Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

National Procedure

Lumykras 120 mg film-coated tablets

(sotorasib)

PLGB 13832/0051

Amgen Limited

LAY SUMMARY

Lumykras 120 mg film-coated tablets (sotorasib)

This is a summary of the Public Assessment Report (PAR) for Lumykras 120 mg film-coated tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Lumykras in this lay summary for ease of reading.

For practical information about using Lumykras, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Lumykras and what is it used for?
This application is a full-dossier application. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that this medicine is suitable for treating the specified indications.

Lumykras is used to treat adults with advanced stages of a type of lung cancer called non-small cell lung cancer (NSCLC) that has spread to other parts of the body.

Lumykras can only be prescribed if the patient has been previously treated for their lung cancer with other medicines, and if their cancer has an abnormal *KRAS G12C* gene.
The patient's doctor will test their cancer and make sure that Lumykras is right for them.

How does Lumykras work?
Lumykras contains the active substance sotorasib and belongs to a group of medicines known as antineoplastic agents (anti-cancer medicines).

Lumykras is a medicine that blocks the abnormal *KRAS G12C* protein, which is involved in the growth of cells. Lumykras binds to *KRAS G12C* protein and blocks its function, which may slow down or stop the growth of cancer.

How is Lumykras used?
The pharmaceutical form of this medicine is a film-coated tablet and the route of administration is oral (via the mouth).

- The recommended dose is eight tablets (960 mg) once a day. The patient should take their daily dose of Lumykras once a day at the same time each day.
- If the patient's doctor or pharmacist decreases their dose, they should take either four tablets or two tablets once a day at the same time each day.
- Lumykras can be taken with or without food.
- The patient should swallow the tablets whole, unless they have difficulty swallowing tablets.
- If the patient cannot swallow Lumykras tablets whole they should:
    1. Place their daily dose of Lumykras in half a glass (not less than 120 mL) of non-carbonated room temperature water without crushing the tablets. Do not use any other liquids.

2. Swirl gently until the tablets are in small pieces (the tablets will not completely dissolve). The appearance of the mixture may range from pale to bright yellow.
3. Drink the Lumykras and water mixture right away.
4. Rinse the glass with an additional half a glass of water and drink right away to make sure that they have taken the full dose of Lumykras.
5. If the patient does not drink all of the mixture immediately, they should stir the mixture again before they finish drinking it. All of the mixture should be drunk within two hours of preparation.

If the patient needs to take a medicine to reduce stomach acid, Lumykras should be taken either 4 hours before or 10 hours after that medicine (see section 2 of the PIL).

For further information on how Lumykras is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure. The patient should not change their dose or stop taking Lumykras unless their doctor or pharmacist tells them to. The patient's doctor or pharmacist may decrease the dose or stop their medicine depending on how well they tolerate it.

What benefits of Lumykras have been shown in studies?
Lumykras has been studied in patients with lung cancer who had previously received at least one prior line of treatment. Of the patients who took Lumykras, 37% had a response (complete or partial) to treatment.

What are the possible side effects of Lumykras?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

The most common side effects with Lumykras (which may affect more than 1 in 10 people) are:

- Liver problems
- Diarrhoea
- Joint, muscle or back pain
- Nausea
- Feeling tired
- Vomiting
- Cough
- Stomach pain

- Constipation
- Low red blood cell count (anaemia)
- Shortness of breath
- Headache
- Fever or high temperature

Why was Lumykras approved?
It was concluded that Lumykras has been shown to be effective in the treatment of advanced stages of NSCLC that has spread to other parts of the body in patients who have had previous treatments with other medicines. Furthermore, the side effects observed with use of this product are considered to be typical for this type of treatment. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that this medicine can be approved for use.

Lumykras has been authorised with a Conditional Marketing Authorisation (CMA). CMAs are intended for medicinal products that address an unmet medical need, such as a lack of alternative therapy for a serious and life-threatening disease. CMAs may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon.

What measures are being taken to ensure the safe and effective use of Lumykras?
A Risk Management Plan (RMP) has been developed to ensure that Lumykras is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Lumykras
A Marketing Authorisation for Lumykras was granted in Great Britain (GB, consisting of England, Scotland and Wales) on 08 September 2021.

The full PAR for Lumykras follows this summary.

This summary was last updated in November 2021.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Lumykras 120 mg film-coated tablets (PLGB 13832/0051) could be approved.

Lumykras 120 mg film-coated tablets are indicated as monotherapy for the treatment of adult patients with *KRAS G12C*-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), who have progressed on, or are intolerant to, platinum-based chemotherapy and/or anti PD-1/PD-L1 immunotherapy.

Sotorasib is a potent and highly selective $KRAS^{G12C}$ (Kirsten rat sarcoma viral oncogene homolog) inhibitor, which covalently and irreversibly binds to the unique cysteine of $KRAS^{G12C}$. Inactivation of $KRAS^{G12C}$ by sotorasib blocks tumour cell signalling and survival, inhibits cell growth, and promotes apoptosis selectively in tumours harbouring $KRAS^{G12C}$, an oncogenic driver of tumourigenesis across multiple cancer types. The potency and selectivity of sotorasib is enhanced through the unique binding to both the P2 pocket and the His95 surface groove, locking the protein in an inactive state that prevents downstream signalling, without affecting wild-type KRAS.

Sotorasib demonstrated *in vitro* and *in vivo* inhibition of $KRAS^{G12C}$ with minimal detectable off-target activity against other cellular proteins and processes. Sotorasib impaired oncogenic signalling and tumour cell survival at clinically relevant exposures in numerous pre-clinical models expressing $KRAS^{G12C}$. Sotorasib also enhanced antigen presentation and inflammatory cytokine production only in tumour cells with $KRAS^{G12C}$. Sotorasib induced anti-tumour inflammatory responses and immunity, driving permanent and complete tumour regressions in immunocompetent mice implanted with $KRAS^{G12C}$ expressing tumours.

This application was approved under Regulation 50 of The Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended), a full-dossier application. All non-clinical data submitted were from studies conducted in accordance with Good Laboratory Practice (GLP). All clinical data submitted were from studies conducted in accordance with Good Clinical Practice (GCP).

This application was evaluated as part of Project Orbis, which is a programme coordinated by the US Food and Drug Administration (FDA) involving the regulatory authorities of Australia (TGA), Canada (Health Canada), Singapore (HSA), Brazil (ANVISA), Switzerland (Swissmedic) and the MHRA (UK), to review and approve promising cancer treatments. Project Orbis provides a framework for concurrent submission and review of oncology products among selected international partners. Each regulator makes independent decisions regarding approval of the application.

This product has been authorised as a Conditional Marketing Authorisation (CMA). CMAs are granted in the interest of public health and are intended for medicinal products that fulfil an unmet medical need and the benefit of immediate availability outweighs the risk posed from less comprehensive data than normally required. Unmet medical needs include, for example, treatment or diagnosis of serious and life-threatening diseases where no satisfactory treatment methods are available. CMAs may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon. Adequate evidence of safety and efficacy to enable the MHRA to conclude that the benefits are greater than the risks is required, and has been provided for Lumykras 120 mg film-coated tablets. The CMA for Lumykras 120 mg film-coated tablets, including the provision of any new

information, will be reviewed every year and this report will be updated as necessary.

This application was evaluated for fulfilment of orphan drug designation criteria and was examined by the Commission on Human Medicines (CHM). The Applicant proceeded to a marketing authorisation approval without orphan drug designation.

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a full product specific waiver P/0091/2020.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 08 April 2021 and 01 July 2021 who on the evidence before them had reason to think that on grounds relating to efficacy, they might be unable to advise the grant of this application. In response to the CHM advice, the applicant provided further data to address these concerns. The information provided was adequate and the issues were resolved and the Marketing Authorisation was granted for this product in Great Britain on 08 September 2021.

II QUALITY ASPECTS

II.1 Introduction

Each film-coated tablet contains 120 mg of sotorasib.

In addition to sotorasib, this product also contains the excipients:

Tablet core

Microcrystalline cellulose, lactose monohydrate, croscarmellose sodium and magnesium stearate.

Film-coating

Polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc and iron oxide yellow.

The finished product is packaged in:

- PVC/PE/PVDC blisters with aluminium foil backing packed into a carton. Each blister contains 8 film-coated tablets and is available in a pack size of 240 film-coated tablets (1 carton of 30 blisters).
- HDPE bottle with a child-resistant polypropylene cap and aluminium foil induction seal liner packed into a carton. Each bottle contains 120 film-coated tablets and is available in a pack size of 240 film-coated tablets (1 carton of 2 bottles).

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

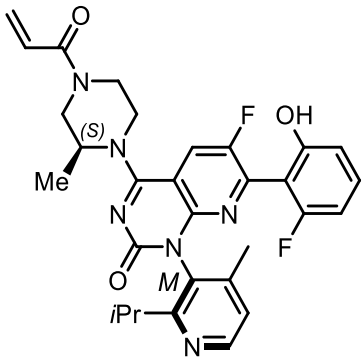
II.2 ACTIVE SUBSTANCE

rINN: Sotorasib

Chemical Name: 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1*M*)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2*S*)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]pyrido[2,3-*d*]pyrimidin-2(1*H*)-one

Molecular Formula: $C_{30}H_{30}F_2N_6O_3$

Chemical Structure:



Molecular Weight: 560.6 g/mol

Appearance: White to off-white to yellow to light brown powder

Solubility The general properties of sotorasib have been established including the solubility in a range of physiologically relevant media.

Sotorasib is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant batch analysis data.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory batch analysis data have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for the non-compendial excipient.

With the exception of lactose monohydrate, no excipients of animal or human origin are used in the final products.

The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has shown satisfactory results.

Finished Product Specifications

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Batch analysis data have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years, with no storage conditions, is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
Lumykras (Sotorasib) 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).

Sotorasib is a novel, first-in-class, potent, and highly selective small molecule inhibitor that covalently binds to the Kirsten rat sarcoma viral oncogene homolog (KRAS) protein with a G12C amino acid substitution (KRASG12C) and locks it in a guanine diphosphate (GDP)-bound, inactive state. By doing so, sotorasib specifically binds and irreversibly inhibits the KRASG12C mutant protein.

Sotorasib potently inhibits recombinant KRASG12C but has minimal effect on wild-type KRAS or other mutant versions of KRAS. The covalent, irreversible binding and inhibition of KRASG12C by sotorasib requires a reactive thiol group adjacent to the sotorasib binding pocket. This thiol is provided by the cysteine at KRAS position 12 (G12C), resulting in a precise interaction that is specific for KRASG12C. The inhibitor contains a thiol-reactive portion that covalently modifies the cysteine residue and locks KRASG12C in the inactive, GDP-bound conformation. This blocks the interaction of KRAS with effectors such as rapidly accelerated fibrosarcoma (RAF), thereby preventing downstream proliferation and survival signalling, including the phosphorylation of extracellular signal-regulated kinase (ERK). Sotorasib treatment impairs tumour cell growth and induces apoptosis only in tumour cell lines and xenografts that have the *KRAS p.G12C* mutation. Blockade of *KRAS p.G12C* signalling by sotorasib also enhances antigen-presentation and inflammatory cytokine production in tumours to induce an inflamed tumour microenvironment and drive permanent antitumor immunity. At physiologically relevant concentrations, sotorasib targets only the KRASG12C protein and will affect the signalling and growth of only those tumour cells that have the *KRASp.G12C* mutation.

III.2 Pharmacology
Sotorasib was demonstrated to be a potent and selective covalent inhibitor of KRASG12C. Sotorasib binds irreversibly to the P2 pocket of KRASG12C through an interaction with the histidine 95 groove and a precise covalent reaction with cysteine 12. Binding of sotorasib locks KRASG12C in the inactive GDP-bound conformation and prevents exchange of GDP with GTP. This blocks the interaction with downstream effectors like RAF, thus preventing phosphorylation of ERK (p-ERK). In biochemical assays, 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. It also impaired viability in all but one *p.G12C*-mutant cell lines and did not affect non-*p.G12C* cell lines.

These findings suggest that sotorasib will show potent activity only in settings with the *KRAS p.G12C* mutation.

In vivo sotorasib covalently modified KRASG12C and significantly inhibited p-ERK in human tumour xenografts at doses as low as 3 mg/kg. Sotorasib inhibition peaked at approximately 2 hours and persisted for at least 48 hours after a single dose. Sotorasib significantly inhibited tumour growth at doses from 3 mg/kg and at 100 mg/kg achieved up to 62% tumour regression.

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 46% regression at 100 mg/kg.

In vitro in combination studies, sotorasib displayed synergistic cell killing 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. 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.

A syngeneic murine colorectal tumour model (CT-26) was engineered to endogenously express *KRASp.G12C.* 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. Combination of sotorasib with an immune checkpoint inhibitor (anti-PD-1) significantly enhanced anti-tumour activity at a suboptimal dose of sotorasib. 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. Re-challenge experiments established that cured mice had developed an anti-tumour immune response to CT-26, irrespective of the *KRAS* mutation status. These studies establish that sotorasib can induce anti-tumour inflammation and immunity and that it might be especially effective in combination with agents that block PD-1 signalling.

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. In NCI-H358 cells, cysteine-proteome profiling indicated that sotorasib engaged only the Cys12-contaning peptide from KRASG12C.

Overall, safety pharmacology studies did not identify any cardiovascular concerns . The hERG IC50 was 54.8 μM. 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 hemodynamic parameters in a GLP cardiovascular safety pharmacology study in telemetered dogs. There were no effects on ECG parameters in the 28-day dog repeat-dose toxicology study.

Evaluation of the potential effects of sotorasib on the central nervous system (CNS) and the respiratory system were incorporated into repeat dose toxicity studies in the dog. The results indicated that there was no significant effect on either system.

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 maintained 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. In vitro hERG assays for these metabolites did not indicate any clinically relevant or significant interactions.

III.3 Pharmacokinetics (PK)

Sotorasib was quantified in mouse, rat, dog, monkey and rabbit plasma using specific analytical procedures.

The pharmacokinetics (PK) of sotorasib was studied in nude and Balb/c mice, Sprague Dawley rat, beagle dog, and cynomolgus monkey following single-dose IV or PO administration.

Following IV dosing, sotorasib exhibited moderate clearance in mouse and dog and high clearance (approaching liver blood flow) in rat and monkey. The Vss was moderate in all the species relative to total body water; approximately 0.74 L/kg in mouse, 2.0 L/kg in rat, 0.73 L/kg in dog, and 0.76 L/kg in monkey. The $t_{1/2,z}$ of sotorasib following IV administration was approximately 0.42 hours in nude mouse, 0.47 hours in Balb/c mouse, 0.49 hours in rat, 0.41 hours in dog, and 0.71 hours in monkey. Following PO administration, mean t_{max} of sotorasib ranged from approximately 0.25 to 1.2 hours in all species. Sotorasib exhibited low to moderate oral bioavailability in mouse, rat, and dog; approximately 35% in mouse, 30% in rat, and 34% in dog.

Sotorasib has moderate binding to plasma proteins and did not preferentially distribute into blood cells when assessed in vitro in mouse, rat, dog, and human, which indicates that plasma concentrations are suitable to assess exposure of sotorasib in human as well as rat and dog, the two species used in the repeat-dose toxicology studies. Binding of sotorasib to mouse, rat, dog, and human plasma was assessed from 0.25 to 25 μM. The free fraction of sotorasib to mouse, rat, dog, and human plasma across the concentration range tested varied less than 2-fold (with an average in vitro unbound fraction of approximately 0.071, 0.054, 0.21, and 0.11 in mouse, rat, dog, and human, respectively). The sotorasib blood-to-plasma partition ratio in mouse, rat, dog, and human ranged from 0.60 to 0.84.

A whole body distribution study in male Long Evens (LE) or male or female SD rats showed that [14C]-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 post-dose. Tissues with the highest radioactivity exposures common to both rat strains were liver, kidney, thyroid, pancreas, exorbital lacrimal gland, and the intra-orbital lacrimal gland. In general, the tissue distribution patterns were similar in LE and SD male rats after a single PO dose of [14C]-sotorasib. Blood and plasma AUC_t values of [14C]-sotorasib-derived radioactivity after PO administration were higher in females than males, but the differences were < 2-fold. Elimination of [14C]-sotorasib-derived radioactivity was nearly complete for most tissues by

336 hours post-dose. By the final sampling time of 672 hours post-dose, only blood and highly perfused tissues such as kidney, lung, myocardium and spleen had measurable concentrations of [14C]-sotorasib-derived radioactivity.

The metabolism of sotorasib was studied using pooled liver microsomes and hepatocytes from mouse, rat, dog, and human. Metabolites M10, M18, and M24 were the predominant sotorasib metabolites formed using human hepatocytes. The in vitro metabolites of sotorasib formed by pooled human liver microsomes and hepatocytes were also produced by pooled liver microsomes and hepatocytes from the rat and dog. No unique human metabolites of sotorasib were observed *in vitro* when compared with incubations from rat and dog..

The metabolism and excretion of [^{14}C]-sotorasib were evaluated in non-cannulated male and female rats or in bile duct cannulated (BDC) male rats after a single PO dose of sotorasib (60 mg/kg). Overall, the data indicated that sotorasib was readily absorbed after a PO dose to non-cannulated male and female rats or BDC male rats; [^{14}C]- sotorasib -derived radioactivity was excreted primarily through biliary and faecal pathways. Sotorasib biotransformation 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.

Sotorasib biotransformation 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 accounts for up to approximately 10% of dose in non-cannulated male and female 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 overall mean recoveries of sotorasib-derived radioactivity were nearly complete with 89.6%, 91.6%, and 95.2% for non-cannulated male, non-cannulated female, and BDC rats, respectively.

The metabolism and excretion of [14C]- sotorasib were evaluated in non-cannulated male and female dogs after a single PO (500 mg/kg) dose of sotorasib. 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 and female dogs.

Mixed plasma matrix experiments were performed to characterise circulating metabolites after multiple doses of sotorasib in male and female rats, dogs, 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 glutathione transferases, human liver cytosol, or human liver S9 fractions demonstrated that M12 formation from sotorasib is primarily

nonenzymatic, with limited contribution from glutathione transferases. Formation of M24 from sotorasib was predominantly catalysed by CYP3A.

The potential for sotorasib and its metabolites M10, M18, and M24 to cause CYP-mediated drug-drug interactions (DDI) was evaluated *in vitro*. These experiments indicated that sotorasib and its metabolites have potential to cause CYP3A-mediated DDI due to reversible inhibition, time-dependent inhibition, and induction; therefore, a clinical CYP3A DDI study was run. Based on sotorasib concentrations observed in the clinic and the *in vitro* and kinetic characteristics of sotorasib, minimal risk for CYP-mediated DDIs is expected with sotorasib for other CYPs.

Sotorasib had high passive permeability and was a substrate of P-glycoprotein (P-gp) in vitro but was not a breast cancer resistance protein (BCRP) substrate. The potential for sotorasib and its metabolites M10, M18, and M24 to cause transporter mediated DDI was evaluated *in vitro*. Sotorasib was characterised as an *in vitro* inhibitor of BCRP (IC50 = 120 μM), multidrug and toxin extrusion protein 1 (MATE1, IC50 = 0.440 μM), multidrug and toxin extrusion protein 2-K (MATE2-K, IC50 =2.39 μM) and P-gp (IC50 = 60.2 μM); therefore, clinical DDI studies for MATE1/MATE2-K and P-gp were run. Based on sotorasib concentrations observed in the clinic and the in vitro characteristics of sotorasib, minimal risk for transporter-mediated DDIs is expected with sotorasib for other transporters.

III.4 Toxicology

All of the pivotal nonclinical studies were conducted in compliance with GLP.
The Sprague Dawley rat and beagle dog were selected as the species for the toxicity studies.

In the 28-day rat toxicity study at 30, 100, and 200 mg/kg/day the main treatment- related changes were reported as minimal to slight which included increased spleen weight, increased leukocytes, a decrease in red blood cell (RBC) mass (hemoglobin, RBC count, and hematocrit) that was associated with changes in reticulocytes and RBC indices. Light microscopy revealed renal tubular epithelial degeneration/necrosis in the proximal tubules in the outer stripe of the outer medulla (OSOM). The renal tubular injury partially reversed after a 28-day recovery period, with evidence of ongoing resolution/repair. However, a few tubules were surrounded by fibroplasia. Sotorasib -related increased spleen weight was not observed after the 28-day recovery period and all the hematology parameters were comparable to control.

In the 3-month rat toxicity study with a 2-month recovery period, higher dose levels were evaluated (60, 180, and 750 mg/kg), which were associated with systemic exposure that exceeded the human clinical exposures. The sotorasib-related changes in the rat were a minimal to moderate decrease in RBC mass at ≥ 60 mg/kg, a minimal to moderate increase in total bilirubin at ≥ 180 mg/kg and gamma-glutamyltransferase at 750 mg/kg, a slight increase in cholesterol at ≥ 60 mg/kg, slight to marked decrease in triglycerides at ≥ 180 mg/kg, and a minimal to moderate decrease in globulins at 750 mg/kg. The main sotorasib-related change was renal tubular degeneration/necrosis with similar characteristics as those observed in the 28-day study (e.g. proximal tubules of the OSOM) associated with clinical pathology, macroscopic and kidney weight changes. By light microscopy, renal tubular degeneration/necrosis primarily located in the proximal tubules in the OSOM increased in both incidence and severity (minimal to marked) compared to the renal changes in the 28-day study, which was attributed to the longer study duration and higher systemic exposures to sotorasib. At the end of the recovery period, there was partial recovery of sotorasib -related renal changes at all dose levels but was accompanied with interstitial fibrosis and

glomerulosclerosis, which would not be expected to be reversible. There were no sotorasib -related changes in any of the other parameters in the recovery phase.

In the 28-day dog toxicity study at 30, 100, and 300 mg/kg the main sotorasib-related changes consisted of a minimal to slight decrease in RBC mass associated with decreased reticulocytes. In the 3-month dog toxicity study, higher dose levels were evaluated (200, and 1000 mg/kg/day administered as 100 and 500 mg/kg twice daily) to achieve higher systemic exposure; however, the exposure even at 1000 mg/kg/day was not as high as in the 3-month rat study.Sotorasib -related changes including abnormal content in the gall bladder, minimal to slight changes in hematology (decrease in RBC mass) and minimal to mild changes in 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 changes were attributed to an adaptive or secondary response to hepatocellular enzyme induction.

It is noteworthy that no renal toxicity was identified in the dog at up to a 3-month administration duration and up to the highest dose tested. However, the systemic exposure even at the top dose was not as high as in the 3-month rat study. This toxicity was reported in only one of the test species, that is, the rat. Renal toxicity in the rat was attributed to the local formation of a putative nephrotoxic reactive metabolite following metabolism of sotorasib by the mercapturate and cysteine S-conjugate β-lyase pathways. Cysteine S-conjugate β-lyase activity is greater in rat renal tissue than in human suggesting that rats may be more susceptible to this type of renal toxicity. The clinical data revealed that renal AEs were seen in the clinical studies in around 12-17 % of subjects. The most common was hyponatremia (8% in the NSCLC population), followed by hypoalbuminemia, raised creatinine, hyperkalaemia, hypophosphatemia. Most renal toxicity adverse events of any grade resolved (53 resolved events versus 9 unresolved events) and all 5 grade ≥3 events resolved. From the clinical viewpoint there no major issues with safety related to renal toxicity.

In summary the two main findings in the test animals i.e. renal toxicity in the rat and liver/pituitary/thyroid findings in the dog were attributed to species-specific metabolic pathways and adaptive changes, respectively. The findings of slight decrease of RBC mass reported in the rat and dog do not appear to have a clinical corelate since this finding is not reported in section 4.8 of the SmPC “Summary of the safety profile”. Clinically, sotorasib has been associated with transient elevations of serum transaminases (ALT and AST). This is included in section 4.4 of the SmPC “Special warnings and precautions for use”.

Sotorasib was negative for genotoxicity in the GLP bacterial mutation assay and the combined in vivo mammalian erythrocyte micronucleus test and alkaline comet assay in the rat.

In the rat and rabbit embryo-fetal development toxicology studies, there were maternal effects including decreased body weight gain and food consumption at systemic exposures of approximately 4 (rat) and 2 (rabbit) times the exposure at the clinical dose (960 mg). Sotorasib was not teratogenic. In the rat, there were no effects on embryo-fetal development up to the high dose (540 mg/kg) tested. In the rabbit, lower fetal body weights and a reduction in the number of ossified metacarpals in fetuses were observed only at the dose level (100 mg/kg) associated with decreased body weight gain and food consumption in dams during dosing phase. The reduced ossification, as evidence of growth retardation associated

with reduced fetal body weight, was interpreted as a non-specific fetal effect in the presence of significant maternal toxicity. The SmPC states: “Pregnancy: There are no data from the use of sotorasib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Patients must be informed of the potential hazards to the foetus if lumykras is used during pregnancy, or if the patient becomes pregnant while taking lumykras.”

Sotorasib was not phototoxic in vitro.

Human circulating metabolites M24, M18, and M10 were assessed for 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.

Specified impurities listed at levels greater than the qualification threshold in the sotorasib drug substance were qualified in line with ICH Q3A and ICH Q3B guidelines.

III.5 Ecotoxicity/Environmental Risk Assessment

A full Environmental Risk Assessment (ERA) was submitted with this application.

Phase 1

The octanol water partition coefficient of sotorasib (log Pow <3 in the pH range of 5-9) did not exceed the value of 4.5 so an evaluation of the persistence, bioaccumulation and toxicity (PBT) of sotorasib was not required.

The worst-case scenario for the Phase I predicted environmental concentration (PECSW) of sotorasib was calculated to be 4.8 µg/L. Thus, the PECSW exceeded the value for a Phase II Tier A risk assessment (>0.01 µg/L).

Phase II Tier A

Surface water/Ground water

The outcome of the Phase II Tier A assessment confirmed that sotorasib is unlikely to represent a risk to surface water, groundwater or to microorganisms.
As the Koc in sewage sludge was <1000 L/kg, sotorasib is unlikely to reach the soil compartment as a result of spreading of sewage sludge onto agricultural land. Therefore, the exposure and effects assessments for soil were not conducted.

Sotorasib should be considered as being very persistent (DT50 in freshwater sediment >180 days).

As sotorasib is not readily biodegradable and more than 10% was present in sediment, a study to investigate the effects on sediment organisms was conducted. Based on this study sotorasib is unlikely to pose a risk to sediment dwelling organisms.

The assessment of sotorasib for secondary poisoning or bioaccumulation in fish was not required. Sotorasib is unlikely to pose a risk to the soil environment.

Conclusions

Sotorasib is unlikely to pose a risk to the aquatic or soil environments.
Sotorasib is not expected to have the potential for secondary poisoning nor be bio-accumulative in fish. AMG 510 is very persistent (vP) in fresh-water sediment.

Precautionary and Safety Measures to be Taken for Disposal
Environmental risk assessment studies have shown that Sotorasib has the potential to be persistent to the environment. There is no potential for bioaccumulation or toxicity. This medicinal product may pose a risk to the environment. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

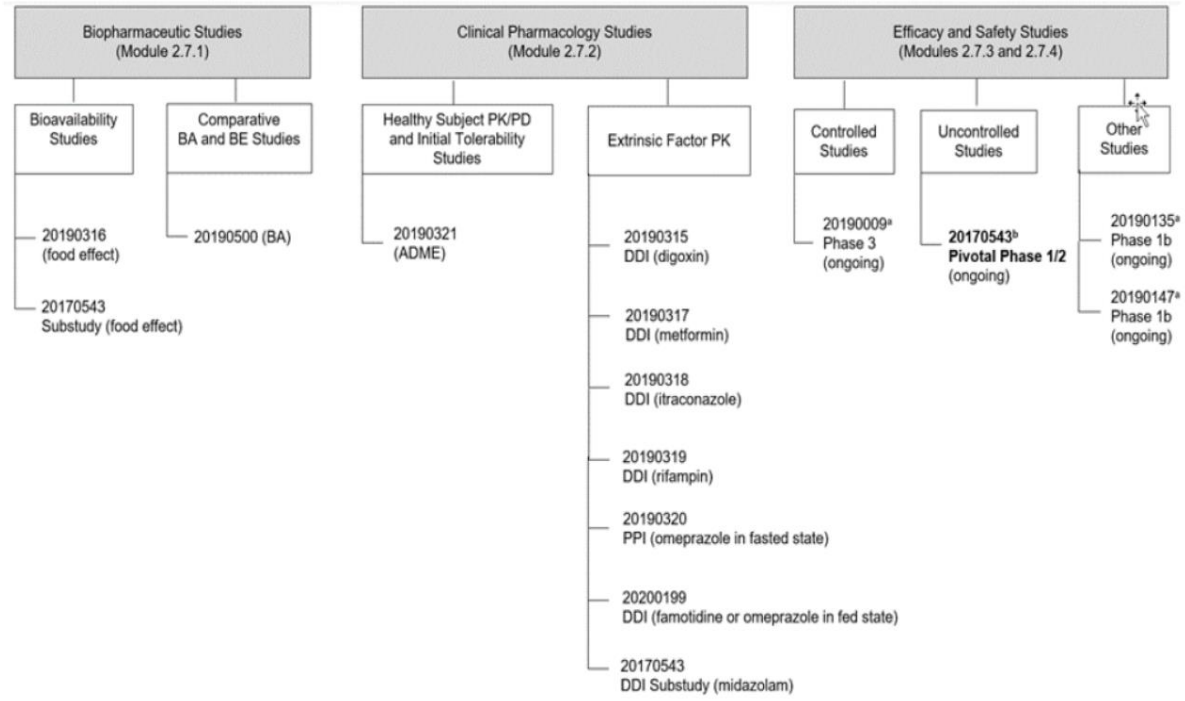
IV.1 Introduction
To characterise the initial safety, tolerability, pharmacokinetic (PK), pharmacodynamic (PD), and exposure response (ER) properties of sotorasib, the marketing authorisation application included 9 clinical pharmacology studies and 2 clinical pharmacology sub-studies. In addition, population PK and ER analyses were performed using data from subjects enrolled in the phase 1/2 Study 20170543.
The clinical pharmacology of sotorasib was assessed as an aspect of 9 conducted clinical studies:

- Study 20170543 was a phase 1/2 open-label, dose expansion/dose exploration study evaluating efficacy, safety, tolerability, and PK (including but not limited to single dose and steady-state area under the drug concentration-time curve [AUC] and maximum plasma concentration [C_{max}]) of sotorasib.30
- Study 20190321 evaluated the absorption, metabolism, and excretion of ^{14}[C] sotorasib in healthy subjects.
- Sotorasib was evaluated as a victim in drug-drug interaction (DDI) studies (20190317, 20190318, 20190319, 20190320, and 20200199). These studies were conducted to determine the effect of coadministration with metformin (clinical probe MATE-1/2K substrate), itraconazole (strong CYP3A4/P-gp inhibitor), rifampin (strong CYP3A4/P-gp inducer with multiple-dose and strong OATP1B1/1B3 inhibitor with single-dose), omeprazole (proton pump inhibitor) under fasted conditions, or famotidine (histamine-2 receptor antagonist) or omeprazole under fed conditions, respectively, on sotorasib PK.
- Sotorasib was also evaluated as a perpetrator in 3 DDI studies.
  i. Study 20170543 included a DDI substudy designed to evaluate the PK of midazolam (sensitive CYP3A4 substrate) when administered with and without sotorasib.
  ii. Study 20190315 evaluated the PK of digoxin (clinical probe P-gp substrate) when administered with and without sotorasib.
  iii. Study 20190317 evaluated the PK of metformin when administered with and without sotorasib.

The relationship of sotorasib exposure to change in baseline corrected QT interval, renal impairment, and hepatic impairment were assessed based on data from the phase 1/2 Study 20170543.

All studies were conducted in line with current Good Clinical Practice (GCP).

Figure 1. Organogram of Sotorasib Clinical Studies in This Marketing Application



IV. 2 Pharmacokinetics

Absorption

In vitro absorption

The solubility of the drug substance over the physiologic pH range was measured. Sotorasib drug substance is soluble at lower pH (eg, pH 1.0) with presence of hydrolytic degradation, but insoluble at higher pH (eg, pH 4.5 and 6.8). Based on the pH solubility data of sotorasib drug substance, an acidic pH is not desired for the consideration of achieving discriminating power of a dissolution medium, as the drug substance has more than 10 times the required solubility at pH ≤ 2. Sotorasib was highly permeable *in vitro* (5.6 to 11.2 x 10-6 cm/s) across polarised Madin Darby canine kidney epithelial cells.

Given the pH-dependent solubility of sotorasib, with it being soluble at pH 1.0 but not at pH 4.5 or 6.8. This warrants further investigation with food- and acid-reducing drug-interaction studies (below).

Clinical pharmacokinetics

Study 20190321 (ADME)

Subjects received a single oral dose of 720 mg sotorasib containing approximately 1 µCi of [^{14}C]-sotorasib after an overnight fast on Day 1. Blood, urine, and faecal samples were collected at predetermined timepoints through Day 14 to characterise plasma concentrations of sotorasib and total radioactivity. A total of 8 healthy men were enrolled and completed the study.

Following single oral administration of 720 mg sotorasib containing approximately 1 µCi of [^{14}C]- sotorasib, plasma sotorasib, and total radioactivity in plasma and whole blood attained similar peak concentrations between 0.50 and 2.00 hours. Plasma sotorasib comprised approximately 20% of total radioactivity in plasma. There was no preferential association of radioactivity with red blood cells. Faecal excretion was the primary route of elimination. On average, 1.47% of the dose was excreted unchanged in the urine.

Study 20170543

In the phase 1 portion of Study 20170543, sotorasib was administrated PO in subjects with KRAS p.G12C-mutated advanced solid tumours in both monotherapy and combination therapy dosing regimens. In the dose exploration (Part 1), sotorasib was either administered PO once daily (QD) as a monotherapy over a dose range of 180 to 960 mg (Part 1a and Part 1d), PO twice daily (BID) as a monotherapy at 480 mg (Part 1b), or PO QD in combination with pembrolizumab over the sotorasib dose range of 360 to 960 mg (Part 1c).

Table: Sotorasib Pharmacokinetic Parameter Estimates Following Oral Administration of 180, 360, 720, or 960 mg Sotorasib QD in Subjects With KRAS p.G12C-Mutated Advanced Solid Tumours (Day 1 and Day 8)

Treatment	tmax (hour)	Cmax (ng/mL)	AUCinf (hour•ng/mL)	AUC0-24h (hour•ng/mL)	t1/2,z (hour)	CL/F (L/hour)	Vz/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)l	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%)i	5.07 (1.08)j	29.6 (37.8, 67%)i	208 (252, 63%)j	0.532 (0.587, 45%)k

For study 20170543 sotorasib was administered orally either QD as a monotherapy over a dose range of 180 to 960mg, BID as a monotherapy at 480mg to subjects with KRAS p.G12C-Mutated Advanced Solid Tumours. Geometric mean C_{max} and AUC from time 0 to 24hours post-dose (AUC0- 24h) With 480-mg BID dosing, geometric mean AUC_{0-24h}increased, compared with 960- mg QD dosing, on both day1 and day8 of dosing.

Based on the data provided, t_{max} was reached between 1 to 2 hours (fasted). C_{max} following a single 180 mg dose was 6880 ng/mL, 6190 ng/mL following a 360 mg dose, 7570 ng/mL following a 720 mg dose and 8400 ng/mL following a 960 mg dose. $AUC_{0-\infty}$ following a single 180 mg dose was 40,700ng×h/mL, 60,700 ng×h/mL following a 360 mg dose, 80,800 ng×h/mL following a 720 mg dose and 67,000 ng×h/mL following a 960 mg dose. The C_{max} and AUC_{0-24h} parameters for both day 1 and day 8 were less than dose proportional. The

elimination half-life was approximately 5 to 6 hours on both day 1 and day 8.

On Day 8, the accumulation ratio is following the 180 mg doses is 0.726, 0.666 following the 360 mg doses, 0.604 following 720 mg doses and 0.532 following the 960 mg dose. This is indicative that there is no accumulation was observed with multiple dosing, but there is increase clearance following multiple dosing.

The same core tablet formulation was used throughout the clinical studies however uncoated tablets were used in phase 1 and early phase 2 studies and film-coated tablets were used in phase 1, 2, and 3 studies. Both formulations showed similar *in vitro* dissolution.

The results of the relative bioavailability study (sotorasib administered as tablets and as a water dispersion in Study 20190500) indicate that administration of sotorasib as film-coated tablets pre-dispersed in water does not affect the PK of sotorasib.

No formal bioequivalence studies were performed nor deemed necessary as both formulations (uncoated and coated tablets) showed similar *in vitro* dissolution.

Influence of food
Study 20190316
The effect of food (high-fat meal) was examined in Study 20190316 conducted in healthy subjects and in a subset of subjects with *KRAS p.G12C*-mutated solid tumours within the phase 1 portion of Study 20170543.

Following a single oral dose of 360 mg sotorasib, the ratios (test/reference) of the geometric least square means of sotorasib administered in the fed state compared to sotorasib administered in the fasted state were 1.376, 1.381, and 1.026 for AUC_{inf}, AUC_{last}, and C_{max}, respectively. Furthermore, a high-fat meal delayed sotorasib median t_{max} by 1.25 hours (from 0.500 to 1.75 hours). The impact of a high-fat meal on M24 was consistent to that on sotorasib.

Study 20170543
Data from an analysis of subjects who completed the crossover-design food effect sub study of Study 20170543 suggest that administration of sotorasib in the fed state increased steady-state AUC_{0-24} by 1.25-fold, on average (Study 20170543 Phase 1).

AUC-based exposure appears to be approximately 25-38% higher in the fed state versus (vs) the fasted state, while for C_{max} results were variable, therefore no definite conclusions can be drawn from the small studies. However the population PK model indicated that a high fat meal increases the bioavailability and absorption of sotorasib resulting in increased exposure (+13%in $C_{max,ss}$ and +33%in $AUC_{tau,ss}$).

Distribution
Plasma protein binding appears to be concentration dependent with an average free fraction of approximately 0.11. The blood-to-plasma partition ratio indicates that the majority of sotorasib is constrained to plasma. Apparent volume of distribution is dose -dependent, as bioavailability of the drug is unknown it is not known if the apparent volume of distribution is due to large extent of distribution or low bioavailability.

Elimination

Excretion

Sotorasib is primarily eliminated in faeces, with approximately 74% of the dose recovered in faeces and 6% (1% unchanged) recovered in urine. The elimination half-life is approximately 5 to 6 hours.

Metabolism

Sotorasib is metabolised to M24 via CYP3A4/5, the M12 metabolite is formed by glutathione conjugation. Mass Balance study showed M10, sotorasib, and M24 were present at 26.8%, 17.1%, and 7.8% of total radioactivity in plasma. Only M18 maintains primary pharmacology effects, but the effect is markedly reduced compared to sotorasib.

The *in vitro* studies carried out in physiologically relevant systems, such as human liver microsomes, indicate that CYP2C8 is not involved in the metabolism of sotorasib.

Pharmacokinetics of metabolites

Following QD administration of sotorasib, M10 exposure (as assessed by C_{max} and $AUC_{0\text{-}24h}$) was highest, followed by M24 and M18. Peak plasma concentrations for all metabolites were greater than 3-fold lower than sotorasib C_{max} on day 8. M18 is the only active metabolite, albeit with reduced activity.

Dose proportionality and time dependency

No accumulation was observed at the dose levels tested (180 mg to 960 mg), however the accumulation ratio on Day 8 ranged from 0.53 to 0.73. This is indicative that there is no accumulation observed with multiple dosing, but there is increase clearance following multiple dosing. The population PK model suggest that induction of relative bioavailability and clearance reaches steady state in 2-3 weeks.

Intra- and inter-individual variability

The population PK model identified moderate inter-individual variability on various parameters.

Pharmacokinetics in target population

Various methods to assess the sotorasib population PK model were used including pcVPC, bootstrapping, and goodness of fit plots. The population PK model is considered fit-for-purpose i.e. adequate to describe the PK data and identify covariates.

Healthy Subjects Versus Subjects With Advanced Solid Tumours

Lower albumin was associated with decreased sotorasib clearance and higher sotorasib exposure. Subjects with low albumin (<34 g/L, median albumin 30 g/L) were estimated to have higher sotorasib exposure (+7.5% in $C_{max,ss}$ and +41% in $AUC_{tau,ss}$) compared to subjects with normal albumin (≥ 34 g/L, median albumin 40 g/L). Baseline disease characteristics (patients vs healthy, tumour size and ECOG score) were estimated to affect sotorasib clearance. Subjects with lower baseline tumour size (≤70 mm) were estimated to have lower sotorasib exposures (-1.8% in $C_{max,ss}$ and -11 $AUC_{tau,ss}$) than the subjects with higher baseline tumour size (>70 mm). Subjects with ECOG score of 0 were estimated to have lower sotorasib exposures (-2.3% in $C_{max,ss}$ and -13% $AUC_{tau,ss}$) than subjects with an ECOG score of 1.

Special populations
Gender
Sex was identified as significant covariate for sotorasib apparent clearance (CL) and volume of distribution (V2). Male patients have larger CL and larger V2 than those of female patients.

Race
Race was identified as a significant covariate, with Asian subjects having a higher clearance compared to other races (White, Black or African American). The consequence of this is a decrease (-18%) $AUC_{tau,ss}$ in Asian patients compared to a typical patient, the impact on $C_{max,ss}$ is negligible. The SmPC states that this is not a clinically meaningful difference.

Weight and age
Weight and age were not considered a significant covariate for either clearance or volume of distribution.

Interactions
In vitro
***In vitro* CYP inhibition:** The potential for sotorasib to inhibit cytochrome P450-mediated metabolism was examined in vitro using human hepatic microsomes. Sotorasib at concentrations up to 100 μM was an in vitro inhibitor of CYP2C8, CYP2D6, and CYP3A.

***In vitro* CYP induction:** Sotorasib was an inducer of CYP3A4, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 *in vitro*. No induction of CYP1A2 was observed after incubation with sotorasib. The metabolite M24 was an inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP2C19.

***In vitro* transporter inhibition:**. Sotorasib was not an inhibitor of human OCT2. Sotorasib was characterised as an inhibitor of human OAT3, OATP1B1, MATE1, MATE2-K and P-gp; incomplete inhibition was observed up to the highest test concentration for human OAT1, OCT1, OATP1B3 and BCRP . The metabolite M24 was not an inhibitor of human OCT1 and OCT2.
AMG3368167 was characterized as an inhibitor of human OAT1, OAT3, OATP1B1, OATP1B3, MATE1 and P-gp; incomplete inhibition was observed up to the highest test concentration for human MATE2-K and BCRP.

In vivo
The drug-drug interaction studies performed with sotorasib are summarised below:

Table: Summary of drug-drug interaction studies

Study Number	Evaluation	Results
20190315	Digoxin (P-gp substrate) DDI	*Sotorasib as perpetrator:* Geometric least squares mean ratio (test/reference) of digoxin AUC_{inf} and C_{max} were 1.214 and 1.914, respectively, when comparing digoxin coadministered with sotorasib (test) and digoxin administered alone (reference).
20190317	Metformin (MATE1 and MATE2-K substrate) DDI	*Sotorasib as perpetrator:* Geometric least squares mean ratio (test/reference) of metformin AUC_{inf} and C_{max} were 0.985 and 0.996, respectively, when comparing metformin coadministered with sotorasib (test) and metformin administered alone (reference). *Sotorasib as victim:* Geometric least squares mean ratio (test/reference) of sotorasib AUC_{inf} and C_{max} were 0.910 and 0.812, respectively, when comparing sotorasib coadministered with metformin (test) and sotorasib administered alone (reference).
20190318	Itraconazole DDI (CYP3A4 and P-gp Inhibitor)	*Sotorasib as victim:* Geometric least squares mean ratio (test/reference) of sotorasib AUC_{inf} and C_{max} were 1.261 and 1.040, respectively, when comparing sotorasib coadministered with itraconazole (test) and sotorasib administered alone (reference).
20190319	Rifampin DDI (OATP inhibitor and CYP3A4 inducer)	*Sotorasib as victim:* Geometric least squares mean ratio (test/reference) of sotorasib AUC_{inf} and C_{max} were 0.766 and 0.840, respectively, when comparing sotorasib coadministered with single-dose rifampin (test) and sotorasib administered as tablets (reference). Geometric least squares mean ratio (test/reference) of sotorasib AUC_{inf} and C_{max} were 0.487 and 0.647, respectively, when comparing sotorasib coadministered with multiple daily dosing of rifampin (test) and sotorasib administered alone (reference).
20190320	Omeprazole DDI	*Sotorasib as victim:* Geometric least squares mean ratio (test/reference) of sotorasib AUC_{inf} and C_{max} were 0.582 and 0.431, respectively, when comparing sotorasib administered with omeprazole in the fasted condition (test) and sotorasib administered alone in the fasted condition (reference).
20200199	Famotidine or omeprazole in fed state (PPI)	*Sotorasib as victim:* Geometric least-square mean ratios of sotorasib AUC_{inf} and C_{max} were 0.622 and 0.654, respectively when comparing sotorasib coadministered with famotidine (test) and sotorasib alone (reference) in fed conditions. Geometric least-square mean ratios of sotorasib AUC_{inf} and C_{max} were 0.430 and 0.349, respectively when comparing sotorasib coadministered with omeprazole (test) and sotorasib alone (reference) in fed conditions.
20170543 Substudy	Midazolam DDI (CYP 3A4 substrate)	*Sotorasib as inhibitor/inducer of CYP3A4:* Geometric least squares mean ratio (test/reference) of sotorasib AUC_{inf} and C_{max} were 0.47 and 0.52, respectively, when comparing midazolam coadministered with sotorasib (test) and midazolam administered alone (reference).

***Sotorasib as victim**:*
Coadministration of proton pump inhibitors, histamine-2 receptor antagonists, and strong CYP3A4 inducers may lead to decreased sotorasib exposure. This is reflected in the SmPC. There is negligible impact on sotorasib exposure by strong CYP3A4/P-gp inhibitors, and strong OATP1B1/1B3 inhibitors.

Sotorasib as perpetrator:
Clinical studies indicate that there is minimal impact of sotorasib on the exposure of MATE1/2K substrates, CYP2D6 substrates. However, as sotorasib is a clinically relevant inhibitor of P-gp and CYP3A4, caution is advised with coadministration of substrates of P-gp and sensitive CYP3A4 substrates.

Exposure relevant for safety evaluation
The exposure following a single dose of sotorasib 960 mg is 8400 ng/mL for C_{max} and 67000 ng.h/mL for $AUC_{0\text{-}inf}$. The elimination half-life is approximately 5.5 hours.

Conclusion on PK
The pharmacokinetics of sotorasib has been well characterised and described using a population PK model. The pharmacokinetics of sotorasib and related covariates have been reasonably well described.

IV.3 Pharmacodynamics
In support of the application, the following studies were submitted:

Amgen Study No.	Study Title	Status
Primary Pharmacodynamics – In Vitro		
R20150198	Biochemical Characterization of AMG 510 and Metabolites in $KRAS^{G12C/C118A}$ and $KRAS^{C118A}$ Nucleotide Exchange Assays	Non-GLP Final
R20150199	Cellular Characterization of AMG 510	Non-GLP Final
R20190078	Effects of AMG 510 on KRAS Signaling in NCI-H358 and MIA PaCa-2 Cells In Vitro o	Non-GLP Final
153894	In Vitro Combination Effects of AMG 510 with MAPK Pathway, PI3K Pathway, and Other Targeted Inhibitors	Non-GLP Final
Primary Pharmacodynamics – In Vivo		
R20150188	AMG 510 Inhibits Phospho-ERK1/2 Signaling in *KRAS p.G12C* Pancreatic MIA PaCa-2 T2 Tumors in Female Athymic Nude Mice	Non-GLP Final
R20190129	AMG 510 Inhibits ERK1/2 Phosphorylation Signaling and Results in Covalent Occupancy of $KRAS^{G12C}$ in *KRAS p.G12C* NSCLC NCI-H358 Tumors in Female Athymic Nude Mice	Non-GLP Final
R20150192	Effect of AMG 510 on Phospho-ERK1/2 Signaling at Early Timepoints (0.25 to 2 hours) in *KRAS p.G12C* Pancreatic MIA PaCa-2 T2 Tumors in Female Athymic Nude Mice	Non-GLP Final
R20150189	The Effect of Once-daily Dosing of AMG 510 on Tumor Growth in the *KRAS p.G12C* Pancreatic MIA PaCa-2 T2 Xenograft Model in Female Athymic Nude Mice	Non-GLP Final
R20150190	The Effect of Once-daily Dosing of AMG 510 on Tumor Growth in the *KRAS p.G12C* NSCLC H358 Xenograft Model in Female Athymic Nude Mice	Non-GLP Final
R20150191	The Effect of Once-dailing Dosing of AMG 510 on Tumor Growth in the *KRAS p.G12V* Colorectal Carcinoma SW480-1AC Xenograft Model in Female Athymic Nude Mice	Non-GLP Final
R20190130	AMG 510 Inhibited ERK 1/2 Phosphorylation in a Time and Dose Dependent Manner in Human KRAS *p.G12C* CRC Patient-derived Xenograft Tumors in Female NOD/SCID IL2rg (NSG) Mice	Non-GLP Final
R20190131	Once Daily Dosing of AMG 510 Inhibited Tumor Growth in a Human *KRAS p.G12C* CRC Patient-dervied Xenograft Model in Female NSG Mice	Non-GLP Final
R20180033	The Effect of AMG 510 in Combination with MEK Inhibitor 1009089 (PD-0325901) in the *KRAS p.G12C* NSCLC H358 Xenograft Model in Female Athymic Nude Mice	Non-GLP Final
153358	Effect of AMG 510 in Combination with Afatinib on Tumor Growth in the *KRAS p.G12C* NSCLC NCI-H358 Xenograft Model in Female Athymic Nude Mice	Non-GLP Final
153397	The Effect of AMG 510 in Combination with RMC-4550 (SHP2i), on Tumor Growth in the *KRAS p.G12C* NSCLC NCI-H358 Xenograft Model in Female Athymic Nude Mice	Non-GLP Final
R20180032	The Effect of AMG 510 in Combination with Carboplatin on Tumor Growth in the *KRAS p.G12C* NSCLC H358 Xenograft Model in Female Athymic Nude Mice	Non-GLP Final
R20180002	AMG 510 Inhibits ERK1/2 Phosphorylation in Murine Colorectal CT-26 *KRAS p.G12C*-H10 Tumors in Female BALB/c Mice	Non-GLP Final
R20190110	AMG 510 Inhibits ERK1/2 Phosphorylation in Murine Colorectal CT-26 *KRAS p.G12C*-H10 Tumors in Female BALB/c Mice	Non-GLP Final
R20190128	The Effect of Once-daily Dosing of AMG 510 on Tumor Growth in the Parental CT-26 *KRAS p.G12D* Colorectal Carcinoma Syngeneic Model in Female BALB/c Mice	Non-GLP Final
R20180034	The Effect of AMG 510 in Combination with anti-PD-1 antibody on Tumor Growth in the Murine Colorectal CT-26 *KRAS p.G12C*-H10 Syngeneic Model in Female BALB/c Mice	Non-GLP Final
R20180035	The Effect of AMG 510 on Tumor Infiltrating Lymphocytes in CT-26 *KRAS p.G12C*-H10 Colorectal Tumors in Female BALB/c Mice	Non-GLP Final

R20190105	The Effect of AMG 510 and/or Anti-PD-1 on CT-26 *KRAS p.G12C*-H10 Colorectal Tumors by Immunohistochemistry (IHC) in the Female BALB/c Mouse	Non-GLP Final
R20180036	The Effect of AMG 510 on Gene Expression and T-Cell Priming in CT-26 *KRAS p.G12C*-H10 Colorectal Tumors in Female BALB/c Mice	Non-GLP Final

BALB/c = Bagg albino, immunodeficient inbred mouse strain; CT-26 = murine colorectal tumor model; CRC = colorectal carcinoma; GLP = Good Laboratory Practices; hERG = human ether-à-go-go-related gene; IHC = immunohistochemistry; KRAS = Kirsten rat sarcoma viral oncogene homolog (gene); MAPK = mitogen-activated protein kinase; MIA PaCa-2 = human pancreatic cancer cell line; mRNA = messenger ribonucleic acid; NCI-H358 = human lung cancer cell line; NSCLC = non-small cell lung cancer; NOD/SCID = nonobese diabetic/severe combined immunodeficiency; PI3K = phosphoinositide-3 kinase; PDX = patient-derived xenograft; SW480-1AC = human colorectal carcinoma cell line.
a AMG 510 was previously known as 3365648 or AMG3365648.
b Studies 124452 and 124453: 3365626 was another KRASG12C inhibitor in early development that was not developed further.

There were 3 human circulating metabolites (AMG3368167 [M24], AMG3375854 [M10], and AMG3413829 [M18]) identified. Among the 3 metabolites, M18 has the same covalent warhead as sotorasib while M24 and M10 lack it. Consistently, only M18 maintains some effect on primary pharmacology endpoints; however, the effect was markedly reduced when compared to sotorasib.

Secondary pharmacology
Sotorasib selectivity was assessed *in vitro* against various targets including receptors, enzymes, ion channels, and transporters; minimal activity was observed, suggesting AMG 510 is highly selective for KRASG12C. In NCI-H358 cells, cysteine-proteome profiling demonstrated that sotorasib engaged only the cysteine at amino acid position 12 (Cys12) peptide from KRASG12C.

The sotorasib human ether-à-go-go-related gene (hERG) IC50 was 54.8 µM, and no clinically significant interaction with the hERG channel is expected over the proposed clinical dose range.

In a Good Laboratory Practices (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 hemodynamic parameters.

Secondary pharmacology screenings for the metabolites did not indicate any clinically relevant or significant off-target pharmacological activities. In vitro hERG assays for these metabolites did not indicate any clinically relevant or significant interactions.

Conclusion of pharmacodynamics
The mechanism of action of sotorasib is based on its binding to the KRASpG12C, thereby blocking its interaction with downstream effectors. The described mechanism of action is relevant to the clinical condition in which the proposed indication is sought. Preclinical studies show minimal effect KRAS wild type. Among the 3 metabolites, only M18 maintains some effect on primary pharmacology endpoints; however, the effect was markedly reduced when compared to sotorasib.

Secondary pharmacology screenings for sotorasib and the metabolites did not indicate any clinically relevant or significant off-target pharmacological activities. There was no clear correlation between concentration and effect with no statistically significant difference in the exposure-response analysis results between the 960 mg dose and the lower doses.
These results are confounded by the independent effects of baseline disease with subjects with lower baseline disease burden exhibited higher clearance and lower sotorasib exposure. No significant exposure-response relationships for treatment-related adverse events of

interest were identified.

IV.4 Clinical efficacy

The primary evidence for the efficacy of the proposed indication is based on results from the pivotal phase II portion of Study 20170543 in subjects with *KRAS p.G12C*-mutated advanced NSCLC who received 960 mg QD.

Efficacy data for NSCLC from the phase I portion of Study 20170543 were analysed separately and discussed as supportive data for efficacy.

The sotorasib development program also includes:

- An ongoing confirmatory, active-controlled phase III study for the treatment of NSCLC (Study 20190009; CodeBreaK 200),
- An ongoing phase I pharmacokinetics study in subjects of Chinese descent (Study20190147; CodeBreaK 105), and
- An ongoing phase 1b master protocol study with sotorasib administered in investigational regimens (as monotherapy and in various combination regimens) in subjects with *KRASp.G12C*-mutated advanced solid tumours (Study 20190135; CodeBreaK 101).

To characterise the initial safety, tolerability, pharmacokinetics, pharmacodynamics, and exposure response properties of sotorasib, the marketing authorisation application also includes 9 clinical pharmacology studies and pharmacokinetic data from the subjects in the pivotal phase 1/2 Study 20170543.

The applicant has summarised response data from 123 subjects (the phase II full analysis set) and overall survival data from 126 subjects (the phase 2 safety analysis set) with NSCLC treated with 960 mg QD sotorasib monotherapy (phase II NSCLC group) from primary analysis of the phase-2 portion of the study that occurred at the data cut-off date 01 September 2020. Also provided and discussed is the efficacy data from 124 subjects with NSCLC who were enrolled across 7 different sotorasib monotherapy dose cohorts (phase I NSCLC group) from interim analysis of the phase-I portion of study that occurred at the data cut-off date 06 July 2020.

Dose-response studies and main clinical studies

Study 20170543 is an ongoing phase I/II, open-label, single-group study evaluating sotorasib in the treatment of subjects with *KRAS p.G12C*-mutated solid tumours. The Phase I study included dose exploration (Part 1), dose expansion (Part 2).

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

Dose response study/ Dose finding study: STUDY 20170543 Phase I

The phase I part of the Study 20170543 was a first-in-human (FIH) dose exploration/expansion portion of the study.

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

The phase I portion of the study was conducted in 2 parts: part 1 – dose exploration and part 2 –dose expansion.

Part 1 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 I 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 sub-study of sotorasib with midazolam.

For the part 1a dose exploration, the dose level review team (DLRT) reviewed the safety data after each cohort completed enrolment and DLT evaluation and decided on the next dose level to be explored for the estimate of RP2D/MTD based on a Bayesian logistics regression model design (BLRM).

Antitumour activity was also monitored in terms of objective response rate (ORR) by tumour types.

For phase I portion of the study, sample sizes were based on practical considerations and were consistent with conventional oncology studies with the objective to estimate the MTD and evaluate initial safety and tolerability. Up to 283 subjects were to be enrolled, approximately 49 subjects in part 1 (dose exploration) and 154 subjects in part 2 (dose expansion). Additionally, a total of 40 to 80 subjects were allowed to be enrolled as backfill into 1 or more cohorts in phase 1 at doses that had been deemed to be safe and tolerable.

Phase 1
Subject Disposition
A total of 214 subjects were enrolled in the phase I part of the study. Out of these, a total of 124 subjects in phase 1 NSCLC group were enrolled in 7 dose cohorts in phase-1 portion of the study to be treated with sotorasib monotherapy.

Baseline Demographics

- Sex: 46 men (37.1%); 78 women (62.9%)
- Age: mean (SD; range): 67.6 (7.9; 49, 86) years
- Race: 101 white (81.5%); 12 Asian (9.7%); 6 black (4.8%); 5 other (4.0%)

Of 124 subjects, 121 (97.6%) had treatment-emergent adverse events, 72 subjects (58.1%) had grade ≥ 3 adverse events, and 59 subjects (47.6%) had serious adverse events. Twenty-one subjects (16.9%) had fatal adverse events; none of the events were considered related to sotorasib per investigator. Forty subjects (32.3%) had adverse events leading to dose modification of sotorasib and 12 subjects (9.7%) had adverse events leading to discontinuation of sotorasib.

No dose-limiting toxicities were observed in any cohort. The RP2D for sotorasib was determined to be 960 mg QD, which was the highest dose tested. Sotorasib was safe and had acceptable tolerability across dose levels tested in monotherapy.

Of 34 subjects in the ORR analysis set for phase 1 NSCLC 960 mg QD sotorasib monotherapy (fasted) dose cohort, 16 subjects had confirmed partial response, for an ORR of 47.1% (95% CI: 29.78, 64.87). The median (range) follow-up time for duration of response (DOR) was 9.0 (1.5, 15.0) months. The Kaplan-Meier estimate of median DOR was not reached (95% CI: 4.2, NE). Among 16 responders, the DOR was at least 3 months in 12 subjects (75.0%),at least 6 months in 5 subjects (31.3%), at least 9 months in 4 subjects (25.0%), and 1 subject (6.3%) had a DOR of at least 12 months.

Sotorasib exposure after QD administration, as assessed by C_{max} and AUC_{0-24h}, increased in a less than dose-proportional manner in the dose range of 180 mg to 960 mg. No accumulation was observed at the dose levels tested (180 mg to 960 mg). After 960 mg QD sotorasib administration to subjects in the fasted or fed states, the applicant states that the sotorasib exposure was similar between the fed state and the fasted state.

The 960 mg QD was selected as the proposed dose for the intended patient population.

Pharmacokinetics:
During dose exploration (part 1 of phase 1), sotorasib was administered orally either QD as a monotherapy over a dose range of 180 mg to 960 mg or BID as a monotherapy at 480 mg.

Geometric mean maximum plasma concentration (C_{max}) and area under the plasma concentration time curve (AUC) from time zero to 24 hours post dose (AUC_{0-24h}) parameters for both day 1 and day 8 were less than dose proportional. No accumulation was observed with multiple dosing at all dose levels tested. With 480 mg BID dosing, geometric mean AUC_{0-24h} increased, compared with 960 mg QD dosing, on both day 1 and day 8 of dosing.

During dose expansion (part 2), sotorasib was administered QD at the 960 mg dose to subjects with *KRAS p.G12C*-mutated advanced solid tumours as a monotherapy in the fasted and fed states (part 2a and part 2d). Geometric mean C_{max} and AUC_{0-24h} were similar to the results observed for the 960 mg QD dose cohorts during dose exploration (part 1).

As a post-marketing commitment to support approval in the United States, a dose comparison sub-study is being added to the phase 2 portion of Study 20170543 (phase 2 Part B). Study 20170543 is the phase 1/2 study in which the phase 2 non-small cell lung cancer (NSCLC) cohort (Part A) formed the primary basis of the sotorasib Marketing Authorisation

Application submitted globally for the treatment of patients with KRAS G12C-mutated non-small cell lung cancer (NSCLC). The aim of the sub-study is to compare the safety and efficacy of sotorasib 960 mg daily (QD) versus a lower daily dose (240 mg QD), as well as to further characterise serious adverse events, including gastrointestinal toxicity, in subjects with locally advanced or metastatic *KRAS p.G12C*-mutated NSCLC who have received at least 1 prior systemic therapy.

The study will include a broader population, where the KRAS p G12C mutation status will be identified by local or central testing. Subjects will be randomised 1:1 to receive sotorasib at either 240 mg QD or 960 mg QD. A 240 mg QD dose, administered as two 120mg tablets, will be used as the lower dose in this dose comparison study.

The study design is considered acceptable. The proposed sample size estimate of 200 was based on objective response rate difference between the two groups. The proposed sample size is considered reasonable given the assumptions made.

Main study- STUDY 20170543 Phase II
The phase II part of the Study 20170543 is the pivotal open-label, non-randomised single-group portion of the study designed to evaluate efficacy and safety/tolerability of sotorasib as monotherapy in subjects with KRAS p.G12C-mutated advanced solid tumours (NSCLC, CRC, and other tumours).

Methods
Based on nonclinical evidence suggesting that sotorasib had no therapeutic effect on tumours lacking KRAS p.G12C mutation, study 20170543 only enrolled subjects with tumours that had this mutation.

Approximately 250 subjects (at least 105 with NSCLC and 60 with CRC) were to be enrolled.

Sotorasib was administered orally once daily (QD) and without interruption (i.e., no planned off treatment days). Daily treatment with sotorasib was to continue without interruption (i.e., no planned off treatment days) until disease progression (unless subject is eligible for continued treatment) or until discontinuation of treatment due to protocol-defined reasons including subject request, adverse event, intolerance to sotorasib treatment, noncompliance, or requirement for alternative treatment.

Study duration is approximately 4 years (28-day screening, 6 to 12 months of treatment, and 3 years of long-term follow-up) for each subject.

Tumour response was measured by contrast enhanced CT/MRI and assessed per RECIST 1.1 by an independent radiological central laboratory.

Interim safety reviews were conducted after 30, 50, 70, and 100 subjects had been enrolled and treated with sotorasib for at least 21 days (enrolment was not to be held for completion of these safety reviews). Interim futility analyses were conducted.

Subjects were to have a safety follow-up visit 30 days (±7 days) after the last dose of sotorasib, before any new anticancer treatment was started. After the safety follow-up visit, subjects were to be followed long-term for health condition, disease status, and subsequent anticancer treatment every 12 weeks (± 2 weeks) up to 3 years after the last subject was

enrolled or until withdrawal of consent, loss to follow-up, or subject death, whichever occurred first.

The primary analysis of the phase II portion of Study 20170543 was planned for approximately 8.5 months after enrolment of 105 subjects with NSCLC or 60 subjects with colorectal cancer in the phase 2 portion of the study.

The primary analysis data cut-off date was determined based on the assumption that most responders achieved responses by the first or second scan (i.e., 1.5 to 3 months from the start of treatment).

Eligible subjects were men or women ≥ 18 years of age, with KRAS p.G12C-mutated advanced NSCLC, colorectal cancer, or other solid tumours.

Patients chosen were to have progressed after receiving prior therapy.

A confirmatory phase III trial is ongoing comparing sotorasib against docetaxel in the treatment of patients with locally advanced, unresectable or metastatic NSCLC with mutated KRASpG12C. The Phase 3 inclusion criteria specifies that NSCLC subjects must receive prior platinum therapy and PD-L1 therapy, unless there is a medical contraindication.

Treatments
The dose (and schedule) administered in phase 2 was the RP2D of 960 mg QD. Sotorasib was provided as 120 mg tablets.

Daily treatment with sotorasib was to continue without interruption (i.e., no planned off treatment days) until disease progression (unless subject is eligible for continued treatment) or until discontinuation of treatment due to protocol-defined reasons including subject request, adverse event, intolerance to sotorasib treatment, noncompliance, or requirement for alternative treatment.

For the phase II 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.

Efficacy endpoints and statistical methods

Efficacy Endpoint	Definition	Primary Summary and Analysis Method
Primary[a]		
objective response rate (ORR)	Proportion of subjects with a best overall response of confirmed complete response or confirmed partial response, measured by CT or MRI and assessed per RECIST 1.1 by blinded independent central review (BICR). Complete response and partial response required CT or MRI repeat assessment at least 4 weeks after the first detection of response.	The number and percentage of subjects with a best overall response of complete response, partial response, stable disease, progressive disease, not evaluable was provided. Objective response rate was summarized with Clopper-Pearson exact 95 CI[b]. Subjects without a post-baseline tumor assessment were considered non-responders.
Secondary[a]		
duration of response (DOR)	Time from first partial response or complete response 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 partial response or complete response per RECIST 1.1.	Summarized with Kaplan-Meier median, quartiles and rates for select durations (eg, 3, 6, 9, 12 months)
disease control rate (DCR)	Proportion of subjects whose best overall response was complete response, partial response, or stable disease > 5 weeks.	Summarized as for ORR.
time to response (TTR)	Time from the date of the first dose of sotorasib to the date of the first partial response or complete response. The TTR was calculated only for subjects who achieved a confirmed best overall response of partial response or complete response per RECIST 1.1.	Summarized by the non-missing sample size (n), mean, standard deviation, median, minimum, and maximum for responders.
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.	Summarized with Kaplan-Meier curves, median, quartiles, and rates for selected timepoints (e.g., 6 and 12 months).
overall survival (OS)	Time from the date of the first dose of sotorasib until the date of death due to any cause.	Summarized with Kaplan-Meier curves, median, quartiles, and rates for selected timepoints (e.g., 12 months).
duration of stable disease (phase 1 only)	Time from the date of the first dose of sotorasib to the date of disease progression or death due to any cause. Only calculated in subjects with best overall response of stable disease.	Summarized as for DOR.

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

[a] Primary and secondary endpoints in this table are based on the phase-2 portion of the study and the phase-1 parts other than part 2e. All efficacy endpoints were primary endpoints for phase 1 part 2e.

[b] Clopper and Pearson, 1934

Source: Study 20170543 Statistical Analysis Plan

Results

The study is ongoing. This study is being conducted at 59 centres in the United States, Canada, France, Belgium, Germany, Switzerland, Austria, Japan, South Korea, Australia, and Brazil. The data presented includes results from the date of first subject enrolment into the phase II portion of the study to the analysis data cut-off date (01 September 2020).

Numbers analysed (NSCLC)

Analysis Set	Definition
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.
Phase 2 safety analysis set	All subjects that enrolled in phase 2 and received at least 1 dose of sotorasib. This analysis set was to be used to evaluate safety and overall survival in the primary and final analyses.
Pharmacokinetic analysis set	All enrolled subjects who received ≥ 1 dose of sotorasib and had ≥ 1 pharmacokinetic sample collected. Subjects were excluded from the data set if they had significant protocol deviations affecting the data analysis or if key dosing or sampling information was missing. This analysis set was used to evaluate the pharmacokinetic parameters of sotorasib.
Phase 2 ORR analysis set	All subjects in the phase 2 full analysis set who had the opportunity to be followed for at least 7 weeks starting from day 1. Subjects who stopped disease assessments prior to 7 weeks were included if the data cutoff was at least 7 weeks after their first dose date. This analysis set was used for the interim futility analysis and interim summary of ORR/DOR/TTR in CRC and Other solid tumors cohorts.

BICR = blinded independent central review; DLT = dose-limiting toxicity; ORR = objective response rate; DOR = duration of response; TTR = time to response; RP2D = recommended phase 2 dose

Phase 2 960 mg QD Fasted	126 (48.3)
Safety analysis set	126 (48.3)
Full analysis set	123 (47.1)
ORR analysis set	123 (47.1)
Investigator efficacy analysis set	126 (48.3)
Investigator ORR analysis set	126 (48.3)

Of a total of 126 subjects with NSCLC, 123 subjects were included in the full analysis set, and 3 subjects were excluded as they did not have ≥1 measurable lesion according to BICR.

Outcomes and estimation

The primary endpoint of ORR (complete response + partial response) 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 123 subjects; 95% CI: 28.84, 46.58); 2 subjects (1.6%) achieved complete response and 44 subjects (35.8%) achieved partial response.

Subgroup analyses were conducted to explore the consistency of the treatment effect between subgroups. Subjects who had not received prior platinum-based chemotherapy had a higher response rate compared to the full cohort and to those who had received prior platinum-based therapy. Subjects with brain metastasis had lower response rate compared to the full cohort and to those without brain metastasis. However, the subgroup analysis interpretation in a single cohort study with small sample size in each subgroup may be limited.

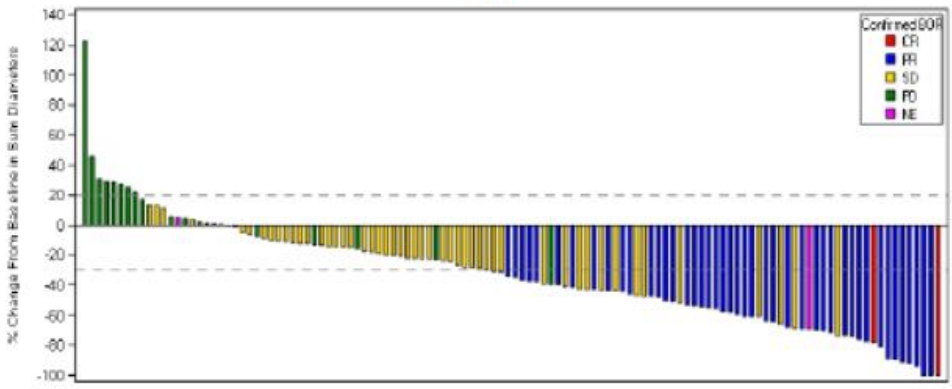
Sensitivity analyses were conducted for best overall tumour response to evaluate concordance between assessments by BICR laboratory and the study centre investigator. The concordance rates between central review and investigator for objective response, best overall response, and disease progression were 82.9%, 72.7%, and 78.0%, respectively.

Summary of Objective Response (Assessed by BICR per RECIST 1.1 Criteria) (Phase 2 NSCLC in Full Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 123)
Best objective response - n (%)	
Complete response (CR)	2 (1.6)
Partial response (PR)	44 (35.8)
Stable disease	53 (43.1)
Progressive disease (PD)	20 (16.3)
Not evaluable (NE)	2 (1.6)
Not done	2 (1.6)
Objective response rate (ORR)	
Number of overall responders - N1 (%)	46 (37.4)
95% CI[a]	(28.84, 46.58)

BICR = blinded independent central review; N = Number of subjects in the analysis set; n = Number of subjects with observed data; NSCLC = non-small cell lung cancer; QD = once daily; RECIST 1.1 = response evaluation criteria in solid tumors
Phase 2 data cutoff date of 01 September 2020.
[a] Exact 95% confidence interval was calculated using the Clopper-Pearson method.
Source: Study 20170543 Phase 2 CSR Table 14n-4.1.1

Waterfall Plot of Best Tumour Shrinkage by Central Review (Phase 2 NSCLC Full Analysis Set)



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

Program: /usr/sdata/stat/amg510/ond20170543/analysis/primary_202009_post-hoc/figures/f-wfall-tmr-no-clo-p2fas.sas
Output: f14n-04-001-401-wfall-tmr-no-clo-p2fas.rtf (Date Generated: 20OCT2019:40) Source Data: adam.adsl, adam.adrs, adam.adtr

BOR = best overall response; CR = complete response; PD = progressive disease; PR = partial response; NE = not evaluable; NSCLC = non-small cell lung cancer; SD = stable disease
Percent change from baseline in sum of diameters only considers tumor assessments before and including the first assessment where time point response is progressive disease. Three subjects without baseline target lesions and 3 subjects without post-baseline percent changes are not shown.
One CR whose reduction < 100% is because target lesions are in lymph nodes.
Source: Figure 14n-4.1.401 of Study 20170543 Phase 2

Subgroup analyses

Table: Subgroup analysis of Objective Response by Central Review (Phase 2 NSCLC in full analysis set)

	NSCLC (N = 123) Events[a]/Subjects (%) (95% CI)
Age at baseline	
< 65 years	21/65 (32.3) (21.2, 45.1)
≥ 65 years	25/58 (43.1) (30.2, 56.8)
Prior lines of anti-cancer therapy	
1	22/53 (41.5) (28.1, 55.9)
2	14/43 (32.6) (19.1, 48.6)
> 2	10/27 (37.0) (19.4, 57.6)
Prior anti PD-1 or anti PD-L1	
Yes	41/112 (36.6) (27.7, 46.2)
No	5/11 (45.5) (16.7, 76.6)
Prior platinum-base chemotherapy	
Yes	37/110 (33.6) (24.9, 43.3)
No	9/13 (69.2) (38.6, 90.9)
Prior platinum-base chemotherapy and prior anti PD-1 or anti PD-L1	
Yes	32/99 (32.3) (23.3, 42.5)
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%	9/22 (40.9) (20.7, 63.6)
≥ 50%	9/34 (26.5) (12.9, 44.4)
ECOG status at baseline	
0	16/37 (43.2) (27.1, 60.5)
1	30/86 (34.9) (24.9, 45.9)
Race	
White	42/101 (41.6) (31.9, 51.8)
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)

Table: Subgroup analysis of Objective Response by Central Review (Phase 2 NSCLC in full analysis set)

	NSCLC (N = 123) Events*/Subjects (%) (95% CI)
Sex	
Male	26/61 (42.6) (30.0, 55.9)
Female	20/62 (32.3) (20.9, 45.3)
Histopathology type	
Squamous	0/1 (0.0) (0.0, 97.5)
Non-squamous	46/122 (37.7) (29.1, 46.9)
Metastatic	
Yes	44/119 (37.0) (28.3, 46.3)
No	2/4 (50.0) (6.8, 93.2)
Liver metastasis	
Yes	9/26 (34.6) (17.2, 55.7)
No	37/97 (38.1) (28.5, 48.6)
Brain metastasis	
Yes	4/26 (15.4) (4.4, 34.9)
No	42/97 (43.3) (33.3, 53.7)
Bone metastasis	
Yes	19/58 (32.8) (21.0, 46.3)
No	27/65 (41.5) (29.4, 54.4)
Smoking history	
Never	1/5 (20.0) (0.5, 71.6)
Current	4/15 (26.7) (7.8, 55.1)
Former	41/100 (41.0) (31.3, 51.3)
Region	
North America	35/79 (44.3) (33.1, 55.9)
Europe	8/28 (28.6) (13.2, 48.7)
Asia	1/11 (9.1) (0.2, 41.3)
Rest of the world	2/5 (40.0) (5.3, 85.3)

Table: Concordance In Assessment of Objective Response by Central Review and by Site Investigator 9Phase 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)

The primary analysis success threshold has been met with ORR of 37.4% (95% CI: 28.84, 46.58). The lower bound of the 95% CI for ORR excludes 23%. The results however are borderline. The majority of subjects achieved complete or partial response and only 2 patients achieved complete response.

The ORR using investigator assessment was lower compared to central review with ORR of 30.2% (95% CI: 22.31, 38.97).

The subgroup analyses, including subgroups defined by prior platinum therapy and Anti PD-1 status, are generally supportive of the primary analysis.
There was more agreement between central and local review in the absence of CR/PR in 57.7% of the cases.

The potential sources of variability between investigator and central assessment mainly due to evaluation variability are noted. However, assessment of agreement should be restricted to only those lesions where central and investigator assessment are done on the same lesion and the same lesion counts and using the same criteria.

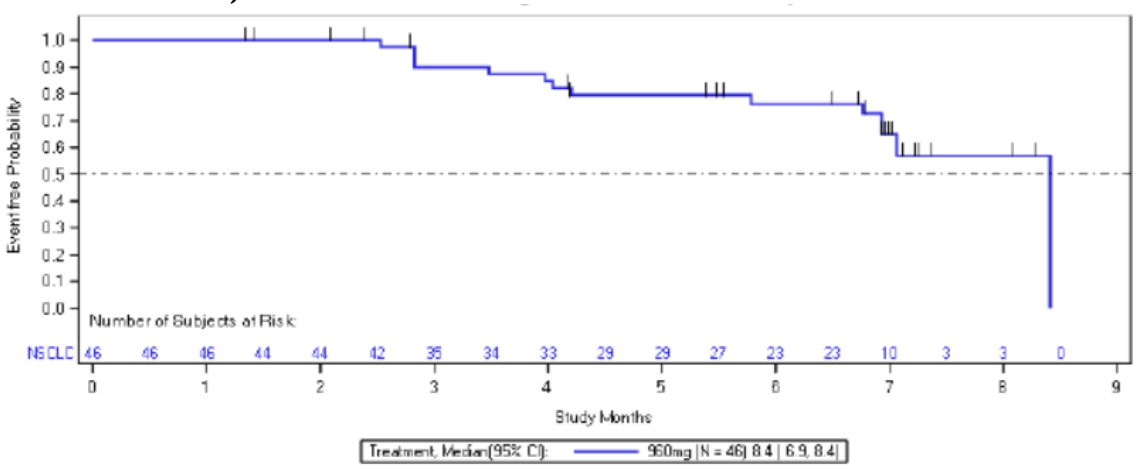
The agreement between the central and local investigator radiologic reviews was assessed by Cohen's kappa statistics. This is an appropriate statistic for assessing agreement. The concordance rate between assessments of best overall response between central and investigator review was 73.0%, with a Cohen's kappa statistic of 0.57 (95% CI: 0.45, 0.70), which indicates a moderate level of agreement between central and investigator assessment. The results should be interpreted with caution given the concern about the potential sources of variability.

Secondary Efficacy Endpoints
Duration of response (DOR) Results
Table: Duration of Response (response assessed by BICR per RECIST 1.1 Criteria)

	Phase 2 NSCLC 960 mg QD Fasted (N = 123)
Duration of objective response (DOR)[a]	
Observed duration ≥ 3 months - n (%)	35 (76.1)
Observed duration ≥ 6 months - n (%)	23 (50.0)
Observed duration ≥ 9 months - n (%)	0 (0.0)
Observed duration ≥ 12 months - n (%)	0 (0.0)
Duration of response (KM) (months)	
25th percentile (95% CI)	6.8 (3.5, 7.1)
Median (95% CI)	8.4 (6.9, 8.4)
75th percentile (95% CI)	8.4 (NE, NE)
Min, Max (+ for censored)	1.3+, 8.4
Kaplan-Meier estimate (95% CI)[b]	
At 3 months	89.9 (75.3, 96.1)
At 6 months	76.2 (59.1, 86.9)
At 9 months	0.0 (NE, NE)
At 12 months	0.0 (NE, NE)
Follow-up time for DOR[c] (KM) (months)	
25th percentile (95% CI)	5.5 (2.8, 6.7)
Median (95% CI)	6.9 (5.6, 7.0)
75th percentile (95% CI)	7.1 (7.0, 8.1)
Min, Max (+ for censored)	1.3, 8.4+

Phase 2 data cut-off date 01 September 2020.
BICR = blinded independent central review; CI = confidence interval; DOR = duration of response; N = Number of subjects in the analysis set; n = Number of subjects with observed data; KM = Kaplan-Meier; N = Number of subjects in the analysis set. N = Number of subjects with observed data; NE = not estimable; NSCLC = non-small cell lung cancer; QD = once daily; RECIST 1.1 = response evaluation criteria in solid tumours
; Months are derived as days x (12/365.25).
[a] Duration of response is 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: Study 20170543 Phase 2 CSR Table 14n-4.1.

Figure: Kaplan-Meier Plot of Duration of Response (response assessed by BICR per RECIST 1.1 Criteria)



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

Program: /userdata/stat/amg510/onc/20170543/analysis/primary/figure/f-eff-km.sas
Output: f14n-04-001-001-eff-km-dor-nsclc-p2fas.rtf (Date Generated: 19OCT20 19:19) Source Data: adam.adtl, adam.adtte

BICR = blinded independent central review; CI = confidence interval; NSCLC = non-small cell lung cancer; QD = once daily; RECIST 1.1 = response evaluation criteria in solid tumors
Phase 2 data cutoff date of 01 September 2020. Censor indicated by vertical bar. Radiological progression or death (whichever occurs earlier after confirmed partial response or confirmed complete response) is an event.
Source: Study 20170543 Phase 2 CSR Figure 14n-4.1.1

Disease Control Rate (DCR)

The DCR (defined as the proportion of subjects whose best objective response was confirmed complete response, partial response, or stable disease ≥ 5 weeks per RECIST 1.1 criteria assessed by BICR) for subjects in phase 2 NSCLC group was 80.5% (95% CI: 72.37; 87.08). Of 123 subjects in the full analysis set of the phase 2 NSCLC group, 53 subjects (43.1%) had stable disease.

Disease Control Rate (Response Assessed By BICR per RECIST 1.1 Criteria) (Phase 2 NSCLC Responders in Full Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 123)
Disease control rate (DCR) - n (%)	99 (80.5)
95% CI[a]	(72.37, 87.08)

BICR = blinded independent central review; CI = confidence interval; N = Number of subjects in the analysis set; n = Number of subjects with observed data; NSCLC = non-small cell lung cancer; QD = once daily; RECIST 1.1 = response evaluation criteria in solid tumors
Phase 2 data cutoff date of 01 September 2020.
[a] Exact 95% confidence interval was calculated using the Clopper-Pearson method
Source: Study 20170543 Phase 2 CSR Table 14n-4.1.1

A median duration of response of 6.9 months and a disease control rate of 80.5% are shown. These could be considered clinically relevant in a heavily treated population.

Time to Response

Time to response was measured from the date of the first dose of sotorasib to the date of the first complete response or partial response observed; calculated only for subjects who achieved a best objective response of confirmed partial response or better per RECIST 1.1 criteria assessed by BICR.

Time to Response (Response Determined per RECIST 1.1 Criteria by BICR) (Phase 2 NSCLC in Full Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 123)
Time to objective response (months)[a]	
Number of subjects with objective response	46
Mean (SD)	1.95 (1.23)
Median	1.35
Q1, Q3	1.25, 2.69
Min, max	1.2, 6.1

BICR = blinded independent central review; N = Number of subjects in the analysis set; NSCLC = non-small cell lung cancer; QD = once daily; RECIST 1.1 = response evaluation criteria in solid tumours

[a] Time to response are calculated among confirmed responders N1.

Source: Study 20170543 Phase 2 CSR Table 14n-4.1.1

Progression-free survival

Progression-free survival was measured from the date of the first dose of sotorasib to the date of disease progression (as determined per RECIST 1.1 criteria by BICR) or death due to any cause, whichever occurred first. Subjects who had no disease progression and did not die while on study were censored at the last disease assessment date.

Summary of Progression-Free Survival (Progression Assessed By BICR per RECIST 1.1 Criteria) (Phase 2 NSCLC in Full Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 123)
Subject Status	
Events - n (%)	70 (56.9)
Progressive disease	60 (48.8)
Death due to any cause	10 (8.1)
Censored - n (%)	53 (43.1)
On study without disease progression	40 (32.5)
No evaluable post-baseline disease assessment	0 (0.0)
Missed more than 1 consecutive assessments	4 (3.3)
Started new anticancer therapy	6 (4.9)
Withdrew consent	3 (2.4)
Off study due to sponsor decision	0 (0.0)
Lost to follow-up	0 (0.0)
Progression-free survival (KM) (months)	
25th percentile (95% CI)	2.8 (1.6, 3.9)
Median (95% CI)	6.7 (4.9, 8.1)
75th percentile (95% CI)	11.5 (9.6, 11.5)
Min, Max (+ for censored)	0.3+, 11.5
Kaplan-Meier estimate (95% CI)[a]	
At 3 months	67.5 (58.2, 75.2)
At 6 months	51.5 (41.9, 60.4)
At 9 months	36.2 (26.7, 45.8)
At 12 months	0.0 (NE, NE)
Follow-up time for PFS[b] (KM) (months)	
25th percentile (95% CI)	6.8 (5.4, 8.2)
Median (95% CI)	8.3 (8.2, 8.3)
75th percentile (95% CI)	8.4 (8.3, 9.5)
Min, Max (+ for censored)	0.3, 11.5+

BICR = blinded independent central review; CI = confidence interval; 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; RECIST 1.1 = response evaluation criteria in solid tumours.

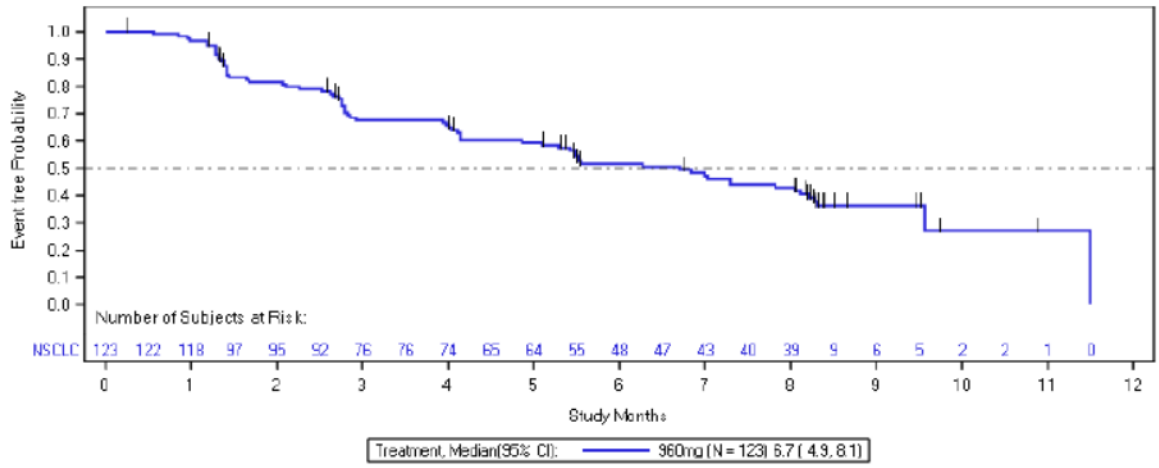
Phase 2 data cut-off date of 01 September 2020

[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.

Source: Study 20170543 Phase 2 CSR Table 14n-4.2.1

Kaplan-Meier Plot of Progression-Free Survival (Progression Assessed By BICR per RECIST 1.1 Criteria) (Phase 2 NSCLC in Full Analysis Set)



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

Program: /userdata/stat/amg510/ond20170543/analysis/primary/figures/f-eff-km.sas
Output: f14n-04-002-001-eff-km-pfs-nsclc-p2fas.rtf (Date Generated: 18OCT20 19:18) Source Data: adam.adsl, adam.adtte

BICR = blinded independent central review; CI = confidence interval; NSCLC = non-small cell lung cancer; RECIST 1.1 = response evaluation criteria in solid tumors
Phase 2 data cutoff date of 01 September 2020.
Censor indicated by vertical bar. Radiological progression or death (whichever occurs earlier) is an event.
Source: Study 20170543 Phase 2 CSR Figure 14n-4.2.1

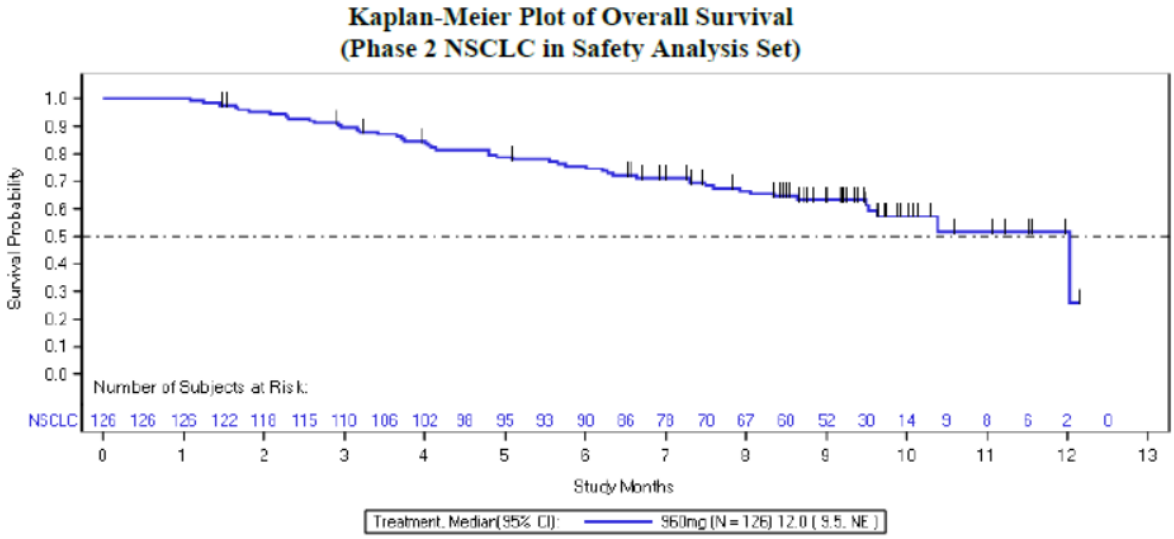
Overall Survival

The median (range) follow-up time for OS was 9.3 (1.1+, 12.2) months. As of the data cut-off date, of 126 subjects in the phase 2 NSCLC safety analysis set, 48 subjects (38.1%) died and 78 subjects (61.9%) were censored. Of those 78 subjects, 69 subjects (54.8%) were alive at the last follow-up visit and 9 subjects (7.1%) withdrew consent.
The Kaplan-Meier estimate of median (95% CI) OS was 12.0 months (9.5, NE). The Kaplan-Meier estimates of survival were 89.5% at 3 months, 75.5% at 6 months, 63.4% at 9 months, and 51.6% at 12 months.

Summary of Overall Survival
(Phase 2 NSCLC in Safety Analysis Set)

	Phase 2 NSCLC 960 mg QD Fasted (N = 126)
Subject Status	
Events - n (%)	48 (38.1)
Death due to any cause	48 (38.1)
Censored - n (%)	78 (61.9)
Alive at last follow-up	69 (54.8)
Lost to follow-up	0 (0.0)
Withdrew consent	9 (7.1)
Off study due to sponsor decision	0 (0.0)
Overall survival (KM) (months)	
25th percentile (95% CI)	6.0 (4.1, 7.9)
Median (95% CI)	12.0 (9.5, NE)
75th percentile (95% CI)	NE (12.0, NE)
Min, max (+ for censored)	1.1, 12.2+
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	63.4 (53.8, 71.5)
At 12 months	51.6 (36.7, 64.5)
Follow-up time for OS[b] (KM) (months)	
25th percentile (95% CI)	8.5 (7.3, 8.8)
Median (95% CI)	9.3 (9.0, 9.5)
75th percentile (95% CI)	9.8 (9.6, 10.2)
Min, Max (+ for censored)	1.1+, 12.2

CI = confidence interval; KM = Kaplan-Meier; N = Number of subjects in the analysis set; NE = not evaluable; NSCLC = non-small cell lung cancer; OS = overall survival; QD = once daily.
Phase 2 data cut-off date of 01 September 2020
[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.
Source: Study 20170543 Phase 2 CSR Table 14n-4.3.1



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

Program: /userdata/stat/amg510/onc/20170543/analysis/primary/figures/f-eff-km.sas
Output: f14n-04-003-001-eff-km-osm-nsclc-p2saf.rtf (Date Generated: 18OCT2019:19) Source Data: adam.adsl, adam.adtte

CI = confidence interval; NSCLC = non-small cell lung cancer
Phase 2 data cut-off date of 01 September 2020.
Censor indicated by vertical bar. Death is an event.
Source: Study 20170543 Phase 2 CSR Figure 14n-4.3.1

Summary of efficacy for trial 20170543 Phase 2 portion

Endpoint	Median	95% CI	Median Follow-up Time (Range) (Months)
ORR (%)[a]	37.4	28.84, 46.58	-
DCR (%)[a]	80.5	72.37, 87.08	-
DOR (months)[a]	8.4	6.9, 8.4	6.9 (1.3, 8.4+)
TTR (months)[a]	1.35 (range: 1.2, 6.1)	-	-
PFS (months)	6.7	4.9, 8.1	8.3 (0.3, 11.5+)
KM estimate at 3 months	67.5	58.2, 75.2	
KM estimate at 6 months	51.5	41.9, 60.4	-
OS (months)	12.0	9.5, NE	9.3 (1.1+, 12.2)
KM estimate at 6 months	75.5	66.8, 82.2	-
KM estimate at 12 months	51.6	36.7, 64.5	-

- = not applicable; + = censored; BICR = blinded independent central review; DCR = disease control rate, DOR = duration of response; KM = Kaplan-Meier; NE = not estimable; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = response evaluation criteria in solid tumours; TTR = time to response

[a] The tumour response was evaluated by contrast-enhanced magnetic resonance imaging/computed tomography (MRI/CT) according to RECIST 1.1 by BICR. Radiographic response (complete response, partial response) required confirmation by a repeat scan at least 4

Analysis of efficacy endpoints including PFS and OS to cut-off date 01 December 2020
(providing 90 days of additional data submitted during MHRA assessment from the results provided with the original marketing authorisation application)

Efficacy results for Primary Analysis and Efficacy Update

	Primary Analysis 01 September 2020 data cut-off	Efficacy Update 01 December 2020 data cut-off
Number of responders/N (evaluable)	46/123	46/124
ORR (95% CI)	37.4% (28.8, 46.6)	37.1% (28.6, 46.2)
Median DOR (95% CI), months	8.4 (6.9, 8.4)	10.0 (6.9, 11.1)
Median PFS (95% CI), months	6.7 (4.9, 8.1)	6.8 (5.1, 8.2)
Median OS (95% CI), months	12.0 (9.5, NE)	12.5 (10.0, NE)
Median TTR (min, max), months	1.35 (1.2, 6.1)	1.35 (1.2, 10.1)

N = number of evaluable subjects; DOR = duration of response; NE = not evaluable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; TTR = time to response

Source: Table 5 of Module 2.5, Clinical Overview; Table 14n-4.1.1, Table 14n-4.2.1, and Table 14n-4.3.1 of 20170543 Supplemental CSR

In summary, sotorasib monotherapy continued to demonstrate a clinically meaningful and durable objective response among subjects with advanced NSCLC, with an ORR of 37.1% (95% CI: 28.60, 46.23) and a median DOR of 10.0 months (95% CI: 6.9, 11.1).
The updated analyses support the evidence of benefit as concluded in the previous analyses.

The applicant has provided a list of treatments that could be used in the second line setting in NSCLC (not target based). These are valid options that would be used the patients with NSCLC that may be KRASpG12C mutation positive. The comparison is indirect. There is a suggestion that sotorasib may provide improved survival over some of the available therapies. However, the survival may be better with some of the treatments, including checkpoint inhibitors. These have also now moved to earlier line therapy for patients with NSCLC. The proposed indication clarifies that sotorasib is meant to be used after progression following chemotherapy and/or immunotherapy.

Patient-reported Outcomes (PRO)
The PRO-related objective in phase 2 was to explore the changes in cancer-specific symptoms and overall health status using PRO instruments validated for use in lung cancer. Overall, compliance with the protocol specified schedule for PRO completion was high, which allowed for an informative exploration of the PRO data. At baseline, 78% of subjects completed at least 1 PRO assessment and the PRO compliance rate at each timepoint (percent of subjects completing a PRO assessment among those expected to complete an assessment) was > than 85% for cycles 2 to 6, > 70% for cycles 7 to 13, and < 60% during later cycles. At enrolment into the study, subjects in the phase 2 NSCLC group reported a high symptomatic burden and impaired physical function and quality of life which was comparable to normative values for patients with NSCLC and higher than the general population. Over time, a trend toward improvement (or stabilisation) was observed in the severity of key lung cancer symptoms of cough, dyspnoea and chest.

Clinical studies in special populations
Natural History of Patients With KRAS p.G12C-mutated NSCLC
To better characterise the natural history of and outcomes for patients with KRAS pG12C-mutated advanced NSCLC, and therefore the unmet medical need, the Applicant conducted 3 real-world evidence studies in the United States:

- Study 20200097 (N = 743), a retrospective cohort study of patients with *KRAS p.G12C*-mutated advanced NSCLC in the Flatiron Health Foundation Medicine Clinico-Genomic Database.

- Study 20200132 (N = 7069), companion study to Study 20200097, a retrospective cohort study of patients with advanced NSCLC (ie, regardless of *KRAS p.G12C* mutation), in the Flatiron Health-Foundation Medicine Clinico-Genomic Database.
- Study 20180277 (N = 416), a retrospective study of patients with *KRAS p.G12C*-mutated metastatic NSCLC in the American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) database.

These studies showed that outcomes in second or later lines of therapy for patients with KRAS p.G12C mutated advanced NSCLC were as poor as the overall patient population with advanced NSCLC.

Efficacy Results: Phase I part of the study 20170543
The tumour response was evaluated by contrast-enhanced magnetic resonance imaging/computed tomography (MRI/CT) according to RECIST 1.1 by BICR. Radiographic response (complete response, partial response) required confirmation by a repeat scan at least 4 weeks after the first documentation of response and could have been delayed until the next scheduled scan to avoid unnecessary procedures.

As the phase I portion of Study 20170543 study was a FIH study, the effect of food on safety, tolerability, and PK of sotorasib was also evaluated in a food effect assessment substudy. The results of this substudy indicate that sotorasib can be taken with or without food.

The phase I portion of the study had 2 dose cohorts for which 960 mg QD sotorasib monotherapy was administered to previously untreated NSCLC subjects: 1 cohort for subjects in the fasted state (part 1a and part 2a) and 1 dose cohort for subjects in the fed state (part 1d and part 2d).

Efficacy results for subjects with previously untreated NSCLC in phase 1 NSCLC 960 mg QD sotorasib monotherapy (fasted) dose cohort are provided in the table below.

Summary of Efficacy Results for Subjects With Previously Treated NSCLC in Phase 1 960 mg QD Sotorasib Monotherapy (Fasted) Dose Cohort (N = 34)

Endpoint	Median	95% CI	Median Follow-up Time (Range) (Months)
ORR (%)	47.1	29.78, 64.87	-
DCR (%)	94.1	80.32, 99.28	-
DOR (months)	NE	4.2, NE	9.0 (1.5, 15.0)
Duration of stable disease (months)	2.9	2.6, 5.2	12.5 (1.3, 12.5)
TTR (months)	1.41 (range: 0.8, 8.3)	-	-
PFS (months)	5.3	3.1, 8.1	11.1 (1.2+, 16.3)
KM estimate at 6 months	42.9	25.5, 59.2	-
KM estimate at 12 months	31.2	15.6, 48.2	-
OS (months)	7.6	6.3, NE	12.2 (2.5+, 17.1)
KM estimate at 6 months	72.2	53.3, 84.4	-
KM estimate at 12 months	41.2	23.8, 57.9	-

- = not applicable; + = censored; BICR = blinded independent central review; DCR = disease control rate, DOR = duration of response; KM = Kaplan-Meier; NE = not estimable; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = response evaluation criteria in solid tumors; TTR = time to response
[a] The tumor response was evaluated by contrast-enhanced magnetic resonance imaging/computed tomography (MRI/CT) according to RECIST 1.1 by BICR. Radiographic response (complete response, partial response) required confirmation by a repeat scan at least 4 weeks after the first documentation of response and could have been delayed until the next scheduled scan to avoid unnecessary procedures.

Conclusions on clinical efficacy
The evidence of clinical efficacy in the proposed patient population is provided by the single arm phase I/II study. The 960-mg dose was selected as the proposed dose for the intended previously treated patient population. However, there is no clear exposure response correlation to support the chosen dose and a dose finding study has been planned and details of the study have been supplied. This is acceptable.

The primary objective endpoint chosen was overall objective response rate. In addition, data on duration of response, disease control rate, progression free survival and overall survival have been provided. The objective response rate of 37.4% appears clinically relevant and compares favourably with the real world evidence provided by the applicant.

The progression free survival and overall survival results are supportive of a positive benefit concluded on the basis of the objective response rate. However, the results are from a single arm study and difficult to contextualise and the applicant has provided comparative data with other available therapies which could be used in this treatment population.

The proposed indication reflects the evaluated study population (patients who have progressed on, or are intolerant to, platinum-based chemotherapy and/or anti PD-1/PD-L1 immunotherapy).

IV.5 Clinical safety

The analysis of the safety profile of sotorasib is primarily based on the pooled monotherapy data from the phase I and II portions of ongoing Study 20170543 (data cut-offs of 06 July 2020 and 01 September 2020, respectively). The analyses are presented by the applicant to characterise the safety profile of sotorasib in the proposed indication of the treatment of patients with previously treated *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC.

Patient exposure
As of the data cut-off dates for the phase I and phase II portions of Study 20170543, a total of 427 subjects were treated with sotorasib monotherapy across all doses and tumour types. This includes 339 subjects who were treated with the intended sotorasib dose of 960 mg once-daily (fasted) for all tumour types; of whom, 190 subjects had *KRAS p.G12C*-mutated NSCLC.

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

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

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

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

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

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

Demographics were generally consistent for subjects treated at 960 mg once-daily for all tumour types and for the total monotherapy population.

Adverse events
Most subjects with NSCLC who received 960 mg QD sotorasib monotherapy (187 of 190 subjects [98.4%]) had ≥1 adverse event during the study. Of these, 114 subjects (60%) had adverse events ≥grade 3 in severity.

Serious adverse events were reported for 99 subjects (52.1%). Adverse events leading to reduction/interruption or discontinuation of sotorasib monotherapy were reported for 67 subjects (35.5%) and 18 subjects (9.5%), respectively. Thirty-one subjects (16.3%) had fatal adverse events; none of the deaths were considered by the investigator as related to sotorasib treatment.

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

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

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

Safety analysis set is defined as all enrolled subjects in Study 20170543 who received ≥ 1 dose of sotorasib as monotherapy. Treatment-related adverse events are treatment-emergent adverse events considered related to investigational product by the investigator.

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

The types of adverse events reported for subjects with NSCLC treated with 960 mg QD sotorasib were generally similar to those reported for subjects treated with 960 mg QD for all tumour types and the total monotherapy population (any dose/ any tumour type).

The applicant has provided a description of their methodology for analysis of adverse drug reactions.

To provide a robust dataset at the intended dose and to maximise the potential for identifying adverse events that were related to sotorasib use, adverse drug reactions were evaluated based on the 359 subjects with any tumour type who were treated with sotorasib monotherapy at 960 mg QD. Medical review was based on a broad evaluation of all adverse events (including their severity, onset, duration, and outcome), changes in laboratory values, and vital signs. Adverse reactions were determined to be those events that were reported ≥ 15% in subjects with any 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 (e.g., cardiac and neurological events), or those commonly associated with drug use (e.g., rash).

Additional considerations such as temporal association, biological plausibility, and medical judgment were then applied for a probable causal drug event association to determine the final adverse drug reactions.

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

The resulting list of adverse drug reactions for sotorasib are summarised below and reflected in the applicant's SmPC:

Table: Adverse reactions

MedDRA system organ class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)
Blood and lymphatic system disorders	Anaemia	
Nervous system disorders	Headache	
Respiratory, thoracic and mediastinal disorders	Dyspnoea Cough[a]	
Cardiovascular disorders		Hypertension
Gastrointestinal disorders	Diarrhoea Nausea Vomiting Abdominal pain[b] Constipation	
Hepatobiliary Disorders	Hepatotoxicity[c]	
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[d]	
General disorders and administration site conditions	Fatigue Pyrexia	Peripheral oedema
Metabolism and nutrition disorders		Decreased appetite Hypokalaemia Hyponatraemia Hypocalcaemia
Infections		Pneumonia Urinary tract infection
Skin and subcutaneous tissue disorders		Rash
Investigations		Blood alkaline phosphatase increased

[a] Cough includes cough, productive cough, and upper-airway cough syndrome.
[b] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower
[c] Hepatotoxicity includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, drug-induced liver injury, hepatitis, hepatotoxicity, liver function test increased, and transaminases increased.
[d] Musculoskeletal pain includes arthralgia, myalgia and back pain

Description of selected adverse reactions:
Occurrence of interstitial lung disease/pneumonitis
Among 359 patients who received sotorasib in CodeBreaK 100, ILD/pneumonitis occurred in 0.8% of patients, all cases were Grade 3 or 4 at onset. The median time to first onset for ILD/pneumonitis was 2 weeks (range: 2 to 18 weeks). Sotorasib was discontinued due to ILD/pneumonitis in 0.6% of patients.

The applicant has provided details of the 3 subjects that had adverse events of pneumonitis and 1 subject that had acute respiratory distress syndrome. It is acknowledged that the subjects had received prior therapies that are associated with pneumonitis.

This needs further evaluation through safety follow up of subjects from the conducted trials and other patients that may receive sotorasib.

Importantly, warnings about the incidence of pneumonitis has been added to the product information and this is at present considered appropriate to address the safety concern.

Hepatotoxicity
Among 359 patients who received sotorasib in CodeBreaK 100, a total of 17% of patients who received sotorasib had increased alanine aminotransferase (ALT)/increased aspartate aminotransferase (AST); 6% were Grade 3 and 0.6% were Grade 4. The median time to first onset of increased ALT/AST was 8 weeks (range: 0.3 to 42). Increased ALT/AST leading to dose interruption or reduction occurred in 7% of patients. Sotorasib was discontinued due to increased ALT/AST in 1.7% of patients. In addition to dose interruption or reduction, 5% of patients received corticosteroids for the treatment of hepatotoxicity.

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

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

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

Treatment-related Fatal Adverse Events
No treatment-related fatal adverse events have been reported as of the respective data cut-off dates in the integrated analysis set nor in any study in the sotorasib clinical development program.

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

Conclusion on clinical safety

98.4% of the subjects with NSCLC who received 960 mg QD sotorasib monotherapy had ≥1 adverse event during the study. 60% of the subjects had adverse events ≥grade 3 in severity. Serious adverse events were reported for 52.1% of subjects. Adverse events leading to reduction/interruption or discontinuation of sotorasib monotherapy were reported for 35.5% of subjects and 9.5% of subjects, respectively.

There were thirty-one subjects (16.3%) who had fatal adverse events. However, none of the deaths were considered by the investigator as related to sotorasib treatment.

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

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

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

An important risk associated with sotorasib treatment has been transient elevations of serum transaminases (ALT and AST), including asymptomatic cases in clinical studies. These elevations improved or resolved with interruption of treatment and did not result in cases of Hy's Law (i.e., concurrent increase of AST/ALT and bilirubin with normal ALP in the absence of alternative etiology), liver failure, or fatal cases. Increased AST and ALT are considered adverse drug reactions. The risk of increased liver enzymes may be successfully managed with more frequent testing, by dose modification, or with temporary interruption until resolution.

Occurrence of specific adverse events such as interstitial lung disease/pneumonitis and hepatoxicity were also reported.

The applicant has incorporated the above safety information into the relevant sections of the SmPC (4.2, 4.4, 4.8 and 5.3). This is acceptable.

IV.6 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL 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.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of this product as monotherapy for the treatment of adult patients with *KRAS G12C*-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), who have progressed on, or are intolerant to, platinum-based chemotherapy and/or anti PD-1/PD-L1 immunotherapy.

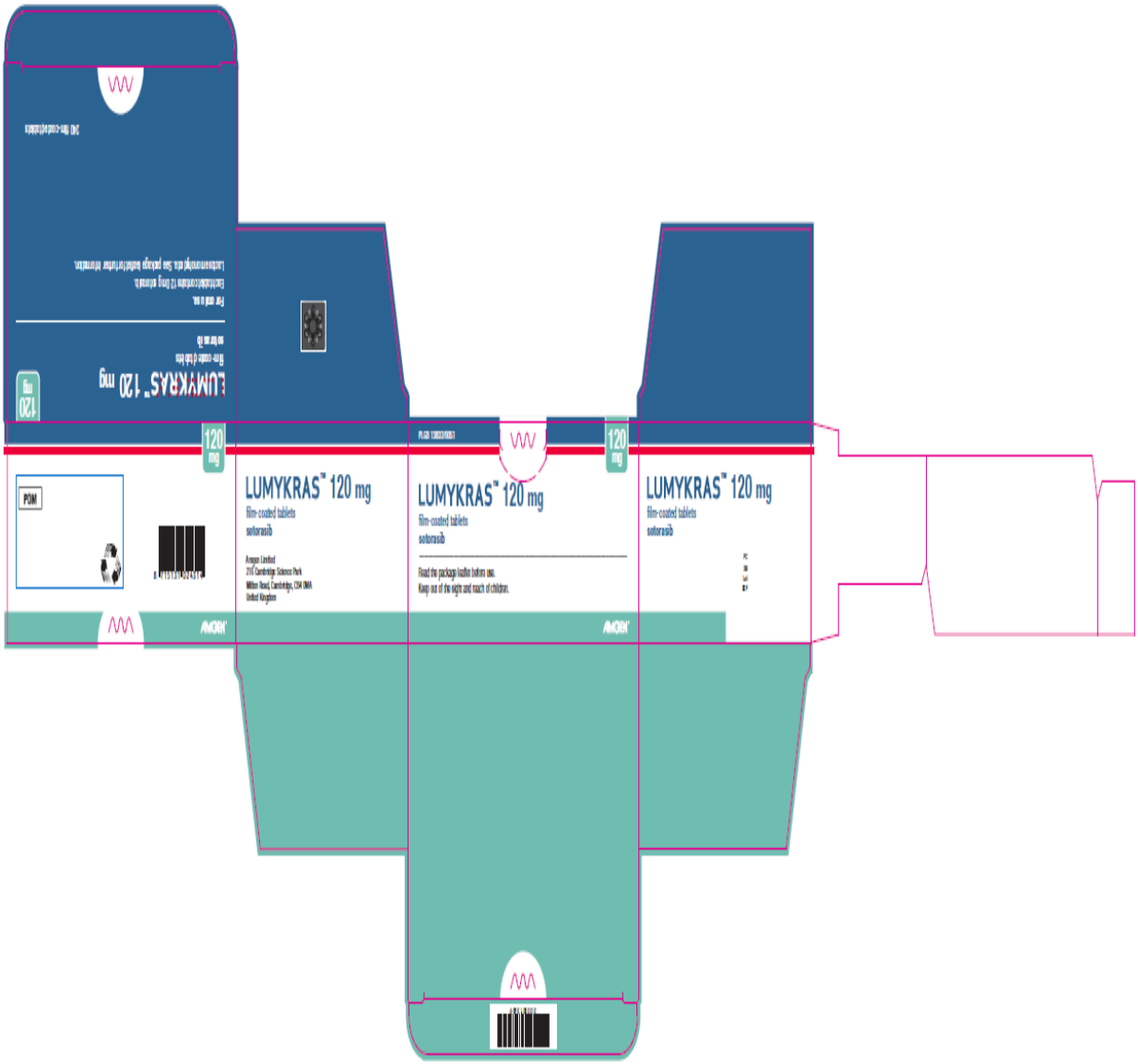
Lumykras 120 mg film-coated tablets has been authorised with a Conditional Marketing Authorisation (CMA). The Marketing Authorisation Holder shall complete, within the stated timeframe, the following measures:

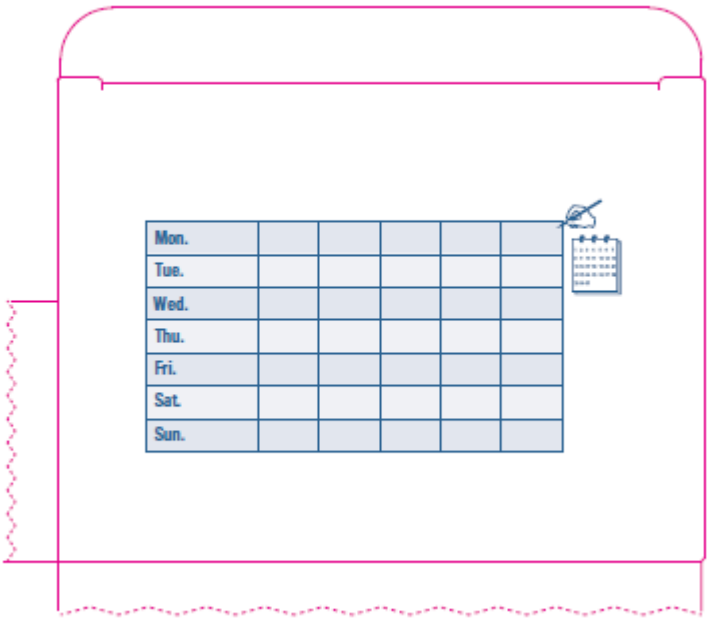
Description	Due date
1. In order to assess the long-term effect of sotorasib in the treatment of adult patients with KRAS G12C mutated locally advanced or metastatic non-small cell lung cancer, who have progressed on, or are intolerant to, platinum based chemotherapy and/or anti PD-1/PD-L1 immunotherapy, the applicant will submit additional efficacy and safety follow-up data from the phase 2, open-label study CodeBreak 100.	30/06/2023.
2. In order to confirm the efficacy and safety of sotorasib in the treatment of adult patients with KRAS G12C mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), who have progressed on, or are intolerant to, platinum-based chemotherapy and/or anti PD-1/PD-L1 immunotherapy, the applicant will submit the results from multicentre, randomised clinical study CodeBreak 200.	31/07/2022
3. Conduct and submit results of the multicentre, randomized clinical trial to further characterize serious adverse events, including gastro-intestinal toxicity and compare the safety and efficacy of sotorasib 960 mg daily versus a lower daily dose in patients with locally advanced or metastatic, KRAS G12C mutated, non-small cell lung cancer who have received at least one prior systemic therapy.	30/06/2023
4. Conduct and submit results of the hepatic impairment clinical trial to determine a safe and appropriate dose of sotorasib in patients with moderate and severe hepatic impairment.	31/10/2022
5. Conduct and submit results of the clinical drug interaction study to assess the effect of concomitant sotorasib administration on the systemic exposure of BCRP transporter substrates.	31/05/2022

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved GB versions of the SmPC and PIL for this product is available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.


LUMYKRAS™ 120 mg
film-coated tablets
sotorasib
120 mg
POM
Amgen Limited
Keep out of the sight and reach of children.

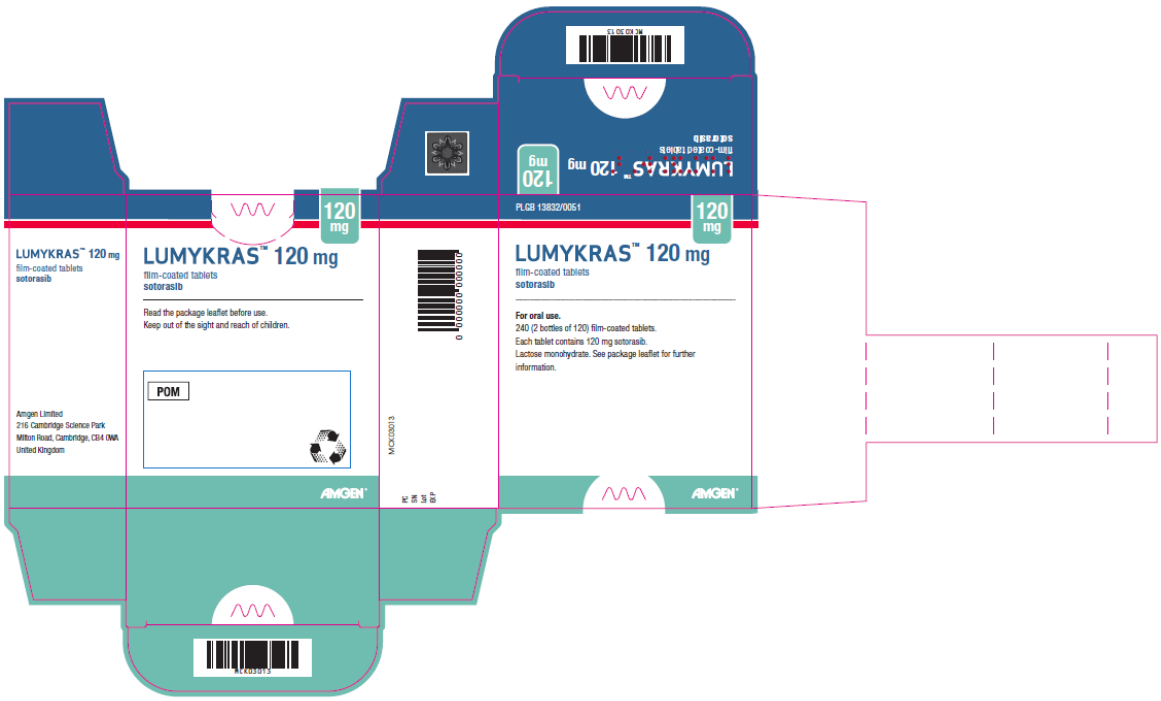


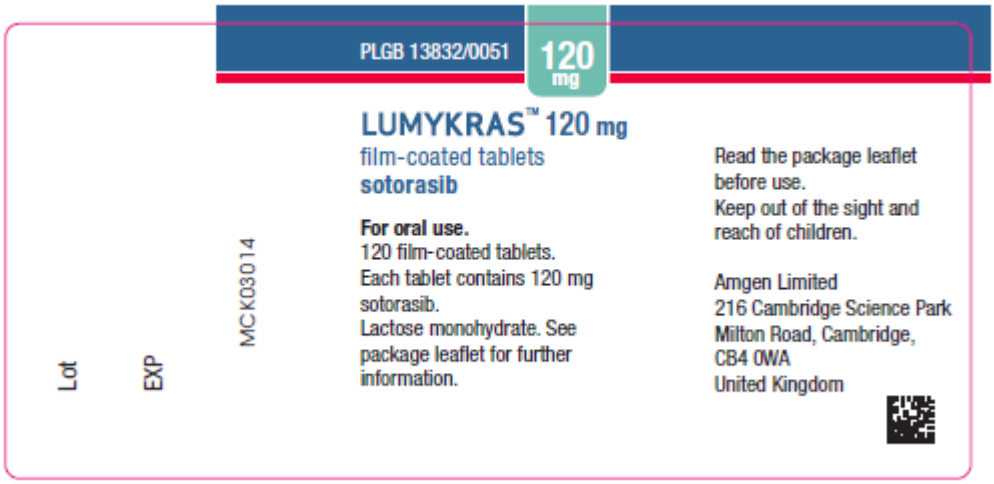
Lot EXP

LUMYKRAS™ 120 mg
film-coated tablets
sotorasib

LUMYKRAS™ 120 mg
film-coated tablets
sotorasib

Amgen Limited
2000013658


LUMYKRAS™ 120 mg
film-coated tablets
sotorasib
120 mg
Read the package leaflet before use.
Keep out of the sight and reach of children.
POM
Amgen Limited
216 Cambridge Science Park
Milton Road, Cambridge, CB4 0WA
United Kingdom
MCK03013
AMGEN
PLGB 13832/0051
For oral use.
240 (2 bottles of 120) film-coated tablets.
Each tablet contains 120 mg sotorasib.
Lactose monohydrate. See package leaflet for further information.


PLGB 13832/0051
120 mg
LUMYKRAS™ 120 mg
film-coated tablets
sotorasib
For oral use.
120 film-coated tablets.
Each tablet contains 120 mg sotorasib.
Lactose monohydrate. See package leaflet for further information.
Read the package leaflet before use.
Keep out of the sight and reach of children.
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Milton Road, Cambridge,
CB4 0WA
United Kingdom
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TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**