

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

KRAZATI 200 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg adagrasib.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, oval shaped, film-coated tablet with a stylised “M” on one side and “200” marked on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

KRAZATI as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with *KRAS* G12C mutation and have progressive disease after prior therapy with, or intolerance to, platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy.

4.2 Posology and method of administration

Treatment with KRAZATI should be initiated by a physician experienced in the use of anti-cancer medicinal products.

The presence of a *KRAS* G12C mutation must be confirmed using a validated test prior to initiation of therapy with KRAZATI (see section 5.1).

Posology

The recommended dose of KRAZATI is 600 mg (three 200 mg tablets) orally twice daily, with or without food.

Duration of treatment

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

Delayed or missed doses

Patients should be advised that if less than 4 hours have passed since the scheduled time of dosing, the patient should take the dose as normal. If a dose is missed by more than 4 hours, the dose should be skipped, and dosing should resume at the next scheduled dose. If vomiting occurs after taking a dose, patients should be advised not to take an additional dose. The next dose should be taken as prescribed.

Dose adjustments during treatment

The recommended dose reduction levels for the management of adverse reactions are outlined in Table 1.

Table 1: Recommended dose reduction levels for adverse reactions

Dose reduction level	Reduced dosage
First dose reduction	Two 200 mg tablets (400 mg) twice daily
Second dose reduction	Three 200 mg tablets (600 mg) once daily

The recommended dose modifications for adverse reactions are provided in Table 2. Severe (e.g. Grade 3) or intolerable adverse reactions require interruption of KRAZATI until sufficient improvement is observed before dosing is resumed.

Table 2: Recommended dosage modifications for adverse reactions

Adverse reaction	Severity ^a	Treatment modification
Nausea or vomiting despite appropriate supportive care (including anti-emetic therapy)	Grade 3 or 4	Withhold KRAZATI until recovery to $\leq$ Grade 1 or return to baseline Resume KRAZATI at the next lower dose level
Diarrhoea despite appropriate supportive care (including anti-diarrhoeal therapy)	Grade 3 or 4	Withhold KRAZATI until recovery to $\leq$ Grade 1 or return to baseline Resume KRAZATI at the next lower dose level
Hepatotoxicity	Grade 2 AST or ALT increase	Decrease KRAZATI to the next lower level, if considered necessary
	Grade 3 or 4 AST or ALT increase	Withhold KRAZATI until $\leq$ Grade 1 or return to baseline Resume KRAZATI at the next lower dose level
	AST or ALT $> 3 \times$ ULN with total bilirubin $> 2 \times$ ULN in the absence of alternative causes	Permanently discontinue KRAZATI
QTc Prolongation	Grade 3 (QTc ≥ 501 ms or > 60 ms change from baseline)	Withhold KRAZATI until $\leq$ Grade 1 or return to baseline Resume KRAZATI at the next lower dose level
	Grade 4 (ventricular arrhythmia)	Permanently discontinue KRAZATI
Pneumonitis/ILD	Any Grade	Withhold KRAZATI if pneumonitis/ILD is suspected. Permanently discontinue KRAZATI if pneumonitis/ILD is confirmed.
Other adverse reactions	Grade 3 or 4	Withhold KRAZATI until $\leq$ Grade 1 or return to baseline Resume KRAZATI at the next lower dose level

ALT = alanine aminotransferase; AST = aspartate aminotransferase;

ULN = upper limit of normal

^a Grading defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0

Special populations

Paediatric population

The safety and efficacy of KRAZATI in children aged 0 to 18 years have not been established. No data are available (see section 5.1).

Method of administration

KRAZATI is for oral use. The tablets should be swallowed whole with water.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Gastrointestinal Adverse Reactions

Gastrointestinal (GI) adverse reactions can occur with adagrasib (see section 4.8).

Patients should be monitored and managed using supportive care, including anti-diarrhoeals, antiemetics, and fluid replacement, as indicated. Based on the severity of the adverse reaction, the dose of KRAZATI should either be reduced, temporarily withheld until a return to $\leq$ Grade 1 or baseline then resumed at a reduced dose (see section 4.2).

Hepatotoxicity

Increased transaminases occurred in some patients treated with adagrasib (see section 4.8).

Liver laboratory tests, including ALT, AST and alkaline phosphatase, should be monitored prior to the start of treatment and monthly for 3 months after starting treatment with KRAZATI and as clinically indicated, with more frequent testing in patients who develop transaminase and/or alkaline phosphatase elevations. Based on the severity of the adverse reaction, the adagrasib dose should either be reduced, temporarily withheld until a return to $\leq$ Grade 1 or baseline then resumed at a reduced dose, or permanently discontinued. Specific guidance regarding dose management of KRAZATI in patients with increased transaminases is provided in section 4.2.

QT Prolongation

QTc interval prolongation can occur in patients treated with KRAZATI. No arrhythmias related to QTc prolongation or sudden death has been observed.

When possible, the use of KRAZATI should be avoided in patients with congenital long QT syndrome and in patients with concurrent QTc prolongation. Baseline

electrocardiogram (ECG) should be considered prior to treatment. Periodic monitoring of ECGs and electrolytes should be performed in patients with congestive heart failure, bradyarrhythmias, or electrolyte abnormalities, and in patients who are taking medications that are known to prolong the QT interval. Based on the severity of the adverse reaction, treatment with KRAZATI can be continued with a reduced dose or should be temporarily discontinued and may be resumed at a reduced dose after a return to $\leq$ Grade 1 or baseline. In patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia, KRAZATI should be permanently discontinued (see section 4.2 and 4.8).

Pneumonitis / Interstitial lung disease (ILD)

Pneumonitis/ILD can occur in patients treated with KRAZATI. Monitor patients for new or worsening respiratory symptoms indicative of pneumonitis/ILD (e.g., increased dyspnoea, cough, fever) during treatment with KRAZATI. Withhold KRAZATI in patients with suspected pneumonitis/ILD and permanently discontinue KRAZATI if no other potential causes of pneumonitis/ILD are identified (see section 4.2).

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have rarely been reported in patients treated with KRAZATI.

Monitor for skin reactions as signs or symptoms of SCAR when receiving KRAZATI alone or concomitantly with medicinal products associated with SCAR. Withhold KRAZATI if a SCAR is suspected and refer the patient to a dermatologist for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue KRAZATI.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro studies showed that adagrasib is metabolised primarily by CYP3A4 and is a reversible inhibitor of CYP2B6, CYP2C9, CYP2D6 and CYP3A4, as well as a time-dependent inhibitor of CYP3A4. In vitro, adagrasib is a substrate of BCRP and inhibits P-gp, BCRP, MATE-1/MATE2-K, OATP1B1, and OCT1.

Effects of other medicinal products on adagrasib

Strong CYP3A inducers

Coadministration of multiple doses of rifampicin 600 mg QD (strong CYP3A4 inducer) with a single 600 mg dose of adagrasib decreased adagrasib $C_{\max}$ by 88% and AUC by 95% in healthy subjects. Coadministration of multiple doses of rifampicin (600 mg QD) with multiple doses of adagrasib (600 mg BID) in patients is predicted to decrease adagrasib $C_{\max}$ by 61% and AUC by 66%, which may decrease the efficacy. Concomitant use of strong CYP3A inducers (e.g., carbamazepine, phenytoin, phenobarbital, rifampicin) should be avoided.

Strong CYP3A4 inhibitors

Adagrasib $C_{\max}$ increased by 2.4-fold and AUC increased by 4-fold following concomitant use of a single dose of 200 mg (0.33 times the approved recommended dose) with itraconazole (a strong CYP3A inhibitor). No clinically significant differences in the pharmacokinetics of adagrasib at steady state were predicted when used concomitantly with itraconazole. Concomitant use of strong CYP3A inhibitors (e.g., itraconazole, ketoconazole, ritonavir) should be avoided until adagrasib concentrations have reached steady state (after approximately 8 days).

Strong CYP2C8 inhibitors

Based on in vitro data, adagrasib is a substrate of CYP2C8. If adagrasib is administered with medicinal products that are strong inhibitors of CYP2C8, an increase in adagrasib concentration is possible. Caution should be exercised with concomitant use of strong inhibitors of CYP2C8 (e.g., gemfibrozil).

Effects of adagrasib on other medicinal products

Substrates of Cytochrome P450 (CYP) enzymes

CYP3A4 substrates: Coadministration of oral midazolam (a sensitive CYP3A4 substrate) with multiple doses of adagrasib (400 mg BID) increased midazolam AUC by approximately 21-fold in healthy subjects. Administration of multiple doses of adagrasib at 600 mg BID in patients is predicted to increase oral midazolam AUC by 31-fold. Avoid concomitant use of adagrasib with sensitive CYP3A4 substrates (e.g., alfuzosin, amiodarone, cisapride, pimozide, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, sildenafil, simvastatin, sirolimus, midazolam, triazolam, ticagrelor and tacrolimus) unless otherwise recommended in the SmPC for these substrates.

CYP2C9 substrates: Coadministration of warfarin (a sensitive CYP2C9 substrate) with multiple doses of adagrasib at 600 mg BID in patients is predicted to increase warfarin AUC by 2.9-fold. Avoid concomitant use of adagrasib with sensitive CYP2C9 substrates where minimal concentration changes may lead to serious adverse reaction (e.g., warfarin) unless otherwise recommended in the SmPC for these substrates.

CYP2D6 substrates: Coadministration of dextromethorphan (a sensitive CYP2D6 substrate) with multiple doses of adagrasib (400 mg BID) increased dextromethorphan AUC by 1.8-fold in healthy subjects. Administration of adagrasib at 600 mg BID in patients is predicted to increase dextromethorphan AUC by 2.4-fold. Avoid concomitant use of adagrasib with sensitive CYP2D6 substrates where minimal concentration changes may lead to serious adverse reactions (e.g., pimozide, propafenone, thioridazine) unless otherwise recommended in the SmPC for these substrates.

Transporter systems

P-glycoprotein (P-gp) substrates: Administration of adagrasib at 600 mg BID in patients is predicted to increase digoxin (a P-gp substrate) $C_{\max}$ and AUC by

1.9-fold and 1.5-fold, respectively. Avoid concomitant use of adagrasib with P-gp substrates where minimal concentration changes may lead to serious adverse reactions (e.g., colchicine, dabigatran, digoxin) unless otherwise recommended in the SmPC for these substrates.

Breast Cancer Resistance Protein (BCRP) or Organic Anion-Transporting Polypeptides 1B1 (OATP1B1) substrates

No clinically significant differences in the pharmacokinetics of rosuvastatin (a BCRP/OATP1B1 substrate) were observed when coadministered with adagrasib.

MATE and OCT substrates

Based on *in vitro* data, adagrasib may have the potential to alter the exposure of substrates of the transporters MATE1/2-K and OCT1/2. The most clinically relevant example substrate of these transporters is metformin. Monitoring of the clinical effects of metformin is recommended during co-administration with adagrasib.

Medicinal products that prolong the QTc interval

The effect of coadministration of medicinal products known to prolong the QTc interval with adagrasib is unknown. The use of medicinal products known to prolong the QTc interval, such as some antiarrhythmic medicinal products (e.g., quinidine, disopyramide, amiodarone, sotalol, dofetilide, ibutilide), antibiotic medicinal products (e.g., azithromycin, ciprofloxacin, moxifloxacin), methadone, antipsychotics (e.g. haloperidol), etc., should be avoided. If concomitant administration of such medicinal products cannot be avoided, periodic ECG monitoring should be conducted (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of adagrasib in pregnant women. Based on findings from animal studies, there are no direct effects of adagrasib on embryo-foetal development (see section 5.3). KRAZATI is not recommended during pregnancy or in women of childbearing potential not using contraception.

Breast-feeding

There are no data on the presence of adagrasib or its metabolites in human milk, effects of adagrasib on the breastfed child, or on milk production. Because of the potential for serious adverse reactions in breastfed children, lactating women should be advised not to breastfeed during treatment with KRAZATI and for at least 7 days after the final dose.

Fertility

No clinical data are available on the possible effects of adagrasib on fertility.

4.7 Effects on ability to drive and use machines

Adagrasib has minor influence on the ability to drive and use machines. Dizziness (including vertigo and fatigue) may occur following administration of adagrasib (see section 4.8). Patients should be advised that dizziness may occur and that, if affected, they should not drive, use machines, or take part in other activities where this would put themselves or others at risk.

4.8 Undesirable effects

Summary of the safety profile

Adagrasib was evaluated in patients with *KRAS* G12C-mutated solid tumours (n = 821). The adverse events and safety evaluation as seen in adagrasib clinical trials are presented.

The most common adverse reactions were diarrhoea (65.2%), nausea (59.9%), fatigue or asthenia (54.3%), vomiting (50.3%), decreased appetite (32.9%), anaemia (32.4%), increased blood creatinine (31.7%), increased aspartate aminotransferase (AST) (29.0%), increased alanine aminotransferase (ALT) (28.3%), peripheral oedema (23.0%), hyponatraemia (17.1%), and dizziness (17.1%) (includes vertigo).

The most common (>1%) severe (grade ≥ 3) adverse reactions were fatigue or asthenia (9.0%), anaemia (7.2%), increased ALT (6.6%), increased lipase (4.8%), increased AST (4.6%), nausea (4.6%), hyponatraemia (4.0%), lymphocyte count decreased (4.0%), QT prolongation (3.4%), decreased appetite (2.7%) increased blood alkaline phosphatase (2.4%), and pneumonitis/ILD (1.2%).

Serious adverse reactions in $\geq 2\%$ of patients were pneumonia (6.9%), dyspnoea (2.9%), vomiting (2.8%), acute kidney injury (2.2%), nausea (2.1%), pyrexia (2.1%), and sepsis (2.1%). Fatal adverse reactions occurred in 15.2% of patients who received adagrasib due to respiratory failure (1.1%), pneumonia (1.0%), cardiac failure (0.2%), pulmonary embolism (0.2%), cerebrovascular accident (0.1%), mental status change (0.1%), and pulmonary haemorrhage (0.1%).

Permanent discontinuation of adagrasib due to an adverse reaction occurred in 11.6% of patients. Adverse reactions that resulted in permanent discontinuation of adagrasib occurring in more than two patients each (>0.2%) were acute kidney injury, ALT increased, cerebrovascular accident, decreased ejection fraction, dysphagia, dyspnoea, fatigue, nausea, neutropenia pneumonia and pneumonitis and seizure.

Dose interruptions of adagrasib due to an adverse reaction occurred in 72.5% of patients. Adverse reactions requiring dosage interruption in $\geq 2\%$ of patients who received adagrasib included nausea, hepatotoxicity, fatigue, vomiting, pneumonia, diarrhoea, QTc interval prolongation, anaemia, dyspnoea, increased lipase, decreased appetite, dizziness, pyrexia, blood creatinine increase, and blood alkaline phosphatase increased.

Dose reductions of adagrasib due to an adverse reaction occurred in 48.4% of patients. Adverse reactions which required dose reductions in $\geq 2\%$ of patients who

received adagrasib included hepatotoxicity, fatigue, nausea, diarrhoea, vomiting, blood creatinine increased, QTc interval prolongation, and decreased appetite.

Tabulated list of adverse reactions

Adverse reactions reported in clinical trials are displayed below. Frequency categories are defined as follows: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from available data). Within each system organ class, adverse reactions are presented in the order of decreasing seriousness.

Adverse reaction frequencies have been derived from 821 patients exposed at adagrasib 600 mg twice daily as monotherapy for a median duration of 5.2 months (range 0.03 months to 53.82 months) in clinical studies of patients with *KRAS* G12C mutation-positive for all solid tumours.

The adverse reaction frequencies from clinical trials are displayed as all-cause adverse event frequencies; a proportion of the events included in the frequency estimate for an adverse reaction may have causes other than KRAZATI, such as the disease being treated, concomitant medication, or other unrelated causes.

Table 3: Adverse reactions reported in patients treated with adagrasib

System Organ Class	Preferred term	
	Very common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)
Blood and lymphatic system disorders	Anaemia	
Metabolism and nutrition disorders	Hyponatraemia	
	Decreased appetite	
Nervous system disorders	Dizziness ¹	
Gastrointestinal disorders	Nausea	
	Diarrhoea	
	Vomiting	
Hepatobiliary disorders	Hepatotoxicity ³	
Renal and Urinary disorders	Renal impairment ⁴	
Respiratory, thoracic and mediastinal disorders		Pneumonitis/ILD
General disorders and administration	Fatigue ²	
	Oedema peripheral	

System Organ Class	Preferred term	
	Very common (≥1/10)	Common (≥1/100 to <1/10)
site conditions		
Investigations	Electrocardiogram QT prolonged	Lymphocyte count decreased
	Lipase increased	Platelet count decreased
	Amylase increased	Blood potassium decreased
		Blood magnesium decreased
		Blood albumin decreased

¹ Includes dizziness and vertigo

² Includes fatigue and asthenia

³ Includes AST increased, ALT increased, Blood alkaline phosphatase increased, Blood bilirubin increased, Gamma-glutamyltransferase increased, hepatic enzyme increased, liver function test increased and mixed liver injury

⁴ Renal impairment includes acute kidney injury and blood creatinine increased

Description of selected adverse reactions

Gastrointestinal Adverse Reactions

Gastrointestinal (GI) adverse reactions that occurred with adagrasib treatment include diarrhoea (65.2%; ≥Grade 3, 5.1%), nausea (59.9%; ≥Grade 3, 4.6%), and vomiting (50.3%; ≥Grade 3, 3.3%). Diarrhoea, nausea, and vomiting resulted in dose interruption and/or reduction in 13.3%, 14.7% and 13.4% of patients respectively.

Hepatotoxicity

Elevations of serum transaminases were observed in clinical studies (see section 4.4).

Elevations of ALT occurred in 28.3% (≥ Grade 3, 6.6%) of patients and elevations of AST in 29.0% (≥ Grade 3, 4.6%) of patients, with a median time to first onset of Grade ≥3 was 21.7 days. Elevations of ALT resulted in dose interruption and/or reduction in 10.2% of patients, and elevations of AST resulted in dose interruption and/or reduction in 7.3% of patients.

QT Prolongation

Prolongation of the QT interval was observed in clinical studies (see section 4.4).

Corrected QT interval prolongation (QTcF) greater than 500 msec occurred in 5.4% of 810 patients. Increase in QTcF interval >60 msec from baseline occurred in 10.8% of patients. Based on the concentration-QTcF relationship, the mean (90 % CI) QTcF change from baseline (ΔQTcF) was 17.93 ms (15.13 – 20.73 ms) at the population geometric mean steady-state maximum concentration ($C_{max,ss}$) in patients after administration of adagrasib 600 mg twice daily. The median time to first onset of QT interval prolongation reported as a severe adverse event (CTCAE Grade 3 and above)

was 12.6 days (range 0.7-289 days). QT interval prolongation resulted in dose interruption and/or reduction in 3.4% of patients.

Pneumonitis/ILD

Pneumonitis/ILD occurred in 4.3%; 1.2% were $\geq$ Grade 3. The median time to first onset for Grade ≥ 3 pneumonitis was 83 days (range: 72-219 days). Pneumonitis/ILD resulted in dose interruption and/or reduction in 2.6% of patients. Adagrasib was discontinued due to pneumonitis/ILD in 0.9% of patients.

Increased Amylase and Lipase

Elevations in amylase and lipase occurred in 10.7% and 12.9% of patients, respectively. Elevations in amylase and lipase resulted in dose interruptions or dose reductions in 1.3% and 3.5% of patients, respectively.

Special populations

Elderly

In patients receiving 600 mg twice daily, fatigue, anaemia and dizziness were more common in ≥ 65 -year-old patients compared to those < 65 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In case of overdose, treatment should be interrupted, and general supportive measures initiated as appropriate. There is no specific antidote or treatment for adagrasib overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: L01XX77

Mechanism of action

Adagrasib is a selective, irreversible inhibitor of KRAS G12C that covalently binds to the mutant cysteine in KRAS G12C and locks the mutant KRAS protein in its inactive, GDP-bound conformation, which prevents KRAS-dependent downstream signalling without affecting wild-type KRAS protein. Adagrasib demonstrates near maximal inhibition of KRAS G12C protein throughout the entire dosing interval resulting in durable inhibition of KRAS-dependent signal transduction. Adagrasib inhibits tumour cell growth and viability in cells harbouring *KRAS* G12C mutations and results in regression in *KRAS* G12C-positive nonclinical tumour models with minimal off-target activity.

Following oral administration in mice, adagrasib exhibited free brain exposure above the cellular IC₅₀ value and demonstrated tumour regression and increased survival in a preclinical *KRAS* G12C-mutant intracranial mouse xenograft model of brain metastasis (LU99).

Clinical efficacy and safety

KRYSTAL-1 NSCLC

The efficacy of adagrasib was evaluated in KRYSTAL-1, a multicentre, open-label multiple expansion cohort study. The study enrolled patients with locally advanced or metastatic NSCLC with confirmed *KRAS* G12C mutation who previously received treatment with a platinum-based regimen and an immune checkpoint inhibitor. Identification of a *KRAS* G12C mutation in cohort A was prospectively determined in tumour tissue by local laboratories using next generation sequencing (NGS), polymerase chain reaction (PCR) or Sanger sequencing. Adult patients received adagrasib 600 mg orally twice daily until unacceptable toxicity or disease progression. Continued treatment after disease progression was allowed if a patient was clinically stable and was considered to be deriving clinical benefit by the investigator.

A total of 116 patients with NSCLC characterised by a *KRAS* G12C mutation identified in a sponsor-approved test were enrolled into cohort A of KRYSTAL-1 and evaluated for efficacy by blinded, independent central review.

The median age was 64.0 years (range: 25 to 89 years); 56.0% were female; 83.6% were White; 7.8% were Black; 4.3% were Asian, and 4.3% were other. ECOG performance status was 0 (15.5%) or 1 (83.6%). Tumour histology was adenocarcinoma for 97.4% of patients, and 88.8% of patients had metastatic disease. Patients received a median of 2 prior systemic therapies (range: 1 to 7); 43.1% received 1 line, 34.5% received 2 lines, 10.3% received 3 lines, and 12.1% received 4 or more lines; 98.3% received both prior platinum and prior anti-PD-1/PD-L1 therapy. Sites of extra-thoracic disease included bone 39.7%, brain 20.7%, adrenals 19.0%, and liver 16.4%.

The major efficacy outcome measures were confirmed objective response rate (ORR) and duration of response (DOR) in accordance with RECIST v1.1. Additional efficacy outcome measures included progression-free survival (PFS) and overall survival (OS).

Efficacy results are summarised in Table 4 for cohort A along with a pooled analysis with supportive cohorts B (where *KRAS* G12C mutation was identified in ctDNA) and Phase 1/1b.

*Table 4: Efficacy results for patients with confirmed *KRAS* G12C metastatic NSCLC in KRYSTAL-1 previously treated with platinum chemotherapy and an immune checkpoint inhibitor*

Endpoint	Pivotal Cohort A (n = 116^a)	Pooled Analysis (n = 192^b)
Objective response rate (95% CI)	42.9 (33.5, 52.6)	40.6 (33.6, 47.9)
Complete response rate, %	0.9	2.1
Partial response rate, %	42.0	38.5
Time to response		
Median ^c in weeks	6.0	6.0
% Patients with response within 8 weeks of treatment initiation	75.0	76.9
Duration of response		
Median ^c in months (95% CI)	8.5 (6.2, 13.8)	9.6 (5.8, 15.1)
% Patients with duration ≥ 6 months	58.3	55.1
Progression-free survival		
Median ^c in months (95% CI)	6.5 (4.7, 8.4)	6.6 (5.4, 8.1)
6-month event-free rate ^c	51.6 (41.1, 61.2)	52.5 (44.5, 59.8)
9-month event-free rate ^c	37.3 (27.3, 47.2)	37.0 (29.5, 44.6)
12-month event-free rate ^c	29.3 (19.6, 39.7)	32.0 (24.4, 39.8)
Overall survival		
Median ^c in months (95% CI)	12.6 (9.2, 19.2)	12.6 (9.2, 16.3)
6-month event-free rate ^c	70.6 (61.1, 78.3)	72.0 (64.9, 78.0)
9-month event-free rate ^c	60.0 (50.1, 68.6)	59.6 (52.0, 66.4)
12-month event-free rate ^c	50.8 (40.9, 60.0)	50.2 (42.1, 57.8)

CI = Confidence interval; NE = Not evaluable

^a Of 116 enrolled patients, 116 are included in the analysis of overall survival; 112 of 116 patients with measurable disease at baseline as assessed by Blinded Independent Central Review (BICR) using RECIST v1.1 are included in the analyses of objective response rate and progression-free survival; 48 patients with a confirmed response are included in the analyses of time to response and duration of response as assessed by BICR.

^b Pooled analysis of pivotal cohort A and other cohorts based on BICR. Of 192 enrolled patients, 192 are included in the analyses of objective response rate, progression-free survival, and overall survival, and 78 patients with a confirmed response are included in the analyses of time to response and duration of response by BICR.

^c Estimated using Kaplan-Meier method

KRYSTAL-12 NSCLC

The efficacy of adagrasib was evaluated in KRYSTAL-12 (Study 849-012), a multicentre, open-label randomised clinical trial comparing the efficacy of adagrasib versus docetaxel in patients with NSCLC with *KRAS* G12C mutation and who have received prior therapy with a platinum-based regimen and an immune checkpoint inhibitor.

Patients with locally advanced or metastatic NSCLC with *KRAS* G12C mutation who previously received treatment with a platinum-based regimen and an immune checkpoint inhibitor were enrolled. Identification of a *KRAS* G12C mutation was prospectively determined in tumour tissue by local laboratories using next generation sequencing (NGS), polymerase chain reaction (PCR) or Sanger sequencing. Patients with active brain metastases, carcinomatous meningitis, history of recent significant haemoptysis or haemorrhage, or prior treatment with a *KRAS* G12C inhibitor were excluded from study. Patients received adagrasib 600 mg orally twice daily as monotherapy until unacceptable toxicity or disease progression.

A total of 453 patients were enrolled and randomly assigned to a treatment arm. The duration of treatment with adagrasib was for a median of 3.9 months and a mean of 5.6 months and with docetaxel for 2.7 months and 3.2 months respectively.

The median age was 64 years (range: 34 to 83 years); 33% were female; 48% were White; 24% were Asian. Eastern Cooperative Oncology Group (ECOG) performance status was 0 (32%) or 1 (68%). Tumour histology was adenocarcinoma for 95% of patients, and 94% of patients had metastatic disease; 28% received 2 prior lines, 6.4% received 3 prior lines and 2.2% received 4 or more prior lines, 100% received both prior platinum and prior anti-PD-1/PD-L1 therapy. Sites of extra-thoracic disease included lymph node 62%, bone 24%, brain 18%, adrenals 20%, and liver 14%.

The primary efficacy endpoint was progression-free survival (PFS) in accordance with RECIST v1.1. Secondary endpoints included objective response rate (ORR) and duration of response (DOR). All endpoints were evaluated using blinded independent central review.

Efficacy results are summarised in Table 5.

*Table 5: Efficacy results for patients with confirmed *KRAS* G12C metastatic NSCLC in KRYSTAL-12 previously treated with platinum chemotherapy and an immune checkpoint inhibitor*

Endpoint	KRAZATI (n = 301)	Docetaxel (n = 152)
Progression-free survival^a		
Hazard Ratio (95% CI)	0.58 (95% CI: 0.45 to 0.76)	
p-value (2-sided, stratified)	< 0.0001	

log-rank test)		
Median in months (95% CI)	5.5 (4.5, 6.7)	3.8 (2.7, 4.7)
6-month event-free rate ^b (95% CI)	44.6 (37.8, 51.1)	30.1 (21.2, 39.5)
9-month event-free rate ^b (95% CI)	31.8 (25.1, 38.6)	15.2 (8.4, 23.9)
Objective Response Rate (95% CI)^a	31.9 (26.7, 37.5)	9.2 (5.1, 15.0)
p-value (2-sided, stratified Cochran-Mantel-Haenszel test)	< 0.0001	
Complete response rate, %	1.0	0
Partial response rate, %	30.9	9.2
Duration of Response^a		
Median ^b in months (95% CI)	8.3 (6.0, 10.3)	5.4 (2.9, 8.5)
% Patients with duration ≥6 months	37.5	21.4

^a Assessed by Blinded Independent Central Review (BICR)

^b Estimate using Kaplan-Meier method

The median PFS by BICR using an extended definition of events (ie, the time from randomization to the date of progression or death due to any cause, whichever occurs first; the extended definition includes progression or death events even after alternative cancer treatment or concomitant procedure for primary diagnosis or after ≥2 consecutive missed or non-evaluable tumor assessments) was 5.7 months (95% CI: 4.6 to 6.8 months) vs. 3.8 months (95% CI: 2.7 to 5.3 months) on the adagrasib arm vs. the docetaxel arm, respectively. The hazard ratio was 0.60 (95% CI: 0.47 to 0.78).

Paediatric population

The MHRA has waived the obligation to submit the results of studies with adagrasib in all subsets of the paediatric population for treatment of all solid and haematological malignancies (see section 4.2 for information on paediatric use).

Conditional marketing authorisation

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme. This means that further evidence on this medicinal product is awaited.

The MHRA will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetics of adagrasib have been characterised in healthy subjects and in patients with *KRAS* G12C-mutated solid tumours, including NSCLC. Adagrasib exhibits more than dose proportional increases in AUC and C_{max} over the dose range of 150 mg to 600 mg. With 600 mg twice daily dosing regimen in patients, adagrasib steady state was reached within 8 days of dosing, and adagrasib accumulated approximately 6-fold relative to a single dose. Daily fluctuations in adagrasib plasma concentrations were low (mean peak-to-trough ratio at steady state of 1.07).

Absorption

The median T_{max} of adagrasib is approximately 6 hours.

Effect of Food

No clinically significant differences in the pharmacokinetics of adagrasib were observed following administration of a high-fat and high-calorie meal.

Distribution

The geometric mean (CV%) apparent volume of distribution of adagrasib (V_z/F) is 942 L (57%). *In vitro*, human plasma protein binding of adagrasib is approximately 98.3%.

Elimination

The mean (CV%) terminal elimination half-life in patients is 23 hours (16%). The geometric mean (CV%) apparent oral clearance (CL/F) is 36.5 L/h (54%).

Metabolism

Adagrasib is metabolised primarily by CYP3A4.

Excretion

Following a single oral dose of radiolabelled adagrasib, approximately 75 % of the dose was recovered in faeces and 4.5 % recovered in urine.

Special populations

Based on a population pharmacokinetic analysis, no clinically meaningful differences in the pharmacokinetics of adagrasib were observed based on age (19 to 89 years), sex, race (White, Black and Asian), body weight (36 to

139 kg), ECOG PS (0, 1), or tumour burden. No clinically significant differences in the pharmacokinetics of adagrasib are expected in patients with mild to severe renal impairment (CL_{Cr} 15 to <90 mL/min estimated by Cockcroft-Gault equation) or in patients with mild to severe hepatic impairment (Child-Pugh classes A to C).

5.3 Preclinical safety data

Repeat Dose Toxicity

In repeat dose non-clinical safety studies with adagrasib, the primary finding in rats and dogs, administered with 150 mg/kg/day and 15 mg/kg/day respectively, was reversible phospholipidosis in multiple organs. In the rat, the target tissues included lung, trachea, heart, skeletal muscle, bone marrow, spleen, pancreas and female sex organs. In the dog, target tissues included bone marrow, lung, heart and spleen. The extent of vacuolation and the presence of foamy macrophages were more prominent in the rat as compared to dogs, and these effects occurred at systemic exposures (based on AUC) below those in humans administered adagrasib at 600 mg twice daily. Doses of 300 mg/kg/day in the rat and 30 mg/kg/day in dog were not tolerated. The main effects at this level in both species were weight loss, anorexia, emesis, inactivity, and respiratory distress. Main biochemical changes in blood included increased AST, cholesterol and fibrinogen. Changes in internal organs included enlarged adrenals, liver and spleen, and atrophied thymus.

Lower doses were generally well tolerated; however, aggregation of foamy macrophages and gross lung discolouration did not completely reverse in rats treated with 150 mg/kg/day but did decrease in severity suggesting that these effects are reversible. In dogs, impaired erythropoiesis associated with reticulocytopenia, erythrocytopenia and anaemia was observed at 25 mg/kg/day, indicating toxic effects of adagrasib on bone marrow. Margins of safety in both rat and dog compared with maximum recommended human dose (MHRD) were below 1.

Genotoxicity / Carcinogenicity

Adagrasib was not mutagenic or genotoxic in a battery of in vitro and in vivo assays. Carcinogenicity studies have not been conducted with adagrasib.

Reproductive Toxicity

Dedicated fertility studies with adagrasib have not been conducted in animals. In the general toxicology studies conducted in rats and dogs, orally administered adagrasib did not result in adverse effects on reproductive organs. However, there was evidence of vacuolation in female sex organs (ovaries, uterus and vagina) that was suggestive of phospholipidosis and reversed after cessation of dosing.

Adagrasib administration to pregnant rats at doses up to 270 mg/kg/day during periods of organogenesis led to maternal toxicities; however, at 90 mg/kg/day there were no adverse effects on maternal or foetal development. In rabbits, at doses of 30 mg/kg/day there were no adverse effects on dams and foetuses. Higher doses in rabbits led to maternal toxicities. In both the rat and rabbit studies, the exposures associated with no adverse effect dose levels were lower (less than 1-fold) compared to those obtained in humans at the clinical dose of 600 mg twice daily.

Photosensitivity

In vitro photosensitisation assays did not indicate phototoxic potential of adagrasib.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose (E 460)
Mannitol (E 421)
Crospovidone
Colloidal silicon dioxide (E 551)
Magnesium stearate (vegetable)

Film-coating

Hypromellose
Titanium dioxide (E 171)
Polydextrose (E 1200)
Talc (E 553b)
Maltodextrin
Medium chain triglycerides (vegetable)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

6.5 Nature and contents of container

Each carton contains one white opaque HDPE bottle with white, child resistant polypropylene closure with an aluminium foil heat induction seal. Each HDPE bottle contains two 1 g of silica gel desiccant containers.

Pack sizes: bottles with 120 and 180 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 15105/0194

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

09/06/2026

10 DATE OF REVISION OF THE TEXT

09/06/2026