11 November 2021
EMA/706135/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lumykras

International non-proprietary name: sotorasib

Procedure No. EMEA/H/C/005522/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

AACR	American Association for Cancer Research
ADR	adverse drug reaction
AE	adverse event
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
SOTORASIB	sotorasib
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-t}	AUC from time 0 to time t
AUC_{inf}	AUC from time 0 to infinite time
AUC_{last}	AUC from time 0 to the last quantifiable timepoint
AUC_{tau}	AUC over the dosing interval
BCRP	breast cancer resistance protein
BCS	biopharmaceutics classification system
BIC	Bayesian information criterion
BICR	blinded independent central review
BID	twice daily
BOR	best overall response
BRAF	B-raf gene
BTSR	best tumor size response
BUN	blood urea nitrogen
14C	carbon-14
CAR	constitutive androstane receptor
CGDB	Clinico-Genomics Database
CL/F	apparent clearance (expressed as a function of bioavailability)
CMA	conditional marketing authorisation
C_{max}	maximum plasma concentration
CHMP	Committee for Medicinal Products for Human Use
COVID-19	coronavirus disease 2019
CQA	Critical Quality Attribute
CR	complete response
C-RAF	RAF proto-oncogene serine/threonine-protein kinase
CRC	colorectal cancer
CrCL	creatinine clearance
CRF	case report form
CT	computed tomography
CTCAE	common terminology criteria for adverse events
C_{trough}	trough concentration
CV%	coefficient of variation percentage
CYP	cytochrome P450
Cys12	cysteine at amino acid position 12
DCR	disease control rate
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
DOR	duration of response
DRM	drug-related material
Emax	maximal fold induction
DRT	data review team
EC	European commission
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EU	European Union
ER	exposure-response, efflux ratio
ERK	extracellular signal-regulated kinase
F	(absolute) bioavailability
F1	relative bioavailability
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded

FIH	first-in-human
FMI	Foundation Medicine
FTIR	Fourier transform infrared
f_u	unbound fraction
GDP	guanosine diphosphate
G12A	glycine 12 to alanine
G12C	glycine 12 to cysteine
G12D	glycine 12 to aspartic acid
G12R	glycine 12 to arginine
G12S	glycine 12 to serine
G12V	glycine 12 to valine
G13D	glycine 13 to aspartic acid
G13S	glycine 13 to serine
G13V	glycine 13 to valine
GENIE	Genomics Evidence Neoplasia Information Exchange
GFR	glomerular filtration rate
GLP	God Laboratory Practice
GST	glutathione transferase
HDPE	High-density polyethylene
HER2	human epidermal growth factor receptor 2
hERG	human ether-à-go-go-related gene
HLMs	human liver microsomes
HPLC	high pressure liquid chromatography
HRAS	Harvey rat sarcoma viral oncogene homolog
I	inhibitor concentration
$[I]_{50}$	apparent binding affinity
IC_{50}	half maximal inhibitory concentration
ICH	International Council for Harmonisation
I_{max}	maximal inhibition
INN	International Nonproprietary Name
INR	International normalized ratio
ISS	integrated summary of safety
I_{total}	total inhibition
IV	intravenous
K_a	absorption rate constant
k_i	inhibition constant
KIM-1	kidney injury molecule 1
k_{obs}	observed rate of covalent bond formation
k_{inact}	rate of enzyme inactivation
KRAS	Kirsten rat sarcoma viral oncogene homolog (protein)
KRAS	Kirsten rat sarcoma viral oncogene homolog (DNA)
KRASG12C	KRAS protein with a G12C amino acid substitution
LC-MS/MS	Liquid chromatography mass spectrometry
LDPE	Low-density polyethylene
LLOQ	lower limit of quantitation
LoQ	list of questions
MAA	marketing authorisation application
MATE	multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
MEK	MAP kinase
MRI	magnetic resonance imaging
MS	Mass spectrometry
MTD	maximum tolerated dose
NE	not evaluable
NGS	Next-Generation Sequencing
NMR	Nuclear Magnetic Resonance
NOR	Normal Operating Range
NSCLC	non-small cell lung cancer
OAT	organic anion transporter
OATP	organic anion transporter
OFV	objective function value
OCT	organic cation transporter
ORR	objective response rate
OS	overall survival

PAR	Proven Acceptable Range
PBPK	physiologically based pharmacokinetic model
PCR	polymerase chain reaction
pcVPC	prediction corrected visual predictive check
PD	pharmacodynamic(s)
PD-1	programmed cell death-1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PI3K	phosphoinositide 3-kinase
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PO	oral(ly)
PPI	proton pump inhibitor
PPK	population pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcomes
PT	prothrombin time
PTT	partial thromboplastin time
PXR	pregnane X receptor
QD	once daily
Q3W	every three week
QTc	corrected QT (interval)
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	response evaluation criteria in solid tumors
RGQ	Rotor-Gene Q
RNA	ribonucleic acid
ROS1	proto-oncogene tyrosine-protein kinase ROS
RP2D	recommended phase 2 dose
RWD	real world data
rwPFS	real-world progression-free survival
SCS	summary of clinical safety
SD	standard deviation
SmPC	summary of product characteristics
STK11	serine/threonine kinase 11
ss	steady state
TBIL	total bilirubin
TDI	time-dependent inhibition
TGI	tumour growth inhibition
$t_{1/2,z}$	terminal half-life
TKI	tyrosine kinase inhibitor
t_{max}	time to achieve Cmax
TMB	tumor mutational burden
TPS	tumor proportion score
TP53	tumor protein 53
TRAE	treatment related adverse event
TTR	time to response
UDP	uridine diphosphate
UGT	uridine 5'-diphospho-glucuronosyltransferase (UDP-glucuronosyltransferase)
ULN	upper limit of normal
USP	United States Pharmacopeia
V_{ss}	volume of distribution at steady state
WT	wild-type

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Amgen Europe B.V. submitted on 18 December 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Lumykras, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 12 December 2019.

The applicant applied for the following indication:

"Lumakras is indicated as monotherapy for the treatment of adult patients with previously treated KRAS G12C mutated locally advanced or metastatic non-small cell lung cancer (NSCLC)."

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0091/2020 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. Conditional marketing authorisation

The applicant requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of the above-mentioned regulation.

1.5.2. New active Substance status

The applicant requested the active substance sotorasib contained in the above medicinal product to be

considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the approved indication from the CHMP:

Date	Reference	SAWP co-ordinators
25/07/2019	EMA/CHMP/SAWP/400744/2019	Dr Kristian Wennmalm and Dr Paolo Foggi
17/10/2019	EMA/CHMP/SAWP/551987/2019	Prof. Flora Musuamba Tshinanu and Dr Armin Koch
30/01/2020	EMA/CHMP/SAWP/26316/2020	Dr Paolo Foggi and Dr Olli Tenhunen
31/01/2020	EMA/CHMP/SAWP/25062/2020	Ms Audrey Sultana and Dr Linda Trauffler

The scientific advice pertained to the following quality and clinical aspects:

- starting materials for commercial manufacture of DS; the use of clinical DS for the DP PPQ campaigns; the proposed PPQ plan and concurrent DS validation approach; the stability data package for drug substance and drug product; the data to support registration of all three DS manufacturing sites; the control strategy for mutagenic impurities;
- the proposed approach to investigate the potential for drug-drug interactions, the need for ADME studies, the approach to assess the potential for QT prolongation and the effect of altered renal and hepatic function on the pharmacokinetics (PK) of AMG 510 using population PK modelling;
- the existence of an unmet medical need in patients with previously treated KRAS p.G12C mutated locally advanced or metastatic NSCLC, and whether AMG 510 treatment could fulfil the unmet need;
- the design of the phase 1/2 study 20170543 to support a Conditional Marketing Authorisation (CMA) based on the anticipate effect size in terms of ORR;
- the use of Real World Evidence (RWE) regarding treatment outcomes in patients with KRAS p.G12C mutation treated with currently available therapies;
- the size of the overall safety database to support a CMA;
- the study design for the planned phase 3 randomised clinical study 20190009, in particular: the eligibility criteria, the use of docetaxel as comparator, the choice of endpoints, the statistical analysis plan and interim analyses, the relevance of the proposed patient-reported outcome (PROs) measures.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau Co-Rapporteur: Johanna Lähteenvuo

The application was received by the EMA on	18 December 2020

The procedure started on	21 January 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	13 April 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 April 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	26 April 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	20 May 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	14 July 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	28 October 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	02 September 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	16 September 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	11 October 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	28 October 2021
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Lumykras on	11 November 2021
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	11 November 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant is seeking a conditional marketing approval (CMA) for the medicinal product Lumykras (sotorasib) with the following clinical indication: as monotherapy for the treatment of adult patients with previously treated *KRAS G12C* mutated locally advanced or metastatic non-small cell lung cancer (NSCLC).

2.1.2. Epidemiology and risk factors

NSCLC is the most common type of lung cancer covering approximately 84% of all lung cancers. In 2020, lung cancer is the leading cause of cancer death with over 257 000 deaths across the European Union (EU) (JRC, 2020). NSCLC is the most frequent lung cancer subtype and patients with advanced NSCLC (stage IIIB and IV) have a low 5-year survival rate of 5.2% (SEER, 2019). Advanced NSCLC is defined to include tumours ≥4 cm, T3 or T4 tumours (based on the American Joint Committee on Cancer, 6th edition), and/or tumours that received neoadjuvant chemotherapy, but also other criteria have been presented.

KRAS mutations are the most frequent gain-of-function alterations in patients with advanced NSCLC being more common in the lung adenocarcinoma (LADC) and Caucasians. Altogether, KRAS mutations occur in 20–40% of lung adenocarcinomas and approximately 42% of the KRAS related lung cancers harbour G12C mutation with only 10% of NSCLC in the Asian patients harbouring this mutation. The estimated incidence of KRAS mutations is up to 25–35% in smokers (Dearden et al, Ann Oncol 24, 2013) with KRAS p.G12C found more often among the former or current smokers (Dogan S et al, Clin Cancer Res 18, 2012), while the other KRAS mutation subtypes p.G12D and p.G12A are met more often in non-smokers (Dogan S et al, Clin Cancer Res 18, 2012; Riely GJ et al, Clin Cancer Res 14, 2008). The smokers have also been reported to have more often complex KRAS-mutant tumours, higher mutational burden, and higher frequency of major co-occurring mutations in TP53 or STK11. The age, gender, or the duration of smoking is not associated with KRAS mutation incidence (Riely GJ et al, Clin Cancer Res 14, 2008). KRAS mutations are ethnicity driven, since they are found in only 10% of Asian patients.

2.1.3. Biologic features

The RAS family of proto-oncogenes consists of 3 closely related genes that encode guanosine triphosphatases (GTPases) responsible for regulating cellular proliferation and survival (Simanshu DK et al, Cell 2017; Barbacid M, Annual rev Biochem 1987). Different tumour types are associated with mutations in certain isoforms of RAS, with Kirsten rat sarcoma viral oncogene homolog (KRAS) being the most frequently mutated isoform in most cancers (Prior IA et al, Cancer Res 2012).

Of the KRAS mutations, an estimated 80% occur at codon 12. The KRAS p.G12C structural change results in a defect in the association of guanosine triphosphatase-activating proteins (GAPs), thereby reducing the hydrolysis of guanosine triphosphate (GTP) by the KRAS protein. The resulting accumulation of active, GTP-bound KRAS leads to proliferative and survival signalling in tumour cells (Jones RP et al, Br J Cancer 2017).

Of the KRAS-related lung cancers approximately 42% are related to G12C mutation, while the proportion of other KRAS mutations G12V, G12D, G12A and other G12 and G13 mutations is 21%, 17%, 10% and 12% of cases, respectively (Dogan S et al. Clin Cancer Res 2012). The KRAS mutation rate is estimated to be 10- to 100-fold that of EGFR-mutated or KRAS wild-type tumours having high correlation with the STK11 and P53 mutations (Dogan S et al, Clin Cancer Res 2012 and Imielinski M et al, Cell 2012).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

NSCLC patients who are positive for KRAS mutations are typically white and have a history of cigarette smoking. Age, gender, or the number of pack-years are not associated with KRAS mutation incidence. Higher proportions of women, former or current smokers, and non-squamous cell carcinoma histology are observed in the patients with KRAS p.G12C-mutated advanced NSCLC. (Sattler et al., 2021)

For patients with lung cancer, the most significant symptoms affecting their daily lives have been identified as fatigue, shortness of breath, and chronic pain. Other symptoms include insomnia, anxiety, and depression (US FDA, 2013, Liao et al, 2011; Tishelman et al, 2007; Tishelman et al, 2005; Cooley et al, 2003; Study 20200090).

The literature is not conclusive about the prognostic of patients with KRAS-mutated NSCLC, including KRAS p.G12C-mutated NSCLC. Some studies reported no prognostic difference with the overall patient with advanced NSCLC (Sattler et al., 2020) whereas in others KRAS mutations have been considered to be associated with poorer prognosis and have been estimated to lead to a 30% relative mortality over-risk (Mascaux C et al, Br J Cancer 2005 and Meng D et al, Lung Cancer 2013). Furthermore, types of mutated codons seem to have a prognostic value with codon 12 mutations appearing to be a more potent oncogenic driver compared to the codon 13 mutations with a higher level of resistance to apoptosis and a predisposition to anchorage-independent growth (Guerrero S et al, Cancer Res. 2000). KRAS mutations have also been assumed to present a negative predictive role of responsiveness and to chemotherapy (Macerelli M et al, Lung Cancer 2014).

2.1.5. Management

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

The National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) treatment guidelines call for testing of all patients with NSCLC for oncogenic driver mutations (Ettinger et al, 2019; Planchard et al, 2018). However, KRAS mutations are qualified as an undruggable target and no anticancer therapies are currently approved in the EU for the treatment of patients with NSCLC that specifically target tumours that have the KRAS p.G12C mutation (Román et al, 2018; McCormick, 2016). Further, oncogenic KRAS mutations rarely occur concomitantly with these other actionable oncogenic mutations (Studies 20200097, 20180277, and 20190344; Scheffler et al, 2019; Martorell et al, 2017; Gainor et al, 2013). Thus, most patients with oncogenic KRAS mutations, including the KRAS p.G12C mutation, are not candidates for currently approved targeted therapies and consequently are typically treated as patients without targetable mutations (i.e. with chemotherapy, immunotherapy, or antiangiogenic agents) (Planchard et al, 2018; Van Cutsem et al, 2014).

In first-line therapy, patients with NSCLC without actionable oncogenic driver mutations are typically treated with checkpoint inhibitors with or without platinum-containing doublets chemotherapy such as

cisplatin/pemetrexed. Patients requiring subsequent second-line or later therapy are commonly treated with taxane chemotherapy with or without a vascular endothelial growth factor (VEGF) inhibitor or checkpoint inhibitors/platinum-containing doublet chemotherapy (if not already given in first line).

Standard-of-care outcomes for patients with advanced/metastatic NSCLC (who are not candidates for currently approved targeted therapy) in ≥ second-line therapies, who had received first-line platinum-containing chemotherapy doublets (typically cisplatin/pemetrexed), have demonstrated objective response rates (ORRs; objective response = complete response + partial response) between 5.5% to 13% with chemotherapy (typically a taxane) and between 9.7% to 22.5% with chemotherapy plus a vascular endothelial growth factor receptor (VEGFR) inhibitor (Gridelli et al, 2018; Rittmeyer et al, 2017; Herbst et al, 2016; Borghaei et al, 2015; Herbst et al, 2007). These studies have also demonstrated progression-free survival (PFS) and overall survival (OS) of 2.8 to 4.2 months and 6 to 11.4 months, respectively, for chemotherapy alone and 4.8 to 5.4 months and 9.9 to 12.6 months, respectively, for chemotherapy with a VEGFR inhibitor. The treatment intent in 2nd line therapy is usually aimed to prolong life and alleviate symptoms caused by the advanced cancer. Second line therapy does not usually lead to permanent cure.

It has been debated in the literature whether the presence or absence of a KRAS mutation or the type of KRAS substitution, codon type or the presence of MASI has a differential benefit from adjuvant chemotherapy (Villaruz LC et al, Cancer 2013, Camps C et al, Lung Cancer 2011, Kalikaki A et al, Lung Cancer 2010). In these publications no significant difference were observed. However, the data from the French National Cancer Institute indicate that patients with KRAS-mutated NSCLC show a lower proportion of responses to cytotoxic chemotherapy and decreased survival compared with the overall population of patients with NSCLC (Barlesi et al, 2016), and this finding has been supported by other data indicating that patients with KRAS-mutated NSCLC have a poor prognosis (Wiesweg et al, 2019; Park et al, 2017; Hames et al, 2016; Svaton et al, 2016; Johnson et al, 2013). Similar findings were reported in Chinese patients, with a shorter median OS observed in patients with the KRAS p.G12C mutation compared with patients with wildtype tumours (Liu et al, 2020). The evaluation of patients with KRAS p.G12C-mutated NSCLC in Western populations showed that OS was similar with patients with other KRAS mutations (Arbour et al, 2020; Cui et al, 2020a; Cui et al, 2020b) and Japanese patients with the KRAS p.G12C or p.G12V mutation had a longer median PFS compared with patients with other KRAS mutations (Tamiya et al, 2020).

2.2. About the product

Sotorasib is a selective KRASG12C (Kirsten rat sarcoma viral oncogene homolog) inhibitor, which blocks tumour cell signalling and survival, inhibits cell growth, and promotes apoptosis selectively in tumours harbouring KRASG12C, an oncogenic driver of tumorigenesis across multiple cancer types. Sotorasib is bound both to the P2 pocket and the His95 surface groove, locking the protein in an inactive state that prevents downstream signalling. Sotorasib also enhance antigen presentation and inflammatory cytokine production and induce anti-tumour inflammatory responses.

The CHMP considers the following indication approvable:

Lumykras as monotherapy is indicated for the treatment of adults with advanced non-small cell lung cancer (NSCLC) with *KRAS G12C* mutation and who have progressed after at least one prior line of systemic therapy.

The recommended dose is 960 mg sotorasib (eight 120 mg tablets) once daily, at the same time each day.

Duration of treatment

Treatment with Lumykras is recommended until disease progression or unacceptable toxicity.

Missed doses or vomiting

If less than 6 hours have passed since the scheduled time of dosing, the patient should take the dose as normal. If more than 6 hours have passed since the scheduled time of dosing, the patient must not take the dose. Treatment should be continued as prescribed the next day.

If vomiting occurs after taking Lumykras, the patient must not take an additional dose on the same day, and treatment must be continued as prescribed the next day.

Dose modifications

Dosing should be modified based on Lumykras toxicity. The dose reduction rules outlined in section 4.2 are based on clinical data. Pharmacokinetic data do suggest a similar exposure at lower sotorasib doses. Dose reduction levels are summarised in table 1. Dose modifications for adverse reactions are provided in table 2.

If toxicity events occur, a maximum of two dose reductions are permitted. Lumykras must be discontinued if patients are unable to tolerate the minimum dose of 240 mg once daily.

Table 1: Recommended sotorasib dose reduction levels

Dose reduction level	**Dose**
Starting dose	960 mg (eight 120 mg tablets) once daily
First dose reduction	480 mg (four 120 mg tablets) once daily
Second dose reduction	240 mg (two 120 mg tablets) once daily

Table 2: Recommended dose modifications for sotorasib

Adverse reaction	**Severity**[a]	**Dose modification**
Hepatotoxicity	Grade 2 AST or ALT with symptoms or Grade ≥ 3 AST or ALT	• Stop treatment until recovered to ≤ grade 1 or to baseline grade • After recovery, resume treatment at the next dose reduction level
	AST or ALT > 3 × ULN with total bilirubin > 2 × ULN, in the absence of alternative causes	• Permanently discontinue treatment
Interstitial Lung Disease (ILD)/ pneumonitis	Any grade	• Stop treatment if ILD/pneumonitis is suspected. • Permanently discontinue treatment if ILD/pneumonitis is confirmed.
Nausea, vomiting, or diarrhoea persisting despite supportive care (including anti-emetic or anti-diarrhoeal therapy)	Grade ≥ 3	• Stop treatment until recovered to ≤ grade 1 or to baseline grade • After recovery, resume treatment at the next dose reduction level
Other medicinal product-related toxicity	Grade ≥ 3	• Stop treatment until recovered to ≤ grade 1 or to baseline grade • After recovery, resume treatment at the next dose reduction level

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal
[a] Grading defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0

Method of administration

Lumykras is for oral use. The tablets must be swallowed whole. There are no data to support the administration of Lumykras if the tablets are chewed, crushed, or split but the tablets can be dispersed in water (see below). The tablets can be taken with or without food.

Administration to patients who have difficulty swallowing solids

Patients should disperse tablets in 120 mL of non-carbonated, room-temperature water, without crushing them. Other liquids must not be used. Patients should stir until tablets are dispersed into small pieces (the tablet will not dissolve completely) and drink immediately. The appearance of the mixture may range from pale to bright yellow. The container must be rinsed with an additional 120 mL of water, which should be drunk immediately. If it is not drunk immediately, patients must stir again to ensure that the tablets are dispersed. The dispersion must be discarded if it is not drunk within 2 hours.

2.3. Type of application and aspects on development

The applicant requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.

The applicant considers that the benefit risk is positive based on:

Efficacy: ORR of 37.4% (95% CI: 28.8, 46.6), which was durable, with a median (95% CI) DOR of 8.4 (6.9, 8.4) months. The applicant considers that the ORR, exceeding the pre-specified benchmark for Study 20170543, which was based on the ORR observed for the pivotal study with ramucirumab combined with docetaxel, demonstrates the clinical benefit of Lumykras treatment.

Safety: Sotorasib was generally safe and well tolerated, based on the evidence currently available from the total safety population enrolled in clinical trials. It is considered that the risks associated with sotorasib can be managed through routine pharmacovigilance and risk communication through the proposed prescribing information, labelling, and packaging.

- It is likely that the applicant will be able to provide comprehensive data.

The proposed confirmatory trial is an ongoing Phase 3 study (Study 20190009; CodeBreaK 200, N=approximately 330), 2-arms, randomised, open-label trial of the safety and efficacy of sotorasib monotherapy administered at 960 mg QD daily and docetaxel administered at dose of 75 mg/m2 over 1 hour every 3 weeks for a treatment cycle of 21 days for subjects with previously treated advanced NSCLC with the KRAS p.G12C mutation. The first patient was enrolled in the 4th of June 2020 and the enrolment is expected to be complete in Q4 2021. Primary PFS analysis and interim OS analysis (67% of events) is anticipated in Q1/early Q2 2022.Several immunotherapies and pemetrexed chemotherapy have been approved recently. The efficacy and safety of these novel therapeutic agents in the current subset of patients is not yet well-known. Therefore, the applicant claims that docetaxel represents a reasonable and valid alternative for the comparator in Phase 3 trial representing Standard of Care (SOC) in the second line treatment after the first line therapies, such as platinum doublet and checkpoint inhibitor with or without platinum-containing doublets chemotherapy, have been given.

- Unmet medical needs will be addressed, as:

No inhibitors specifically targeting KRAS p.G12C mutations have been successfully developed until recently. The applicant claims that oncogenic KRAS mutations, including the KRAS p.G12C mutation, rarely occur concomitantly with other actionable mutations. In studies 20180277 and 20200097, EGFR mutations were observed in 0.2 - 1.2% of patients, ROS1 mutations in 0.2 - 0.3%, and BRAF mutations

in 0.9-1.0%, and no ALK alterations were reported. A low number of subjects enrolled in phase 2 of Study 20170543 had co-mutations (10.3% of subjects for TP53, 5.6% for serine/threonine kinase 11(STK11), 2.4% for EGFR, and 1.6% all other co-mutations; no subjects had co-mutations in ALK or ROS. Most patients with oncogenic KRAS mutations, including the KRAS p.G12C mutation, are thus not candidates for currently approved targeted therapies and consequently are typically treated as patients without targetable mutations (i.e., with chemotherapy, immunotherapy, or antiangiogenic agents). The applicant has provided an overview of available treatment options for patients with previously treated KRAS p.G12C mutated advanced NSCLC, including afatinib, docetaxel, erlotinib, nintedanib/docetaxel, pemetrexed, ramucirumab/docetaxel; and for patients not previously treated with the check-point inhibitors, atezolizumab, nivolumab, and pembrolizumab. The ORR in the provided studies varies between 4.7-20%, with highest response rate reported for ramucirumab/docetaxel (22.9%).

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

The durable ORR observed could be expected to translate to a favourable OS for treated patient when compared to current available treatments for patients with previously-treated KRAS p.G12C-mutated locally advanced or metastatic NSCLC.

A Conditional Approval of sotorasib would make available a treatment with a potential major therapeutic advantage versus currently available therapies, with compelling evidence of anti-tumour activity and a tolerable safety profile. Sotorasib would otherwise not be available to patients until comprehensive data are available, anticipated to be Q1/Q2 2022. The applicant claims that the current treatment would offer an additional option after treatment attempts with other therapies have been failed.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablet containing 120 mg of sotorasib.

Other ingredients are: microcrystalline cellulose, (E460(i)), lactose monohydrate, croscarmellose sodium (E468), magnesium stearate (E470b). Components of the film-coating agent are: polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 4000 (E1521), talc (E553b) and iron oxide yellow (E172).

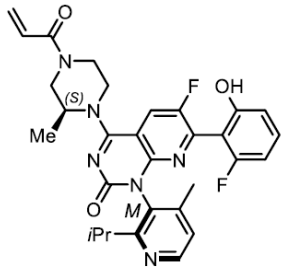
The product is available in PVC/PE/PVDC blisters with aluminium foil backing or in HDPE bottle with a child-resistant polypropylene cap and aluminium foil induction seal liner, as described in section 6.5 of the SmPC.

2.4.2. Active substance

General information

The chemical name of sotorasib is 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1M)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2S)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]pyrido[2,3-d]pyrimidin-2(1H)-one corresponding to the molecular formula $C_{30}H_{30}F_2N_6O_3$. It has a relative molecular mass of 560.6 and the following structure:

Figure 1: **Active substance structure**



The chemical structure of sotorasib was elucidated by a combination of elemental analysis, NMR analysis (^{1}H, ^{13}C, ^{15}N, and ^{19}F NMR), mass spectroscopy, absorption ultraviolet/visible, infrared spectroscopy and single crystal X-ray diffraction. The solid-state properties of the active substance were measured by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and dynamic vapor sorption (DVS).

Sotorasib is a white to off-white to yellow to light brown powder. Sotorasib is slightly hygroscopic. The solubility of sotorasib is highest at pH 1.2, very slightly soluble at pH 3.6 and practically insoluble over a pH range of 4.6 to 6.8. Given its low solubility and high permeability, sotorasib is classified as a BCS Class 2.

Sotorasib exhibits stereoisomerism due to the presence of two chiral centres. Enantiomeric purity is controlled at the level of the starting materials and active substance specification (by chiral HPLC).

Polymorphism has been observed for sotorasib. Sixteen crystalline forms, including 3 anhydrous forms and 13 solvate forms, have been discovered to date. Based on crystal form screening and characterisation studies, sotorasib anhydrous free base Form I, the desired form for this MAA, was determined experimentally to be the most thermodynamically stable form.

Manufacture, characterisation and process controls

Sotorasib is synthesised in five main chemical steps; the synthesis uses commercially available well-defined starting materials with acceptable specifications.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme. The types of bond connections and order of reaction steps have remained unchanged over the course of development. Process development changes have consisted of changes to solvents, reagents, processing conditions, and starting materials. Similar impurity profiles are observed for batches produced using the previous and the current commercial processes. Changes introduced have been presented in sufficient detail and have been justified.

The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process. Additionally, it is has been shown that one form has been consistently produced throughout the development of the manufacturing process of the active substance.

The active substance is packaged in double low-density polyethylene (LDPE) bags, closed with a cable tie, the LDPE bags comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance release and stability specification includes tests for description, identification (FTIR), enantiomer identification (HPLC/RT), assay (HPLC), organic impurities (HPLC), chiral impurities (HPLC), residual solvents (GC), residue on ignition (ph. Eur.), elemental impurities (ICP-MS, Ph. Eur.), trifluoroacetic acid (IC) and particle size distribution (laser diffraction measurement, Ph. Eur.).

Impurities above the qualification threshold of ICH Q3A have been qualified at the established levels using data from preclinical safety studies. With regards to mutagenic impurities, a hybrid ICH S9/ICH M7 approach has been applied. Since ICH M7(R1) guideline does not apply to active substances and finished products intended for advanced cancer indications, this is accepted as it is more restrictive than the requirements. Only the solvents used in the last steps of the commercial process are routinely controlled in line with ICH Q3C (option 1).

A test for particle size (PSD) was added in the active substance specification during the procedure The whole control strategy for the polymorphic form is considered adequate. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data (7 commercial scale batches) of the active substance, per active substance manufacturer, are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from six commercial batches of active substance from the proposed manufacturers stored in in a container closure system representative of that intended for the market for up to 18 months under long term conditions (30ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* assay (HPLC), organic impurities (HPLC), chiral impurities (HPLC), water content (Karl fisher, Ph. Eur.), and visual appearance. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications. No trend of degradation is observed.

Photostability testing following the ICH guideline Q1B was performed on one batch of the active substance. Sotorasib as solid state is susceptible to colour change under stressed 3 x ICH light conditions. However, no change in purity, assay, mass balance, or peak purity was observed under these conditions.

Results on stress conditions (hydrolytic, oxidative, thermal) were also provided on one batch of the active substance. All stressed samples were evaluated for changes in physical appearance, impurity profile, assay, mass balance, and sotorasib peak purity in comparison with the unstressed controls. Sotorasib in solution exhibits significant degradation when exposed to hydrolysis (acidic and basic) and oxidative degradation. The main degradation product observed is 3368167 (DS Dione). Sotorasib as solid state is not degraded under heat and humidity.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 24 months when stored below 30°C, protected from light, in the proposed container.

2.4.3. Finished medicinal product

Description of the product and pharmaceutical development

The finished product is an immediate-release film-coated tablet containing 120 mg of sotorasib.

The dosage form is a yellow oblong (7 mm × 16 mm) tablet debossed with "AMG" on one side and "120" on the opposite side.

The composition of the finished product is presented.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards, with the exception of iron oxide yellow, which complies with NF and JPE, this is acceptable. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The dosage form has been developed for the adult population. The recommended daily dose is 960 mg sotorasib (eight 120 mg tablets) once daily; the dose is reduced on an individual basis, down to 240 mg once daily (two 120 mg tablets), based on the toxicity experienced by the patient. The administration of eight concomitant tablets is not ideal; the applicant is recommended to develop a presentation with higher drug load to allow for fewer tablets per dose. For patients having difficulty to swallow, an alternative method of administration by dispersing the tablets in water is proposed. Additionally, the applicant is recommended to conduct a feasibility study of sotorasib 120 mg film-coated tablets administration through an enteral feeding tube for adult patients within 6 months of approval of the MAA. In consideration of the therapeutic indication, and given the possible alternative administration method, the formulation is considered acceptable.

Development studies support the PI information regarding dispersion of tablets. Only water should be used as dispersion medium, as the active substance degrades in acidic conditions, hence fruit juices are not suitable. Since the PI stated that '..tablets are in small pieces (the tablet will not completely dissolve)' the Ph. Eur. requirement for fineness of the dispersion can be waived for this immediate release pharmaceutical form. Stability data support the two-hour in-use period, as proposed in the SmPC, of the dispersed tablets.

Uncoated tablets were used in Phase 1 and early Phase 2 studies. During Phase 2, the proposed commercial film-coated tablet was introduced to support on-going Phase 1 and Phase 2 clinical studies. The same core tablet formulation has been used throughout clinical trials. The core tablets were manufactured using the same dry granulation by roller compaction. The formulation used during the pivotal clinical studies is the same as that intended for marketing.

The pharmaceutical development of the finished product contains QbD elements. In addition to traditional manufacturing process optimisation, consisting of univariate experiments (initial blending, roller compaction, final blending/lubrication, compression) and scale-up studies, the formulation and manufacturing development have been evaluated through the use of the use of risk assessment design of experiments (DoE) to identify the critical product quality attributes and critical process parameters. In one DoE study the effect of the active substance particle size and the amount of the excipients croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, and magnesium stearate (extra-granular) on manufacturing process and on the finished product characteristics was evaluated. The amount of excipients in the formulation was optimised. Different particle sizes lead to different dissolutions profiles of the finished product. The particle size distribution impact on PK values (i.e., C_{max} and AUC) was further assessed using GastroPlus software, which indicated that the differences in dissolution observed for the batches manufactured with large particle size may not be significant *in vivo*. However, considering the low solubility of the active substance, a specification limit for active

substance PSD, in line with particle size tested clinically, has been added to the active substance specification.

In a second DoE the spray rates and exhaust temperatures of the final coating were evaluated; all batches had acceptable coating quality. Supplementary information has been provided during the procedure regarding the polymorphism of the active substance in the finished product, which further confirms the consistency, stability and adequate monitoring of polymorph I.

The critical process parameters have been adequately identified. The manufacturing process mainly includes target values for process parameters, with limited ranges corresponding to not more than normal variability; based on this process characterisation studies are considered sufficient and they adequately support the commercial manufacturing process operating conditions.

The QC dissolution conditions are considered acceptable. During the procedure a major objection (MO) was raised on the dissolution method conditions and specifications. The level of surfactant (0.2 %) has been thoroughly justified to address the MO: SDS levels below 0.2%, i.e. 0.1% and 0.15%, have been tested but were shown to be not sufficient to provide complete release in a reasonable timeframe. Solubility data in SDS 0.15% indicate that sink conditions are not met at this concentration in pH 6.8 buffer.

The discriminatory power of the dissolution method has been demonstrated by investigating tablets manufactured with active substance having a particle size outside the specification limits and with tablets subjected to humidity stress. Additionally, in order to provide greater discriminatory capacity, dissolution specification has been revised as requested as part of the MO raised on the dissolution method. The QC sampling point has been tightened from 30 minutes to 15 minutes with Q = 80%.

The primary packaging is PVC/PE/PVDC blisters with aluminium foil backing or HDPE bottle with a child-resistant polypropylene cap and aluminium foil induction seal liner. The material of both presentations complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. Child-resistance complies to ISO 8317.

Manufacture of the product and process controls

The manufacturing process is considered to be a standard manufacturing process.

Manufacturing process is adequately described. Sufficient details are provided, including equipment type and capacity, mesh screen sizes, and process parameters target values with normal operating ranges. Process robustness is supported by development data from the development to the commercial scale. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Validation batches will be completed prior to marketing. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification (HPLC/UV, HPLC/RT), assay (HPLC), organic impurities (HPLC), content Uniformity (HPLC, Ph. Eur.), dissolution (Ph. Eur.), water content (Karl Fisher, Ph. Eur.) and microbial limits (Ph. Eur.).

The tests and controls applied for the finished product at release and throughout shelf life are appropriate for the dosage form. The specifications comply with the Ph. Eur. requirements and with ICH guidelines. Several specification limits (assay, DS-dione, dissolution and water content) have been

tightened during the procedure and are considered acceptable. The lack of chirality test in the finished product specifications is supported as the risk of racemisation or epimerisation during the manufacturing process of the active substance and finished product is considered low, as also supported by batch data.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on 3 batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment, and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The same reference standards used in the active substance analysis are also used in the finished product and are considered satisfactory.

Batch analysis results are provided for 9 pilot scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three pilot scale batches (primary stability batches) for each presentation (blister and bottle) and additional supportive pilot scale batches (5 for the blister and 8 for the bottle) of finished product stored for up to 18 months (blister presentation) and 24 months (bottle presentation) under long term conditions (30ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing, were manufactured using active substance batches from both the active substance manufacturers and were packed in the primary packaging proposed for marketing.

Samples were tested for the shelf-life specification. The analytical procedures used are stability indicating. No significant changes have been observed.

In addition, 1 batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant were observed. Stress stability studies (60°C / 33% RH and 60°C / 75% RH for up to 4 weeks) was performed on one batch of the finished product; the results from the stress study showed that the film-coated finished product is stable with respect to temperature and slightly sensitive to humidity (assay and impurity results were within the specification limit). Samples were also exposed to forced degradation conditions: 85°C (1 week); 85°C (2 weeks); 85°C / 85% RH (1 week); 85°C / 85% RH (2 weeks); Light stressed (3 x ICH); 0.1 N HCl (24 Hrs.) neutralised; 0.1 N NaOH (2 Hrs.) neutralised; 20% H_2O_2 (24 hours). Through the forced degradation study, it was concluded that the main degradation pathways are hydrolysis and oxidation. Also, the

main peak remains spectrally pure in all the stressed samples. The results indicate that the HPLC method is specific and stability indicating and is suitable for release and stability testing.

Stability and stress data give no indication that the drug product is susceptible to deterioration. Each bottle contains 120 tablets which should cover 15 days of treatment; however, for patients with dose reduction, a bottle could be used up to 60 days (worst case). Based on stress studies and updated ICH long-term stability studies, justification that in-use stability studies do not need to be undertaken can be accepted.

Based on available stability data, the proposed shelf-life of 24 months and no special storage conditions, as stated in the SmPC (section 6.3), are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The MOs raised during the procedure on the redefinition of acryloyl chloride as starting material and on the choice of the conditions and acceptance criteria of the dissolution method have been adequately addressed.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to the development of a formulation with a higher drug load and the provision of studies to support administration through an enteral feeding tube for adult patients. These points are put forward and agreed as recommendations for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The applicant is recommended to:

1) To provide the data from a study to assess the feasibility of sotorasib 120 mg film-coated tablets administration through an enteral feeding tube for adult patients within six months from granting of the MAA.

2) To develop a higher drug load presentation to reduce the number of tablets needed for each single dose.

2.5. Non-clinical aspects

2.5.1. Introduction

Sotorasib is a potent and selective covalent inhibitor of KRASG12C and is being developed for the treatment of patients with advanced malignancies that have the p.G12C mutation of KRAS. Sotorasib binds irreversibly to the P2 pocket of KRASG12C through a novel interaction with the histidine 95 groove and a precise covalent reaction with cysteine. Binding of sotorasib locks KRASG12C in the inactive GDP bound conformation and prevents loading of GTP. This blocks the interaction with downstream effectors like RAF, thus preventing p-ERK.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In a biochemical assay (Study R20150198), sotorasib potently inhibited the activation of recombinant KRASG12C, but did not inhibit activation of WT KRAS. Sotorasib also potently inhibited MAPK signalling only in KRAS p.G12C-mutant cell lines (Study R20190078). It also impaired viability in all but one p.G12C-mutant cell lines and did not affect non p.G12C cell lines (Study R20150199).

In vivo sotorasib covalently modified KRASG12C and significantly inhibited p-ERK in human tumour xenografts at doses as low as 3 mg/kg (Studies R20150188 and R20190129). Sotorasib inhibition peaked at approximately 2 hours and persisted for at least 48 hours after a single dose. Sotorasib also significantly inhibited tumour growth at doses as low as 3 mg/kg and at 100 mg/kg achieved up to 62% tumour regression (Studies R20150189, R20150190 and R20150191). Sotorasib had no effect in non-KRAS p.G12C tumour models and did not impact body weight in any study. In a patient-derived xenograft (PDX) model of KRAS p.G12C colorectal carcinoma, sotorasib inhibited p ERK and tumour growth in a dose-dependent manner and resulted in 45% regression at 100 mg/kg (Study R20190131).

In combination studies, sotorasib displayed synergistic cell killing *in vitro* in multiple KRAS p.G12C cell lines with inhibitors of every tested node of the MAPK pathway upstream and downstream of RAS and with inhibitors of the AKT pathway (Studies 153397, R20180032, 153894). Significantly enhanced anti-tumour activity was also observed *in vivo* with combinations of sotorasib with inhibitors of EGFR/pan-ErbB, SHP 2, or MEK, and with carboplatin chemotherapy (Studies R20180033, 153358).

In a syngeneic murine colorectal tumour model (CT-26) engineered to endogenously express KRAS p.G12C, sotorasib treatment *in vitro* inhibited p-ERK and viability and also enhanced MHC class I antigen and inflammatory cytokine expression (Canon et al, 2019). Dosing of sotorasib in immunocompetent mice bearing CT-26 KRAS p.G12C tumours resulted in permanent complete regression of tumours in 80% of the animals (Study R20190128). Combination of sotorasib with an immune checkpoint inhibitor (anti-PD-1) significantly enhanced anti-tumour activity at a suboptimal dose of sotorasib (Canon et al, 2019). Mechanistic studies revealed that sotorasib treatment induced an inflamed tumour microenvironment by enhancing inflammatory cytokine production and MHC class I expression in the tumours, which led to infiltration of anti-tumour immune cell subsets including proliferating effector T cells, dendritic cells, and macrophages (Study R20180035). Rechallenge

experiments established that cured mice had developed an anti-tumour immune response to CT-26, irrespective of the KRAS mutation status (Canon et al, 2019).

2.5.2.2. Secondary pharmacodynamic studies

The general selectivity of sotorasib *in vitro* was assessed against various targets including receptors, enzymes, ion channels, and transporters; minimal activity was observed, suggesting sotorasib is highly selective for KRASG12C (Studies 124452 and 124453). In NCI-H358 cells, cysteine proteome profiling indicated that sotorasib engaged only the Cys12-contaning peptide from KRASG12C (Study R20150219; Patricelli et al, 2016).

2.5.2.3. Safety pharmacology programme

The sotorasib hERG IC50 was 54.8 µM (Study 150431); no clinically significant interaction with the hERG channel is expected over the proposed clinical dose range. *In vivo*, sotorasib at doses up to 300 mg/kg did not result in changes to qualitative ECG, quantitative ECG, or haemodynamic parameters in a GLP cardiovascular safety pharmacology study in telemetered dogs (Study 150458). Likewise, there were no effects on ECG parameters in the 28-day dog repeat-dose toxicology study. Overall, no cardiovascular concerns have been identified for sotorasib (Study 150429).

Human circulating metabolites (AMG3368167 [M24], AMG3375854 [M10], and AMG3413829 [M18]) were assessed for potential primary or secondary pharmacology effects and for effects on *in vitro* hERG potassium channel. Among the 3 metabolites, M18 has the same covalent warhead as sotorasib, while M24 and M10 lack it. Consistently, only M18 maintains primary pharmacology effects; however, the effect is markedly reduced when compared to sotorasib. Secondary pharmacology screenings for these 3 metabolites did not indicate any clinically relevant or significant off-target pharmacological activities although M24 at 10 µM showed 61.0 and 52.3 percent inhibition, respectively, for Neurokinin NK1 and NK2 receptors (Study 124807). *In vitro* hERG assays for these metabolites did not indicate any clinically relevant or significant interactions (Studies 124803 and 153419).

2.5.2.4. Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies have not been conducted.

2.5.3. Pharmacokinetics

The absorption, distribution, metabolism, excretion and PK characteristics of sotorasib were evaluated in mouse, rat, dog, and monkey. The analytical methods are generally well validated according to the FDA guideline. The methods are sensitive, selective, accurate, and reproducible. Sotorasib is stable during storage, processing, and analysis.

Sotorasib was readily absorbed after a PO dose to non-cannulated male and female rats and BDC male rats. The absorption of sotorasib was studied in mouse, rat, dog and monkey. Following oral administration, mean tmax of sotorasib ranged from approximately 0.25 to 1.2 hours in all species. Sotorasib exhibited low to moderate F_{oral} in mouse, rat, and dog; approximately 35% in mouse, 30% in rat, and 34% in dog.

Sotorasib biotransformation through primary glutathione conjugation was major and accounted for up to approximately 21% to 33% of the dose from intact male and female rats, respectively, and up to approximately 41% of the dose in male BDC rats. Sotorasib underwent biotransformation in dogs to eleven identified metabolites. The major circulating metabolite M24 was observed in all nonclinical

species, however the AUC of this metabolite varied between 33-391% of sotorasib AUC between species. The AUC of metabolite M12 (glutathione conjugate) varied from 46.9% in dogs to 37.3% of sotorasib AUC in monkeys.

Sotorasib and the main metabolites have a varying plasma protein binding profile. The free fraction of sotorasib to mouse, rat, dog, and human plasma across the concentration range tested varied less than 2-fold when comparing the human value to the values found with animal plasma (with an average *in vitro* unbound fraction of approximately 0.071, 0.054, 0.21, and 0.11 in mouse, rat, dog, and human. The metabolite M10 showed the highest fraction unbound at 50 µM, whereas the metabolite M18 showed the lowest fraction unbound at 50 µM and the highest at 1 µM.

Sotorasib exhibits moderate to high clearance, a moderate volume of distribution and a low to moderate bioavailability in nonclinical species. The $t_{1/2,z}$ of sotorasib in nonclinical species following intravenous administration ranged between 0.41 and 0.71 hours. Sotorasib and three of its metabolites (M10, M18, and M24) have moderate binding to plasma proteins and did not preferentially distribute into blood cells when assessed *in vitro* in rat, dog, and human, which indicates that plasma concentrations are suitable to assess exposure in human as well as rat and dog, which were the two nonclinical species used in repeat-dose toxicology studies.

A whole-body distribution study in male LE or male or female Sprague Dawley (SD) rats showed that [^{14}C]-Sotorasib-derived radioactivity distributed reversibly to most tissues after a single PO dose (60 mg/kg), with C_{max} occurring in most tissues at 0.5 hour postdose. Tissues with the highest sotorasib-related radioactivity exposures common to both rat strains were liver, kidney, thyroid, pancreas, exorbital lacrimal gland, and the intra-orbital lacrimal gland. Elimination of sotorasib-related radioactivity was nearly complete for most tissues by 336 hours postdose. By the final sampling time of 672 hours postdose, only highly perfused tissues including blood, kidney, lung, myocardium and spleen had measurable concentrations of sotorasib-related radioactivity. Sotorasib was highly permeable *in vitro* (5.67 x 10-6 cm/s – 11.2 x 10-6 cm/s) across polarised Madin-Darby canine kidney epithelial cells (MDCKII). Circulating metabolite M24 was also highly permeable *in vitro* (25.6 x 10-6 cm/s – 27.7 x 10-6 cm/s) across polarised MDCKII cells (Study 150563).

The metabolism of sotorasib was studied *in vitro* using pooled liver microsomes and hepatocytes. Metabolites M10, M18, and M24 were the predominant sotorasib metabolites formed using human hepatocytes. The *in vitro* sotorasib metabolites formed by pooled human liver microsomes and hepatocytes were also produced by pooled liver microsomes and hepatocytes from the rat and dog, the nonclinical species used in repeat-dose toxicology studies. No unique human metabolites of sotorasib were observed *in vitro*. All human *in vitro* metabolites of sotorasib were observed from *in vitro* incubations with rat and dog.

The metabolism and excretion of [^{14}C]-sotorasib were evaluated in non-cannulated male or female rats as well as in BDC male rats after a single PO dose of sotorasib (60 mg/kg). Overall, the data indicated that sotorasib was readily absorbed after an PO dose to non-cannulated male and female rats and BDC male rats, underwent extensive biotransformation, and was eliminated primarily by non-enzymatic conjugation and metabolic clearance; [^{14}C]-sotorasib-derived radioactivity was excreted primarily through biliary and faecal pathways. Biotransformation of sotorasib was mediated primarily by non-enzymatic glutathione conjugation, oxidation, and to a lesser extent, reduction and dealkylation. Secondary sotorasib metabolism was substantive and included amide hydrolysis, cysteine-conjugate cleavage, N-acetylation, methylation, glucuronidation, and sulfonation. Biotransformation of sotorasib through primary glutathione conjugation was major and accounted for up to approximately 21% to 33% of dose from intact male and female rats, respectively, and up to approximately 41% of dose in male BDC rats. Sotorasib metabolites originating from primary oxidation account for up to approximately 20% of dose in non-cannulated rats and for approximately 10% of dose in BDC rats. Reduction of the

sotorasib acrolein moiety account for up to approximately 10% of dose in non-cannulated male and female rats and approximately 2.7% of dose in BDC rats, whereas dealkylation at the piperazine moiety accounted for approximately 10 to 13% of dose in non-cannulated rats and for approximately 6% of dose in BDC rats.

The metabolism and excretion of [^{14}C]-sotorasib were evaluated in non-cannulated male and female dogs after a single PO (500 mg/kg) dose of sotorasib. Sotorasib accounted for 6.65% or 9.22% of total plasma radioactivity exposure in male and female dogs, respectively. Co-eluting sotorasib metabolites M10/M48 (des (methylpipe razinylpropenone [MPPO])-oxy-sotorasib dione glucuronide) and M24 accounted for 64.4% and 21.3%, respectively, of total plasma radioactivity exposure in male dogs and 60.2% and 20.2%, respectively, of total plasma radioactivity in female dogs. Overall, [^{14}C]-sotorasib-derived radioactivity was minimally absorbed and was eliminated predominantly as unchanged sotorasib in faeces following a single 500 mg/kg dose to male or female dogs.

Table 3: Pharmacokinetic parameter estimates of sotorasib metabolite M10, M18 and M24 in human, rat and dog

Metabolite	Molecular weight	Unbound fraction	Study 20190321	Study 20170543 (960 mg QD, N=4) [a]			Multiple vs 10 μM[e]	Rat mass balance study (152495) (60 mg/kg single dose)	
			Plasma TRA (%)	Day 1 C_{max} (ng/mL)	Day 8 C_{max} (ng/mL)	Day 8 C_{max} (μM)[d]		Male C_{max} (ng eq/mL)	Female C_{max} (ng eq/mL)
M10	681.76	0.026 [f]	26.8	1200 (2580, 138%)	2610 (3340, 79%)	0.73 (3.8)	14	6590	10800
M18	576.60	0.19 [b]	<5.0	830 (1000, 54%)	806 (848, 40%)	0.42 (1.4)	24	1730	1700
M24	424.41	0.3 [c]	7.81	470 (538, 56%)	1180 (1280, 44%)	0.072 (2.8)	138	568	375

$AUC_{0\text{-}24h}$ = area under the concentration-time curve from time 0 to 24 hours postdose; C_{max} = maximum observed drug concentration; CV = coefficient of variation; KRAS = Kirsten rat sarcoma viral oncogene homolog protein; PK = pharmacokinetic; QD = once daily; TRA = total radioactivity; t_{max} = time to reach C_{max} [a] Data presented as Geometric Mean (Mean, CV%) for all PK Parameters except for t_{max} which is presented as Median (Range). Values are reported to 3 significant figures except for t_{max} and CV% which are presented as 2 significant figures and the nearest integer, respectively.

[b] M10 showed nonlinear plasma protein binding with an *in vitro* unbound fraction of 0.16 at 1 μM, 0.19 at 5 μM, 0.29 at 20 μM, and 0.35 at 50 μM (Study 153486). [c] M18 showed nonlinear plasma protein binding, with an *in vitro* unbound fraction of 0.30 at 1 μM, 0.17 at 5 μM, 0.14 at 20 μM, and 0.050 at 50 μM (Study 153486). [d] unbound concentration (total concentration)

[e] Multiples of 10 μM used in the *in vitro* secondary/safety pharmacology screenings relative to unbound fraction of each metabolite in clinical[f] Study 150530

Mixed plasma matrix experiments were performed to characterise circulating metabolites after multiple doses of sotorasib in male or female rat, dog, or humans. Overall, the data presented in the mixed matrix experiments indicate that sotorasib underwent oxidative N-dealkylation, glutathione conjugation, oxidation, and to a lesser extent, hydrogenation, lysine conjugation, and glucuronide conjugation, with similar circulating metabolites observed across rat, dog, and humans.

In vitro experiments were run to characterise the enzymes or mechanisms involved with the formation of the sotorasib metabolites M12 (glutathione adduct) and M24 (oxidative dealkylation). *In vitro* studies using recombinant GSTs, human liver cytosol, or human liver S9 fractions demonstrated that M12 formation from sotorasib is primarily non-enzymatic (Michael addition), with limited contribution from GST enzymes. Formation of M24 from sotorasib was predominantly catalysed by CYP3A.

The potential for sotorasib to inhibit cytochrome P450 mediated metabolism was examined *in vitro* using HLMs. Sotorasib was shown to inhibit CYP2C8 (inhibition constant [K_i] = 25.6 μM), CYP2D6 (K_i =

18.2 μM), and CYP3A (K_i = 4.82 μM, midazolam; K_i = 17.8 μM, testosterone). Sotorasib was a time-dependent inhibitor of CYP3A with an inactivation constant (K_I) of 1.92 μM and k_{inact} of 0.016 min^{-1}. Sotorasib metabolite M24 was an inhibitor of CYP2B6 (K_i = 22.0 μM), CYP2C8 (K_i = 10.1 μM), CYP2C9 (K_i = 4.47 μM), CYP2C19 (K_i = 36.3 μM), CYP2D6 (K_i = 51.9 μM), and CYP3A (K_i = 14.5 μM, midazolam; K_i = 21.2 μM, testosterone). Sotorasib metabolite M24 was a time-dependent inhibitor of CYP3A with a K_I of 32.7 μM and k_{inact} of 0.010 min^{-1} *in vitro*. Sotorasib M18 was an inhibitor of CYP2C8 (IC_{50} = 68.11 μM), and CYP3A (IC_{50} = 28.40 μM, midazolam; IC_{50} = 26.68 μM, testosterone) and a time-dependent inhibitor of CYP3A (IC_{50} = 4.13 μM, midazolam; IC_{50} = 3.48 μM, testosterone) *in vitro*.

The potential for sotorasib and metabolite M24 to induce human cytochrome P450 isoforms was assessed *in vitro* after treatment of human hepatocytes in primary culture with sotorasib and M24. Following incubation with 0.0005 to 30 μM sotorasib for up to 72 hours, CYP3A4 mRNA levels increased by 8- to 37-fold with a mean EC_{50} of 1.12 μM; additionally, M24 incubation with 0.0005 to 30 μM for up to 72 hours increased CYP3A4 mRNA levels by 8- to 18-fold with a mean EC_{50} of 2.07 μM. Sotorasib was also an inducer of CYP2B6 (35% to 70% of positive control), CYP2C8 (11% to 55% of positive control), CYP2C9 (27% to 60% of positive control) and CYP2C19 (25% to 62% of positive control). Sotorasib M24 was an inducer of CYP1A2 (8% to 12% of positive control), CYP2B6 (28% to 46% of positive control), CYP2C8 (67% to 90% of positive control), CYP2C9 (38% to 54% of positive control) and CYP2C19 (50% to 60% of positive control).

The potential for sotorasib metabolites M10 and M18 to induce the expression of CYP1A2, CYP2B6, CYP3A4, CYP2C8, CYP2C9, and CYP2C19 was assessed *in vitro* in human hepatocytes across a concentration range of 0.1 to 100 μM (Study 153424). Sotorasib metabolite M10 showed the potential to induce CYP2B6 in two of the three hepatocyte donors tested, with respective EC_{50} and maximal fold induction (E_{max}) values of 30.4 to 34.7 μM and 2.55 to 2.74-fold. Sotorasib metabolite M18 showed the potential to induce CYP2B6 in one donor only, with respective EC_{50} and E_{max} values of 11.1 μM and 2.25-fold. Sotorasib metabolite M10 showed the potential to induce CYP3A4 in all three hepatocyte donors, with respective EC_{50} and E_{max} values of 31.8 to 36.0 μM and 14.1 to 36.3-fold. Sotorasib metabolite M18 also showed the potential to induce CYP3A4 in all three hepatocyte donors, with respective EC_{50} and E_{max} values of 10.4 to 14.0 μM and 3.59 to 6.65-fold. Sotorasib metabolite M10 showed the potential to induce CYP2C8 in all three hepatocyte donors, with respective EC_{50} and E_{max} values of 35.3 to 39.4 μM and 3.15 to 4.99-fold. Sotorasib metabolite M10 showed the potential to induce CYP2C9 in one hepatocyte donor, with respective EC_{50} and E_{max} values of 35.1 μM and 3.16-fold, respectively.

In vitro, sotorasib is a P-gp substrate (net efflux ratio [ER] = 57.8 ± 5.82); thus, active transport by P-gp may affect sotorasib absorption and elimination (Study 150540). Sotorasib is not a BCRP substrate *in vitro*. Sotorasib was characterised as an *in vitro* inhibitor of human OATP1B1 (IC_{50} = 29.3 μM), MATE1 (IC_{50} = 0.440 μM), MATE2-K (IC_{50} = 2.39 μM), and P-gp (IC_{50} = 60.2 μM) (Study 150539). Incomplete inhibition curves for sotorasib (concentration-dependent loss in activity observed with greater than 25% activity remaining at the highest concentration tested) was observed up to the highest test concentration for human OAT1 (IC_{50} = 64.7 μM), OAT3 (IC_{50} = 42.8 μM), OCT1 (IC_{50} = 58.3 μM), OATP1B3 (IC_{50} = 54.2 μM), and BCRP (IC_{50} = 120 μM) *in vitro*.

Sotorasib metabolite M24 was characterised as an *in vitro* inhibitor of human OAT1 (IC_{50} = 10.2 μM), OAT3 (IC_{50} = 5.28 μM), OATP1B1 (IC_{50} = 6.63 μM), OATP1B3 (IC_{50} = 31.8 μM), MATE1 (IC_{50} = 0.632 μM), and P-gp (IC_{50} = 41.1 μM). Incomplete inhibition curves for sotorasib metabolite M24 (concentration-dependent loss in activity observed with greater than 25% activity remaining at the highest concentration tested) were observed up to the highest test concentration for human MATE2-K (IC_{50} = 81.2 μM) and BCRP (IC_{50} = 72.7 μM) *in vitro*.

The potential for two additional metabolites of sotorasib, M10 and M18, to cause transporter-mediated DDI was evaluated *in vitro*. M10 was characterised as *in vitro* inhibitor of human OAT3 (IC_{50} = 32.6 μM) and MATE2-K (IC_{50} = 18.5 μM) (Study 153425). Incomplete inhibition curves for SOTORASIB metabolite M10 (concentration-dependent loss in activity observed with greater than 25% activity remaining at the highest concentration tested) were observed up to the highest test concentration for human MATE1 (IC_{50} = 46.6 μM) *in vitro*. Sotorasib metabolite M18 was characterised as *in vitro* inhibitor of human OAT3 (IC_{50} = 5.86 μM), OCT1 (IC_{50} = 12.7 μM), OATP1B1 (IC_{50} = 11.6 μM), OATP1B3 (IC_{50} = 17.9 μM), and MATE1 (IC_{50} = 7.53 μM). Incomplete inhibition curves for M18 (concentration-dependent loss in activity observed with greater than 25% activity remaining at the highest concentration tested) were observed up to the highest test concentration for human OAT1 (IC_{50} = 76.2 μM) and MATE2-K (IC_{50} = 21.3 μM) *in vitro*.

Information on observed concentrations of sotorasib from clinical studies (C_{max} = 9.12 μg/mL, Study 20170543) were integrated with measured *in vitro* and kinetic parameters to estimate DDI risk for both CYPs and transporters; estimates were only carried out for CYPs or transporters where inhibition was observed *in vitro*.

Initial DDI risk estimates were calculated using basic models of reversible inhibition, as described in the EMA and FDA Guidance on Drug Interactions (FDA, 2020; EMA, 2013). For CYP2C8 and CYP2D6, estimates based mechanistic static models or physiologically based pharmacokinetic modeling, respectively, indicated that a clinical study was not necessary, as estimated increases in AUC upon co-administration with CYP-isoform selective substrates were within the 1.25-fold criteria defined by the EMA and FDA guidance. For CYP3A, a clinical study was run due to the complex nature of the anticipated DDI (simultaneous CYP inhibition, inactivation, and induction). For transporters, estimated DDIs for BCRP, MATE-1, MATE-2K, and P-gp exceeded the recommended guidance thresholds; clinical DDI studies for MATE-1/MATE-2K and P-gp were run.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Single-dose toxicity studies were not conducted.

2.5.4.2. Repeat dose toxicity

The repeat dose toxicological assessment of sotorasib has been conducted in the Rat/Sprague Dawley and Dog/Beagle by oral gavage administration of sotorasib up to 3 months duration (including supportive toxicokinetic evaluations).

Two repeat dose GLP studies evaluated the potential toxicity and measured toxicokinetics of sotorasib in Sprague Dawley rats when administered by daily oral dosing up to or 200 mg/kg for 28 days (followed by a 28-day recovery) and up to 750 mg/Kg for 3-month (followed by 2-month recovery).

The administration of sotorasib by once daily oral gavage was well tolerated in animals dosed up to 200 mg/kg (the highest dose in the 28 day-study) and up to 180 mg/Kg (the mean dose tested in the 3-month study).

The kidney was identified as a target organ of toxicity in the rat. Minimal to moderate degeneration/necrosis of renal tubular epithelium was observed. The incidence and severity of tubular degeneration/necrosis were generally dose dependent and involved primarily the outer stripes of the outer medulla of the kidney.

At the severely toxic dose in 10% of the rats (STD10; 180 mg/Kg) determined in the 3-month repeat dose study, mild tubular degeneration/necrosis were accompanied by morphologic features in the tubular epithelium involving large portions of the outer and/or inner stripes of the outer medulla (OSOM and ISOM, respectively). In the OSOM, there was cytoplasmic basophilia with or without focal necrosis of isolated or small segments of tubular epithelium. In the ISOM, there was scattered acute necrosis of tubule epithelium characterised by shrunken hypereosinophilic cytoplasm and pyknotic nuclei. Moderate tubular degeneration was accompanied with tubular necrosis in the OSOM, characterised by numerous short segments of tubular epithelium with granular to hypereosinophilic cytoplasm and pyknotic or absent nuclei. Sotorasib related changes in clinical chemistry, urinalysis, urine chemistry, and urine biomarkers were generally consistent with renal tubular injury and dysfunction. A full recovery of those parameters was observed at the end of treatment period.

A mechanistic exploratory 7-Day Oral Toxicology Study in the Male Sprague Dawley Rat (Study 153127) was conducted in order to address the renal toxicity in the rat characterised by tubular epithelial degeneration/necrosis primarily restricted to the proximal tubules in the OSOM. The formation of a putative toxic reactive metabolite in the rat kidney was involved in the mechanism of renal toxicity. Therefore, the renal findings were considered a rat-specific toxicity, not expected to be relevant for Humans (*see*: Other Studies, Mechanistic studies).

Sotorasib related changes in haematology parameters were also observed during the treatment period. The increased haematopoiesis in the spleen, liver, and bone marrow was predominantly composed of erythroid precursors and was considered a normal physiologic response to the sotorasib related minimal decrease in RBC mass. However, those changes in the haematological parameters were completely reversed at the end of the recovery phase. Moreover, none of the sotorasib related clinical pathology findings and microscopic changes were considered to be severely toxic.

Based on these results, the severely toxic dose in 10% of animals (STD10) was considered to be > 200 mg/kg in the 28-day study (200 mg/kg Day 27 C_{max} and AUC_{last} values of 2.35 µg/mL and 12.6 hr*µg/mL for the males and 8.61 µg/mL and 53.7 hr*µg/mL for the females) and to be 180 mg/kg in the 3-month study (180 mg/kg Day 91 C_{max}: 10.1 µg/mL and AUC_{last}: 63.7 hr*µg/mL; the exposure multiples). The exposure multiples based on unchanged sotorasib concentration in plasma from patients dosed 960 mg sotorasib tended to be low (1.7).

Two repeat dose GLP studies evaluated the potential toxicity and measured toxicokinetics of sotorasib in the Beagle Dog when administered by daily oral dosing up to 300 mg/kg for 28 days and up to 1000 mg/kg (500 mg/Kg BID) for 3-month.

Sotorasib was well tolerated following daily oral administration in the 28-day study up to 300 mg/kg. Key sotorasib related changes were limited to minimal to mild decrease in RBC mass associated with decreased reticulocytes. The highest non-severely toxic dose (HNSTD) was considered to be ≥ 300 mg/kg (correlated to Day 27 C_{max}/ AUC_{last} values of 3.68 µg/mL/ 15.8 hr* µg/mL).

Table 4: Mean ± SD toxicokinetic parameters for sotorasib after daily oral administration for 28 days in the Beagle dog (sexes combined)

Day	AMG 510 Dose (mg/kg)	T_{max} (hr)	C_{max} (µg/mL)	AUC_{last} (µg•hr/mL)
1	30	0.5 to 2	1.09 ± 0.741	1.94 ± 1.13
	100	0.25 to 1	3.54 ± 3.59	5.76 ± 4.98
	300	0.5 to 2	3.31 ± 2.02	13.1 ± 12.1
27	30	0.25 to 0.5	1.35 ± 0.515	4.75 ± 3.35
	100	0.25 to 8	3.90 ± 2.49	12.3 ± 5.13
	300	0.25 to 2	3.68 ± 2.32	15.8 ± 8.18

AUC_{last} = area under the concentration-time curve from time zero to the time of the last quantifiable concentration (up to 24 hours); C_{max} = maximum observed drug concentration during a dosing interval; T_{max} = time to reach C_{max}, reported as the range.
AMG 510 concentrations were not quantifiable in plasma samples collected from the control group.
Source: Study 150429

In the GLP 3-month dog toxicology study (Study 150433), higher dose levels were evaluated (up to 500 mg/kg BID) to achieve higher systemic exposure; however, the exposure even at 1000 mg/kg/day was lower than the exposure observed in the 3-month rat toxicology study.

The administration of sotorasib by twice daily oral gavage was well tolerated in beagle dogs at levels of 1000 mg/kg/day. Sotorasib related changes included abnormal content in the gall bladder, minimal to mild changes in haematology (decrease in RBC mass) and serum chemistry parameters (increase in total bilirubin, alkaline phosphatase, cholesterol and triglycerides). Light microscopic changes were observed in the liver (hepatocellular hypertrophy with increased liver weight), pituitary (hypertrophy of basophils with increased pituitary weight), and the thyroid gland (decreased colloid and hypertrophy of follicular epithelium with decreased thyroid weight). These microscopic changes were considered to be either non-severely toxic and attributed to an adaptive or secondary response to hepatocellular enzyme induction.

No toxicological findings in the kidney were identified in the repeat dose toxicity studies conducted in the dog. The highest non-severely toxic dose (HNSTD) was 1000 mg/kg/day (correlated to Day 90 C_{max}/ AUC_{last} values of 4.63 µg/mL/ 14.1 hr* µg/mL). The exposure multiples based on unchanged sotorasib concentration in plasma from patients dosed 960 mg sotorasib are lower than 1.

Table 5: Mean ± SD toxicokinetic parameters for sotorasib after daily oral administration for 3 months in the Beagle dog

Day	AMG 510 Dose (mg/kg BID)	T_{max} [a] (hr)	C_{max} (µg/mL)	AUC_{last} (µg•hr/mL)
1	100	0.5 to 13	3.07 ± 1.07	10.5 ± 5.41
	500	0.5 to 16	4.15 ± 2.77	18.6 ± 15.0
43	100	13	4.31 ± 2.01	9.56 ± 4.66
	500	0.5 to 13	3.28 ± 2.68	10.5 ± 9.76
90	100	0.5 to 13	4.11 ± 1.68	12.7 ± 7.62
	500	0.5 to 14	4.63 ± 1.17	14.1 ± 6.46

AUC_{last} = area under the concentration-time curve from time zero to the time of the last quantifiable concentration (up to 24 hours); BID = twice daily; C_{max} = maximum observed drug concentration during a dosing interval; T_{max} = time to reach C_{max}, reported as the range.
[a] t_{max} collection intervals determined from the first daily dose (t_{max} values greater than 12 hours occurred after the second daily dose).
AMG 510 concentrations were not quantifiable in plasma samples collected from the control group.
Source: Study 150433

In order to address changes in the liver, pituitary and thyroid in the dog 3-month study, a study on cytochrome P450 and UDP glucuronosyltransferase induction in cultured Beagle dog hepatocytes

(Study 153409) was performed. An adaptive response to reduced thyroid hormone levels by induced hepatic UGTs was identified.

2.5.4.3. Genotoxicity

Sotorasib was not mutagenic in a bacterial mutagenicity (Ames) assay (Study 124824). Sotorasib was not genotoxic in the *in vivo* rat micronucleus and comet assays.

2.5.4.4. Carcinogenicity

Carcinogenicity studies were not conducted

2.5.4.5. Reproductive and developmental toxicity

The reproductive and developmental safety assessment of sotorasib is focused on embryofetal toxicology studies. Data from a non-pivotal maternal tolerability study performed in rabbits and two GLP-embryo-fetal studies conducted in the Sprague Dawley Rat and New Zealand White rabbits was provided (including supportive toxicokinetic evaluations). The set of available reproductive and developmental toxicological information is in line with ICH S9 requirements to support the marketing of pharmaceuticals for the treatment of patients with advanced cancer.

The non-clinical assessment of potential adverse effects of sotorasib in male and female reproductive organs has been addressed within the scope of repeat dose toxicity studies. No toxicological findings in the reproductive organs were mentioned in studies conducted in rats and dogs.

Potential safety concerns on embryo-foetal development have been assessed in the Sprague Dawley Rat and New Zealand White rabbits orally dosed with sotorasib from Gestation Day (GD)7 to GD17 and from GD7 to GD19, respectively.

Sotorasib was administered to pregnant Sprague Dawley CD (Crl:CD[SD]) female rats once daily by oral gavage from GD 7 through GD 17 at doses up to 540 mg/kg. Sotorasib was tolerated at all dose levels with maternal effects on body weights, body weight gains, and food consumption at the highest dose, 540 mg/kg (corresponding to a systemic exposure 3.9 times higher than the exposure at the human dose of 960 mg based on AUC). There were no effects on any ovarian, uterine or litter parameters. In addition, there were no effects on embryo-fetal survival or fetal body weights at any dose. Sotorasib did not produce any fetal external, visceral, or skeletal malformations or variations.

In the study conducted in rabbits, female New Zealand White [Hra: (NZW)SPF] rabbits were orally administered sotorasib from GD 7 through GD 19 at doses up to 100 mg/Kg. Sotorasib related maternal effects included early euthanasia of one female on GD 21 and lower maternal body weight gain and food consumption at 100 mg/Kg (i.e., 2.2 times higher than the systemic exposure at the human dose of 960 mg based on AUC). There were no effects on embryo-fetal survival, but there were sotorasib related reductions in mean fetal body weights and a delay in skeletal ossification (fewer metacarpals) at 100 mg/Kg. Those fetal findings were observed only at the dose level associated with decreased body weight gain and food consumption in dams during the dosing phase. Maternal administration of sotorasib did not produce any fetal external, visceral, or skeletal malformations or variations. A delay in the skeletal ossification, as evidence of growth retardation associated with reduced fetal body weight in the presence of significant maternal toxicity, might be interpreted as a non-specific effect of sotorasib in the embryo-fetal development.

2.5.4.6. Local tolerance

Local tolerance of sotorasib was evaluated after oral dosing in the repeat-dose studies; no evidence of local irritant effects was observed in the digestive tract.

2.5.4.7. Other toxicity studies

Several screening assessments were performed for 3 circulating metabolites, AMG3368167 (M24), AMG3375854 (M10), and AMG3413829 (M18), identified in human, rat and dog. The screening assessments included potential primary or secondary pharmacology effects and for effects on *in vitro* hERG potassium channel and mutagenicity. The results indicated no clinically relevant safety concerns.

There are 9 specified impurities in total warranting nonclinical qualification; all of them were qualified with bacterial reverse mutation assay (Ames test) and general 28-day repeat-dose toxicology studies in the rat or dog in line with the ICH guidance (ICH Q3A, 2006; ICH Q3B, 2006).

A study was conducted to determine the phototoxic potential of AMG3365648. Sotorasib at concentrations from 0.032 to 100 μg/mL was negative in an exploratory *in vitro* study using 3T3 fibroblasts.

2.5.5. Ecotoxicity/environmental risk assessment

Table 6: Summary of main study results

Substance (INN/Invented Name): sotorasib			
CAS-number (if available): 2296729-00-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log Kow (pH 5) = 2.36 log Kow (pH 7) = 2.44 log Kow (pH 9) = 2.77	Potential PBT N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2.44	not B
	BCF		B/not B
Persistence	DT50	>180 days	vP
Toxicity	NOEC	>10 µg/L	notT
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	1.8	µg/L	> 0.01 threshold Y
Other concerns (e.g. chemical class)			N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Koc_{sludge} =125 Koc_{sludge}=118 $Koc_{sandy\ loam}$=87.5 $Koc_{clay\ loam}$ = 281.0 $Koc_{sandy\ clay\ loam}$ = 125	terrestrial studies not triggered
Ready Biodegradability Test	OCDE 301	Not conducted	Not ready biodegradable

Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	CALS/ELS $DT_{50, 12\ °C, water}$ = 53.9 / 74.5 d $DT_{50, 12\ °C, sediment}$ = 26.7 / 633 d $DT_{50, 12\ °C, total\ system}$ = 83.6 / 124 d Mean % shifting to sediment = 7.2 / 15.8 (day 100) % Non-extractables = 50.3 / 52.9 % mineralisation = 0.124 / 0.294			metabolite G>10%
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Raphidoceis subcapitata*	OECD 201	NOEC	8400	µg/L	
Daphnia magna Reproduction Test	OECD 211	NOEC	10000	µg/L	
Fish, Early Life Stage Toxicity Test/*Pimephales promelas*	OECD 210	NOEC	11000	µg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	100	µg/L	
Phase IIb Studies					
Sediment dwelling organism *Chironomus riparius*	OECD 218	NOEC	1200 6000	mg/kg dw	o.c. 2% normalised 10% o.c,

2.5.6. Discussion on non-clinical aspects

Pharmacology

The effects of sotorasib monotherapy *in vitro* studies consisted of structural, biochemical and cellular characterisation of sotorasib. Primary pharmacodynamics *in vivo* studies included 1) effects of sotorasib monotherapy (consisting of pharmacodynamic, pharmacokinetics and occupancy studies of sotorasib), 2) effects of sotorasib combination therapy and 3) effects of sotorasib on anti-tumour inflammatory response. The studies were well planned and clearly indicated that sotorasib targets specifically tumours with KRAS p.G12C mutation, and inhibits growth of these tumours.

In combination studies of tumour cell viability *in vitro*, significantly enhanced anti-tumour activity of sotorasib was observed with the MAPK pathway upstream and downstream of RAS inhibitors, and with inhibitors of EGFR/pan- erb-b2 receptor tyrosine kinase family (ErbB), SHP 2, or MAPK/ERK kinases. Combination of sotorasib with an immune checkpoint inhibitor (PD1 antibody) enhanced tumour regression at a lower sotorasib dose. Sotorasib was shown to induce a pro-inflammatory microenvironment. The genes affected included those involved in interferon signalling, chemokine production (including Cxcl11), antigen processing, cytotoxic and natural killer cell activity, and markers of innate immune system stimulation.

Overall, *in vitro* and *in vivo* primary pharmacology data support the intended clinical use. Moreover, the *in vivo* models and the sotorasib dose range studied are considered mostly relevant for the clinical situation.

Sotorasib did not show significant activity *in vitro* against various targets including receptors, enzymes, ion channels, and transporters. In NCI-H358 tumour cells, cysteine-proteome profiling demonstrated that sotorasib engaged only the cysteine at amino acid position 12 (Cys12) peptide from KRASG12C. General off-target selectivity of 3 major human circulating metabolites, M24, M18 and M10 was assessed in the same way as sotorasib. The concentration of these metabolites in the *in vitro* assays was 14 to 138-fold greater than the unbound fraction of the metabolites observed in human (Table 3). The only positive signal in screening studies, M24 at 10 µM showed inhibition for Neurokinin NK1 and NK2 receptors. However, this effect is not considered to be clinically significant as the concentration of 10 µM is 138-folder higher than the free fraction of M24 in human plasma at 960 mg.

IC_{50} for human ether-à-go-go-related gene (hERG) was 54.8 µM sotorasib, therefore clinically significant interaction with the hERG are not expected at therapeutic doses. In a GLP cardiovascular safety pharmacology study in telemetered dogs, sotorasib at doses up to 300 mg/kg did not result in changes to electrocardiogram (ECG) or haemodynamic parameters.

Pharmacokinetics

Methods of analysis for SOTORASIB were adequately validated. However, studies of SOTORASIB were performed with the (S) isomer, while no information is provided for the potential isomerisation *in vitro* or *in vivo*. Sotorasib is used as (S, M) isomer. Sotorasib molecule has both chiral centre and chiral axis. The desired (S, M)-isomer has chiral centre in S-configuration and chiral axis in M-configuration. In the applicant's answer it is talked about rotamers, which points to chiral axis. Chiral axis forms in sotorasib molecule so that spin of the pyridine ring of the lower part of the molecule around the first bond is not free due to presence of substituents attached to the pyridine ring. Therefore, sotorasib can exist as following forms: 1. (S, M), desired form; 2. (S, P); 3. (R, M); 4. (R, P). In the specifications of DS there are limits for those chiral impurities. Chemically (S, M) isomer is stabile (28 days, 80 C). However, what happens *in vivo* remains to be solved. The applicant has demonstrated that no conversion of sotorasib to its rotamers was observed at 37ºC during *in vitro* studies, using human plasma, over 2 hours. As per EMA guideline on "Investigation of Chiral Active Substances", the possibility of the formation of the other enantiomer "*in vivo*" should be considered in relation to the chemical structure at an early stage in order to justify the need for any enantiospecific bioanalysis. The potential for interconversion of sotorasib rotomers was evaluated using clinical samples at day 1 and day 8 from clinical study 20170543 and reported in Study 155849. No conversion of sotorasib to its rotomers was observed in the clinical samples.

Sotorasib was readily absorbed after a PO dose to non-cannulated male and female rats and BDC male rats. Primary sotorasib biotransformation was mediated by non-enzymatic glutathione conjugation.

The absorption of sotorasib was studied in mouse, rat, dog and monkey. The major circulating metabolite M24 was observed in all nonclinical species. In humans, M24 is not the main circulating metabolite.

Sotorasib and its metabolite M24 were highly permeable *in vitro* across canine kidney epithelial cells in MDCK Transwell Assay. Caco-2 monolayer cells derived from colon cancer cells can be considered the gold standard for *in vitro* permeability assay. MDR1-tranfected MDCK cell systems are useful to characterise P-gp transporter activity and inhibition *in vitro*. Sotorasib is a P-gp substrate; thus, active transport by P-gp may affect sotorasib absorption and elimination. MDR1-tranfected MDCK cell system can be considered an appropriate permeability assay for sotorasib as an alternative to Caco-2 assay.

Overall, [^{14}C] -sotorasib-derived radioactivity was minimally absorbed and was eliminated predominantly as unchanged sotorasib in faeces following a single 500 mg/kg dose to male or female dogs.

Sotorasib is an amphoteric molecule, with basic pKa of 4.56 and acidic pKa of 8.06. In dogs, which have some unique characteristics in gastrointestinal physiology, incomplete sotorasib dissolution in the suspension or tablet formulations led to incomplete absorption and lower systemic exposure when compared to the solution dose.

Based on the radiolabelled mass balance studies in rat (Study 152495), dog (Study 153304), and human (Study 20190321), sotorasib metabolite M10 was the major circulating metabolite observed in rat, dog, and human.

Although a preliminary *in vitro* metabolite assessment using human hepatocytes indicated that metabolites M10, M18 and M24 were the predominant sotorasib metabolites, M10 metabolite was determined as a single major metabolite (> 10% of total radioactivity) based on the human mass balance study (Study 20190321). It is agreed that the 3-month repeat-dose toxicology study in the rat evaluated sufficiently the safety of not only unchanged sotorasib, but also human major metabolite M10. Moreover, results from cross-species studies (150531) on the metabolism of sotorasib *in vitro* in hepatocytes from mouse, rat, dog, monkey and human show that M10 was formed in all species (percent of total MS response 2.5, 2.6, 12.1, 6.8 and 9.9%, respectively). Thus, per ICHS9 M10 is not a unique human major metabolite.

Non-clinical studies with metabolites for anticancer pharmaceuticals are not warranted based on ICH S9 (ICH S9, 2009) and ICH S9 Q&A clarification (ICH S9 Q&A, 2018). Therefore, exposures to key metabolites (including M10) were not directly measured within any GLP toxicology studies. However, based on the results from the rat mass balance study (Study 152495), systemic exposure to M10 metabolite in the 3-month rat study can be extrapolated, and the predicted exposures to M10 metabolite in the rat are considered to be greater than those in humans. The dose level used in the single-dose rat mass balance study with 14C-sotorasib was 60 mg/kg. The Cmax of metabolite M10 in the rat were approximately 5.5- to 9-fold greater than those in humans that received a single dose of sotorasib at the highest clinical dose of 960 mg (Table 3). The dose levels used in the 3-month rat study were 60, 180 and 750 mg/kg. Although there were no steady-state M10 metabolite exposure data in the rat, M10 metabolite exposure in the rat at the lowest dose of 60 mg/kg was already higher than that in human at the highest clinical dose; therefore, M10 metabolite exposures in the rat at both of the higher doses of 180 and 750 mg/kg are expected to be greater compared to the human. Thus, the 3-month repeat-dose toxicology study in the rat (at least one species) evaluated the safety of not only unchanged sotorasib but also human major metabolite M10.

In vitro studies indicate that sotorasib is metabolised by cytochrome P450 (CYP) 2C8, CYP3A4, and CYP3A5, and is a substrate of P glycoprotein (P gp). Sotorasib was an inducer of CYP3A4, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 *in vitro*. Sotorasib is an *in vitro* inhibitor of CYP2C8, CYP2D6, and CYP3A. *In vitro* studies indicate that sotorasib is an inhibitor of human organic anion transporter (OAT)3, OATP1B1, Breast Cancer Resistance Protein (BCRP) and P-gp (see section 4.5 of the SmPC).

Toxicology

Potential acute effects of sotorasib were evaluated in the repeat-dose rat and dog toxicology studies. There were no sotorasib related acute adverse effects in the rat or dog. The lack of dedicated single dose toxicity studies is acceptable. The non-clinical set of repeat dose toxicity studies are in line with ICH S9. The repeat dose toxicological assessment of sotorasib has been conducted in the Rat/Sprague Dawley and Dog/Beagle by oral gavage administration of sotorasib up to 3 months duration (including supportive toxicokinetics evaluations). Primary pharmacology-related on-target effects are not expected in "non-tumour-bearing" rats and dogs used in repeat dose toxicological assessment.

Two repeat dose GLP studies evaluated the potential toxicity and measured toxicokinetics of sotorasib in Sprague Dawley rats when administered by daily oral dosing up to or 200 mg/kg for 28 days

(followed by a 28-day recovery) and up to 750 mg/Kg for 3-month (followed by 2-month recovery). The administration of sotorasib by once daily oral gavage was well tolerated in animals dosed up to 200 mg/kg (the highest dose in the 28 day-study) and up to 180 mg/Kg (the mean dose tested in the 3-month study).

Consistent with tumour-specific target distribution, there were no primary pharmacology-related on-target effects identified from pivotal repeat-dose toxicology studies. The kidney was identified as a target organ of toxicity in the rat. Minimal to moderate degeneration/necrosis of renal tubular epithelium was observed. The incidence and severity of tubular degeneration/necrosis were generally dose dependent and involved primarily the outer stripes of the outer medulla of the kidney. In the 28-day study, 2 of 20 animals at 200 mg/kg (the highest dose tested) had renal tubular degeneration/necrosis, and this change was minimal to mild. In the 3-month rat study, the same renal change progressed to a more chronic nature that involved more of the renal tubule; this was attributed to higher exposures and longer study duration. Based on the results of mechanistic studies as well as the metabolic pathways of sotorasib, the renal toxicity was attributed to the formation of a putative toxic reactive metabolite following metabolism of sotorasib by the mercapturate pathway. Rat-specific renal toxicity and a low risk in the clinic are supported by sotorasib metabolism and safety data, as well as published information (Anders, 2004b; Gul Altuntas and Kharasch, 2002; Iyer and Anders, 1996; Mccarthy et al, 1994; Green et al, 1990; Lash et al, 1990). Similar toxicity was not observed in the dog toxicology studies and there have been no similar signals of acute renal toxicity in the sotorasib clinical trials to date. Clinical trials with sotorasib have included monitoring of renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance along with microscopic examination of urine sediment. The applicant confirmed that there has been no signal identified in the clinical studies suggestive of similar renal toxicity characterised in the rat toxicology studies.

Sotorasib related changes in haematology parameters were also observed during the treatment period. However, those changes were completely reversed at the end of the recovery phase. Moreover, none of the sotorasib related clinical pathology findings and microscopic changes were considered to be severely toxic. Based on these results, the severely toxic dose in 10% of animals (STD10) was considered to be > 200 mg/kg in the 28-day study and to be 180 mg/kg in the 3-month study. The exposure multiples based on unchanged sotorasib concentration in plasma from patients dosed 960 mg sotorasib tended to be low (1.7).

Two repeat dose GLP studies evaluated the potential toxicity and measured toxicokinetics of sotorasib in the Beagle Dog when administered by daily oral dosing up to 300 mg/kg for 28 days and up to 1000 mg/kg (500 mg/kg BID) for 3-month. Sotorasib was well tolerated following daily oral administration in the 28-day study up to 300 mg/kg. Key sotorasib related changes were limited to minimal to mild decrease in RBC mass associated with decreased reticulocytes. In the GLP 3-month dog toxicology study, higher dose levels were evaluated (up to 500 mg/kg BID) to achieve higher systemic exposure; however, the exposure even at 1000 mg/kg/day was lower than the exposure observed in the 3-month rat toxicology study.

In the dog 3-month study there were adaptive changes in the liver, pituitary, and thyroid, secondary to hepatocellular enzyme induction. If effects on the thyroid do occur, they are clinically monitorable.

The mean observed sotorasib clinical exposures from 180, 360, 720, and 960 mg once daily (QD) dosing in subjects (Study 20170543) were lower than the exposures observed at the STD10 of 180 mg/kg in rats in the 3-month GLP repeat-dose toxicology study (Study 150432), but higher than the exposures observed at the HNSTD of 1000 mg/kg/day in dogs in the 3-month GLP repeat-dose toxicology study (Study 150433).

The comparison of C_{max} and AUC values in the last TK sampling day confirms the low exposure of sotorasib in repeat-dose toxicity studies in rats and dogs compared to exposure in human plasma after a single dose (Day 1, Study 20170543). On Day 8 C_{max} was 25% lower in human plasma suggesting that steady-dose C_{max} of sotorasib is presumably further decreasing along the dosing due to autoinduction of its own metabolism.

When considering the exposure multiples based on steady-state sotorasib concentration in human plasma relative to exposure in plasma of animal species used in toxicology studies, it was challenging to establish the optimal study design of repeat-dose toxicology studies, especially in the dog, due to low sotorasib systemic exposure. In pivotal repeat-dose toxicity studies only TK of the parent drug was measured and therefore, it is now known the amount of the circulating metabolites in the plasma of toxicology species. Neither are there specific safety data of the main metabolites available and their impact on nonclinical toxicology evaluation and safety margins is not known.

The higher exposures for the sum of sotorasib and its metabolites in rat and dog as compared to the exposures observed in clinic do not fully support that the nonclinical toxicology evaluation sufficiently assessed potential safety liabilities for the clinic. Especially in the dog, the interrelationship of the physiologic characteristics of the canine gastrointestinal tract and those of a particular compound can be difficult to unravel (Tibbits 2003).

Sotorasib was not mutagenic in a bacterial mutagenicity (Ames) assay. Sotorasib was not genotoxic in the *in vivo* rat micronucleus and comet assays.

Carcinogenicity studies have not been performed with sotorasib which is acceptable in line with ICHS9.

In rat (Sprague Dawley) and rabbit (New Zealand White) embryo-foetal development studies (as described by ICH S5(R3), 2020), oral sotorasib was not teratogenic. Moreover, data from a non-pivotal maternal tolerability study performed in rabbits has been provided.

In the rat, there were no effects on embryo-fetal development up to the highest dose tested (540 mg/kg, corresponding to a systemic exposure 3.9 times higher than the exposure at the maximum recommended human dose [MRHD] of 960 mg based on area under the curve [AUC]).

In the rabbit, lower fetal body weights and a reduction in the number of ossified metacarpals in foetuses were observed only at the highest dose level tested (100 mg/kg, corresponding to a systemic exposure 2.2 times higher than the exposure at the MRHD of 960 mg based on AUC), which was associated with maternal effects such as decreased body weight gain and food consumption during the dosing phase. Reduced ossification, as evidence of growth retardation associated with reduced foetal body weight, was interpreted as a non-specific effect in the presence of significant maternal toxicity (see section 5.3 of the SmPC).

Primary pharmacology-related on-target effects on embryofetal development will not be expected in normal "non-tumour-bearing" animals.

Sotorasib was not phototoxic *in vitro*. Human circulating metabolites, M24, M10 and M18 raised no clinically relevant safety concerns based on primary or secondary pharmacology screening, *in vitro* hERG or mutagenicity assessment.

As per ICH guideline S9 on non-clinical evaluation for anticancer pharmaceuticals, exceeding the established limits for impurities identified in ICH Q3A and Q3B guidelines could be appropriate for anticancer pharmaceuticals. There are 9 specified impurities in total warranting nonclinical qualification; all of them were qualified with bacterial reverse mutation assay (Ames test) and general 28 day repeat dose toxicology studies in the rat or dog in line with the ICH guidance (ICH Q3A, 2006; ICH Q3B, 2006).

Sotorasib is not a PBT substance. Considering the above data, sotorasib should be used according to the precautions stated in the SmPC (section 6.6) in order to minimise any potential risks to the environment.

2.5.7. Conclusion on the non-clinical aspects

The primary pharmacodynamic studies provided adequate evidence that sotorasib is highly selective small molecule inhibitor that covalently binds to the KRASG12C and impairs downstream oncogenic signalling exclusively in KRAS p.G12C tumour cells. The KRAS p.G12C mutation has only been reported in tumour tissue and is not present in normal tissue. Consistent with tumour specific target distribution, there were no apparent primary pharmacology related on target effects identified.

From the pharmacokinetic point of view, sotorasib has a very complex metabolism. The main metabolites have accumulation potential in the plasma. Sotorasib and the main metabolites had several interactions *in vitro* with CYP isoforms and human transporters, some of which may be clinically relevant.

Overall, the toxicology programme revealed that sotorasib had low toxicity potential in pivotal toxicity studies.

Overall, the nonclinical pharmacology, pharmacokinetics and toxicology programme may support the marketing authorisation of sotorasib for treatment of *KRAS p.G12C*-mutated tumours.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 7: Summary of all clinical studies included in the marketing application

Phase	Study	Description	Comment
Phase 1	20190315	PK of digoxin alone and in combination with sotorasib; safety and tolerability: single oral dose of 960 mg sotorasib tablets single oral doses of 0.5 mg digoxin tablets	14 healthy volunteers. Not included in population PK analysis *Report 152921*
Phase 1	20190316	Bioavailability study: single oral doses of 360 mg sotorasib tablets in a fasted or fed state	14 healthy volunteers included in population PK analysis *Report 152921*

Phase	Study	Description	Comment
Phase 1	20190317	PK of metformin and sotorasib, safety, tolerability, antihyperglycemic PD effect: single oral doses of 960 mg sotorasib tablets single oral doses of 850 mg metformin tablets	13 healthy volunteers included in population PK analysis *Report 152921*
Phase 1	20190318	drug-drug interaction effect of itraconazole with sotorasib; PK, safety, and tolerability: single oral doses of 360 mg sotorasib tablets 200 mg itraconazole capsules PO BID	14 healthy volunteers included in population PK analysis *Report 152921*
Phase 1	20190319	drug-drug interaction effect of rifampin with sotorasib; PK, safety, and tolerability; PK of metabolite M24: single oral doses of 960 mg sotorasib tablets 600 mg rifampin capsules PO QD	14 healthy volunteers included in population PK analysis *Report 152921*
Phase 1	20190320	drug-drug interaction effect of omeprazole with sotorasib; PK, safety, and tolerability: single oral doses of 960 mg sotorasib tablets 40 mg omeprazole delayed release tablet PO QD	14 healthy volunteers included in population PK analysis *Report 152921*
Phase 1	20190321	Healthy Subject PK and Initial Tolerability: single oral dose of 720 mg containing approximately 1 µCi of ^{14}[C]-sotorasib administered as a suspension	8 healthy volunteers. Not included in population PK analysis *Report 152921*
Phase 1	20190500	Comparative Bioavailability/Bioequivalence: single oral doses of 960 mg sotorasib administered as either tablets or a water dispersion	14 healthy volunteers. Not included in population PK analysis *Report 152921*
Phase 1	20200199	Effect of acid reducing agents, famotidine or omeprazole in fed state; PK, safety, and tolerability: sotorasib 960 mg PO administered alone and in combination with either 40 mg famotidine or 40 mg omeprazole	14 healthy volunteers. Not included in population PK analysis *Report 152921*
Phase 1	20190147	Safety, tolerability, PK, efficacy in Chinese subjects : sotorasib 720 mg (cohort 1) or 960 (cohort 2) mg PO QD	Ongoing. Not included in population PK analysis *Report 152921*
Phase 1b	20190135	Safety, tolerability, PK, and efficacy Subprotocol A: sotorasib (960 mg) PO QD + trametinib (1 mg, 2 mg, or 0.5 mg) PO QD or sotorasib (960 mg) PO QD + trametinib (1 mg, 2 mg, or 0.5 mg) PO QD + panitumumab (3.6 mg/kg, 4.8 mg/kg, or 6 mg/kg) IV Q2W	Ongoing. Not included in population PK analysis *Report 152921*

Phase	Study	Description	Comment
		Subprotocol C: sotorasib (960 mg) QD + RMC-4630 (50 to 300 mg) PO twice weekly Subprotocol D: sotorasib (960 mg) QD + afatinib (20 to 40 mg) PO QD Subprotocol E: sotorasib (960, 720, 360, 240, or 120 mg) QD + atezolizumab (1200 mg) IV Q3W Subprotocol H: sotorasib (960, 720, 480 mg) PO QD + panitumumab (6 or 3 mg/kg) IV Q2W or panitumumab (6 or 3 mg/kg) + FOLFIRI IV Q2W	
Phase 1/2	20170543	Safety, tolerability, efficacy, PK, PD: monotherapy and in combination, non-randomised, open-label, dose exploration **Phase 1** Part 1a: 180, 360, 720, or 960 mg sotorasib QD Part 1b: 480 mg sotorasib BID with food Part 1c: 360, 720, or 960 mg sotorasib + 200 mg pembrolizumab IV Q3W Part 1d: 960 mg sotorasib QD with food Part 2a: 960 mg sotorasib QD Part 2b: 480 mg sotorasib BID with food Part 2c: recommended dose of sotorasib QD from Part 1c + 200 mg pembrolizumab IV Q3W Part 2d: 960 mg sotorasib QD with food Part 2e: 960 mg sotorasib QD Part 2e substudy: single oral dose of 960 mg sotorasib tablets single oral doses of 2 mg midazolam **Phase 2 - pivotal** 960 mg sotorasib PO QD	258 patients with NSCLC, 113 patients with rectal or colon cancer, and 60 patients with other types of tumours (overall n=431) included in population PK analysis Report 152921 Phase 2 ongoing
Phase 3	20190009	Efficacy, safety, tolerability, PROs, PK: sotorasib 960 mg PO QD docetaxel 75 mg/m_2 IV Q3W	Ongoing. Not included in population PK analysis *Report 152921*

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Sotorasib is an orally available, first in class small molecule that specifically binds and irreversibly inhibits the KRASp.G12C mutant protein (KRASG12C).

In addition to non-clinical pharmacokinetics studies (*in vitro* metabolite profiling, CYP inhibition and induction, and P-gp substrate evaluation, protein binding …), the clinical pharmacology investigations of sotorasib consisted of 9 clinical studies performed in healthy volunteers and one in patients (Study 20170543, Pivotal study).

The PK of sotorasib have not been investigated in special populations such as hepatic dysfunction. PopPK analysis and two exposure-response analysis were performed.

Methods

- Bioanalysis

Plasma concentration of sotorasib and its metabolites (M10, M18 and M24) were determined using a liquid chromatography mass-spectrometry method (LC-MS/MS), two separates methods were used.

- Pharmacokinetic analysis

Standard non-compartmental (model-independent) pharmacokinetic methods were used to calculate PK parameters using Phoenix® WinNonlin version 8.1 (Certara, Princeton, NJ).

Pharmacokinetics of sotorasib were investigated by population modelling using a nonlinear mixed effects modelling approach with NONMEM software program (version 7.2, ICON Development Solutions, Ellicot City, MD).

Exposure-response analysis (efficacy and safety) were also performed using predicted PK metrics from the population pharmacokinetic model.

Absorption

Following single oral dose of sotorasib in healthy volunteers or patients and after multiple-dosing of sotorasib at doses between 180 mg to 960 mg, median Tmax ranged from 0.73 to 1.5h in HV and from 1 to 1.5 h in patients.

In patients Cmax ranged from 6190 to 8600 ng/mL at Day 1 and from 5390 to 6440 ng/mL at Day 8. As shown at Day 1 and more particularly at Day 8, PK exposure parameters are similar between a 180 mg and a 960 mg QD dose (Table 8).

Table 8: PK parameter estimates following oral administration of sotorasib QD from 180 mg to 960 mg

Treatment	t_{max} (hour)	C_{max} (ng/mL)	AUC_{inf} (hour•ng/mL)	AUC_{0-24h} (hour•ng/mL)	$t_{1/2,z}$ (hour)	CL/F (L/hour)	V_z/F (L)	AR
Phase 1 Part 1A (Fasted)				Day 1				
Part 1A cohort 1 180 mg, n = 6	1.0 (0.50 – 2.0)	6880 (7870, 51%)	40700 (46800, 64%)[a]	43600 (50200, 57%)	5.71 (0.815)[a]	4.42 (4.96, 50%)[a]	36.1 (41.1, 57%)[a]	NC
Part 1A cohort 2 360 mg, n = 26	1.1 (0.57 – 6.2)	6190 (8390, 64%)	60700 (76700, 63%)[c]	58400 (74300, 63%)[b]	6.45 (1.80)[c]	5.93 (8.35, 108%)[c]	53.1 (80.6, 122%)[c]	NC
Part 1A cohort 3 720 mg, n = 11	1.2 (0.50 – 4.1)	7570 (10300, 59%)	80800 (90500, 52%)[d]	84000 (96300, 57%)[e]	6.45 (1.95)[d]	8.91 (9.91, 48%)[d]	79.8 (83.3, 32%)[d]	NC
Part 1A cohort 4 960 mg, n = 24	1.5 (0.25 – 4.8)	8400 (10600, 59%)	67000 (85800, 88%)[c]	67700 (86700, 77%)[b]	5.49 (2.14)[c]	14.3 (17.4, 62%)[c]	106 (121, 49%)[c]	NC
Phase 1 Part 1A (Fasted)				Day 8				
Part 1A cohort 1 180 mg, n = 6	0.73 (0.50 – 1.2)	6440 (7630, 67%)	NC	31700 (40800, 89%)	5.13 (1.99)[a]	5.68 (6.81, 56%)	37.6 (40.8, 43%)	0.726 (0.769, 42%)
Part 1A cohort 2 360 mg, n = 24	1.0 (0.50 – 4.0)	6310 (7330, 43%)	NC	38900 (43700, 49%)[b]	5.53 (1.84)[f]	9.25 (10.5, 55%)[b]	67.9 (81.0, 95%)[f]	0.666 (0.805, 80%)[g]
Part 1A cohort 3 720 mg, n = 11	1.1 (0.53 – 4.0)	5450 (6760, 50%)	NC	42100 (48500, 49%)	4.75 (1.16)[i]	17.1 (20.9, 82%)	153 (653, 264%)[h]	0.604 (0.641, 36%)[e]
Part 1A cohort 4 960 mg, n = 24	1.1 (0.22 – 6.5)	5390 (6820, 65%)	NC	32400 (42300, 75%)[j]	5.07 (1.08)[j]	29.6 (37.8, 67%)[j]	208 (252, 63%)[j]	0.532 (0.587, 45%)[k]

Formal clinical investigation (mass balance study 20190321) does not support a fairly high degree (≥85%) of absorption of sotorasib in humans. The overall recovery of radioactivity was low 80.6%, with 74.4 % of the dose recovered in faeces and 5.81% recovered in urine. Approximately 54.4% of [14C]-sotorasib was recovered unchanged in faeces, whereas less than 2% was recovered unchanged in urine. Absorption of sotorasib is clear affected by a preponderant pre-systemic elimination process.

Sotorasib is a low permeable drug (<85%) and is a low soluble drug (pH dependent), therefore sotorasib is a BCS class 4 drug.

Absolute bioavailability

The absolute bioavailability is unknown. However based on the results of the mass balance study (despite the fact that only 80% of the total radioactivity was recovered), F could be estimated around 26%, unless it could be demonstrated that all the sotorasib unchanged part (=54,5%) excreted in faeces is firstly absorbed in the systemic circulation then excreted unchanged in faeces.

Relative bioavailability/Bioequivalence

The claimed recommended dose of sotorasib is 960 mg suggesting QD intake of 8 tablets of 120 mg. Therefore, the applicant investigated an alternative method of administration where sotorasib will be predispersed in water.

Results of study 20190500 show that PK exposure parameters (Cmax, AUCs) remain similar with or without predispersed SOTORASIB in water. Based on this study, the applicant statement that sotorasib can be taken with this alternative method is acceptable

Food effect

In study 20190316, the effect of a high fat meal on sotorasib PK was investigated in 14 healthy volunteers who were administered a single oral dose of 360 mg sotorasib in the fasted and the fed states. PK results indicated that administration of a high fat meal delayed by 1.25 (median Tmax) the absorption of sotorasib. Following administration of sotorasib with a high-fat, high-calorie meal, there was no effect on Cmax, and AUC increased by 38% compared to administration under fasted conditions.

In study 20170543, the effect of high fat meal was performed in a subset of patients, who were administered oral dose of 360 (n=2) or 960 mg (n=8) sotorasib in the fasted and the fed states.

PK results indicated that administration of a high fat meal delayed the absorption of sotorasib by 3h with a median Tmax of 4h. In the fed state the AUC and Cmax of sotorasib were 75% and 38% higher respectively, compared to the fasted state at the dose of 360 mg. At a 960 mg dose Cmax decreased by 34% and AUC increased by 25% compared to fasted state.

Based on these data, the applicant preconise that sotorasib can be administered with or without food.

Effects with acid reducing agents

In study 20200199, the effects of acidic reducing agents (omeprazole and famotidine) in fed state on sotorasib PK was investigated in 14 healthy volunteers who were administered 960 mg sotorasib in the fed state.

Under fed conditions (standard calorie moderate-fat meals), co-administration of multiple doses of omeprazole with a single dose of 960 mg sotorasib decreased sotorasib Cmax by 65% and AUC by 57%. Co-administration of a single dose of famotidine given 10 hours prior and 2 hours after a single dose of 960 mg sotorasib decreased sotorasib Cmax by 35% and AUC by 38%.

Under fasted conditions, co administration of multiple doses of omeprazole with a single dose of 960 mg sotorasib decreased sotorasib Cmax by 57% and AUC by 42%

Distribution

In vitro, plasma protein binding of sotorasib was 89% and sotorasib bound preferentially to alpha-1-acid glycoprotein *in vitro* (Study 155351).

In the human AME study (Study 20190321), the blood-to-plasma radioactivity ratios was determined to be 1 (range min-max: 0.8-1.29), suggesting lack of meaningful distribution of sotorasib into blood cells. Based on *in vitro* investigation mean B/P was estimated at 0.69.

Following oral dosing, in healthy volunteers the sotorasib Vz/F was estimated at 242 L, thus indicating high distribution in tissues. The geometric mean apparent volume of distribution after 960 mg PO QD for 8 consecutive days of sotorasib was 211 L (determined using noncompartmental analysis).

Elimination

In patients (study 20170543) receiving doses of 180, 360, 720, and 960 mg as film-coated tablets (except for the 180 mg dose containing 30 and 120 mg as uncoated tablet), sotorasib clearance (CL/F) varied between geometric mean of 4.42 and 14.3 L/h (48 – 108 %CV) on day 1. At Day 8, following multiple dose of 960 mg sotorasib once daily, geometric mean CL/F was estimated at 26.2 L/h and the mean half-life was 5h.

The main elimination route was hepatic metabolism via CYP3A4 enzyme and excretion of metabolites in both urine and faeces. Sotorasib is mainly excreted as unchanged drug in faeces (53%) and in urine with a fraction excreted less than 2 % (1.74%).

- Mass balance

The mass balance study 20190321 consisted of the administration of a single oral dose of 720 mg containing approximately 1µCi of [14C]-sotorasib to 8 healthy volunteers. Results are summarised in Table 9 (plasma and plasma total radioactivity) and Figure 2.

Table 9: Summary of PK parameters of plasma and total radioactivity in plasma of SOTORASIB

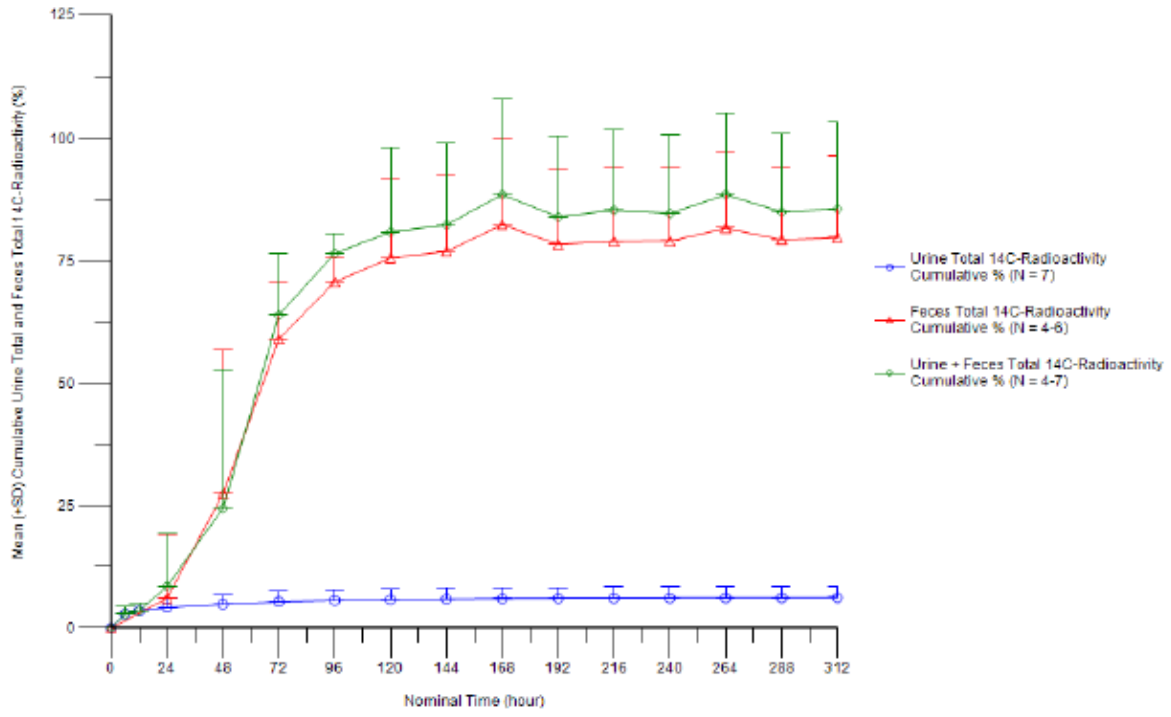
Matrix: Plasma; Analyte: AMG 510

Parameter	720 mg of AMG 510 containing approximately 1 µCi of [^{14}C]-AMG 510 (N=8)
AUC_{inf} (h*ng/mL)	26100 (36.6) [8]
AUC_{last} (h*ng/mL)	25900 (36.6) [8]
AUC_{0-312} (h*ng/mL)	26100 (36.6) [8]
C_{max} (ng/mL)	6690 (35.6) [8]
t_{max} (h)	0.750 (0.500-1.50) [8]
t_{last} (h)	36.0 (24.0-72.0) [8]
$t_{1/2}$ (h)	6.35 (4.07) [8]
CL/F (L/h)	27.6 (36.6) [8]
V_z/F (L)	224 (33.5) [8]
AUC_{inf} Plasma AMG 510 / Total Radioactivity Ratio	0.180 (50.1) [4]
AUC_{0-312} Plasma AMG 510 / Total Radioactivity Ratio	0.196 (32.5) [7]

Matrix: Plasma; Analyte: Total Radioactivity

Parameter	720 mg of AMG 510 containing approximately 1 µCi of [^{14}C]-AMG 510 (N=8)
AUC_{inf} (h*ngEq/mL)	150000 (89.6) [4]
AUC_{last} (h*ngEq/mL)	136000 (60.1) [7]
AUC_{0-312} (h*ngEq/mL)	137000 (59.0) [7]
C_{max} (ngEq/mL)	9000 (27.2) [7]
t_{max} (h)	1.00 (0.500-2.00) [7]
t_{last} (h)	312 (216-312) [7]
$t_{1/2}$ (h)	128 (73.4) [5]

Figure 2: Arithmetic mean (+SD) cumulative urinary and faecal recovery (% Radioactive dose) vs time



Following oral administration, approximately 5.81% of the radioactive dose was recovered in urine with unchanged sotorasib of 1.39% and 74.4% in the faeces with unchanged sotorasib of 52.97%. Renal clearance was found to be low and estimated at 0.41 L/h.

Metabolism

Sotorasib was extensively metabolised following oxidative and conjugation process as shown in **Error! Reference source not found.**. Following direct injection of diluted plasma, sotorasib accounted for 17.1% of the total radioactivity and one major metabolite was detected, M10 which account for 26.8%. Other metabolites such as M24, M18 and M12 accounted for 7.81%, 4.28% and 3.28%, respectively.

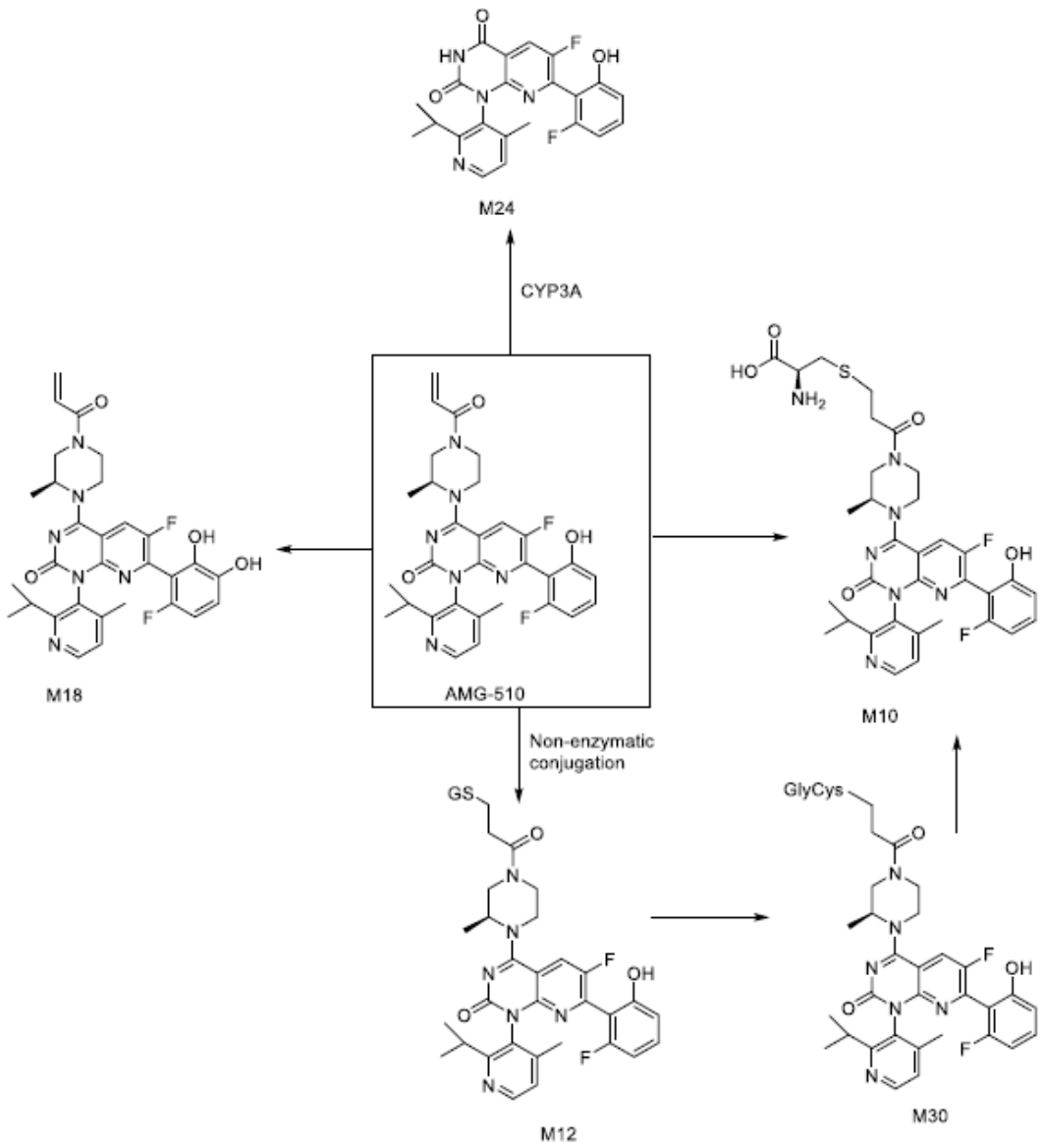
Results of the metabolite profiling indicated that sotorasib was the main component excreted in faeces with 52.97% of dose. M8, M10, M18 and M24 accounted for less than 1.49%, AMG3414811 was not detected in faeces, nor in plasma. In urine AMG510 and M10 was the main components excreted with

1.39% and 1.49% respectively. Therefore whereas 86% of the dose excreted in the urine was identified, approximately 80% of the dose excreted in faeces was identified.

Based on in vitro investigations using human recombinant CYP enzymes, sotorasib was found to be predominantly metabolised by CYP3A4 and to a lesser extent by CYP3A5 and 2C8.

Following single oral administration of a radioactive sotorasib dose of 720 mg, a cysteine adduct (M12, formed through hydrolysis of a glutathione adduct) and an oxidative metabolite (M24) resulting from CYP3A-mediated cleavage of the piperazine acrylamide moiety were the primary circulating metabolites. Neither of these metabolites were pharmacologically active.

Figure 3: Proposed metabolic scheme for sotorasib in humans



- Interconversion

Sotorasib has an asymmetric (S) carbon and a chiral axe (M). However the manufacturing process is designed to develop only sotorasib (S,M). Therefore any endogenous inter-conversion is unlikely.

- Pharmacokinetic of metabolites

M10, M18 and M20 PK was characterised in a subset of patient during study 20170543. Only M18 was found to be active but lesser than sotorasib.

Based on the PK profiles, M10 appears to accumulate with an AR of 17.2, whereas both M18 and M24 had minor accumulation (AR approximately of 3).

M24 is considered inactive. However since M24 formation was mediated by CYP 3A effects on CYP inhibition and induction was investigated. M24 was found *in vitro* to be a time-dependent inhibitor of CYP3A and an inducer of CYP 1A2, 2B6, 2C8, 2C9 and 2C19.In addition M24 was also characterised as a P-gp substrate and an inhibitor of P-gp.

Dose proportionality and time dependencies

Dose proportionality of sotorasib was investigated following single and multiple oral doses in patients during Study 20170543.

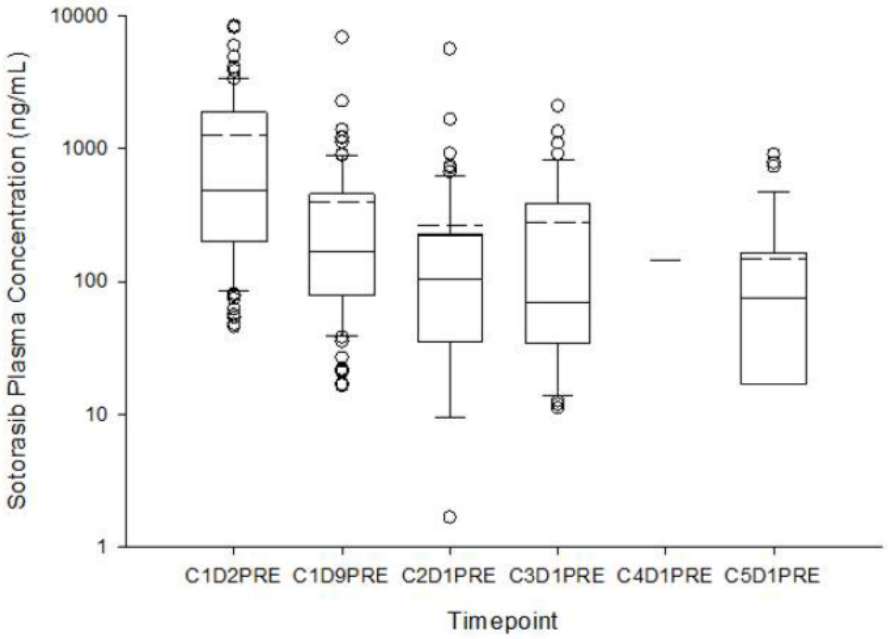
Following single oral dose of sotorasib from 180 mg to 960 mg, both C_{max} and AUC_{inf} appears overall similar, with increasing CL and V as dose increase. Following multiple dose the same trend is observed for both the PK exposure metrics (C_{max} and AUC_{inf}) and PK parameters (CL and V).

Geometric mean C_{max} and AUC_{0-24h} were less than dose proportional, with 1.4 and 1.9-fold increases, respectively, for a 5.3 increase in dose over the dose range of 180 to 960 mg. Similarly, C_{max} and AUC_{0-24h} increase by 1- to 1.3-fold with the same dose range at Day 8, this is particularly highlighted in **Error! Reference source not found.**.

Only patients received multiple dose of sotorasib. Following QD dosing in patients the applicant claimed that steady state is expected to be reached after 3 weeks as shown in Figure 4. Whereas estimated half-life of sotorasib was 6.5h, after repeated administration, no accumulation of the product is expected.

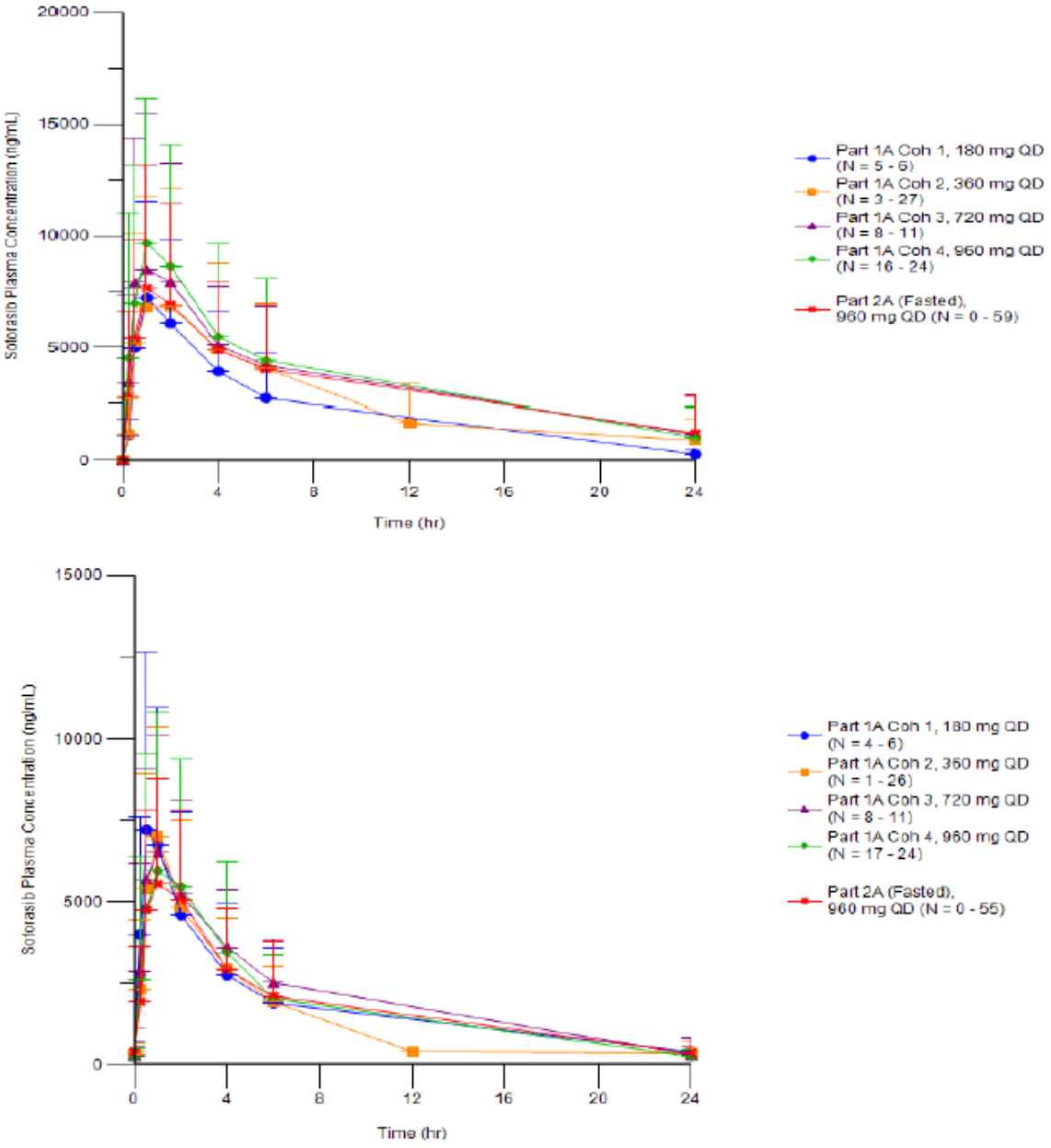
The discrepancy between the estimated half-life and the reaching of steady state, rely, according to the applicant, on an auto-induction phenomenon. Interestingly the auto-induction process appears more pronounced when the QD dose increased from 180 to 960 mg. Such behavior has been handled in the PopPK analysis.

Figure 4: Individual sotorasib plasma concentrations at predose timepoints



C1D2PRE = cycle 1, day 2 predose; C1D9PRE = cycle 1, day 9 predose; C2D1PRE = cycle 2, day 1 predose; C3D1PRE = cycle 3, day 1 predose; C4D1PRE = cycle 4, day 1 predose; C5D1PRE = cycle 5, day 1 predose

Figure 5: Mean (+SD) Plasma sotorasib concentration –time profiles (Day 1 and Day 8) following administration of 180, 360, 720 and 960 mg of sotorasib.



Pharmacokinetic in target population

Population pharmacokinetic (PK) modelling was performed to characterise and predict the PK of sotorasib (report 152921). Data from six studies were utilised; five Phase 1 studies in 69 healthy volunteers (n=14 each from studies 20190316, 20190318, 20190319, 20190320, and n=13 from study 20190317), and one Phase 1/2 study (study 20170543) is being performed in oncology patients with 258 patients with NSCLC, 113 patients with rectal or colon cancer, and 60 patients with other types of tumours (overall n=431 from study 20170543). The PK analysis dataset included concentration-time data from all patients receiving at least one dose at data cutoff of September 2nd, 2020. The analysis dataset consisted of 7476 quantifiable sotorasib concentration time samples from 500 volunteers. Overall, 276 of 7752 samples, 3.56 % samples below the limit of quantification were excluded from the analysis.

The population PK model was updated using additional data. Additional data from studies 20190500 (comparative Bioavailability/Bioequivalence: single oral doses of 960 mg sotorasib administered as either tablets or a water dispersion) and 20200199 (effect of acid reducing agents, famotidine or omeprazole in fed state; PK, safety, and tolerability: sotorasib 960 mg PO administered alone and in combination with either 40 mg famotidine or 40 mg omeprazole) in healthy were added to the dataset.

The number of patients for study 20170543 included in the population PK analysis are presented in

Table **10**. There were 4706 intensive PK samples and 2770 sparse PK samples included in the original population PK analysis from one Phase 1/2 patient study and five Phase 1 healthy subject studies. After including PK data from Studies 20190500 and 20200199, additional 328 intensive PK samples from healthy subjects were included in the updated population PK analysis.

Table 10: Number of participants for study 20170543 included in the population PK analysis

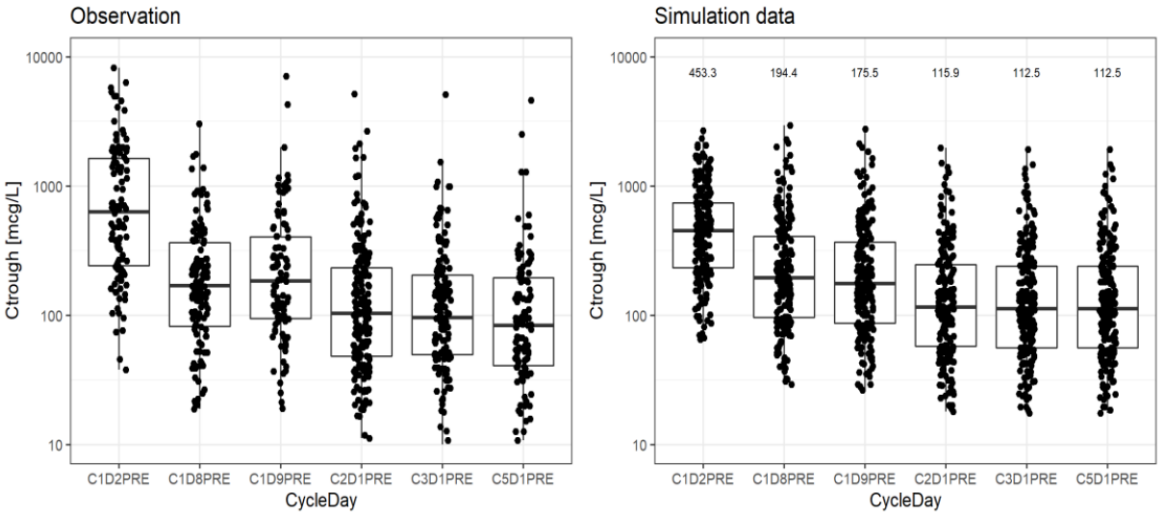
Dose	NSCLC	CRC	Other	Total
180mg	3	3	0	6
360mg	20	10	1	31
480mg	20	4	0	24
720mg	8	4	1	13
960mg	207	92	58	357
Total	258	113	60	431

The final model structure is a two-compartment disposition model with three transit compartments and a first order elimination. In order to describe the observed non-linear dose-exposure relationship and the induction effect following multiple dosing, the model was parameterised with different relative bioavailability values (F1) by doses using 960 mg dose as reference. Changes in exposure due to the induction effect were modeled using an exponential function with a first order rate coefficient parameter (KIND_F), such that the relative bioavailability (F1) and clearance (CL) were modulated by KIND_F from baseline ($F1_{BS}$ and CL_{BS}) to steady state of the induction ($F1_{SS}$ and CL_{SS}).

Relative bioavailability (F1, reference fixed to 1 for 960 mg QD dosing) at sotorasib doses of 180, 360, 480, 720, and 960 mg at baseline (day 1) and steady-state of induction effect was less than dose proportional varying between 4.95 and 1.53 (180 and 960 mg, respectively) at day 1 and between 4.58 and 1.00 at steady state. The induction effect on F1 seems to be higher at higher doses.

Sotorasib apparent CL was estimated by the model to increase by 91 % at steady-state relative to day 1 over time while the F1 was estimated to decrease by 35 % over time. The induction half-life corresponding to the estimated induction rate constant of 0.00845 1/h is 3.4 days, suggesting the induction reaches its state-steady in 2-3 weeks. The model-predicted and observed C_{trough} (pre-dose sotorasib concentration in NSCLC patients receiving 960 mg Sotorasib in the first 5 cycles) over time are presented in Figure 5 below.

Figure 6: Model-predicted and observed Ctrough values in NSCLC patients over time following 960 mg QD dosing of sotorasib



The co-administration with PPIs and high-fat meal were found to have an effect on bioavailability F for both and on ka for a high-fat meal.

The updated final model is a three-compartment model with first order absorption. A delay in absorption is described using two transit models with the same rate constant (KA). Like in the previous model, a time-dependent increase in clearance was included by an exponential function with a first order rate coefficient parameter (KIND). Again, different relative bioavailability (F1) for different doses were applied (reference dose: 960 mg) with induction effect (=KIND), leading to bioavailability values from 1 (960 mg) to 4.66 (180 mg). Interindividual variability (IIV) were found for on KA (67.6 %CV), V2 (54.4 %CV), CL (54.8 %CV). The following covariates were identified: albumin, race, gender, baseline tumour size (categorical) on CL, high-fat meal on KA, use of PPI and High-fat meal on F1, and gender on V2. A combined error model was selected (exponential = 0.622 (2.91% RSE), additive = 2.26 (109 % RSE)). As opposed to the previous model, ECOG baseline was not found a statistically significant covariate on CL anymore.

Sotorasib has shown time-dependent induction of CYP3A4 in *in vitro* studies. In study 20170543, sotorasib exposure decreased after repeated dosing. In the midazolam sub-study, midazolam exposure was decreased after co-administrated with sotorasib following 14 days of repeated sotorasib dosing, suggesting possible autoinduction of CYP3A4 by sotorasib. The autoinduction of CYP3A4 enzyme, which may be present in the gut and liver, may reduce relative bioavailability (F1) and increase clearance (CL) of sotorasib. To model the induction effect on F1 and CL, the time-dependent effect was described by an exponential function with a first-order rate coefficient parameter (KIND).

Parameter estimates of the updated model are presented in Table 11.

Table 11: Parameter estimates for the updated population PK model

Parameter Description (unit)	Parameter	Mean	%RSE
First-order absorption parameter in between transit compartments and the last transit compartment to the central compartment (1/hr)	TVKA	5.16	4.5
Clearance at baseline (L/hr)	CLBS	22.3	15.1
Clearance at steady state (L/hr)	CLSS	44.5	13.5
Induction rate (1/hr)	KIND	0.00636	13.9
Apparent volume of distribution of central compartment (L)	TVS2	207	6.3
Rate constant from central to 1st peripheral compartment (1/hr)	K24	0.0311	14.6
Rate constant from 1st peripheral to central compartment (1/hr)	K42	0.0792	11.8
Rate constant from central to 2nd peripheral compartment (1/hr)	K25	0.0108	33.1
Rate constant from 2nd peripheral to central compartment (1/hr)	K52	0.00117	144.4
Relative bioavailability at baseline (ratio to F1SS_DG5):			
• Dose: 180 mg (including 120 mg and 240 mg)	F1BS_DG1	4.99	24.3
• Dose: 360 mg	F1BS_DG2	3.5	9.7
• Dose: 480 mg	F1BS_DG3	2.96	14.0
• Dose: 720 mg (including 600 mg and 840 mg)	F1BS_DG4	2.29	14.9
• Dose:960 mg	F1BS_DG5	1.52	4.9
Relative bioavailability at steady state of induction (ratio to F1SS_DG5):			
• Dose: 180 mg (including 120 mg and 240mg)	F1SS_DG1	4.66	26.2
• Dose: 360 mg	F1SS_DG2	2.86	10.1
• Dose: 480 mg	F1SS_DG3	1.41	16.2
• Dose: 720 mg (including 600 mg and 840 mg)	F1SS_DG4	1.63	9.8
• Dose: 960 mg (reference, fixed)	F1SS_DG5	1	-
Covariate Effects			
Baseline tumor size on CL (proportional change)			
• Patient with tumor size >70mm (reference)		0	-
• Patient with tumor size ≤70mm	CLTUM_BS1	0.122	60.0
• Healthy (0mm)	CLTUM_BS2	0.822	31.6

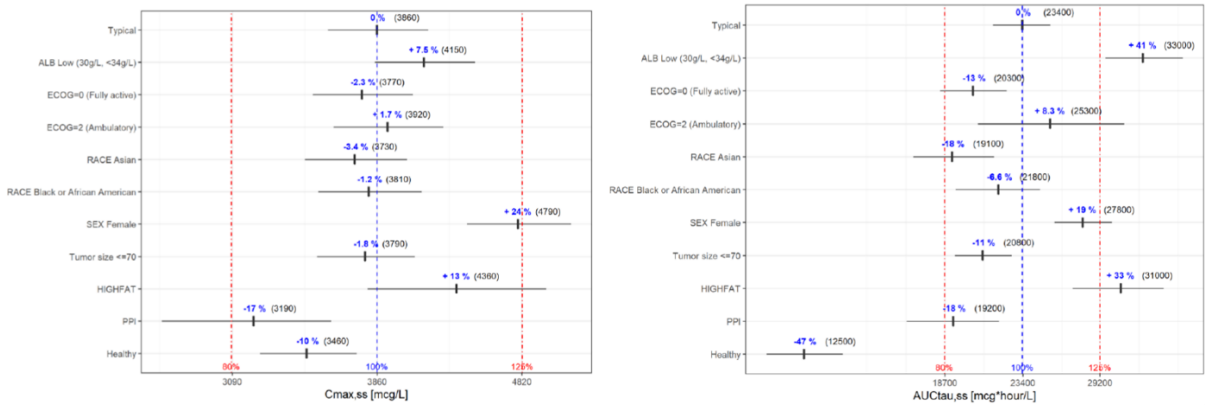
Parameter Description (unit)	Parameter	Mean	%RSE
Albumin on CL ((L/hr)/(g/dL))	CLALB	0.0335	31.6
Race on CL (proportional change)		0	-
• Caucasian (reference)			
• Asian	CLRACE1	0.254	32.5
• Black or African American	CLRACE2	0.0445	185
• Other or Multiple	CLRACE3	0.141	67.5
• Native Hawaiian or Other Pacific Islander	CLRACE4	-0.558	25.1
• American Indian or Alaska Native	CLRACE5	0.224	69.2
High-fat meal on F1 (proportional change)	F1HF	0.331	26.7
PPI on F1 (proportional change)	F1PPI	-0.19	40.0
High-fat meal on KA (proportional change)	KAHF	-0.647	9.5
SEX on V2/F (proportional change)			
• Male (reference)		0	-
• Female	S2SEX1	-0.21	20.3
Inter-Individual Variability			
Apparent volume (V2/F)	OMEGA.1.1	54.4 (%CV)	
Correlation between volume and clearance (V2/F-CL)	OMEGA.2.1	0.648 (correlation)	
Clearance (CL)	OMEGA.2.2	54.8 (%CV)	
Correlation between volume and absorption rate (S2-KA)	OMEGA.3.1	-0.324 (correlation)	
Correlation between clearance and absorption rate (CL-KA)	OMEGA.3.2	0.101 (correlation)	
Absorption rate (KA)	OMEGA.3.3	67.6 (%CV)	
Residual Error			
Exponential residual	RES_EXP	0.622	2.91 (%RSE)
Additive residual (ng/mL)	RES_ADD	2.26	109 (%RSE)

CV = coefficient of variation; RSE = relative standard error; - = not available

Special populations

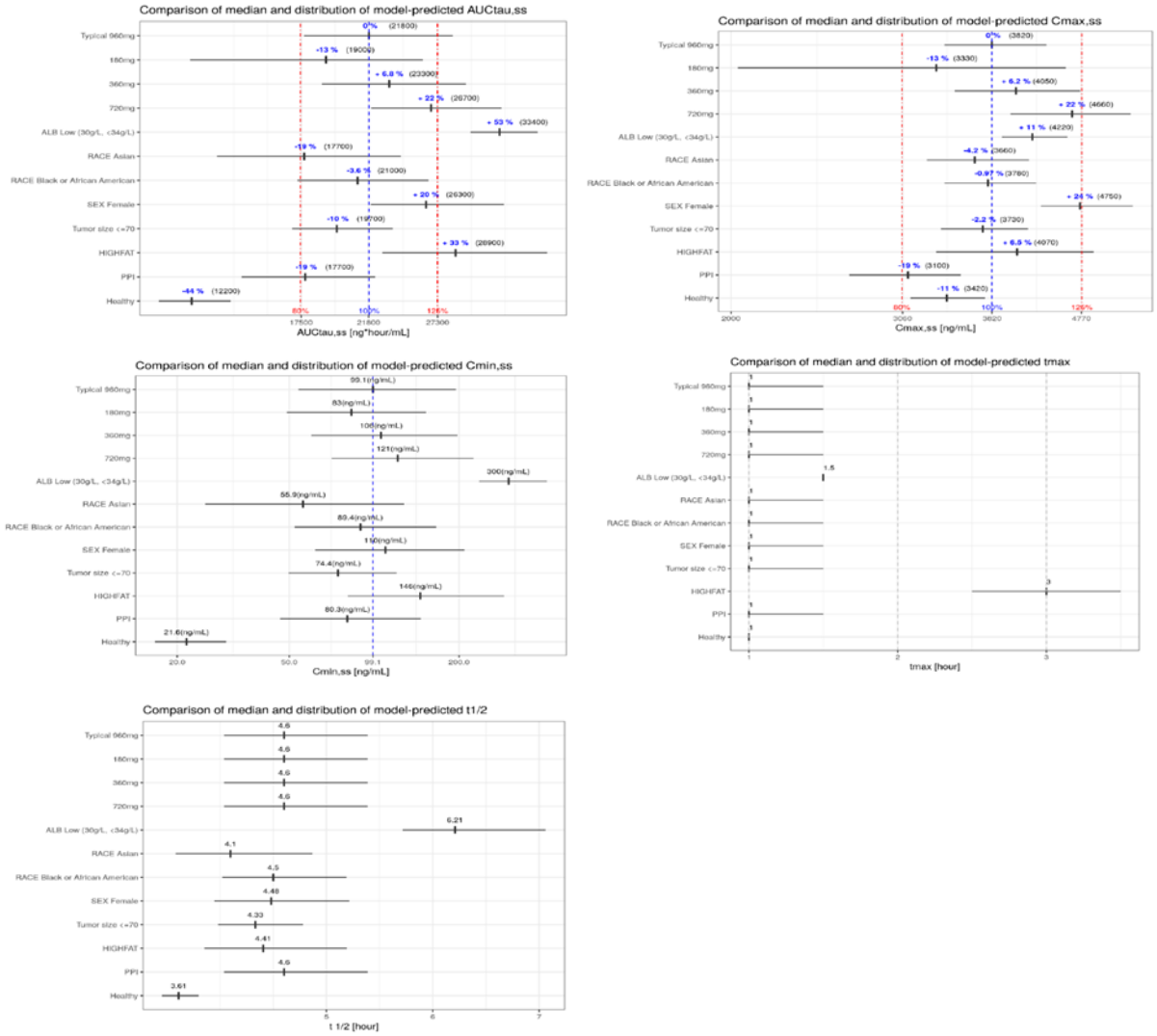
The effects of several covariates were investigated on sotorasib exposure PK ($AUC_{tau,ss}$ and $C_{max,ss}$) using Monte-Carlo simulations following the PopPK analysis.

Figure 7: Covariate effect on sotorasib Cmax (left) and AUC (right) at steady-state following 960 mg QD



PK and exposure metrics including $AUC_{tau,ss}$, $C_{max,ss}$, $C_{min,ss}$, t_{max}, and $t_{½}$ were estimated using 1000 simulations based on the updated final population PK model. The covariate effects on PK and PK differences in subpopulations, as assessed by the covariate analyses, are provided as forest plots in Figure 8. The typical subject (vertical dotted blue line) is defined as NSCLC Caucasian male with baseline tumour size >70mm, normal baseline albumin level (>34g/L) who received 960 mg QD sotorasib under fasted condition without PPI use.

Figure 8: Covariate effect on sotorasib AUC (left upper panel) C_{max} (right upper panel), C_{min} (left middle), t_{max} (right middle), and $t_{1/2}$ (left down) at steady-state following 960 mg QD



- Renal impairment

No formal PK study was performed to investigate the potential effect of renal impairment on the PK of sotorasib. Besides, this effect was investigated and tested as a covariate in the population PK model.

A slight decrease in clearance of sotorasib was observed patients with moderate renal impairment. However, it should be noted that the number of these patients (n=37, 7.54 % of all patients) was relatively smaller compared to those with mild renal impairment and normal renal function. No information was provided for patients with severe renal impairment.

No PK/clinical data in patients with severe renal impairment and end-stage renal disease are available.

- Hepatic impairment

No formal PK study was performed to investigate the potential effect of hepatic impairment on the PK of sotorasib. Besides, this effect was investigated and tested as a covariate in the population PK model.

The degree of hepatic impairment (i.e. mild or moderate) seem not to affect the clearance of sotorasib markedly. However, it should be noted that the number of these patients with moderate hepatic impairment was low (n=3, 0.6 % of all patients) precluding any valid conclusion from the population analysis regarding this subgroup. No information was provided for patients with severe hepatic impairment. Thus these results require cautious interpretation. Moreover, these results are based on a population PK model that is currently not considered reliable, thus are not conclusive at the time being.

- Gender

Sex was found a statistically significant covariate on CL and V2. Simulations predicted that the differences were associated with an increase exposure for the female population (+24 % in $C_{max,ss}$ and +19 % in $AUC_{tau,ss}$).

- Race

Asians showed a slightly higher clearance of sotorasib, associated with slight increase in exposure. The differences in CL and V2 between Japanese and non-Japanese Asian patients seem limited.

- Weight

Weight was found not being significantly associated with CL and V2 and thus with exposure.

- Elderly

Age was found not being significantly associated with CL and V2 and thus with exposure.

Table 12: Number of elderly subjects in Study 20170543 included in the noncompartmental analysis

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK data collected	152 / 431	42 / 431	2 / 431

The number of PK observations per each group of age for patients are represented in Table 13.

Table 13: **Summary PK exposures at steady-state by age groups for patients**

Age Group	Number of Subjects	Number of PK observations	$AUC_{tau, ss}$ (2.5-97.5 percentiles) [ng*hour/mL]	$C_{max, ss}$ (2.5-97.5 percentiles) [ng/mL]	$C_{min, ss}$ (2.5-97.5 percentiles) [ng/mL]
<65	235	3,456	23,158 (6,887-72,871)	4,469 (1,553-13,100)	80.5 (9.65-824)
65-74	152	2,311	23,896 (7,157-63,871)	4,183 (1,550-13,065)	103 (11.6-893)
75-84	42	666	20,958 (5,935-57,786)	3,624 (1,249-11,916)	76.3 (6.43-430)
>=85	2	41	17,277 (12,276-22,277)	3,903 (3,671-4,134)	58.5 (24.9-92.2)
All	431	6,474	23,155 (6,988-64,748)	4,288 (1,533-12,895)	89.4 (9.14-825)

- Laboratory parameter

Baseline albumin levels was a statistically significant covariate on CL and associated with a higher exposure (+7.5 % in $C_{max,ss}$ and +41 % in $AUC_{tau,ss}$ for median albumin 30 g/L compared to normal with ≥ 34 g/L and median albumin 40 g/L) for patients with lower albumin baselines. Thus, patients with low albumin baseline levels may require dose adjustments.

- Disease status

Higher ECOG score and greater tumour size at baseline, were associated with lower clearance and higher exposure. Patients had a higher exposure compared to healthy volunteers. Thus, some patients may require dose adjustments. Using the updated model, ECOG baseline was not found a statistically significant covariate on CL anymore.

- Children

The pharmacokinetics of sotorasib was not investigated in children.

Pharmacokinetic interaction studies

Effect of other drug on sotorasib (victim drug)

In vitro studies showed sotorasib, parent drug, was substrate of CYP3A4 and P-gp.

Co administration of sotorasib with multiple doses of a strong CYP3A4 inducer (rifampicin) decreased sotorasib Cmax by 35% and AUC by 51%.

CYP3A4 contribution to sotorasib metabolism was shown to be moderate, of roughly 30%.

Effect of sotorasib on other drugs (perpetrator drug)

Sotorasib was identified *in vitro* as CYP3A4 time-dependent inhibitor and inducer. The net effect was further investigated in Part 2e of Study 20170543 conducted with midazolam, CUP3A4 probe substrate. Co administration of sotorasib with midazolam (a sensitive CYP3A4 substrate) decreased midazolam Cmax by 48% and AUC by 53%.

In addition to sotorasib CYP3A4 induction potential, sotorasib was *in vitro* an inducer of CYP enzymes CYP2B6, CYP2C8, CYP2C9, and CYP2C19. No induction of CYP1A2 was observed after incubation with sotorasib (Study 150536).

Sotorasib was also identified *in vitro* as an inhibitor of CYP2D6. In addition to the initial PBPK model submitted to describe sotorasib following single administration, a new model was submitted to describe sotorasib PK at steady state in NSCLC patients by decreasing the apparent clearance (CL/F) from 37.5 L/h, the single dose model value to 25 L/h to fit steady-state PK data in target population. Consequently, depending on the dosing regimen single or multiple administrations, the model to use varies. The provided model was not demonstrated to be able to robustly describe sotorasib PK, following single and multiple dose administration, and across dose levels. Therefore, interaction prediction with CYP2D6 based on the proposed PBPK model cannot be endorsed. (See discussion on clinical pharmacology).

Sotorasib was identified *in vitro* as an inhibitor of P-gp, BCRP, OAT1, OAT3, OCT1, OATP1B1, OATP1B3.

With regards to P-gp inhibition, in study 20190315 conducted in healthy subjects, digoxin showed an increase in digoxin exposure by 21% (ratio of 1.214 with 90% CI = 1.105, 1.334) and an increase in Cmax by 91% (ratio of 1.914 with 90% CI = 1.574, 2.328).

MATE1 and MATE2-K inhibition was also evaluated in study 20190317 conducted in healthy subjects with co-administration of metformin. The results showed sotorasib did not affect metformin PK (based on AUC last and AUC inf with the estimated ratios of 0.990 (90% CI 0.914, 1.073) and 0.985 (90% CI 0.909, 1.067). Therefore, sotorasib is not expected to affect substrate transport mediated by MATE1/MATE2K or OCT2.

2.6.2.2. Pharmacodynamics

Relationship between plasma concentration and response

Exposure-response (ER) analyses for efficacy and safety of sotorasib in patients with advanced solid tumours with a specific KRAS mutation were performed (report 152922). PK exposure metrics predicted by the PopPK analysis ($AUC_{tau,ss}$, $C_{max,ss}$, $C_{trough,ss}$) were used as input for both analyses.

Data from Phase 1/2 study 20170543 were analysed. The analysis dataset for ER analysis for efficacy and safety consisted of patient data with a phase 1 data cut-off date of July 6th, 2020 and a phase 2 data cut-off date of September 1st, 2020. NSCLC patients with at least one post-treatment plasma concentration measurement and one evaluation of corresponding efficacy endpoints were included in the ER analysis for efficacy.

Exposure-response-efficacy

PD endpoints consisted of ORR, DCR, PFS, OS, DOR and TTR (time to respond) and BTSR (best tumour size response). Time to respond (TTR) and best tumour size response (BTSR) were evaluated using linear regression. Objective response rate (ORR), and disease control rate (DCR) were evaluated using logistic regression model. Time-to-event endpoints progression free survival (PFS), overall survival (OS), and duration of response (DOR) were evaluated using a Cox proportional hazard model or an abbreviated to Cox model.

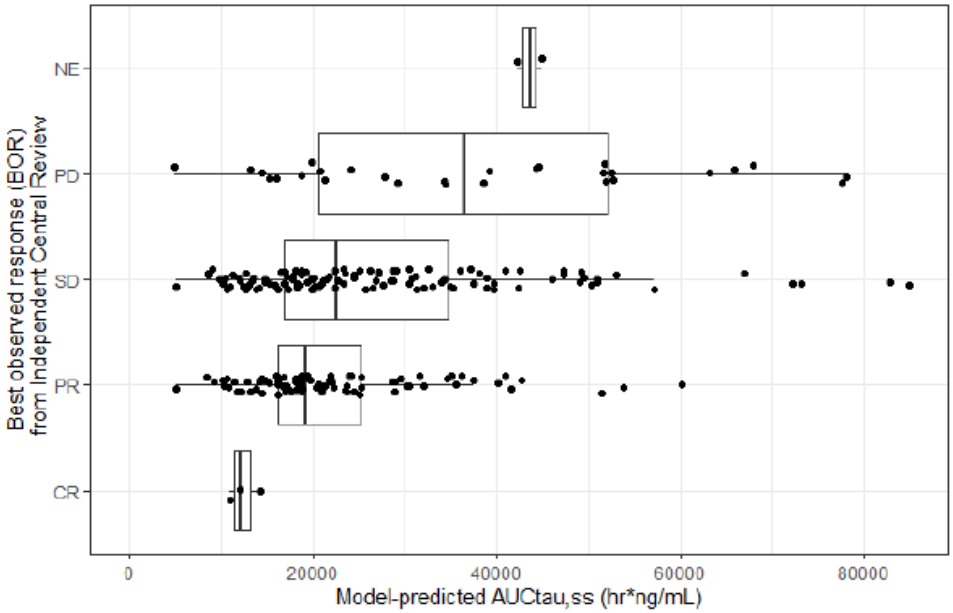
The dataset for efficacy consisted of 248 NSCLC patients with at least one post-treatment plasma concentration and at least one evaluation of efficacy endpoints from Study 20170543. The dataset for safety consisted of 421 patients with solid tumours (n=248 with NSCLC, n=113 CRC, and n=60 other types of solid tumours).

Graphical analyses for efficacy reveal that smaller tumour size (< 70 mm), ECOG=0 were associated with a longer progression free survival and overall survival. Kaplan Meier curves for PFS, OS and DOR with AUC in NSCLC patients indicate that increasing exposure is not associated with an improved outcome.

Moreover, an increase in exposure was associated with decreasing response for BOR, ORR, DCR, OS, and PFS and it seems that exposure and dose are not correlated to efficacy (e.g. baseline sum of lesion diameters, brain metastasis) as shown in

for BOR and **Error! Reference source not found.** for ORR and DCR.

Figure 9: Box-plot of model predicted AUCtauss by BOR



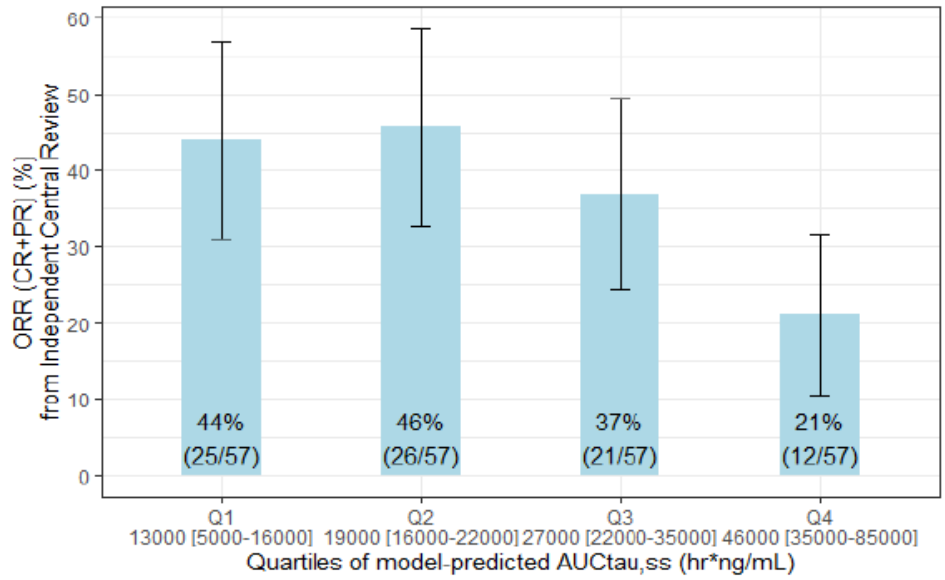
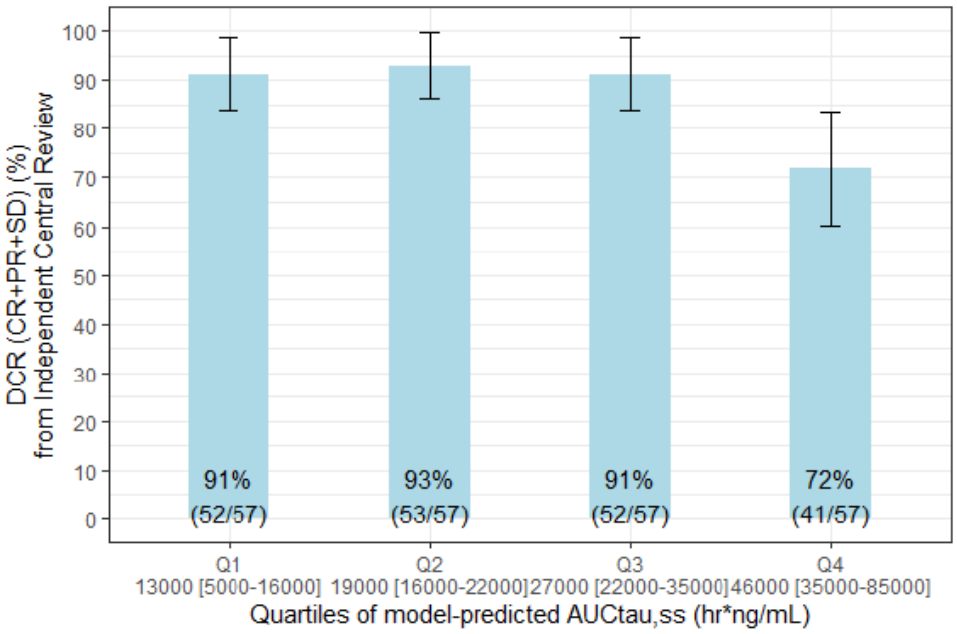


Figure 10: Relationship between ORR (up) and DCR (down) vs Model-predicted AUCtauss



In contrast, a significant inverse ER relationship was observed. A dose-response analysis showed that the 960 mg QD dose was not statistically significantly superior for ORR, BTSR, PFS and OS when compared to lower doses of 180, 360 and 720 mg QD (p=0.194 to 0.589) as shown in Table 14 below.

Table 14: Result of dose-response analysis for efficacy

Response Variable	Predictor Variable	Estimate	Standard Error	P-value
	Logistic Regression Analysis			
Objective Response Rate, ORR	960 mg QD vs Other Dose Groups	0.2474	0.4582	0.589
	Regression Analysis			
Progression Free Survival, PFS	960 mg QD vs Other Dose Groups	0.7233	0.2492	0.194
Overall Survival, OS	960 mg QD vs Other Dose Groups	0.8449	0.3080	0.584
	Linear Regression Analysis			
Best Tumor Size Response, BTSR	960 mg QD vs Other Dose Groups	-7.945	7.562	0.294675

Hazard ratio by exponentiating the parameter estimate, and the corresponding standard error were reported for Cox regression analysis

Exposure-response safety

PD endpoints consisted mainly of TRAE associated with hepatic disorders (ALT, AST, TBIL) and other factors. TRAEs were evaluated using logistic regression. No relation was found between sotorasib PK and any TRAEs.

2.6.3. Discussion on clinical pharmacology

Sotorasib, a new chemical entity, is an orally available, first in class small molecule that specifically binds and irreversibly inhibits the KRASp.G12C mutant protein.

Sotorasib is a BCS class IV drug, with probably very low absolute bioavailability due to a marked pre-systemic elimination process and low solubility at intestinal pH. The drug exhibits a pronounced nonlinear PK behaviour and is extensively metabolised mainly by CYP3A4. Three metabolites (M10, M18 and M24) were investigated during the clinical development programme, mainly M24.

Based on the food effect study (and substudy in patients), the applicant recommends that sotorasib can be administered with or without food. In healthy volunteers (HV) or patients following a 360 mg dose, a high fat meal was associated with an increase of AUC of 38% and 75% respectively. Whereas the study in HV is adequately designed, results from the patient sub-study should be viewed cautiously. The applicant was asked to discuss if an increase in the AUC by at least 38% is clinically relevant when sotorasib is administered with a high fat meal. The increase AUC of 38% was not discussed. Nevertheless, the applicant provided an in-depth discussion related to the safety events observed in the patients that received sotorasib in the fed/fasted states however, given the number of subjects in each state (14 vs 200), no clear conclusions can be drawn.

In the mass-balance study (720 mg single dose) sotorasib accounted only for 22.2% of circulating radioactivity. Exposure to sotorasib decreases over time, presumably due to autoinduction of metabolism, whereas exposure to metabolites is expected to increase. It is unfortunate that the mass-balance study was conducted using a single dose even though it was recommended in the CHMP scientific advice to conduct the study at steady state to mimic the therapeutic situation. Such design would have been helpful to assess the accumulation potential of sotorasib's main metabolites. Presently the applicant has not presented reliable data on metabolite accumulation following administration of multiple doses. Therefore, the accumulation of sotorasib metabolites should be investigated particularly during the ongoing dose comparison study (Recommendation).

Sotorasib exhibited nonlinear pharmacokinetics over a range of single and multiple oral administration doses studied between 180 to 960 mg QD as Cmax and AUC0-24 hour were less than dose proportional. The average Cmax and $AUC_{0\text{-}24h}$ values following multiple doses were similar for all dosing regimens from 180 mg QD to 960 mg QD. Exposure to sotorasib decreases over time following 960 mg QD dosing regimen until steady state is reached. Steady state plasma concentrations were achieved by approximately 3 weeks across the phase 1 and phase 2 clinical studies across all sotorasib doses (see section 5.2 of the SmPC).

Co-administration of sotorasib with a PPI (omeprazole) or an H2 receptor antagonist (famotidine) led to a decrease in sotorasib concentrations. Co-administration of PPIs and H2 receptor antagonists with sotorasib is not recommended because the impact on sotorasib efficacy is unknown. If treatment with an acid-reducing agent is required, sotorasib should be taken 4 hours before or 10 hours after administration of a local antacid (see sections 4.2 and 4.5 of the SmPC).

Co-administration of multiple-dose itraconazole (a strong CYP3A4 and P-gp inhibitor) did not increase sotorasib exposures to a clinically significant extent. No dose adjustment of sotorasib is recommended when co-administered with CYP3A4 inhibitors.

Co-administration of strong CYP3A4 inducers (e.g. rifampicin, carbamazepine, enzalutamide, mitotane, phenytoin and St. John's wort) with sotorasib is not recommended because they may decrease sotorasib exposure.

Sotorasib is a moderate CYP3A4 inducer. Co administration of sotorasib with CYP3A4 substrates led to a decrease in their plasma concentrations, which may reduce the efficacy of these substrates.

Co-administration of sotorasib with CYP3A4 substrates with narrow therapeutic indices, including but not limited to alfentanil, ciclosporin, dihydroergotamine, ergotamine, fentanyl, hormonal contraceptives, pimozide, quinidine, sirolimus and tacrolimus, should be avoided. If co-administration cannot be avoided, adjust the CYP3A4 substrate dosage in accordance with the current summary of product characteristics.

In vitro data indicated that sotorasib may have the potential to induce CYP2B6, CYP2C8, CYP2C9 and CYP2C19; the clinical relevance of these findings is unknown. When sotorasib is co-administered with medicinal products metabolised by these enzymes, appropriate monitoring is recommended.

Interactions of sotorasib with CYP2D6 substrates was investigated by *in silico* approaches. Two PBPK models were presented to describe sotorasib PK following single dose in heathy populations and multiple dose in NSCLC patients respectively. To describe sotorasib PK at steady-state in target population, the apparent clearance (CL/F) was reduced from 37.5 L/h, the single dose model value to 25 L/h to fit steady-state PK data in target population. The use of two different models depending on the dosing regimen is not considered acceptable, especially considering the decrease in clearance at steady-state was attributed to sotorasib auto-induction which may be accounted by PBPK models, given their mechanistic nature. In addition, the platform qualification for CYP2D6 inhibition, which enzyme is subject to polymorphism, is considered insufficiently qualified. As a consequence, the following data has been reflected in section 4.5 of the SmPC: *in vitro* data indicated that sotorasib may have the potential to inhibit CYP2D6, the clinical relevance of these findings is unknown. When sotorasib is co-administered with CYP2D6 substrates (e.g. flecainide, propafenone, metoprolol), appropriate monitoring is recommended.

In vitro data indicated that sotorasib may have the potential to inhibit BCRP; the clinical relevance of these findings is unknown. When sotorasib is co-administered with BCRP substrates (e.g. methotrexate, mitoxantrone, topotecan and lapatinib), appropriate monitoring is recommended.

Co-administration of sotorasib with P gp substrates with narrow therapeutic indices is not recommended. If co administration cannot be avoided, adjust the P gp substrate dosage in accordance with the current summary of product characteristics.

The applicant is recommended to conduct a clinical drug-drug interaction study to investigate the effect of coadministration of sotorasib on the pharmacokinetics of a BCRP substrate (rosuvastatin) the MAH shall submit the final clinical study report of a phase I, open-label, fixed sequence crossover study in healthy subjects (Recommendation).

One population PK analysis and two ER analysis were performed. The population PK model was not considered reliable. Consequently the ER analysis based on this model cannot be considered reliable. An updated population PK model was submitted during the procedure but not considered robust (parameter estimates with low precision, and diagnostic plots revealing lack of descriptive and predictive performance) and not considered reliable to simulate doses less than 960 mg. A population PK model refinement using data from the forthcoming dose comparison part of Study 20170543 (240 mg vs. 960 mg) should be conducted. If deemed appropriate, the SmPC will be updated according to the results of the refined model using the dose comparison data part of Study 20170543 (240 mg vs. 960 mg) (Recommendation). To this end the applicant agrees to submit such analysis, the refined model is expected until 30 September 2023.

The applicant has not conducted dedicated PK studies in special populations. The effects of impaired renal and hepatic function and other intrinsic factors were evaluated only in the population PK analysis.

No dose adjustment is recommended for patients with mild renal impairment (creatine clearance, CrCL, $\geq$ 60 mL/min). Sotorasib has not been studied in patients with moderate or severe renal impairment (CrCL < 60 mL/min). Therefore, caution should be exercised when treating patients with

moderate, severe and end stage renal impairment. No dose adjustment is recommended for patients with mild hepatic impairment (AST or ALT < 2.5 × ULN or total bilirubin < 1.5 × ULN). However, administration of sotorasib in subjects with moderate and severe hepatic impairment is not recommended. The applicant will conduct a formal PK study in subjects with hepatic impairment (Study 20200362) (see RMP).

The claimed dose of 960 mg QD is not soundly justified from a PK perspective. On 09 March 2021 the applicant proposed an update for a dose comparison part for patients with NSCLC to be added to Study 20170543 (phase 2 Part B). Sotorasib has demonstrated a non-linear pharmacokinetic profile, with responses noted at all dose levels ranging from 180 mg to 960 mg. A dose of 240 mg QD has been selected for further exploration in this dose comparison part of the study to investigate whether a lower dose can be as safe and efficacious as 960 mg QD. The applicant proposes to use 240 mg QD (administered as two 120 mg tablets) as the lower dose in this dose-comparison study. Exposure at the 240 mg dose is expected to be above the concentration associated with 90 % inhibition *in vitro* and is anticipated to generate an exposure profile where robust clinical responses have been observed in advanced cancer patients. This dose would have a meaningfully different tablet burden compared with the higher dose (2 tablets versus 8 tablets). From the PK perspective, the investigation of lower doses than 960 mg are endorsed and highly encouraged. The results of the ongoing dose comparison part of Study 20170543 (phase 2 Part B) investigating a 240 mg QD dose will be submitted (Recommendation).

2.6.4. Conclusions on clinical pharmacology

Overall, the PKs of sotorasib have been characterised in healthy subjects and in the target patients based on formal phase 1 and 2 studies. The claimed dose of 960 mg QD is not soundly justified from a PK perspective. To this end the results from the ongoing dose comparison part for patients with NSCLC to be added to Study 20170543 (phase 2 Part B) where a 240 mg QD dose will be investigated, are awaited.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study(ies)

The Phase-1 portion of the study 20170543 was the first-in-human (FIH) study of sotorasib and was conducted in 2 parts: part 1 - dose exploration and part 2 - dose expansion.

Part 1 (dose exploration) had several dose cohorts that evaluated sotorasib administered under different conditions in subjects with *KRAS p.G12C*-mutated advanced solid tumours:

- Part 1a: escalating dosing of once daily (QD) sotorasib monotherapy administered orally (180 mg to 960 mg).
- Part 1b: 480 mg sotorasib monotherapy twice daily (BID) administered with food.
- Part 1d: 960 mg sotorasib QD administered with food.
- In part 1c cohort, 360, 720, and 960 mg sotorasib QD in combination with pembrolizumab were evaluated in subjects with NSCLC (combination therapy).

The phase 1 dose expansion (part 2) was to open when the MTD and/or a RP2D had been determined in part 1. Part 2 comprised several cohorts that evaluated sotorasib administered under different conditions in subjects with *KRAS p.G12C*-mutated advanced solid tumours:

- Part 2a: 960 mg sotorasib monotherapy QD.
- Part 2b: 480 mg sotorasib monotherapy BID administered with food.
- Part 2d: 960 mg sotorasib QD administered with food.
- In Part 2c, sotorasib QD in combination with pembrolizumab will be evaluated in subjects with NSCLC
- Part 2e: evaluated safety, tolerability, preliminary efficacy, PK and pharmacodynamic parameters of 960 mg QD dosing for sotorasib monotherapy in subjects with previously untreated *KRAS p.G12C*-mutated metastatic NSCLC. In addition, approximately 4 to 6 subjects enrolled in part 2e could participate in a drug-drug interaction substudy of sotorasib with midazolam.

The primary objectives were to evaluate the safety and tolerability of sotorasib and to estimate the maximum tolerated dose (MTD) and/or a recommended phase 2 dose (RP2D) of sotorasib in adult subjects with *KRAS p.G12C*-mutated advanced solid tumours.

The secondary objectives of this study were the evaluation of tumour response (for all study parts, except part 2e) and pharmacokinetics.

The full analysis set included all subjects who received ≥ 1 dose of sotorasib and had ≥1 or more measurable lesions at baseline as assessed by blinded independent central review using RECIST 1.1. The monotherapy phase-1 ORR analysis set included all subjects in the phase-1 full analysis set who had the opportunity to be followed for ≥ 7 weeks starting from day 1.

The RP2D for sotorasib was determined to be 960 mg QD, which was the highest dose tested.

2.6.5.2. Main study

A Phase 1/2, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of AMG 510 Monotherapy in Subjects With Advanced Solid Tumors With KRAS p.G12C Mutation and AMG 510 Combination Therapy in Subjects With Advanced NSCLC With KRAS p.G12C Mutation (CodeBreak 100)

Methods

- **Study Participants**

Inclusion criteria:

- Adult patients with pathologically documented, locally-advanced or metastatic malignancy with KRAS p.G12C mutation identified through molecular testing. For phase 2, the mutation will be confirmed by central testing prior to enrolment for NSCLC and CRC tumour types only.

- Phase 2 subjects must have progressed after receiving anti-PD1 or anti-PD-L1 immunotherapy (unless contraindicated) AND/OR platinum-based combination chemotherapy AND targeted therapy if actionable oncogenic driver mutations were identified (ie, EGFR, ALK, and ROS1).

- Subjects must have received no more than 3 prior lines of therapy.

- Measurable disease per RECIST 1.1 criteria

- Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2 (phase 1) or ≤ 1 (phase 2)

- QTc ≤ 470 msec (based on average of screening triplicates)

Exclusion Criteria:

- Active brain metastases from non-brain tumours.

- Subjects who have had brain metastases resected or have received radiation therapy ending at least 4 weeks prior to study day 1 were eligible if they meet all of the following criteria: a) residual neurological symptoms grade ≤ 2; b) on stable doses of dexamethasone, if applicable; and c) follow-up MRI performed within 30 days shows no new lesions appearing.

- Patients with history or presence of haematological malignancies, with myocardial infarction within 6 months of study day 1, symptomatic congestive heart failure (New York Heart Association > class II), unstable angina, or cardiac arrhythmia requiring, with Gastrointestinal (GI) tract disease causing the inability to take oral medication, malabsorption syndrome, requirement for intravenous alimentation, uncontrolled inflammatory GI.

- Patients with previous treatment with a direct $KRAS^{G12C}$ inhibitor.

- **Treatments**

Sotorasib was provided as 120 mg tablets and was administered orally once daily (QD) and without interruption (ie, no planned off-treatment days). The RP2D was 960 mg PO QD.

Daily treatment with sotorasib in phase 2 was to continue without interruption) until disease progression, treatment intolerance, withdrawal of consent, or death.

- **Objectives**

For the phase 2 portion of the study, the primary objective was to evaluate the objective response rate (ORR) for sotorasib as monotherapy in subjects with *KRAS p.G12C*-mutated advanced solid tumours.

Secondary objectives for both portions of the study included other measures of sotorasib efficacy (endpoints of duration of response, disease control rate, time to response, progression-free survival [PFS], and overall survival [OS]), safety, and pharmacokinetics.

- **Outcomes/endpoints**

Table 15: Objectives and endpoints of the phase-2 portion of the study 20170543

Objectives	Endpoints
Phase 2 – Primary	
Monotherapy (Once Daily [QD] Dosing) – Advanced Solid Tumours	
• to evaluate tumour objective response rate (ORR) assessed by response evaluation criteria in solid tumours (RECIST) 1.1 criteria of SOTORASIB (sotorasib) as monotherapy in subjects with *KRAS p.G12C*-mutated advanced tumours (non-small cell lung cancer [NSCLC], colorectal cancer [CRC], and other tumour types)	• objective response (complete response [CR] + partial response [PR]), measured by computed tomography [CT] or magnetic resonance imaging [MRI] and assessed per RECIST 1.1 Response was assessed by blinded independent central review (BICR). Complete response and PR required confirmatory CT or MRI repeat assessment at least 4 weeks after the first detection of response.
Phase 2 – Secondary	

• to evaluate other measures of sotorasib efficacy as monotherapy in subject with *KRAS p.G12C*-mutated advanced tumours by RECIST 1.1 (NSCLC, CRC, and other tumour types)	– duration of response (DOR) – disease control – time to response (TTR) – progression-free survival (PFS) – overall survival (OS) – 6-month PFS and 12-month PFS – 12-month OS
• to evaluate the safety and tolerability of sotorasib in adult subjects with *KRAS p.G12C*-mutated advanced solid tumours (NSCLC, CRC, and other tumour types)	• Incidence and severity of adverse events
• to evaluate the pharmacokinetics (PK) of sotorasib following administration as an oral tablet formulation	• PK parameters of sotorasib (SOTORASIB) including, but not limited to, maximum plasma concentration (Cmax), area under the plasma concentration-time curve (AUC), clearance, and time to achieve Cmax (tmax)
Exploratory	
Objective	Endpoint
• to explore biomarkers of response and resistance in tumour and blood specimens prior to exposure to sotorasib (SOTORASIB) and at the time of progression	• biomarkers of response and resistance to sotorasib (SOTORASIB) at the time of progression - quantification of biomarker expression at protein, RNA, and DNA levels, as appropriate - potential biomarkers by biochemical and/or genetic analysis of blood and/or tumour tissue samples
• to explore the subject experience with sotorasib (SOTORASIB) treatment using patient-reported outcome instruments with respect to the following core concepts:	– Changes in cancer-specific symptoms and overall health status using subject-reported outcome instruments: • impact of treatment on disease-related symptoms and HRQOL (instruments; EORTC QLQ-C30 + disease-specific modules QLQ LC13 and NSCLC SAQ for NSCLC, and QLQ Pan 26 for pancreatic cancer; PGIS and PGIC in cough, dyspnoea and chest pain among NSCLC patients) • treatment-related symptoms and impact on the subject (EORTC QLQ-C30, selected questions from the PRO-CTCAE library and a single item about symptom bother, item GP5 of the FACT-G) • physical function (instrument: EORTC QLQ-C30, Physical function scale)

EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30; FACT-G = Functional Assessment Of Cancer Therapy - General; HRQOL = health-related quality-of-life; NSCLC = non-small cell lung cancer; PRO-CTCAE = patient-reported outcomes version of the common terminology criteria for adverse events; QLQ LC13 = Quality-Of-Life Questionnaire Lung Cancer Module; QLQ Pan 26 = Quality-of-Life Questionnaire Pancreatic Cancer Module; SAQ = symptom assessment questionnaire

- **Sample size**

Approximately 250 subjects were to be enrolled in phase 2 (at least 105 subjects with NSCLC and 60 subjects with CRC). The phase 2 part of the study targeted an ORR higher than a prespecified benchmark rate to be excluded. The threshold was based on the lower limit of the 95% CI for the observed ORR for each tumour type (NSCLC or CRC).

For subjects with NSCLC, a large phase 3 clinical trial (REVEL) in the second-line treatment after disease progression on platinum-based therapy showed an ORR of 23% (95% CI: 20, 26) with ramucirumab plus docetaxel treatment (Garon et al, 2014; Cyramza Prescribing Information). Thus, the benchmark ORR to exclude was selected as 23% for the NSCLC study.

For subjects with CRC, while treatment with regorafenib or TAS 102 in subjects who had ≥ third-line treatment the ORRs of 1% to 4% were observed. These therapies had also demonstrated survival benefits (Li et al, 2015; Mayer et al, 2015; Grothey et al, 2013).

To justify the use of the surrogate endpoint ORR in the Phase 2 study for the subjects with CRC, a higher benchmark ORR was selected. Thus, the benchmark ORR to exclude was selected as 10% for the CRC study.

A sample size of 105 subjects for NSCLC and 60 subjects with CRC provide approximately a 90% probability that the lower limit of the ORR 95% CI exceeds the tumour-specific benchmark ORR.

The minimum observed ORRs that would exclude the benchmark ORR with 105 subjects with NSCLC and 60 subjects with CRC are 32% and 20%, respectively. No benchmark ORR was set for the other tumour types because of expected low enrolment.

- **Randomisation and Blinding (masking)**

Not applicable.

- **Statistical methods**

Primary endpoint analyses

The primary analysis of the phase 2 portion of the study estimated ORR (CR+PR) measured by CT or MRI and assessed by RECIST 1.1 by BICR. The analysis was performed by tumour type. For NSCLC, a benchmark rate was selected as 23% based on a phase 3 trial (REVEL) for second-line treatment after disease progression on platinum-based therapy, which showed a 23% ORR with ramucirumab + docetaxel. According to the protocol and SAP, the primary NSCLC analysis was to be considered successful if the 95% confidence interval excluded the 23% pre-specified benchmark rate, corresponding to an ORR estimate ≥ 32%.

The percentage of subjects with an OR in Phase 2 ORR Analysis Set were summarised along with a Clopper-Pearson exact confidence interval. Subjects without a post-baseline tumour assessment were considered as non-responders.

BICR was used for the primary analysis, with investigator assessment used for sensitivity analysis. Concordance between central review and investigator assessments was summarised by tumour type.

Secondary endpoint analyses

- Disease control rate (DCR) was summarised as for ORR
- Progression-free survival (PFS), overall survival (OS) and duration of response (DOR) were summarised with Kaplan-Meier median, quartiles and rates for selected time points. DOR was summarised for subjects who achieved confirmed partial or complete response only
- Time to response (TTR) was summarised for subjects who achieved a confirmed partial or complete response only, with mean, standard deviation, median, minimum and maximum

The censoring rules for PFS are described in the table below:

Situation up to DCO/EOS	Date of Event or Censor	Outcome
No evaluable post-baseline tumor assessments per BICR, no death recorded	Date of randomization (or first dose date of IP in non-randomized trials)	Censor
PD per BICR	First detection of PD per BICR	Event
No PD per BICR, but death recorded	Date of death	Event
Start of new anti-cancer therapy prior to any PD per BICR or death	Date of last evaluable assessment per BICR before or on start of new anti-cancer therapy	Censor
No PD per BICR, no death recorded, no start of new anti-cancer therapy	Date of last evaluable assessment per BICR	Censor
Death or PD per BICR immediately after consecutively missed more than one tumor assessment	Date of last evaluable assessment per BICR with documented non-progression prior to missing assessment(s) [a]	Censor

DCO = Data Cutoff; EOS = End of Study; PD = Progressive disease
[a] This supersedes the previous rules that result in PFS event at date of PD or death.

DOR censoring rules were following the same strategy as for PFS. Regarding OS, subjects who did not die were censored at the date of last contact.

Futility interim analyses

The interim futility analyses were conducted in a continuous manner using Bayesian predictive probability for NSCLC. It began after approximately 25 response-evaluable subjects, defined as received at least 1 dose of sotorasib and had at least 7 weeks response data starting from day 1. Following this initial interim analysis, subsequent interim analyses were performed after every 10 subjects becomes response evaluable. The futility analyses were reviewed at interim futility data review team (DRT) meetings.

The Go criterion was met if the probability that the true ORR exceeds the benchmark ORR is ≥ to a high probability of:

- Go criterion for NSCLC: probability [ORR > 0.23] ≥ 80%
- Go Criterion for CRC: probability [ORR > 0.1] ≥ 95%

Given the existing observed data during the continuous monitoring stage, the Bayesian predictive probability was obtained by calculating the probability of reaching a Go Criterion should the treatment group be enrolled and evaluated to the maximum planned final sample size of 105 NSCLC subjects.

Futility was met if it was predicted that there is a small probability of reaching a Go Criterion upon full enrolment of 105 NSCLC given the existing observed data. A non-informative prior distribution of beta (1, 1) was used. Futility for the NSCLS was when the predictive probability of a Go decision was below 5%.

The analysis population for the primary endpoint:

Phase 2 full analysis set

All subjects in phase 2 who received ≥1 dose of sotorasib and have 1 or more measurable lesions at baseline as assessed by BICR using RECIST 1.1. This analysis set was to be used to evaluate response-related endpoints in the primary and final analyses.

Results

The results presented are related to the period from the date when the first subject enrolled into the phase 2 portion of the study to the analysis data cutoff date (01 September 2020).

- **Participant flow**

Table 16: **Subject disposition with discontinuation reason (Phase 2 Sotorasib Monotherapy– All enrolled subjects)**

	Phase 2 NSCLC 960 mg QD Fasted (N = 126) n (%)
Enrolled – n (%)	126 (100.0)
Investigational product accounting – n (%)	
Subjects who never received sotorasib	0 (0.0)
Subjects who received sotorasib	126 (100.0)
Subjects who discontinued sotorasib	95 (75.4)
Adverse event	11 (8.7)
Decision by sponsor	0 (0.0)
Lost to follow-up	0 (0.0)
Death	2 (1.6)
Subject request	5 (4.0)
Pregnancy	0 (0.0)
Noncompliance	1 (0.8)
Disease progression	75 (59.5)
Requirement for alternative therapy	1 (0.8)
Protocol specified criteria	0 (0.0)
Study completion accounting – n (%)	
Subjects continuing study	56 (44.4)
Subjects who discontinued study	70 (55.6)
Decision by sponsor	0 (0.0)
Lost to follow-up	2 (1.6)
Death	58 (46.0)
Withdrawal of consent from study	10 (7.9)

Phase 2 data cutoff date 01DEC2020.
N = Number of enrolled subjects, n = Number of subjects with observed data.
Percentages based on subjects enrolled.
Source: Table 14b-1.1 of 20170543 Supplemental CSR

- **Recruitment**

This study is being conducted at 59 centres in the United States (39 sites and 75 patients enrolled), Canada (5 sites, 4 patients), France (6 sites, 10 patients), Belgium (4 sites, 7 patients), Germany 3 sites, 7 patients), Switzerland (3 sites, 5 patients), Austria 4 sites, 5 patients), Japan (12 sites, 11 patients), South Korea (5 sites, 1 patient), Australia (4 sites, 5 patients), and Brazil (6 sites, 0 patients).

The first subject was enrolled on 13 August 2019 into the phase 2 part of the study and the analysis cut-off date was 01 September 2020.

- **Conduct of the study**

The original protocol (dated 12 May 2018) was amended 6 times. A summary of the protocol amendments is provided in Table 17 below:

Table 17: Summary of protocol amendments for Phase 2

Amendment	Major Changes
Original Protocol 12 May 2018	–
Amendment 1 12 July 2018	• updated eligibility criteria and schedule of assessments for the phase 1 portion of the study (phase 1 is reported separately)
Amendment 2 13 March 2019	• added the phase 2 portion to the study: multicenter, non-randomized, open-label design to evaluate efficacy and safety/tolerability of sotorasib as monotherapy in subjects with ***KRAS p.G12C***-mutated advanced solid tumors (NSCLC, CRC, and other tumors) • updated the number of study centers • added clarification regarding response evaluation criteria in solid tumors (RECIST)
Superseding Amendment 2	
28 March 2019	• corrected an error in Section 4.2 (exclusion criterion 209) and in Section 10.4.1.3.2 (Futility)
02 April 2019	• this superseding protocol amendment was done to create a single protocol amendment 2 document and a single summary of changes document
Amendment 3 22 May 2019	• use of standard RECIST 1.1 for analysis of tumor response • time to response was added as a secondary endpoint to describe timing aspect of sotorasib response profile • revised eligibility criteria in terms of the extent of prior therapies for NSCLC and CRC; removed the inclusion criteria requirement for alkaline phosphatase, and updated birth control method requirements • adjusted sample size for NSCLC and CRC based on new benchmark rates: – NSCLC: revised the benchmark rate to 23% to exclude from the lower limit of the 95% confidence interval for observed ORR – CRC: revised the benchmark rate to 10% to exclude from the lower limit of the 95% confidence interval for observed ORR • clarified that efficacy analysis to be conducted using only phase 2 data; removed interim analysis for efficacy • updated futility interim analysis to allow continuous monitoring using Bayesian predictive probability method • added patient-reported outcomes • added urine pregnancy test on day 1 of every cycle for female subjects of child bearing potential

Amendment 4 25 September 2019	• PGIS and PGIC were added to patient-reported outcomes
Amendment 5 11 February 2020	• increased the planned number of subjects from 200 to 250 subjects • clarified minimal time interval for determination of stable disease • updated text describing timing of primary analysis and analysis sets • clarified dose modification guidance and updated hepatotoxicity stopping rules with new guidelines for liver function tests
Amendment 6 10 June 2020	• added language to allow continued treatment with sotorasib after disease progression for subjects who continue to have clinical benefit in the investigator's opinion • added language for proton-pump inhibitor interaction with sotorasib • updated the frequency of tumor assessments

BID = twice daily; CRC = colorectal cancer; DLRM = dose level review meeting; DLT = dose-limiting toxicity; HIV = human immunodeficiency virus; NSCLC = non-small cell lung cancer; ***KRAS p.G12C*** = KRAS DNA with a mutation resulting in a G12C mutation at the protein level; ORR = objective response rate; PD-1[L1] = programmed cell death-1 [ligand 1]; PGIC = patient global impression change; PGIS = patient global impression survey; QD = once daily; RECIST = response evaluation criteria in solid tumors; RP2D = recommended phase 2 dose

Table 18: **Summary of important protocol deviations (Phase 2 NSCLC in safety analysis set)**

	Phase 2 NSCLC 960 mg QD Fasted (N = 126) n (%)
Number of subjects with at least one important protocol deviation	51 (40.5)
Total number of important protocol deviations[a]	89
Total number of missing data (other than TA or TC)[a]	66
Missing data (other than TA or TC)	40 (31.7)
Missing key safety or laboratory samples	28 (22.2)
Missing screening assessments	12 (9.5)
Missing End of Treatment or Safety Follow Up procedures	6 (4.8)
Missing Imaging	2 (1.6)
Missing Pre-dose assessments	2 (1.6)
Missing key PK data	1 (0.8)
Total number of other deviations[a]	10
Other deviations	10 (7.9)
Good Clinical Practice	10 (7.9)
Total number of entered study even though entry criteria was not satisfied[a]	4
Entered study even though entry criteria was not satisfied	4 (3.2)
Inform consent	2 (1.6)
Exclusion of hepatitis infection	1 (0.8)
Pathologically documented, locally-advanced or metastatic malignancy with KRAS p.G12C mutation and history of prior treatment	1 (0.8)
Total number of received the wrong treatment or incorrect dose[a]	4
Received the wrong treatment or incorrect dose	4 (3.2)
Incorrect, incomplete or partial dose of IP	4 (3.2)
Total number of developed withdrawal criteria but was not withdrawn[a]	3
Developed withdrawal criteria but was not withdrawn	3 (2.4)
Non-withdrawal after meeting criteria	3 (2.4)
Total number of off-schedule procedures (other than TA or TC)[a]	2
Off-schedule procedures (other than TA or TC)	2 (1.6)
Pre-dose procedure(s)	1 (0.8)
Safety or laboratory samples	1 (0.8)

Phase 1 data cut-off date 06JUL2020. Phase 2 data cut-off date 01SEP2020.
N = Number of subjects in the analysis set; n = Number of subjects with observed data; TA = Received the wrong treatment or incorrect dose; TC = Other treatment compliance
[a] Each occurrence is counted, including multiple events of the same important protocol deviation for a single subject.
Deviation categories are not mutually exclusive. Multiple deviations within the same category are counted once per subject.

Table 19: **Summary of COVID-19 related important protocol deviations (Phase 2 NSCLC in safety analysis set)**

	Phase 2 NSCLC 960 mg QD Fasted (N = 126) n (%)
Number of subjects with at least one important protocol deviation related to COVID-19	13 (10.3)
Missing data (other than TA or TC)	10 (7.9)
Missing key safety or laboratory samples	7 (5.6)
Missing Imaging	2 (1.6)
Missing End of Treatment or Safety Follow Up procedures	1 (0.8)
Received the wrong treatment or incorrect dose	3 (2.4)
Incorrect, incomplete or partial dose of IP	3 (2.4)
Off-schedule procedures (other than TA or TC)	1 (0.8)
Safety or laboratory samples	1 (0.8)

Page 1 of 1

Phase 1 data cut-off date 06JUL2020. Phase 2 data cut-off date 01SEP2020.
N = Number of subjects in the analysis set; n = Number of subjects with observed data; TA = Received the wrong treatment or incorrect dose; TC = Other treatment compliance
Deviation categories are not mutually exclusive. Multiple deviations within the same category are counted once per subject.

- **Baseline data**

Table 20: Baseline demographics (Phase 2 NSCLC in Safety Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 126)	Phase 2 CRC 960 mg QD Fasted (N = 62)	Phase 2 Other Tumors 960 mg QD Fasted (N = 36)	Phase 2 Total (N = 224)
Sex - n (%)				
Male	63 (50.0)	28 (45.2)	21 (58.3)	112 (50.0)
Female	63 (50.0)	34 (54.8)	15 (41.7)	112 (50.0)
Ethnicity - n (%)				
Hispanic or Latino	2 (1.6)	5 (8.1)	1 (2.8)	8 (3.6)
Not Hispanic or Latino	116 (92.1)	56 (90.3)	34 (94.4)	206 (92.0)
Missing	8 (6.3)	1 (1.6)	1 (2.8)	10 (4.5)
Race - n (%)				
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	19 (15.1)	17 (27.4)	9 (25.0)	45 (20.1)
Black or African American	2 (1.6)	0 (0.0)	1 (2.8)	3 (1.3)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (1.6)	0 (0.0)	1 (0.4)
White	103 (81.7)	42 (67.7)	25 (69.4)	170 (75.9)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	2 (1.6)	2 (3.2)	1 (2.8)	5 (2.2)
Age (years)				
n	126	62	36	224
Mean	62.9	55.7	60.6	60.5
SD	9.3	11.3	12.3	10.8
Median	63.5	56.0	62.5	61.0
Q1, Q3	56.0, 70.0	49.0, 61.0	55.5, 70.0	54.0, 69.0
Min, Max	37, 80	31, 85	33, 82	31, 85
Age group - n (%)				
18 - 64 years	67 (53.2)	48 (77.4)	22 (61.1)	137 (61.2)
65 - 74 years	49 (38.9)	11 (17.7)	10 (27.8)	70 (31.3)
75 - 84 years	10 (7.9)	2 (3.2)	4 (11.1)	16 (7.1)
≥ 85 years	0 (0.0)	1 (1.6)	0 (0.0)	1 (0.4)

Data cutoff date 01SEP2020.
N = Number of subjects in the analysis set; n = Number of subjects in the corresponding category;
Q1 = First Quartile; Q3 = Third Quartile; SD = Standard Deviation.
Source Table 14.b.21

Table 21: Baseline characteristics (Phase 2 NSCLC in Safety Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 126)
ECOG status at baseline[a] - n (%)	
0	38 (30.2)
1	88 (69.8)
2	0 (0.0)
Weight (kg)	
n	126
Mean	71.08
SD	17.14
Median	70.65
Q1, Q3	57.70, 83.00
Min, Max	36.8, 122.7
Height (cm)	
n	123
Mean	167.83
SD	9.20
Median	168.80
Q1, Q3	161.00, 175.00
Min, Max	146.0, 188.0
Type of cancer - n (%)	
Non small cell lung	126 (100.0)
Prior line of anti-cancer therapy - n (%)	
0	0 (0.0)
1	54 (42.9)
2	44 (34.9)
3	28 (22.2)
≥ 4	0 (0.0)
Median (number of prior lines)	2
Type of prior anti-cancer therapy[b] - n (%)	
Chemotherapy	115 (91.3)
Platinum-base chemotherapy	113 (89.7)
Immunotherapy	116 (92.1)
Checkpoint inhibitor	116 (92.1)
Anti PD-1 or anti PD-L1	115 (91.3)
Platinum-base chemotherapy and anti PD-1 or anti PD-L1[c]	102 (81.0)
Hormonal therapy	0 (0.0)
Targeted biologics	30 (23.8)
Anti-VEGF biological therapy	25 (19.8)
Targeted small molecules	9 (7.1)
Other	1 (0.8)

Disease stage at initial diagnosis - n (%)	
Stage I	11 (8.7)
Stage II	14 (11.1)
Stage III	22 (17.5)
Stage IV	78 (61.9)
Missing	1 (0.8)
Disease stage at screening - n (%)	
Stage I	0 (0.0)
Stage II	0 (0.0)
Stage III	5 (4.0)
Stage IV	121 (96.0)
Differentiation - n (%)	
Well differentiated	6 (4.8)
Moderately differentiated	15 (11.9)
Poorly differentiated	24 (19.0)
Undifferentiated	0 (0.0)
Other	0 (0.0)
Unknown	81 (64.3)
PD-L1 protein expression - n (%)	
< 1%	33 (26.2)
≥ 1% and < 50%	24 (19.0)
≥ 50%	35 (27.8)
Unknown	34 (27.0)
Histopathology type - n (%)	
Squamous	1 (0.8)
Adenosquamous carcinoma	0 (0.0)
Squamous cell carcinoma	1 (0.8)
Non-squamous	125 (99.2)
Adenocarcinoma	120 (95.2)
Mucinous	8 (6.3)
Large cell carcinoma	3 (2.4)
Bronchoalveolar carcinoma	2 (1.6)
Sarcomatoid	0 (0.0)
Undifferentiated	0 (0.0)
Other	0 (0.0)

Mutations[d] - n (%)	
ATM	1 (0.8)
BRAF	1 (0.8)
CTNNB1	1 (0.8)
EGFR	3 (2.4)
FBXW7	1 (0.8)
GNAS	2 (1.6)
KEAP1	1 (0.8)
KIT	1 (0.8)
KRAS	126 (100.0)
MET	2 (1.6)
MYC	1 (0.8)
PIK3CA	2 (1.6)
RB1	1 (0.8)
SMARCA4	1 (0.8)
SMARCB1	1 (0.8)
STK11	7 (5.6)
TP53	13 (10.3)
Metastatic - n (%)	
Yes	122 (96.8)
No	4 (3.2)
Number of body sites of metastatic disease - n (%)	
0	4 (3.2)
1	51 (40.5)
2	30 (23.8)
3	24 (19.0)
> 3	17 (13.5)
Liver metastasis - n (%)	
Yes	26 (20.6)
No	100 (79.4)
Brain metastasis - n (%)	
Yes	26 (20.6)
No	100 (79.4)
Bone metastasis - n (%)	
Yes	61 (48.4)
No	65 (51.6)

Smoking history - n (%)	
Never	6 (4.8)
Current	15 (11.9)
Former	102 (81.0)
Missing	3 (2.4)
Region - n (%)	
North America	79 (62.7)
Europe	30 (23.8)
Asia	12 (9.5)
Rest of the world	5 (4.0)
Best response to last prior line of therapy[e] - n (%)	
Complete response	1 (0.8)
Partial response	12 (9.5)
Stable disease	33 (26.2)
Progressive disease	48 (38.1)
Unevaluable	1 (0.8)
Unknown / not applicable / not done	27 (21.4)
Missing	4 (3.2)
Centrally confirmed KRAS G12C (Tissue) - n (%)	
Positive	125 (99.2)
Negative	0 (0.0)
Unknown	1 (0.8)

Phase 1 data cut-off date 06JUL2020. Phase 2 data cut-off date 01SEP2020.
N = Number of subjects in the analysis set; n = Number of subjects in the corresponding category; Q1 = First Quartile; Q3 = Third Quartile; SD = Standard Deviation.
[a] Baseline ECOG is measured at C1D1 pre-dose. Subject may satisfy ECOG enrollment eligibility during screening period, but subsequently had baseline ECOG = 2 prior to first dose. ECOG 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2 = Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours; 3 = Capable of only limited selfcare, confined to bed or chair more than 50% of
waking hours; 4 = Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair; 5 = Dead.
[b] Each subject may have multiple prior therapies. Types of prior anti-cancer therapies were adjudicated and include therapies given in any treatment setting.
[c] Platinum-base chemotherapy and anti PD-1 or anti PD-L1 could be in combination or across different lines.
[d] Based on available data at local site as entered on CRF.
[e] Subjects with 0 prior line of therapy are excluded. Number of prior lines and best response on prior lines of therapy include therapies in metastatic disease and adjuvant therapy immediately before metastasis where progression occurred on or within 6 months of treatment ending.

- **Numbers analysed**

Of a total of 126 subjects with NSCLC, 124 subjects were included in the full analysis set (FAS), and 3 subjects were excluded as they did not have ≥ 1 measurable lesion at baseline according to BICR.

- **Outcomes and estimation**

Primary Efficacy Endpoint – Objective Response Rate

ORR measured by CT or MRI and assessed per RECIST 1.1 by BICR laboratory for subjects with *KRAS p.G12C*-mutated NSCLC was 37.4% (46 of 124 subjects; 95% CI: 28.6, 46.3); 3 subjects (2.4%) achieved complete response and 43 subjects (34.7%) achieved partial response (see table below).

Table 22: Summary of objective response assessed by central review (01 December 2020 data cutoff) (Phase 2 NSCLC in Full Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 124)
Best objective response - n (%)	
Complete response (CR)	3 (2.4)
Partial response (PR)	43 (34.7)
Stable disease	54 (43.5)
Progressive disease (PD)	20 (16.1)
Not evaluable (NE)	2 (1.6)
Not done	2 (1.6)
Objective response rate (ORR)	
Number of overall responders - N1 (%)	46 (37.1)
95% CI[a]	(28.60, 46.23)

Phase 2 data cut-off date 01DEC2020.
N = Number of subjects in the analysis set; n = Number of subjects with observed data;
NSCLC = non-small cell lung cancer; QD = once daily
[a] Exact 95% CI was calculated using the Clopper Pearson method.
Source: Table 14n-4.1.1 of 20170543 Supplemental CSR

Secondary efficacy endpoints

Duration of response (DCO 20 June 2021)

As of the 20 June 2021 data cutoff date, the Kaplan-Meier estimate of median (95% CI) DOR for the 46 objective responders was 11.1 months (6.9, 15.0) months. The Kaplan-Meier estimates for DOR at 6, 9, and 12 months were 71.2%, 55.7%, and 45.1%, respectively. The Kaplan-Meier estimate of median (95% CI) follow-up time for DOR was 15.3 (15.2, 15.8) months

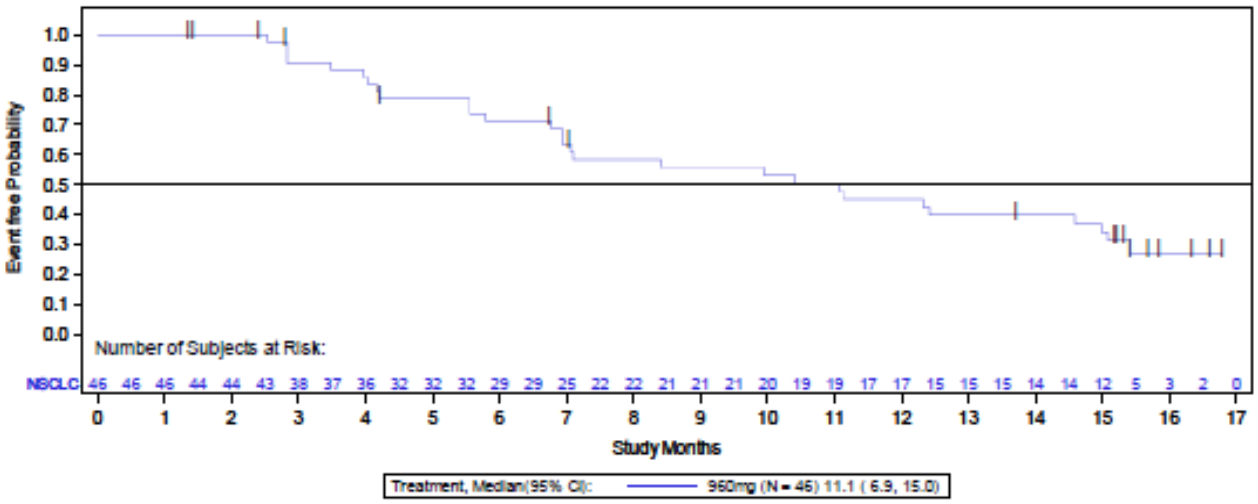
Among the 46 objective responders (4 subjects with complete response and 42 with partial response) in the full analysis set for the phase 2 (part A; pivotal portion of study) NSCLC group, 18 subjects (39.1%) were censored; of those, 10 subjects (21.7%) were on treatment without disease progression at the time of data cutoff.

Table 23: Summary of objective response by central review (20 June 2021 data cutoff) (Phase 2 Part A NSCLC in Full Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 124)
Duration of objective response (DOR)[a]	
Observed duration ≥ 3 months - n (%)	38 (82.6)
Observed duration ≥ 6 months - n (%)	29 (63.0)
Observed duration ≥ 9 months - n (%)	21 (45.7)
Observed duration ≥ 12 months - n (%)	17 (37.0)
Subject status - n (%)	
Events	28 (60.9)
Progressive disease	23 (50.0)
Death	5 (10.9)
Related to COVID-19	0 (0.0)
Censored	18 (39.1)
On study without disease progression	10 (21.7)
No evaluable post-baseline disease assessment	0 (0.0)
Missed more than one consecutive assessments	2 (4.3)
Related to COVID-19	0 (0.0)
Started new anti-cancer therapy	5 (10.9)
Withdrew consent	1 (2.2)
Related to COVID-19	0 (0.0)
Off study due to sponsor decision	0 (0.0)
Related to COVID-19	0 (0.0)
Lost to follow-up	0 (0.0)
Related to COVID-19	0 (0.0)
Duration of response (KM) (months)	
25th percentile (95% CI)	5.6 (3.5, 7.1)
Median (95% CI)	11.1 (6.9, 15.0)
75th percentile (95% CI)	NE (12.4, NE)
Min, Max (+ for censored)	1.3+, 16.8+
Kaplan-Meier estimate (95% CI)[b]	
At 3 months	90.5 (76.7, 96.3)
At 6 months	71.2 (54.9, 82.5)
At 9 months	55.7 (39.1, 69.4)
At 12 months	45.1 (29.2, 59.7)
Follow-up time for DOR[c] (KM) (months)	
25th percentile (95% CI)	15.2 (4.2, 15.2)
Median (95% CI)	15.3 (15.2, 15.8)
75th percentile (95% CI)	16.3 (15.3, NE)
Min, Max (+ for censored)	1.3, 16.8

Phase 2 data cut-off date 20JUN2021.
DOR = duration of response; KM = Kaplan-Meier; N = number of subjects in the analysis set; n = number of subjects with observed data; NE = not estimable; NSCLC = non-small cell lung cancer; QD = once daily
Months are derived as days x (12/365.25). Events marked "Related to COVID-19" were identified from available information collected on CRF and protocol deviation data.
[a] Time to response and duration of response are calculated among confirmed responders N1.
[b] 95% CIs are based on estimated variance for log-log transformation of the Kaplan-Meier survival estimate.
[c] Follow-up time is measured by reversing the status indicator for censored and events.
Source: Table 14n-4.1.1

Figure 11: Kaplan-Meier plot of duration of response by central review – 20 June 2021 data cut-off (Phase 2 Part A Responders in Full Analysis



Phase 2 data cut-off date 20JUN2021.
Censor indicated by vertical bar |
NE = Not Estimable.
Radiological Progression or Death (whichever occurs earlier after confirmed CR/PR) is an event.

Disease control rate

The disease control rate (95%CI) for subjects with NSCLC was 80.6% (72.58, 87.19). Of 124 subjects in the full analysis set of the phase 2 NSCLC group, 54 subjects (43.5%) had stable disease.

Table 24: Disease control rate assessed by central review (01 December data cutoff) (Phase 2 NSCLC Responders in Full Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 124)
Disease control rate (DCR) - n (%)	100 (80.6)
95% CI[a]	(72.58, 87.19)

Data cutoff date of 01 December 2020
N = Number of subjects in the analysis set; n = Number of subjects with observed data; NSCLC = non-small cell lung cancer; QD = once daily
[a] Exact 95% confidence interval was calculated using the Clopper-Pearson method
Source: Table 14n-4.1.1 of 20170543 Supplemental CSR

Time to Response

Among the 46 responders in the NSCLC group, the median (range) time to response was 1.35 (1.2, 10.1) months with 70% of responses occurring within the first 7 weeks.

Progression free survival

As of the DCO date of 1 Dec 2020, 56.5% of subjects with NSCLC had events of disease progression and 10.5% had an event of death (see figure and table below). A total of 41 subjects (33.1%) were censored, and of those, 25 subjects (20.2 %) were on study without disease progression.

The Kaplan-Meier PFS probability estimates at 6, 9, and 12 months were 52.2% (95% CI: 42.6, 60.9), 37.2% (95% CI: 28.1, 46.3), and 16.3% (95% CI: 7.4, 28.2), respectively. Median PFS was 6.8 (5.1, 8.2) months.

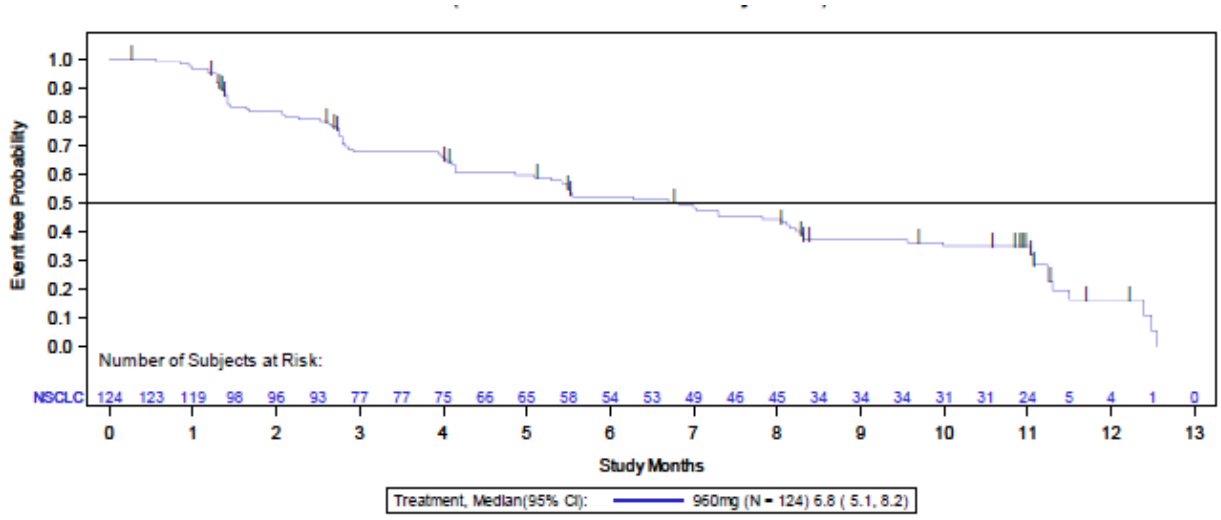
Table 25: Summary of progression-free survival by tumour type (Phase 2 Sotorasib 960 mg QD Monotherapy – Full Analysis Sets)

	Phase 2 NSCLC 960 mg QD Fasted (N = 124)
Subject status	
Events - n (%)	83 (66.9)
Progressive disease	70 (56.5)
Death due to any cause	13 (10.5)
Related to COVID-19	0 (0.0)
Censored - n (%)	41 (33.1)
On study without disease progression	25 (20.2)
No evaluable post-baseline disease assessment	0 (0.0)
Missed more than one consecutive assessments	5 (4.0)
Related to COVID-19	0 (0.0)
Started new anti-cancer therapy	7 (5.6)
Withdrew consent	3 (2.4)
Related to COVID-19	0 (0.0)
Off study due to sponsor decision	0 (0.0)
Related to COVID-19	0 (0.0)
Lost to follow-up	1 (0.8)
Related to COVID-19	1 (0.8)
Progression-free survival (KM) (months)	
25th percentile (95% CI)	2.8 (1.6, 3.9)
Median (95% CI)	6.8 (5.1, 8.2)
75th percentile (95% CI)	11.2 (11.0, 12.4)
Min, Max (+ for censored)	0.3+, 12.6
Kaplan-Meier estimate (95% CI)[a]	
At 3 months	67.8 (58.5, 75.4)
At 6 months	52.2 (42.6, 60.9)
At 9 months	37.2 (28.1, 46.3)
At 12 months	16.3 (7.4, 28.2)
Follow-up time for PFS[b] (KM) (months)	
25th percentile (95% CI)	8.4 (5.5, 10.8)
Median (95% CI)	11.0 (10.8, 11.1)
75th percentile (95% CI)	11.7 (11.1, NE)
Min, Max (+ for censored)	0.3, 12.6+

Page 2 of 2

Phase 2 data cutoff date of 01 December 2020
KM = Kaplan-Meier; N = Number of subjects in the analysis set; NE = not evaluable; NSCLC = non-small cell lung cancer; PFS = progression-free survival; QD = once daily
[a] 95% CIs are based on estimated variance for log-log transformation of the Kaplan-Meier survival estimate.
[b] Follow-up time is summarized by reversing the status indicator for censored and events.
Events marked "Related to COVID-19" were identified from available information collected on CRF and protocol deviation data.
Source: Table 14n-4.2.1 of 20170543 Supplemental CSR

Figure 12: Kaplan-Meier plot of progression-free survival by central review (Phase 2 NSCLC Full Analysis Set)



Phase 2 data cutoff date 01 December 2020
Censor indicated by vertical bar |
Radiological progression or death is an event.

Overall survival

The Kaplan-Meier estimate of survival was 89.5% (82.7, 93.8) at 3 months, 75.5% (66.8, 82.2) at 6 months, 63.5% (54.3, 71.4) at 9 months, and 51.4% (41.9, 60.1) at 12 months. The median (range) follow-up time was 12.2 (1.1, 15.6) months. The Kaplan-Meier estimate of median (95% CI) OS was 12.5 months (10.0, NE). No notable treatment-by-subgroup effects were observed for subjects with NSCLC (see table below).

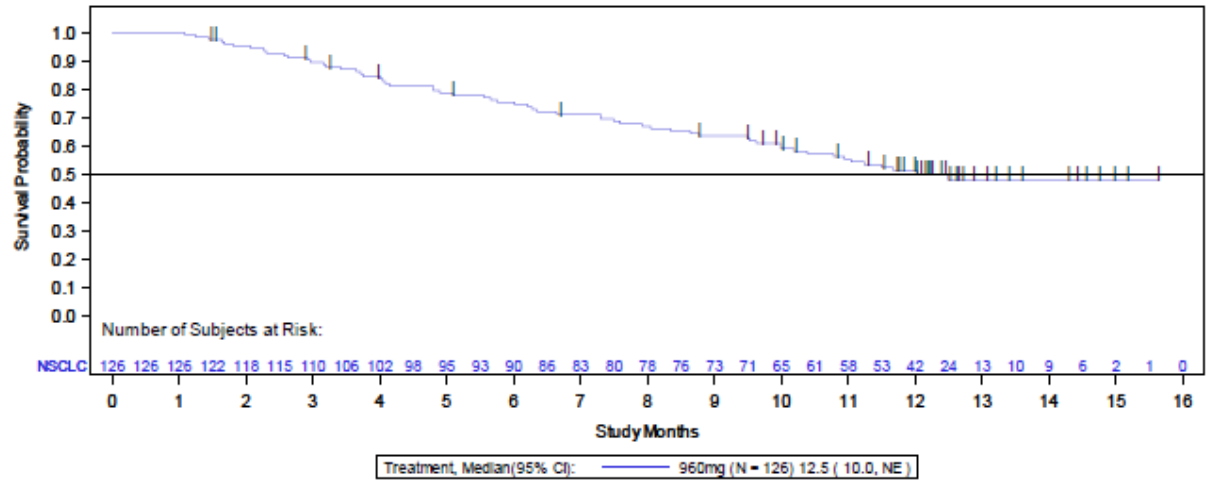
Table 26: Summary of overall survival by tumour Type (Phase 2 Sotorasib 960 mg QD Monotherapy – Safety Analysis Sets)

	Phase 2 NSCLC 960 mg QD Fasted (N = 126)
Subject status	
Events - n (%)	59 (46.8)
Death due to any cause	59 (46.8)
Censored - n (%)	67 (53.2)
Alive at last follow-up	56 (44.4)
Lost to follow-up	2 (1.6)
Related to COVID-19	1 (0.8)
Withdrew consent	9 (7.1)
Related to COVID-19	1 (0.8)
Off study due to sponsor decision	0 (0.0)
Related to COVID-19	0 (0.0)
Overall survival (KM) (months)	
25th percentile (95% CI)	6.0 (4.1, 7.9)
Median (95% CI)	12.5 (10.0, NE)
75th percentile (95% CI)	NE (NE, NE)
Min, Max (+ for censored)	1.1, 15.6+
Kaplan-Meier estimate (95% CI)[a]	
At 3 months	89.5 (82.7, 93.8)
At 6 months	75.5 (66.8, 82.2)
At 9 months	63.5 (54.3, 71.4)
At 12 months	51.4 (41.9, 60.1)
Follow-up time for OS[b] (KM) (months)	
25th percentile (95% CI)	11.8 (10.8, 12.0)
Median (95% CI)	12.2 (12.0, 12.5)
75th percentile (95% CI)	12.7 (12.6, 13.6)
Min, Max (+ for censored)	1.1+, 15.6

Page 1 of 1

Phase 2 data cut-off date 01 December 2020.
KM = Kaplan-Meier; NE = Not Estimable.
[a] 95% CIs are based on estimated variance for log-log transformation of the Kaplan-Meier survival estimate.
[b] Follow-up time is summarized by reversing the status indicator for censored and events.
Survival status may include publicly available records (where permitted) searched by investigator after subject ended study.
Events marked "Related to COVID-19" were identified from available information collected on CRF and protocol deviation data.

Figure 13: Kaplan-Meier plot of overall survival (Phase 2 NSCLC Safety Analysis Set)



Phase 2 data cutoff date 01 December 2020
Censor indicated by vertical bar |
NE = not estimable

- **Ancillary analyses**

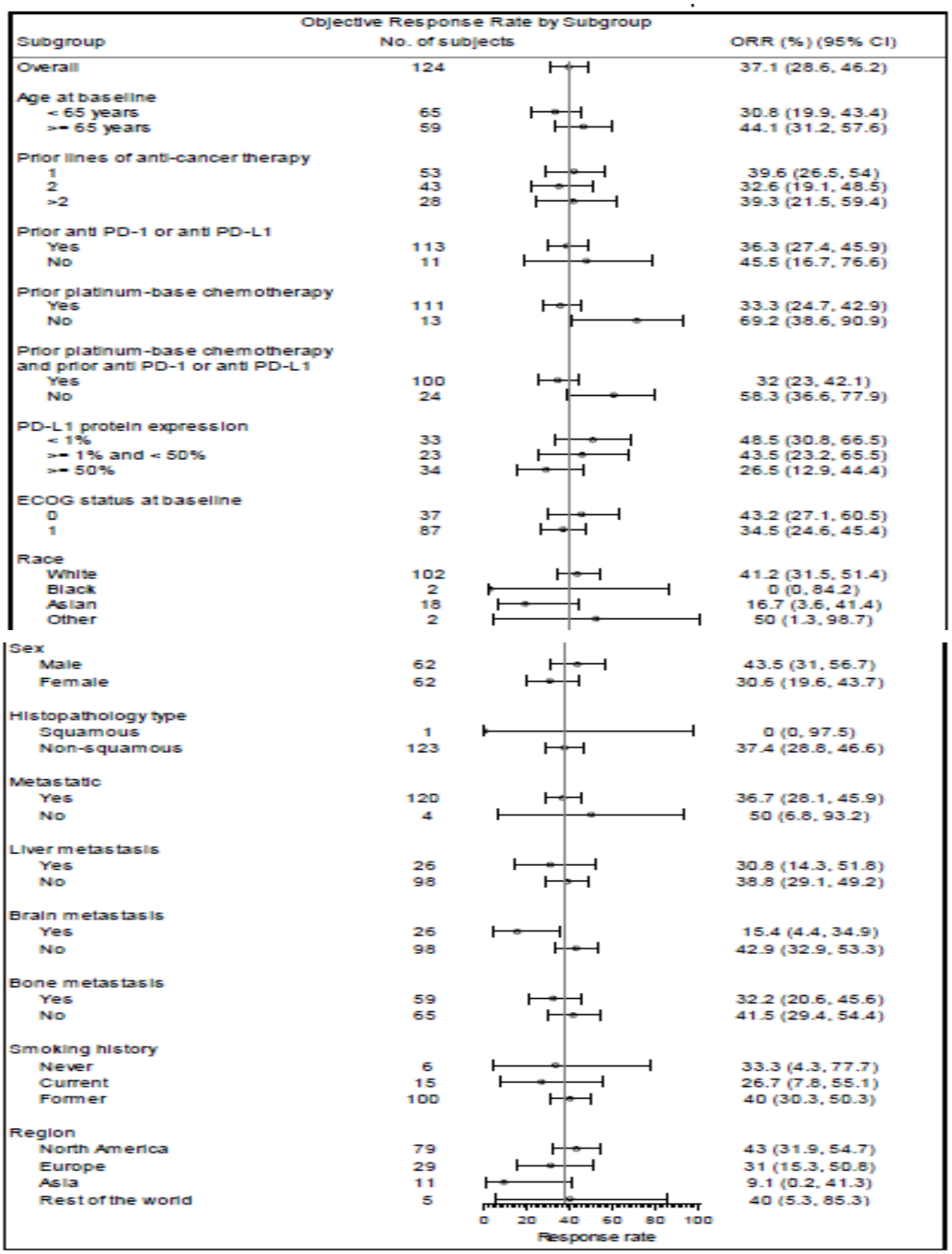
Subgroup analyses of ORR

Table 27: Subgroup analysis of objective response by central review (01 December 2020 data cutoff) (Phase 2 NSCLC in Full Analysis Set)

	NSCLC (N = 124) Events*/Subjects (%) (95% CI)
Age at baseline	
< 65 years	20/65 (30.8) (19.9, 43.4)
≥ 65 years	26/59 (44.1) (31.2, 57.6)
Prior lines of anti-cancer therapy	
1	21/53 (39.6) (26.5, 54.0)
2	14/43 (32.6) (19.1, 48.5)
> 2	11/28 (39.3) (21.5, 59.4)
Prior anti PD-1 or anti PD-L1	
Yes	41/113 (36.3) (27.4, 45.9)
No	5/11 (45.5) (16.7, 76.6)
Prior platinum-base chemotherapy	
Yes	37/111 (33.3) (24.7, 42.9)
No	9/13 (69.2) (38.6, 90.9)
Prior platinum-base chemotherapy and prior anti PD-1 or anti PD-L1	
Yes	32/100 (32.0) (23.0, 42.1)
No	14/24 (58.3) (36.6, 77.9)
PD-L1 protein expression	
< 1%	16/33 (48.5) (30.8, 66.5)
≥ 1% and < 50%	10/23 (43.5) (23.2, 65.5)
≥ 50%	9/34 (26.5) (12.9, 44.4)
ECOG status at baseline	
0	16/37 (43.2) (27.1, 60.5)
1	30/87 (34.5) (24.6, 45.4)
Race	
White	42/102 (41.2) (31.5, 51.4)
Black	0/2 (0.0) (0.0, 84.2)
Asian	3/18 (16.7) (3.6, 41.4)
Other	1/2 (50.0) (1.3, 98.7)
Sex	
Men	27/62 (43.5) (31.0, 56.7)
Women	19/62 (30.6) (19.6, 43.7)
Histopathology type	
Squamous	0/1 (0.0) (0.0, 97.5)
Non-squamous	46/123 (37.4) (28.8, 46.6)
Metastatic	
Yes	44/120 (36.7) (28.1, 45.9)
No	2/4 (50.0) (6.8, 93.2)
Liver metastasis	
Yes	8/26 (30.8) (14.3, 51.8)
No	38/98 (38.8) (29.1, 49.2)
Brain metastasis	
Yes	4/26 (15.4) (4.4, 34.9)
No	42/98 (42.9) (32.9, 53.3)
Bone metastasis	
Yes	19/59 (32.2) (20.6, 45.6)
No	27/65 (41.5) (29.4, 54.4)
Smoking history	
Never	2/6 (33.3) (4.3, 77.7)
Current	4/15 (26.7) (7.8, 55.1)
Former	40/100 (40.0) (30.3, 50.3)
Region	
North America	34/79 (43.0) (31.9, 54.7)
Europe	9/29 (31.0) (15.3, 50.8)
Asia	1/11 (9.1) (0.2, 41.3)
Rest of the world	2/5 (40.0) (5.3, 85.3)

Phase 2 data cut-off date 01 December 2020.
* Events are Confirmed Responder (PR/CR).
Types of prior anticancer therapies were adjudicated and include therapies given in any treatment setting.
Number of prior lines of therapy include therapies in metastatic disease and adjuvant therapy immediately before metastasis where progression occurred on or within 6 months of treatment ending.
Subject(s) with unknown or missing subgroup value are not included.
Exact 95% confidence interval was calculated using the Clopper Pearson method.

Figure 14: Forest plot of o response rate by central review in subgroups (01 December 2020 data cutoff) (Phase 2 NSCLC in Full Analysis Set)



Sensitivity analyses of ORR (DCO 1 Sept 2020)

Based on investigator assessment, the ORR sensitivity analysis was 30.2% (95% CI: 22.31, 38.97). The concordance rates between central review and investigator for objective response, best overall response, and disease progression were 82.9%, 72.7%, and 78.0%, respectively (see tables below).

Table 28: Sensitivity analysis of objective response using investigator assessment (Phase 2 NSCLC in Investigator Efficacy Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 126)
Best overall response - n (%)	
Complete response (CR)	1 (0.8)
Partial response (PR)	37 (29.4)
Stable disease (SD)	69 (54.8)
Progressive disease (PD)	15 (11.9)
Not evaluable (NE)	2 (1.6)
Not done	2 (1.6)
Objective response rate (ORR)	
Number of overall responders - N1 (%)	38 (30.2)
95% CI[a]	(22.31, 38.97)
Disease control rate (DCR) - n (%)	107 (84.9)
95% CI[a]	(77.46, 90.67)
Duration of objective response (DOR)[b]	
Observed duration ≥ 3 months - n (%)	33 (86.8)
Observed duration ≥ 6 months - n (%)	20 (52.6)
Observed duration ≥ 9 months - n (%)	0 (0.0)
Observed duration ≥ 12 months - n (%)	0 (0.0)
Subject status - n (%)	
Events	11 (28.9)
Progressive disease	9 (23.7)
Death	2 (5.3)
Related to COVID-19	0 (0.0)
Censored	27 (71.1)
On study without disease progression	26 (68.4)
No evaluable post-baseline disease assessment	0 (0.0)
Missed more than one consecutive assessments	0 (0.0)
Related to COVID-19	0 (0.0)
Started new anti-cancer therapy	1 (2.6)
Withdrew consent	0 (0.0)
Related to COVID-19	0 (0.0)
Off study due to sponsor decision	0 (0.0)
Related to COVID-19	0 (0.0)
Lost to follow-up	0 (0.0)
Related to COVID-19	0 (0.0)
Duration of response (KM) (months)	
25th percentile (95% CI)	6.7 (4.2, 8.4)
Median (95% CI)	8.4 (6.8, 8.4)
75th percentile (95% CI)	8.4 (8.4, 8.4)
Min, Max (+ for censored)	1.2+, 8.4
Kaplan-Meier estimate (95% CI)[c]	
At 3 months	97.2 (81.9, 99.6)
At 6 months	81.5 (63.3, 91.3)
At 9 months	0.0 (NE, NE)
At 12 months	0.0 (NE, NE)

	Phase 2 NSCLC 960 mg QD Fasted (N = 126)
Follow-up time for DOR[d] (KM) (months)	
25th percentile (95% CI)	5.6 (2.8, 6.8)
Median (95% CI)	6.9 (5.6, 6.9)
75th percentile (95% CI)	7.0 (6.9, 8.3)
Min, Max (+ for censored)	1.2, 8.4+
Time to objective response (months)[b]	
Number of subjects with objective response	38
Mean (SD)	2.20 (1.43)
Median	1.43
Q1, Q3	1.31, 2.73
Min, Max	1.2, 7.0

Phase 1 data cut-off date 06JUL2020. Phase 2 data cut-off date 01SEP2020.
CI = Confidence Interval; KM = Kaplan-Meier; NE = Not Estimable.q
Months are derived as days x (12/365.25).
a Exact 95% confidence interval was calculated using the Clopper Pearson method.
b Time to response and duration of response are calculated among confirmed responders N1.
c 95% CIs are based on estimated variance for log-log transformation of the Kaplan-Meier survival estimate.
d Follow-up time is measured by reversing the status indicator for censored and events.
Events marked "Related to COVID-19" were identified from available information collected on CRF and protocol deviation data.

Table 29: Concordance in assessment of objective response by central review and by site investigator (Phase 2 NSCLC in Full Analysis Set)

	Central Review Assessment		
Investigator Assessment	Confirmed CR/PR n (%)	Not CR/PR n (%)	Total n (%)
Phase 2 NSCLC (N = 123)			
Confirmed CR/PR	31 (25.2)	6 (4.9)	37 (30.1)
Not CR/PR	15 (12.2)	71 (57.7)	86 (69.9)
Total	46 (37.4)	77 (62.6)	123 (100.0)
Concordance rate n (%)			102 (82.9)

Phase 1 data cut-off date 06JUL2020. Phase 2 data cut-off date 01SEP2020.
N = Number of subjects in the analysis set. n = Number of subjects with observations in both categories.
CR = Complete Response; PR = Partial Response.
Concordance rate is defined as the proportion of subjects with the same objective response status as assessed by both central review and site investigator.

Table 30: Concordance in assessment of best overall response by central review and by site investigator (Phase 2 NSCLC in Full Analysis Set)

	Central Review Assessment						
Investigator Assessment	CR n (%)	PR n (%)	SD n (%)	PD n (%)	NE n (%)	Not Done n (%)	Total n (%)
Phase 2 NSCLC (N = 123)							
CR	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
PR	1 (0.8)	29 (23.6)	6 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)	36 (29.3)
SD	0 (0.0)	15 (12.2)	45 (36.6)	7 (5.7)	0 (0.0)	0 (0.0)	67 (54.5)
PD	0 (0.0)	0 (0.0)	2 (1.6)	12 (9.8)	1 (0.8)	0 (0.0)	15 (12.2)
NE	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.8)	0 (0.0)	2 (1.6)
Not done	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)	2 (1.6)
Total	2 (1.6)	44 (35.8)	53 (43.1)	20 (16.3)	2 (1.6)	2 (1.6)	123 (100.0)
Concordance rate n (%)							88 (72.7)

Phase 2 data cut-off date 01SEP2020.
N = Number of subjects in the analysis set. n = Number of subjects with observations in both categories. CR = Complete Response; NE = Not Evaluable; PD = Progressive Disease; PR = Partial Response; SD = Stable Disease.
Concordance rate is defined as the proportion of subjects with the same best overall response as assessed by both central review and site investigator. Subjects with "not done" assessment by both central review and site investigator are excluded in concordance rate calculation.

Table 31: Concordance in disease progression by central review and by site investigator (Phase 2 NSCLC in Full Analysis Set)

	Central Review Assessment		
Investigator Assessment	PD	Non-PD	Total
Phase 2 NSCLC (N = 123)			
PD	48	15	63
Investigator agrees with central review on timing	32		
Investigator declares PD earlier than central review	1		
Investigator declares PD later than central review	15		
Non-PD	12	48	60
Total	60	63	123
Concordance rate for PD status		96/123 (78.0%)	
Concordance rate for PD status and timing		80/123 (65.0%)	

Phase 1 data cut-off date 06JUL2020. Phase 2 data cut-off date 01SEP2020.
N = Number of subjects in the analysis set. PD = Progressive Disease.
Concordance rate for PD status is defined as the proportion of subjects with the same PD status as assessed by local investigator and Central Review.
Concordance rate for PD status and timing is defined as the proportion of subjects with PD where investigator agrees with Central Review on timing + proportion of non-PD by both Investigator and Central Review.

Subgroups analysis of PFS (DCO 1 Sept 2020)

Table 32: Subgroup analysis of progression-free survival by central review (Phase 2 NSCLC in Full Analysis Set)

	Events[a]/Subjects	Median (95% CI) (Months)	6 Months KM Estimate (95% CI) (%)	12 Months KM Estimate (95% CI) (%)
Age at baseline				
< 65 years	39/65	5.5 (2.9, 8.1)	47.5 (34.4, 59.5)	0.0 (NE, NE)
≥ 65 years	31/58	7.0 (4.9, 11.5)	56.0 (41.5, 68.3)	0.0 (NE, NE)
Prior lines of anti-cancer therapy				
1	29/53	7.8 (5.4, 11.5)	56.2 (40.8, 69.0)	0.0 (NE, NE)
2	27/43	4.1 (2.7, 8.3)	41.5 (26.3, 56.0)	NE (NE, NE)
> 2	14/27	7.0 (4.1, NE)	59.3 (37.3, 75.8)	NE (NE, NE)
Prior anti PD-1 or anti PD-L1				
Yes	63/112	6.8 (4.9, 8.2)	53.5 (43.3, 62.6)	0.0 (NE, NE)
No	7/11	5.4 (1.3, NE)	32.7 (8.3, 60.6)	NE (NE, NE)
Prior platinum-base chemotherapy				
Yes	66/110	5.5 (4.1, 7.0)	46.1 (36.1, 55.6)	0.0 (NE, NE)
No	4/13	9.6 (8.0, 9.6)	100.0 (NE, NE)	0.0 (NE, NE)
Prior platinum-base chemotherapy and prior anti PD-1 or anti PD-L1				
Yes	59/99	5.5 (4.1, 7.3)	47.7 (37.0, 57.6)	0.0 (NE, NE)
No	11/24	9.6 (5.4, 9.6)	67.9 (44.1, 83.3)	0.0 (NE, NE)
PD-L1 protein expression				
< 1%	14/33	11.5 (5.5, 11.5)	69.5 (49.2, 83.0)	0.0 (NE, NE)
≥ 1% and < 50%	14/22	5.3 (1.4, NE)	43.3 (22.0, 63.0)	NE (NE, NE)
≥ 50%	21/34	5.5 (2.8, 8.3)	47.3 (28.9, 63.6)	0.0 (NE, NE)
ECOG status at baseline				
0	14/37	NE (5.4, NE)	59.8 (40.8, 74.5)	NE (NE, NE)
1	56/86	5.5 (2.9, 7.3)	48.0 (36.7, 58.5)	0.0 (NE, NE)
Race				
White	57/101	7.0 (5.3, 8.3)	53.1 (42.4, 62.7)	0.0 (NE, NE)
Black	2/2	2.6 (1.3, 3.9)	0.0 (NE, NE)	0.0 (NE, NE)
Asian	10/18	2.9 (1.4, NE)	48.8 (22.9, 70.5)	NE (NE, NE)
Other	1/2	NE (2.8, NE)	50.0 (0.6, 91.0)	NE (NE, NE)
Sex				
Male	33/61	6.8 (4.1, 11.5)	52.4 (38.2, 64.8)	0.0 (NE, NE)
Female	37/62	6.7 (2.9, 8.1)	50.6 (37.2, 62.6)	NE (NE, NE)
Histopathology type				
Squamous	1/1	1.4 (NE, NE)	0.0 (NE, NE)	0.0 (NE, NE)
Non-squamous	69/122	6.7 (5.1, 8.2)	52.0 (42.3, 60.8)	0.0 (NE, NE)
Metastatic				
Yes	69/119	6.7 (4.1, 8.1)	51.1 (41.4, 60.1)	0.0 (NE, NE)
No	1/4	NE (5.5, NE)	66.7 (5.4, 94.5)	NE (NE, NE)
Liver metastasis				
Yes	20/26	2.9 (1.6, 6.8)	31.7 (14.8, 50.0)	NE (NE, NE)
No	50/97	7.3 (5.4, 11.5)	57.1 (46.0, 66.7)	0.0 (NE, NE)
Brain metastasis				
Yes	16/26	4.9 (2.5, 8.3)	48.8 (27.5, 67.0)	NE (NE, NE)
No	54/97	6.7 (5.3, 8.3)	52.3 (41.4, 62.1)	0.0 (NE, NE)
Bone metastasis				
Yes	37/58	4.1 (2.8, 7.8)	38.3 (25.0, 51.5)	0.0 (NE, NE)
No	33/65	7.3 (5.5, NE)	62.5 (49.1, 73.4)	NE (NE, NE)

Smoking history				
Never	5/5	2.8 (1.2, 5.5)	0.0 (NE, NE)	0.0 (NE, NE)
Current	8/15	6.3 (1.4, NE)	56.0 (26.6, 77.6)	NE (NE, NE)
Former	56/100	7.0 (5.1, 8.3)	53.1 (42.3, 62.8)	0.0 (NE, NE)
Region				
North America	43/79	7.3 (5.4, 8.3)	55.5 (43.1, 66.2)	0.0 (NE, NE)
Europe	18/28	4.1 (2.8, NE)	40.9 (22.5, 58.5)	NE (NE, NE)
Asia	7/11	2.8 (0.9, NE)	40.0 (12.3, 67.0)	NE (NE, NE)
Rest of the world	2/5	NE (4.1, NE)	80.0 (20.4, 96.9)	NE (NE, NE)

Phase 1 data cut-off date 06JUL2020. Phase 2 data cut-off date 01SEP2020.
CI = Confidence Interval; KM = Kaplan-Meier; NE = Not Estimable.
[a] Events are disease progression and death.
Types of prior anti-cancer therapies were adjudicated and include therapies given in any treatment setting. Number of prior lines of therapy include therapies in metastatic disease and adjuvant therapy immediately before metastasis where progression occurred on or within 6 months of treatment ending.
95% CIs are based on estimated variance for log-log transformation of the Kaplan-Meier survival estimate.
Subject(s) with unknown or missing subgroup value are not included.

Sensitivity analysis of PFS (DCO 1 Sept 2020)

According to the sensitivity analysis of PFS by investigator assessment, of the 126 NSCLC patients, 64 patients (50.8%) had events of disease progression and 11 patients (8.7%) had an event of death. The median PFS was 6.8 months (95% CI: 5.5, 8.3) with a median follow-up time of 8.3 months (0.3, 11.5+).

According to the sensitivity analysis of PFS by investigator assessment considering clinical progression, of the 126 NSCLC patients, 73 patients (57.9%) had events of disease progression and 7 patients (5.6%) had an event of death. The median PFS was 6.8 months (95% CI: 5.4, 8.2) with a median follow-up time of 8.3 months (0.3+, 11.5+).

Subgroup analysis of OS

Table 33: Subgroup analysis of overall survival (Phase 2 NSCLC in Safety Analysis Set)

	Events/Subjects	Median (95% CI) (Months)	6 Months KM Estimate (95% CI) (%)	12 Months KM Estimate (95% CI) (%)
Age at baseline				
< 65 years	26/67	10.4 (8.0, NE)	75.6 (63.3, 84.3)	47.9 (26.8, 66.3)
≥ 65 years	22/59	12.0 (9.5, 12.0)	75.4 (62.1, 84.7)	56.6 (39.0, 70.8)
Prior lines of anti-cancer therapy				
1	23/54	10.4 (7.9, NE)	75.0 (60.9, 84.7)	45.2 (22.0, 65.9)
2	16/44	NE (8.6, NE)	74.1 (58.1, 84.7)	NE (NE, NE)
> 2	9/28	NE (7.5, NE)	78.6 (58.4, 89.8)	NE (NE, NE)
Prior anti PD-1 or anti PD-L1				
Yes	44/115	12.0 (9.5, NE)	74.8 (65.7, 81.9)	56.1 (44.6, 66.1)
No	4/11	10.4 (4.8, NE)	81.8 (44.7, 95.1)	NE (NE, NE)
Prior platinum-base chemotherapy				
Yes	47/113	10.4 (8.6, NE)	72.8 (63.4, 80.1)	47.3 (32.1, 61.0)
No	1/13	NE (NE, NE)	100.0 (NE, NE)	NE (NE, NE)

	Events/Subjects	Median (95% CI) (Months)	6 Months KM Estimate (95% CI) (%)	12 Months KM Estimate (95% CI) (%)
Prior platinum-base chemotherapy and prior anti PD-1 or anti PD-L1				
Yes	43/102	12.0 (8.3, NE)	71.8 (61.8, 79.6)	51.4 (39.1, 62.4)
No	5/24	NE (10.4, NE)	91.3 (69.5, 97.8)	NE (NE, NE)
PD-L1 protein expression				
< 1%	14/33	10.4 (8.3, 12.0)	78.3 (59.8, 89.0)	46.7 (21.0, 69.0)
≥ 1% and < 50%	7/24	NE (7.5, NE)	78.8 (56.2, 90.6)	68.3 (44.3, 83.6)
≥ 50%	18/35	9.5 (5.7, NE)	63.8 (45.1, 77.5)	NE (NE, NE)
ECOG status at baseline				
0	6/38	NE (NE, NE)	86.3 (70.2, 94.1)	77.7 (51.5, 90.8)
1	42/88	9.5 (7.5, 12.0)	70.8 (59.9, 79.2)	42.1 (26.9, 56.6)

	Events/Subjects	Median (95% CI) (Months)	6 Months KM Estimate (95% CI) (%)	12 Months KM Estimate (95% CI) (%)
Race				
White	39/103	12.0 (9.5, NE)	75.2 (65.6, 82.5)	52.4 (36.7, 65.9)
Black	2/2	4.7 (1.8, 7.6)	50.0 (0.6, 91.0)	0.0 (NE, NE)
Asian	7/19	NE (6.3, NE)	77.3 (50.1, 90.8)	NE (NE, NE)
Other	0/2	NE (NE, NE)	100.0 (NE, NE)	NE (NE, NE)
Sex				
Male	20/63	12.0 (9.5, NE)	83.1 (70.9, 90.5)	62.5 (45.6, 75.5)
Female	28/63	10.4 (7.5, NE)	68.2 (55.2, 78.2)	NE (NE, NE)
Histopathology type				
Squamous	0/1	NE (NE, NE)	100.0 (NE, NE)	NE (NE, NE)
Non-squamous	48/125	12.0 (9.5, NE)	75.3 (66.6, 82.0)	51.4 (36.6, 64.4)
Metastatic				
Yes	47/122	12.0 (9.5, NE)	75.5 (66.7, 82.3)	50.2 (34.6, 63.9)
No	1/4	NE (3.2, NE)	75.0 (12.8, 96.1)	NE (NE, NE)
Liver metastasis				
Yes	14/26	8.8 (4.0, NE)	60.0 (38.4, 76.1)	NE (NE, NE)
No	34/100	12.0 (10.4, NE)	79.4 (69.9, 86.2)	57.1 (39.5, 71.3)
Brain metastasis				
Yes	12/26	10.4 (4.1, 10.4)	71.8 (49.7, 85.4)	0.0 (NE, NE)
No	36/100	12.0 (9.5, NE)	76.5 (66.8, 83.7)	59.4 (47.1, 69.7)
Bone metastasis				
Yes	33/61	8.6 (5.7, 12.0)	63.7 (49.9, 74.7)	35.9 (21.0, 51.1)
No	15/65	NE (10.4, NE)	86.0 (74.8, 92.5)	67.5 (43.4, 83.1)
Smoking history				
Never	2/6	NE (4.0, NE)	60.0 (12.6, 88.2)	NE (NE, NE)
Current	5/15	NE (5.7, NE)	78.6 (47.2, 92.5)	NE (NE, NE)
Former	41/102	10.4 (9.5, NE)	74.9 (65.2, 82.3)	49.3 (32.5, 64.1)

Region				
North America	30/79	12.0 (9.5, NE)	75.2 (63.9, 83.4)	55.0 (38.3, 68.8)
Europe	12/30	9.5 (7.9, NE)	76.5 (57.0, 88.1)	NE (NE, NE)
Asia	5/12	NE (1.7, NE)	73.3 (37.9, 90.6)	NE (NE, NE)
Rest of the world	1/5	NE (5.6, NE)	80.0 (20.4, 96.9)	NE (NE, NE)

Phase 1 data cut-off date 06JUL2020. Phase 2 data cut-off date 01SEP2020.
CI = Confidence Interval; KM = Kaplan-Meier; NE = Not Estimable.
Types of prior anti-cancer therapies were adjudicated and include therapies given in any treatment setting. Number of prior lines of therapy include therapies in metastatic disease and adjuvant therapy immediately before metastasis where progression occurred on or within 6 months of treatment ending.
95% CIs are based on estimated variance for log-log transformation of the Kaplan-Meier survival estimate.
Subject(s) with unknown or missing subgroup value are not included.

- **Summary of main efficacy results**

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 34: Summary of efficacy for sotorasib for the study 20170543

Title: A Phase 1/2, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of SOTORASIB Monotherapy in Subjects With Advanced Solid Tumors With KRAS p.G12C Mutation and SOTORASIB Combination Therapy in Subjects With Advanced NSCLC With KRAS p.G12C Mutation (CodeBreak 100)			
Study identifier	EudraCT Number: 2018-001400-11 NCT Number: NCT03600883		
Design	Prospective, nonrandomised, open-label, multicentre clinical trial		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		1 year (between 1st enrolment and DCO date) not applicable not applicable
Hypothesis	Exploratory: threshold predetermined by the applicant for a positive outcome (ORR > 32% and lower limit of the 95% CI for ORR > 23%)		
Treatments group	Sotorasib		Treatment: Sotorasib 960 mg taken orally once daily Duration of treatment: until unacceptable toxicity or documented disease progression. 126 subjects enrolled of whom 123 subjects in the FAS
Endpoints and definitions	Primary endpoint: overall response rate	ORR	Proportion of subjects with a best overall response of confirmed CR or confirmed PR, measured by CT or MRI and assessed per RECIST 1.1 by blinded independent central review (BICR). CR and PR required confirmatory CT or MRI repeat assessment at least 4 weeks after the first detection of response.
	Secondary endpoint: duration of response	DOR	Time from first PR or CR to disease progression per RECIST 1.1 or death, whichever was earlier. The DOR was calculated only for subjects who achieved a confirmed best overall response of PR or CR per RECIST 1.1.

	Secondary endpoint: disease control rate	DCR	Proportion of subjects whose best overall response was CR, PR, or SD > 5 weeks
	Secondary endpoint: time to response	TTR	Time from the date of the first dose of sotorasib to the date of the first PR or CR. The TTR was calculated only for subjects who achieved a confirmed best overall response of PR or CR per RECIST 1.1.
	Secondary endpoint: Progression-free survival	PFS	Time from the date of the first dose of sotorasib to the date of disease progression (assessed per RECIST 1.1 by BICR) or death due to any cause.
	Secondary endpoint: Overall survival	OS	Time from the date of the first dose of sotorasib until the date of death due to any cause.
Database lock	01 December 2020		

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	other: exploratory, full analysis set	
Descriptive statistics and estimate variability	Treatment group	NSCLC 960mg QD Fasted
	Number of subjects	124
	ORR, % (95% CI)	37.1 (28.6, 46.2)
	Median DOR months (95% CI)	11.1 (6.9, 15.0) (DCO 20 June 2021)
	DCR, % (95% CI)	80.6 (72.6, 87.2)
	Median TTR (range)	1.35 (1.2, 10.1)
	Median PFS (95% CI)	6.8 (5.1, 8.2)
	Median OS (95% CI)	12.5 (10.0, NE)

2.6.5.3. Clinical studies in special populations

Table 35: Number of patients included in the clinical development per age group

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Non-Controlled trials	165/463	46/463	5/463

2.6.5.4. Supportive study(ies)

The phase-1 portion of the study 20170543 has been submitted in support of the application.

Objectives, outcomes and endpoints

Table 36: Objectives and endpoints of the phase-1 portion of the study 20170543

Objectives	Endpoints
Phase 1 — Primary	
Part 1a and Part 2a Monotherapy Cohorts (Once Daily [QD] Dosing) – Advanced Solid Tumors	
• to evaluate the safety and tolerability of sotorasib in adult subjects with *KRAS p.G12C*-mutated advanced solid tumors	• incidence of treatment-emergent adverse events, treatment-related adverse events, and clinically significant changes in vital signs, physical examinations, electrocardiograms (ECGs), and clinical laboratory tests
• to estimate the maximum tolerated dose (MTD) and/or a recommended phase 2 dose (RP2D) in adult subjects with *KRAS p.G12C*-mutated advanced solid tumors	• incidence of dose-limiting toxicity (DLT)
Part 1b and Part 2b Monotherapy Cohorts (Twice Daily [BID] Dosing) – Advanced Solid Tumors *Part 1d and Part 2d Monotherapy Cohorts (QD Dosing) – Advanced Solid Tumors (Fed State)*	
• to evaluate the safety and tolerability of sotorasib in adult subjects with *KRAS p.G12C*-mutated advanced solid tumors	• incidence of DLTs, treatment-emergent adverse events, treatment-related adverse events, and changes in vital signs, ECGs, and clinical laboratory tests

Objectives	Endpoints
Phase 1 — Secondary	
Part 1a and Part 2a Monotherapy Cohorts (QD Dosing) – Advanced Solid Tumors *Part 1b and Part 2b Monotherapy Cohorts (BID Dosing) – Advanced Solid Tumors* *Part 1d and Part 2d Monotherapy Cohorts (QD Dosing) – Advanced Solid Tumors (Fed State)*	
• to characterize the pharmacokinetics (PK) of sotorasib after administration as an oral tablet formulation	• PK parameters of sotorasib including, but not limited to, maximum plasma concentration (C_{max}), time to achieve C_{max} (t_{max}), and area under the plasma concentration-time curve (AUC)
• to evaluate tumor response assessed by RECIST 1.1 of sotorasib as monotherapy in advanced solid tumors with *KRAS p.G12C* mutation	• OR, DOR, disease control, PFS, duration of stable disease, and TTR measured by CT or MRI and assessed per RECIST 1.1 Response was assessed by BICR. Complete response and PR required confirmatory CT or MRI repeat assessment at least 4 weeks after the first detection of response. • Overall survival (OS)
• to evaluate the effect of food on the oral PK of sotorasib (substudy of part 1a only)	• PK parameters of sotorasib including, but not limited to, C_{max}, t_{max}, and AUC in the fed and/or fasted state
• to evaluate the relationship between changes in corrected QT interval (QTc) and sotorasib exposure (part 1a and part 2a only)	• Sotorasib exposure/QTc interval relationship

Outcomes and estimation

The efficacy results for 34 subjects with previously treated NSCLC in the ORR analysis set of the phase 1 NSCLC 960 mg QD sotorasib monotherapy (fasted) dose cohort are presented below.

The results for efficacy endpoints for other dose cohorts in the phase 1 NSCLC group are provided in the tables below.

Table 37: Summary of objective response (Response assessed by BICR per RECIST 1.1 criteria) (Phase 1 NSCLC monotherapy in ORR Analysis Set)

	Phase 1 NSCLC 180 mg QD Fasted (N = 3)	Phase 1 NSCLC 360 mg QD Fasted (N = 16)	Phase 1 NSCLC 720 mg QD Fasted (N = 6)	**Phase 1 NSCLC 960 mg QD Fasted (N = 34)**	Phase 1 NSCLC 480 mg BID Fed (N = 21)	Phase 1 NSCLC 960 mg QD Fed (N = 11)	Phase 1 NSCLC 1L 960 mg QD Fasted (N = 28)
Best overall response - n (%)							
Complete response (CR)							
Confirmed	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	1 (9.1)	0 (0.0)
Confirmed and unconfirmed awaiting confirmatory scan	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	1 (9.1)	2 (7.1)
Partial response (PR)							
Confirmed	1 (33.3)	4 (25.0)	3 (50.0)	**16 (47.1)**	3 (14.3)	2 (18.2)	8 (28.6)
Confirmed and unconfirmed awaiting confirmatory scan	1 (33.3)	4 (25.0)	3 (50.0)	**16 (47.1)**	5 (23.8)	4 (36.4)	9 (32.1)
Stable disease (SD)	2 (66.7)	10 (62.5)	3 (50.0)	**16 (47.1)**	12 (57.1)	6 (54.5)	14 (50.0)
Progressive disease (PD)	0 (0.0)	1 (6.3)	0 (0.0)	**2 (5.9)**	3 (14.3)	0 (0.0)	2 (7.1)
Not evaluable	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)
Not done	0 (0.0)	1 (6.3)	0 (0.0)	**0 (0.0)**	3 (14.3)	2 (18.2)	4 (14.3)
Objective response rate (ORR)							
Confirmed - N1 (%)	1 (33.3)	4 (25.0)	3 (50.0)	**16 (47.1)**	3 (14.3)	3 (27.3)	8 (28.6)
95% CI[a]	(0.84, 90.57)	(7.27, 52.38)	(11.81, 88.19)	**(29.78, 64.87)**	(3.05, 36.34)	(6.02, 60.97)	(13.22, 48.67)
Confirmed and unconfirmed awaiting confirmatory scan - n (%)	1 (33.3)	4 (25.0)	3 (50.0)	**16 (47.1)**	5 (23.8)	5 (45.5)	11 (39.3)
95% CI[a]	(0.84, 90.57)	(7.27, 52.38)	(11.81, 88.19)	**(29.78, 64.87)**	(8.22, 47.17)	(16.75, 76.62)	(21.50, 59.42)
Disease control rate (DCR) - n (%)	3 (100.0)	14 (87.5)	6 (100.0)	32 (94.1)	15 (71.4)	9 (81.8)	22 (78.6)
95% CI[a]	(29.24, 100.00)	(61.65, 98.45)	(54.07, 100.00)	(80.32, 99.28)	(47.82, 88.72)	(48.22, 97.72)	(59.05, 91.70)
Duration of objective response (DOR)[b]							
Observed duration ≥ 3 mon - n (%)	1 (100.0)	4 (100.0)	2 (66.7)	12 (75.0)	0 (0.0)	1 (33.3)	2 (25.0)
Observed duration ≥ 6 mon - n (%)	1 (100.0)	2 (50.0)	2 (66.7)	5 (31.3)	0 (0.0)	0 (0.0)	0 (0.0)
Observed duration ≥ 9 mon - n (%)	1 (100.0)	1 (25.0)	1 (33.3)	4 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Observed duration ≥ 12 mon - n (%)	0 (0.0)	1 (25.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Subject status - n (%)							
Events	1 (100.0)	3 (75.0)	3 (100.0)	5 (31.3)	0 (0.0)	0 (0.0)	0 (0.0)
Progressive disease	1 (100.0)	2 (50.0)	2 (66.7)	4 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	1 (25.0)	1 (33.3)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Censored	0 (0.0)	1 (25.0)	0 (0.0)	11 (68.8)	3 (100.0)	3 (100.0)	8 (100.0)
On study without disease progression	0 (0.0)	1 (25.0)	0 (0.0)	9 (56.3)	3 (100.0)	2 (66.7)	8 (100.0)
Missed more than 1 consecutive assessment	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrew consent	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (33.3)	0 (0.0)
Duration of response (KM) (months)							
25th percentile (95% CI)	-	-	-	**4.7 (3.0, NE)**	-	-	-
Median (95% CI)	-	-	-	**NE (4.2, NE)**	-	-	-
75th percentile (95% CI)	-	-	-	**NE (5.1, NE)**	-	-	-
Min, Max (+ for censored)	9.5, 9.5	3.1, 13.6	2.8, 10.9	**1.5+, 15.0+**	1.4+, 1.5+	1.4+, 4.9+	1.3+, 4.1+
Kaplan-Meier estimate (95% CI)[c]							
At 3 months	-	-	-	**92.3 (56.6, 98.9)**	-	-	-
At 6 months	-	-	-	**53.7 (21.0, 78.1)**	-	-	-
At 9 months	-	-	-	**53.7 (21.0, 78.1)**	-	-	-
At 12 months	-	-	-	**53.7 (21.0, 78.1)**	-	-	-
Follow-up time for DOR[d] (KM) (months)							
25th percentile (95% CI)	-	-	-	**4.1 (1.5, 9.0)**	-	-	-
Median (95% CI)	-	-	-	**9.0 (4.1, 11.0)**	-	-	-
75th percentile (95% CI)	-	-	-	**9.8 (9.0, 15.0)**	-	-	-
Min, Max (+ for censored)	9.5+, 9.5+	3.1+, 13.6+	2.8+, 10.9+	**1.5, 15.0**	1.4, 1.5	1.4, 4.9	1.3, 4.1

	Phase 1 NSCLC 180 mg QD Fasted (N = 3)	Phase 1 NSCLC 360 mg QD Fasted (N = 16)	Phase 1 NSCLC 720 mg QD Fasted (N = 6)	**Phase 1 NSCLC 960 mg QD Fasted (N = 34)**	Phase 1 NSCLC 480 mg BID Fed (N = 21)	Phase 1 NSCLC 960 mg QD Fed (N = 11)	Phase 1 NSCLC 1L 960 mg QD Fasted (N = 28)
Duration of stable disease[b]							
Observed duration ≥ 3 months - n (%)	2 (100.0)	4 (40.0)	2 (66.7)	**7 (43.8)**	1 (8.3)	3 (50.0)	5 (35.7)
Observed duration ≥ 6 months - n (%)	1 (50.0)	0 (0.0)	1 (33.3)	**3 (18.8)**	0 (0.0)	0 (0.0)	0 (0.0)
Observed duration ≥ 9 months - n (%)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (6.3)**	0 (0.0)	0 (0.0)	0 (0.0)
Observed duration ≥ 12 months - n (%)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (6.3)**	0 (0.0)	0 (0.0)	0 (0.0)
Duration of stable disease (KM) (months)							
25th percentile (95% CI)	-	2.6 (2.2, 3.6)	-	**2.6 (2.5, 2.8)**	2.8 (2.6, 3.2)	-	2.8 (2.6, 4.1)
Median (95% CI)	-	3.6 (2.2, 4.0)	-	**2.9 (2.6, 5.2)**	3.2 (2.6, 3.2)	-	4.1 (2.6, 4.1)
75th percentile (95% CI)	-	4.0 (2.6, 4.8)	-	**5.3 (2.9, NE)**	3.2 (NE, NE)	-	4.1 (2.8, 4.1)
Min, Max (+ for censored)	4.4, 8.3	1.0+, 4.8	2.2, 7.8	**1.3+, 12.5+**	1.2+, 3.2	2.6+, 4.1+	1.2+, 4.1
Follow-up time for duration of stable disease[d] (KM) (months)							
25th percentile (95% CI)	-	2.4 (1.0, NE)	-	**12.5 (1.3, 12.5)**	2.0 (1.2, 2.8)	-	1.4 (1.2, 3.9)
Median (95% CI)	-	NE (1.0, NE)	-	**12.5 (NE, NE)**	2.8 (1.3, 3.0)	-	3.9 (1.4, 4.1)
75th percentile (95% CI)	-	NE (NE, NE)	-	**12.5 (NE, NE)**	3.0 (2.8, NE)	-	4.1 (3.9, NE)
Min, Max (+ for censored)	4.4+, 8.3+	1.0, 4.8+	2.2+, 7.8+	**1.3, 12.5**	1.2, 3.2+	2.6, 4.1	1.2, 4.1+
Time to objective response (months)[b]							
Number of subjects with objective response	1	4	3	**16**	3	3	8
Mean (SD)	1.25 (NE)	1.65 (0.59)	2.74 (1.46)	**2.24 (2.16)**	1.28 (0.11)	1.25 (0.07)	1.84 (0.71)
Median	1.25	1.36	2.79	**1.41**	1.22	1.25	1.36
Min, max	1.2, 1.2	1.3, 2.5	1.2, 4.2	**0.8, 8.3**	1.2, 1.4	1.2, 1.3	1.3, 2.7

BID = twice a day; mono = sotorasib monotherapy; KM = Kaplan-Meier; NE = not estimable; NSCLC = non-small cell lung cancer; NSCLC 1L = previously untreated subjects with NSCLC; Q1 = first quartile; Q3 = third quartile; QD = once daily; SD = standard deviation.
Phase 1 data cutoff date of 06 July 2020. Months are derived as days x 12/365.25.Kaplan-Meier estimates were not provided if the analysis set had < 10 subjects.
Only minimum and maximum values were provided.
a Exact 95% confidence interval was calculated using the Clopper-Pearson method.
b Time to response and duration of response are calculated among confirmed responders N1. Duration of stable disease is calculated among subjects with best overall
response of stable disease.
c 95% CIs are based on estimated variance for log-log transformation of the Kaplan-Meier survival estimate.
d Follow-up time is measured by reversing the status indicator for censored and events.

Table 38: Summary of progression-free survival (progression assessed by BICR per RECIST 1.1 criteria) (Phase 1 NSCLC monotherapy Full Analysis Set)

	Phase 1 NSCLC 180 mg QD Fasted (N = 3)	Phase 1 NSCLC 360 mg QD Fasted (N = 16)	Phase 1 NSCLC 720 mg QD Fasted (N = 6)	**Phase 1 NSCLC 960 mg QD Fasted (N = 34)**	Phase 1 NSCLC 480 mg BID Fed (N = 21)	Phase 1 NSCLC 960 mg QD Fed (N = 14)	Phase 1 NSCLC 1L 960 mg QD Fasted (N = 30)
Subject status							
Events - n (%)	3 (100.0)	11 (68.8)	6 (100.0)	**21 (61.8)**	7 (33.3)	2 (14.3)	10 (33.3)
Progressive disease	3 (100.0)	8 (50.0)	3 (50.0)	**17 (50.0)**	6 (28.6)	1 (7.1)	6 (20.0)
Death due to any cause	0 (0.0)	3 (18.8)	3 (50.0)	**4 (11.8)**	1 (4.8)	1 (7.1)	4 (13.3)
Censored - n (%)	0 (0.0)	5 (31.3)	0 (0.0)	**13 (38.2)**	14 (66.7)	12 (85.7)	20 (66.7)
On study without disease progression	0 (0.0)	1 (6.3)	0 (0.0)	**10 (29.4)**	12 (57.1)	8 (57.1)	16 (53.3)
No evaluable post-baseline disease assessment	0 (0.0)	1 (6.3)	0 (0.0)	**0 (0.0)**	2 (9.5)	3 (21.4)	2 (6.7)
Missed more than 1 consecutive assessments	0 (0.0)	2 (12.5)	0 (0.0)	**2 (5.9)**	0 (0.0)	0 (0.0)	0 (0.0)
Started new anticancer therapy	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	2 (6.7)
Withdrew consent	0 (0.0)	1 (6.3)	0 (0.0)	**1 (2.9)**	0 (0.0)	1 (7.1)	0 (0.0)
Off study due to sponsor decision	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)
Progression-free Survival (KM) (months)							
25th percentile (95% CI)	-	2.6 (1.2, 3.9)	-	**2.8 (2.5, 4.3)**	2.6 (1.1, 3.2)	NE (0.7, NE)	2.6 (0.9, 4.1)
Median (95% CI)	-	4.0 (2.6, 6.7)	-	**5.3 (3.1, 8.1)**	3.2 (2.6, 3.2)	NE (2.7, NE)	4.1 (2.8, NE)
75th percentile (95% CI)	-	6.7 (3.9, 14.9)	-	**NE (6.3, NE)**	3.2 (NE, NE)	NE (NE, NE)	NE (4.1, NE)
Min, max (+ for censored)	4.4, 10.7	0.0+, 14.9	2.2, 13.7	**1.2, 16.3+**	0.0+, 3.2	0.0+, 6.0+	0.0+, 5.7+
Kaplan-Meier estimate (95% CI)[a]							
At 3 months	-	68.1 (35.4, 86.8)	-	**69.3 (50.4, 82.2)**	61.2 (31.0, 81.5)	79.5 (39.3, 94.5)	62.7 (39.9, 78.8)
At 6 months	-	25.5 (6.2, 51.2)	-	**42.9 (25.5, 59.2)**	0.0 (NE, NE)	79.5 (39.3, 94.5)	NE (NE, NE)
At 9 months	-	17.0 (2.7, 41.9)	-	**31.2 (15.6, 48.2)**	0.0 (NE, NE)	NE (NE, NE)	NE (NE, NE)
At 12 months	-	17.0 (2.7, 41.9)	-	**31.2 (15.6, 48.2)**	0.0 (NE, NE)	NE (NE, NE)	NE (NE, NE)
Follow-up time for PFS[b] (KM) (months)							
25th percentile (95% CI)	-	2.4 (0.0, NE)	-	**10.9 (3.0, 11.1)**	1.3 (0.0, 2.7)	1.3 (0.0, 2.7)	1.4 (1.2, 4.0)
Median (95% CI)	-	8.3 (2.4, NE)	-	**11.1 (5.6, 12.5)**	2.7 (1.3, 2.8)	2.7 (0.0, 4.1)	4.0 (2.6, 4.1)
75th percentile (95% CI)	-	NE (8.3, NE)	-	**12.5 (11.1, 16.3)**	2.8 (2.7, NE)	4.1 (2.7, 6.0)	4.1 (4.0, 5.7)
Min, max (+ for censored)	4.4+, 10.7+	0.0, 14.9+	2.2+, 13.7+	**1.2+, 16.3**	0.0, 3.2+	0.0, 6.0	0.0, 5.7

BID = twice a day; mono = sotorasib monotherapy; KM = Kaplan-Meier; NE = not estimable; NSCLC = non-small cell lung cancer; NSCLC 1L = previously untreated subjects with NSCLC; Q1 = first quartile; Q3 = third quartile; QD = once daily; SD = standard deviation.
Phase 1 data cutoff date of 06 July 2020.
Kaplan-Meier estimates was not provided if the analysis had < 10 subjects. Only minimum and maximum values were provided.
a 95% CIs are based on estimated variance for log-log transformation of the Kaplan-Meier survival estimate.
b Follow-up time is summarised by reversing the status indicator for censored and events.

Table 39: Summary of overall survival (Phase 1 – NSCLC monotherapy Safety Analysis Set)

	NSCLC 180 mg QD Fasted (N = 3)	NSCLC 360 mg QD Fasted (N = 16)	NSCLC 720 mg QD Fasted (N = 6)	**NSCLC 960 mg QD Fasted (N = 34)**	NSCLC 480 mg BID Fed (N = 21)	NSCLC 960 mg QD Fed (N = 14)	NSCLC 1L 960 QD Fasted (N = 30)
Subject status							
Events - n (%)	2 (66.7)	7 (43.8)	5 (83.3)	**19 (55.9)**	4 (19.0)	1 (7.1)	6 (20.0)
Death due to any cause	2 (66.7)	7 (43.8)	5 (83.3)	**19 (55.9)**	4 (19.0)	1 (7.1)	6 (20.0)
Censored - n (%)	1 (33.3)	9 (56.3)	1 (16.7)	**15 (44.1)**	17 (81.0)	13 (92.9)	24 (80.0)
Alive at last follow-up	0 (0.0)	7 (43.8)	1 (16.7)	**12 (35.3)**	15 (71.4)	10 (71.4)	24 (80.0)
Withdrew consent	1 (33.3)	2 (12.5)	0 (0.0)	**3 (8.8)**	2 (9.5)	3 (21.4)	0 (0.0)
OS (KM) (months)							
25th percentile (95% CI)	-	4.4 (2.2, 8.2)	-	**5.2 (3.2, 7.1)**	4.1 (1.2, 6.7)	NE (0.7, NE)	NE (1.1, NE)
Median (95% CI)	-	8.2 (4.1, NE)	-	**7.6 (6.3, NE)**	4.1 (4.1, 6.7)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	-	NE (8.2, NE)	-	**NE (8.1, NE)**	6.7 (4.1, 6.7)	NE (NE, NE)	NE (NE, NE)
Min, max (+ for censored)	7.8, 18.6	0.5+, 18.2+	2.2, 15.1+	**2.5, 17.1+**	1.2, 6.7	0.4+, 6.6+	0.5, 6.7+
Kaplan-Meier estimate (95% CI)[a]							
At 3 months	-	93.3 (61.3, 99.0)	-	**97.1 (80.9, 99.6)**	88.9 (61.8, 97.2)	92.3 (56.6, 98.9)	82.8 (63.4, 92.5)
At 6 months	-	71.8 (41.1, 88.4)	-	**72.2 (53.3, 84.4)**	44.4 (1.1, 86.5)	92.3 (56.6, 98.9)	78.2 (57.4, 89.7)
At 9 months	-	47.9 (20.0, 71.4)	-	**41.2 (23.8, 57.9)**	0.0 (NE, NE)	NE (NE, NE)	NE (NE, NE)
At 12 months	-	47.9 (20.0, 71.4)	-	**41.2 (23.8, 57.9)**	0.0 (NE, NE)	NE (NE, NE)	NE (NE, NE)
Follow-up time for OS[b] (KM) (months)							
25th percentile (95% CI)	-	7.8 (0.5, 8.4)	-	**11.3 (6.0, 12.2)**	2.4 (1.4, 2.9)	1.6 (0.4, 4.1)	3.2 (1.3, 4.4)
Median (95% CI)	-	8.4 (6.9, 9.8)	-	**12.2 (11.3, 13.5)**	3.1 (2.2, 3.5)	4.1 (1.3, 4.6)	4.4 (3.7, 5.0)
75th percentile (95% CI)	-	9.8 (8.2, 18.2)	-	**13.5 (12.2, 17.1)**	3.6 (3.2, NE)	4.6 (4.1, 6.6)	5.0 (4.6, 5.9)
Min, max (+ for censored)	7.8+, 18.6+	0.5, 18.2	2.2+, 15.1	**2.5+, 17.1**	1.2+, 6.7+	0.4, 6.6	0.5+, 6.7

- = not calculated; BID = twice daily; CI = confidence interval; KM = Kaplan-Meier; NE = not estimable; NSCLC = non-small cell lung cancer; NSCLC 1L = previously untreated subjects with NSCLC; QD = once daily; OS = overall survival
Data cutoff date 06 July 2020
OS was defined as the interval from the start of treatment to death due to any cause (whichever came first).
KM estimates were not provided if the analysis set had fewer than 10 subjects. Only min, max were provided.
a 95% CIs were based on estimated variance for log-log transformation of the KM survival estimate.
b Follow-up time was summarised by reversing the status indicator for censored and events.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The primary support for the proposed indication is based on efficacy results from subjects with KRAS p.G12C-mutated advanced NSCLC enrolled in the pivotal phase 2 portion of Study 20170543 (CodeBreaK 100). This study is an ongoing phase 1/2, open label, single-group study of sotorasib in subjects with KRAS p.G12C-mutated advanced or metastatic NSCLC, colorectal cancer, and other solid tumours. Further efficacy support is provided based on the results from the phase-1 portion assessing sotorasib as monotherapy.

Main study

Phase-1 portion

The Phase-1 portion of study 20170543 was the first-in-human (FIH) study of sotorasib and was conducted in 2 parts: part 1 - dose exploration and part 2 - dose expansion. During the dose exploration (part 1) of the phase 1, no dose-limiting toxicities were observed in any cohort but the RP2D for sotorasib was determined to be 960 mg QD, which was the highest dose tested. However, Sotorasib has demonstrated a non-linear pharmacokinetic profile (see section 2.6.1 Pharmacokinetics), with an important dose non-linearity. Responses were observed at all dose levels from 180 mg to 960 mg and a significant inverse ER relationship was observed. The 960 mg QD dose used in the Phase-2 portion of the study 20170543 is thus not considered justified.

Then, since the 960 mg QD dose is not justified, the applicant has planned to add a dose comparison part (part B) to the phase-2 portion of the study 20170543 in order to determine the optimal dose in subjects with previously treated locally advanced and unresectable or metastatic KRAS p.G12C mutant advanced NSCLC. The dose of 240 mg QD has been selected for further exploration in this dose comparison part of the study. The results of this study extension are highly relevant for dose optimisation.

Phase-2 portion

The target population for the pivotal study were adult patients with advanced solid tumours (NSCLC, CRC, and other solid tumours) and the enrolment was restricted to subjects with KRAS p.G12C-mutation as assessed by molecular testing. The pivotal study population for the currently claimed indication were patients with previously treated locally advanced or metastatic non-small cell lung cancer (NSCLC) with centrally confirmed KRAS p.G12C mutation in pre-dose tumour biopsy (N=126 patients). By the inclusion criteria the study subjects had ≥ 1 prior line(s) of anticancer therapy, progressed on prior line(s) of therapy, had measurable disease per RECIST 1.1 criteria and had ECOG performance status of ≤ 1.

The inclusion criteria of disease progression after received prior line therapies (checkpoint inhibitor, platinum-based therapy or their combination, targeted therapy against oncogenic driver mutations) were not defined in detail regarding the treatment duration or the number of the progressed tumour locations or their site and whether the clinical or radiologic progression was applied as a progression criteria. In the definition of measurable lesion, radiotherapy was not excluded and the applicant was requested to clarify how this could have potentially affected the evaluation of ORR results. Uncertainties remain in the response evaluation in several patients in which the previous radiotherapy may have influenced the response evaluation. However, these uncertainties are not expected to substantially impact the key outcomes of the study and hence this issue is not pursued further.

Targeted biological therapies included anti-VEGF (bevacizumab, ramucirumab), anti PD-1, anti PD-L1, or other checkpoint inhibitor (atezolizumab, pembrolizumab, nivolumab, durvalumab, ipilimumab, MedImmune D6840, TSR-042), and RANK-L inhibitor (denosumab) targeted biologic. The following are the targeted small molecules that were used: capmatinib, nintedanib, trametinib, vorolanib, RMC-4630, sitravatinib, cobimetinib. It is considered that the difference in ORR between subgroups of subjects with or without brain metastases is mostly prognostic. This is supported by historical evidence of poor outcomes in patients with brain metastases compared to patients without. Ongoing study 20190135 in subjects with NSCLC and brain metastases should further inform the effect in this population. On the other hand, no scientific basis could be found by the applicant for differences observed between subgroups of patients with/without prior platinum-based chemotherapy and patients with/without both prior platinum-based chemotherapy and anti-PD-1 or anti PD-L1 therapies. These differences are most likely observed due to the small sample sizes of these subgroups. These subgroups (amongst other baseline characteristics) will be explored in the larger phase 3 study.

The applicant noted that oncogenic KRAS mutations, including the KRAS p.G12C mutation, rarely occur concomitantly with other actionable mutations. However, co-mutations were reported in 39 subjects (31.1%) and among them actionable driver mutations were identified in 6 patients; 3 patients (2.4%) with EGFR mutation, 2 patients (1.6%) with MET mutation and 1 patient (0.8%) with BRAF mutation. No subjects had co-mutations in ALK or ROS. Since the mutation data reported by the study centre did not provide specific mutations, actionability of the mutation is unknown. While ideally patients should get targeted therapy early in their treatment course if their tumour has an actionable driver mutation, these 6 subjects did not receive it as their first line of therapy and 4 of these subjects had not received a targeted therapy after 3 lines of therapy. Further information about the previous treatments of the subjects having actionable driver mutations was received from the applicant as requested during the

evaluation. Based on the applicant´s responses, the treatment outcome was not negatively affected by these co-mutations, even though the data is limited. There were almost as many patients with PD-L1 expression <1%, ≥1% and <50% and ≥50% with respectively 33 subjects (26.2%), 24 subjects (19.0%) and 35 subjects (27.8%). For 34 subjects (27.0%) the PD-L1 expression was unknown. Indeed, in Study 20170543, PD-L1 expression level was not required data. Therefore, this information was not available for every enrolled subject even though queries were made in an attempt to collect this information. Of these 34 subjects with PD-L1 status "unknown," 88.2% (30 subjects) had prior PD-1 and/or PD-L1 therapy, alone or in combination with chemotherapy, similar to the entire study population. Among the 4 subjects who did not receive checkpoint inhibitor therapy, all 4 received at least platinum doublet chemotherapy. Overall, the significance of PD-L1 expression on the outcome of the pivotal trial remains unclear and this topic needs to be addressed in further clinical studies, including the ongoing Phase III study.

All subjects in the Phase 2 trial received sotorasib as monotherapy administered orally 960 mg (8 tablets of 120 mg) once daily (QD) without interruption until disease progression.

The primary objective of the Phase 2 trial was the evaluation of tumour objective response rate (ORR) (CR + PR) assessed by RECIST 1.1 criteria of sotorasib as monotherapy in subjects with KRAS p.G12C-mutated advanced tumours (NSCLC, CRC, and other tumour types). The secondary objectives and endpoints were DOR, DCR, TTR, PFS (including also 6-month and 12-month outcome), and OS (including also 12-month OS). In addition, the PK parameters (C_{max}, AUC, Cl, t_{max}) were measured. Overall, the proposed endpoints selected as well as the objectives seem reasonable, though, interpretation of OS and PFS results is hampered by the study design.

The choice of ORR as the primary endpoint is justified in a Phase 2 single-arm study. It is acknowledged that the selected primary endpoint in contrast to OS excludes the impact of natural history of the tumour unrelated to the intervention interfering the outcome. The DOR secondary endpoint is important to contextualise the primary outcome, but it has the same limitations as the primary endpoint regarding the intrinsic factors in trial setting potentially biasing the evaluation against published data.

Overall, it seems that the current study population has approximately a 10% lower proportion of patients with a high PD-L1 expression compared to the cohort in the RWE studies submitted to support the claim for unmet medical need. The significance of PD-L1 expression on the outcome in this this trial is unclear and this topic needs to be addressed in further clinical studies, including the ongoing Phase III study. This is of prime importance while knowing that the prognosis of NSCLC is highly dependent also on the PD-L1 level, which contributes to the response rate obtained.

The sample size for the NSCLC group was based on the approximation of a 90% probability that the lower limit of the ORR 95% CI exceeds the tumour-specific benchmark ORR of 23% derived from the REVEL study in the second-line treatment setting with ramucirumab plus docetaxel after disease progression on platinum-based therapy (Garon et al, 2014). The use of the REVEL study, although seeming to have more favourable study population compared to the current study in terms of treatment lines and smoking history, leaves many uncertainties regarding the disease progression potential (e.g. prognostic PD-L1 expression level and various driver gene co-mutations were not studied in the reference study) and by lacking adequate baseline information to compare and justify the similar characteristics in the study populations. The REVEL study was also conducted before immunotherapies were approved which makes hard to contextualise the relevance of these data. In the CHMP scientific advice the targeted lower limit for the ORR of 23% was not agreed on and due to the inter-trial setting, an ORR of at least 32% [0.24 – 0.42] was considered more suitable (EMEA/H/SA/4171/1/2019/II).

The minimum sample size for the observed ORRs to exclude 32% benchmark point-estimate was estimated to be 105 study subjects for the advanced NSCLC.

Statistical methods and endpoint definitions are appropriate. However, almost all patients enrolled in the NSCLC group (123/126) were included in the FAS population with only 3 patients being excluded due to the non-measurable lesion, who were included in the study by an obvious protocol violation.

The statistical analysis plan was amended four times and in three of these after the first patient was

The reported protocol violations are not expected to have a significant impact on the efficacy evaluation. The treatment compliance in the NSCLC group was high with only one patient discontinuing due to non-compliance.

Efficacy data and additional analyses

A total of 126 subjects with NSCLC were enrolled and all the 126 subjects received sotorasib. Among them, 123 subjects were included in the full analysis set (FAS), and 3 subjects were excluded as they did not have ≥ 1 measurable lesion at baseline according to BICR. However, the dataset used for sensitivity analysis of response-related efficacy endpoints using assessment per investigator comprised 126 subjects.

Primary endpoint

As of the DCO of 1 December 2020, the ORR (CR + PR) assessed per RECIST 1.1 by BICR was 37.1 % (46 of 124 subjects; 95% CI: 28.6, 46.23) consisting of 3 subjects (2.4%) who achieved CR and 43 subjects (34.7%) who achieved PR.

The concordance rates between central review and investigator for objective response, best overall response, and disease progression were 82.9%, 72.7%, and 78.0%, respectively at the DCO of 1 September 2020. The concordance rate for objective response was 83.1% at the DCO of 1 December 2020.

Subgroup analyses were conducted to explore the consistency of the ORR between subgroups. In the context of a single arm study with small sample size in each subgroup, the interpretation of subgroup analyses is hampered, and no formal conclusion could be done whether these factors are predictive or prognostic.

Secondary endpoints

The disease control rate (DCR) (95% Cl) for subjects with NSCLC was relatively high, 99/123 (80.5%, 95% CI: 72.37, 87.08) with 43.1% of subjects having stable disease, and the time to response was short 1.35 (1.2, 6.1) months. The value of the observation is limited with relatively short minimal time interval criteria defined for the SD on which DCR was based on.

As of the 20 June 2021 data cut-off date, the Kaplan-Meier estimate of median (95% CI) DOR for the 46 objective responders was 11.1 months (6.9, 15.0) months. As of the data cut-off date, the Kaplan-Meier estimates for DOR at 6, 9, and 12 months were 71.2%, 55.7%, and 45.1%, respectively. The Kaplan-Meier estimate of median (95% CI) follow-up time for DOR was 15.3 (15.2, 15.8) months.

Although the duration of previous treatment response was not collected in Study 20170543, the immediate prior treatment start and discontinuation dates were known for all 123 subjects. Based on the available data the median duration on treatment was numerically higher for sotorasib (5.5 months, 95% CI: 4.1, 7.6) than for the previous therapy (4.2 months, 95% CI: 3.0, 5.6). This might indicate at least similar treatment response with sotorasib to prior treatment. The applicant did not provide the data on correlation between the prior treatment length and the response with sotorasib, but the data

seem to support similar or slightly better response with sotorasib overall, despite it being the later treatment line.

As of the DCO of 1 December 2020 of the 46 responders in the NSCLC group, the median time to response was 1.35 (1.2, 10.1) months.

At the DCO of 1 December 2020, the median PFS was 6.8 months with a median follow-up time of 11 months (min, max: 0.3, 12.6+) and the 95% CI range from 10.8 to 11.1 months by the Kaplan-Meier analysis. Results of subgroup analysis of PFS by central review were presented. However, in the context of a single arm study with an overall small study size and some unbalanced subgroups it is difficult to draw conclusion. The presented PFS data are also limited due to the short duration of follow-up.

At the DCO of 1 December 2020, the median OS was 12.5 months (95% CI: 10.0 NE) by Kaplan-Meier analysis. The Kaplan-Meier estimate of survival was 89.5% (82.7, 93.8) at 3 months, 63.5% (54.3, 71.4) at 9 months, and 51.4% (41.9, 60.1) at 12 months. Overall, the interpretation of time-to-event endpoints (OS and PFS) is hampered by the fact that there is no randomised comparator and, therefore, no robust conclusions can be drawn.

Supportive studies – Phase-1 portion of the study 20170543

Further efficacy support is provided based on the results from the phase-1 portion assessing sotorasib as monotherapy. During the phase-1 portion of study 20170543, 34 subjects with previously treated NSCLC received 960 mg QD sotorasib monotherapy (fasted) dose. Since the sotorasib dose used in this cohort was identical to the dose used in the phase-2 portion of the study, the efficacy data are supportive of the phase 2 NSCLC efficacy data package.

As of the DCO date (06 July 2020) of 34 subjects with previously treated NSCLC in the monotherapy 960-mg QD (fasted) dose cohort (parts 1a, 2a), the ORR was 47.1% (95%CI: 29.78, 64.87), consisting of 16 subjects (47.1%) who achieved partial responses. No patients achieved a complete response. The DCR was 94.1% (95%CI: 80.32, 99.28) with 16 subjects with PR and 16 subjects with SD.

Out of the 16 objective responders, the KM estimate of median DOR was not reached (95%CI: 4.2, NE) with a median (range) follow-up time for DOR of 9.0 months (1.5, 15.0). However, due to the low number of events with more than two third of patients who were censored at the time of analysis, no conclusion can be drawn regarding the expected durability of response.

The median (range) TTR was 1.41 months (0.8, 8.3).

As of the DCO date, the KM estimate of median PFS was 5.3 months (95%CI: 3.1, 8.1) with a median (range) follow-up time for PFS of 11.1 months (1.2+, 16.30). The KM PFS probability estimate (95%CI) was 42.9% (25.5, 59.2) at 6 months and 31.2% (15.6, 48.2) at 12 months.

The KM estimate of median OS was 7.6 months (95%CI: 6.3, NE) with a median (range) follow-up time for OS was 12.2 months (2.5+, 17.1). The Kaplan-Meier estimate (95%CI) of survival was 72.2% (53.3, 84.4) at 6 months and 41.2% (23.8, 57.9) at 12 months.

Moreover, among the 25 subjects treated with the different doses of sotorasib monotherapy (180 mg to 720 mg QD [fasted]; phase 1, part 1a and part 2a) in the phase 1 ORR analysis set, 8 subjects (32%) had a confirmed partial response. Among these 8 responders, the DOR was at least 3 months in 7 subjects (87.5%), at least 6 months in 5 subjects (62.5%), at least 9 months in 3 subjects (37.5%), at least 12 months in 1 subject (12.5%).

Overall, efficacy data between the phase 1 and 2 are rather consistent.

In vitro biomarker test

For NSCLC in the phase-2 portion of study 20170543, the mutation was confirmed by central testing (therascreen® KRAS RGQ PCR from Qiagen) prior to enrolment. The baseline tissue samples used were archival FFPE blocks or slides, less than 5 years since collection. Baseline plasma samples were collected before a subject's first dose on Cycle 1 Day 1. Total nucleic acids were extracted from the FFPE tissue samples, RNA was purified, DNA libraries prepared, and target DNA amplified. Both target-captured DNA and target-captured RNA were sequenced and used to detect single and multi-nucleotide alterations, insertions and deletions, copy number variants, and translocations. Cell-free DNA was isolated from plasma samples and sequenced for detection of single nucleotide variants, insertions and deletions, fusions and copy number variations. Samples were processed and analysed using standard tissue and plasma tests for the genes of interest (EGFR pathway and related genes).

Moreover, based on the Phase 1 data (with limited sample size), no clear co-mutation or biomarker profile was identified to be correlated with response or resistance to sotorasib in NSCLC. However, the results of the exploratory biomarker analyses for the phase 2 portion of the study 20170543 have not been provided and are now expected to understand the outcome and the prognostic within this heterogeneous patient population.

Assessment of paediatric data on clinical efficacy

A waiver was requested for the treatment of children, from birth to ≤ 18 years of age with non-small cell lung cancer (NSCLC) on the grounds that NSCLC is a condition that predominantly occurs in the adult population and the extreme rarity of paediatric tumours with the KRAS p.G12C mutation, and the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric population.

Additional efficacy data needed in the context of a conditional MA

The evidence for efficacy of sotorasib is limited to uncontrolled data from one single arm phase 2 study. As comprehensive data are not available, a conditional marketing authorisation was requested by the applicant in the initial submission based on response rate. The current trial is considered sufficient to support the conditional marketing authorisation but has limitations in the demonstration of longer-term effect and time related endpoints (PFS and OS) remain descriptive. Therefore, additional controlled efficacy data on survival endpoints are needed as a SOB.

To provide more comprehensive data in the proposed indicated population, a confirmatory, active-controlled, phase 3 study is currently ongoing in the same population of patients. Study 20190009 (CodeBreaK 200), is designed to assess the efficacy and safety of sotorasib administered at 960 mg QD daily versus docetaxel and have the ability to provide confirmatory evidence, provided that a successful PFS result is supported by the totality of the data, including a favourable effect on OS /no negative trend as described in the CHMP anticancer product guideline. Results from this study are intended to provide a comprehensive data package and potentially convert the conditional MA into a full MA.

2.6.7. Conclusions on the clinical efficacy

Based on the available data the observed ORR of 37% is considered clinically meaningful in the patient population with advanced NSCLC carrying p.G12C mutation, and it is also higher than the ORRs observed with non-targeted treatments and docetaxel in overall NSCLC patient population. Furthermore, considering that almost all patients in the current study had metastatic disease and had already received platinum-based therapy and nearly 91% also the checkpoint inhibitor therapy leading

to the treatment resistant disease, the current response rate is considered relevant in this heavily pretreated population.

DOR of 11.1 months (95% CI 6.9, 15.0) at the latest data cut-off of 21 June 2021, supports clinically relevant response duration and clinical benefit.

Based on these aspects, sotorasib might offer an alternative treatment option for patients who have already experienced different chemotherapies with poor response and do not have any standard or care treatments available.

The CHMP considers the following measure necessary to address the missing efficacy data in the context of a conditional MA:

In order to confirm the efficacy and safety of sotorasib in the treatment of patients with KRAS G12C-mutated NSCLC, the MAH should submit the clinical study report for the phase III CodeBreaK 200 study (Study 20190009) comparing sotorasib versus docetaxel for the treatment of previously treated KRAS G12C-mutated NSCLC. The clinical study report will be submitted by 31 March 2023.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Overall Extent of Exposure

Table 37: Summary of sotorasib exposure (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 200)	CRC (N = 87)	Other Tumor Types (N = 72)	Any Tumor Type (N = 359)	Total Any Tumor Type/Any Dose (N = 456)
Number of cycles started					
Mean	9.0	7.0	5.5	7.8	7.6
SD	6.3	5.2	4.2	5.8	5.8
Median	7.0	6.0	4.0	6.0	6.0
Q1, Q3	4.0, 14.0	4.0, 8.0	2.0, 7.5	4.0, 12.0	3.0, 11.5
Min, Max	1, 31	1, 26	1, 25	1, 31	1, 31
Number of doses per subject					
Mean	183.1	140.4	103.8	156.9	161.0
SD	133.3	104.7	88.2	122.8	126.5
Median	163.0	123.0	83.0	123.0	126.0
Q1, Q3	65.0, 298.0	84.0, 169.0	42.0, 145.5	62.0, 240.0	63.0, 244.5
Min, Max	7, 580	21, 547	1, 528	1, 580	1, 583
Duration on treatment (weeks)					
Mean	27.56	20.79	15.38	23.48	22.84
SD	19.38	15.39	12.57	17.92	17.61
Median	23.93	18.00	12.14	18.00	18.00
Q1, Q3	12.00, 44.93	12.00, 27.00	6.07, 21.00	9.86, 35.86	9.14, 35.14
Min, Max	1.0, 92.1	3.0, 78.1	0.1, 75.3	0.1, 92.1	0.1, 92.1

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 200)	CRC (N = 87)	Other Tumor Types (N = 72)	Any Tumor Type (N = 359)	Total Any Tumor Type/Any Dose (N = 456)
Number and percentage of subjects with treatment duration					
< 3 months	65 (32.5)	34 (39.1)	40 (55.6)	139 (38.7)	185 (40.6)
≥ 3 months	135 (67.5)	53 (60.9)	32 (44.4)	220 (61.3)	271 (59.4)
≥ 6 months	92 (46.0)	22 (25.3)	9 (12.5)	123 (34.3)	152 (33.3)
≥ 9 months	58 (29.0)	8 (9.2)	3 (4.2)	69 (19.2)	79 (17.3)
≥ 12 months	20 (10.0)	5 (5.7)	1 (1.4)	26 (7.2)	30 (6.6)
≥ 18 months	2 (1.0)	0 (0.0)	0 (0.0)	2 (0.6)	3 (0.7)
Average dose delivered (mg) per day[a]					
Mean	865.74	920.69	893.13	884.55	847.23
SD	179.23	89.70	158.48	159.06	198.33
Median	960.00	960.00	960.00	960.00	960.00
Q1, Q3	878.60, 960.00	928.70, 960.00	942.64, 960.00	908.31, 960.00	829.68, 960.00
Min, Max	145.1, 1000.0	465.7, 960.0	218.2, 1004.7	145.1, 1004.7	145.1, 1004.7
Relative dose intensity (%)[b]					
Mean	90.18	95.91	93.03	92.14	92.61
SD	18.67	9.34	16.51	16.57	15.75
Median	100.00	100.00	100.00	100.00	100.00
Q1, Q3	91.52, 100.00	96.74, 100.00	98.19, 100.00	94.62, 100.00	94.79, 100.00
Min, Max	15.1, 104.2	48.5, 100.0	22.7, 104.7	15.1, 104.7	15.1, 104.7

CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QD = once-daily

* 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: 90DSU ISS Table 14a-5.1 and 90DSU ISS Table 14b-5.1

Table 38: Baseline demographics (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 200)	CRC (N = 87)	Other Tumor Types (N = 72)	Any Tumor Type (N = 359)	Total Any Tumor Type/Any Dose (N = 456)
Sex (n [%])					
Men	92 (46.0)	43 (49.4)	44 (61.1)	179 (49.9)	215 (47.1)
Women	108 (54.0)	44 (50.6)	28 (38.9)	180 (50.1)	241 (52.9)
Ethnicity (n [%])					
Hispanic or Latino	4 (2.0)	6 (6.9)	1 (1.4)	11 (3.1)	14 (3.1)
Not Hispanic or Latino	186 (93.0)	79 (90.8)	67 (93.1)	332 (92.5)	420 (92.1)
Missing	10 (5.0)	2 (2.3)	4 (5.6)	16 (4.5)	22 (4.8)
Race (n [%])					
Asian	31 (15.5)	23 (26.4)	16 (22.2)	70 (19.5)	76 (16.7)
Black or African American	6 (3.0)	1 (1.1)	3 (4.2)	10 (2.8)	14 (3.1)
Native Hawaiian or other Pacific Islander	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.3)	1 (0.2)
White	158 (79.0)	59 (67.8)	51 (70.8)	268 (74.7)	349 (76.5)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)
Other	5 (2.5)	3 (3.4)	2 (2.8)	10 (2.8)	14 (3.1)
Age (years)					
Mean	64.6	57.0	60.7	62.0	62.2
SD	9.3	11.4	11.0	10.6	10.8
Median	66.0	58.0	60.5	63.0	63.0
Q1, Q3	57.0, 72.0	50.0, 65.0	55.5, 69.5	55.0, 70.0	55.0, 71.0
Min, Max	37, 86	31, 85	33, 82	31, 86	31, 86
Age group (n [%])					
18 to 64 years	89 (44.5)	65 (74.7)	43 (59.7)	197 (54.9)	243 (53.3)
65 to 74 years	89 (44.5)	16 (18.4)	23 (31.9)	128 (35.7)	164 (36.0)
75 to 84 years	21 (10.5)	5 (5.7)	6 (8.3)	32 (8.9)	46 (10.1)
≥ 85 years	1 (0.5)	1 (1.1)	0 (0.0)	2 (0.6)	3 (0.7)

CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QD = once-daily
Source: 90DSU ISS Table 14a-2.1 and 90DSU ISS Table 14b-2.1

Table 39: Baseline disease characteristics (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 200) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 72) n (%)	Any Tumor Type (N = 359) n (%)	Total Any Tumor Type/Any Dose (N = 456) n (%)
Region					
North America	144 (72.0)	47 (54.0)	37 (51.4)	228 (63.5)	305 (66.9)
Europe	31 (15.5)	13 (14.9)	18 (25.0)	62 (17.3)	63 (13.8)
Asia	18 (9.0)	21 (24.1)	15 (20.8)	54 (15.0)	59 (12.9)
Rest of the world	7 (3.5)	6 (6.9)	2 (2.8)	15 (4.2)	29 (6.4)
Eastern Cooperative Oncology Group performance status at baseline					
0	58 (29.0)	46 (52.9)	21 (29.2)	125 (34.8)	149 (32.7)
1	140 (70.0)	41 (47.1)	46 (63.9)	227 (63.2)	295 (64.7)
≥ 2	2 (1.0)	0 (0.0)	5 (6.9)	7 (1.9)	12 (2.6)
Number of prior anticancer therapy[a]					
0	38 (19.0)[b]	0 (0.0)	0 (0.0)	38 (10.6)[b]	38 (8.3)[b]
1	67 (33.5)	4 (4.6)	19 (26.4)	90 (25.1)	115 (25.2)
2	55 (27.5)	25 (28.7)	21 (29.2)	101 (28.1)	123 (27.0)
3	33 (16.5)	26 (29.9)	16 (22.2)	75 (20.9)	98 (21.5)
≥ 4	7 (3.5)	32 (36.8)	16 (22.2)	55 (15.3)	82 (18.0)
Median	1.0	3.0	2.0	2.0	2.0
Type of prior anticancer therapy[c]					
Chemotherapy	158 (79.0)	87 (100.0)	72 (100.0)	317 (88.3)	412 (90.4)
Immunotherapy	148 (74.0)	7 (8.0)	19 (26.4)	174 (48.5)	240 (52.6)
Platinum-based chemotherapy and anti-PD-1 or anti-PD-L1[d]	134 (67.0)	5 (5.7)	16 (22.2)	155 (43.2)	218 (47.8)
Targeted biologics	38 (19.0)	78 (89.7)	17 (23.6)	133 (37.0)	178 (39.0)
Targeted small molecules	18 (9.0)	22 (25.3)	8 (11.1)	48 (13.4)	68 (14.9)
Other	2 (1.0)	29 (33.3)	15 (20.8)	46 (12.8)	67 (14.7)
Unknown	31 (15.5)	0 (0.0)	0 (0.0)	31 (8.6)	32 (7.0)
Metastatic disease					
Yes	193 (96.5)	87 (100.0)	71 (98.6)	351 (97.8)	447 (98.0)
No	7 (3.5)	0 (0.0)	1 (1.4)	8 (2.2)	9 (2.0)
Smoking history					
Never	14 (7.0)	47 (54.0)	37 (51.4)	98 (27.3)	125 (27.4)
Current	23 (11.5)	7 (8.0)	9 (12.5)	39 (10.9)	48 (10.5)
Former	160 (80.0)	30 (34.5)	25 (34.7)	215 (59.9)	276 (60.5)
Missing	3 (1.5)	3 (3.4)	1 (1.4)	7 (1.9)	7 (1.5)

Page 2 of 2

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] Number of prior lines includes therapies in metastatic disease and adjuvant therapy immediately before metastasis where progression occurred on or within 6 months of treatment ending.

[b] Includes 36 subjects enrolled in the treatment naïve cohort in the phase 1 portion of the study.

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

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

Adverse events

2.6.8.2. Adverse events

Adverse Events

As of the 01 December 2020, the he 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 tumour types and for the total monotherapy population.

Table 40: Summary of treatment-emergent adverse events (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 200) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 72) n (%)	Any Tumor Type (N = 359) n (%)	Total Any Tumor Type/Any Dose (N = 456) n (%)
All treatment-emergent adverse events	197 (98.5)	83 (95.4)	66 (91.7)	346 (96.4)	441 (96.7)
Grade ≥ 2	172 (86.0)	58 (66.7)	53 (73.6)	283 (78.8)	366 (80.3)
Grade ≥ 3	122 (61.0)	31 (35.6)	37 (51.4)	190 (52.9)	243 (53.3)
Grade ≥ 4	44 (22.0)	3 (3.4)	19 (26.4)	66 (18.4)	88 (19.3)
Serious adverse events	105 (52.5)	24 (27.6)	38 (52.8)	167 (46.5)	206 (45.2)
Leading to discontinuation of investigational product	18 (9.0)	1 (1.1)	3 (4.2)	22 (6.1)	28 (6.1)
Serious	12 (6.0)	0 (0.0)	3 (4.2)	15 (4.2)	18 (3.9)
Nonserious	7 (3.5)	1 (1.1)	0 (0.0)	8 (2.2)	11 (2.4)
Fatal adverse events	35 (17.5)	2 (2.3)	18 (25.0)	55 (15.3)	72 (15.8)
Treatment-related treatment-emergent adverse events	137 (68.5)	44 (50.6)	28 (38.9)	209 (58.2)	270 (59.2)
Grade ≥ 2	77 (38.5)	18 (20.7)	14 (19.4)	109 (30.4)	143 (31.4)
Grade ≥ 3	41 (20.5)	7 (8.0)	5 (6.9)	53 (14.8)	67 (14.7)
Grade ≥ 4	3 (1.5)	1 (1.1)	0 (0.0)	4 (1.1)	7 (1.5)
Serious adverse events	14 (7.0)	1 (1.1)	3 (4.2)	18 (5.0)	23 (5.0)
Leading to discontinuation of investigational product	12 (6.0)	1 (1.1)	0 (0.0)	13 (3.6)	17 (3.7)
Serious	5 (2.5)	0 (0.0)	0 (0.0)	5 (1.4)	6 (1.3)
Nonserious	7 (3.5)	1 (1.1)	0 (0.0)	8 (2.2)	11 (2.4)
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: 90DSU ISS Table 14a-6.1.1 and 90DSU ISS Table 14b-6.1.1

Table 41: Summary of treatment-emergent adverse events - pooled fasted and fed analysis (Safety Analysis Set)

Preferred Term	Sotorasib Monotherapy 960 mg QD Fasted and Fed			
	NSCLC (N = 214) n (%)	CRC (N = 91) n (%)	Other Tumor Types (N = 72) n (%)	Any Tumor Types (N = 377) n (%)
All treatment-emergent adverse events	211 (98.6)	87 (95.6)	66 (91.7)	364 (96.6)
Grade ≥ 2	184 (86.0)	61 (67.0)	53 (73.6)	298 (79.0)
Grade ≥ 3	128 (59.8)	32 (35.2)	37 (51.4)	197 (52.3)
Grade ≥ 4	47 (22.0)	4 (4.4)	19 (26.4)	70 (18.6)
Serious adverse events	110 (51.4)	25 (27.5)	38 (52.8)	173 (45.9)
Leading to discontinuation of investigational product	19 (8.9)	1 (1.1)	3 (4.2)	23 (6.1)
Serious	12 (5.6)	0 (0.0)	3 (4.2)	15 (4.0)
Nonserious	8 (3.7)	1 (1.1)	0 (0.0)	9 (2.4)
Fatal adverse events	38 (17.8)	3 (3.3)	18 (25.0)	59 (15.6)
Treatment-related treatment-emergent adverse events	146 (68.2)	46 (50.5)	28 (38.9)	220 (58.4)
Grade ≥ 2	82 (38.3)	19 (20.9)	14 (19.4)	115 (30.5)
Grade ≥ 3	43 (20.1)	7 (7.7)	5 (6.9)	55 (14.6)
Grade ≥ 4	3 (1.4)	1 (1.1)	0 (0.0)	4 (1.1)
Serious adverse events	14 (6.5)	1 (1.1)	3 (4.2)	18 (4.8)
Leading to discontinuation of investigational product	13 (6.1)	1 (1.1)	0 (0.0)	14 (3.7)
Serious	5 (2.3)	0 (0.0)	0 (0.0)	5 (1.3)
Nonserious	8 (3.7)	1 (1.1)	0 (0.0)	9 (2.4)
Fatal adverse events	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: 90DSU ISS Table 14d-6.1.401

Common Adverse Events

Table 42: Summary of treatment-emergent adverse events by preferred term (occurring in at least 5% of subjects in any group) (Safety Analysis Set)

Preferred Term	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 200) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 72) n (%)	Any Tumor Type (N = 359) n (%)	Total Any Tumor Type/Any Dose (N = 456) n (%)
Number of subjects with treatment-emergent adverse events	197 (98.5)	83 (95.4)	66 (91.7)	346 (96.4)	441 (96.7)
Diarrhoea	**87 (43.5)**	**25 (28.7)**	**10 (13.9)**	**122 (34.0)**	**157 (34.4)**
Nausea	**56 (28.0)**	**20 (23.0)**	**13 (18.1)**	**89 (24.8)**	**115 (25.2)**
Fatigue	**49 (24.5)**	**13 (14.9)**	**12 (16.7)**	**74 (20.6)**	**99 (21.7)**
Aspartate aminotransferase increased	**40 (20.0)**	**9 (10.3)**	7 (9.7)	**56 (15.6)**	**71 (15.6)**
Arthralgia	**39 (19.5)**	8 (9.2)	3 (4.2)	**50 (13.9)**	**71 (15.6)**
Alanine aminotransferase increased	**38 (19.0)**	7 (8.0)	5 (6.9)	**50 (13.9)**	**65 (14.3)**
Back pain	**38 (19.0)**	6 (6.9)	6 (8.3)	**50 (13.9)**	**61 (13.4)**
Constipation	**35 (17.5)**	8 (9.2)	5 (6.9)	**48 (13.4)**	**60 (13.2)**
Vomiting	**34 (17.0)**	**16 (18.4)**	**14 (19.4)**	**64 (17.8)**	**80 (17.5)**
Dyspnoea	**33 (16.5)**	5 (5.7)	2 (2.8)	**40 (11.1)**	**53 (11.6)**
Anaemia	**29 (14.5)**	**11 (12.6)**	6 (8.3)	**46 (12.8)**	**61 (13.4)**
Cough	**28 (14.0)**	7 (8.0)	6 (8.3)	**41 (11.4)**	**53 (11.6)**
Blood alkaline phosphatase increased	**26 (13.0)**	5 (5.7)	3 (4.2)	34 (9.5)	41 (9.0)
Decreased appetite	**24 (12.0)**	5 (5.7)	5 (6.9)	34 (9.5)	**51 (11.2)**
Headache	**24 (12.0)**	**11 (12.6)**	2 (2.8)	**37 (10.3)**	**50 (11.0)**
Oedema peripheral	**24 (12.0)**	5 (5.7)	5 (6.9)	34 (9.5)	42 (9.2)
Pneumonia	**23 (11.5)**	1 (1.1)	4 (5.6)	28 (7.8)	35 (7.7)
Abdominal pain	**21 (10.5)**	**11 (12.6)**	**16 (22.2)**	**48 (13.4)**	**63 (13.8)**
Pyrexia	**20 (10.0)**	**11 (12.6)**	6 (8.3)	**37 (10.3)**	44 (9.6)
Pleural effusion	18 (9.0)	3 (3.4)	3 (4.2)	24 (6.7)	27 (5.9)

Productive cough	18 (9.0)	0 (0.0)	1 (1.4)	19 (5.3)	25 (5.5)
Dizziness	17 (8.5)	5 (5.7)	2 (2.8)	24 (6.7)	38 (8.3)
Insomnia	17 (8.5)	5 (5.7)	2 (2.8)	24 (6.7)	34 (7.5)
Pruritus	17 (8.5)	5 (5.7)	2 (2.8)	24 (6.7)	30 (6.6)
Hypokalaemia	16 (8.0)	2 (2.3)	3 (4.2)	21 (5.8)	24 (5.3)
Hyponatraemia	16 (8.0)	0 (0.0)	2 (2.8)	18 (5.0)	22 (4.8)
Myalgia	15 (7.5)	7 (8.0)	3 (4.2)	25 (7.0)	34 (7.5)
Hypertension	15 (7.5)	2 (2.3)	4 (5.6)	21 (5.8)	24 (5.3)
Anxiety	14 (7.0)	4 (4.6)	3 (4.2)	21 (5.8)	24 (5.3)
Pain	14 (7.0)	0 (0.0)	2 (2.8)	16 (4.5)	19 (4.2)
Weight decreased	13 (6.5)	3 (3.4)	1 (1.4)	17 (4.7)	20 (4.4)
Rash maculo-papular	13 (6.5)	2 (2.3)	3 (4.2)	18 (5.0)	19 (4.2)
Pain in extremity	12 (6.0)	8 (9.2)	1 (1.4)	21 (5.8)	28 (6.1)
Lymphocyte count decreased	12 (6.0)	1 (1.1)	0 (0.0)	13 (3.6)	18 (3.9)
Fall	11 (5.5)	3 (3.4)	1 (1.4)	15 (4.2)	18 (3.9)
Upper respiratory tract infection	10 (5.0)	6 (6.9)	2 (2.8)	18 (5.0)	29 (6.4)
Urinary tract infection	10 (5.0)	5 (5.7)	6 (8.3)	21 (5.8)	28 (6.1)
Rash	10 (5.0)	3 (3.4)	3 (4.2)	16 (4.5)	19 (4.2)
Neck pain	10 (5.0)	0 (0.0)	0 (0.0)	10 (2.8)	11 (2.4)
Abdominal distension	8 (4.0)	3 (3.4)	2 (2.8)	13 (3.6)	23 (5.0)
Blood bilirubin increased	7 (3.5)	5 (5.7)	2 (2.8)	14 (3.9)	16 (3.5)
Gastrooesophageal reflux disease	4 (2.0)	3 (3.4)	5 (6.9)	12 (3.3)	14 (3.1)
Ascites	2 (1.0)	1 (1.1)	5 (6.9)	8 (2.2)	8 (1.8)
Tumour pain	1 (0.5)	1 (1.1)	6 (8.3)	8 (2.2)	9 (2.0)
Small intestinal obstruction	0 (0.0)	5 (5.7)	4 (5.6)	9 (2.5)	11 (2.4)
Cholangitis	0 (0.0)	3 (3.4)	4 (5.6)	7 (1.9)	7 (1.5)
Pancreatic carcinoma metastatic	0 (0.0)	0 (0.0)	6 (8.3)	6 (1.7)	6 (1.3)
Pancreatic carcinoma	0 (0.0)	0 (0.0)	4 (5.6)	4 (1.1)	4 (0.9)

CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QD = once-daily
Adverse events were coded using Medical Dictionary for Regulatory Activities version 23.1.
Bold text identifies adverse events with a ≥ 10% subject incidence in any group.
Source: 90DSU ISS Table 14a-6.2.1 and 90DSU ISS Table 14b-6.2.1

Grade ≥3 Adverse Events

Table 43: 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 = 200) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 72) n (%)	Any Tumor Type (N = 359) n (%)	Total Any Tumor Type/Any Dose (N = 456) n (%)
Number of subjects with grade ≥ 3 adverse events	122 (61.0)	31 (35.6)	37 (51.4)	190 (52.9)	243 (53.3)
Pneumonia	**15 (7.5)**	1 (1.1)	**4 (5.6)**	**20 (5.6)**	**25 (5.5)**
Alanine aminotransferase increased	**15 (7.5)**	1 (1.1)	0 (0.0)	16 (4.5)	22 (4.8)
Aspartate aminotransferase increased	**13 (6.5)**	2 (2.3)	0 (0.0)	15 (4.2)	21 (4.6)
Pleural effusion	**12 (6.0)**	2 (2.3)	2 (2.8)	16 (4.5)	17 (3.7)
Diarrhoea	**10 (5.0)**	2 (2.3)	2 (2.8)	14 (3.9)	19 (4.2)
Back pain	9 (4.5)	1 (1.1)	0 (0.0)	10 (2.8)	11 (2.4)
Non-small cell lung cancer	9 (4.5)	0 (0.0)	0 (0.0)	9 (2.5)	11 (2.4)
Blood alkaline phosphatase increased	8 (4.0)	1 (1.1)	1 (1.4)	10 (2.8)	13 (2.9)
Respiratory failure	8 (4.0)	0 (0.0)	0 (0.0)	8 (2.2)	9 (2.0)
Dyspnoea	7 (3.5)	0 (0.0)	0 (0.0)	7 (1.9)	11 (2.4)
Hypertension	5 (2.5)	0 (0.0)	3 (4.2)	8 (2.2)	8 (1.8)
Pulmonary embolism	5 (2.5)	1 (1.1)	1 (1.4)	7 (1.9)	8 (1.8)
Gamma-glutamyltransferase increased	5 (2.5)	1 (1.1)	0 (0.0)	6 (1.7)	7 (1.5)
Anaemia	4 (2.0)	**5 (5.7)**	0 (0.0)	9 (2.5)	16 (3.5)
Fatigue	4 (2.0)	1 (1.1)	3 (4.2)	8 (2.2)	10 (2.2)
Lung cancer metastatic	4 (2.0)	0 (0.0)	0 (0.0)	4 (1.1)	7 (1.5)
Arthralgia	4 (2.0)	0 (0.0)	0 (0.0)	4 (1.1)	6 (1.3)
Lymphocyte count decreased	4 (2.0)	0 (0.0)	0 (0.0)	4 (1.1)	6 (1.3)
Hypokalaemia	4 (2.0)	0 (0.0)	0 (0.0)	4 (1.1)	5 (1.1)
Hyponatraemia	4 (2.0)	0 (0.0)	0 (0.0)	4 (1.1)	4 (0.9)
Abdominal pain	3 (1.5)	1 (1.1)	**4 (5.6)**	8 (2.2)	11 (2.4)
Vomiting	3 (1.5)	1 (1.1)	**4 (5.6)**	8 (2.2)	8 (1.8)
Nausea	2 (1.0)	0 (0.0)	2 (2.8)	4 (1.1)	4 (0.9)

Treatment-related Adverse Events

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

Treatment-related adverse events were reported for 137 subjects (68.5%) with NSCLC treated at 960 mg once-daily. Consistent with the primary analysis, 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 (41.5%) and investigations (23.5%). Consistent with the primary analysis, 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 diarrhoea (28.0%), nausea (16%), increased ALT (15.5%), increased AST (15.5%), and fatigue (11.5%).

All Tumour Types, 960 mg Once-daily Fasted

Treatment-related adverse events were reported for 209 subjects (58.2%) treated at 960 mg once-daily for all tumour types. Consistent with the primary analysis, the most frequently reported (≥20% of subjects) treatment-related adverse event in subjects treated at 960 mg once-daily for all tumour types by system organ class was gastrointestinal disorders (34.0%).

Consistent with the primary analysis, the most frequently reported (≥10% of subjects) treatment-related adverse events in subjects treated at 960 mg once-daily for all tumour types by preferred term were diarrhoea (21.7%), nausea (12.5%), increased AST (10.6%), and increased ALT (10.3%).

All Tumour Types, All Doses

Treatment-related adverse events were reported for 270 subjects (59.2%) in the total monotherapy population. Consistent with the primary analysis, the most frequently reported (≥ 20% of subjects) treatment-related adverse event in the total monotherapy population by system organ class was gastrointestinal disorders (34.6%). Consistent with the primary analysis, the most frequently reported (>10%of subjects) treatment-related adverse events in the total monotherapy population by preferred term were diarrhoea (22.6%), nausea (11.8%), increased AST (10.7%), and increased ALT (10.5%).

Adverse drug reactions

Medical review was based on a broad evaluation of all adverse events (including their severity, onset, duration, and outcome), changes in laboratory values, and vital signs. Adverse reactions were determined to be those events that were reported ≥ 10% in subjects with any tumour type who were treated with sotorasib monotherapy at 960 mg QD. In addition, medical review of all adverse events reported was undertaken, with special attention to common events, grade ≥3 and serious adverse events. A review of all the frequently occurring adverse events was performed, with consideration of the events expected to occur at a particular incidence in patients with known underlying diseases to identify an appropriate initial threshold for identifying adverse drug reactions. Based on this review, adverse drug reactions for sotorasib were initially selected by evaluating adverse events that occurred with a ≥ 15% overall incidence rate, grade ≥ 3 adverse events with a ≥ 2% overall incidence rate, or serious adverse events with ≥ 2% overall incidence rate. An assessment was also performed on adverse events not meeting any of these thresholds that could represent potentially serious toxicities (eg, cardiac and neurological events), or those commonly associated with drug use (eg, rash). Additional considerations such as temporal association, biological plausibility, and medical judgment were then applied for a probable causal drug event association to determine the final adverse drug reactions.

Table 44: **Adverse drug reactions with sotorasib**

System Organ Class	Adverse Reaction	Frequency Category[a]	Overall Subject Incidence (N = 359) n (%)
Blood and lymphatic system disorders			
	Anaemia	Very common	46 (12.8)
Nervous system disorders			
	Headache	Very common	37 (10.3)
Respiratory, thoracic and mediastinal disorders			
	Cough	Very common	41 (11.4)

System Organ Class	Adverse Reaction	Frequency Category[a]	Overall Subject Incidence (N = 359) n (%)
	Dyspnoea	Very common	40 (11.1)
	ILD/pneumonitis	Uncommon	3 (0.8)
Gastrointestinal disorders			
	Diarrhoea	Very common	122 (34.0)
	Nausea	Very common	89 (24.8)
	Abdominal pain[b]	Very common	65 (18.1)
	Vomiting	Very common	64 (17.8)
	Constipation	Very common	48 (13.4)
Hepatobiliary disorders			
	Drug-induced liver injury	Common	5 (1.4)
Musculoskeletal and connective tissue disorders			
	Arthralgia	Very common	50 (13.9)
	Back pain	Very common	50 (13.9)
General disorders and administration site conditions			
	Fatigue	Very common	74 (20.6)
	Pyrexia	Very common	37 (10.3)
Investigations			
	Aspartate aminotransferase increased	Very common	56 (15.6)
	Alanine aminotransferase increased	Very common	50 (13.9)
	Blood alkaline phosphatase increased	Common	34 (9.5)
	Blood bilirubin increased	Common	14 (3.9)
	Gamma-glutamyltransferase increased	Common	12 (3.3)

Monotherapy 960mg QD sotorasib for subjects with any tumour type are included. Snapshot date 01DEC2020.
[a] Very common (≥ 10%), common (≥ 1% to < 10%), uncommon (≥ 0.1% to < 1%), rare (≥ 0.01% to < 0.1%) and very rare (< 0.01%).
[b] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower.
Coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.1. Graded using Common Terminology Criteria for Adverse Events version 5.0 criteria.

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 programme.

2.6.8.3. Serious adverse event/deaths/other significant events

Serious Adverse Events

Table 45: 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 = 200) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 72) n (%)	Any Tumor Type (N = 359) n (%)	Total Any Tumor Type/Any Dose (N = 456) n (%)
Number of subjects with serious adverse events	105 (52.5)	24 (27.6)	38 (52.8)	167 (46.5)	206 (45.2)
Pneumonia	**16 (8.0)**	1 (1.1)	**4 (5.6)**	**21 (5.8)**	**26 (5.7)**
Non-small cell lung cancer	**9 (4.5)**	0 (0.0)	0 (0.0)	**9 (2.5)**	**11 (2.4)**
Pleural effusion	**8 (4.0)**	**2 (2.3)**	**2 (2.8)**	**12 (3.3)**	**14 (3.1)**
Respiratory failure	**8 (4.0)**	0 (0.0)	0 (0.0)	**8 (2.2)**	**9 (2.0)**
Dyspnoea	**5 (2.5)**	0 (0.0)	0 (0.0)	5 (1.4)	8 (1.8)
Lung cancer metastatic	**4 (2.0)**	0 (0.0)	0 (0.0)	4 (1.1)	7 (1.5)
Abdominal pain	3 (1.5)	1 (1.1)	**3 (4.2)**	7 (1.9)	8 (1.8)
Vomiting	2 (1.0)	0 (0.0)	**2 (2.8)**	4 (1.1)	4 (0.9)
Ascites	1 (0.5)	0 (0.0)	**2 (2.8)**	3 (0.8)	3 (0.7)
Large intestinal obstruction	1 (0.5)	**2 (2.3)**	0 (0.0)	3 (0.8)	3 (0.7)
Small intestinal obstruction	0 (0.0)	**5 (5.7)**	**4 (5.6)**	**9 (2.5)**	**11 (2.4)**
Cholangitis	0 (0.0)	**3 (3.4)**	**4 (5.6)**	7 (1.9)	7 (1.5)
Pancreatic carcinoma metastatic	0 (0.0)	0 (0.0)	**6 (8.3)**	6 (1.7)	6 (1.3)
Pancreatic carcinoma	0 (0.0)	0 (0.0)	**4 (5.6)**	4 (1.1)	4 (0.9)
Tumour pain	0 (0.0)	1 (1.1)	**2 (2.8)**	3 (0.8)	4 (0.9)
Cholangiocarcinoma	0 (0.0)	0 (0.0)	**2 (2.8)**	2 (0.6)	2 (0.4)
Duodenal obstruction	0 (0.0)	0 (0.0)	**2 (2.8)**	2 (0.6)	2 (0.4)

CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QD = once-daily
Adverse events were coded using Medical Dictionary for Regulatory Activities version 23.1.
Bold text identifies adverse events with a ≥ 2% subject incidence in any group.
Source: 90DSU ISS Table 14a-6.3.16 and 90DSU ISS Table 14b-6.3.16

Treatment-related Serious Adverse Events

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

Treatment-related serious adverse events were reported for 14 subjects (7.0%) with NSCLC treated at 960 mg once-daily. Consistent with the primary analysis, 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 (2.5%).

Consistent with the primary analysis, 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 1.0%).

All Tumour Types, 960 mg Once-daily Fasted

Treatment-related serious adverse events were reported for 18 subjects (5.0%) treated at 960 mg once-daily for all tumour types. Consistent with the primary analysis, no treatment-related serious adverse events were reported by system organ class for ≥2% of subjects or by preferred term for ≥1% of subjects treated at 960 mg once-daily for all tumour types.

All Tumour Types, All Doses

Treatment-related serious adverse events were reported for 23 subjects (5.0%) in the total monotherapy population. Consistent with the primary analysis, the most frequently reported (≥2% of subjects) treatment-related serious adverse event in the total monotherapy population by system organ class was investigations (2.0%).

Consistent with the primary analysis, the most frequently reported (≥1% of subjects) treatment-related serious adverse events in the total monotherapy population by preferred term were increased ALT (1.3%) and increased AST (1.1%).

Pooled fed and fasted status non-small cell lung cancer, 960 mg once-daily treatment-related serious adverse events were reported for 14 subjects (6.5%) with NSCLC treated at 960 mg once-daily in either the fed or fasted state.

Consistent with the fasted analysis, the most frequently reported (≥ 2% of subjects) treatment-related serious adverse event in subjects with NSCLC treated at 960 mg once-daily regardless of fed/fasted state by system organ class was investigations (2.3%).

No treatment-related serious adverse events were reported for ≥ 1% of subjects with NSCLC treated at 960 mg once-daily regardless of fed/fasted state. In contrast to the fasted state analysis, in the pooled fed/fasted analysis, increased ALT, nausea, and pneumonitis (each 0.9%) were not reported for ≥ 1% of subjects with NSCLC treated at 960 mg once-daily.

Deaths

Table 46: Fatal adverse events by preferred term (Safety Analysis Set)

	Sotorasib Monotherapy 960 mg QD Fasted and Fed			
Preferred Term	NSCLC (N = 214) n (%)	CRC (N = 91) n (%)	Other Tumor Types (N = 72) n (%)	Any Tumor Types (N = 377) n (%)
Number of subjects with fatal adverse events	38 (17.8)	3 (3.3)	18 (25.0)	59 (15.6)
Non-small cell lung cancer	**9 (4.2)**	0 (0.0)	0 (0.0)	**9 (2.4)**
Respiratory failure	**5 (2.3)**	0 (0.0)	0 (0.0)	**5 (1.3)**
Lung cancer metastatic	**4 (1.9)**	0 (0.0)	0 (0.0)	**4 (1.1)**
Pneumonia	**3 (1.4)**	0 (0.0)	0 (0.0)	**3 (0.8)**
Cardiac arrest	**2 (0.9)**	0 (0.0)	0 (0.0)	**2 (0.5)**
Lung neoplasm malignant	**2 (0.9)**	0 (0.0)	0 (0.0)	**2 (0.5)**
Non-small cell lung cancer metastatic	**2 (0.9)**	0 (0.0)	0 (0.0)	**2 (0.5)**
Adenocarcinoma	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)
Bronchial carcinoma	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)
Cardiac failure	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)
Gastric ulcer	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)
Haemorrhage intracranial	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)
Hypovolaemic shock	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)
Large intestinal obstruction	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)
Lung adenocarcinoma	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)
Lung adenocarcinoma stage IV	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)
Non-small cell lung cancer stage IV	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)
Systemic inflammatory response syndrome	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)
Pancreatic carcinoma metastatic	0 (0.0)	0 (0.0)	**6 (8.3)**	**6 (1.6)**
Pancreatic carcinoma	0 (0.0)	0 (0.0)	**4 (5.6)**	**4 (1.1)**
Cholangiocarcinoma	0 (0.0)	0 (0.0)	**2 (2.8)**	**2 (0.5)**
Small intestinal obstruction	0 (0.0)	**2 (2.2)**	0 (0.0)	**2 (0.5)**
Adenocarcinoma pancreas	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.3)

Aspiration	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.3)
Cholangitis	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.3)
Colon cancer	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.3)
Endometrial adenocarcinoma	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.3)
Large cell lung cancer	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.3)
Malignant neoplasm of unknown primary site	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.3)

CRC – colorectal cancer; NSCLC – non-small cell lung cancer; QD – once-daily
Adverse events were coded using Medical Dictionary for Regulatory Activities version 23.1.
Bold text identifies adverse events with ≥ 2 subjects in any group.
Source: 90DSU ISS Table 14d-6.3.432

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 programme.

Adverse events of special interest

Hepatotoxicity

None of the cases of hepatotoxicity adverse events in any subjects had laboratory values consistent with Hy's Law. Compared with the primary analysis, no new adverse events were reported as drug-induced liver injury as of 01 December 2020.

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

In subjects with NSCLC treated at 960 mg once-daily, hepatotoxicity adverse events of interest were reported for 57 subjects (28.5%). Consistent with the primary analysis, the most frequently reported (≥5% of subjects) hepatotoxicity adverse events of any grade were increased AST (20.0%), increased ALT (19.0%), and increased blood ALP (13.0%). No adverse events of liver failure were reported. Grade ≥ 3 hepatotoxicity adverse events of interest were reported for 30 subjects (15.0%) with NSCLC treated at 960 mg once-daily. Consistent with the primary analysis, the most frequently reported (≥2% of subjects) grade ≥3 hepatotoxicity adverse events were increased ALT (7.5%), increased AST (6.5%), increased blood ALP (4.0%), and increased gamma-glutamyltransferase (2.5%).

Serious hepatotoxicity adverse events of interest were reported for 9 subjects (4.5%) with NSCLC treated at 960 mg once-daily. Consistent with the primary analysis, the most frequently reported (≥1% of subjects) serious hepatotoxicity adverse events were increased ALT and drug-induced liver injury (each 1.0%).

Most subjects with NSCLC treated at 960 mg once-daily were able to continue treatment. Hepatotoxicity events of interest leading to dose modification (dose reduced, dose increased, drug interrupted) or discontinuation of sotorasib were reported for 25 subjects (12.5%) and 9 subjects (4.5%), respectively. Consistent with the primary analysis, the most frequently reported (≥1% of subjects) hepatotoxicity adverse events leading to discontinuation of sotorasib were increased ALT (1.5%), increased AST (1.5%), drug-induced liver injury (1.5%), increased blood ALP (1.0%), and increased transaminases (1.0%). Consistent with the primary analysis, the most frequently reported (≥ 1% of subjects) hepatotoxicity adverse events leading to dose modification of sotorasib were increased ALT (8.0%), increased AST (8.0%), increased blood ALP (3.5%), drug-induced liver injury (1.0%), and abnormal hepatic function (1.0%).

No fatal hepatotoxicity adverse events of interest were reported.

All Tumour Types, 960 mg Once-daily Fasted

In subjects treated at 960 mg once-daily for all tumour types, hepatotoxicity adverse events of interest were reported for 92 subjects (25.6%). Consistent with the primary analysis, the most frequently

reported hepatotoxicity adverse events of any grade were increased AST (15.6%), increased ALT (13.9%, and increased blood ALP (9.5%). No adverse events of liver failure were reported.

Grade ≥3 hepatotoxicity adverse events of interest were reported for 40 subjects (11.1%) treated at 960 mg once-daily for all tumour types. Consistent with the primary analysis, the most frequently reported grade ≥ 3 hepatotoxicity adverse events were increased ALT (4.5%), increased AST (4.2%), and increased blood ALP (2.8%).

Serious hepatotoxicity adverse events of interest were reported for 13 subjects (3.6%) treated at 960 mg once-daily for all tumour types. no serious hepatotoxicity adverse events were reported for ≥ 1% of subjects.

Hepatotoxicity events of interest leading to dose modification or discontinuation of sotorasib were reported for 35 subjects (9.7%) and 9 subjects (2.5%) treated at 960 mg once-daily for all tumour types, respectively. No hepatotoxicity adverse events led to discontinuation of sotorasib for ≥ 1% of subjects treated at 960 mg once-daily for all tumour types. Consistent with the primary analysis, the most frequently reported hepatotoxicity adverse events leading to dose modification of sotorasib were increased ALT (6.1%), increased AST (6.1%), and increased blood ALP (2.8%).

No fatal hepatotoxicity adverse events of interest were reported.

Table 47: Summary of hepatotoxicity treatment-emergent adverse events of interest (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
Hepatotoxicity	NSCLC (N = 200) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 72) n (%)	Any Tumor Type (N = 359) n (%)	Total Any Tumor Type/Any Dose (N = 456) n (%)
Treatment-emergent adverse events	57 (28.5)	18 (20.7)	17 (23.6)	92 (25.6)	111 (24.3)
Leading to interruption of investigational product	24 (12.0)	7 (8.0)	3 (4.2)	34 (9.5)	43 (9.4)
Leading to discontinuation of investigational product	9 (4.5)	0 (0.0)	0 (0.0)	9 (2.5)	13 (2.9)
Serious	9 (4.5)	0 (0.0)	4 (5.6)	13 (3.6)	17 (3.7)
Grade ≥ 3	30 (15.0)	5 (5.7)	5 (6.9)	40 (11.1)	48 (10.5)
Grade ≥ 4	3 (1.5)	0 (0.0)	0 (0.0)	3 (0.8)	5 (1.1)
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 23.1. Severity was graded using Common Terminology Criteria for Adverse Events version 5.0.
Hepatotoxicity is based on the hepatic disorders (SMQB) search strategy.
Source: 90DSU ISS Table 14a-6.5 and 90DSU ISS Table 14b-6.5

Table 48: 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 = 200) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 72) n (%)	Any Tumor Type (N = 359) n (%)	Total Any Tumor Type/Any Dose (N = 456) n (%)
Subjects with hepatoxicity treatment-emergent adverse events of interest	57 (28.5)	18 (20.7)	17 (23.6)	92 (25.6)	111 (24.3)
Aspartate aminotransferase increased	**40 (20.0)**	**9 (10.3)**	**7 (9.7)**	**56 (15.6)**	**71 (15.6)**
Alanine aminotransferase increased	**38 (19.0)**	**7 (8.0)**	**5 (6.9)**	**50 (13.9)**	**65 (14.3)**
Blood alkaline phosphatase increased	**26 (13.0)**	**5 (5.7)**	**3 (4.2)**	**34 (9.5)**	**41 (9.0)**
Blood bilirubin increased	**7 (3.5)**	**5 (5.7)**	**2 (2.8)**	**14 (3.9)**	**16 (3.5)**
Gamma-glutamyltransferase increased	**7 (3.5)**	**2 (2.3)**	**3 (4.2)**	**12 (3.3)**	**13 (2.9)**
Hypoalbuminaemia	**7 (3.5)**	1 (1.1)	1 (1.4)	**9 (2.5)**	**11 (2.4)**
Drug-induced liver injury	**4 (2.0)**	0 (0.0)	1 (1.4)	**5 (1.4)**	**5 (1.1)**
Transaminases increased	**3 (1.5)**	1 (1.1)	1 (1.4)	**5 (1.4)**	**5 (1.1)**
Liver function test abnormal	**3 (1.5)**	0 (0.0)	0 (0.0)	**3 (0.8)**	**3 (0.7)**
Ascites	**2 (1.0)**	1 (1.1)	**5 (6.9)**	**8 (2.2)**	**8 (1.8)**
Hepatic function abnormal	**2 (1.0)**	1 (1.1)	1 (1.4)	**4 (1.1)**	**4 (0.9)**
International normalised ratio increased	**2 (1.0)**	0 (0.0)	0 (0.0)	**2 (0.6)**	**3 (0.7)**
Liver function test increased	**2 (1.0)**	0 (0.0)	0 (0.0)	**2 (0.6)**	**2 (0.4)**
Jaundice	1 (0.5)	**2 (2.3)**	0 (0.0)	**3 (0.8)**	**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 23.1.
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: 90DSU ISS Table 14a-6.6.1 and 90DSU ISS Table 14b-6.6.1

Table 49: Summary of hepatotoxicity treatment-emergent adverse events of interest - pooled fasted and fed analysis (Safety Analysis Set)

	Sotorasib Monotherapy 960 mg QD Fasted and Fed			
Hepatotoxicity	NSCLC (N = 214) n (%)	CRC (N = 91) n (%)	Other Tumor Types (N = 72) n (%)	Any Tumor Types (N = 377) n (%)
Treatment-emergent adverse events	61 (28.5)	18 (19.8)	17 (23.6)	96 (25.5)
Leading to interruption of investigational product	25 (11.7)	7 (7.7)	3 (4.2)	35 (9.3)
Leading to discontinuation of investigational product	10 (4.7)	0 (0.0)	0 (0.0)	10 (2.7)
Serious	9 (4.2)	0 (0.0)	4 (5.6)	13 (3.4)
Grade ≥ 3	31 (14.5)	5 (5.5)	5 (6.9)	41 (10.9)
Grade ≥ 4	3 (1.4)	0 (0.0)	0 (0.0)	3 (0.8)
Fatal	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 23.1. Severity was graded using Common Terminology Criteria for Adverse Events version 5.0.
Hepatotoxicity is based on the hepatic disorders (SMQB) search strategy.
Source: 90DSU ISS Table 14d-6.5.400

Table 50: Treatment-emergent hepatotoxicity events of interest (occurring in at least 2 subjects in any group) - pooled fasted and fed analysis (Safety Analysis Set)

	Sotorasib Monotherapy 960 mg QD Fasted and Fed			
Preferred Term	NSCLC (N = 214) n (%)	CRC (N = 91) n (%)	Other Tumor Types (N = 72) n (%)	Any Tumor Types (N = 377) n (%)
Subjects with hepatoxicity treatment-emergent adverse events of interest	61 (28.5)	18 (19.8)	17 (23.6)	96 (25.5)
Aspartate aminotransferase increased	**42 (19.6)**	**9 (9.9)**	**7 (9.7)**	**58 (15.4)**
Alanine aminotransferase increased	**41 (19.2)**	**7 (7.7)**	**5 (6.9)**	**53 (14.1)**
Blood alkaline phosphatase increased	**28 (13.1)**	**5 (5.5)**	**3 (4.2)**	**36 (9.5)**
Blood bilirubin increased	**7 (3.3)**	**5 (5.5)**	**2 (2.8)**	**14 (3.7)**
Gamma-glutamyltransferase increased	**7 (3.3)**	**2 (2.2)**	**3 (4.2)**	**12 (3.2)**
Hypoalbuminaemia	**7 (3.3)**	1 (1.1)	1 (1.4)	**9 (2.4)**
Drug-induced liver injury	**4 (1.9)**	0 (0.0)	1 (1.4)	**5 (1.3)**
Transaminases increased	**3 (1.4)**	1 (1.1)	1 (1.4)	**5 (1.3)**
Liver function test abnormal	**3 (1.4)**	0 (0.0)	0 (0.0)	**3 (0.8)**
Ascites	**2 (0.9)**	1 (1.1)	**5 (6.9)**	**8 (2.1)**
Hepatic function abnormal	**2 (0.9)**	1 (1.1)	1 (1.4)	**4 (1.1)**
International normalised ratio increased	**2 (0.9)**	0 (0.0)	0 (0.0)	**2 (0.5)**
Liver function test increased	**2 (0.9)**	0 (0.0)	0 (0.0)	**2 (0.5)**
Jaundice	1 (0.5)	**2 (2.2)**	0 (0.0)	**3 (0.8)**

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 23.1.
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: 90DSU ISS Table 14d-6.6.401

Renal Toxicity

Table 51: 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 = 200) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 72) n (%)	Any Tumor Type (N = 359) n (%)	Total Any Tumor Type/Any Dose (N = 456) n (%)
Treatment-emergent adverse events	34 (17.0)	7 (8.0)	4 (5.6)	45 (12.5)	55 (12.1)
Leading to interruption of investigational product	1 (0.5)	1 (1.1)	0 (0.0)	2 (0.6)	2 (0.4)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious	2 (1.0)	1 (1.1)	0 (0.0)	3 (0.8)	4 (0.9)
Grade ≥ 3	6 (3.0)	2 (2.3)	1 (1.4)	9 (2.5)	10 (2.2)
Grade ≥ 4	3 (1.5)	0 (0.0)	0 (0.0)	3 (0.8)	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 23.1. 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: 90DSU ISS Table 14a-6.5 and 90DSU ISS Table 14b-6.5

Table 52: 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 = 200) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 72) n (%)	Any Tumor Type (N = 359) n (%)	Total Any Tumor Type/Any Dose (N = 456) n (%)
Subjects with renal toxicity treatment-emergent adverse events of interest	34 (17.0)	7 (8.0)	4 (5.6)	45 (12.5)	55 (12.1)
Hyponatraemia	**16 (8.0)**	0 (0.0)	**2 (2.8)**	**18 (5.0)**	**22 (4.8)**
Blood creatinine increased	**8 (4.0)**	**2 (2.3)**	0 (0.0)	**10 (2.8)**	**11 (2.4)**
Hypoalbuminaemia	**7 (3.5)**	1 (1.1)	1 (1.4)	**9 (2.5)**	**11 (2.4)**
Hyperkalaemia	**7 (3.5)**	1 (1.1)	0 (0.0)	**8 (2.2)**	**10 (2.2)**
Hypocalcaemia	**4 (2.0)**	1 (1.1)	0 (0.0)	**5 (1.4)**	**6 (1.3)**
Hyperphosphataemia	**4 (2.0)**	1 (1.1)	0 (0.0)	**5 (1.4)**	**5 (1.1)**
Acute kidney injury	1 (0.5)	**2 (2.3)**	1 (1.4)	**4 (1.1)**	**5 (1.1)**
Proteinuria	1 (0.5)	0 (0.0)	1 (1.4)	**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 23.1.
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: 90DSU ISS Table 14a-6.6.1 and 90DSU ISS Table 14b-6.6.1

Table 53: Summary of renal toxicity treatment-emergent adverse events of interest - pooled fasted and fed analysis (Safety Analysis Set)

	Sotorasib Monotherapy 960 mg QD Fasted and Fed			
Renal Toxicity	NSCLC (N = 214) n (%)	CRC (N = 91) n (%)	Other Tumor Types (N = 72) n (%)	Any Tumor Types (N = 377) n (%)
Treatment-emergent adverse events	35 (16.4)	7 (7.7)	4 (5.6)	46 (12.2)
Leading to interruption of investigational product	1 (0.5)	1 (1.1)	0 (0.0)	2 (0.5)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious	2 (0.9)	1 (1.1)	0 (0.0)	3 (0.8)
Grade ≥ 3	6 (2.8)	2 (2.2)	1 (1.4)	9 (2.4)
Grade ≥ 4	3 (1.4)	0 (0.0)	0 (0.0)	3 (0.8)
Fatal	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 23.1. 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: 90DSU ISS Table 14d-6.5.400

Table 54: Treatment-emergent renal toxicity events of interest (occurring in at least 2 subjects in any group) - pooled fasted and fed analysis (Safety Analysis Set)

	Sotorasib Monotherapy 960 mg QD Fasted and Fed			
Preferred Term	NSCLC (N = 214) n (%)	CRC (N = 91) n (%)	Other Tumor Types (N = 72) n (%)	Any Tumor Types (N = 377) n (%)
Subjects with renal toxicity treatment-emergent adverse events of interest	35 (16.4)	7 (7.7)	4 (5.6)	46 (12.2)
Hyponatraemia	**16 (7.5)**	0 (0.0)	**2 (2.8)**	**18 (4.8)**
Blood creatinine increased	**8 (3.7)**	**2 (2.2)**	0 (0.0)	**10 (2.7)**
Hyperkalaemia	**8 (3.7)**	1 (1.1)	0 (0.0)	**9 (2.4)**
Hypoalbuminaemia	**7 (3.3)**	1 (1.1)	1 (1.4)	**9 (2.4)**
Hyperphosphataemia	**4 (1.9)**	1 (1.1)	0 (0.0)	**5 (1.3)**
Hypocalcaemia	**4 (1.9)**	1 (1.1)	0 (0.0)	**5 (1.3)**
Acute kidney injury	1 (0.5)	**2 (2.2)**	1 (1.4)	**4 (1.1)**
Proteinuria	1 (0.5)	0 (0.0)	1 (1.4)	**2 (0.5)**

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 23.1.
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: 90DSU ISS Table 14d-6.6.401

2.6.8.4. Laboratory findings

Table 55: 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 = 200) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 72) n (%)	Any Tumor Type (N = 359) n (%)	Total Any Tumor Type/Any Dose (N = 456) n (%)
Chemistry							
Alanine aminotransferase	Increase	3	19 (9.5)	3 (3.4)	0 (0.0)	22 (6.1)	25 (5.5)
	Increase	4	3 (1.5)	0 (0.0)	0 (0.0)	3 (0.8)	4 (0.9)
Albumin	Decrease	3	1 (0.5)	0 (0.0)	1 (1.4)	2 (0.6)	3 (0.7)
Alkaline phosphatase	Increase	3	5 (2.5)	0 (0.0)	0 (0.0)	5 (1.4)	8 (1.8)
Aspartate aminotransferase	Increase	3	17 (8.5)	3 (3.4)	0 (0.0)	20 (5.6)	22 (4.8)
	Increase	4	2 (1.0)	0 (0.0)	0 (0.0)	2 (0.6)	3 (0.7)
Calcium (corrected)	Increase	3	0 (0.0)	0 (0.0)	3 (4.2)	3 (0.8)	3 (0.7)
	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)	1 (1.4)	4 (1.1)	5 (1.1)
	Increase	4	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.3)	2 (0.4)
Creatinine	Increase	3	0 (0.0)	0 (0.0)	2 (2.8)	2 (0.6)	3 (0.7)
	Increase	4	0 (0.0)	0 (0.0)	1 (1.4)	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)

Chemistry (continued)							
Gamma glutamyltransferase	Increase	3	5 (2.5)	0 (0.0)	0 (0.0)	5 (1.4)	5 (1.1)
Glucose	Decrease	4	2 (1.0)	0 (0.0)	0 (0.0)	2 (0.6)	2 (0.4)
Magnesium	Increase	3	2 (1.0)	2 (2.3)	0 (0.0)	4 (1.1)	4 (0.9)
	Decrease	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Potassium	Increase	4	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
	Decrease	3	9 (4.5)	0 (0.0)	1 (1.4)	10 (2.8)	11 (2.4)
Sodium	Decrease	3	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
	Decrease	4	2 (1.0)	0 (0.0)	0 (0.0)	2 (0.6)	2 (0.4)
Total bilirubin	Increase	3	3 (1.5)	0 (0.0)	0 (0.0)	3 (0.8)	5 (1.1)
Coagulation							
Activated partial thromboplastin time	Increase	3	3 (1.5)	0 (0.0)	0 (0.0)	3 (0.8)	4 (0.9)
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 (1.0)	0 (0.0)	0 (0.0)	2 (0.6)	2 (0.4)
	Decrease	3	5 (2.5)	4 (4.6)	0 (0.0)	9 (2.5)	13 (2.9)
	Decrease	4	1 (0.5)	0 (0.0)	1 (1.4)	2 (0.6)	2 (0.4)
Platelets	Decrease	4	1 (0.5)	0 (0.0)	2 (2.8)	3 (0.8)	3 (0.7)
Total neutrophils	Decrease	3	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
	Decrease	4	2 (1.0)	1 (1.1)	1 (1.4)	4 (1.1)	6 (1.3)
White blood cells	Decrease	3	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.3)	2 (0.4)
	Decrease	4	2 (1.0)	0 (0.0)	1 (1.4)	3 (0.8)	3 (0.7)
Urinalysis							
Urine protein	Increase	3	9 (4.5)	1 (1.1)	1 (1.4)	11 (3.1)	15 (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: 90DSU ISS Table 14a-7.2.2, 90DSU ISS Table 14a-7.2.4, 90DSU ISS Table 14a-7.2.7, 90DSU ISS Table 14a-7.2.8, 90DSU ISS Table 14a-7.2.9, 90DSU ISS Table 14a-7.2.18, 90DSU ISS Table 14a-7.2.19, 90DSU ISS Table 14a-7.4, 90DSU ISS Table 14b-7.2.2, 90DSU ISS Table 14b-7.2.4, 90DSU ISS Table 14b-7.2.7, 90DSU ISS Table 14b-7.2.8, 90DSU ISS Table 14b-7.2.9, 90DSU ISS Table 14b-7.2.18, 90DSU ISS Table 14b-7.2.19, and 90DSU ISS Table 14b-7.4

Vital Signs

Table 56: Abnormal changes in vital signs (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 200) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 72) n (%)	Any Tumor Type (N = 359) n (%)	Total Any Tumor Type/Any Dose (N = 456) n (%)
Pulse rate					
> 120 bpm	9 (4.5)	3 (3.4)	2 (2.8)	14 (3.9)	28 (6.1)
< 50 bpm	4 (2.0)	2 (2.3)	7 (9.7)	13 (3.6)	17 (3.7)
Systolic blood pressure					
≥ 160 mmHg	39 (19.5)	9 (10.3)	13 (18.1)	61 (17.0)	74 (16.2)
≤ 90 mmHg	15 (7.5)	2 (2.3)	6 (8.3)	23 (6.4)	35 (7.7)
Diastolic blood pressure					
≥ 105 mmHg	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.4)
≤ 50 mmHg	23 (11.5)	4 (4.6)	4 (5.6)	31 (8.6)	39 (8.6)
Weight					
Decease ≥ 10% from baseline	10 (5.0)	4 (4.6)	8 (11.1)	22 (6.1)	31 (6.8)
Increase ≥ 10% from baseline	25 (12.5)	6 (6.9)	3 (4.2)	34 (9.5)	46 (10.1)
Body temperature					
> 39°C	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.4)

CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QD = once-daily
Source: 90DSU ISS Table 14a-8.1 and 90DSU ISS Table 14b-8.1

Electrocardiograms

Table 57: Summary of electrocardiogram parameter categories (Safety Analysis Set)

Parameter	Sotorasib Monotherapy 960 mg QD Fasted NSCLC (N = 200) n (%)	Sotorasib Monotherapy 960 mg QD Fasted CRC (N = 87) n (%)	Sotorasib Monotherapy 960 mg QD Fasted Other Tumor Types (N = 72) n (%)	Sotorasib Monotherapy 960 mg QD Fasted Any Tumor Type (N = 359) n (%)	Sotorasib Monotherapy Any Dose Total Any Tumor Type/Any Dose (N = 456) n (%)
QTcF interval					
Baseline					
≤ 450 msec	184 (92.0)	83 (95.4)	68 (94.4)	335 (93.3)	416 (91.2)
> 450 to 480 msec	6 (3.0)	1 (1.1)	1 (1.4)	8 (2.2)	13 (2.9)
> 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	10 (5.0)	3 (3.4)	3 (4.2)	16 (4.5)	26 (5.7)
Maximum postbaseline					
≤ 450 msec	178 (89.0)	76 (87.4)	64 (88.9)	318 (88.6)	393 (86.2)
> 450 to 480 msec	13 (6.5)	8 (9.2)	4 (5.6)	25 (7.0)	37 (8.1)
> 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	8 (4.0)	3 (3.4)	4 (5.6)	15 (4.2)	24 (5.3)
Maximum increase from baseline					
≤ 30 msec	168 (84.0)	73 (83.9)	62 (86.1)	303 (84.4)	377 (82.7)
> 30 to 60 msec	18 (9.0)	8 (9.2)	5 (6.9)	31 (8.6)	42 (9.2)
> 60 msec	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	14 (7.0)	6 (6.9)	5 (6.9)	25 (7.0)	37 (8.1)
Heart rate					
≥ 25% decrease from baseline to < 50 bpm	1 (0.5)	2 (2.3)	2 (2.8)	5 (1.4)	5 (1.1)
≥ 25% increase from baseline to > 100 bpm	6 (3.0)	3 (3.4)	5 (6.9)	14 (3.9)	19 (4.2)
PR interval					
≥ 25% increase to PR > 200 msec	2 (1.0)	1 (1.1)	0 (0.0)	3 (0.8)	5 (1.1)
QRS interval					
≥ 25% increase to QRS > 120 msec	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)

Page 2 of 2

CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QD = once-daily; QTcF = QT interval corrected for heart rate using Fridericia's formula
Source: 90DSU ISS Table 14a-7.6 and 90DSU ISS Table 14b-7.6

2.6.8.5. In vitro biomarker test for patient selection for safety

2.6.8.6. Safety in special populations

Race

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

Table 58: Summary of treatment-emergent adverse events by subgroup of race (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 200) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 72) n (%)	Any Tumor Type (N = 359) n (%)	Total Any Tumor Type/Any Dose (N = 456) n (%)
Race: White					
Number of subjects in this subgroup	158	59	51	268	349
All TEAEs	157 (99.4)	56 (94.9)	49 (96.1)	262 (97.8)	341 (97.7)
Grade ≥ 3	97 (61.4)	23 (39.0)	30 (58.8)	150 (56.0)	191 (54.7)
Grade ≥ 4	32 (20.3)	2 (3.4)	15 (29.4)	49 (18.3)	70 (20.1)
Serious adverse events	83 (52.5)	18 (30.5)	30 (58.8)	131 (48.9)	164 (47.0)
Leading to discontinuation of investigational product	16 (10.1)	1 (1.7)	3 (5.9)	20 (7.5)	24 (6.9)
Fatal adverse events	27 (17.1)	2 (3.4)	15 (29.4)	44 (16.4)	60 (17.2)
Treatment-related TEAEs	109 (69.0)	27 (45.8)	22 (43.1)	158 (59.0)	207 (59.3)
Race: Black					
Number of subjects in this subgroup	6	1	3	10	14
All TEAEs	6 (100.0)	1 (100.0)	3 (100.0)	10 (100.0)	14 (100.0)
Grade ≥ 3	4 (66.7)	0 (0.0)	1 (33.3)	5 (50.0)	9 (64.3)
Grade ≥ 4	2 (33.3)	0 (0.0)	0 (0.0)	2 (20.0)	2 (14.3)
Serious adverse events	4 (66.7)	0 (0.0)	2 (66.7)	6 (60.0)	9 (64.3)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)
Fatal adverse events	1 (16.7)	0 (0.0)	0 (0.0)	1 (10.0)	1 (7.1)
Treatment-related TEAEs	4 (66.7)	1 (100.0)	1 (33.3)	6 (60.0)	10 (71.4)
Race: Asian					
Number of subjects in this subgroup	31	23	16	70	76
All TEAEs	29 (93.5)	22 (95.7)	12 (75.0)	63 (90.0)	69 (90.8)
Grade ≥ 3	18 (58.1)	6 (26.1)	5 (31.3)	29 (41.4)	32 (42.1)
Grade ≥ 4	9 (29.0)	1 (4.3)	4 (25.0)	14 (20.0)	14 (18.4)
Serious adverse events	17 (54.8)	4 (17.4)	6 (37.5)	27 (38.6)	27 (35.5)
Leading to discontinuation of investigational product	2 (6.5)	0 (0.0)	0 (0.0)	2 (2.9)	2 (2.6)
Fatal adverse events	7 (22.6)	0 (0.0)	3 (18.8)	10 (14.3)	10 (13.2)
Treatment-related TEAEs	21 (67.7)	14 (60.9)	4 (25.0)	39 (55.7)	43 (56.6)
Race: Others					
Number of subjects in this subgroup	5	4	2	11	17
All TEAEs	5 (100.0)	4 (100.0)	2 (100.0)	11 (100.0)	17 (100.0)
Grade ≥ 3	3 (60.0)	2 (50.0)	1 (50.0)	6 (54.5)	11 (64.7)
Grade ≥ 4	1 (20.0)	0 (0.0)	0 (0.0)	1 (9.1)	2 (11.8)
Serious adverse events	1 (20.0)	2 (50.0)	0 (0.0)	3 (27.3)	6 (35.3)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)
Fatal adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.9)
Treatment-related TEAEs	3 (60.0)	2 (50.0)	1 (50.0)	6 (54.5)	10 (58.8)

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.

Age

Table 59: Summary of treatment-emergent adverse events by subgroup of age (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 200) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 72) n (%)	Any Tumor Type (N = 359) n (%)	Total Any Tumor Type/Any Dose (N = 456) n (%)
Age: < 65					
Number of subjects in this subgroup	89	65	43	197	243
All TEAEs	87 (97.8)	61 (93.8)	41 (95.3)	189 (95.9)	233 (95.9)
Grade ≥ 3	57 (64.0)	22 (33.8)	23 (53.5)	102 (51.8)	126 (51.9)
Grade ≥ 4	19 (21.3)	2 (3.1)	9 (20.9)	30 (15.2)	39 (16.0)
Serious adverse events	48 (53.9)	14 (21.5)	24 (55.8)	86 (43.7)	103 (42.4)
Leading to discontinuation of investigational product	8 (9.0)	0 (0.0)	1 (2.3)	9 (4.6)	11 (4.5)
Fatal adverse events	16 (18.0)	1 (1.5)	8 (18.6)	25 (12.7)	32 (13.2)
Treatment-related TEAEs	58 (65.2)	31 (47.7)	18 (41.9)	107 (54.3)	133 (54.7)
Age: ≥ 65 years					
Number of subjects in this subgroup	111	33	29	162	213
All TEAEs	110 (99.1)	22 (100.0)	25 (86.2)	157 (96.9)	208 (97.7)
Grade ≥ 3	65 (58.6)	9 (40.9)	14 (48.3)	88 (54.3)	117 (54.9)
Grade ≥ 4	25 (22.5)	1 (4.5)	10 (34.5)	36 (22.2)	49 (23.0)
Serious adverse events	57 (51.4)	10 (45.5)	14 (48.3)	81 (50.0)	103 (48.4)
Leading to discontinuation of investigational product	10 (9.0)	1 (4.5)	2 (6.9)	13 (8.0)	17 (8.0)
Fatal adverse events	19 (17.1)	1 (4.5)	10 (34.5)	30 (18.5)	40 (18.8)
Treatment-related TEAEs	79 (71.2)	13 (59.1)	10 (34.5)	102 (63.0)	137 (64.3)
Age: < 75 years					
Number of subjects in this subgroup	178	81	66	325	407
All TEAEs	175 (98.3)	77 (95.1)	62 (93.9)	314 (96.6)	394 (96.8)
Grade ≥ 3	109 (61.2)	30 (37.0)	34 (51.5)	173 (53.2)	215 (52.8)
Grade ≥ 4	40 (22.5)	3 (3.7)	17 (25.8)	60 (18.5)	79 (19.4)
Serious adverse events	96 (53.9)	23 (28.4)	35 (53.0)	154 (47.4)	186 (45.7)
Leading to discontinuation of investigational product	17 (9.6)	0 (0.0)	2 (3.0)	19 (5.8)	24 (5.9)
Fatal adverse events	31 (17.4)	2 (2.5)	16 (24.2)	49 (15.1)	63 (15.5)
Treatment-related TEAEs	119 (66.9)	41 (50.6)	24 (36.4)	184 (56.6)	234 (57.5)
Age: ≥ 75 years					
Number of subjects in this subgroup	22	6	6	34	49
All TEAEs	22 (100.0)	6 (100.0)	4 (66.7)	32 (94.1)	47 (95.9)
Grade ≥ 3	13 (59.1)	1 (16.7)	3 (50.0)	17 (50.0)	28 (57.1)
Grade ≥ 4	4 (18.2)	0 (0.0)	2 (33.3)	6 (17.6)	9 (18.4)
Serious adverse events	9 (40.9)	1 (16.7)	3 (50.0)	13 (38.2)	20 (40.8)
Leading to discontinuation of investigational product	1 (4.5)	1 (16.7)	1 (16.7)	3 (8.8)	4 (8.2)
Fatal adverse events	4 (18.2)	0 (0.0)	2 (33.3)	6 (17.6)	9 (18.4)
Treatment-related TEAEs	18 (81.8)	3 (50.0)	4 (66.7)	25 (73.5)	36 (73.5)

Sex

Table 60: Summary of treatment-emergent adverse events by subgroup of sex (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 200) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 72) n (%)	Any Tumor Type (N = 359) n (%)	Total Any Tumor Type/Any Dose (N = 456) n (%)
Sex: Men					
Number of subjects in this subgroup	92	43	44	179	215
All TEAEs	90 (97.8)	41 (95.3)	42 (95.5)	173 (96.6)	209 (97.2)
Grade ≥ 3	52 (56.5)	17 (39.5)	22 (50.0)	91 (50.8)	112 (52.1)
Grade ≥ 4	16 (17.4)	2 (4.7)	10 (22.7)	28 (15.6)	36 (16.7)
Serious adverse events	43 (46.7)	11 (25.6)	24 (54.5)	78 (43.6)	92 (42.8)
Leading to discontinuation of investigational product	9 (9.8)	1 (2.3)	2 (4.5)	12 (6.7)	15 (7.0)
Fatal adverse events	13 (14.1)	1 (2.3)	9 (20.5)	23 (12.8)	30 (14.0)
Treatment-related TEAEs	60 (65.2)	23 (53.5)	20 (45.5)	103 (57.5)	123 (57.2)
Sex: Women					
Number of subjects in this subgroup	108	44	28	180	241
All TEAEs	107 (99.1)	42 (95.5)	24 (85.7)	173 (96.1)	232 (96.3)
Grade ≥ 3	70 (64.8)	14 (31.8)	15 (53.6)	99 (55.0)	131 (54.4)
Grade ≥ 4	28 (25.9)	1 (2.3)	9 (32.1)	38 (21.1)	52 (21.6)
Serious adverse events	62 (57.4)	13 (29.5)	14 (50.0)	89 (49.4)	114 (47.3)
Leading to discontinuation of investigational product	9 (8.3)	0 (0.0)	1 (3.6)	10 (5.6)	13 (5.4)
Fatal adverse events	22 (20.4)	1 (2.3)	9 (32.1)	32 (17.8)	42 (17.4)
Treatment-related TEAEs	77 (71.3)	21 (47.7)	8 (28.6)	106 (58.9)	147 (61.0)

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: 90DSU ISS Table 14a-6.1.6, 90DSU ISS Table 14a-6.1.7, 90DSU ISS Table 14b-6.1.6, and 90DSU ISS Table 14b-6.1.7

Region

Table 61: Summary of treatment-emergent adverse events by subgroup of region (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 200) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 72) n (%)	Any Tumor Type (N = 359) n (%)	Total Any Tumor Type/Any Dose (N = 456) n (%)
Region: North America					
Number of subjects in this subgroup	144	47	37	228	305
All TEAEs	142 (98.6)	45 (95.7)	36 (97.3)	223 (97.8)	298 (97.7)
Grade ≥ 3	87 (60.4)	16 (34.0)	21 (56.8)	124 (54.4)	167 (54.8)
Grade ≥ 4	31 (21.5)	0 (0.0)	10 (27.0)	41 (18.0)	59 (19.3)
Serious adverse events	74 (51.4)	13 (27.7)	21 (56.8)	108 (47.4)	139 (45.6)
Leading to discontinuation of investigational product	11 (7.6)	0 (0.0)	3 (8.1)	14 (6.1)	20 (6.6)
Fatal adverse events	26 (18.1)	0 (0.0)	10 (27.0)	36 (15.8)	50 (16.4)
Treatment-related TEAEs	99 (68.8)	17 (36.2)	17 (45.9)	133 (58.3)	182 (59.7)
Region: Europe					
Number of subjects in this subgroup	31	13	18	62	63
All TEAEs	31 (100.0)	12 (92.3)	17 (94.4)	60 (96.8)	61 (96.8)
Grade ≥ 3	21 (67.7)	5 (38.5)	9 (50.0)	35 (56.5)	36 (57.1)
Grade ≥ 4	7 (22.6)	1 (7.7)	5 (27.8)	13 (21.0)	14 (22.2)
Serious adverse events	18 (58.1)	3 (23.1)	9 (50.0)	30 (48.4)	31 (49.2)
Leading to discontinuation of investigational product	4 (12.9)	0 (0.0)	0 (0.0)	4 (6.5)	4 (6.3)
Fatal adverse events	5 (16.1)	1 (7.7)	5 (27.8)	11 (17.7)	11 (17.5)
Treatment-related TEAEs	19 (61.3)	10 (76.9)	5 (27.8)	34 (54.8)	35 (55.6)
Region: Asia					
Number of subjects in this subgroup	18	21	15	54	59
All TEAEs	17 (94.4)	20 (95.2)	11 (73.3)	48 (88.9)	53 (89.8)
Grade ≥ 3	11 (61.1)	6 (28.6)	5 (33.3)	22 (40.7)	25 (42.4)
Grade ≥ 4	6 (33.3)	1 (4.8)	4 (26.7)	11 (20.4)	11 (18.6)
Serious adverse events	11 (61.1)	4 (19.0)	6 (40.0)	21 (38.9)	21 (35.6)
Leading to discontinuation of investigational product	2 (11.1)	0 (0.0)	0 (0.0)	2 (3.7)	2 (3.4)
Fatal adverse events	4 (22.2)	0 (0.0)	3 (20.0)	7 (13.0)	7 (11.9)
Treatment-related TEAEs	12 (66.7)	13 (61.9)	4 (26.7)	29 (53.7)	33 (55.9)
Region: Rest of world					
Number of subjects in this subgroup	7	6	2	15	29
All TEAEs	7 (100.0)	6 (100.0)	2 (100.0)	15 (100.0)	29 (100.0)
Grade ≥ 3	3 (42.9)	4 (66.7)	2 (100.0)	9 (60.0)	15 (51.7)
Grade ≥ 4	0 (0.0)	1 (16.7)	0 (0.0)	1 (6.7)	4 (13.8)
Serious adverse events	2 (28.6)	4 (66.7)	2 (100.0)	8 (53.3)	15 (51.7)
Leading to discontinuation of investigational product	1 (14.3)	1 (16.7)	0 (0.0)	2 (13.3)	2 (6.9)
Fatal adverse events	0 (0.0)	1 (16.7)	0 (0.0)	1 (6.7)	4 (13.8)
Treatment-related TEAEs	7 (100.0)	4 (66.7)	2 (100.0)	13 (86.7)	20 (69.0)

Page 2 of 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: 90DSU ISS Table 14a-6.1.12, 90DSU ISS Table 14a-6.1.13, 90DSU ISS Table 14a-6.1.14, 90DSU ISS Table 14a-6.1.15, 90DSU ISS Table 14b-6.1.12, 90DSU ISS Table 14b-6.1.13, 90DSU ISS

2.6.8.7. Immunological events

Not applicable.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Co-administration of sotorasib with a strong CYP3A4 inducer, proton pump inhibitor, or H2 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.

2.6.8.9. Discontinuation due to adverse events

Adverse Events Leading to Dose Reduction or Interruption of Sotorasib

Table 62: Summary of sotorasib dose modification (Safety Analysis Set)

	Sotorasib Monotherapy				
	960 mg QD Fasted				Any Dose
	NSCLC (N = 200)	CRC (N = 87)	Other Tumor Types (N = 72)	Any Tumor Type (N = 359)	Total Any Tumor Type/Any Dose (N = 456)
Number of subjects with any dose change (n [%])	35 (17.5)	6 (6.9)	7 (9.7)	48 (13.4)	60 (13.2)
Primary reason(s) for dose change[a]					
Adverse event	30 (15.0)	4 (4.6)	4 (5.6)	38 (10.6)	47 (10.3)
Noncompliance	3 (1.5)	0 (0.0)	0 (0.0)	3 (0.8)	4 (0.9)
Dose administration error	2 (1.0)	1 (1.1)	0 (0.0)	3 (0.8)	5 (1.1)
Per protocol	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
PI decision	2 (1.0)	1 (1.1)	0 (0.0)	3 (0.8)	3 (0.7)
Other	6 (3.0)	2 (2.3)	3 (4.2)	11 (3.1)	12 (2.6)
Number of dose change per subject					
Mean	21.7	3.8	2.5	13.5	12.3
SD	77.4	18.8	14.0	59.5	56.1
Median	0.0	0.0	0.0	0.0	0.0
Min, Max	0, 567	0, 139	0, 115	0, 567	0, 567
Number of subjects grouped by number of dose change (n [%])					
0	165 (82.5)	81 (93.1)	65 (90.3)	311 (86.6)	396 (86.8)
1	6 (3.0)	2 (2.3)	2 (2.8)	10 (2.8)	11 (2.4)
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 (14.5)	4 (4.6)	5 (6.9)	38 (10.6)	48 (10.5)

Number of subjects with any dose withheld (n [%])	103 (51.5)	35 (40.2)	23 (31.9)	161 (44.8)	210 (46.1)
Primary reason(s) for dose withheld*					
Adverse event	67 (33.5)	24 (27.6)	16 (22.2)	107 (29.8)	139 (30.5)
Noncompliance	19 (9.5)	13 (14.9)	6 (8.3)	38 (10.6)	46 (10.1)
Dose administration error	2 (1.0)	0 (0.0)	0 (0.0)	2 (0.6)	5 (1.1)
Per protocol	12 (6.0)	4 (4.6)	0 (0.0)	16 (4.5)	26 (5.7)
PI decision	14 (7.0)	3 (3.4)	2 (2.8)	19 (5.3)	23 (5.0)
Other	23 (11.5)	4 (4.6)	7 (9.7)	34 (9.5)	45 (9.9)
Number of dose withheld per subject					
Mean	11.6	5.4	4.7	8.7	8.6
SD	23.7	11.9	10.5	19.4	18.7
Median	1.0	0.0	0.0	0.0	0.0
Min, Max	0, 193	0, 64	0, 50	0, 193	0, 193
Number of subjects grouped by number of dose withheld (n [%])					
0	97 (48.5)	52 (59.8)	49 (68.1)	198 (55.2)	246 (53.9)
1	15 (7.5)	6 (6.9)	3 (4.2)	24 (6.7)	30 (6.6)
2	6 (3.0)	2 (2.3)	1 (1.4)	9 (2.5)	14 (3.1)
3	4 (2.0)	3 (3.4)	3 (4.2)	10 (2.8)	12 (2.6)
> 3	78 (39.0)	24 (27.6)	16 (22.2)	118 (32.9)	154 (33.8)

CRC – colorectal cancer; NSCLC – non-small cell lung cancer; PI – principal investigator; QD – once-daily
* Subjects may be counted more than once. Multiple modifications with the same reason are counted once per subject.

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

Adverse events leading to dose reduction or interruption of sotorasib were reported for 71 subjects (35.5%) with NSCLC treated at 960 mg once-daily. Consistent with the primary analysis, the most frequently reported adverse events leading to dose reduction or interruption of sotorasib in subjects with NSCLC treated at 960 mg once-daily were investigations (12.0%) and gastrointestinal disorders (10.0%). In contrast to the primary analysis, as of 01 December 2020, infections and infestations (5.0%) was also reported for ≥5% of subjects; however, respiratory, thoracic and mediastinal disorders (4.5%) was no longer reported for ≥ 5% of subjects.

Consistent with the primary analysis, the most frequently reported adverse events leading to dose reduction or interruption of sotorasib in subjects with NSCLC treated at 960 mg once-daily were diarrhoea (8.0%), increased ALT (8.0%), increased AST (8.0%), increased blood ALP (3.5%), nausea (3.0%), and pneumonia (3.0%). In contrast to the primary analysis, as of 01 December 2020, fatigue (2.5%) was also reported for ≥2% of subjects.

All Tumour Types, 960 mg Once-daily Fasted

Adverse events leading to dose reduction or interruption of sotorasib were reported for 112 subjects (31.2%) treated at 960 mg once-daily for all tumour types.

Consistent with the primary analysis, the most frequently reported adverse events leading to dose reduction or interruption of sotorasib in subjects treated at 960 mg once-daily for all tumour types were diarrhoea (6.4%), increased ALT (6.1%), increased AST (6.1%), nausea (3.3%), increased blood ALP (2.8%), and vomiting (2.2%).

Pooled Fed and Fasted Status Non-small Cell Lung Cancer, 960 mg Once-daily

Adverse events leading to dose reduction or interruption of sotorasib were reported for 75 subjects (35.0%) with NSCLC treated at 960 mg once-daily in either the fed or fasted state. Consistent with the fasted analysis, the most frequently reported adverse events leading to dose reduction or interruption of sotorasib in subjects with NSCLC treated at 960 mg once-daily regardless of fed/fasted state by system organ class were investigations (12.1%) and gastrointestinal disorders (10.3%). In contrast to

the fasted state analysis, in the pooled fed/fasted analysis, infections and infestations (4.7%) was not reported for ≥5% of subjects with NSCLC treated at 960 mg once-daily.

Consistent with the fasted analysis, the most frequently reported adverse events leading to dose reduction or interruption of sotorasib in subjects with NSCLC treated at 960 mg once-daily regardless of fed/fasted state were diarrhoea (8.4%), increased ALT (7.9%), increased AST (7.9%), increased blood ALP (3.3%), nausea (2.8%), pneumonia (2.8%), and fatigue (2.3%).

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

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

Treatment-related adverse events leading to dose reduction or interruption of sotorasib were reported for 42 subjects (21.0%) with NSCLC treated at 960 mg once-daily.

Consistent with the primary analysis, the most frequently reported treatment-related adverse events leading to dose reduction or interruption of sotorasib in subjects with NSCLC treated at 960 mg once-daily were diarrhoea (7.5%), increased AST (7.5%), increased ALT (7.0%), nausea (3.0%), increased blood ALP (2.5%), vomiting (1.5%), and abnormal hepatic function (1.0%). In contrast to the primary analysis, as of 01 December 2020, fatigue (1.5%) was also reported for ≥ 1% of subjects.

All Tumour Types, 960 mg Once-daily Fasted

Treatment-related adverse events leading to dose reduction or interruption of sotorasib were reported for 59 subjects (16.4%) treated at 960 mg once-daily for all tumour types;

Consistent with the primary analysis, the most frequently reported treatment-related adverse events leading to dose reduction or interruption of sotorasib in subjects treated at 960 mg once-daily for all tumour types were diarrhoea (5.6%), increased AST (5.6%), increased ALT (5.3%), nausea (2.5%), and increased blood ALP (2.2%). In contrast to the primary analysis, as of 01 December 2020, fatigue (1.4%) and vomiting (1.1%) were also reported for ≥1% of subjects.

Adverse Events Leading to Treatment Discontinuation

Table 63: 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 = 200) n (%)	CRC (N = 87) n (%)	Other Tumor Types (N = 72) n (%)	Any Tumor Type (N = 359) n (%)	Total Any Tumor Type/Any Dose (N = 456) n (%)
Number of subjects with adverse events leading to withdrawal of investigational product	18 (9.0)	1 (1.1)	3 (4.2)	22 (6.1)	28 (6.1)
Alanine aminotransferase increased	**3 (1.5)**	0 (0.0)	0 (0.0)	**3 (0.8)**	**6 (1.3)**
Aspartate aminotransferase increased	**3 (1.5)**	0 (0.0)	0 (0.0)	**3 (0.8)**	**6 (1.3)**
Drug-induced liver injury	**3 (1.5)**	0 (0.0)	0 (0.0)	**3 (0.8)**	**3 (0.7)**
Blood alkaline phosphatase increased	**2 (1.0)**	0 (0.0)	0 (0.0)	**2 (0.6)**	**3 (0.7)**
Pneumonitis	**2 (1.0)**	0 (0.0)	0 (0.0)	**2 (0.6)**	**2 (0.4)**
Transaminases increased	**2 (1.0)**	0 (0.0)	0 (0.0)	**2 (0.6)**	**2 (0.4)**
Cardiac arrest	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	**2 (0.4)**
Pneumonia	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.3)	**2 (0.4)**

CRC = colorectal cancer; NSCLC = non-small cell lung cancer; QD = once-daily
Adverse events were coded using Medical Dictionary for Regulatory Activities version 23.1.
Bold text identifies adverse events with ≥ 2 subjects in any group.
Source: 90DSU ISS Table 14a-6.3.33 and 90DSU ISS Table 14b-6.3.33

Table 64: Summary of adverse events leading to withdrawal of sotorasib by preferred term (occurring in at least 2 subjects in any group) - pooled fasted and fed analysis (Safety Analysis Set)

	Sotorasib Monotherapy 960 mg QD Fasted and Fed			
Preferred Term	NSCLC (N = 214) n (%)	CRC (N = 91) n (%)	Other Tumor Types (N = 72) n (%)	Any Tumor Types (N = 377) n (%)
Number of subjects with adverse events leading to withdrawal of investigational product	19 (8.9)	1 (1.1)	3 (4.2)	23 (6.1)
Alanine aminotransferase increased	**4 (1.9)**	0 (0.0)	0 (0.0)	**4 (1.1)**
Aspartate aminotransferase increased	**4 (1.9)**	0 (0.0)	0 (0.0)	**4 (1.1)**
Drug-induced liver injury	**3 (1.4)**	0 (0.0)	0 (0.0)	**3 (0.8)**
Blood alkaline phosphatase increased	**2 (0.9)**	0 (0.0)	0 (0.0)	**2 (0.5)**
Pneumonitis	**2 (0.9)**	0 (0.0)	0 (0.0)	**2 (0.5)**
Transaminases increased	**2 (0.9)**	0 (0.0)	0 (0.0)	**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 23.1.
Bold text identifies adverse events with ≥ 2 subjects in any group.
Source: 90DSU ISS Table 14d-6.3.433

Treatment-related Adverse Events Leading to Treatment Discontinuation

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

Treatment-related adverse events leading to discontinuation of sotorasib were reported for 12 subjects (6.0%) with NSCLC treated at 960 mg once-daily. Consistent with the primary analysis, the most frequently reported (≥2% of subjects) treatment-related adverse event leading to discontinuation of sotorasib in subjects with NSCLC treated at 960 mg once-daily by system organ class was investigations (3.0%).

Consistent with the primary analysis, the most frequently reported (≥ 1% of subjects) treatment-related adverse events leading to discontinuation of sotorasib in subjects with NSCLC treated at 960 mg once-daily by were drug-induced liver injury (1.5%), increased ALT (1.5%), increased AST (1.5%), increased blood ALP (1.0%), increased transaminases (1.0%), and pneumonitis (1.0%).

All Tumour Types, 960 mg Once-daily Fasted

Treatment-related adverse events leading to discontinuation of sotorasib were reported for 13 subjects (3.6%) treated at 960 mg once-daily for all tumour types. Consistent with the primary analysis, 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 tumour types.

2.6.8.10. Post marketing experience

Sotorasib is not yet a marketed product.

2.6.9. Discussion on clinical safety

Safety results of sotorasib monotherapy at the intended dose (960 mg once daily) in the proposed indication (KRAS p.G12C-mutated NSCLC), are mainly coming from the phase 1/2, open-label study 20170543. The safety population in the target population of non-small cell lung cancer (NSCLC) is relatively small, n = 200 with a lack of comparative data and a limited follow-up period. At the latest data cut-off date of 01 December 2020, a total of 456 subjects have been exposed to sotorasib monotherapy across all doses and tumour types, (colorectal cancer at the intended dose n=87, all other tumour types at the intended dose n=72, pool of any tumour type at the intended dose n=359), and only 200 of them in NSCLC at the intended dose.

Supportive safety data from study 20190009 (Phase 3 study of sotorasib versus docetaxel in the NSCLC subjects with Mutated KRAS p.G12C), study 20190147 (Phase 1, in Subjects of Chinese Descent with Advanced/Metastatic Solid Tumours with KRAS p.G12C Mutation) and study 20190135 (in combination with tametinib, RMC-4630, afatinib, atezolizumab and panitumumab/FOLFIRI) have been provided. All these studies are phase I/II open-label and one-arm treatment trials except the ongoing phase 3 study 20190009, evaluating sotorasib versus docetaxel which started on 4th of June 2020. However, only 21 subjects received at least 1 dose of sotorasib. At the present time, there is no available safety data of sotorasib compared to other available therapies.

At the latest data cut-off date of 01 December 2020, 141 subjects (70%) with NSCLC treated at 960 mg once-daily had discontinued treatment; the most frequently reported reason for treatment discontinuation was disease progression (54%) and AEs (9%).

Demographics were generally consistent for subjects treated at the intended dose for all tumour types and for the total monotherapy population at any dose. A smaller proportion of subjects with NSCLC treated at 960 mg once-daily were < 65 years of age compared with subjects treated at the intended dose for all tumour types or with the total monotherapy population at any dose (44.5% versus 54.9% and 53.3% respectively). This difference is mainly attributable to the CRC population with subjects that were mostly <65 years of age (75%).

Subjects with NSCLC were treated with sotorasib monotherapy for a median of 24 weeks, with 46% and 10% of subjects receiving treatment for ≥6 and ≥12 months, respectively. Exposure was slightly lower for all tumour types or the total monotherapy population (median 18.0 weeks, respectively), than for subjects with NSCLC.

Mean Relative dose intensity was 90% for NSCLC patients.

Adverse Events: 98.5% of NSCLC patients (197 of 200 subjects) reported at least 1 TEAE and 68.5% of these patients reported TEAEs that were considered drug-related. The incidence of adverse events was higher for subjects with NSCLC treated at 960 mg once-daily compared with subjects treated at 960 mg once-daily for all tumour types and for the total any dose monotherapy population. This difference is largely attributable to the lower incidence of adverse events in subjects with colorectal cancer treated at 960 mg once-daily; Grade ≥3 TEAEs (61% vs 35.6%), SAEs (52.5% vs 27.6%), TEAEs leading to discontinuation of sotorasib (9.0% vs 1.1%), fatal AEs (17.5% vs 2.3%) and related grade ≥3 TEAE (20.5% vs 8%). This could be explained by the difference in some baseline demographics like age, ECOG status and by the type of prior treatments.

Most common TEAEs NSCLC population (vs all tumour type at 960 mg once-daily) were diarrhoea (43.5% vs 34%), nausea (28% vs 25.2%), fatigue (24.5% vs 20.6%), increased aspartate aminotransferase (AST) (20% vs 15.6%), increased alanine aminotransferase (ALT) (19% vs 13.9%), back pain (19% vs 13.9%), constipation (17.5% vs 13.2%) dyspnoea (16.5% vs 11.1%), vomiting (17% vs 17.8%), cough (14% vs 11.4%), increased blood alkaline phosphatase (ALP) (13% vs 9.5%), arthralgia (19.5% vs 13.9%), decreased appetite (12% vs 9.5%), anaemia (14.5% vs 12.8%), peripheral oedema (12% vs 9.5%), pneumonia (11.5% vs 7.8%), and headache (12.0% vs 10.3%).

TEAEs any tumour/any dose pooled results did not show any significant difference nor any trend in relation to the incidence by the dose.

The most frequently reported (≥10% of subjects) treatment-related adverse events in subjects with NSCLC treated at 960 mg once-daily were diarrhoea (28%), nausea (16%), increased ALT (15.5%), increased AST (15.5%), and fatigue (11.5%). However, to which degree a certain TEAE may be assumed to be attributable to the underlying disease is difficult to determine given the single-arm study design.

Grade ≥3 adverse events: Grade ≥ 3 TEAEs were reported at least once for 61% (122/200) of the total of the NSCLC patients. The most common Grade ≥ 3 TEAEs reported were pneumonia (7.5%), increased ALT (7.5%), increased AST (6.5%), pleural effusion (6.0%), and diarrhoea (5.0%).

Grade ≥ 3 AE were reported for 190 subjects (53%) in the total monotherapy population at the recommended dose. The most frequently reported grade≥ 3 adverse events were pneumonia (5.6%) and increased ALT (4.5%), AST (4.2%). The profile of the most common AEs of CTCAE Grade ≥ 3 in NSCLC patients is comparable with that observed in the total monotherapy pool at the recommended dose. The exception was cholangitis, pancreatic carcinoma, pancreatic carcinoma metastatic, small intestinal obstruction showing a higher frequency in the monotherapy pool, mainly due to other tumour's type prone for these AEs in the monotherapy pool.

The most frequently reported treatment-related grade ≥3 adverse events in subjects with NSCLC treated at 960 mg once-daily by preferred term were increased ALT (7%), increased AST (5.5%), and diarrhoea (4%).

Serious Adverse events: SAE were reported for 105 of 200 subjects with NSCLC (52.5%) treated with 960 mg QD sotorasib. The most frequently reported serious adverse events for subjects with NSCLC were pneumonia (8%), NSCLC (4.5%), pleural effusion (4%), respiratory failure (4%), back pain (3%), dyspnoea (2.5%) and metastatic lung cancer (2%). Most of these serious AEs were not considered related to treatment, only 7% of serious AEs were considered related to sotorasib. The most frequently reported treatment-related serious adverse events in subjects with NSCLC were increased ALT, nausea, and pneumonitis (each 1%). Cases of pneumonitis lead to treatment discontinuation. Pneumonitis was added to the list of adverse reactions in section 4.8 of the SmPC. Special warning has been included as well in the section 4.4 of the SmPC for monitoring patients for

new or worsening pulmonary symptoms indicative of ILD/pneumonitis. Lumykras should be withhold in patients with suspected ILD/pneumonitis and permanently discontinued if no other potential causes of ILD/pneumonitis are identified.

The types of serious adverse events reported for subjects with CRC and other tumour types (pleural effusion, cholangitis, large intestinal obstruction, small intestinal obstruction, pancreatic carcinoma, pancreatic carcinoma metastatic) treated with 960 mg QD sotorasib were different to those reported for NSCLC subjects, mostly reflecting the type of underlying cancer.

Deaths: Among all the NSCLC patients, 35 cases of Grade 5 TEAEs (17.5%) were reported; Fatal adverse events reported for more than 1 subject included NSCLC (8 subjects [4%]), metastatic lung cancer (4 subjects [2%]), respiratory failure (5 subjects [2.5%]), pneumonia n=3 (1.5%), cardiac arrest (2 subjects [1%]), and malignant lung neoplasm (2 subjects [1%]).

For the total monotherapy population at the recommended dose, fatal adverse events were reported for 55 subjects (15.3%). Fatal adverse events reported for more than 1 subject included NSCLC (8 subjects [2.2%]), metastatic lung cancer (4 subjects [1.1%]), metastatic pancreatic carcinoma (6 subjects [1.7%]), pneumonia n=3 (1.5%), pancreatic carcinoma (4 subjects [1.1%]), respiratory failure (5 subjects [1.4%]), cardiac arrest (2 subjects [0.6%]), cholangiocarcinoma (2 subjects [0.6%]), and malignant lung neoplasm (2 subjects [0.6%]). The respiratory SOC TEAEs leading to death in the pool came mostly from the lung cancer patients. Other Fatal reported AEs were consistent with subject's cancer type.

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.

All Grade 5 TEAEs were considered treatment unrelated by the investigator.

Adverse events of special interest: ALT increased (19%) and AST increased (20%) were the most common TEAEs among NSCLC patients. Hepatotoxicity adverse events of interest were reported for 57 subjects (28.5%) among NSCLC patients. Grade≥3 hepatotoxicity adverse events were reported for 30 subjects (15%). Serious adverse events were reported for 9 subjects (4.5%) with NSCLC. 9 subjects (4.5%) had events of interest leading to discontinuation of sotorasib. Sotorasib can cause hepatotoxicity, which may lead to drug-induced liver injury (DILI) and hepatitis. Patients should be then monitored for liver function (ALT, AST, and total bilirubin) prior to the start of treatment, with more frequent testing in patients who develop transaminase and/or bilirubin elevations. Among patients who experienced hepatotoxicity, 38% had hepatotoxicity leading to dose interruption or dose reduction. Overall, 26% of patients with hepatotoxicity received concurrent corticosteroids for the treatment of hepatotoxicity. The SmPC includes dosing reduction/interruption recommendations based on the severity of the laboratory abnormalities, and hepatotoxicity in sections 4.2 and 4.4.

Renal toxicity was identified as an event of interest. Non-clinical toxicology data suggested the potential for renal toxicity. In the integrated safety analysis set for study 20170543, renal toxicity adverse events were reported for 34 of 200 subjects (17%) with NSCLC. The most frequently reported renal toxicity adverse event was hyponatremia (8%). Six subjects (3%) had grade $\geq$ 3 renal toxicity adverse events; the most frequently reported was hyponatremia (2%). Events of hyponatremia were reported as serious adverse events for 2 subjects (1%). One subject (0.5%) had a renal toxicity event leading to interruption of sotorasib (hyponatremia); no subjects discontinued sotorasib due to renal toxicity adverse events. No fatal renal toxicity adverse events were reported. A total of 5 subjects in the monotherapy population had acute kidney injury, including 1 of the 200 subjects with NSCLC.

The medical review of the 5 events did not suggest causality between sotorasib and the event of acute kidney injury. Renal toxicity should continue to be monitored in the postmarketing setting.

No specific pattern in change of blood pressure (BP) was observed in patients treated with sotorasib, although there was variability in both systolic and diastolic BP. No significant change in weight was observed in patients treated with sotorasib.

As regards QT prolongation, 500 ms QT absolute QT value and delta QT of 60 ms are the thresholds provided in the ICH E14 guideline to state that there is a QT prolonging effect. In subjects with NSCLC, elevated post-baseline QTcF intervals were reported infrequently, with maximum post-baseline QTcF intervals> 450 to 480 msec or >480 to 500 msec reported for 6.5% and 0.5%, respectively; no subjects with NSCLC had a post-baseline QTcF interval >500 msec and no subjects had changes from baseline in QTcF interval >60 msec. One subject in the total monotherapy population at any dose had a post-baseline QTcF interval > 500 msec. This subject had a baseline QTcF of 481 msec. This subject did not have any adverse events at the time of the increased QTcF as of cardiac disorders or nervous system disorders, or other potential clinical correlations.

In addition to the increase in AT, other liver function tests were elevated. Thus, in NSCLC patients, ALP was increased in 13% of patients, with Grade ≥3 in 4.2%; and GGT was increased in 3.5% of patients, with Grade ≥3 in 2.6%. Total bilirubin was increased in 3.5%, with only 1.6% having a Grade ≥3 AE.

No overall differences in safety or efficacy were observed between elderly patients (≥ 65 years old) and younger patients. There is limited data on the safety and efficacy of sotorasib in patients aged 75 years and older but these do not suggest that a dose adjustment is required in elderly patients.

The incidence of adverse events tended to be numerically lower for men compared with women. Whether these represent true differences in toxicity by sex group or reflect other circumstances is not possible to know. The proportion of patients reporting TEAEs were generally consistent between patients based on region.

The incidence of adverse events (including Grade>3, and serious AE) tended to be numerically lower for Asian subgroup compared with white subgroup. Subgroups of black and Asian were of very limited size (n=16).

Dose interruption/reduction for the management of a TEAE was reported in 35.5% of subjects with NSCLC (71 of 200 subjects). The most common TEAEs leading to dose reduction/interruption were diarrhoea (8%), increased ALT (8%), increased AST (8%), increased blood ALP (3.5%), nausea (3%), and pneumonia (3%). Treatment-related adverse events leading to dose reduction or interruption of sotorasib were reported for 42 subjects (21%). The most frequently reported (≥1% of subjects) were diarrhoea (7.5%), increased AST (7.5%), increased ALT (7%), nausea (3%), increased blood ALP (2.5%), abnormal hepatic function (1 %), and vomiting (1.5%).

Adverse events leading to dose reduction or interruption of sotorasib were reported for 145 subjects (31.8%) in the total monotherapy population. Overall, the types of adverse events leading to both sotorasib treatment interruption/dose reduction were generally similar to those reported for subjects with NSCLC.

Eighteen (18) of 200 subjects with NSCLC (9%) had adverse events leading to sotorasib discontinuation. The most frequently reported were drug-induced liver injury (1.5%), increased ALT (1.5%), increased AST (1.5%), increased blood ALP (1%), pneumonitis (1%), and increased transaminases (1%).

Adverse drug reactions in the SmPC section 4.8 are based on subjects with KRAS p.G12C mutated advanced solid tumours who received 960 mg orally once daily as monotherapy (n=359), to maximise the potential for identifying adverse events that were related to sotorasib use, which is considered acceptable. The criteria used to identify ADRs are considered acceptable.

The dose modification criteria as reflected on SmPC are based solely on dose modification criteria used in the clinical studies. In line with the overall dose selection rationale, the negligible differences in exposure levels within the range of doses used were not taken into account, leading to uncertainty about the efficiency of the approach. While it is acknowledged that the dose reductions are not expected to lead to significantly lower exposure based on PK modelling, based on available clinical data the safety profile is manageable, also in situations where dose modifications are required due to adverse events. Among the 30 subjects with NSCLC who had dose reduction due to adverse events, the objective response rate (ORR) per central review was 40% (12 of 30 subjects), which is comparable with the overall ORR of 37.4% observed in subjects with NSCLC in phase 2. Currently, limited data is available on the impact of the dose modification criteria on resolution of adverse events. As the same criteria are used in the on-going confirmatory Study 20190009, more data will be available to confirm the impact of the dose modifications on management of adverse events.

Additional safety data needed in the context of a conditional MA

Additional safety data including comparative data will be provided as part of the specific obligation in order to fulfil a CMA. Study 201900091 will allow a better characterisation of the long-term safety and a contextualisation of the safety data compared to the control arm.

2.6.10. Conclusions on the clinical safety

The totality of evidence generated at this time point indicates that sotorasib was generally well tolerated, with adverse events mainly related to gastrointestinal reactions, increased liver enzymes and general disorders, and a low number of adverse events leading to treatment discontinuation (9% in the NSCLC 960-mg sotorasib monotherapy). The key risk with sotorasib is hepatotoxicity with laboratory abnormalities for serum transaminases, mostly mild-moderate, but require monitoring and resulted in dose modification, or temporary interruption or use of steroids until resolution. Appropriate routine risk minimisation measures, as described in the SmPC have also been put in place to mitigate the adverse reaction of pneumonitis. Sotorasib toxicity could overall be considered clinically manageable in the context of a conditional MA.

The entire safety database is limited and based on data from single-arm phase 1/2 trial in different diseases. To provide more comprehensive efficacy and safety data in the proposed indicated population, the results of an ongoing, confirmatory, active-controlled, phase 3 study will be submitted by the applicant in the same population of patients as a specific obligation in the context of the conditional MA. The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

In order to confirm the efficacy and safety of sotorasib in the treatment of patients with KRAS G12C-mutated NSCLC, the MAH should submit the clinical study report for the phase III CodeBreaK 200 study (Study 20190009) comparing sotorasib versus docetaxel for the treatment of previously treated KRAS G12C-mutated NSCLC. The clinical study report will be submitted by 31 March 2023.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 65: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use in patients with hepatic impairment

2.7.2. Pharmacovigilance plan

Table 66: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 - Required additional pharmacovigilance activities				
Study 20200362 An open label study to evaluate the pharmacokinetics of AMG 510 in healthy subjects with normal hepatic function and subjects with moderate and severe hepatic impairment Planned	Primary objectives: • To evaluate the PK of a single 960 mg oral dose of AMG 510 administered in subjects with normal hepatic function and subjects with moderate and severe hepatic impairment Secondary objectives: • To evaluate the safety and tolerability of AMG 510 administered in subjects with normal hepatic function and subjects with moderate and severe hepatic impairment	Use in patients with hepatic impairment	Protocol submission Final CSR	Q1 2021 Q4 2022

CSR = clinical study report; PK = pharmacokinetic; TBD = to be determined.

2.7.3. Risk minimisation measures

Table 67. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
None		
Important Potential Risks		
None		
Missing Information		
Use in patients with hepatic impairment	Routine risk minimisation measures: • SmPC Sections 4.2 and 5.2 • PL Sections 2 and 4 • Restricted medical prescription Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Study 20200362

Routine risk minimisation measures are considered sufficient to manage the risks associated with use of sotorasib.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 28.05.2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, LUMYKRAS (sotorasib) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It is approved under a conditional marketing authorisation [REG Art 14-a]

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The authorised indication is: "LUMYKRAS as monotherapy is indicated for the treatment of adults with advanced non-small cell lung cancer (NSCLC) with *KRAS G12C* mutation and who have progressed after at least one prior line of systemic therapy."

3.1.2. Available therapies and unmet medical need

Currently, KRAS-related advanced NSCLC is treated in a conventional manner with the initial platinum-based chemotherapy regimens and/or regimens, including checkpoint inhibitors in the first- and second-line treatments. Additional second-line or subsequent lines of therapy include taxane chemotherapy with or without a vascular endothelial growth factor (VEGF) inhibitor or checkpoint inhibitors/platinum-containing doublet chemotherapy (if not already given in first line). The objective response rates (ORRs; objective response = complete response + partial response) have been reported to be between 5.5% to 13% with chemotherapy (typically a taxane) and between 9.7% to 22.5% with chemotherapy plus a vascular endothelial growth factor receptor (VEGFR) inhibitor (Gridelli et al, 2018; Rittmeyer et al, 2017; Herbst et al, 2016; Borghaei et al, 2015; Herbst et al, 2007). The respective outcomes for the PFS and OS were 2.8 to 4.2 months and 6 to 11.4 months with chemotherapy alone and 4.8 to 5.4 months and 9.9 to 12.6 months with chemo plus VEGFR inhibitor.

Based on current data, there is unmet medical need for patients with advanced NSCLC harbouring the KRAS mutation based on unavailability of the targeted treatment, poor results obtained with approved therapies and severe AEs often accompanying the cytotoxic therapies.

3.1.3. Main clinical studies

The primary support for the proposed indication is based on the phase 2 portion of Study 20170543 (CodeBreaK 100). This study is an ongoing phase ½, open label, single-group study of sotorasib in subjects with KRAS p.G12C-mutated advanced or metastatic NSCLC, colorectal cancer, and other solid tumours. Further efficacy support is provided based on the results from the phase-1 portion assessing sotorasib as monotherapy.

In addition, the multicentre, randomised (1:1), open-label active-controlled confirmatory Phase 3 study is enrolling adult locally-advanced and unresectable or metastatic NSCLC patients with KRAS p.G12C mutation and who have failed ≥1 prior systemic therapy. In the Phase 3 trial sotorasib 960 mg PO QD treatment is compared against docetaxel 75 mg/m2 IV q3w in efficacy, safety PROs and PK. The data from the ongoing confirmatory Phase 3 study are not yet available.

3.2. Favourable effects

At the DCO date (01 December 2020), out of the 124 patients included in the FAS, the ORR (CR + PR) assessed per RECIST 1.1 by BICR was 37.1% (46 of 124 subjects; 95% CI: 28.6, 46.2) consisting of 3 subjects (2.4%) who achieved CR and 43 subjects (34.7%) who achieved PR. The study achieved the threshold predetermined by the applicant for a positive outcome (ORR > 32% and lower limit of the 95% CI for ORR > 23%). The sensitivity analysis of ORR based on investigator assessment was 30.2% (95% CI: 22.31, 38.97) consisting of 1 subject (0.8%) who achieved CR and 37 subjects (29.4%) who achieved PR. The concordance rates between the central review and investigator for objective response, best overall response, and disease progression were 83.1%, 73.0%, and 74.2%, respectively.

As of the 21 June 2021 data cut-off date, of the 46 objective responders, the median DOR was 11.1 months (95% CI: 6.9, 15.0) with a median follow-up time of 15.3 months (95% CI: 15.2, 15.8). The median time to response was 1.35 months (range: 1.2, 10.1).

The median PFS was 6.8 months (95% CI: 5.1, 8.2) with a median follow-up time of 11.0 months (min, max: 0.3, 12.6) and the median OS was 12.5 months (95% CI: 10.0, NE) with a median follow-up time of 12.2 months (min, max: 1.1, 15.6).

3.3. Uncertainties and limitations about favourable effects

Study 20170543 is a single-arm clinical trial aimed at investigating the efficacy of sotorasib in patients with previously treated KRAS G12C-mutated locally advanced or metastatic NSCLC. There are obvious uncertainties related to the design of a single arm phase 1/2 study without any control of the type I error. Determining efficacy in single-arm studies can be challenging due to the lack of comparator and due to the potential selection bias, especially in a heterogeneous population for whom the prognostic of the patients is not clearly established. The literature is indeed not conclusive about the prognostic of patients with KRAS-mutated NSCLC, including p.G12C-mutated NSCLC. Some studies reported that patients with KRAS mutations have a poor prognostic while other studies have demonstrated no prognostic difference with the overall patients with advanced NSCLC (Sattler et al., 2020). Thus, definitive conclusions cannot be drawn on time to event endpoints from a single arm trial. Results of PFS and OS are thus considered exploratory in this context. However, confirmatory PFS results supported by the totality of the data, including a favourable effect on OS /no negative trend are awaited from the ongoing phase 3 trial comparing the efficacy of sotorasib versus docetaxel.

The sample size is another limitation (for main results and subgroup assessments), as well as the relatively short follow-up time which limits the interpretation of several study endpoints.

Finally, the claimed dose of 960 mg is not justified from both a PK and PK/PD perspective. An important dose nonlinearity and a significant inverse ER relationship were indeed observed. The sotorasib 960 mg QD regimen has exceeded the exposure-response saturation level and the applicant is intending to incorporate an additional study arm to the currently ongoing Phase 2 trial to find the optimal dose.

3.4. Unfavourable effects

As of the data cut-off dates for the phase 1 and phase 2 portions of study 20170543, the safety database comprises 456 patients across all doses and tumour types, (colorectal cancer at the intended dose n=87, all other tumour types at the intended dose n=72, pool of any tumour type at the intended dose n=359), of which 200 are patients with NSCLC.

Nearly all patients experienced at least one TEAEs.

Grade ≥3 AEs and SAEs were experienced, respectively, by 61% and 52.5% of patients with NSCLC and by 53.3 % and 45.2% of patients in total any tumour type/any dose pool. The most frequently reported serious adverse events among NSCLC patients were pneumonia (8%), NSCLC (4.5%), pleural effusion (4%), respiratory failure (4%), back pain (3%), dyspnoea (2.5) and metastatic lung cancer (2%).

The most frequent AEs in NSCLC patients belong to gastrointestinal disorders SOC (71.5%) including occurrence of nausea, diarrhoea, constipation and vomiting, abdominal pain; musculoskeletal and connective tissue disorders SOC (51.5%) including back pain and arthralgia; and general disorders and administration site conditions SOC (49.5%) including fatigue, oedema peripheral and pyrexia.

AESI cases of hepatotoxicity are notable in about 28.5% of patients with NSCLC (15% Grade ≥3). ALT increased (19%) and AST increased (20%) were the most common TEAEs among NSCLC patients. AST increased and ALT increased TEAEs were severe (grade ≥3) in 6.5% and 7.5% of patients respectively. 5 cases of DILI were reported among 456 patients in the total any tumour type/any dose pool.

Renal toxicity was identified as an event of interest. Renal toxicity adverse events were reported for 34 of 200 subjects (17%) with NSCLC (3% grade ≥ 3). The most frequently reported renal toxicity adverse event of interest was hyponatremia (8%) (2% grade ≥ 3). A total of 5 subjects in the monotherapy any tumour/any dose population had acute kidney injury, including 1 of the 200 subjects with NSCLC receiving 960 mg QD sotorasib and 4 of the 359 subjects treated with 960 mg QD sotorasib for all tumour types.

Pneumonitis were reported in 3 patients (1.1%), all were serious and 2 cases led to treatment discontinuation.

SAEs most commonly reported as treatment-related by investigators concerned increased ALT, nausea, and pneumonitis;

Treatment discontinuation due to AEs occurred in about 9% of patients, and dose interruption / reductions in about 35.5% of patients, which is not negligible.

A substantial proportion of patients (about 17.5%) had fatal AEs. All were considered drug unrelated by investigator.

3.5. Uncertainties and limitations about unfavourable effects

The number of patients with NSCLC is limited (200 patients) and the single-cohort design of the phase I/II study 20170543 precludes a causality assessment. There is no direct comparison of the sotorasib safety profile with current standard of care therapy (chemotherapy and immunotherapy).

The median duration of exposure of about 6 months is considered limited, with only 46% and 10% of subjects receiving treatment for ≥6 and ≥12 months, respectively; long-term safety data are not available.

Safety data in patients with the most advanced age (>75 years) remain limited. Patients with ECOG status 0 and 1 have been enrolled and data in frail patients, of most relevance for late lines of therapy, is missing. A key uncertainty in the safety of sotorasib relates to hepatotoxicity, which seems to be an unpredictable adverse reaction with an unknown mechanism. Although the discontinuation rate due to hepatotoxicity was found to be low (4.5%) and no fatal cases were reported, the number of hepatotoxicity adverse events and unresolved cases is notable. Section 4.4 of the SmPC reflects the overall use of steroids for the treatment of hepatotoxicity in study 20170543 (24/359=6.7%).

The dose modifications rules evolved during the study 20170543 and the larger dose reduction from 960 mg to 480 mg (in line with the current SmPC), was only applied later in the trial with Protocol amendment 6. Therefore, only 36.8% of subjects had dose reduction from 960 mg to 480 mg, most subjects having a reduction from 960 mg to 720 mg (57.9%). Given the non-linear PK, these SmPC dose modification recommendations are not ideal, but were nevertheless applied in the pivotal study 20170543. It is recognised that the currently proposed dose modification rules are also applied in the ongoing Phase 3 study. The comparison of 960 mg QD to 240 mg QD in the context of the study 20170543 will further shed light to the issue of optimal dosing.

3.6. Effects Table

Table 68: Effects table for sotorasib in the study 20170543 (data cut-off: 01 September 2020)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ORR	CR + PR by BICR	% (95% CI)	37.1 (28.6, 46.2)	NA	Considered successful according to the threshold predetermined by the applicant. Sensitivity analysis based on investigator assessment was not considered successful.	
Median DOR		Months (95% CI)	11.1 (6.9,15.0)	NA	Trend of durability in response in longer term follow up.	As of the 20 June 2021 DCO
Median PFS		Months	6.8 (5.1, 8.2)	NA	66.9% maturity Drug effect unknown. Not interpretable as a measure of efficacy in this uncontrolled trial.	
Median OS		Months	12.5 (10.0, NE)	NA	46.8% maturity Drug effect unknown. Not interpretable as a measure of efficacy in this uncontrolled trial.	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Unfavourable Effects						
TEAE any grade, all-cause TEAE treatment-related TEAE Grade ⩾ 3 Serious TEAE (SAE) TEAE leading to dose interruption/reduction TEAE leading to permanent discontinuation TEAE treatment-related leading to permanent discontinuation TEAEs leading to death TEAE treatment-related leading to death		%	98.5 68.5 61 52.5 35.5 9 6 17.5 0		Percentage of patients with adverse event	
AST increased ALT increased Nausea Diarrhoea Fatigue		%	20(grade ⩾3: 6.5) 19 (grade ⩾3: 7.5) 28 43.5 24.5			

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The activity data available for Lumykras is considered meaningful for the targeted group of patients with KRAS p.G12C mutated locally advanced and metastatic NSCLC. The primary endpoint ORR showed over 37% overall response rate (ORR) in patients of whom the majority had received several previous treatment lines and had been treated with anti-PD1 or anti-PD-L1 with or without platinum-based combination chemotherapy as well as targeted therapies against actionable oncogenic driver mutations, if present.

Only 5 patients with stage III disease at study screening were included in the phase II study. Extrapolation of indication to locally advanced disease is considered reasonable since the proposed treatment option is aimed for a population that has already received at least one line of treatment in the advanced disease setting and in line with previously approved biomarker targeted therapy indications in NSCLC.

In indirect comparisons, the ORR observed compares favourably to the response observed with conventional treatments, including pembrolizumab, in the 2nd line overall NSCLC population in which response rates up to about 30% ORR have been observed. However, direct comparisons are not available. The activity of Lumykras is even more important considering the large part of the patients (35%) in the current study having already experienced 2 or more treatment lines with progression and 22% at least 3 prior treatment lines with progression. Considering that the current product, being a monotherapy without any additional backbone chemotherapy, emphasises further the value of the current data in a patient population with limited treatment options available.

The design of the study and the observed activity are however of limited value in establishing the magnitude of effects in terms of important clinical endpoints in terms of OS, PFS, and Harmol. However, the observed activity in terms of response rate and response duration is such that one can conclude that a clinically relevant effect in terms of efficacy is established even if the magnitude cannot be precisely estimated based on the available data.

To provide comprehensive efficacy and safety data in the proposed indicated population, an ongoing, confirmatory, active-controlled, phase 3 study will be submitted by the applicant in the same population of patients.

Sotorasib was generally well tolerated, with AEs mainly related to gastrointestinal reactions, increased liver enzymes and general disorders. The key risk with sotorasib is hepatotoxicity with laboratory abnormalities for serum transaminases (AST (20%) and ALT (19%)) mostly mild-moderate, but require monitoring and resulted in dose modification, or temporary interruption or use of steroids until resolution.

The totality of evidence generated at this time point indicates that sotorasib was generally well tolerated, with a low number of adverse events leading to treatment discontinuation (9% in the NSCLC 960-mg sotorasib monotherapy). Sotorasib toxicity could overall be considered clinically manageable in the context of a conditional MA.

3.7.2. Balance of benefits and risks

The benefit-risk balance of sotorasib is considered positive. Although the magnitude of benefits needs to be confirmed, the available activity data allows to conclude that efficacy is established. The toxicity profile is considered acceptable.

Despite important uncertainties about the precise magnitude of the benefits, sotorasib benefits outweigh the harms for the second line treatment setting and beyond (2L+) of patients with KRAS G12C-mutated locally advanced or metastatic NSCLC. The pivotal trial supports the conditional marketing authorisation and the SOB will provide comprehensive data on the impact on time-dependent endpoint, as well as comparative safety.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a seriously debilitating and life-threatening disease.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- Ability to provide comprehensive data. It is likely that the applicant will be able to provide comprehensive data. The ongoing multicentre, randomised (1:1), open-label active-controlled confirmatory Phase 3 study is intended to enrol 330 locally-advanced and unresectable or metastatic NSCLC patients with KRAS p.G12C mutation and who have failed ≥1 prior systemic therapy. In this Phase 3 trial sotorasib 960 mg PO QD treatment is compared against docetaxel 75 mg/m2 IV q3w. The interim analysis timing was adjusted to be at approximately 70% information fraction when approximately 160 PFS events observed from both groups. Cross-over from docetaxel control group is allowed, hampering the ability of the study to demonstrate OS benefit compared to docetaxel in the target population.

Nevertheless, the phase 3 trial have the ability to provide confirmatory evidence, provided that a successful PFS result is supported by the totality of the data, including a favourable effect on OS /no negative trend as described in the guideline on the "Evaluation of anticancer medicinal products in man" (EMA/CHMP/205/95 Rev.6). The due date for the submission of the final study results is 31 March 2023.

- Unmet medical needs will be addressed, as sotorasib may provide a therapeutic advantage for patients with KRAS p.G12C-mutated advanced NSCLC. Efficacy results observed in studies with other available treatments including afatinib, docetaxel, erlotinib, nintedanib/docetaxel, pemetrexed ramucirumab/docetaxel, atezolizumab, nivolumab, and pembrolizumab have been presented by the applicant. While the limitations related to indirect comparisons between studies are acknowledged, ORRs in the provided studies are all lower than that observed with sotorasib (ORR 37%), with highest response rate reported for pembrolizumab (30%).The justification for major therapeutic advantage, providing an overview of available treatment options in 2nd line setting is considered to be sufficient by the CHMP. Moreover, providing a new treatment option with a new mechanism of action, oral administration and with a different safety profile is considered to be a relevant therapeutic advantage.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. In the population defined by the claimed indication the benefit/risk is considered to be positive. Approval based on non-comprehensive data from a single arm study could lead to earlier availability of the treatment. Today enrolment of study 20190009 has been completed (18 countries globally, including 12 countries and 67 sites in Europe) and thus no impact of the approval of sotorasib is anticipated on the ability of the applicant to complete the SOB.

3.8. Conclusions

The overall benefit/risk balance of Lumykras is positive, subject to the conditions stated in section 'Recommendations'.

Divergent position is appended to this report.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the benefit-risk balance of Lumykras is favourable in the following indication:

Lumykras as monotherapy is indicated for the treatment of adults with advanced non-small cell lung cancer (NSCLC) with KRAS G12C mutation and who have progressed after at least one prior line of systemic therapy.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of sotorasib in the treatment of patients with KRAS G12C-mutated NSCLC, the MAH should submit the clinical study report for the phase III CodeBreaK 200 study (Study 20190009) comparing sotorasib versus docetaxel for the treatment of previously treated KRAS G12C-mutated NSCLC. The clinical study report will be submitted by:	31 March 2023

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that sotorasib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

5. Appendix

5.1. Divergent position to the majority recommendation dated 11 November 2021

5.2. CHMP AR on New Active Substance (NAS) dated 11 November 2021

APPENDIX

DIVERGENT POSITION DATED 11 November 2021

DIVERGENT POSITION DATED 11 November 2021

Lumykras EMEA/H/C/005522/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Lumykras (Sotorasib) for the following indication:

LUMYKRAS as monotherapy is indicated for the treatment of adults with advanced NSCLC with KRAS G12C mutation and who have progressed after at least one prior line of systemic therapy.

The reasons for the divergent opinion are as follows:

The evidence for efficacy of Sotorasib based on the single arm trial (Study 20170543) is considered insufficient:

- The overall response rate (ORR) in patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) (37.4%; 95% CI: 28.84, 46.58), associated with a very low rate of complete response (1.6%), and the duration of response (DoR) (11.1 months; 95% CI: 6.9, 15.0) are unconvincing and not outstanding as would be required for a single-arm trial.
- In the absence of an outstanding ORR and DoR, time-related endpoints would have been needed to establish clinical benefit, but the impact of treatment with Sotorasib on PFS and OS cannot be reliably estimated and PFS and OS results remain therefore descriptive and non-inferential.

Thus, due to major uncertainties regarding efficacy combined with considerable toxicity of Sotorasib, we cannot conclude on a positive B/R.

CHMP Members expressing a divergent opinion:

DE CHMP member