≤ 450 msec	137 (72.1)	65 (74.7)	55 (88.7)	257 (75.8)	321 (75.2)
> 450 to 480 msec	11 (5.8)	6 (6.9)	3 (4.8)	20 (5.9)	31 (7.3)
> 480 to 500 msec	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
> 500 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Missing	41 (21.6)	16 (18.4)	4 (6.5)	61 (18.0)	73 (17.1)
Maximum increase from baseline					
≤ 30 msec	133 (70.0)	62 (71.3)	52 (83.9)	247 (72.9)	311 (72.8)
> 30 to 60 msec	14 (7.4)	7 (8.0)	5 (8.1)	26 (7.7)	37 (8.7)
> 60 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	43 (22.6)	18 (20.7)	5 (8.1)	66 (19.5)	79 (18.5)
Heart rate					
≥ 25% decrease from baseline to < 50 bpm	1 (0.5)	2 (2.3)	2 (3.2)	5 (1.5)	5 (1.2)
≥ 25% increase from baseline to > 100 bpm	5 (2.6)	2 (2.3)	4 (6.5)	11 (3.2)	15 (3.5)

Footnotes are defined on the last page of the table.

Table 18. Summary of Electrocardiogram Parameter Categories (Safety Analysis Set)

Parameter	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
PR interval					
≥ 25% increase to PR > 200 msec	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	3 (0.7)
QRS interval					
≥ 25% increase to QRS > 120 msec	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)

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CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QD = once-daily; QTcF = QT interval corrected for heart rate using Fridericia's formula
Source: ISS Table 14a-7.6 and ISS Table 14b-7.6

An exposure-QTc analysis found no clinically relevant effect of sotorasib on QT interval (Section 4 of Module 2.7.2, Summary of Clinical Pharmacology).

5. Safety in Special Groups and Situations

5.1 Intrinsic Factors

Adverse events were analyzed by intrinsic factor subgroups of race, age, and sex, which are presented in the sections that follow. Subgroup analyses by tumor type (eg, NSCLC) are presented throughout this Summary of Clinical Safety and in the ISS. Small sample sizes in some subgroups limit the ability to draw conclusions.

5.1.1 Race

The incidence of adverse events was generally similar across subgroups of race.

For subjects with NSCLC treated at 960 mg once-daily, adverse events were reported for 151 of 152 white subjects (99.3%), 28 of 30 Asian subjects (93.3%), 4 of 4 black subjects (100%), and 4 of 4 subjects of other race (100%) (Table 19). Treatment-related adverse events were reported for 103 white subjects (67.8%), 21 Asian subjects (70.0%), 1 black subject (25.0%), and 3 subjects of other race (75.0%). Grade $\geq$ 3 and serious adverse events, respectively, were reported for 92 white subjects (60.5%) and 80 white subjects (52.6%), 17 Asian subjects (56.7%) and 16 Asian subjects (53.3%), 3 black subjects (75.0%) and 3 black subjects (75.0%), and 2 subjects of other race (50.0%) and 0 subjects of other race (0%). Fatal adverse events were reported for 24 white subjects (15.8%), 6 Asian subjects (20.0%), 1 black subject (25.0%), and no subjects of other race. Adverse events leading to sotorasib monotherapy discontinuation were reported for 16 white subjects (10.5%), 2 Asian subjects (6.7%), no black subjects, and no subjects of other race.

As with the adverse event incidence overall, the subject incidence of adverse events for subgroups of white and Asian subjects was slightly lower for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population; the subgroups of black subjects and subjects of other race were too small to draw conclusions.

Table 19. Summary of Treatment-emergent Adverse Events by Subgroup of Race (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Race: White					
Number of subjects in this subgroup	152	59	45	256	332
All TEAEs	151 (99.3)	56 (94.9)	43 (95.6)	250 (97.7)	323 (97.3)
Grade ≥ 3	92 (60.5)	21 (35.6)	28 (62.2)	141 (55.1)	178 (53.6)
Grade ≥ 4	29 (19.1)	2 (3.4)	13 (28.9)	44 (17.2)	60 (18.1)
Serious adverse events	80 (52.6)	17 (28.8)	27 (60.0)	124 (48.4)	152 (45.8)
Leading to discontinuation of investigational product	16 (10.5)	1 (1.7)	3 (6.7)	20 (7.8)	23 (6.9)
Fatal adverse events	24 (15.8)	2 (3.4)	13 (28.9)	39 (15.2)	51 (15.4)
Treatment-related TEAEs	103 (67.8)	27 (45.8)	17 (37.8)	147 (57.4)	194 (58.4)
Race: Black					
Number of subjects in this subgroup	4	1	3	8	12
All TEAEs	4 (100.0)	1 (100.0)	3 (100.0)	8 (100.0)	12 (100.0)
Grade ≥ 3	3 (75.0)	0 (0.0)	1 (33.3)	4 (50.0)	8 (66.7)
Grade ≥ 4	1 (25.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (8.3)
Serious adverse events	3 (75.0)	0 (0.0)	1 (33.3)	4 (50.0)	7 (58.3)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)
Fatal adverse events	1 (25.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (8.3)
Treatment-related TEAEs	1 (25.0)	1 (100.0)	1 (33.3)	3 (37.5)	7 (58.3)

Footnotes are defined on the last page of the table.

Table 19. Summary of Treatment-emergent Adverse Events by Subgroup of Race (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Race: Asian					
Number of subjects in this subgroup	30	23	12	65	67
All TEAEs	28 (93.3)	22 (95.7)	7 (58.3)	57 (87.7)	58 (86.6)
Grade ≥ 3	17 (56.7)	6 (26.1)	3 (25.0)	26 (40.0)	27 (40.3)
Grade ≥ 4	8 (26.7)	1 (4.3)	3 (25.0)	12 (18.5)	12 (17.9)
Serious adverse events	16 (53.3)	3 (13.0)	4 (33.3)	23 (35.4)	23 (34.3)
Leading to discontinuation of investigational product	2 (6.7)	0 (0.0)	0 (0.0)	2 (3.1)	2 (3.0)
Fatal adverse events	6 (20.0)	0 (0.0)	3 (25.0)	9 (13.8)	9 (13.4)
Treatment-related TEAEs	21 (70.0)	14 (60.9)	4 (33.3)	39 (60.0)	40 (59.7)
Race: Others					
Number of subjects in this subgroup	4	4	2	10	16
All TEAEs	4 (100.0)	4 (100.0)	2 (100.0)	10 (100.0)	16 (100.0)
Grade ≥ 3	2 (50.0)	2 (50.0)	1 (50.0)	5 (50.0)	10 (62.5)
Grade ≥ 4	1 (25.0)	0 (0.0)	0 (0.0)	1 (10.0)	2 (12.5)
Serious adverse events	0 (0.0)	2 (50.0)	0 (0.0)	2 (20.0)	5 (31.3)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)
Treatment-related TEAEs	3 (75.0)	2 (50.0)	1 (50.0)	6 (60.0)	10 (62.5)

CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QD = once-daily;
TEAEs = treatment-emergent adverse events
Severity was graded using Common Terminology Criteria for Adverse Events version 5.0.
Source: ISS Table 14a-6.1.8, ISS Table 14a-6.1.9, ISS Table 14a-6.1.10, ISS Table 14a-6.1.11, ISS Table 14b-6.1.8, ISS Table 14b-6.1.9, ISS Table 14b-6.1.10, and ISS Table 14b-6.1.11

5.1.1.1 Common Adverse Events by Race

No meaningful differences were observed in the types of adverse events reported across subgroups of race.

For white subjects, the most frequently reported (≥ 20% of subjects) adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were gastrointestinal disorders (74.3%); musculoskeletal and connective tissue disorders (54.6%); general disorders and administration site conditions (51.3%); respiratory, thoracic and mediastinal disorders (48.7%); infections and infestations (45.4%); investigations (40.1%); metabolism and nutrition disorders (39.5%); nervous system disorders (29.6%); and skin and subcutaneous tissue disorders (24.3%) (ISS Table 14b-6.3.8). Adverse events by preferred term reported with a ≥ 10% subject incidence for white subjects with NSCLC treated at 960 mg once-daily included diarrhea (46.7%), nausea (30.3%), fatigue (27.0%), increased AST (20.4%), increased ALT (19.7%), back pain (19.7%), constipation (19.1%), dyspnea (19.1%), vomiting (17.8%), cough (15.8%), peripheral edema (14.5%), arthralgia (13.2%), increased blood ALP (13.2%), decreased appetite (11.8%), anemia (11.2%), and abdominal pain (10.5%).

For Asian subjects, the most frequently reported (≥ 20% of subjects) adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were gastrointestinal disorders (63.3%); respiratory, thoracic and mediastinal disorders (43.3%); metabolism and nutrition disorders (40.0%); general disorders and administration site conditions (33.3%); skin and subcutaneous tissue disorders (33.3%); investigations (30.0%); infections and infestations (26.7%); musculoskeletal and connective tissue disorders (26.7%); and psychiatric disorders (20.0%) (ISS Table 14b-6.3.10). Adverse events by preferred term reported with a ≥ 10% subject incidence for Asian subjects with NSCLC treated at 960 mg once-daily included diarrhea (26.7%); decreased appetite (20.0%); increased AST (16.7%), nausea (16.7%), pneumonia (16.7%), pruritus (16.7%), hyponatremia (13.3%), increased ALT (13.3%), vomiting (13.3%), and back pain, constipation, cough, decreased weight, fatigue, headache, increased blood ALP, insomnia, maculo-papular rash, and pyrexia (each 10.0%).

For black subjects, the most frequently reported (≥ 2 subjects) adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were gastrointestinal disorders; investigations; metabolism and nutrition disorders; respiratory, thoracic and mediastinal disorders; and vascular disorders (each 50.0%) (ISS Table 14b-6.3.9). The only adverse event by preferred term reported for ≥ 2 black subjects with NSCLC treated at 960 mg once-daily was productive cough (50.0%).

For subjects of other race, the most frequently reported (≥ 2 subjects) adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were investigations (75.0%); nervous system disorders (75.0%); gastrointestinal disorders (50.0%); and musculoskeletal and connective tissue disorders (50.0%) (ISS Table 14b-6.3.11). Adverse events by preferred term reported for ≥ 2 subjects of other race with NSCLC treated at 960 mg once-daily included increased ALT (75.0%), increased AST (75.0%), increased blood ALP (50.0%), back pain (50.0%), and diarrhea (50.0%).

Results were generally similar for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population (ISS Table 14a-6.3.8, ISS Table 14a-6.3.9, ISS Table 14a-6.3.10, and ISS Table 14a-6.3.11).

5.1.1.2 Serious Adverse Events by Race

No meaningful differences were observed in the types of serious adverse events reported across subgroups of race.

For white subjects, the most frequently reported (≥ 5% of subjects) serious adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were respiratory, thoracic and mediastinal disorders (13.2%); benign, malignant and unspecified neoplasms (incl cysts and polyps) (12.5%); infections and infestations (12.5%); gastrointestinal disorders (9.2%); musculoskeletal and connective tissue disorders (7.9%); and injury, poisoning and procedural complications (5.9%) (ISS Table 14b-6.3.23). Serious adverse events by preferred term reported with a ≥ 2% subject incidence for white subjects with NSCLC treated at 960 mg once-daily included pneumonia (6.6%), NSCLC (4.6%), pleural effusion (4.6%), respiratory failure (3.9%), back pain (3.3%), metastatic lung cancer (2.6%), diarrhea (2.0%), and pulmonary embolism (2.0%).

For Asian subjects, the most frequently reported (≥ 10% of subjects) serious adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were respiratory, thoracic and mediastinal disorders (26.7%); gastrointestinal disorders (13.3%); metabolism and nutrition disorders (13.3%); and infections and infestations (10.0%) (ISS Table 14b-6.3.25). Serious adverse events by preferred term reported for ≥ 2 Asian subjects with NSCLC treated at 960 mg once-daily included pneumonia

(10.0%) and fatigue, hyponatremia, NSCLC, pleural effusion, and pneumonitis (each 6.7%).

For black subjects with NSCLC treated at 960 mg once-daily, no serious adverse events were reported for ≥ 2 subjects by system organ class or preferred term (ISS Table 14b-6.3.24).

No serious adverse events were reported for subjects of other race with NSCLC treated at 960 mg once-daily (ISS Table 14b-6.3.26).

Results were generally similar for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population (ISS Table 14a-6.3.23, ISS Table 14a-6.3.24, ISS Table 14a-6.3.25, and ISS Table 14a-6.3.26).

5.1.2 Age

The incidence of adverse events was generally similar across subgroups of age.

For subjects with NSCLC treated at 960 mg once-daily, adverse events were reported for 86 of 87 subjects (98.9%) < 65 years of age, 101 of 103 subjects (98.1%) ≥ 65 years of age, 166 of 169 subjects (98.2%) < 75 years of age, and 21 of 21 subjects (100%) ≥ 75 years of age (Table 20). Treatment-related adverse events were reported for 56 subjects (64.4%) < 65 years of age, 72 subjects (66.9%) ≥ 65 years of age, 112 subjects (66.3%) < 75 years of age, and 16 subjects (76.2%) ≥ 75 years of age. Grade ≥ 3 and serious adverse events, respectively, were reported for 55 subjects (63.2%) and 48 subjects (55.2%) < 65 years of age, 59 subjects (57.3%) and 51 subjects (49.5%) ≥ 65 years of age, 102 subjects (60.4%) and 91 subjects (53.8%) < 75 years of age, and 12 subjects (57.1%) and 8 subjects (38.1%) ≥ 75 years of age. Fatal adverse events were reported for 15 subjects (17.2%) < 65 years of age, 16 subjects (15.5%) ≥ 65 years of age, 28 subjects (16.6%) < 75 years of age, and 3 subjects (14.8%) ≥ 75 years of age. Adverse events leading to sotorasib monotherapy discontinuation were reported for 8 subjects (9.2%) < 65 years of age, 10 subjects (9.7%) ≥ 65 years of age, 17 subjects (10.1%) < 75 years of age, and 1 subject (4.8%) ≥ 75 years of age.

As with the adverse event incidence overall, the subject incidence of adverse events for subgroups of subjects < 65 and < 75 years of age was slightly lower for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population; the incidence of adverse events were similar across these groups for subjects ≥ 65 and ≥ 75 years of age.

Table 20. Summary of Treatment-emergent Adverse Events by Subgroup of Age (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Age: < 65					
Number of subjects in this subgroup	87	65	37	189	230
All TEAEs	86 (98.9)	61 (93.8)	36 (97.3)	183 (96.8)	222 (96.5)
Grade ≥ 3	55 (63.2)	20 (30.8)	20 (54.1)	95 (50.3)	116 (50.4)
Grade ≥ 4	18 (20.7)	2 (3.1)	7 (18.9)	27 (14.3)	34 (14.8)
Serious adverse events	48 (55.2)	12 (18.5)	19 (51.4)	79 (41.8)	94 (40.9)
Leading to discontinuation of investigational product	8 (9.2)	0 (0.0)	1 (2.7)	9 (4.8)	11 (4.8)
Fatal adverse events	15 (17.2)	1 (1.5)	7 (18.9)	23 (12.2)	28 (12.2)
Treatment-related TEAEs	56 (64.4)	31 (47.7)	16 (43.2)	103 (54.5)	126 (54.8)
Age: ≥ 65 years					
Number of subjects in this subgroup	103	22	25	150	197
All TEAEs	101 (98.1)	22 (100.0)	19 (76.0)	142 (94.7)	187 (94.9)
Grade ≥ 3	59 (57.3)	9 (40.9)	13 (52.0)	81 (54.0)	107 (54.3)
Grade ≥ 4	21 (20.4)	1 (4.5)	9 (36.0)	31 (20.7)	41 (20.8)
Serious adverse events	51 (49.5)	10 (45.5)	13 (52.0)	74 (49.3)	93 (47.2)
Leading to discontinuation of investigational product	10 (9.7)	1 (4.5)	2 (8.0)	13 (8.7)	16 (8.1)
Fatal adverse events	16 (15.5)	1 (4.5)	9 (36.0)	26 (17.3)	34 (17.3)
Treatment-related TEAEs	72 (69.9)	13 (59.1)	7 (28.0)	92 (61.3)	125 (63.5)

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Footnotes are defined on the last page of the table.

Table 20. Summary of Treatment-emergent Adverse Events by Subgroup of Age (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Age: < 75 years					
Number of subjects in this subgroup	169	81	57	307	380
All TEAEs	166 (98.2)	77 (95.1)	52 (91.2)	295 (96.1)	364 (95.8)
Grade ≥ 3	102 (60.4)	28 (34.6)	31 (54.4)	161 (52.4)	197 (51.8)
Grade ≥ 4	36 (21.3)	3 (3.7)	15 (26.3)	54 (17.6)	68 (17.9)
Serious adverse events	91 (53.8)	21 (25.9)	30 (52.6)	142 (46.3)	169 (44.5)
Leading to discontinuation of investigational product	17 (10.1)	0 (0.0)	2 (3.5)	19 (6.2)	23 (6.1)
Fatal adverse events	28 (16.6)	2 (2.5)	15 (26.3)	45 (14.7)	55 (14.5)
Treatment-related TEAEs	112 (66.3)	41 (50.6)	21 (36.8)	174 (56.7)	219 (57.6)
Age: ≥ 75 years					
Number of subjects in this subgroup	21	6	3	32	47
All TEAEs	21 (100.0)	6 (100.0)	3 (60.0)	30 (93.8)	45 (95.7)
Grade ≥ 3	12 (57.1)	1 (16.7)	2 (40.0)	15 (46.9)	26 (55.3)
Grade ≥ 4	3 (14.3)	0 (0.0)	1 (20.0)	4 (12.5)	7 (14.9)
Serious adverse events	8 (38.1)	1 (16.7)	2 (40.0)	11 (34.4)	18 (38.3)
Leading to discontinuation of investigational product	1 (4.8)	1 (16.7)	1 (20.0)	3 (9.4)	4 (8.5)
Fatal adverse events	3 (14.3)	0 (0.0)	1 (20.0)	4 (12.5)	7 (14.9)
Treatment-related TEAEs	16 (76.2)	3 (50.0)	2 (40.0)	21 (65.6)	32 (68.1)

CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QD = once-daily;
TEAEs = treatment-emergent adverse events
Severity was graded using Common Terminology Criteria for Adverse Events version 5.0.
Source: ISS Table 14a-6.1.2, ISS Table 14a-6.1.3, ISS Table 14a-6.1.4, ISS Table 14a-6.1.5, ISS Table 14b-6.1.2, ISS Table 14b-6.1.3, ISS Table 14b-6.1.4, and ISS Table 14b-6.1.5

5.1.2.1 Common Adverse Events by Age

No meaningful differences were observed in the types of adverse events reported across subgroups of age.

For subjects < 65 years of age, the most frequently reported (≥ 20% of subjects) adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were gastrointestinal disorders (71.3%); musculoskeletal and connective tissue disorders (52.9%); general disorders and administration site conditions (48.3%); respiratory, thoracic and mediastinal disorders (48.3%); metabolism and nutrition disorders (40.2%); infections and infestations (39.1%); investigations (35.6%); nervous system disorders (28.7%); and skin and subcutaneous tissue disorders (24.1%) (ISS Table 14b-6.3.2). Adverse events by preferred term reported with a ≥ 10% subject incidence for subjects < 65 years of age with NSCLC treated at 960 mg once-daily included diarrhea (44.8%), nausea (28.7%), increased AST (21.8%), increased ALT (20.7%), fatigue (19.5%), vomiting (18.4%), dyspnea (17.2%), back pain (16.1%), constipation (16.1%), anemia (14.9%), arthralgia (14.9%), cough (14.9%), increased blood ALP (14.9%), headache (12.6%), insomnia (11.5%), pneumonia (11.5%), decreased appetite (10.3%), peripheral edema (10.3%), and pleural effusion (10.3%).

For subjects ≥ 65 years of age, the most frequently reported (≥ 10% of subjects) adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were gastrointestinal disorders (71.8%); general disorders and administration site conditions (46.6%); musculoskeletal and connective tissue disorders (46.6%); respiratory, thoracic and mediastinal disorders (46.6%); infections and infestations (42.7%); investigations (42.7%); metabolism and nutrition disorders (38.8%); nervous system disorders (28.2%); and skin and subcutaneous tissue disorders (26.2%) (ISS Table 14b-6.3.3). Adverse events by preferred term reported with a ≥ 5% subject incidence for subjects ≥ 65 years of age with NSCLC treated at 960 mg once-daily included diarrhea (41.7%), fatigue (26.2%), nausea (26.2%), increased AST (20.4%), back pain (20.4%), increased ALT (19.4%), constipation (17.5%), dyspnea (16.5%), vomiting (15.5%), decreased appetite (14.6%), cough (13.6%), peripheral edema (13.6%), increased blood ALP (12.6%), abdominal pain (10.7%), arthralgia (10.7%), and productive cough (10.7%).

For subjects < 75 years of age, the most frequently reported (≥ 20% of subjects) adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were gastrointestinal disorders (71.0%); musculoskeletal and connective tissue disorders (51.5%); general disorders and administration site conditions (48.5%); respiratory, thoracic and mediastinal disorders (47.3%); infections and infestations (42.0%);

metabolism and nutrition disorders (40.8%); investigations (37.3%); nervous system disorders (29.0%); and skin and subcutaneous tissue disorders (26.0%) (ISS Table 14b-6.3.4). Adverse events by preferred term reported with a ≥ 10% subject incidence for subjects < 75 years of age with NSCLC treated at 960 mg once-daily included diarrhea (42.6%), nausea (28.4%), fatigue (22.5%), increased AST (20.7%), back pain (19.5%), increased ALT (19.5%), dyspnea (17.2%), vomiting (17.2%), constipation (16.0%), arthralgia (14.2%), cough (14.2%), increased blood ALP (14.2%), anemia (12.4%), decreased appetite (12.4%), peripheral edema (12.4%), pneumonia (11.2%), headache (10.7%), abdominal pain (10.1%), and pyrexia (10.1%).

For subjects ≥ 75 years of age, the most frequently reported (≥ 20% of subjects) adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were gastrointestinal disorders (76.2%); investigations (57.1%); respiratory, thoracic and mediastinal disorders (47.6%); general disorders and administration site conditions (38.1%); infections and infestations (33.3%); musculoskeletal and connective tissue disorders (33.3%); metabolism and nutrition disorders (28.6%); vascular disorders (28.6%); and nervous system disorders (23.8%) (ISS Table 14b-6.3.5). Adverse events by preferred term reported with a ≥ 10% subject incidence for subjects ≥ 75 years of age with NSCLC treated at 960 mg once-daily included diarrhea (47.6%), fatigue (28.6%), constipation (23.8%), increased ALT (23.8%), increased AST (23.8%), nausea (19.0%), and cough, decreased appetite, decreased weight, decreased white blood cell count, dyspnea, pleural effusion, and vomiting (each 14.3%).

Results were generally similar for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population (ISS Table 14a-6.3.2, ISS Table 14a-6.3.3, ISS Table 14a-6.3.4, and ISS Table 14a-6.3.5).

5.1.2.2 Serious Adverse Events by Age

No meaningful differences were observed in the types of serious adverse events reported across subgroups of age.

For subjects < 65 years of age, the most frequently reported (≥ 5% of subjects) serious adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were benign, malignant and unspecified neoplasms (incl cysts and polyps) (16.1%); infections and infestations (16.1%); respiratory, thoracic and mediastinal disorders (14.9%); and gastrointestinal disorders (11.5%) (ISS Table 14b-6.3.17).

Serious adverse events by preferred term reported with a ≥ 2% subject incidence for subjects < 65 years of age with NSCLC treated at 960 mg once-daily included pneumonia (10.3%), NSCLC (8.0%), dyspnea (3.4%), metastatic lung cancer (3.4%), pleural effusion (3.4%), pneumonitis (3.4%), and abdominal pain, back pain, cellulitis, diarrhea, nausea, respiratory failure, and vomiting (each 2.3%).

For subjects ≥ 65 years of age, the most frequently reported (≥ 5% of subjects) serious adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were respiratory, thoracic and mediastinal disorders (14.6%); infections and infestations (8.7%); gastrointestinal disorders (7.8%); musculoskeletal and connective tissue disorders (7.8%); benign, malignant and unspecified neoplasms (incl cysts and polyps) (6.8%); cardiac disorders (6.8%); and injury, poisoning and procedural complications (5.8%) (ISS Table 14b-6.3.18). Serious adverse events by preferred term reported with a ≥ 2% subject incidence for subjects ≥ 65 years of age with NSCLC treated at 960 mg once-daily included pleural effusion (5.8%), pneumonia (4.9%), respiratory failure (4.9%), and back pain (2.9%).

For subjects < 75 years of age, the most frequently reported (≥ 5% of subjects) serious adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were respiratory, thoracic and mediastinal disorders (13.6%); infections and infestations (13.0%); benign, malignant and unspecified neoplasms (incl cysts and polyps) (11.2%); gastrointestinal disorders (8.9%); musculoskeletal and connective tissue disorders (6.5%); and cardiac disorders (5.3%) (ISS Table 14b-6.3.19). Serious adverse events by preferred term reported with a ≥ 2% subject incidence for subjects < 75 years of age with NSCLC treated at 960 mg once-daily included pneumonia (7.7%), NSCLC (5.3%), pleural effusion (4.1%), respiratory failure (3.6%), and back pain (3.0%).

For subjects ≥ 75 years of age, the most frequently reported (≥ 2 subjects) serious adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were respiratory, thoracic and mediastinal disorders (23.8%); gastrointestinal disorders (14.3%); and benign, malignant and unspecified neoplasms (incl cysts and polyps) (9.5%) (ISS Table 14b-6.3.20). The only serious adverse event by preferred term reported for ≥ 2 subjects ≥ 75 years of age with NSCLC treated at 960 mg once-daily was pleural effusion (9.5%).

Results were generally similar for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population (ISS Table 14a-6.3.17, ISS Table 14a-6.3.18, ISS Table 14a-6.3.19, and ISS Table 14a-6.3.20).

5.1.3 Sex

The incidence of adverse events tended to be numerically lower for men compared with women. However, review of the events, including fatal adverse events, did not reveal any clinically meaningful differences across sexes.

For subjects with NSCLC treated at 960 mg once-daily, adverse events were reported for 86 of 88 men (97.7%) and 101 of 102 women (99.0%) (Table 21). Treatment-related adverse events were reported for 58 men (65.9%) and 70 women (68.6%). Grade ≥ 3 and serious adverse events, respectively, were reported for 50 men (56.8%) and 41 men (46.6%) and 64 women (62.7%) and 58 women (56.9%). Fatal adverse events were reported for 11 men (12.5%) and 20 women (19.6%). Adverse events leading to sotorasib monotherapy discontinuation were reported for 9 men (10.2%) and 9 women (8.8%).

As with the adverse event incidence overall, the subject incidence of adverse events for subgroups of men and women was slightly lower for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population.

Table 21. Summary of Treatment-emergent Adverse Events by Subgroup of Sex (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Sex: Men					
Number of subjects in this subgroup	88	43	38	169	200
All TEAEs	86 (97.7)	41 (95.3)	34 (89.5)	161 (95.3)	191 (95.5)
Grade ≥ 3	50 (56.8)	16 (37.2)	19 (50.0)	85 (50.3)	104 (52.0)
Grade ≥ 4	14 (15.9)	2 (4.7)	8 (21.1)	24 (14.2)	31 (15.5)
Serious adverse events	41 (46.6)	11 (25.6)	19 (50.0)	71 (42.0)	83 (41.5)
Leading to discontinuation of investigational product	9 (10.2)	1 (2.3)	2 (5.3)	12 (7.1)	14 (7.0)
Fatal adverse events	11 (12.5)	1 (2.3)	8 (21.1)	20 (11.8)	26 (13.0)
Treatment-related TEAEs	58 (65.9)	23 (53.5)	16 (42.1)	97 (57.4)	114 (57.0)
Sex: Women					
Number of subjects in this subgroup	102	44	24	170	227
All TEAEs	101 (99.0)	42 (95.5)	21 (87.5)	164 (96.5)	218 (96.0)
Grade ≥ 3	64 (62.7)	13 (29.5)	14 (58.3)	91 (53.5)	119 (52.4)
Grade ≥ 4	25 (24.5)	1 (2.3)	8 (33.3)	34 (20.0)	44 (19.4)
Serious adverse events	58 (56.9)	11 (25.0)	13 (54.2)	82 (48.2)	104 (45.8)
Leading to discontinuation of investigational product	9 (8.8)	0 (0.0)	1 (4.2)	10 (5.9)	13 (5.7)
Fatal adverse events	20 (19.6)	1 (2.3)	8 (33.3)	29 (17.1)	36 (15.9)
Treatment-related TEAEs	70 (68.6)	21 (47.7)	7 (29.2)	98 (57.6)	137 (60.4)

CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QD = once-daily;
TEAEs = treatment-emergent adverse events
Severity was graded using Common Terminology Criteria for Adverse Events version 5.0.
Source: ISS Table 14a-6.1.6, ISS Table 14a-6.1.7, ISS Table 14b-6.1.6, and ISS Table 14b-6.1.7

5.1.3.1 Common Adverse Events by Sex

No meaningful differences were observed in the types of adverse events reported across subgroups of sex.

For women, the most frequently reported (≥ 20% of subjects) adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were gastrointestinal disorders (73.5%); musculoskeletal and connective tissue disorders (51.0%); general disorders and administration site conditions (49.0%); respiratory, thoracic and mediastinal disorders (46.1%); infections and infestations (42.2%); metabolism and nutrition disorders (40.2%); investigations (36.3%); nervous system disorders (32.4%); and skin and subcutaneous tissue disorders (24.5%) (ISS Table 14b-6.3.6). Adverse events by preferred term reported with a ≥ 10% subject incidence for women with NSCLC treated at 960 mg once-daily included diarrhea (45.1%), nausea (32.4%), back pain (22.5%), fatigue (21.6%), increased AST (20.6%), increased ALT (19.6%), constipation (18.6%), vomiting (16.7%), anemia (15.7%), arthralgia (13.7%), dyspnea (13.7%), decreased appetite (12.7%), increased blood ALP (12.7%), cough (11.8%), abdominal pain (10.8%), and peripheral edema (10.8%).

For men, the most frequently reported (≥ 20% of subjects) adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were gastrointestinal disorders (69.3%); respiratory, thoracic and mediastinal disorders (48.9%); musculoskeletal and connective tissue disorders (47.7%); general disorders and administration site conditions (45.5%); investigations (43.2%); infections and infestations (39.8%); metabolism and nutrition disorders (38.6%); skin and subcutaneous tissue disorders (26.1%); and nervous system disorders (23.9%) (ISS Table 14b-6.3.7). Adverse events by preferred term reported with a ≥ 10% subject incidence for men with NSCLC treated at 960 mg once-daily included diarrhea (40.9%), fatigue (25.0%), nausea (21.6%), increased AST (21.6%), dyspnea (20.5%), increased ALT (20.5%), cough (17.0%), vomiting (17.0%), constipation (14.8%), increased blood ALP (14.8%), back pain (13.6%), peripheral edema (13.6%), pneumonia (13.6%), decreased appetite (12.5%), arthralgia (11.4%), headache (10.2%), pruritus (10.2%), and pyrexia (10.2%).

Results were generally similar for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population (ISS Table 14a-6.3.6 and ISS Table 14a-6.3.7).

5.1.3.2 Serious Adverse Events by Sex

No meaningful differences were observed in the types of serious adverse events reported across subgroups of sex.

For women, the most frequently reported (≥ 5% of subjects) serious adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were benign, malignant and unspecified neoplasms (incl cysts and polyps) (15.7%); respiratory, thoracic and mediastinal disorders (15.7%); infections and infestations (13.7%); and gastrointestinal disorders (9.8%) (ISS Table 14b-6.3.21). Serious adverse events by preferred term reported with a ≥ 2% subject incidence for women with NSCLC treated at 960 mg once-daily included pneumonia (6.9%), NSCLC (5.9%), respiratory failure (5.9%), pleural effusion (4.9%), diarrhea (2.9%), and cellulitis, dyspnea, hemoptysis, malignant lung neoplasm, metastatic lung cancer, and pain (each 2.0%).

For men, the most frequently reported (≥ 5% of subjects) serious adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were respiratory, thoracic and mediastinal disorders (13.6%); infections and infestations (10.2%); musculoskeletal and connective tissue disorders (10.2%); gastrointestinal disorders (9.1%); cardiac disorders (8.0%); and benign, malignant and unspecified neoplasms (incl cysts and polyps) (5.7%) (ISS Table 14b-6.3.22). Serious adverse events by preferred term reported with a ≥ 2% subject incidence for men with NSCLC treated at 960 mg once-daily included pneumonia (8.0%), back pain (4.5%), pleural effusion (4.5%), NSCLC (3.4%), and fatigue, nausea, hyponatremia, increased ALT, metastatic lung cancer, pathological fracture, pneumonitis, pulmonary embolism, and vomiting (each 2.3%).

Results were generally similar for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population (ISS Table 14a-6.3.21 and ISS Table 14a-6.3.22).

5.2 Extrinsic Factors

Adverse events were analyzed by the extrinsic factor subgroup of region, which is presented in the section that follows. Subgroup analyses by dose regimen (eg, 960 mg once-daily) and fed/fasted status are presented throughout this Summary of Clinical Safety and in the ISS.

5.2.1 Region

The incidence of adverse events was generally similar across subgroups of region.

For subjects with NSCLC treated at 960 mg once-daily, adverse events were reported for 133 of 136 subjects (97.8%) from North America, 31 of 31 subjects (100%) from

Europe, 17 of 17 subjects (100%) from Asia, and 6 of 6 subjects (100%) from rest of world (Table 22). Treatment-related adverse events were reported for 91 subjects (66.9%) from North America, 19 subjects (61.3%) from Europe, 12 subjects (70.6%) from Asia, and 6 subjects (100%) from rest of world. Grade ≥ 3 and serious adverse events, respectively, were reported for 80 subjects (58.8%) and 68 subjects (50.0%) from North America, 21 subjects (67.7%) and 18 subjects (58.1%) from Europe, 11 subjects (64.7%) and 11 subjects (64.7%) from Asia, and 2 subjects (33.3%) each from rest of world. Fatal adverse events were reported for 23 subjects (16.9%) from North America, 4 subjects (12.9%) from Europe, 4 subjects (23.5%) from Asia, and no subjects from rest of world. Adverse events leading to sotorasib monotherapy discontinuation were reported for 11 subjects (8.1%) from North America, 4 subjects (12.9%) from Europe, 2 subjects (11.8%) from Asia, and 1 subject (16.7%) from rest of world.

As with the adverse event incidence overall, the subject incidence of adverse events for subgroups of subjects from North America, Europe, and Asia was slightly lower for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population; the subgroup of subjects from rest of world was too small to draw comparisons across groups.

Table 22. Summary of Treatment-emergent Adverse Events by Subgroup of Region (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Region: North America					
Number of subjects in this subgroup	136	47	34	217	291
All TEAEs	133 (97.8)	45 (95.7)	32 (94.1)	210 (96.8)	280 (96.2)
Grade ≥ 3	80 (58.8)	15 (31.9)	20 (58.8)	115 (53.0)	155 (53.3)
Grade ≥ 4	27 (19.9)	0 (0.0)	9 (26.5)	36 (16.6)	50 (17.2)
Serious adverse events	68 (50.0)	13 (27.7)	18 (52.9)	99 (45.6)	127 (43.6)
Leading to discontinuation of investigational product	11 (8.1)	0 (0.0)	3 (8.8)	14 (6.5)	19 (6.5)
Fatal adverse events	23 (16.9)	0 (0.0)	9 (26.5)	32 (14.7)	42 (14.4)
Treatment-related TEAEs	91 (66.9)	17 (36.2)	13 (38.2)	121 (55.8)	169 (58.1)
Region: Europe					
Number of subjects in this subgroup	31	13	14	58	59
All TEAEs	31 (100.0)	12 (92.3)	14 (100.0)	57 (98.3)	58 (98.3)
Grade ≥ 3	21 (67.7)	4 (30.8)	8 (57.1)	33 (56.9)	34 (57.6)
Grade ≥ 4	6 (19.4)	1 (7.7)	4 (28.6)	11 (19.0)	11 (18.6)
Serious adverse events	18 (58.1)	2 (15.4)	8 (57.1)	28 (48.3)	29 (49.2)
Leading to discontinuation of investigational product	4 (12.9)	0 (0.0)	0 (0.0)	4 (6.9)	4 (6.8)
Fatal adverse events	4 (12.9)	1 (7.7)	4 (28.6)	9 (15.5)	9 (15.3)
Treatment-related TEAEs	19 (61.3)	10 (76.9)	4 (28.6)	33 (56.9)	34 (57.6)

Footnotes are defined on the last page of the table.

Table 22. Summary of Treatment-emergent Adverse Events by Subgroup of Region (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 190) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 62) n (%)	Any Tumor Type (N = 339) n (%)	Total Any Tumor Type/Any Dose (N = 427) n (%)
Region: Asia					
Number of subjects in this subgroup	17	21	12	50	51
All TEAEs	17 (100.0)	20 (95.2)	7 (58.3)	44 (88.0)	45 (88.2)
Grade ≥ 3	11 (64.7)	6 (28.6)	3 (25.0)	20 (40.0)	21 (41.2)
Grade ≥ 4	6 (35.3)	1 (4.8)	3 (25.0)	10 (20.0)	10 (19.6)
Serious adverse events	11 (64.7)	3 (14.3)	4 (33.3)	18 (36.0)	18 (35.3)
Leading to discontinuation of investigational product	2 (11.8)	0 (0.0)	0 (0.0)	2 (4.0)	2 (3.9)
Fatal adverse events	4 (23.5)	0 (0.0)	3 (25.0)	7 (14.0)	7 (13.7)
Treatment-related TEAEs	12 (70.6)	13 (61.9)	4 (33.3)	29 (58.0)	30 (58.8)
Region: Rest of world					
Number of subjects in this subgroup	6	6	2	14	26
All TEAEs	6 (100.0)	6 (100.0)	2 (100.0)	14 (100.0)	26 (100.0)
Grade ≥ 3	2 (33.3)	4 (66.7)	2 (100.0)	8 (57.1)	13 (50.0)
Grade ≥ 4	0 (0.0)	1 (16.7)	0 (0.0)	1 (7.1)	4 (15.4)
Serious adverse events	2 (33.3)	4 (66.7)	2 (100.0)	8 (57.1)	13 (50.0)
Leading to discontinuation of investigational product	1 (16.7)	1 (16.7)	0 (0.0)	2 (14.3)	2 (7.7)
Fatal adverse events	0 (0.0)	1 (16.7)	0 (0.0)	1 (7.1)	4 (15.4)
Treatment-related TEAEs	6 (100.0)	4 (66.7)	2 (100.0)	12 (85.7)	18 (69.2)

CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QD = once-daily;
TEAEs = treatment-emergent adverse events
Severity was graded using Common Terminology Criteria for Adverse Events version 5.0.
Source: ISS Table 14a-6.1.12, ISS Table 14a-6.1.13, ISS Table 14a-6.1.14, ISS Table 14a-6.1.15, ISS Table 14b-6.1.12, ISS Table 14b-6.1.13, ISS Table 14b-6.1.14, and ISS Table 14b-6.1.15

5.2.1.1 Common Adverse Events by Region

No meaningful differences were observed in the types of adverse events reported across subgroups of region.

For subjects from North America, the most frequently reported (≥ 20% of subjects) adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were gastrointestinal disorders (72.8%); musculoskeletal and connective tissue disorders (55.9%); respiratory, thoracic and mediastinal disorders (52.2%); general disorders and administration site conditions (49.3%); metabolism and nutrition disorders (39.7%); infections and infestations (39.0%); investigations (39.0%); nervous system disorders (33.8%); skin and subcutaneous tissue disorders (21.3%); psychiatric disorders (20.6%); and vascular disorders (20.6%) (ISS Table 14b-6.3.12). Adverse events by preferred term reported with a ≥ 10% subject incidence for subjects from North America with NSCLC treated at 960 mg once-daily included diarrhea (45.6%), nausea (26.5%), fatigue (25.0%), back pain (22.8%), increased AST (20.6%), increased ALT (19.9%), dyspnea (18.4%), cough (17.6%), vomiting (17.6%), constipation (16.9%), increased blood ALP (13.2%), headache (12.5%), arthralgia (11.8%), decreased appetite (11.8%), insomnia (11.8%), pneumonia (11.8%), abdominal pain (11.0%), anemia (11.0%), peripheral edema (11.0%), dizziness (10.3%), hypokalemia (10.3%), and productive cough (10.3%).

For subjects from Europe, the most frequently reported (≥ 20% of subjects) adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were gastrointestinal disorders (67.7%); infections and infestations (48.4%); investigations (48.4%); general disorders and administration site conditions (41.9%); metabolism and nutrition disorders (35.5%); musculoskeletal and connective tissue disorders (35.5%); respiratory, thoracic and mediastinal disorders (32.3%); and skin and subcutaneous tissue disorders (25.8%) (ISS Table 14b-6.3.13). Adverse events by preferred term reported with a ≥ 10% subject incidence for subjects from Europe with NSCLC treated at 960 mg once-daily included diarrhea (48.4%), nausea (32.3%), increased AST (25.8%), increased ALT (22.6%), peripheral edema (22.6%), constipation (19.4%), dyspnea (19.4%), anemia (16.1%), arthralgia (16.1%), asthenia (16.1%), fatigue (16.1%), increased blood ALP (16.1%), increased gamma-glutamyltransferase (16.1%), pleural effusion (12.9%), vomiting (12.9%), and decreased weight (12.9%).

For subjects from Asia, the most frequently reported (≥ 20% of subjects) adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were gastrointestinal disorders (70.6%); metabolism and nutrition disorders (41.2%);

respiratory, thoracic and mediastinal disorders (41.2%); skin and subcutaneous tissue disorders (41.2%); general disorders and administration site conditions (35.3%); infections and infestations (35.3%); and investigations (23.5%) (ISS Table 14b-6.3.14). Adverse events by preferred term reported with a ≥ 10% subject incidence for subjects from Asia with NSCLC treated at 960 mg once-daily included decreased appetite (23.5%), diarrhea (23.5%), pneumonia (23.5%), anemia (17.6%), increased ALT (17.6%), increased AST (17.6%), nausea (17.6%), pruritus (17.6%), pyrexia (17.6%), vomiting (17.6%), abnormal hepatic function, back pain, cough, increased blood ALP, pain, hypercalcemia, hyperkalemia, hyponatremia, maculo-papular rash, NSCLC, and pleural effusion (each 11.8%).

For subjects from rest of world, the most frequently reported (≥ 2 subjects) adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were musculoskeletal and connective tissue disorders (83.3%); gastrointestinal disorders (66.7%); general disorders and administration site conditions (66.7%); infections and infestations (66.7%); skin and subcutaneous tissue disorders (66.7%); eye disorders (50.0%); investigations (50.0%); metabolism and nutrition disorders (50.0%); nervous system disorders (50.0%); psychiatric disorders (33.3%); and respiratory, thoracic and mediastinal disorders (33.3%) (ISS Table 14b-6.3.15). Adverse events by preferred term reported for ≥ 2 subjects from rest of world with NSCLC treated at 960 mg once-daily included fatigue (66.7%), arthralgia (50.0%), nausea (50.0%), constipation (33.3%), oral candidiasis (33.3%), oropharyngeal pain (33.3%), and pain in extremity (33.3%).

Results were generally similar for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population (ISS Table 14a-6.3.12, ISS Table 14a-6.3.13, ISS Table 14a-6.3.14, and ISS Table 14a-6.3.15).

5.2.1.2 Serious Adverse Events by Region

No meaningful differences were observed in the types of serious adverse events reported across subgroups of region.

For subjects from North America, the most frequently reported (≥ 5% of subjects) serious adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were respiratory, thoracic and mediastinal disorders (15.4%); infections and infestations (13.2%); benign, malignant and unspecified neoplasms (incl cysts and polyps) (11.0%); gastrointestinal disorders (8.1%); musculoskeletal and connective

tissue disorders (7.4%); injury, poisoning and procedural complications (5.9%); and cardiac disorders (5.1%) (ISS Table 14b-6.3.27). Serious adverse events by preferred term reported for ≥ 2% subject incidence for subjects from North America with NSCLC treated at 960 mg once-daily included pneumonia (8.1%), respiratory failure (5.1%), NSCLC (4.4%), pleural effusion (3.7%), back pain (2.9%), metastatic lung cancer (2.9%), diarrhea (2.2%), dyspnea (2.2%), and pulmonary embolism (2.2%).

For subjects from Europe, the most frequently reported (≥ 2 subjects) serious adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were benign, malignant and unspecified neoplasms (incl cysts and polyps) (12.9%); gastrointestinal disorders (12.9%); hepatobiliary disorders (6.5%); immune system disorders (6.5%); investigations (6.5%); and respiratory, thoracic and mediastinal disorders (6.5%) (ISS Table 14b-6.3.28). Serious adverse events by preferred term reported for ≥ 2 subjects from Europe with NSCLC treated at 960 mg once-daily included malignant lung neoplasm and pleural effusion (each 6.5%).

For subjects from Asia, the most frequently reported (≥ 2 subjects) serious adverse events in subjects with NSCLC treated at 960 mg once-daily by system organ class were respiratory, thoracic and mediastinal disorders (29.4%); infections and infestations (17.6%); metabolism and nutrition disorders (17.6%); benign, malignant and unspecified neoplasms (incl cysts and polyps) (11.8%); and gastrointestinal disorders (11.8%) (ISS Table 14b-6.3.29). Serious adverse events by preferred term reported for ≥ 2 subjects from Asia with NSCLC treated at 960 mg once-daily included pneumonia (17.6%), hyponatremia (11.8%), NSCLC (11.8%), and pleural effusion (11.8%).

No serious adverse events were reported for ≥ 2 subjects from rest of world with NSCLC treated at 960 mg once-daily by system organ class or preferred term (ISS Table 14b-6.3.30).

Results were generally similar for subjects treated at 960 mg once-daily for all tumor types and for the total monotherapy population (ISS Table 14a-6.3.27, ISS Table 14a-6.3.28, ISS Table 14a-6.3.29, and ISS Table 14a-6.3.30).

5.3 Drug Interactions

Nonclinical studies demonstrated that sotorasib is metabolized by cytochrome P450 (CYP) enzymes and was an inhibitor and inducer of CYP enzymes (Module 2.6.4,

Pharmacokinetics Written Summary). In vitro, sotorasib was shown to be a substrate of P-glycoprotein and an inhibitor of various transporters.

A number of clinical drug-drug interaction studies have been conducted in healthy subjects or subjects with *KRAS p.G12C*-mutated advanced solid tumors (see Section 2 of Module 2.7.2, Summary of Clinical Pharmacology). Coadministration of sotorasib with a strong CYP3A4 inducer, proton pump inhibitor, or H_2 receptor antagonist led to a decrease in sotorasib concentrations. In addition, sotorasib is a moderate CYP3A4 inducer; coadministration of sotorasib with CYP3A4 substrates led to a decrease in their plasma concentrations. The safety profile of sotorasib in these single-dose studies in healthy subjects was generally similar with and without the coadministered drug (Study [redacted] and Study [redacted]).

5.4 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 was reported in which the patient was exposed to sotorasib during pregnancy through paternal exposure; 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 2). No breastfeeding cases were reported with exposure to sotorasib.

In the rat and rabbit embryo-fetal development toxicology studies, 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 area under the curve). 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 area under the curve), 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 nonspecific effect in the presence of significant maternal toxicity.

5.5 Overdose

There is no clinical experience with overdose with sotorasib.

5.6 Drug Abuse

There is no evidence that sotorasib is habit forming or could lead to dependence.

5.7 Withdrawal and Rebound

No withdrawal or rebound studies were conducted with sotorasib.

5.8 Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

Sotorasib does not have any known effects on the ability to drive or operate machinery or on the impairment of mental ability.

6. Postmarketing Data

Sotorasib is not yet a marketed product.

7. References

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8. Summary of Clinical Safety Appendix

Appendix 1. Clinical Study Narratives

A study narrative for Study [redacted] is provided in Section 2 of Module 2.7.3, Summary of Clinical Efficacy.

Study [redacted]

Study Title: Phase 3 Multicenter, Randomized, Open Label, Active-controlled, Study of [redacted] Versus Docetaxel for the Treatment of Previously Treated Locally Advanced and Unresectable or Metastatic NSCLC Subjects With Mutated *KRAS p.G12C*

Methods: Study [redacted] s an ongoing, phase 3, multicenter, randomized (1:1), open-label, active-controlled study to evaluate the efficacy, safety, and tolerability of sotorasib versus docetaxel in subjects with previously treated locally advanced and unresectable or metastatic NSCLC with the *KRAS p.G12C* mutation. Subjects continue treatment until investigator-determined disease progression, intolerance of treatment leading to treatment discontinuation, initiation of another anticancer therapy, or withdrawal of consent.

The primary objective is to compare the efficacy of sotorasib versus docetaxel as assessed by progression-free survival in previously treated subjects with *KRAS p.G12C*-mutated NSCLC.

Results:

Data are reported in a blinded fashion as of a cutoff date of 01 September 2020. A total of 29 subjects were randomized, and 21 subjects received at least 1 dose of investigational product. [redacted]

Safety Results

No fatal adverse events were reported. Serious adverse events were reported for 2 subjects and include hypoglycemia and nausea (each 1 subject).

No subjects had nonserious adverse events leading to the discontinuation of investigational product or nonserious hepatotoxicity and renal toxicity adverse events of interest.

Additional details and subject narratives are provided in the Study [redacted] Safety Report.

Study [redacted]

Study Title: Phase 1, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of [redacted] in Subjects of Chinese Descent With Advanced/Metastatic Solid Tumors With *KRAS p.G12C* Mutation

Methods: Study [redacted] is an ongoing, nonrandomized, open-label, multicenter phase 1 study to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of sotorasib administered orally once-daily in subjects of Chinese descent with *KRAS p.G12C*-mutant advanced/metastatic solid tumors. Subjects continue sotorasib treatment until there is evidence of disease progression, intolerance to study medication, or withdrawal of consent.

The primary objectives of the study are to evaluate the safety and tolerability of sotorasib in adult subjects of Chinese descent with *KRAS p.G12C*-mutant advanced/metastatic solid tumors and to characterize the pharmacokinetics of sotorasib in subjects of Chinese descent when administered orally.

Results:

Data are reported as of a cutoff date of 01 September 2020. A total of 3 subjects were enrolled and received at least 1 dose of sotorasib. No subjects had discontinued sotorasib.

All 3 subjects were [redacted]

Safety Results

No fatal adverse events were reported. Serious adverse events were reported for 1 subject; the preferred term was dyspnea.

No subjects had nonserious adverse events leading to the discontinuation of investigational product or nonserious hepatotoxicity and renal toxicity adverse events of interest.

Additional details and subject narratives are provided in the Study [redacted] Safety Report.

Study [redacted] Subprotocol A

Study Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of [redacted] in Combination With Trametinib in Subjects With Advanced Solid Tumors With *KRAS p.G12C* Mutation

Methods: Study [redacted] Subprotocol A is an ongoing, phase 1b multicenter, open-label study evaluating the safety, tolerability, pharmacokinetics, and efficacy of sotorasib in combination with trametinib in subjects with previously treated *KRAS p.G12C*-mutant advanced solid tumors. Subjects continue sotorasib treatment until evidence of disease progression, intolerance to study medication, withdrawal of consent, or end of study.

The primary objective of the study is to evaluate the safety and tolerability of sotorasib administered in combination with trametinib in adult subjects with *KRAS p.G12C*-mutant advanced solid tumors.

Results:

Data are reported as of a cutoff date of 01 September 2020. A total of 35 subjects were enrolled and received at least 1 dose of sotorasib. [redacted]

Safety Results

Fatal adverse events were reported for [redacted] subjects and include death and pneumonia [redacted]

Serious adverse events were reported for [redacted] subjects and include small intestinal obstruction ([redacted] subjects) and acute respiratory failure, bacteremia, cancer pain, Clostridium difficile infection, dehydration, intestinal obstruction, pyrexia, visual hallucination, and vomiting ([redacted]).

Nonserious adverse events leading to the discontinuation of investigational product were reported for 1 subject; the preferred term was diarrhea.

Nonserious hepatotoxicity adverse events of interest were reported for [redacted] subjects and include hypoalbuminemia ([redacted] subjects), increased blood ALP ([redacted] subjects), ascites ([redacted] subject), increased ALT ([redacted] subject), and increased AST ([redacted] subject). Nonserious renal

toxicity adverse events of interest were reported for [redacted] subjects and include hypoalbuminemia ([redacted] subjects), hyponatremia ([redacted] subjects), hypokalemia ([redacted] subjects), increased blood creatinine ([redacted] subjects), and proteinuria ([redacted] subjects).

Additional details and subject narratives are provided in the Study [redacted] Substudy A Safety Report.

Study [redacted] Subprotocol C

Study Title: A Phase 1b Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 510 (pINN Sotorasib) in Combination With RMC-4630 in Subjects With Advanced Solid Tumors With *KRAS p.G12C* Mutation

Methods: Study [redacted] Subprotocol C is an ongoing, phase 1b multicenter, open-label study evaluating the safety, tolerability, pharmacokinetics, and efficacy of sotorasib in combination with RMC-4630, an SHP2 inhibitor, in subjects with previously treated *KRAS p.G12C*-mutant advanced solid tumors. Subjects continue sotorasib treatment until evidence of disease progression, intolerance to study medication, withdrawal of consent, or end of study.

The primary objective of the study is to evaluate the safety and tolerability of sotorasib in combination with RMC-4630 in adult subjects with *KRAS p.G12C*-mutant advanced solid tumors.

Results:

Data are reported as of a cutoff date of 01 September 2020. A total of 3 subjects were enrolled and received at least 1 dose of sotorasib. [redacted]

Safety Results

No fatal adverse events were reported. Serious adverse events were reported for 1 subject; the preferred term was increased AST.

Nonserious adverse events leading to the discontinuation of investigational product were reported for 1 subject; the preferred term was increased AST.

Nonserious hepatotoxicity adverse events of interest were reported for 1 subject; the preferred term was increased AST. No subjects had nonserious renal toxicity adverse events of interest.

Additional details and subject narratives are provided in the Study [redacted] Substudy C Safety Report.

Study [redacted] Subprotocol D

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

Methods: Study [redacted] Subprotocol D is an ongoing, phase 1b multicenter, open-label study evaluating the safety, tolerability, pharmacokinetics, and efficacy of sotorasib in combination with afatinib in subjects with previously treated *KRAS p.G12C*-mutant advanced NSCLC. Subjects continue sotorasib treatment until evidence of disease progression, intolerance to study medication, withdrawal of consent, or end of study.

The primary objective of the study is to evaluate the safety and tolerability of sotorasib in combination with afatinib in adult subjects with *KRAS p.G12C*-mutant advanced NSCLC.

Results:

Data are reported as of a cutoff date of 01 September 2020. A total of 5 subjects were enrolled and received at least 1 dose of sotorasib. [redacted]

Safety Results

No fatal adverse events were reported. Serious adverse events were reported for [redacted] subjects and include diarrhea ([redacted] subjects) and hemoptysis, pneumonia, and sepsis ([redacted]

Nonserious adverse events leading to the discontinuation of investigational product were reported for 1 subject; the preferred term was diarrhea.

Nonserious hepatotoxicity adverse events of interest were reported for 1 subject; the preferred terms were increased ALT, increased AST, and increased blood ALP. No subjects had nonserious renal toxicity adverse events of interest.

Additional details and subject narratives are provided in the Study [redacted] Substudy D Safety Report.

Study [redacted] Subprotocol E

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

Methods: Study [redacted] Subprotocol E is an ongoing, phase 1b multicenter, open-label study evaluating the safety, tolerability, pharmacokinetics, and efficacy of sotorasib in combination with atezolizumab in subjects with previously treated *KRAS p.G12C*-mutant advanced NSCLC. Subjects continue sotorasib treatment until evidence of disease progression, intolerance to study medication, withdrawal of consent, or end of study.

The primary objective of the study is to evaluate the safety and tolerability of sotorasib in combination with atezolizumab in adult subjects with *KRAS p.G12C*-mutant advanced NSCLC.

Results:

Data are reported as of a cutoff date of 01 September 2020. A total of 6 subjects were enrolled, and 5 subjects received at least 1 dose of sotorasib. [redacted].

Safety Results

No fatal adverse events were reported. Serious adverse events were reported for 1 subject; the preferred term was urinary tract infection.

No subjects had nonserious adverse events leading to the discontinuation of investigational product or nonserious hepatotoxicity or renal toxicity adverse events of interest.

Additional details and subject narratives are provided in the Study [redacted] Substudy E Safety Report.

Study [redacted] Subprotocol H

Study Title: A Phase 1b Study Evaluating the Safety, Tolerability, and Efficacy of [redacted] in Combination with Panitumumab and in Combination with Panitumumab and FOLFIRI in Subjects with Advanced Solid Tumors with *KRAS p.G12C* Mutation

Methods: Study [redacted] Subprotocol H is an ongoing, phase 1b multicenter, open-label study evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of sotorasib in combination with panitumumab or with panitumumab and FOLFIRI in subjects with previously treated *KRAS p.G12C*-mutant advanced solid tumors. Subjects continue sotorasib treatment until evidence of disease progression, intolerance to study medication, withdrawal of consent, or end of study.

The primary objective of the study is to evaluate the safety and tolerability of sotorasib in combination with panitumumab or with panitumumab and FOLFIRI in adult subjects with *KRAS p.G12C*-mutant advanced solid tumors.

Results:

Data are reported as of a cutoff date of 01 September 2020. A total of 4 subjects were enrolled and received at least 1 dose of sotorasib. No subjects had discontinued sotorasib.

Safety Results

No subjects had a fatal adverse event, other serious adverse event, nonserious adverse event leading to the discontinuation of investigational product, or nonserious hepatotoxicity or renal toxicity adverse event of interest.

Additional details are provided in the Study [redacted] Substudy H Safety Report.