9 November 2023
EMA/552099/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Krazati

International non-proprietary name: adagrasib

Procedure No. EMEA/H/C/006013/0000

Note

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

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List of abbreviations

AAS	Atomic Absorption Spectrometry
AP	Applicant's Part (or Open Part) of an ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
AS	Active substance
ASA	Acetylsalicylic acid
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
BCR	B-cell receptor
BCS	Biopharmaceutics Classification System
CEP	Certificate of Suitability of the Ph. Eur.
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human use
CIA	Collagen induced arthritis
CMA	Conditional marketing authorisation
CMS	Concerned Member State
CoA	Certificate of Analysis
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CRS	Chemical Reference Substance (official standard)
CV	Coefficient of variation
CVMP	Committee for Medicinal Products for Veterinary use
CVS	Cardiovascular studies
DC	Dendritic cells
DCM	Dichloromethane
DCP	Decentralised (Application) Procedure
DMF	Drug Master File = Active Substance Master File
DoE	Design of experiments
DPM	Drug Product Manufacturer
DSC	Differential Scanning Calorimetry
EC	European Commission
EDQM	European Directorate for the Quality of Medicines
EMA	European Medicines Agency
EO	Ethylene oxide
ER	Extraction ratio
EtO	Ethylene oxide
EtOH	Ethanol
EU	European Union
FDA	Food and Drug Administration
FMEA	Failure Mode Effects Analysis
FPM	Finished Product Manufacturer
FT-IR	Fourrier Transform Infrared Spectroscopy
GC	Gas Chromatography
GC-MS	Gas Chromatography-Mass Spectrometry
GLP	good laboratory practice
GMP	good manufacturing practice
HCT	Hydrochlorothiazide
HDPE	High Density Polyethylene
HPLC	High Performance Liquid Chromatography

HRMS	High Resolution Mass Spectrometry
IC	Ion Chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
Imp.	Impurity
IPA	Isopropanol
IPAc	Isopropyl acetate
IPC	In-process control
IR	Infrared
ITAM	Immunoreceptor tyrosine-based activation motif
ITP	Immune thrombocytopenia
IU	International Units
IUPAC	International Union of Pure and Applied Chemistry
KRAS	Kirsten Rat Sarcoma Viral Oncogene Homolog
KF	Karl Fischer
LCMS	Liquid chromatography mass spectrometry
LDPE	Low Density Polyethylene
LOA	Letter of Access
LOD	Limit of Detection
LOQ	(1) Limit of Quantification, (2) List of Questions
LT	Less than
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board
MeOH	Methanol
MS	Mass Spectrometry
ND	Not detected
NIR	Near Infrared Spectroscopy
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NOR	Normal operating range
NSCLC	Non-small cell lung cancer
NT	Not tested
OOS	Out of Specifications
PAR	Proven acceptable range
PCTFE	Polychlorotrifluoroethylene
PDE	Permitted Daily Exposure
PE	Polyethylene
PET	Preservative Efficacy Test
Ph.Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PK	Pharmacokinetics
PP	Polypropylene
PPM	parts per million
PVC	Poly vinyl chloride
QbD	Quality by Design
QC	Quality Control
QOS	Quality Overall Summary

QP	Qualified Person
QTPP	Quality Target Product Profile
QWP	Quality Working Party
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of an ASMF
RRT	Relative retention time
RSD	Relative standard deviation
RTBF	Relative thrombosis blood flow
SM	Starting material
SMQ	Standardised MedDRA Query
SPC	Summary of Product Characteristics
Spec.	(1) Specified, (2) Specification
SYK	Spleen tyrosine kinase
TAMC	Total Aerobic Microbial Count
TGA	Thermo-Gravimetric Analysis
THF	Tetrahydrofuran
TK	Toxicokinetics
TLC	Thin Layer Chromatography
TLR	Theoretic Logarithmic Reduction Factor
T_{max}	Time to achieve C_{max}
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of toxicological concern
TTO	Time to occlusion
TYMC	Total Combined Yeasts/Moulds Count
uHPLC	Ultra-High-Performance Chromatography
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XRD	X-Ray Diffraction
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mirati Therapeutics B.V. submitted on 28 April 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Krazati, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 16 September 2021.

The applicant applied for the following indication:

Krazati as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with KRAS G12C mutation, who have received at least one prior systemic therapy.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

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

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0511/2021 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Applicant's requests for consideration

1.5.1. Conditional marketing authorisation

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

1.5.2. New active substance status

The applicant requested the active substance adagrasib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Aaron Sosa Mejia Co-Rapporteur: Alar Irs

The application was received by the EMA on	28 April 2022
The procedure started on	19 May 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	10 August 2022
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	23 August 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	22 August 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	15 September 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 December 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	2 February 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	9 February 2023
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	23 February 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 April 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 May 2023
The CHMP agreed on a 2nd list of outstanding issues in writing to be sent to the applicant on	25 May 2023

The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	8 June 2023
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	20 June 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a conditional marketing authorisation to Krazati on	20 July 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	20 July 2023

1.8. Steps taken for the re-examination procedure

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

Rapporteur: Peter Mol Co-Rapporteur: Filip Josephson

The applicant submitted written notice to the EMA, to request a re-examination of Krazati CHMP opinion of 20 July 2023 , on	26 July 2023
The CHMP appointed Peter Mol as Rapporteur and Filip Josephson as Co-Rapporteur on	14 September 2023
The applicant submitted the detailed grounds for the re-examination (Appendix 3) on	13 September 2023
The re-examination procedure started on	14 September 2023
The CHMP Rapporteur's re-examination assessment report was circulated to all CHMP members on	17 October 2023
The CHMP Co-Rapporteur's assessment report was circulated to all CHMP members on	16 October 2023
The CHMP Rapporteurs circulated the Joint Assessment Report on the detailed grounds for re-examination to all CHMP members on	31 October 2023
SAG were convened to address questions raised by the CHMP on The CHMP considered the views of the SAG as presented in the minutes of this meeting.	25 October 2023
The detailed grounds for re-examination were presented by the applicant during an oral explanation before the CHMP on	6 November 2023
The CHMP, in the light of the scientific data available and the scientific discussion within the Committee, re-examined its initial opinion and in its final opinion concluded that the application satisfied the criteria for authorisation and recommended the granting of the conditional marketing authorisation on	9 November 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant seeks a conditional marketing authorisation (CMA) for the medicinal product Krazati (adagrasib) with the following therapeutic indication:

Krazati as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with KRAS G12C mutation, who have received at least one prior systemic therapy.

2.1.2. Epidemiology and risk factors

Lung cancer remains the leading cause of cancer-related death in Europe. Approximately 477,534 new cases of lung cancer were estimated to have been diagnosed in Europe in 2020, and 384,176 deaths were attributed to lung cancer (Ferlay, 2020). NSCLC accounts for 80% to 90% of lung cancers, while small-cell lung cancer has been decreasing in frequency in many countries over the past two decades (Planchard, 2018). KRAS G12C mutation occurs in approximately 13% to 14% of NSCLC, and almost exclusively in lung adenocarcinoma.

2.1.3. Biologic features

The RAS family of genes comprises 3 members, KRAS, NRAS, and HRAS, which are mutated in nearly 25% of all human cancers. KRAS is the most frequently mutated gene of the RAS family, with KRAS mutations occurring in approximately 30% of lung adenocarcinomas, 50% of colorectal carcinomas, and 90% of pancreatic ductal adenocarcinomas. The majority of KRAS mutations are missense mutations affecting residues (codons) 12, 13, and 61. Functional genomics studies have demonstrated that NSCLC cell lines exhibiting KRAS mutations are highly dependent on KRAS function for cell growth and survival (McDonald, 2017).

Mutations in KRAS occur in approximately one-third of cases and represent the most frequent driver mutation in lung adenocarcinoma, with KRAS G12C comprising nearly half of all KRAS mutations (Simanshu, 2017). Although most of KRAS-mutant NSCLC are diagnosed in former or active smokers, KRAS mutations can also be detected in never smoker patients with early onset of cancer, thus its mutational state cannot be predicted on the basis of smoking history alone (Riely, 2008). Remarkably, smokers and never smokers have a different spectrum of mutations and codon variants in KRAS. Thus, transition mutations (G12D) are more common in never smokers, whereas transversion mutations (G12C and G12V) are more common in former or current smokers. Moreover, KRAS-mutant NSCLC in smoker patients is genomically more complex, with a higher mutational burden and higher frequency of additional mutations in TP53 or STK11 genes compared to never smoker tumours, as result of antigenic exposure and oxidative stress in epithelial cells (Grazia, 2021).

2.1.4. Clinical presentation, diagnosis and prognosis

The natural history of lung cancer is one of progressive disease that is rapidly fatal (Detterbeck, 2008), and despite the significant advances of chemotherapy and immunotherapy for NSCLC, most patients

ultimately develop progressive disease. The 5-year survival of metastatic NSCLC remains at approximately 6% (Howlader, 2019), indicating that NSCLC is a serious and life-threatening condition with an unmet medical need.

From a clinical point of view, KRAS-mutant cancers have generally been associated with poorer overall survival (OS) compared to KRAS wild type tumours, especially in the advanced stages; however, other studies in early (where the benefit of adjuvant chemotherapy is minimal) or advanced stage of KRAS-mutant lung cancer have provided conflicting results, thus the prognostic value of KRAS alteration is still debated (Grazia, 2021). A systematic review and meta-analysis including 3,620 patients has shown that KRAS mutations confers a significantly worse prognosis in patients with lung adenocarcinoma (Mascaux, 2005).

2.1.5. Management

In the absence of a targeted treatment option, the preferred initial treatment of advanced/metastatic NSCLC is a combination of platinum-based chemotherapy and immune checkpoint inhibitor therapy. Immune checkpoint inhibitors (ICIs), including nivolumab, pembrolizumab, and atezolizumab, were first proven to be effective in the treatment of advanced NSCLC in the second-line setting (Borghaei, 2015; Garon, 2015; Herbst, 2016; Rittmeyer, 2017), followed by studies in the first-line setting demonstrating a survival advantage as monotherapy in patients with untreated, advanced NSCLC characterized by ≥ 50% tumour PD-L1 expression (Reck, 2016; Herbst, 2020), and in combination with a platinum-based chemotherapy regimen in the first-line, advanced disease treatment setting for patients with NSCLC regardless of PD L1 status (Gandhi, 2018; Socinski, 2018).

Docetaxel, alone or in combination with ramucirumab or nintedanib, and pemetrexed remain approved chemotherapy options in patients previously treated with platinum-based chemotherapy and a checkpoint inhibitor. Pemetrexed is much less common as an option in this setting due to earlier administration as part of first-line or maintenance settings (Gandhi, 2018; Planchard, 2018) and histology (Planchard, 2018).

In January 2022, the European Commission granted a Conditional Marketing Authorisation (CMA) to Lumykras (sotorasib) for the treatment of patients with previously treated NSCLC harbouring the KRAS G12C mutation. Such approval was based on pharmacological, efficacy and safety data from the CodeBreak 100 study, which showed favourable results from sotorasib in the overall population, with an ORR of 37.1% (95% CI: 28.6, 46.2) and a median DOR of 11.1 months (95% CI: 6.9, 15.0). Interim results from the confirmatory trial for such CMA (CodeBreak 200) are already available and indicate a median PFS of 5.6 months [95% CI 4.3–7.8] for sotorasib vs 4.5 months [3.0–5.7] for docetaxel; hazard ratio 0.66 [0.51–0.86]; p=0.0017 (de Langen, 2023). Overall survival is confounded due to cross-over.

Despite therapeutic advances, treatment for patients with advanced NSCLC and KRAS G12C mutation remains palliative, and there remains an unmet medical need with additional treatment options warranted.

2.2. About the product

Adagrasib, also known as MRTX849, 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.

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

Treatment with adagrasib was intended until disease progression or unacceptable toxicity.

2.3. Type of application and aspects on development

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

- The benefit-risk balance is positive.

There remains an unmet medical need for further therapeutic options in NSCLC, in particular if harbouring the KRAS G12C mutation, in spite of the availability of approved second-line therapeutic options in the field, demanding effective treatment alternatives with an acceptable safety profile. The available evidence of anti-tumour activity and safety of adagrasib as treatment of adult patients with advanced or metastatic with KRAS G12C mutation and who have received at least one prior systemic therapy, provides a sound and sufficiently robust basis for a preliminary positive risk-benefit evaluation:

o Registrational Study 849-001-Cohort A demonstrates a substantial and durable tumour response to adagrasib at a starting dose of 600 mg BID, administered in 3-week cycles.

o The safety profile of adagrasib is considered acceptable given the serious condition of the study population. There has been no indication of unacceptable risks.

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

With the already initiated and ongoing randomised, controlled Phase 3 Study 849-012, comprehensive and confirmatory clinical data in support of the claimed therapeutic indication will be provided following a CMA.

In addition, clinical studies of MRTX849 have been initiated or are ongoing, which will further contribute to the overall clinical experience with adagrasib.

- Unmet medical needs will be addressed, as adagrasib is a selective inhibitor of KRAS G12C. Based on the mode of action and the evidence gained so far, demonstrating a positive risk-benefit balance, adagrasib fulfils unmet medical needs in the second-line treatment of NSCLC with KRAS G12C mutation. The approval of sotorasib, a selective inhibitor of KRAS G12C, in the EU can be regarded as providing clinical validation for the paradigm of targeting KRAS G12C in NSCLC.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. In view of the anti-tumour activity, the favourable safety profile with no indication of unacceptable toxicities and risks in the patient population studied, and the limitations of available second-line treatment options, it is considered important to make adagrasib available to patients, including some who have no approved options. Adagrasib is deemed to provide additional benefit to public health with early market availability, even though comprehensive and confirmative clinical data are still required for selective KRAS G12C inhibitors. Unacceptable risks for public health have not been identified.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablet containing 200 mg of adagrasib.

Other ingredients are:

Tablet core: microcrystalline cellulose (E 460), mannitol (E 421), crospovidone, silica colloidal anhydrous (E 551), magnesium stearate (vegetable);

Film-coating: hypromellose, titanium dioxide (E 171), polydextrose (E 1200), talc (E 553b), maltodextrin, medium chain triglycerides (vegetable).

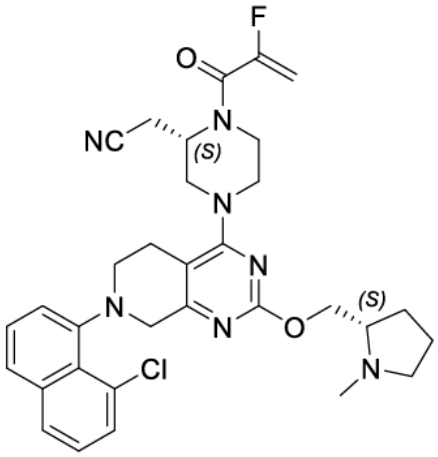
The product is available in a white opaque HDPE bottle with a white child resistant polypropylene closure and an aluminium foil heat induction seal, containing two 1 g of silica gel desiccant containers, as described in section 6.5 of the SmPC.

2.4.2. Active substance

2.4.2.1. General information

The chemical name of adagrasib is 2-[(2*S*)-4-[7-(8-chloronaphthalen-1-yl)-2-[[(2*S*)-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5*H*-pyrido[3,4-d]pyrimidin-4-yl]-1-(2-fluoroprop-2-enoyl)piperazin-2-yl]acetonitrile, corresponding to the molecular formula $C_{32}H_{35}ClFN_7O_2$. It has a relative molecular mass of 604.1 g/mol and the following structure:

Figure 1: active substance structure



The chemical structure of adagrasib was elucidated by a combination of X-ray crystallography, nuclear magnetic resonance (NMR) spectrometry, elemental analysis, Fourrier transformed infrared (FTIR) spectroscopy, electrospray ionisation mass spectrometry (ESI MS), and ultraviolet (UV)-visible spectroscopy. The polymorphic form of the active substance was determined by X-ray powder diffraction.

The active substance is an off-white solid, with low hygroscopicity. Solubilities at 37 °C are listed in Table 1.

Table 1: Solubility of adagrasib in aqueous media, at 37°C

Aqueous Media	Solubility (mg/mL)
HCl pH 1.2	> 262
Citrate Buffer pH 3.0	> 259
Citrate Buffer pH 4.5	0.497
Phosphate pH 6.8	< 0.010
Phosphate pH 7.4	< 0.010

Adagrasib exhibits stereoisomerism due to the presence of two chiral centres; the absolute configuration of both stereocenters is the *S*-configuration.

The sources of stereoisomerism are two of the starting materials and. The specifications for these starting materials contain a limit for the enantiomer impurity, which has been set based on purging experiments.

Also epimerisation of the stereogenic centre on the piperazine ring during the manufacturing process can result in the formation of a diastereomer (*R,S*-stereoisomer). Controls are in place in these steps to limit epimerisation, and the purification process was optimised in Process E to purge the diastereomer in the crystallisation of the final active substance.

Stereoisomeric purity is controlled routinely by chiral HPLC in two intermediates, and in the active substance, by means of a limit for the 3 possible stereoisomeric impurities, i.e. the *R,S*-isomer, the *R,R*-isomer and the *S,R*-isomer.

Polymorphism has been observed for adagrasib. Solid form screening studies demonstrate that there are five crystalline forms including three anhydrous forms designated as Forms 1, 2, and 5, and two hydrated forms, designated as Forms 3 and 4. Form 1 and Form 2, are suitable for development while polymorphic Form 3, Form 4, and Form 5 are considered unsuitable due to their metastable nature. Form 1 and 2 have been characterised by thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD), and dynamic vapor sorption (DVS). The two crystal forms (Form 1 and Form 2) have been shown to be similar with respect to rate of dissolution in physiological relevant media.

The manufacturing process was developed to produce active substance batches containing predominantly the desired polymorphic Form 2.

The polymorphic form 2 is stable during storage at ICH conditions.

Adagrasib is classified as a Class 2 compound according to the Biopharmaceutics Classification System as it is highly soluble at low pH but not highly soluble within the entire pH range of 1-6.8; it has high permeability in a Caco-2 cell monolayer model.

2.4.2.2. Manufacture, characterisation and process controls

Adagrasib is synthesised by a single source in four main steps using well defined starting materials with acceptable specifications. Two of the four starting materials are commercially available. During the procedure, a major objection (MO) was raised on the suitability of one of the proposed starting materials. The applicant responded by demonstrating that the diastereomer of the active substance () mainly forms by racemisation in the penultimate and final synthetic steps, rather than from the upstream chiral impurity of the concerned starting material, which anyhow is not present at levels above 0.1% in the starting material. This claim was further supported by purge studies. The applicant

also tightened the specification for the concerned proposed starting material in line with batch analysis results and restricted the sourcing of this starting material to a single supplier. Based on this, the MO was resolved.

Proven acceptable ranges have been established for all process parameters and the setpoints as well as normal operating ranges for process parameters are provided for each synthesis step. Process parameters considered critical were defined.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented and justified by purging studies. The suitability of analytical methods used for purge studies in the active substance has been demonstrated.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were satisfactorily discussed with regards to their origin and characterised.

Although the specification limits for genotoxic impurities as outlined in ICH M7 do not apply to active substances intended for advanced cancer therapy, all potential impurities have been assessed for being potentially genotoxic/mutagenic. Four impurities that could be present in the active substance when manufactured according to Process E were determined to be either mutagenic or potentially mutagenic substances, and for these a control strategy was defined, which was considered adequate.

The commercial manufacturing process (process E) for the active substance was developed in parallel with the clinical development program.

Impurity levels have been reduced due to improvements in purification, increased process efficiency, and controlling regulatory starting material purity through tightened specifications. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process. Process D was used to manufacture the active substance registration batches (primary stability batches), however formal stability data from the proposed process E have also been provided substantiating that the stability profiles are similar.

The active substance is packaged in sealed double low density polyethylene (LDPE) bags, inside a heat sealed aluminium bag. Silica gel desiccant packs are placed between the secondary LDPE bag and the aluminium bag. The filled bag(s) are placed into high density polyethylene (HDPE) drums. The LDPE bags comply with EC 10/2011 as amended.

2.4.2.3. Specification

The active substance specification shown in includes tests for: appearance (visual), identity (FTIR, HPLC), assay (HPLC), related substances (HPLC), stereoisomeric impurities (chiral HPLC), water content (KF), residual solvents (GC), polymorphic form (XRPD), particle size (laser diffraction), elemental impurities (ICP-MS), and sulphated ash/residue on ignition (Ph. Eur.)

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set in line with the batch- and stability data.

A MO was raised regarding the bridging of polymorphic forms and formulations during clinical development and inadequate control strategy to obtain the desired polymorphic form. Even if the two polymorphic forms have been demonstrated to be bioequivalent, the initially proposed specification limit for polymorphic form was not considered acceptable as the proposed limit was not in line with the process E performance, which produces predominantly form 2. As a response to this MO, the applicant has tightened the specification limit of the active substance to reflect the batch analysis data. An additional MO was raised on acceptability on the control strategy, i.e. inappropriate specifications for the active substance (the proposed limit for unspecified impurities in the active substance not complying with ICH Q3A (R2) requirements, the proposed limits for unspecified and specified impurities and for assay not aligned with the active substance batch release and stability data), for the designated starting materials (low and wide assay limits leading to potential presence of undetected impurities at significant levels in the active substance), and for the isolated intermediates (low and wide assay limits with mass imbalance of more than 10%). The applicant adequately responded by tightening the relevant specifications for the active substance, the starting materials, and the isolated intermediates.

ICHQ3D Class 1 and 2A elemental impurities are included in the specification, as well as palladium, since palladium catalysts are used in Step 1A and Step 2B of the active substance synthesis.

The Class 3 solvents isopropanol and n-heptane, used in the final crystallisation step, and the Class 2 solvent *N,N*-dimethylacetamide (DMAc), used in Step 3 of the active substance synthesis, are controlled to ICH Q3C limits. Benzene is controlled in the isopropanol, n-heptane, and acetone specifications .

Particle size limits for d10 and d50 have been introduced in addition to the initially proposed d90 to ensure a consistent particle size distribution reflecting manufacturing capacity.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data from four batches of active substance produced by the proposed manufacturer according to Process D, at approximately 30% of the production scale, stored in the intended commercial package for up to 12 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

Stability data from one batch of active substance produced by the proposed manufacturer according to Process E at approximately 50% of the production scale , and three process validation batches at full commercial scale, all stored in the intended commercial package for up to 12 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, assay, related substances, water content, stereoisomeric impurities, and polymorphic form. The analytical methods used were the same as for release and were stability indicating.

No changes or trends were observed for the tested parameters, except for a slight increase in the content of a degradant at 40°C/75% RH.

Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions acid, base, oxidation, heat/humidity and heat stress, were also provide on one batch.

Photostability studies revealed that the active substance degrades upon exposure to light.

The stability results justify the proposed retest period.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is an immediate-release film-coated tablet containing 200 mg of adagrasib. The film-coated tablet is white to off-white, oval, size 8.00 x 16.00 x 5.90 mm and debossed with "200" on one side and a stylised "M" on the other size.

Solubility of the active substance has been demonstrated to be pH-dependent (solubility decreases as pH increases) and the substance has been informed as BCS class II (low solubility-high permeability).

Polymorphic form and particle size are controlled in the active substance specification.

The applicant has satisfactorily addressed the different polymorphic forms of the active substance and why Forms 1 and 2 were chosen for development. Adequate control of the polymorphic forms has been ensured in the active substance specification, which was tightened with regard to the allowed amount of Form 1 in the active substance, this to respond to a MO (as described above). Stability of the polymorphic during storage has been demonstrated. It was demonstrated that neither the finished product manufacturing process (including tablet compression process) nor the finished product storage cause polymorph conversion.

The quality target product profile of the product was defined as listed in Table 2.

Table 2: Quality Target Product Profile (QTPP) for adagrasib tablets

QTPP Element	Target	Justification
Patient Population	Oncology patients	Based on clinical data
Route of administration	Oral	Ease of use for patient
Pharmacokinetics	Absorption T_{max} at least 2-10 hours	Based on clinical data
Dosage design	Immediate release	Based on intended clinical use
Dosage form	Tablet	Ease of administration
Dosage strength	200 mg	Anticipated high clinical dose and need for dosing flexibility
Stability	Shelf-life of at least 24 months	Suitable for commercial distribution
Container closure system	Plastic bottle with desiccant and child resistant cap	Need to achieve shelf-life and ensure product integrity for commercial distribution
Drug product quality attributes	Appearance	Quality attributes for drug product performance and safety, consistent with compendial requirements and regulatory guidelines
	Identity	
	Assay	
	Content Uniformity	
	Dissolution	
	Degradation Products	
	Microbial Limits	
	Water Content	

The critical quality attributes identified were: appearance, identity, assay, degradation products and purity, content uniformity, dissolution, water content and microbial limit.

Active substance particle size was demonstrated to have no impact on in vivo performance (clinical exposure-response). Powder density and flowability of the active substance did not impact on processability and finished product critical quality attributes. Nevertheless, active substance particle size is part of the active substance release specifications, to ensure consistency.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Compatibility of active substance with excipients was confirmed in accelerated stability studies during formulation development, and ICH stability studies on the final commercial formulation.

The proposed dissolution QC method comprises a standard test design for an immediate-release formulation with acceptable rotation speed. An MO was raised on dissolution method development, as a result of which the applicant further justified the choice of surfactant concentration and of the agitation speed, and tightened the finished product release and shelf-life dissolution specifications. Taking this response into account, CHMP concluded that the development of the dissolution method, including sink condition and discriminatory nature, has been sufficiently addressed. The discriminative capabilities of the proposed dissolution method were demonstrated to be as follows:

- Discriminating towards finished product core tablet hardness and formula composition of disintegrant (crospovidone) and lubricant (magnesium stearate)
- Not discriminating towards active substance particle size, polymorphic form, tablet coating weight gain and formula composition of glidant (colloidal silicon dioxide).

The applicant has provided a detailed overview of the manufacturing development conducted which allows to conclude that the manufacturing process developed is controlled and is suitable for intended use. Finished product pharmaceutical development and control strategy are considered traditional. Principles of enhanced approach as described in ICH Q8 through Q11 such as definition of a quality target product profile (QTPP), associated finished product critical quality attributes (CQA) as well as formulation and process risk assessments have been utilised in formulation and process development, but no design spaces have been claimed for the manufacturing process of the finished product. Selection, control and improvement on the manufacturing process intended for commercial production batches have been explained. Process/operating parameters have been identified that should be controlled to ensure that the product is of adequate quality. PARs are considered justified by development data presented.

During clinical development, different formulations (capsules and tablets) have been used with varying ratios of Form 1 and 2 adagrasib. An MO was raised on inadequate bridging between development formulations containing different ratios of forms 1 and 2, and the commercial tablet formulation which contains predominantly Form 2. The applicant adequately responded to the MO by providing additional characterisation data on Forms 1 and 2, supporting the similarity of the two crystal forms with respect to the rate of dissolution in physiological relevant media, and by implementing an appropriate specification limit for polymorphic form 1 in the active substance.

The primary packaging is a white opaque HDPE bottle with a white child resistant polypropylene closure and an aluminium foil heat induction seal, containing two 1 g of silica gel desiccant containers. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process consists of nine main steps: pre-blending, de-lumping, intragranular blending and lubrication, dry granulation, final blending and lubrication, compression, film-coating and packaging. The process is considered to be a standard manufacturing process.

The applicant has concluded that there are no critical steps in the process. This conclusion is supported by manufacturing development and the control strategy.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this film-coated tablet manufacturing process.

2.4.3.3. Product specification

The finished product specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (HPLC retention time + UV-spectrum), uniformity of dosage units (Ph.Eur.), assay (HPLC), degradation products (HPLC), dissolution (HPLC, Ph.Eur.), water content (KF, Ph.Eur.), microbial count (Ph.Eur.), absence of E. coli (Ph.Eur.).

Overall, the finished product specification has been adequately set in accordance with EU/ICH, Ph. Eur. and it is recognised to be based on batch and stability data. During the procedure, the applicant tightened the limits for specified degradation products, individual unspecified impurities and total impurities in the finished product release and shelf-life specifications in order to respond to an MO as discussed above.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment (according to option 2b) and the fact that elemental impurities are controlled in the active substance with a validated ICP-MS method, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

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

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and degradants testing has been presented.

Batch analysis results are provided for commercial scale batches manufactured with active substance from process E confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. The finished product is released on the market based on the above release specifications, through traditional final product release testing.

2.4.3.4. Stability of the product

Stability data from four primary stability batches of finished product, corresponding to about 27-50% of proposed commercial scale), stored for up to 18 months under long term conditions (2 ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of adagrasib tablets have been manufactured using active substance obtained from synthetic processes D which is different than process E proposed for marketing, however impurity levels in active substance from process E are lower than in active substance batches from process D, and the stability behaviour of batches of process D and E is considered similar. Hence, it is acceptable to rely on stability data from finished product batches with process D active substance, to set a shelf-life period and storage conditions.

The primary stability batches were packaged as 120 tablets in a 215 cc HDPE bottle with one 1-g desiccant canister, i.e. more headspace and less moisture protection compared to the proposed commercial package (120 tablets in 150 cc bottle and 180 film-coated tablets in a 215 cc bottle, with two 1-g desiccant canisters per bottle), respectively. Therefore, the stability data generated with the primary stability batches can be considered worst-case.

During the procedure, an MO was raised to request the available stability data from three PPQ batches of finished product manufactured at the proposed commercial scale, packaged in the proposed commercial packaging. The applicant responded by providing data for these batches, stored for under long term conditions (25ºC / 60% RH) and accelerated conditions (40ºC / 75% RH) according to the ICH guidelines.

Samples were tested for appearance, assay, degradation Products, chiral purity, dissolution, water content, polymorphic form. The analytical procedures used are the same as for release testing and are stability indicating. Also chiral purity and polymorphic form were tested, with a chiral HPLC and a XRPD method respectively.

In the primary stability study, a slight increase of two degradants and and a resulting increase in total impurities was observed after eighteen months at 25°C/60% RH (approximately 0.1%) and after six months at 40°C/75% RH (approximately 0.2%), but all remained within specification. Epimerisation of the stereogenic centers and polymorphic conversion of the active substance were not observed on storage of the finished product. The water content remained stable and within specification, confirming adequacy of the desiccant. OOS results were observed for unspecified impurities, which were identified to be active substance process related impurities. Due to the optimised impurity profile of process E active substance compared to process D batches, it is assumed that finished product batches with process E active substance will contain less process related impurities, which was confirmed by the available stability data for the PPQ batches, in which no OOS results and no significant changes were observed.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products, and also subjected to a forced degradation study. These studies indicated that potential degradation pathways are acid and oxidative conditions with and two main known degradation products. No significant degradation and no epimerisation were observed in basic conditions and ICH light, heat, and heat/moisture.

Based on available stability data, the proposed shelf-life of 24 months and storage conditions "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." as stated in the SmPC (section 6.3) are acceptable.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. During the procedure, a multidisciplinary MO (quality + pK) was raised on the characterisation and control strategy for the polymorphic forms and the bridging of the different ratios of polymorphic forms 1 and 2 and different formulations (capsules and tablets) used in clinical development, which was adequately responded to by the applicant. Furthermore, a second MO was raised on the suitability of one of the proposed starting materials, to which the applicant demonstrated by means of purge studies that epimerisation mainly occurs in the penultimate and final synthetic steps, rather than from the potential chiral impurity in the concerned starting material. The tightening of the specifications for the concerned starting material in line with batch analysis results, and the restricted sourcing of this starting material to a single supplier further enabled CHMP to resolve the MO.

A third MO was raised on acceptability on the control strategy. The applicant adequately responded by tightening the relevant specifications for the active substance, the starting materials, and the isolated intermediates. A fourth MO was raised on dissolution method development. The applicant further justified the choice of surfactant concentration and of the agitation speed of the dissolution method, and tightened the finished product release and shelf-life dissolution specifications. A fifth MO was raised on impurity limits. In response, the applicant tightened the limits for specified degradation products, individual unspecified impurities and total impurities in the finished product release and shelf-life specifications. Finally, the applicant provided 3-month stability data from three PPQ batches of finished product, manufactured at commercial scale, packaged in the proposed commercial packaging and stored for under long-term conditions (25 ºC / 60% RH) and accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines, which showed no OOS results and no significant changes.

Taken together, the results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.4.6. Recommendation(s) for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Adagrasib (MRTX849) is a mutant-selective small molecule covalent irreversible inhibitor of Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS) G12C and locks it in its inactive, GDP-bound conformation, which prevents KRAS G12C downstream signalling without affecting wild-type KRAS protein. When KRAS is mutated and activated, the MAP kinase pathway can become constitutively phosphorylated and activated leading to uncontrolled cellular growth and a malignant phenotype. Inhibition of mutant KRAS, in contrast, decreases the phosphorylation state of ERK1/2 and S6 and inhibits KRAS-dependent cellular growth and survival. Numerous studies have demonstrated KRAS mutant cancers are dependent on mutant KRAS for cell growth and survival.

In vivo pharmacology studies were conducted in mice as human xenografts growing in immunodeficient mice are a well-established and useful model in studying human tumour biology. In vivo safety pharmacology studies were performed in rats and beagle dogs, species that are well characterized and commonly used in non-clinical studies.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Adagrasib (MRTX849) was tested in a series of in vitro and in vivo pharmacology studies to evaluate its activity as a selective KRAS G12C mutant inhibitor. These studies included biochemical inhibition studies, cell proliferation and in vivo activity anti-tumour studies.

MRTX849 demonstrated high affinity and irreversible covalent modification of the cysteine at codon 12 and inhibition of a recombinant protein variant of KRAS G12C in which all native cysteines are mutated to serine or leucine (KRAS G12C-lite) in a mass spectrometry-based modification assay with an inhibition constant of 1.43 µM. The rate of covalent modification and inactivation of KRAS G12C-lite by MRTX849 was evaluated and the inactivation rate constant value was determined to 0.387 min^{-1} (study No PH-MRTX849-001). The selectivity of MRTX849 toward cysteine 12 of KRAS G12C, versus other surface-exposed cysteine residues present in other proteins, was evaluated in MRTX849-treated NCI-H358 cells utilizing mass spectrometry-based methods. Overall, MRTX849 demonstrated a high degree of selectivity toward Cys12 of KRAS G12C, versus other surface-exposed cysteines in the NCI-H358 proteome (study No PH-MRTX849-003).

Additional studies confirmed that modification of recombinant protein translated into inhibition of KRAS activity and KRAS-dependent signal transduction pathways in cells harbouring a KRAS G12C mutation. In an NCI-H358 cell-based assay MRTX849 inhibited the phosphorylation of ERK1/2, after a 3-hour incubation with an IC50 value of 17 nM (0.0103 µg/mL) (study No PH-MRTX849-002). In a series of 3D ultra-low adherent viability assays across a panel of KRAS G12C mutated and non-mutated cancer cell lines MRTX849 inhibited the growth of all 17 KRAS G12C-mutant cell lines with IC50 values ranging from 0.2 to 1042 nM. In contrast, IC50 values were greater than 3000 nM in three non-G12C-mutant KRAS models evaluated. In the same study concentration-dependent inhibition of phosphorylation of ERK1/2 and S6 of MRTX849 was demonstrated in NCI-H358 and MIA Paca-2 cell lines over a time course of 3 to 48 hours (study No PH-MRTX849-005).

Two MRTX849 human metabolites M11 (study No PH-MRTX849-015) and M68 (study No PH-MRTX849-024) were shown to have limited effects on KRAS-dependent downstream signal transduction and

phosphorylation of ERK1/2. M68 was not active (IC50 ≥ 10,000 nM) and M11 was approximately 80-fold less active (IC50 = 1519 nM) compared to MRTX849 (IC50 = 17 nM) suggesting that the metabolites do not contribute significantly to the pharmacological activity of MRTX849.

To help guide dose selection for pharmacologic evaluation of MRTX849, a 14-day toleration study of MRTX849 was conducted using female CD-1 mice. MRTX849 exhibited a slightly greater dose-proportional increase in AUC24 from 50 to 100 mg/kg/day. At the 100, 200, and 400 mg/mg/day dose levels in mice, increases in AUC24 were slightly less than proportional (study No PH-MRTX849-014).

The pharmacodynamic response to MRTX849 was evaluated over a range of dose levels following administration by oral gavage to NCI-H358 NSCLC tumour xenograft-bearing immunocompromised mice. A dose-dependent increase in plasma levels of MRTX849 was observed which correlated with a dose- and concentration-dependent increase in the fraction of covalently modified KRAS G12C mutant protein (study Nos PH-MRTX849-006 and PH-MRTX849-004). Signalling downstream of KRAS was inhibited following treatment with MRTX849 as measured by decreased pERK1/2 and pS6. Single- vs. multi-dose treatment with MRTX849 demonstrated sustained KRAS modification and inhibition of KRAS-dependent downstream signalling. In repeat-dose studies in the MIA PaCa-2 xenograft model, significant, dose-dependent anti-tumour activity was observed at the 3, 10, 30 and 100 mg/kg/day once daily dose levels and animals in the 30 and 100 mg/kg/day cohorts exhibited evidence of a complete response. Significant and dose-dependent anti-tumour efficacy was also observed in the NCI-H358 model including marked tumour regression at the 30 and 100 mg/kg/day dose levels (study No PH-MRTX849-006). MIA PaCa-2 xenograft-bearing mice were dosed once daily, twice daily or every other day by oral gavage at multiple dose levels to determine the effects of alternative dose schedules on anti-tumour activity. In general, anti-tumour efficacy or degree of tumour regression across different dose schedules was comparable. Plasma AUC24 values across the evaluated dose range were roughly dose-proportional (study No PH-MRTX849-011).
The anti-tumour efficacy of MRTX849 was evaluated at a fixed dose of 100 mg/kg/day once daily in a panel of human KRAS G12C-mutant xenograft models. MRTX849 demonstrated significant tumour regression in 18 of 23 models and marked tumour regressions of greater than 50% were observed in most models. In addition, the anti-tumour activity of MRTX849 was assessed in three non-G12C-mutant KRAS xenograft models, and significant anti-tumour activity was not observed (study Nos PH-MRTX849-012 and PH-MRTX849-013). In a model of brain metastasis using a luciferase-labeled LU99 cell line xenograft tumour model implanted intracranially into immunocompromised mice oral administration of 100 mg/kg MRTX849 twice daily led to significant anti-tumour activity, prolonged survival and marked tumour regression. The 100 mg/kg once daily dose level demonstrated a maximum response in the least sensitive tumour xenograft model and was associated with an AUC24 of 63.0 µg × h/mL and an estimated human Cav of 1544 ng/mL (study No PH-MRTX849-023).

The relationship of plasma concentration of MRTX849 to anti-tumour efficacy over a variety of dose levels and administration schedules was evaluated with particular emphasis on determining plasma exposure and pharmacokinetic parameters that correlated with the observed anti-tumour efficacy. The analysis of time-plasma concentration curves and associated anti-tumour efficacy indicated that AUC and Cav were closely correlated with the extent of anti-tumour efficacy compared with C_{max} or C_{min} (study Nos PH-MRTX849-011 and PH-MRTX849-022).

2.5.2.2. Secondary pharmacodynamic studies

The potential off-target secondary pharmacodynamic activity of adagrasib (MRTX849) was evaluated in vitro using selectivity assays against a panel of 44 enzymes, receptors and ion channels. MRTX849 at 10 µM demonstrated significant binding or inhibition on 18 targets including the potassium channel hERG (human) - [3H] dofetilide (study No PH-MRTX849-007). A follow-up assay further identified four

receptors with Ki values less than 1 µM. The receptors included alpha 1A adrenergic antagonist, muscarinic M2 antagonist, serotonin 5HT1A agonist, and serotonin 5HT1B antagonist, with Ki of 0.15 µM, 0.30 µM, 0.17 µM, and 0.14 µM, respectively. When compared with the observed free steady-state human C_{max} of 0.07 µM in patients treated with adagrasib 600 mg BID, the Ki values exceeded the clinical exposure by approximately 2- to 4-fold (study No PH-MRTX849-008).

2.5.2.3. Safety pharmacology programme

The potential effects of adagrasib (MRTX849) on the CNS were not evaluated in stand-alone studies but as part of the pivotal repeat-dose toxicology studies in rat and dog (study Nos TX-MRTX849-004, TX-MRTX849-012, TX-MRTX849-005 and TX-MRTX849-013). No specific CNS examinations were described in the study plan, nor reported in the study report, apart from general clinical observations and standard histopathological examinations. There were no remarkable clinical signs suggestive of CNS effects, nor were there microscopic changes in neuronal tissues.

No stand-alone respiratory safety studies of adagrasib were conducted. However, clinical signs of respiratory changes and histological examination of pulmonary tissues were examined in the 28-day and 13-week rat (study Nos TX-MRTX849-004, TX-MRTX849-012) and dog (study Nos TX-MRTX849-005, TX-MRTX849-013) repeat-dose toxicology studies. In the 28-day study in rats, the high dose males (300 mg/kg/day) became moribund starting on Day 21. One of the clinical signs in these moribund rats included impaired respiration that was associated with evidence of foamy macrophages suggestive of phospholipidosis. However, in the dog studies (up to 25/15 mg/kg/day), and in the rat 13-week study (up 150 mg/kg/day), there were no clinical signs of respiratory impairment based on general clinical signs despite the presence of foamy macrophages in the lung of some high dose rats and dogs in the 13-week and the 28-day repeat-dose studies, respectively.

Clinical signs of CNS and respiratory changes and microscopy of neuronal and lung tissues evaluated in the 28-day and 13-week repeat-dose toxicology studies in the rat and dog were used to assess CNS and respiratory safety pharmacology. In the 13-week studies: Cage side observations were carried out at least once daily (inside/outside cage), post dose observations were conducted once daily 1 to 4 hours post dose (inside cage or outside if necessary) and detailed clinical observations were performed at least once weekly (outside). In the 28-day studies: Cage side observations were carried out once daily 1 to 2 hours post dose (outside or inside not specified) and detailed observations were performed once weekly 4 hours post dose.

Adagrasib was evaluated for its effect on the hERG potassium channel, stably expressed in Chinese hamster ovary cells. The screening hERG study for adagrasib resulted in an IC50 of 4.8 µM (study No PH-MRTX849-009). In another study, a GLP hERG assay conducted in human embryonic kidney cells, the IC50 for adagrasib was 3.8 µM which is 54-fold above the human free C_{max} (0.07 µM). In addition, within the GLP hERG assay, two adagrasib metabolites MRTX2359 (also known as WX-41090 or M11) and MRTX4928 (also known as WX-42050 or M68) were also profiled for hERG inhibition and did not produce an IC50 at the highest concentration tested (10 µM) (study No PH-MRTX849-025).
M68 was not active (IC50 ≥ 10,000 nM) and M11 was more than 80-fold less active (IC50 = 1519 nM) compared to adagrasib (IC50 = 17 nM). Suggesting that both metabolites do not contribute significantly to the pharmacological activity of adagrasib.

In the isolated Guinea pig Langendorff study, adagrasib increased QTc by 8.4%, increased PR interval by 34.8%, and decreased ventricular development pressure by 44% at 5 µM. A 5 µM free concentration is 71-fold above the free efficacious C_{max} (0.07 µM) at steady state in humans after administration of adagrasib at 600 mg twice daily (study No PH-MRTX849-010).

In a single-dose (0 (vehicle), 5, 10, and 25 mg/kg) cardiovascular study in telemetry implanted dogs using a 4 x 4 Latin Square crossover design, there were no adverse findings in blood pressure, heart rate, or ECG parameters, including no changes in QT interval at adagrasib doses up to 25 mg/kg (study No TX-MRTX849-009).

Cardiovascular safety of adagrasib was also evaluated as part of the pivotal repeat-dose toxicology studies in dog (study Nos TX-MRTX849-004, TX-MRTX849-012, TX-MRTX849-005 and TX-MRTX849-013). Adagrasib induced no test article-related changes on ECG parameters or blood pressure following oral gavage at doses of 0 (vehicle), 5, 10, or 25 mg/kg/day for 28 days to dogs with a 14-day recovery period (study No TX-MRTX849-005). In addition, administration of adagrasib by oral gavage at doses of 0 (control), 5, 10, and 25/15 mg/kg/day for up to 13 weeks had no treatment-related effects on ECG rhythm, morphology, or quantitative measurements (heart rate, RR, PR, QRS, QT, or QTcV interval durations) in male or female dogs (study No TX-MRTX849-013).

Renal effects were monitored during the conduct of the rat (study Nos TX-MRTX849-004, TX-MRTX849-012) and dog (study Nos TX-MRTX849-005, TX-MRTX849-013) 28-day and 13-week repeat dose toxicology studies. In the rat, renal injury was possibly related to the morbidity seen in the 28-day rat study at dose levels of 300 mg/kg/day. However, there was no evidence of kidney injury in the 13-week rat study at doses up to 150 mg/kg/day. In the dog there were no remarkable clinical pathology changes suggestive of renal injury.

2.5.2.4. Pharmacodynamic drug interactions

No specific drug interaction studies have been conducted.

2.5.3. Pharmacokinetics

The nonclinical PK/TK properties of adagrasib were characterized in a series of *in vitro* and *in vivo* studies. Non-GLP *in vivo* PK studies with IV and/or PO administration were conducted in CD-1 mice, Sprague-Dawley rats, Beagle dogs and cynomolgus monkeys. Toxicokinetics were obtained from repeat-dose toxicology studies (2, 4 and 13 weeks) conducted in Wistar Han rats and Beagle dogs; and from embryo-foetal development studies in New Zealand White rabbits and Wistar Han rats (all in compliance with OECD GLP, except for the 2-week toxicology studies (non-GLP) and 4-week toxicology studies in rats/dogs (performed at a non-OECD MAD CRO)). The rat and dog were selected as preclinical species for toxicology studies based on results from *in vitro* and *in vivo* metabolism studies, which is supported. Further, *in vitro* and *in vivo* distribution studies in preclinical species and human, an *in vivo* excretion study in rats, and a range of *in vitro* studies on drug-drug interactions (DDI) were provided as part of the nonclinical PK/TK package for adagrasib.

Methods of analysis

Five validation reports on LC-MS/MS methods used to determine adagrasib concentrations in plasma from rats, dogs and rabbits were submitted by the Applicant. These methods were used in the GLP-compliant toxicology studies in rats and dogs and in the GLP-compliant EFD study in rabbits. Only the validated methods were considered for assessment, however, several qualified LC-MS/MS methods were used in non-GLP exploratory PK studies and TK studies in mice, rats, dogs, rabbits and cynomolgus monkeys.

The LC-MS/MS methods used in GLP-compliant toxicology/EFD studies conducted in rats, dogs and/or rabbits have been suitably validated. The intra- and inter-assay precision and accuracy is acceptable and in line with relevant guidance documents (EMEA/CHMP/EWP/192217/2009 Rev. 1, Corr. 2). Dilution integrity and selectivity as well as short-term stability, stability during freeze-thaw cycles and

long-term stability in plasma was sufficiently addressed. All samples from mentioned studies were analysed within the stability time line specified in the validation reports. Incurred sample reanalysis (ISR) was investigated in the GLP-compliant studies (TX-MRTX849-004, TX-MRTX849-005, TX-MRTX849-012, TX-MRTX849-013, TX-MRTX849-021) and results were acceptable in line with relevant guidance.

In vitro absorption

In vitro, adagrasib was shown to be both a substrate and an inhibitor of P-gp in MDR1-transfected cell lines (LLC-PK1; MDCK-II). Saturation of P-gp-mediated efflux occurred with increasing concentration of adagrasib. Further, it was shown that adagrasib has low absorption potential in Caco-2 cells as well as low brain penetration potential in MDR1-transfected MCDK-II

In vivo single dose PK

After IV-administration of adagrasib (3 mg/kg), half-life was 1.5, 4.1, 6.3 and 7.6 hours in mice, monkeys, rats and dogs, respectively. Estimated volumes of distribution of adagrasib were high across species (2-21 L/kg), indicating extensive distribution to tissue, which was later confirmed in oral studies incorporating [^{14}C]adagrasib administration in rats. Clearance was 20, 44, 30 and 37 ml/min/kg in mice, rats, dogs and monkeys, respectively. Bioavailability following single dose oral administration of adagrasib at 30 mg/kg was highest in mice (63%) and low-to-moderate in rats (30%) and dogs (23%), and peak concentrations (t_{max}) was reached at 1, 3 and 4 hours in mice, rats and dogs, respectively. Following a single oral dose of [^{14}C]adagrasib at 100 mg/kg to male and female rats, approximately 50% of the [^{14}C]adagrasib-derived radioactivity was absorbed.

Dose-escalating studies with PO administration were conducted with adagrasib in mice (50.0-400 mg/kg), rats (3.0-500 mg/kg) and dogs (3.75-300 mg/kg). Overall, C_{max} increased approximately dose-proportionally across species for the low dose ranges, and less than dose-proportionally at higher dose ranges. For AUC_{0-t}, exposure increased slightly greater than dose-proportionally in low dose ranges in mice and rats, and dose-proportionally in dogs. For all species, the same tendency as for C_{max} was observed in higher dose ranges, with less-than dose-proportional AUC_{0-t} with increases in dose.

When adagrasib was dosed orally to dogs (10 mg/kg) as either a suspension or as capsules, feeding slightly increased exposure parameters (AUC_{0-t}, C_{max}) compared to that observed in fasted dogs. A similar slight effect of food on exposure is observed in humans after a single dose of 600 mg adagrasib (SmPC section 5.2), but is not considered clinically significant.

In vivo repeat-dose TK

Repeat-dose toxicokinetics in rats

Adagrasib was administered PO once daily to Wistar Han rats in three repeat-dose TK studies of 14 days, 28 days, or 13-weeks. Across studies, t_{max} for tolerated doses (i.e. ≤150 mg/kg, see toxicology section) ranged from 1-8 hours in rats. In general, increases in dose of adagrasib lead to greater-than dose-proportional increases in exposure (C_{max}, AUC_{0-t}) across the tolerated doses tested (10-150 mg/kg) in all three repeat-dose studies. At the non-tolerated doses (i.e. 450 mg/kg in the 14-day study; 300 mg/kg in the 28-day study) exposure parameters were only available from Day 1, and increases were observed to be less-than dose proportional at these higher dose ranges (i.e. from 150 mg/kg to 300/450 mg/kg), as also observed in the single dose-escalating studies. Accumulation ratios ranged from 1.4-3.5 across the doses tested in the three studies.

In studies where both male and female rats were included (28-day and 13-week studies), exposure parameters were overall similar between the sexes, with a few exceptions: In the 13-week study, an increase in dose from 10 to 150 mg/kg (15-fold increase) lead to markedly greater-than dose-

proportional increases in C_{max} and AUC_{0-t}, however, to a much greater extent in males: 104- and 122-fold increase in AUC_{0-t} on Day 1 and 91 versus 33- and 80-fold increases on the same days for females. The difference in the extent of the greater-than dose-proportional increases on Day 1 between sexes may be explained by t_{last} being only 8 hours in males at 10 mg/kg, thus AUC is based on 1/3 of the time of the obtained AUC_{0-24} from the 150 mg/kg group males. Sex differences in increases in C_{max} with dose were also noted, however, less pronounced. Slightly higher dose-normalized AUC_{0-t}-values were observed for females on both Day 1 and Day 91 at 10 mg/kg.

Repeat-dose toxicokinetics in dogs

Adagrasib was dosed PO once-daily to Beagle dogs in three repeat-dose TK studies for 14 days, 28 days and 13 weeks. Across studies and doses, mean t_{max}-values for adagrasib ranged from 2 to 8 hours. Overall, there were no significant sex-related differences in exposure, in the 28-day and 13-week studies incorporating more than 1/animal/sex/dose (4-5 animals/sex/dose). Exposure parameters (C_{max} and AUC_{0-t}) in these studies generally increased slightly greater than dose-proportional with dose at lower dose levels (5 to 10 mg/kg), and dose-proportional or less-than dose-proportional at higher dose levels (10 to 25/15 mg/kg), a tendency also observed in single dose-escalating studies in dogs and in repeat-dose studies in rats. Accumulation ratios ranged from 1.8-3.5 across studies and dose ranges (28-day and 13-week study).

Repeat-dose toxicokinetics from EFD studies in pregnant rats and rabbits

TK data were available from a GLP dose range-finding EFD study in rats and a definitive GLP EFD study in rabbits. Pregnant rats were dosed orally once daily at 0, 30, 90, 150 or 300 mg/kg adagrasib through gestation days (GD) 6 and 17 and TK was evaluated on GD6 and 17. On GD6, t_{max} was reached between 4-24 hours (increasing with dose); on GD17 t_{max} was reached between 2-4 hours. Across the dose range (30-300 mg/kg), AUC_{0-t} increased greater than dose-proportionally (15- and 34-fold) on GD6 and GD17, whereas increases in C_{max} was dose-proportional on GD6, and greater than dose-proportional on GD 17. Slight accumulation was noted, and increased with dose in the range from 1.65-3.72.

Following once daily oral dosing at 0, 6, 15 or 30 mg/kg adagrasib to pregnant rabbits through GD7-20, t_{max} was reached at 1-4 hours on both GD7 and 20. Both AUC_{0-t} and C_{max} increased greater than dose-proportionally across the dose range on both GD7 and GD20. Accumulation was noted for adagrasib through the dosing period in pregnant rabbits as well, with accumulation ratios between 3.11-4.37.

Interspecies comparison and exposure multiples compared to the clinically relevant dose revealed that for most studies, exposure did not exceed that obtained in the clinic.

In vitro distribution

In vitro, adagrasib was highly bound to plasma protein in all species, with mean reversible protein binding values (at 0.1 µM adagrasib) of 99.1 % (mouse), 97.9 % (rat), 98.3 % (dog), and 98.3 % (human) with suggestion of protein binding saturation with increasing concentration. The binding of adagrasib to human serum albumin and human $alpha_1$-acid glycoprotein was 93.7% and 98.4%, respectively, also showing a trend towards saturation at the highest concentration tested.

Mean *in vitro* blood-to-plasma ratios were 1.08, 1.36, 1.65, and 0.7 for mouse, rat, dog and human, respectively, indicating a greater partitioning of adagrasib to blood in the two nonclinical species used for toxicology studies (rat, dog) compared to human. The mean blood-to-plasma ratio of adagrasib, was further shown to increase over time in an *in vivo* oral single dose distribution study conducted with [^{14}C]-adagrasib in male and female rats, suggesting a longer elimination phase in blood compared to plasma.

Mean unbound fractions of adagrasib in human liver microsomes at increased with adagrasib concentration and decreased with liver microsome protein concentration and ranged from 0.03-0.50. In cryopreserved human, rat, and mouse hepatocyte suspensions, the unbound fraction of adagrasib at 1 and 10 µM was 0.14 and 0.28; 0.20 and 0.21; and 0.12 and 0.16, respectively. Only modest concentration-dependent binding was observed between adagrasib concentrations of 0.1-10 µM (liver microsome study) and 1 and 10 µM (hepatocyte suspension study).

In vivo distribution

The distribution of [^{14}C]-labelled adagrasib following a single oral dose was investigated in fasted Sprague-Dawley (non-pigmented) and Long-Evans (pigmented) male rats, by means of quantitative whole-body autoradiography and radioanalysis. Results indicated that adagrasib is extensively distributed to almost all tissues in rats in agreement with the wide-spread phospholipidosis observed in multiple tissues in repeat-dose toxicity studies. Peak radioactivity concentrations occurred at 4-8 hours postdose, and the vast majority of tissue:plasma (T/P)-ratios were above 1 in both strains at all time points up to 24 hours post dose (except for most brain structures, suggesting less extensive distribution across the blood-brain barrier). Overall, tissue distribution was similar in both strains of rats, except for an affinity of [^{14}C]-adagrasib for pigmented tissues in Long-Evans rats; with quantifiable radioactivity until 168 hours post dose in pigmented skin, and until 672 hours post dose in the uveal tract and meninges, i.e. an affinity for melanin-containing tissues was observed. A phototoxicity study was conducted to address these findings, please refer to the toxicology section.

In the two strains, the highest radioactivity exposures were observed in intra- and extraorbital lacrimal glands, spleen, adrenal gland, Harderian gland (Sprague-Dawley); and in the pituitary gland, Harderian gland, meninges, eye and uveal tract (Long-evans). High exposures were also noted in tissues such as liver, lung, kidney, thyroid gland and salivary glands. Tissues with lowest exposures included spinal cord, brain (cerebellum, cerebrum, medulla, olfactory lobe), eye and bone (Sprague-Dawley), and whole brain, spinal cord, bone and abdominal fat (Long Evans). Radioactivity remained quantifiable by 72 hours post dose for ≈75% of evaluated matrices.

Plasma, brain and CNS exposure to adagrasib was also quantified in female CD-1 mice by LC-MS/MS, after a single oral dose of adagrasib at 100 or 200 mg/kg. At both doses, adagrasib was quantifiable in cerebrospinal fluid (CSF) and brain, with mean brain-to-plasma ratios ranging from 0.0281-0.136 and CSF-to-plasma ratios ranging from 0.000823 – 0.00594 across time points. Brain concentrations increased 3-4-fold from 1 to 8 hours at both dose levels, while CSF concentrations decreased to about half from 1 to 8 hours in the 100 mg/kg group, but approximately doubled from 1 to 8 hours in the 200 mg/kg group. However, the determination of CSF concentrations was associated with considerable variation (CV%: 55.8-99.0), i.e. the quantitative reliability of these results is questionable.

Transplacental transfer and excretion in milk

No data on transplacental transfer or excretion in milk were available.

In vitro metabolism

Hepatic extraction ratios (ERs) in liver microsomes and hepatocytes were intermediate (ERs between 30-70%) for adagrasib, predicting moderate hepatic clearance across species *in vitro* (mice, rats, dogs, humans). *In vitro* data from a study using GSH-supplemented liver cytosol suggests that GSH-mediated metabolism was a minor pathway for adagrasib in humans, while it was moderate in mouse and rat. No data were available from GSH-supplemented liver cytosol in dogs, however in a later *in vitro* study in hepatocytes, GSH-conjugation was shown to be a major metabolic pathway in this species. An *in vitro* stability study with adagrasib in whole blood from humans and preclinical species, showed minimal extrahepatic GSH-mediated metabolization, with >97% remaining adagrasib after incubation across species.

Eleven different metabolites (M1-M11) were identified across species *in vitro* after incubation of adagrasib with hepatocytes from mouse, rat, dog and human. Identified metabolic pathways included oxidation (M6-11) and GSH-conjugation (M1-5), and no unique human metabolites were observed. The most abundant oxidative metabolites were M10 and M11. In agreement with a previous *in vitro* study, the extent of GSH-conjugation was low in human hepatocytes compared to preclinical species. In terms of proportions of oxidative metabolites, similar profiles were observed between humans, rats and dogs.

Human CYP reaction phenotyping using individual recombinant human P450 enzyme isoforms, indicated that adagrasib is metabolized by CYP3A4, CYP2C8 and CYP2D6. The calculated contribution to in vivo clearance was 72% and 28% for CYP3A4 and CYP2C8, respectively. CYP2D6 contributed less than 5%. The potential to induce adagrasib metabolite formation was investigated for a range of recombinant CYP enzymes. CYP2C8, CYP2D6, CYP2J2, CYP3A4 and CYP3A5 induced formation of M10 and M55a; CYP2C8 induced formation of M11 and M66. The abundant human metabolite M68 was not formed by any of the rCYPs investigated. M55a and M10 was additionally formed after incubation with HLM.

In vivo metabolism

Plasma samples from PK studies in dogs, rats and mice were analysed for adagrasib metabolites following either a single dose (mice, rat, dog) or repeated dosing (dog, 14 days). While adagrasib was the major circulating component, five of the 11 metabolites identified *in vitro* were recovered in plasma across species and dosing regimens (M4, M5, M9, M10, M11). Of these, only M11 accounted for more than 10% of total drug in circulation (in male/female rats and in male dogs following a single dose of adagrasib). M11 is one of the two major adagrasib plasma metabolites formed in humans following repeat dosing of 600 mg BID x 8 days, comprising 17% of drug related material (the other being M68; accounting for 24% of DRM).

[^{14}C]Adagrasib underwent extensive metabolism in intact and BDC male and female rats after a single oral dose of 100 mg/kg. In total, 54 metabolites were detected across plasma, urine, bile and feces, whereof 37 were identified or proposed. No metabolite accounted for more than 10% of total plasma radioactivity or dose in the matrices tested. The predominant metabolization pathways for adagrasib were oxidation and glutathione conjugation. More specifically, metabolism in rats was mediated by oxidation, glutathione conjugation, oxidative *N*-demethylation and, to a lesser extent, by oxidative *N*- and *O*-dealkylation, dehydrogenation, oxidative dechlorination, and reductive defluorination. Secondary metabolism included dehydrogenation, hydrogenation, amide hydrolysis, *N*-acetylation, oxidation, glucuronidation, and sulfonation. In humans, adagrasib is metabolized by oxidative metabolism and to a lesser extent amide hydrolysis or oxidative *N*-dealkylation. In total, 26 metabolites were detected in bile in rats, 22 in feces, 7 in urine and 4 in plasma, i.e. the majority of adagrasib elimination occur through hepatic metabolism and fecal excretion.

In humans, screening for metabolites of adagrasib in plasma at steady state (study 849-001, PK-MRTX849-039), yielded 10 metabolites (M10, M9, M11, M57, M66, M68 and four unknown) whereof two (M68 and M11) comprised more than 10% of drug-related material (DRM) as determined by UV spectroscopy (M68: 24%; M11: 17%). M11 and M68 was shown *not* to contribute significantly to pharmacological activity in cell-based potency assays (see pharmacodynamic section). Plasma from rats and dogs collected at termination in the 13-week toxicology studies at the highest tolerated doses were subsequently analyzed for coverage of M11 and M68. By MS analysis, both M11 and M68 were detected in plasma from both rats and dogs, however, in neither species did levels of M68 reach those observed in human steady-state plasma, and were not detectable by UV spectroscopy. In rats, M11 was as abundant in plasma as in humans, as determined by UV spectroscopy, and to a lesser extent in dogs; i.e. under steady state conditions, M68 and M11 (pharmacologically inactive metabolites) are not

unique human metabolites and are covered by the toxicological species, although to a rather limited extent for M68. Following single-dosing of adagrasib to humans (study 849-005), metabolite M55a accounted for 13.6% of DRM but was not detected at steady state. M55a was detected in bile and feces in rats, following a single dose of [^{14}C]adagrasib.

Excretion

Following a single oral dose of 10 mg/kg adagrasib to male bile duct-intact rats, the cumulative recovery of parent compound was 40.3% of the nominal dose in feces and 0.036% in urine. In BDC rats, cumulative recovery was 0.55% in bile.

Following a single oral dose of [^{14}C]adagrasib at 100 mg/kg to bile duct-intact rats, the vast majority of excretion occurred via the fecal route, accounting for 93.7%-94.3% of the dose across sexes. Urinary excretion was minor, accounting for only 0.821%-1.05% of the dose. [^{14}C]adagrasib was the most abundant component of excreted radioactivity through both pathways in bile duct-intact rats. Metabolites of adagrasib were primarily excreted via the fecal route and cumulatively accounted for approximately 21.7% -25.8% of the dose across sexes.

Major excretory routes for [^{14}C]adagrasib in BDC rats were biliary (46.1%/38.1 of dose in male/female) and fecal (37.9%/29.6% of dose in male/female), with urinary excretion contributing to a lesser extent (5.97% and 10.8% of dose in male/female). [^{14}C]adagrasib was the most abundant component of excreted radioactivity through all pathways in BDC rats. Metabolites of adagrasib were present in all excreta and accounted for 0.4-0.8% (urine), 34.6-39.9% (bile), and 3.10-3.60% (feces) of dose in male and female rats.

Collectively, *in vivo* excretion studies showed that the majority of excretion of the parent compound occurs via hepatic metabolism and the fecal route, with only minor contribution from urinary and biliary routes. For the majority of adagrasib-derived metabolites, excretion occurs via the biliary route. In humans, the major excretion pathway for adagrasib is fecal, with limited urinary contribution (study no 849-005)

Pharmacokinetic drug-drug interactions

In vitro data suggests that adagrasib is a substrate for and an inhibitor of P-gp as well as BCRP. Extrapolation of the data also suggests potential inhibition *in vivo* of these transporters. Further, potential inhibition of OATP1B1, OCT1, MATE1, MATE2-K and BSEP was shown for adagrasib *in vitro*, with identification of potential for *in vivo* inhibition (by calculation/extrapolation) for OATP1B1, OCT1 and MATE-1.

Adagrasib was a substrate for recombinant human CYP enzymes with CYP3A4 being the most significant enzyme responsible for metabolization, followed by CYP2C8 and CYP2D6. The respective contribution to in vivo clearance was 78% (CYP3A4), 28% (CYP2C8) and <5% (CYP2D6). In another *in vitro* study, CYP3A4, CYP3A5, CYP2C8, CYP2D6 and CYP2J2 were shown to contribute to the formation of adagrasib metabolites M66, M55a, M11 and M10.

In human liver microsomes, adagrasib was shown to weakly reversibly inhibit CYP1A2, CYP2C8, CYP2C19 and CYP2D6 and to moderately reversibly inhibit CYP2B6, CYP2C9 and CYP3A4. The [I]/Ki values for CYP2B6, CYP2C9, CYP2D6 and CYP3A4 were > 0.02 indicating a potential for adagrasib to increase exposure of co-administered drugs metabolized by these enzymes *in vivo*. The potential of adagrasib to act as a time-dependent inhibitor of CYP2C8, CYP2C9, CYP2D6 and CYP3A4 was also investigated, and time-dependent inhibition by adagrasib on CYP3A4-mediated midazolam hydroxylation was demonstrated *in vitro* (PK-MRTX849-013). The potency of the inhibition was approximately 25% of the positive control (troleandomycin). The $(k_{obs} + k_{deg}) / k_{deg}$ value was >1.25, indicating potential time-dependent inhibition by adagrasib on CYP3A4 *in vivo*.

The potential of adagrasib to induce CYP3A4, CYP2B6 and CYP1A2 enzyme mRNA and activity was evaluated in primary hepatocytes from three individual human donors (PK-MRTX849-014). CYP3A4 mRNA was shown to be concentration-dependently induced by adagrasib in one donor. CYP3A4 enzyme activity decreased in a concentration-dependent manner in all three donors, in agreement with the observation from study PK-MRTX849-013 described above, indicating adagrasib to be a time-dependent inhibitor of CYP3A4.

Other pharmacokinetic studies

The applicant did not submit additional pharmacokinetic studies conducted with adagrasib, which is accepted.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No stand-alone single dose studies have been performed. This is acceptable.

2.5.4.2. Repeat dose toxicity

Exploratory (14 days dosing) and definitive GLP repeat-dose toxicity studies were conducted with MRTX849 in rats and dogs of up to 13 weeks of dosing. In all the repeat-dose toxicology studies, the free form of MRTX849 was prepared as a suspension using 10% (w/v) Vitamin E tocopheryl polyethylene glycol succinate (TPGS) in water. Oral gavage was used as the route of administration in all toxicity studies.

Adagrasib was administered by oral gavage in the repeat-dose studies, using a dose formulation prepared as a suspension using 10% (w/v) Vitamin E tocopheryl polyethylene glycol succinate (TPGS) in water. As the intended clinical administration route is oral, this is supported. TPGS is quoted in literature to exert anti-tumour effects on its own (Neuzil J, Dong LF, Ramanathapuram L, Hahn T, Chladova M, Wang XF. et al. Vitamin E analogues as a novel group of mitocans: anti-cancer agents that act by targeting mitochondria. Mol Aspects Med. 2007;28:607-45). The applicant explained the choice of vehicle for the toxicology studies as the TPGS vehicle produced a formulation that allowed for resuspension upon storage and a homogenous formulation suitable for repeat dose toxicology studies.

In the 14-day repeat-dose study in dogs (TX-MRTX849-003), the high dose male animal (4001) was observed to have severely increased ALT, AST and CK. These findings were correlated in the serum chemistry section with the following clinical signs noted by the attending veterinary: "*The changes correlated with the observations of relative high temperature, convulsions, gums pale and slight dehydration.*"

In several of the repeat-dose studies, mortality was observed, or animals were euthanized in extremis. This was often linked to decreased bodyweight and decreased food consumption, and general clinical signs as well as acute necrosis in one rat (450 mg/kg/day). In the rat 14 days DRF study, moribund animals administered 450 mg/kg/day had elevated liver enzymes that was associated with cytoplasmic vacuolation of hepatocytes, bile duct, and Kupffer cells. A similar effect was observed in rats administered 300 mg/kg/day in the 28-day rat study; however, these changes were considered non-adverse given the lack of elevated liver enzymes.

Adagrasib related changes was observed in several organs, including lung, trachea, heart, skeletal muscle, spleen, ovaries, uterus, and vagina in rats, and lung, heart, bone marrow, and spleen in dog in the 28-day studies. The changes observed mainly consisted of vacuolisation of cells, or infiltration of

tissues with foamy macrophages. Bone marrow effects were associated with decreased erythropoiesis. This effect was seen in the rat in the range-finding study at the non-tolerated dose of 450 mg/kg/day and correlated with a decrease in reticulocyte counts. In the 28-day rat study, similar effects in the bone marrow were associated with decreased erythrocytic precursors, but was not associated with clinical pathology changes and not considered adverse. In the dog studies, decreased erythropoiesis occurred in both males and females which was associated with decreased reticulocytes at ≥ 25 mg/kg/day.

In the rat 28-day study, target organs associated with adverse findings included lung, trachea, heart, skeletal muscle, spleen, ovaries, uterus, and vagina. In the dog 28-day study, target organs associated with adverse findings included the lung, heart, bone marrow, and spleen. In the 13-week studies, microscopic findings were noted in multiple tissues that were consistent with phospholipidosis; however, these findings were not considered adverse, but dose levels were also lower (high dose level 150 mg/kg/day vs 300 mg/kg/day and 25/15 mg/kg/day vs 25 mg/kg/day for the rat and dog studies respectively).

MRTX849 treatment was associated with phospholipidosis based on the presence of foamy macrophages and vacuolated epithelium most likely containing "myeloid bodies" (Shayman, 2013). These changes occurred in multiple tissues and prominent in rats treated with the non-tolerated dose level of MRTX849 (≥ 300 mg/kg/day). In the dog, vacuolated tissues were present, but the effect appeared to be less severe, but this was also well correlated with lower exposure margins achieved in the dog studies, compared to rat. In most studies and dose levels, the exposure margins were <1 to the human exposure at the MHRD. Although the pathophysiological consequence of phospholipidosis is not well described, the vacuolated changes in the absence of degenerative effects is not considered adverse and these changes are reversible (Chatman, 2009).

In the 28-day repeat dose dog study (TX-MRTX849-005) microscopic changes in the heart were limited to one high dose (25 mg/kg/day) male dog, characterized as subacute myocardial necrosis in the papillary muscle along with mild vacuolation. In addition, one recovery high-dose dog had papillary muscle fibrosis, suggestive of a reparative process after myocardial necrosis. In the 13-week repeat dose dog study microscopic changes of heart were not evaluated (TX-MRTX849-013. The applicant considered that these microscopic changes of heart were MRTX849-induced and speculated that this type of cardiac lesion in dogs is often associated with vasodilators and positive inotropic/vasodilating drugs. It was discussed that since the C_{max} of adagrasib (25 mg/kg/day) was 2-fold lower than the IC50 of the alpha-1-adrenergic receptor in the 28-day dog study (TX-MRTX849-005), it was unlikely to cause vasodilation. This conclusion is supported. The precise mechanism of the adverse cardiac change in one male dog is not known.

The repeat-dose toxicity studies in rats and dogs did not reach exposure levels exceeding the exposure observed in the clinic following administration of 600 mg BID (MHRD). Even dose levels where mortalities were observed, or animals having to be euthanised were similar or below human exposure levels. These severe non-clinical findings are reflected in the SmPC or the RMP.

2.5.4.3. Genotoxicity

The genotoxicity of adagrasib was assessed in a screening bacterial mutation assay (TX-MRTX849-006), a screening in vitro chromosomal aberration assay (TX-MRTX849-007), a definitive bacterial mutation assay (TX-MRTX849-010), and a chromosomal aberration assay (TX-MRTX849-011). The in vitro assays were conducted with and without exogenous Aroclor-induced rat liver S9 and adagrasib concentrations up to those limited by cytotoxicity or solubility. In vivo, the clastogenic effects of adagrasib were evaluated in rats by measuring micronuclei present in peripheral blood reticulocytes

after oral dosing at 250, 500, and 1000 mg/kg/day for two days (TX-MRTX849-016). The 1000 mg/kg/day dose was selected as the maximum tolerated dose based on lack of tolerability at 2000 mg/kg/day in an initial range-finding study.

In summary, adagrasib was negative in all the genotoxicity studies

2.5.4.4. Carcinogenicity

No carcinogenicity studies have been submitted.

2.5.4.5. Reproductive and developmental toxicity

DRF and definitive EFD studies were performed in Wistar rat and NZW rabbits. No fertility, early embryonic development or PPND studies were performed. This is considered acceptable as adagrasib is intended for treatment of advanced cancer, and the ICH S9 guideline applies.

In the EFD studies performed in rats and rabbits, no embryofetal teratogenicity or malformations were observed at dose levels that did not exert maternal toxicity.

At dose levels which were clearly toxic at the maternal level, (50 mg/kg and above) in NWZ rabbits maternal mortality as well as embryofetal toxicity and lethality was observed. In pregnant Wistar rats skeletal variations and malformations were observed at the high dose level of 270 mg/kg/day, which was also clearly toxic to the pregnant dams. Based on maternal body weight loss, lower mean body weight gain, and lower food consumption at 270 mg/kg/day, a dose level of 90 mg/kg/day was considered to be the NOAEL for maternal and embryofetal developmental toxicity for adagrasib in rats.

The lack of any dedicated FEED and PPND studies is acceptable, as adagrasib is intended for treatment of advanced cancer.

In the repeat-dose studies, vacuolation in sex organs were observed in both males and females, at dose levels of 150 mg/kg/day or above (rats) and at the 100 mg/kg/day dose level in dog in the 14-day DRF study. In the dog, similar findings were not observed in the longer duration studies, however, the dose levels were also lower, due to toxicity findings. The vacuolation observed in male sex organs were considered non-adverse, and possibly related to phospolipidosis as also observed in other tissues. This can be accepted, however, it should be noted that the exposure levels achieved were similar or below exposure in humans at MHRD.

In female rats, vacuolisation in corpora lutea in ovaries, glandular epithelium in the uterus, vaginal mucosa and mild atrophy with mucification of the vaginal mucosa in females treated with 300 mg/kg/day adagrasib. Non-adverse vaginal mucification were observed in the 150 mg/kg/day group in the 28-day study. The findings were reversible.

2.5.4.6. Toxicokinetic data

See repeat dose TK studies in section 3.2.3. Pharmacokinetics

2.5.4.7. Local Tolerance

No dedicated tolerance studies were submitted. Vomiting was observed in the dog studies, but histological changes in the stomach was only observed in the rat 14 days DRF study at dose levels of 450 mg/kg. These changes consisted of moderate hyperplasia of the squamous epithelium that was associated with mild to moderate hyperkeratosis, but were not associated with notable inflammation or

evidence of erosion or ulceration. All affected animals had a correlative macroscopic observation of multiple depressions in the mucosa of the non-glandular region. These effects were not seen in other repeat-dose studies (high dose levels 300 mg/kg/day and 150 mg/kg/day). These effects were also not seen at lower doses in the DRF study.

2.5.4.8. Other toxicity studies

No specific studies were performed regarding antigenicity or dependence. This is acceptable.

No specific immunotoxicity studies with MRTX849 were presented. However, as [14C]-MRTX849 distribute to the lymphoid tissues and the repeat dose toxicity studies in rats and dogs (TX-MRT849-004, TX-MRT849-012, TX-MRT849-005) indicated microscopic changes in lymphoid tissues (thymus, spleen, mesenteric lymph nodes), therefore suggesting lymphoid organs may be the potential targets for MRTX849. It is further clarified that adagrasib-induced microscopic changes in lymphoid tissues, do not appear to translate into an immunotoxicity risk is supported. Omission of specific immunotoxicity studies is therefore accepted.

Metabolites

The two major human metabolites M11 and M68 were screened for genotoxic potential in vitro in an limited AMES test (only using strains TA98 and TA100) and in a micronucleus test. In the AMES test, both metabolites were found devoid of mutagenic potential. In the study report TX-MRTX849-0026 the following was concluded; Under the experimental conditions reported herein, WX-41090 and WX-42050 were considered equivocal for inducing micronuclei in TK6 cells up to the limit of cytotoxicity or solubility. Considering the metabolites are formed in rat, and no genotoxicity was observed in studies performed with adagrasib in rats, it is supported that no further studies are required.

Impurities

A number of impurities were tested either in standalone studies of 28 days duration, in screening *in vitro* Ames tests or present in the non-clinical batches used in the TX-MRTX849-004 study was also specified. However, only the degradation products, two impurities and are specified separately in the proposed specification of the adagrasib tablet formulation to be marketed, at a limit which is acceptable based on the standalone 28-day study performed with these two impurities, where rats received 2 mg/kg/day of either impurity. Furthermore, these two impurities were specified in the drug substance used in the repeat-dose toxicity studies in rats and dogs for the 28 days and 13 weeks dosing duration. However, one impurity was not found (<0.05% w/w) and the other was present in the batches used in the 28 day and 13-week study respectively.

Of the impurities mentioned in the quality section, only one of the impurities tested by the applicant was found to be positive for genotoxic potential in silico using a statistical based (Leadscope Model applier) and rule based (Derek-nexus) model. One impurity () was flagged as a potential mutagenic impurity, but a screening AMES test (using only salmonella strains TA98 and TA100) did not show any potential for mutagenicity at concentrations up to 500µg/plate. However, in study TX-MRTX849-008, which flagged as positive for genotoxicity, and were also flagged as positive for genotoxicity.

Phototoxicity

An in vitro study of adagrasib phototoxicity potential was performed in mouse fibroblast BALB/c 3T3 cells. Adagrasib was found to be slightly phototoxic and slightly cytotoxic, but the threshold values were not exceeded, hence the compound is not designated as phototoxic. Adagrasib distributes to pigmented cells including uveal tract (C_{max} was 270000 ng eq/g at the last sampling time of 672 hours postdose in a distribution study in rats). The absorption spectrum provided in the quality section cuts

the scan off at 400 nm as there is no absorption above this wavelength. There is very little absorption between 290 and 700 nm; therefore, there is no risk for phototoxic potential as outlined in ICH S10.

2.5.5. Ecotoxicity/environmental risk assessment

A brief ERA assessment has been submitted by the applicant.
Adagrasib PEC surfacewater value is above the action limit of 0.01 µg/L hence further ERA studies are required.

A preliminary Log Kow (Pow) was stated to be 5.81 (Study report no. CP824U05) using a shakeflask method, however, in this study adagrasib could not be detected in the buffer phase.

Summary of main study results

Substance (INN/Invented Name): adagrasib/Krazati			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	5.81	Potential PBT (Y)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.027	µg/L	> 0.01 threshold (Y)

2.5.6. Discussion on non-clinical aspects

Pharmacology

The in vitro and in vivo primary pharmacodynamic studies provided adequate evidence that adagrasib is a potent and selective inhibitor of KRAS G12C. The general pharmacology studies showed adagrasib is a covalent KRAS G12C inhibitor that inhibits the growth of KRAS G12C-mutant models. Adagrasib selectively inhibited the growth of KRAS G12C-mutant cell lines in vitro and exhibited dose dependent inhibition of KRAS G12C protein and downstream signal transduction in xenograft models. Adagrasib induced tumour regression across a panel of KRAS G12C-mutant human cell line xenograft and patient-derived xenograft models at doses that were well tolerated. Overall, in vitro and in vivo studies of adagrasib were relevant in relation to the disease to be treated and the proposed indication. Proof of concept and mode of action of the substance were demonstrated and is endorsed.

A relatively limited selection of targets (44) led to a rather large number (18) of significant off-target activity of adagrasib. A follow-up assay further identified four receptors with Ki values less than 1 µM. The receptors included alpha 1A adrenergic antagonist, muscarinic M2 antagonist, serotonin 5HT1A agonist, and serotonin 5HT1B antagonist, with Ki of 0.15 µM, 0.30 µM, 0.17 µM, and 0.14 µM, respectively. When compared with the observed free steady-state human C_{max} of 0.07 µM in patients treated with adagrasib 600 mg BID, the Ki values exceeded the clinical exposure by approximately 2- to 4-fold.

The safety pharmacology assessment of MRTX849 was carried out in accordance with the ICH guideline S9. Overall, it was demonstrated that adagrasib poses a low risk for adverse effects on major physiological systems. There were no CNS related effects in the repeat-dose toxicology studies, while in moribund rats treated at 300 mg/kg/day, there were observations of laboured breathing suggestive of altered respiratory function due to accumulation of foamy pulmonary macrophage and the overall moribund nature of this non-tolerated dose in rats.

Based on in vitro hERG binding, in vitro Langendorff study and ECG parameters collected in the repeat-dose dog toxicology studies no safety concern with regard to risk for QT prolongation was identified at the doses tested. Of note in the 28-day repeat-dose study (study No TX-MRTX849-009) in dogs indirect blood pressure recordings were performed from the tail roots or other appropriate sites. However, this method is not considered fit for purpose to obtain accurate measurements and to detect blood pressure fluctuations in a safety pharmacology context. It is accepted that the ECG recordings in the recovery period were not analysed due to lack of cardiac effects at the end of the dosing period.

It should be taken into consideration that low margins of exposure ranging from 0.3 to 2.4 were observed in the 28-day and 13-week repeat-dose studies in rat and dog. And in general, the observed exposure at NOAEL levels were similar or below the exposure level at the maximum human recommended dose.

Adagrasib treatment at 600 mg twice daily poses a low risk for a QT prolonging effect however, clinical observations suggest that a signal exists. The applicant states that mitigation of the risk of QT prolongation and Torsade de pointes specifically includes limiting use in patients with other risk factors (baseline QT prolongation or family history of long QT syndrome, congestive heart failure), avoiding concomitant use with use with drugs known to prolong QT, and supplementing potassium and magnesium if levels are low.

Pharmacokinetics

Overall, the pharmacokinetics of adagrasib were considered adequately described in the nonclinical package provided, and there are no remaining issues to resolve.

Toxicology

The primary MRTX849-related target organ effects were likely caused by phospholipidosis observed in multiple tissues examined in both rats and dogs in the repeat-dose toxicology studies with frequency and severity based on dose. In the rat 28-day study, target organs associated with adverse findings included lung, trachea, heart, skeletal muscle, spleen, pancreas, bone marrow, ovaries, uterus, and vagina. The extent of vacuolisation and the presence of foamy macrophages were more prominent in the rat as compared to dogs. In the dog 28-day study, target organs associated with adverse findings included the lung, heart, bone marrow, and spleen. In the 13-week studies, microscopic findings were noted in multiple tissues that were consistent with phospholipidosis; however, these findings were not considered adverse, but dose levels were also lower (high dose level 150 mg/kg/day vs 300 mg/kg/day and 25/15 mg/kg/day vs 25 mg/kg/day for the rat and dog studies respectively). In most studies and dose levels, the exposure margins were <1 to the human exposure at the MHRD. Although the pathophysiological consequence of phospholipidosis is not well described, the vacuolated changes in the absence of degenerative effects are not considered adverse and the changes observed were reversible. These findings were adequately reflected in the SmPC. Furthermore, the severe toxicity signals at high dose levels which resulted in similar or even lower exposure levels compared to the clinical exposure (mortalities and animals needing to be euthanised) has been included in the SmPC section 5.3 and the RMP.

In the reproductive toxicity studies, no teratogenicity or embryofetal lethality was observed at dose levels that did not show maternal toxicity. However, none of the dose levels achieved allowed for any margin of safety, as they were below the clinically relevant exposure in both rats and rabbits.

The repeat-dose toxicity studies in rats and dogs and the EFD studies in rats and rabbits, did not achieve sufficient exposure levels at NOAEL's exceeding the exposure observed in the clinic following administration of 600 mg BID (MHRD). This is reflected in the SmPC and the RMP.

Overall the submitted studies of potential for genotoxicity suggest that there is no clear signal for genotoxicity for adagrasib. It should be noted that the in vitro tests were performed at a non-OECD MAD CRO. However, the in vivo study was performed at an OECD GLP adherent facility. The outcome of all genotoxicity studies was negative and thus it can reasonably be assumed that there is no genotoxic hazard to humans of adagrasib.

The lack of any carcinogenicity studies is considered acceptable, based on the proposed indication being in the scope of ICH S9.

As the product is intended for oral administration (tablets), and the animals were dosed via oral gavage in the toxicology studies, the lack of any dedicated local tolerance studies is considered acceptable.

There is very little absorption between 290 and 700 nm; therefore, there is no risk for phototoxic potential as outlined in ICH S10.

Environmental risk assessment

The provided ERA consists of a Phase I screening, and it was established that the PECsurfacewater value is above the action limit of 0.01 µg/L. Hence further ERA studies were required. These had not been provided yet, but the Applicant proposed a list of ERA studies to be conducted. As a result of the above considerations, the available data did not allow to conclude definitively on the potential risk of adagrasib to the environment.

The applicant committed to performing the following studies as follow-up measures:

- Adsorption – Desorption study (OECD 106)
- Ready biodegradability study (OECD 301)
- If adagrasib is not readily biodegradable, an aerobic transformation study in aquatic
- Sediment systems (OECD 308) will be performed
- Algae, growth inhibition study (OECD 201)
- Daphnia sp., reproduction study (OECD 211)
- Fish, early life stage toxicity study (OECD 210)
- Activated sludge, respiration inhibition study (OECD 209)
- Fish bioaccumulation study (OECD 305) since adagrasib has Log Kow >3
- OECD 107/117/123 to determine LogKow or LogDow at 3 pH values (e.g. 5, 7 and 9).

The need for any further ERA studies would need to be determined upon completion of the above studies, and the applicant proposed to submit these potential follow-up studies at a later stage.

2.5.7. Conclusion on the non-clinical aspects

Overall, the primary pharmacodynamic studies provided adequate evidence that adagrasib is a potent and selective inhibitor of KRAS G12C. In vitro and in vivo proof of concept, mechanism of action and mode of action were demonstrated. When assessed against a panel of receptors, ion channels, and enzymes significant off-target activity of adagrasib was observed. No safety pharmacological concern was identified with regard to central nervous, respiratory and renal systems. Based on in vitro hERG and ECG parameters collected in the repeat-dose dog toxicology study, adagrasib poses a low risk for QT prolongation. Studies on pharmacodynamic drug interactions were omitted.

Overall, the pharmacokinetic/toxicokinetic profile of adagrasib was adequately characterized in the submitted non-clinical package. Initial PK studies were performed in mice, rat, dog and monkey. The rat and dog were chosen species for toxicology studies.

Overall, the toxicology programme revealed that treatment with adagrasib resulted in phospolipidosis in several tissues, where severity increases related to dose level. These findings were adequately reflected in the SmPC.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Table 3: Clinical and clinical pharmacology studies with adagrasib

Clinical or Clinical Pharmacology Studies	Brief Name	Study Title
849-001	Phase 1/2 First-in-Human in Patients	A Phase 1/2 Multiple Expansion Cohort Trial of MRTX849 in Patients with Advanced Solid Tumors with *KRAS* G12C Mutation
849-003	Hepatic Impairment	A Phase 1, Open-label, Nonrandomized, Single-dose Study to Investigate the Safety, Tolerability, and Pharmacokinetics of MRTX849 in Subjects with Mild, Moderate, and Severe Hepatic Impairment Compared to Subjects with Normal Hepatic Function
849-004	Renal Impairment	A Phase 1, Open-label, Nonrandomized, Single-dose Study to Investigate the Safety, Tolerability, and Pharmacokinetics of MRTX849 in Subjects with Mild, Moderate, or Severe Renal Impairment Compared to Subjects with Normal Renal Function
849-005	Mass Balance	A Phase 1, Open-label Study of the Absorption, Metabolism, Excretion Following a Single Oral Dose of [^{14}C]-MRTX849 in Healthy Male Subjects
849-006	DDI with P-gp/CYP3A4 modulators, PPI, and substrates of CYP2C9, CYP2D6, CYP3A4, BCRP, and P-gp	A Phase 1, Open-label, Parallel, 4-arm, Fixed-sequence Study to Investigate the Effect of Coadministration of P-glycoprotein Inhibitor, CYP3A4 Inhibitor, CYP3A4 Inducer, and Increased Gastric pH on the Pharmacokinetics, Safety, and Tolerability of MRTX849 and the Effect of MRTX849 on the Pharmacokinetics of CYP2C9, CYP2D6, CYP3A4, Breast Cancer Resistance Protein, and P-glycoprotein Probe Substrates in Healthy Subjects

849-011	Relative BA and Food Effect	A Phase 1, Three-part, Open-label, Randomized, Crossover Study to Investigate the Relative Bioavailability and Food Effect of Different Formulations of MRTX849 in Healthy Subjects
849-015	BE	A Phase 1, Fully-Replicate Designed Bioequivalence Study to Compare MRTX849 Capsule and Tablet Formulations in Healthy Adult Subjects

BA = bioavailability; BCRP = breast cancer resistance protein; BE = bioequivalence; CYP = cytochrome P450; DDI = drug-drug interaction; P-gp = P-glycoprotein; PPI = proton-pump inhibitor.

Table 4: Ongoing trials of adagrasib as monotherapy or in combination.

Clinical Phases 1 and 2 – Treatment Combinations			
849-002 US	A Phase 1/2 Trial of MRTX849 in Combination with TNO155 in Patients with Advanced Solid Tumors with *KRAS* G12C Mutation	Phase 1/1b component of the study. MRTX849 at various doses, QD or BID TNO155 at various doses, QD or BID, 2 weeks on/1 week off or continuously	Ongoing
849-007 Global	A Phase 2 Trial of MRTX849 in Combination with Pembrolizumab in Patients with Advanced Non-Small Cell Lung Cancer with *KRAS* G12C Mutation	MRTX849 400 mg BID Pembrolizumab 200 mg IV every 3 weeks	Ongoing
849-014 US	A Phase 1/1b Trial of MRTX849 in Combination with BI 1701963 in Patients with Advanced Solid Tumors with *KRAS* G12C Mutation	Phase 1: Various doses with the starting dose of MRTX849 400 mg BID and BI 1701963 100 mg QD in 3-week cycles. Phase 1b: MRTX849 and BI 1701963 dose levels and regimen as determined in preceding Phase 1 to support selection of recommended Phase 2 dosing regimen.	Ongoing
Clinical Phase 3 – MRTX849 Monotherapy			
849-012 Global	A Randomized Phase 3 Study of MRTX849 versus Docetaxel in Patients with Previously Treated Non-Small Cell Lung Cancer with *KRAS* G12C Mutation	MRTX849 600 mg BID versus Docetaxel 75 mg/m^2 IV every 3 weeks	Ongoing
Clinical Phase 3– Treatment Combinations			
849-010 Global	A Randomized Phase 3 Study of MRTX849 in Combination with Cetuximab Versus Chemotherapy in Patients with CRC with *KRAS* G12C Mutation with	MRTX849 600 mg BID with Cetuximab 500 mg/m^2 IV every 2 weeks versus Standard-of-care chemotherapy (FOLFIRI of mFOLFOX6)	Ongoing
	Disease Progression On or After Standard First-Line Therapy		

BID = twice daily; CRC = colorectal cancer; ctDNA = Circulating tumor deoxyribonucleic acid; IV = intravenous; NSCLC = non-small cell lung cancer; QD = once daily, PDAC = Pancreatic Ductal Adenocarcinoma.
[1] Completed study is defined as a study with a finalised clinical study report.
[2] Phase1/1b dose escalation and expansion and Cohort A have reached their primary completion date.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The clinical pharmacology of adagrasib has been characterized in the Phase 1/2 study in patients with advanced solid tumors with KRAS G12C mutation (849-001) and 6 Phase 1 clinical pharmacology studies: 4 in healthy subjects, 1 in subjects with hepatic impairment, and 1 in subjects with renal impairment. In addition, a PBPK model was developed and population PK analyses were conducted.

Adagrasib exhibits polymorphism. Anhydrous forms, Form 1 and Form 2, are preferred crystalline forms with suitable physiochemical properties. Both forms exhibit similar solubility and dissolution profiles in biorelevant media.

Dose rationale

The Phase 2 starting dose was established in the Phase 1/1b segment of Study 849-001, where 25 patients were enrolled and treated at 5 dose levels. Initially, 4 dose levels (150, 300, 600, and 1200 mg once daily) were assessed using an accelerated titration design. Six patients were then enrolled at 600 mg twice daily using the modified toxicity probability interval design, and the 600 mg twice daily dose level was further evaluated with 2 sequential Phase 1b cohorts of 7 patients. Among the 20

patients treated at 600 mg twice daily during dose escalation/Phase 1b expansion, the safety profile was acceptable. The 600 mg twice daily dose level was selected as the starting dose for the Phase 2 cohorts. It is noted that no ER relationship has been demonstrated.

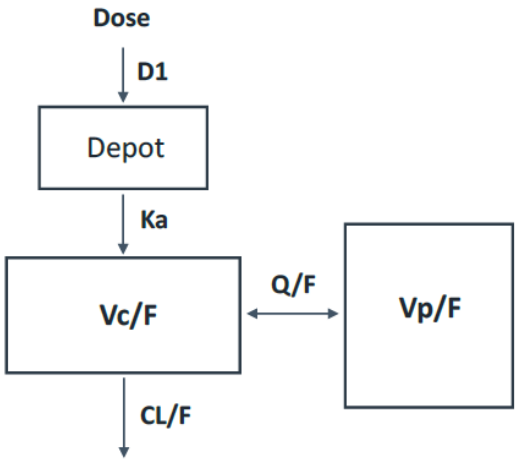
Pharmacokinetic data analysis

Validated bioanalytical methods were used for the quantification of MRTX849 (adagrasib) concentrations in human plasma and urine using LC-MS/MS. The calibration curve ranged from 1.00 to 3000 ng/mL in plasma and from 0.0455 to 45.5 ng/mL in CHAPS treated urine.

Pharmacokinetic parameters were determined by NCA in Phoenix WinNonlin. Population PK analysis was performed using NONMEM. Further analysis of the Pop PK results, exposure-response analyses and C-QTc analysis were performed using various R packages. A PBPK model for adagrasib was developed using Simcyp simulator.

The Pop PK of adagrasib was described by a two-compartment mixed-order absorption model, which included a zero-order process into a depot compartment followed by a first-order Ka into the Vc/F, with linear elimination and a time-dependent effect on CL/F after 7 doses. The residual variability was described by a proportional and an additive error model. The population PK analysis included a total of 353 subjects of which 252 were patients with advanced malignancies. The effect of body weight on disposition parameters was allometrically scaled with estimated exponents. No other covariates were included in the model.

Figure 2: Schematic representation of base population PK model of adagrasib



Where CL/F = apparent clearance; D1 = duration of the zero-order rate of transfer into the depot compartment; Ka = first-order rate constant of absorption; Q/F = apparent peripheral clearance; Vc/F = apparent central volume of distribution; Vp/F = apparent peripheral volume of distribution.

Table 5: Final population PK model of adagrasib – parameter estimates

Parameter	Estimate (RSE)	BSV (RSE)	Shrinkage
Ka (h^{-1})	**0.399 (14.3%)**	103 (13.4%)	33.9%
D1 (h)	**2.96 (8.44)**	4.2 (11.7%)	49.1%
CL/F (L/h)	**35.9 (4.18%)** × $(BW/76.6)^{0.661}$ (18.7%) × 0.720 for ≥7 doses of MRTX849 (1.37%)	57.5% (4.03%)	5.2%
Vc/F (L)	**776 (7.41%)** × $(BW/76.6)^{1.30}$ (9.42%)	64.8% (9.69%)	19.8%
Q/F (L/h)	**21.4 (30.6%)** × $(BW/76.6)^{0.661}$ (18.7%)	NE [a]	NE [a]
Vp/F (L)	**208 (14.8%)** × $(BW/76.6)^{1.30}$ (9.42%)	NE [a]	NE [a]
Error Model			
Proportional (%)	0.276 (0.719%)	NA	NA
Additive (ng/mL)	0.478 (43.0%)	NA	NA

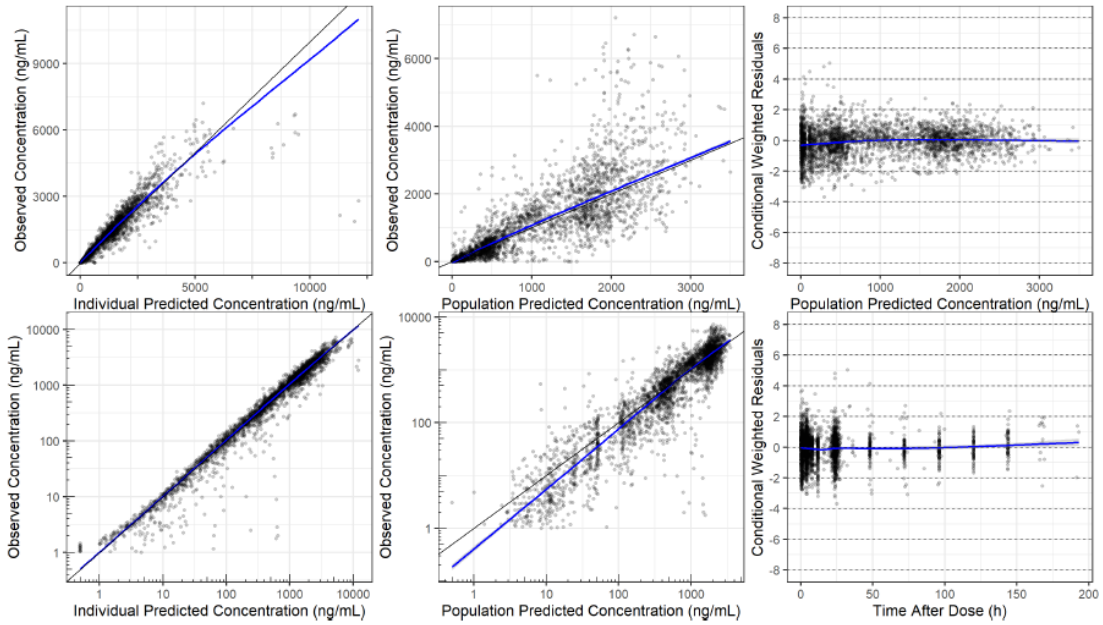
BSV = between-subject variability; CL/F = apparent clearance; D1 = duration of zero-order absorption; ka = first-order rate constant of absorption; NA = not applicable; NE = not estimated; Q/F = clearance of distribution; RSE = relative standard error; Vc/F = apparent volume of distribution of the central compartment; Vp/F = apparent peripheral volume of distribution;

Note: Population PK parameters are given for a typical 76.6-kg subject (the allometric model was centered for a body weight of 76.6 kg, which corresponded to the median body weight in the interim analysis)

[a] BSV (RSE) and shrinkage could not be estimated for peripheral parameters (Q/F and Vp/F)

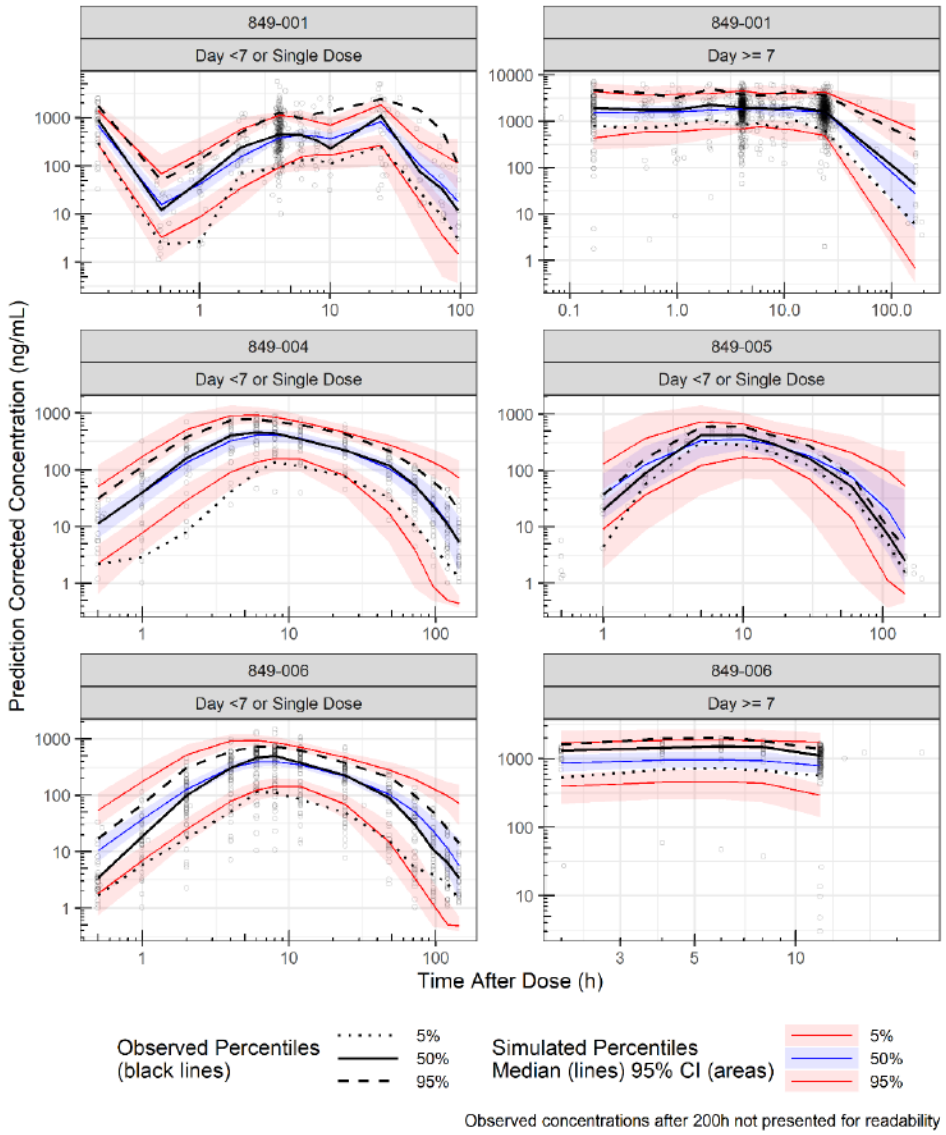
Goodness-of-fit plots and selected pc-VPC's are presented in Figure 3 and Figure 4. The elimination phase was slightly overpredicted following <7 days dosing and underpredicted >7 days of dosing, especially of healthy subjects PK, but the patient PK was well-captured. The exposure simulation for Study 849-001 indicated that 600 mg BID was adequate for the majority of patients to meet the target concentration of 1544 ng/mL.

Figure 3: Goodness-of-fit of Final population PK model of adagrasib: population and predicted vs. observed concentrations – All studies



Black circles = observed data; black line = identity line; blue line = smoothing function. Note: the goodness-of-fit of the final model is the same as the based model since no covariates were included during the covariate analysis.

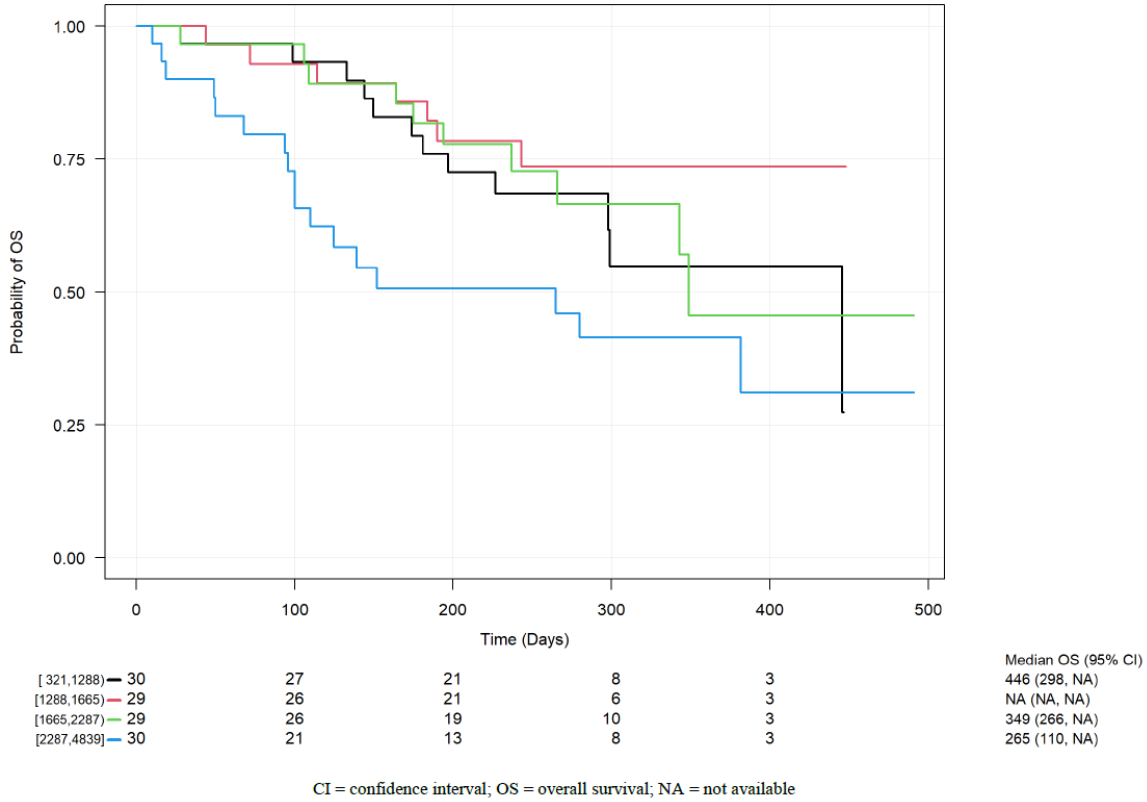
Figure 4: Prediction-corrected visual predictive check of adagrasib by study and occasions: Log-Log scale



Exposure-response modelling

Steady-state exposure parameters C_{min} and Cave from Weeks 2 to 6 derived from Study 849-001 were used to explore exposure-efficacy relationships. The relationship between MRTX849 exposure and ORR was described using a logistic regression model. The relation between MRTX849 exposure and PFS and OS was evaluated by means of Kaplan-Meier plots and log-rank tests. Exposure-response analyses of safety measures were performed using logistic regression models and box plots. No significant exposure-response relations were detected. Weight was a significant covariate that influenced exposure. Weight was not evaluated as a covariate in the E-R analyses. Responses in the lowest exposure quartile (all patients below the target concentration) did not indicate a worse efficacy outcome compared to quartile 2 and 3. In contrast, patients in the highest exposure quartile (Cave,week2-6 exposures >2287 ng/mL) seemed to experience a worse OS and PFS than patients in the other exposure quartiles.

Figure 5: Exposure-response analysis of efficacy – probability of OS – Kaplan-Meier figure – $C_{ave,\ Week2\text{-}6}$ – by quartiles



CI = confidence interval; OS = overall survival; NA = not available

C-QTc modelling

In Study 849-001, triplicate ECGs were collected at pre-dose and around t_{max} after a single dose and at steady state and over a range of 150 to 1200 mg per day. A total of 229 patients with 1038 paired plasma concentrations and ECG measurements were included. Of these, 224 patients received 600 mg BID. Simulation of 14 days concentration-time profile for 600 mg BID were performed using the individual posthoc estimates of the population PK model parameters of 252 patients from Study 849-001.

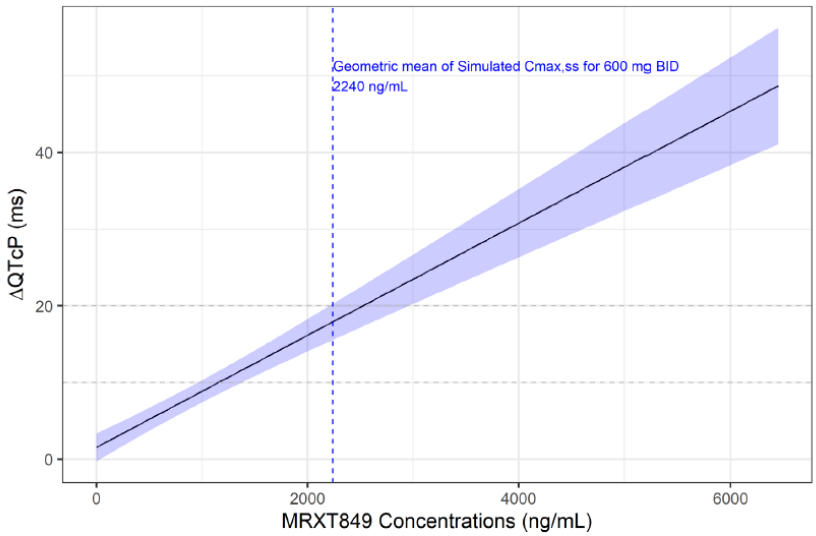
A LME model with time effect was used for concentration-QTc modelling. The model parameters were estimated with adequate precision, except for the intercept. The intercept was determined to -2.07 ms with a %RSE of 64.7 and the 95% CI contained the null. The unexplained error was estimated to 15.9 ms.

Table 6: Sensitivity analysis - parameter estimates and confidence intervals

Data Included	Parameter	Estimate	SE	RSE (%)	CI95
All data	Intercept (θ_0, ms)	-2.07	1.34	64.7	(-4.7, 0.563)
	If visit other than Lead-in of Cycle 1 Day 1	7.93	1.62	20.4	(4.77, 11.1)
	Concentration (θ_1, ms/(ng/mL))	0.00753	0.000806	10.7	(0.00595, 0.00911)
	BSV Intercept (η_0, ms)	6.84	1.2	17.5	(4.89, 9.56)
	BSV slope concentration (η_1, ms/(ng/mL)))	0.0054	0.000545	10.1	(0.00444, 0.00657)
	Residual error (σ, ms)	15.9	0.41	2.58	(15.1, 16.7)
|SRES| ≤ 4	Intercept (θ_0, ms)	-2.99	1.23	41.1	(-5.4, -0.593)
	If visit other than Lead-in of Cycle 1 Day 1	8.44	1.45	17.2	(5.6, 11.3)
	Concentration (θ_1, ms/(ng/mL))	0.00794	0.000769	9.69	(0.00643, 0.00945)
	BSV Intercept (η_0, ms)	7.56	1.03	13.6	(5.8, 9.85)
	BSV slope concentration (η_1, ms/(ng/mL)))	0.00561	0.000532	9.45	(0.00467, 0.00675)
	Residual error (σ, ms)	13.8	0.363	2.62	(13.1, 14.6)

BSV = between subject variability; CI95 = 95% confidence interval; RSE = relative standard error; SE = standard error; |SRES| = standardized residuals

Figure 6: Predictions of 90% confidence interval on mean estimand ΔQTcF values for specific concentrations

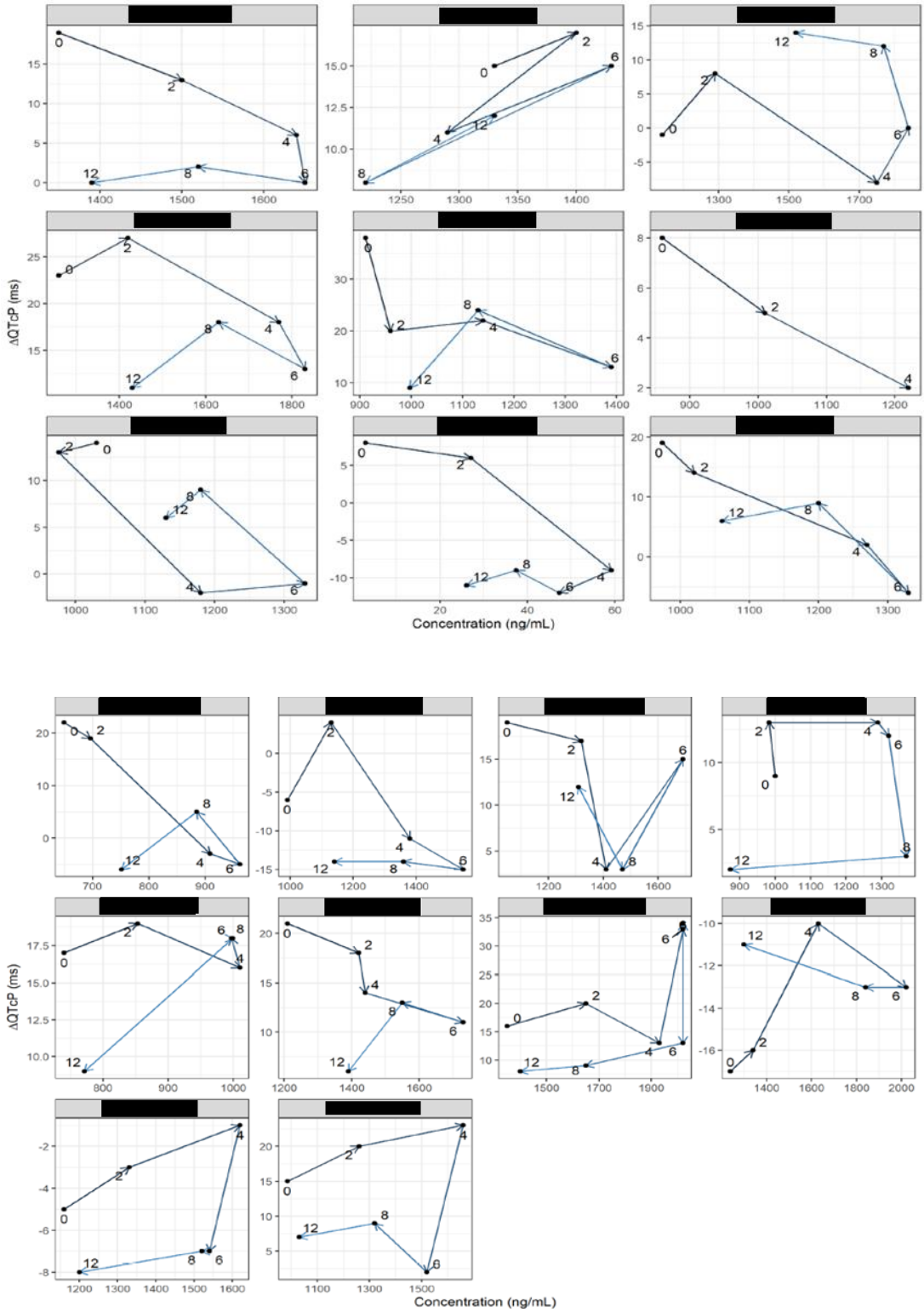


ΔQTcF = QTcF change from baseline; $C_{max,ss}$ = maximum concentration at steady state; QT = ECG QT interval; QTcF = QT corrected using Fridericia's method

Note: the geometric mean of $C_{max,ss}$ was based simulated rich 14 days concentration-times profiles for 600 mg BID treatment with individual posthoc estimates of MRTX849 population PK model parameters in Subjects from study 849-001. The dashed horizontal gray lines represent 20 ms and 10 ms, respectively. The blue purple shaded area represents the 90% confidence intervals.

Hysteresis was evaluated in Study 849-006, Cohort 4 where 19 healthy subjects received a reduced dose of 400 mg BID on Days 6 to 9. Time-matched ECG and PK samples were collected up to 12 hours post-dose at Day 9. The ΔQTcP was largest at the pre-dose timepoint in most subjects and seemed to decline across tau of 12 hours, independently of adagrasib concentration.

Figure 7: Exploratory analysis – Hysteresis plots individual concentration and ΔQTcF –Study 849-006, Cohort 4



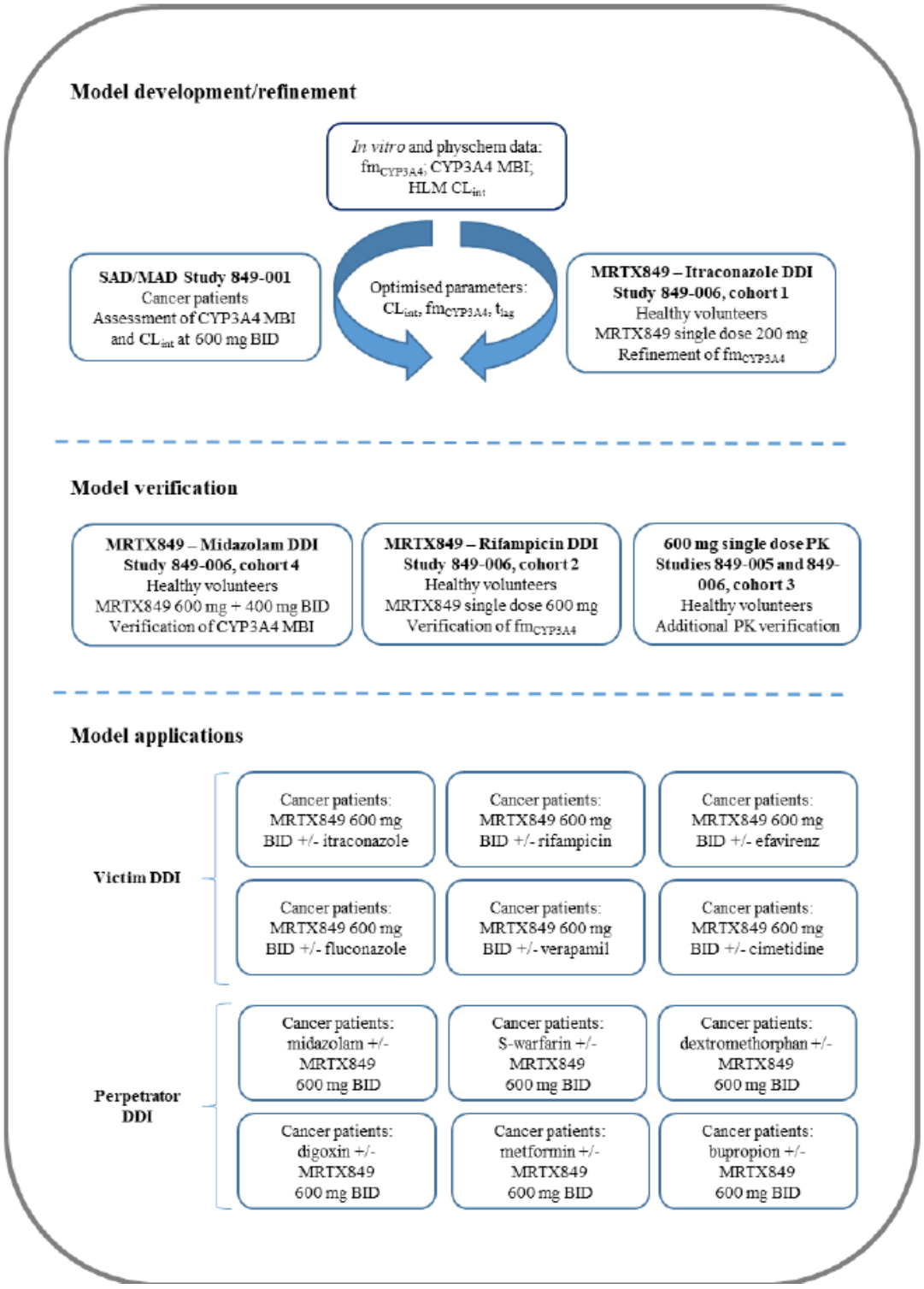
ΔQTcP = QTcP change from baseline; QT = ECG QT interval; QTcP = population corrected QT.

PBPK modelling

A minimal PBPK model was developed for adagrasib (MTRX849) using the Simcyp Simulator (V18 R2).

Absorption was described via a first order model with lag time. Rate and extent of absorption was predicted from permeability data. Distribution was described by a minimal model using physicochemical, plasma protein binding (fu,p) and blood distribution data. Renal clearance of MRTX840 was calculated from the fraction of dose excreted unchanged in urine (fe=0.018) and mean oral clearance. Hepatic clearance of MRTX849 was initially scaled using in vitro HLM intrinsic clearance and fm from rhCYP data and adjusted using clinical data from study 849-001 and study 849-006, Cohort 1. MRTX840 is a time-dependent inhibitor of CYP3A4. This was incorporated in the model using in-vitro data with midazolam as a probe substrate. In-vitro MTRX849 was an inhibitor of a range of CYPs and transporters. The in-vitro Ki values were used as model input or refined using clinical DDI data. The modelling steps are shown in Figure 8.

Figure 8: Schematic showing the key PBPK modelling steps and components of each clinical study used in model building and verification



The original PBPK model were further refined to incorporate contribution of the non-CYP3A4 pathway (CYP2C8).

Absorption

Adagrasib is highly permeable *in vitro*, but the solubility is pH-dependent. It is most soluble at low pH and considered relatively insoluble at pH 6.8. Based on in vitro permeability and solubility data, adagrasib is classified as a biopharmaceutics classification system (BCS) Class 2 compound.

With the intended dose regimen of 600 mg BID, steady state is reached within day 8 and the accumulation of AUC is reported to be approximately 6-fold. At steady state, the geometric mean AUC, C_{max}, and C_{min} was 31600 h x ng/mL (n=4), 3253 ng/mL (n=8), and 2693 ng/mL (n=8), respectively.

Time to maximum concentrations (T_{max}) on C1D1 and C1D8 were 6.03 (2.08–10.00) hours and 2.96 (0.48-4.30) hours, respectively.

Food intake (a high-fat and high-calorie meal) increased adagrasib tablet C_{max} and AUC by approximately 20% and 38%, respectively, following a single 600 mg oral dose of adagrasib in healthy subjects. Inter-individual variability of exposure parameters was found nearly 2 times lower under fed conditions.

Bioavailability and bioequivalence

The relative BA and the BE of different formulations of adagrasib were explored in studies 011 and 015.

In part 1 of study 011, bioequivalence was demonstrated between the Mixed Form tablets and Mixed Form capsules and between the Form 2 capsules and Mixed Form capsules.

In part 2 of the study, BE criteria between the Form 2 tablets and the Mixed Form capsules were not met. The lower boundary of the 90% CI for C_{max}, AUClast, and AUC∞ was slightly below the BE limit of 80.00%. The applicant was of the opinion that an inadequate sample size was the reason for the inability to show BE between the Form 2 tablets and the Mixed Form capsules. Hence, a new study (study 015) with a replicate crossover design was conducted. In this study, BE was demonstrated for AUClast and AUC∞ but not for C_{max}.

Overall, it is noted that in all clinical studies besides the one on food-effect, IR capsules containing mixture of polymorphic forms of the API have been used with the content of Form 1 in Form 2 ranging from 1.3% to 82.7%. The proposed commercial product as stated in the Quality part of the dossier and as defined according to the drug product specifications (section P.5.1) is film-coated tablets containing up to 58% of Form 1 in Form 2 as stated by the Applicant. This formulation containing such mixture of polymorphic forms have not been studied in any clinical study being part of this MAA documentation. Thus, no in vivo data on drug exposure from the final tablet formulation containing 58% of Form 1 in Form 2 are available.

Distribution

The apparent volume of distribution of adagrasib is 942 L (healthy subjects), indicating a high degree of tissue distribution. The protein binding is reported to be 99% in healthy subjects. There was no evidence of preferential binding of drug-related product to blood cells. Following a single oral dose of 600 mg containing approximately 1 µCi of [14C]-adagrasib, the geometric mean whole blood/plasma AUC∞ ratio for total radioactivity was approximately 0.877 (ADME study).

Elimination

Based on a population PK analysis, the estimated terminal elimination half-life ($t_{1/2}$) and apparent oral clearance (CL/F) at steady state in patients are approximately 29 hours and 25.8 L/h, respectively.

Adagrasib is extensively metabolised. In the **ADME study** in healthy subjects, 79.2% of total radioactivity was accounted for with 74.7% of the radioactive dose recovered in feces and 4.5% (1.8% unchanged) recovered in urine.

Table 7 presents the cumulative recovery of total radioactivity in urine and feces during the study.

Table 7: Summary of the recovery of total radioactivity in Urine and faeces within 504 hours following a single oral administration of [^{14}C]-adagrasib (study 849-005)

Matrix	Mean (range) Cumulative Amount of Total Radioactivity Recovery (%)		
	0 to 144 Hours Postdose	0 to 312 Hours Postdose	0 to 504 Hours Postdose[1]
Urine	3.72 (3.29-4.10)	4.12 (3.85-4.57)	4.49 (3.90-5.02)
Feces	66.9 (60.9-71.2)	73.1 (68.8-76.5)	74.7 (71.8-78.5)
Overall (urine + feces)	70.6 (65.0-74.9)	77.2 (73.1-80.4)	79.2 (76.5-82.4)

Source: Study 849-005 CSR, Table 6
[1] Values from 0 to 480 hours postdose were interpolated, as no sample was collected in the 312 to 480 hours postdose period.

The metabolism of adagrasib is complex with some metabolites only detected after a single dose or at steady state. Adagrasib is mainly metabolised through oxidative metabolism by CYP3A4, but can also be metabolised by CYP2C8 or CYP2D6 with the percent contribution calculated to be *in vivo* 71%, 28% and <5%, respectively. No major active metabolites are formed.

Dose proportionality and time dependencies

Due to limited data, dose proportionality is not assessable in the patient population. In healthy subjects, adagrasib exposure increased more than dose proportionally, with increases in geometric mean C_{max} and AUC∞ of approximately 6- and 8-fold, respectively, for a 3-fold increase in dose from 200 mg (n = 15) to 600 mg (n = 29-30). The same extent of non-linear PK is observed in single and multiple dosing.

CYP3A4 is the main enzyme metabolising adagrasib, and, according to the dossier, adagrasib is in itself a strong inhibitor of CYP3A4 (autoinhibition). This contributes to the observed accumulation with multiple dosing.

Intra- and interindividual variability

Based on popPK results, the variability, expressed as CV, in exposure and disposition parameters was 51%-65%, which is considered moderate.

Special populations

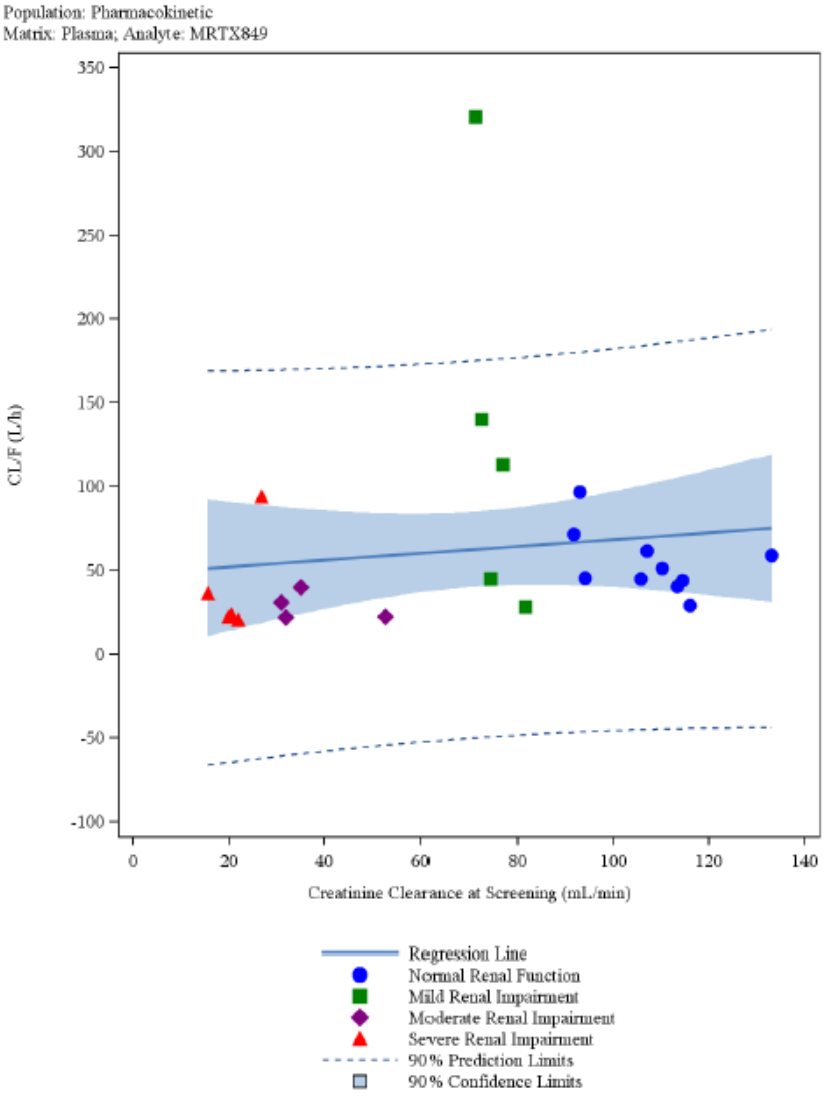
Impaired renal function

The impact of renal impairment on the PK of adagrasib was investigated in a dedicated renal study as well as in the popPK analysis.

In the dedicated renal impairment study, renal impairment did not affect apparent total adagrasib clearance (CL/F) (Figure 9). Based on popPK analysis, geometric mean $AUC_{tau,ss}$ of adagrasib in patients with mild and moderate renal impairment were approximately 6% and 8% lower, respectively,

than in patients with normal renal function. Together, these results reflect the low renal excretion (1.8% unchanged adagrasib).

Figure 9: Apparent total clearance (CL/F) of adagrasib versus creatinine clearance (CL_{CR}) at screening (study 849-004)



$R^2 = 0.01$, P-value for zero slope: 0.5778
CL/F = 48.34 + 0.20 * Creatinine Clearance
Reference: Listing 16.2.6.1-4; Listing 16.2.4-9
Program Location: /cvn/projects/prj/ecb/programs/000000194825/dev/figures/f_stat_corr.sas
Program Status: FINAL Program Run: 29SEP2021 Protocol Reference: 849-004

Impaired hepatic function

The impact of hepatic impairment on the PK of adagrasib was investigated in a dedicated hepatic study as well as in the popPK analysis.

Table 8: Summary of adagrasib PK parameters after administration of a single dose of adagrasib 600 mg under fasted conditions (study 849-003)

Parameter	Normal Hepatic Function (N=11)	Mild Hepatic Impairment (N=7)	Moderate Hepatic Impairment (N=11)	Severe Hepatic Impairment (N=8)
Total (bound + unbound) PK parameters				
AUC_{last} (h*ng/mL)	11490 (45.0) [n=11]	9249 (54.8) [n=6]	9813 (63.4) [n=8]	10630 (20.7) [n=6]
AUC_{∞} (h*ng/mL)	11580 (45.0) [n=11]	9332 (54.7) [n=6]	10370 (65.7) [n=8]	11980 (19.4) [n=6]
C_{max} (ng/mL)	424 (36.3) [n=11]	394 (33.9) [n=6]	315 (57.6) [n=8]	220 (11.4) [n=6]
t_{max} (h)	6.00 (4.00-8.00) [n=11]	5.00 (4.00-8.00) [n=6]	6.00 (2.00-8.00) [n=8]	7.03 (2.00-24.05) [n=6]
$t_{1/2}$ (h)	19.8 (10.3) [n=11]	20.7 (14.6) [n=6]	31.1 (43.0) [n=8]	43.4 (33.7) [n=6]
CL/F (L/h)	51.8 (45.0) [n=11]	64.3 (54.7) [n=6]	57.8 (65.7) [n=8]	50.1 (19.4) [n=6]
V_z/F (L)	1474 (41.8) [n=11]	1898 (56.8) [n=6]	2414 (64.1) [n=8]	2959 (43.5) [n=6]
Unbound PK parameters				
f_u (%)	0.963 (38.9) [n=11]	1.22 (76.6) [n=6]	1.25 (74.7) [n=8]	1.69 (116.2) [n=6]
$AUC_{\infty,u}$ (h*ng/mL)	112 (44.4) [n=11]	114 (72.4) [n=6]	130 (101.2) [n=8]	202 (96.4) [n=6]
$C_{max,u}$ (ng/mL)	4.08 (44.9) [n=11]	4.81 (64.2) [n=6]	3.93 (82.3) [n=8]	3.71 (105.4) [n=6]

Source: Study 849-003 CSR Table 8 and Table 11

AUC_{∞} = area under the plasma concentration-time curve from time zero to infinity; $AUC_{\infty,u}$ = area under the plasma concentration-time curve from time zero to infinity unbound drug in plasma; AUC_{last} = area under the plasma concentration-time curve from time zero to time of last measurable concentration; CL/F = apparent total clearance of the drug from plasma after oral administration; C_{max} = maximum (peak) plasma concentration; $C_{max,u}$ = maximum unbound drug in plasma concentration; CV = coefficient of variation (%); f_u = fraction of unbound drug in plasma; N= number of subjects; n = number of subjects with valid observations; PK = pharmacokinetic; $t_{1/2}$ = elimination half-life; t_{max} = time to reach maximum (peak) plasma concentration following drug administration; V_z/F = apparent volume of distribution during terminal phase after non-intravenous administration.

Note: Geometric mean (CV) statistics presented; for t_{max} median (minimum-maximum) statistics presented; for $t_{1/2}$, arithmetic mean (arithmetic CV) statistics presented.

Table 9: Statistical comparison using a paired t-Test to assess the effect of each hepatic impairment group on the total and unbound adagrasib exposure (study 849-003)

Comparison	Ratio of Geometric Least Squares Mean (90% CI)			
	Total (Bound + Unbound) MRTX849		Unbound MRTX849	
	C_{max}	AUC_{∞}	$C_{max,u}$	$AUC_{\infty,u}$
Mild HI (n=6) vs normal (n=6)	1.01 (0.68, 1.51)	0.87 (0.54, 1.42)	1.18 (0.60, 2.31)	1.01 (0.47, 2.19)
Moderate HI (n=8) vs normal (n=8)	0.70 (0.52, 0.93)	0.88 (0.61, 1.27)	0.82 (0.49, 1.38)	1.03 (0.57, 1.87)
Severe HI (n=6) vs normal (n=6)	0.50 (0.45, 0.55)	0.98 (0.73, 1.32)	0.84 (0.50, 1.43)	1.66 (0.92, 3.00)

Source: Study 849-003CSR, Table 9 and Table 12

AUC_{∞} = area under the plasma concentration-time curve from time zero to infinity; $AUC_{\infty,u}$ = area under the plasma concentration-time curve from time zero to infinity unbound drug in plasma; CI = confidence interval; C_{max} = maximum plasma concentration; $C_{max,u}$ = maximum unbound drug in plasma concentration; HI = hepatic impairment; n = number of subjects with valid observations; vs = versus.

Descriptive statistics of exposure parameters of adagrasib for the 600 mg BID dosing regimen in patients with advanced malignancies (849-001) by degree of hepatic function are presented in Table 10. The hepatic impairment classification system used for the popPK analysis was the NCI-OGWD.

Table 10: Descriptive statistics of adagrasib exposure parameters for 600 mg BID by hepatic function based on NCI-OGWD (Study 849-001)

Parameters	Normal Hepatic Function (N=217)	Mild Hepatic Impairment (N=32)	Moderate Hepatic Impairment (N=3)	Overall (N=252)
$AUC_{tau,day1}$ (ng.h/mL)				
Mean (CV%)	5440 (53.0%)	4400 (56.6%)	2330 (74.2%)	5270 (54.2%)
Median [Q5; Q95]	4770 [1820;10700]	3990 [1500;9470]	2420 [741;3850]	4640 [1680;10700]
Geometric Mean	4740	3820	1750	4560
$AUC_{tau,ss}$ (ng.h/mL)				
Mean (CV%)	28700 (51.9%)	25000 (46.8%)	19300 (45.0%)	28100 (51.6%)
Median [Q5; Q95]	26900 [11500;50700]	23100 [12500;43400]	20300 [11200;26700]	25900 [11500;50300]
Geometric Mean	25700	22700	17800	25200
RAC (AUC)				
Mean (CV%)	5.95 (47.7%)	6.63 (54.8%)	15.9 (113.3%)	6.16 (57.0%)
Median [Q5; Q95]	5.24 [3.02;11.4]	5.63 [3.50;13.8]	6.84 [4.46;33.6]	5.28 [3.04;12.2]
Geometric Mean	5.43	5.95	10.2	5.53
$C_{ave,ss}$ (ng.h/mL)				
Mean (CV%)	2390 (51.9%)	2080 (46.8%)	1610 (45.0%)	2340 (51.6%)
Median [Q5; Q95]	2240 [962;4220]	1920 [1040;3620]	1690 [930;2220]	2160 [954;4190]
Geometric Mean	2140	1890	1480	2100
$C_{max,day1}$ (ng/mL)				
Mean (CV%)	630 (52.3%)	520 (53.8%)	280 (64.3%)	612 (53.3%)
Median [Q5; Q95]	547 [230;1240]	441 [202;1080]	281 [118;443]	525 [226;1240]
Geometric Mean	554	461	235	536
$C_{max,ss}$ (ng/mL)				
Mean (CV%)	2550 (51.2%)	2200 (46.7%)	1660 (44.5%)	2500 (51.1%)
Median [Q5; Q95]	2320 [1060;4630]	2040 [1140;3910]	1700 [981;2310]	2290 [1040;4510]
Geometric Mean	2290	2000	1540	2240
$C_{min,ss}$ (ng/mL)				
Mean (CV%)	2200 (53.3%)	1940 (47.5%)	1540 (45.8%)	2160 (52.9%)
Median [Q5; Q95]	2070 [833;3940]	1780 [919;3450]	1680 [865;2120]	2020 [821;3900]
Geometric Mean	1960	1760	1410	1930

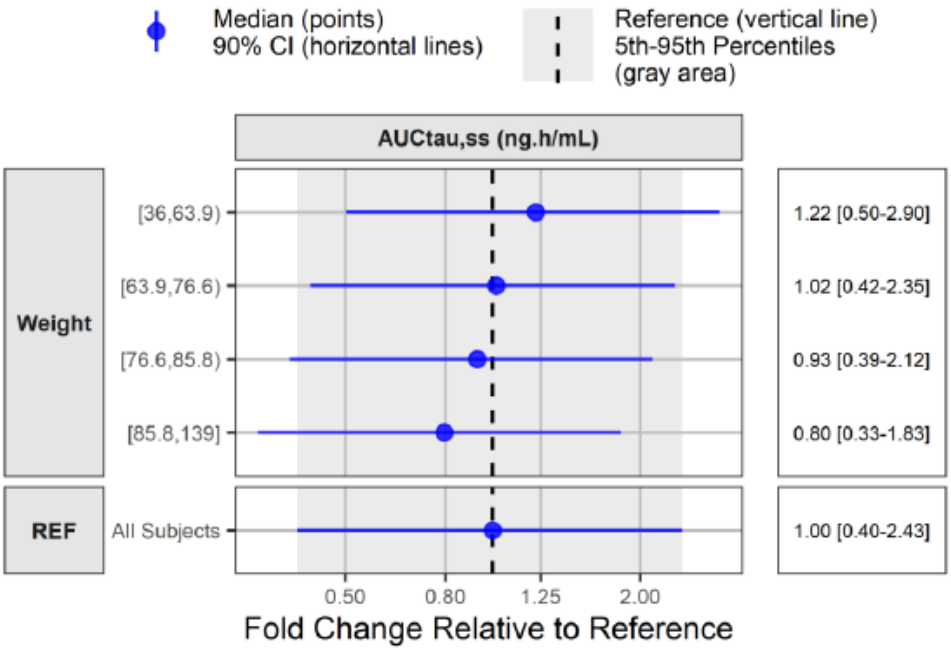
AUC_{tau} Day 1 = area under the curve over the dosing interval on Day 1; $AUC_{tau,ss}$ = area under the curve over the dosing interval under steady state; $C_{ave,ss}$ = average concentration at steady state; $C_{max,ss}$ = maximum concentration at steady state; $C_{min,ss}$ = minimum concentration at steady state; CV = coefficient of variation; Q5 = 5th percentile; Q95 = 95th percentile; RAC = accumulation ratio.

Weight

In the popPK evaluation, CL/F and Vc/F of adagrasib were dependent on body weight. Median weight in the PK population was 76.3 kg (range 36 – 139 kg).

To determine the potential impact of body weight on adagrasib steady-state exposure, body weight in patients with advanced malignancies were separated by quartiles and the impact of body weight on steady-state exposure parameters of adagrasib was explored.

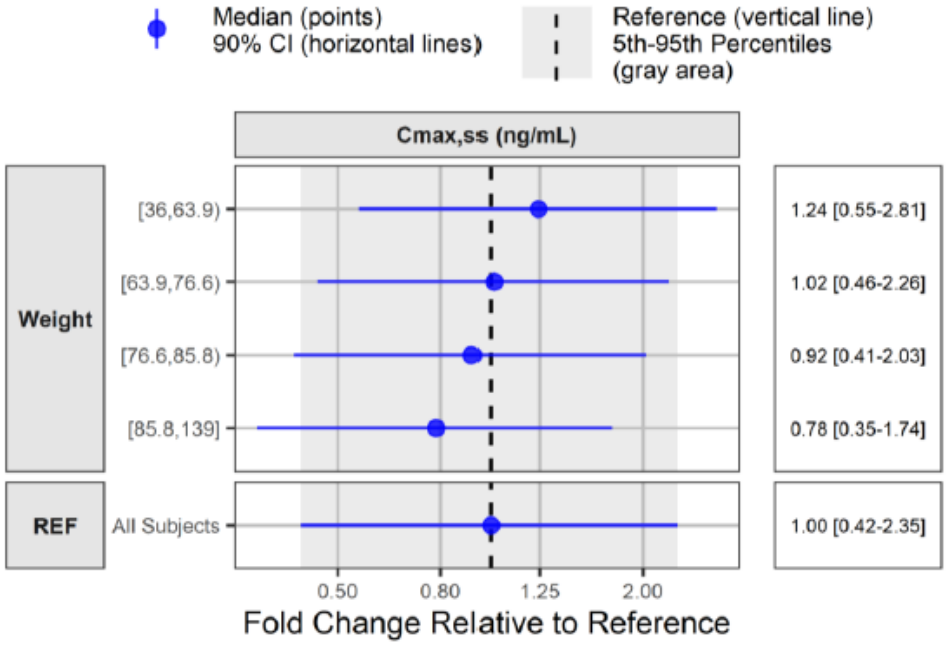
Figure 10: Forest Plot: impact of body weight on $AUC_{tau,ss}$ of adagrasib for 600 mg BID in patients with advanced malignancies



$AUC_{tau,ss}$ = Area under the curve at steady-state.

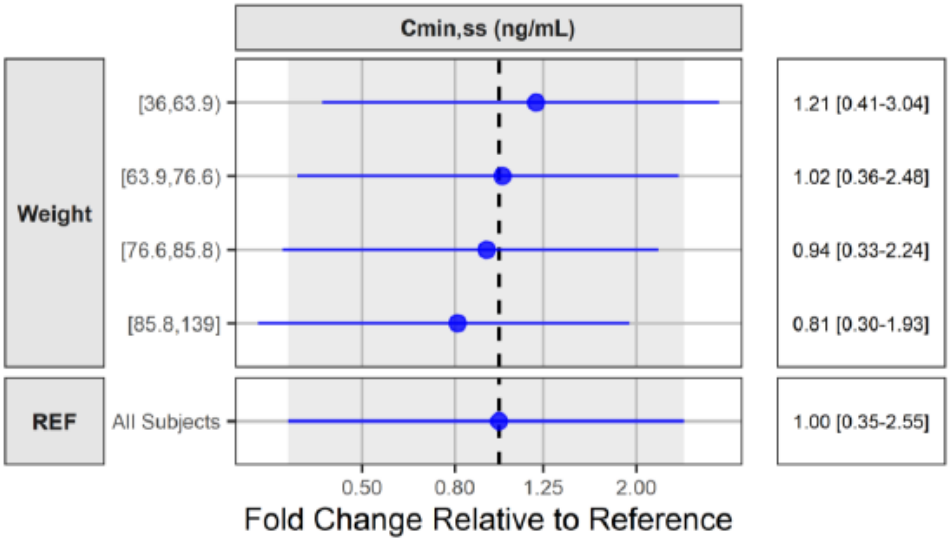
Note: REF represents the body weight range in patients with advanced malignancies (36 to 139 kg). The reference is a typical 76.6-kg patient who received ≥ 7 doses of MRTX849. The shaded area represents the 5th and 95th percentiles of exposure in all subjects

Figure 11: Forest Plot: impact of body weight on $C_{max,ss}$ of adagrasib for 600 mg BID in patients with advanced malignancies



Cmax,ss = Maximum concentration at steady-state.
Note: REF represents the body weight range in patients with advanced malignancies (36 to 139 kg). The reference is a typical 76.6-kg patient who received ≥ 7 doses of MRTX849. The shaded area represents the 5th and 95th percentiles of exposure in all subjects

Figure 12: Forest Plot: impact of body weight on $C_{min,ss}$ of adagrasib for 600 mg BID in patients with advanced malignancies



Cmin,ss = Minimum concentration at steady-state.
Note: REF represents the body weight range in patients with advanced malignancies (36 to 139 kg). The reference is a typical 76.6-kg patient who received ≥ 7 doses of MRTX849. The shaded area represents the 5th and 95th percentiles of exposure in all subjects

Gender, age, race, tumor burden, and ECOG status

The impact of sex, age (19 to 89 years), race (White, Black, Asian), tumor burden, and ECOG performance status on adagrasib PK was evaluated in popPK analyses and these factors explained less than 5% of the variability in PK parameters of adagrasib and were therefore not included in the population PK model.

Table 11: Number of elderly subjects by study included in population PK analysis

Study Number	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
849-001	79/252 (31.3%)	30/252 (11.9%)	2/252 (0.8%)
849-004	10/28 (35.7%)	1/28 (3.6%)	0/28 (0.0%)
849-005	1/6 (16.7%)	0/6 (0.0%)	0/6 (0.0%)
849-006	0/67 (0.0%)	0/67 (0.0%)	0/67 (0.0%)
Overall	90/353 (25.5%)	31/353 (8.8%)	2/353 (0.6%)

Pharmacokinetic interaction studies

In silico

A **PBPK model** based on in vitro and in vivo data relating to the absorption, distribution, metabolism, and excretion (ADME) and PK properties of MRTX849 in healthy subjects and cancer patients was developed using the Simcyp Simulator (V18 R2) to assess the DDI liability of MRTX849 as a victim of CYP3A4-mediated DDIs and as a perpetrator of CYP2B6, CYP2C9, CYP2D6, CYP3A4, P-gp, and MATE mediated DDIs in cancer patients receiving MRTX849 600 mg twice daily. Results of these predictions along with the observed DDI results from Study 849-006 are summarised in Table 12 and Table 13 below.

In vitro

In vitro data showed that MRTX849 is a competitive inhibitor of CYP2B6, CYP2C9, CYP2D6, and CYP3A4, as well as a time-dependent inhibitor of CYP3A4, while it may also induce CYP3A4. MRTX849 also inhibits the drug transporters P-gp, BCRP, and MATE1. Further, it is noted in the dossier that MRTX849 may inhibit OCT1 and OATP1B1 but not BSEP in vivo. Based on the *in vitro* results, a clinical DDI study with several arms was conducted.

Clinical studies

The primary objectives of the clinical DDI study were to evaluate the effect of perpetrator drugs on the PK of adagrasib and the effect of adagrasib as perpetrator on the PK of victim drugs in healthy subjects. In addition to the clinical DDI study, PBPK model simulations of the potential for drug-drug interactions have been provided.

Potential for concomitant medications to alter the PK of MRTX849

The effects of CYP3A4 inhibitors and inducers on MRTX849 single-dose and steady-state exposure based on Study 849-006 and PBPK modeling are summarised in Table 12.

In study 006, co-administration of itraconazole with a single 200 mg dose of adagrasib led to a 4-fold increase in adagrasib AUC. Based on modelling, co-administration of multiple dose itraconazole and multiple dose (600 mg) adagrasib only led to a 10% increase in adagrasib AUC which is considered to be due to the fact that adagrasib itself is a strong 3A4 inhibitor. Rifampin reduced the exposure (AUC) of single dose adagrasib with 95% (study 006) and is expected to reduce the exposure of multiple dose adagrasib with 66% (PBPK).

Adagrasib exhibits pH-dependent solubility.

Table 12: Effects of CYP3A4 inhibitors and inducers on the single-dose and steady-state exposure of adagrasib

CYP3A4 Modulators	MRTX849 Dose	N	Source	Effect on MRTX849	
				C_{max}	AUC_{∞} or AUC_{τ}
Itraconazole 200 mg QD – Strong CYP3A4 inhibitor	200 mg single dose	14	Observed	2.44-fold increase	3.97-fold increase
Itraconazole 200 mg QD – Strong CYP3A4 inhibitor	600 mg BID	250	PBPK modeling	1.10-fold increase	1.10-fold increase
Fluconazole 200 mg QD – Moderate CYP3A4 inhibitor (competitive)	600 mg BID	250	PBPK modeling	1.06-fold increase	1.07-fold increase
Verapamil 80 mg TID - Moderate CYP3A4 inhibitor (MBI)	600 mg BID	250	PBPK modeling	1.01-fold increase	1.01-fold increase
Cimetidine 400 mg TID – Weak CYP3A4 inhibitor	600 mg BID	250	PBPK modeling	1.01-fold increase	1.02-fold increase
Rifampin 600 mg QD – Strong CYP3A4 inducer	600 mg single dose	12	Observed	88% reduction	95% reduction
Rifampin 600 mg QD – Strong CYP3A4 inducer	600 mg BID	250	PBPK modeling	61% reduction	66% reduction
Efavirenz 600 mg QD - Moderate CYP3A4 inducer	600 mg BID	250	PBPK modeling	23% reduction	25% reduction

Source: Observed (Study 849-006 CSR); PBPK modeling (Certara Report MRT/3/B).
AUC_{∞} = area under the plasma concentration-time curve from time zero to infinity; AUC_{τ} = area under the plasma concentration-time curve during a dosage interval; BID = twice daily; C_{max} = maximum plasma concentration; MBI = mechanism-based inhibition; PBPK = physiologically-based pharmacokinetic; QD = once daily; TID = three times daily.

Potential for MRTX849 to alter the PK of concomitant medications

The effects of MRTX849 on exposure of the oral probe substrates of CYPs and drug transporters from Study 849-006 and PBPK modelling are summarised in Table 13.

Co-administration of adagrasib and midazolam (sensitive 3A4 substrate) resulted in an observed 20-fold increase in midazolam AUC with 400 mg adagrasib BID (study 006) and a predicted 31-fold increase in midazolam AUC with 600 mg adagrasib BID (PBPK).

The impact of adagrasib on CYP2D6 was investigated using dextromethorphan as a substrate. The exposure to dextromethorphan increased 90% and 80% for C_{max} and AUC, respectively.

With regard to BCRP substrates, clinical data with single dose rosuvastatin and multiple dose (400 mg BID) adagrasib showed a modest 1.35-fold increase in rosuvastatin AUC. Hence, no dose adjustment for BCRP substrates are necessary during co-administration with adagrasib.

Table 13: Effect of adagrasib on exposure of the oral probe substrate of CYPs and drug transporters

Oral Probe Substrate	MRTX849 Dose	N	Source	Effect on Oral Probe Substrate	
				C_{max}	AUC_{last} or AUC_{∞}
Midazolam 2 mg single dose – CYP3A4 probe substrate	400 mg BID	12-13	Observed	4.81-fold increase	20.5-fold increase
Midazolam 5 mg single dose – CYP3A4 probe substrate	600 mg BID	250	PBPK modeling	3.10-fold increase	31.4-fold increase
Warfarin 10 mg single dose – CYP2C9 probe substrate	600 mg single dose	5	Observed	1.32-fold increase	1.62-fold increase
Warfarin 10 mg single dose – CYP2C9 probe substrate	600 mg BID	250	PBPK modeling	1.05-fold increase	2.93-fold increase
Dextromethorphan 30 mg single dose - CYP2D6 probe substrate	400 mg BID	13	Observed	1.90-fold increase	1.75-fold increase
Dextromethorphan 30 mg single dose - CYP2D6 probe substrate	600 mg BID	250	PBPK modeling	1.73-fold increase	2.37-fold increase
Bupropion 130.2 mg (free base) single dose - CYP2B6 probe substrate	600 mg BID	250	PBPK modeling	1.10-fold increase	1.14-fold increase
Digoxin 0.25 mg single dose/P-gp probe substrate	600 mg single dose	13	Observed	1.05-fold increase	1.38-fold increase

Digoxin 0.5 mg single dose/P-gp probe substrate	600 mg BID	250	PBPK modeling	1.86-fold increase	1.48-fold increase
Rosuvastatin 5 mg single dose/BCRP probe substrate	600 mg single dose	20-21	Observed	1.05-fold increase	No change
Rosuvastatin 5 mg single dose/BCRP probe substrate	400 mg BID	11-13	Observed	1.06-fold increase	1.35-fold increase
Metformin 390 mg (free base) single dose/MATE probe substrate	600 mg BID	250	PBPK modeling	1.03-fold increase	1.05-fold increase

Source: Observed (Study 849-006 CSR); PBPK modeling (Certara Report MRT/3/B)
AUC = area under the plasma concentration curve; AUC_{∞} = area under the plasma concentration-time curve from time zero to infinity; AUC_{last} = area under the plasma concentration-time curve from time zero to time of last measurable concentration; BCRP = breast cancer resistance protein; BID = twice daily; C_{max} = maximum plasma concentration; CYP = cytochrome P450; MATE = multi-antimicrobial extrusion protein; MBI = mechanism-based inhibition; QD = once daily; PBPK = physiologically-based pharmacokinetic; P-gp = P-glycoprotein; TID = three times daily.

2.6.2.2. Pharmacodynamics

Mechanism of action

Adagrasib is a rat sarcoma (virus) gene (RAS) GTPase family inhibitor that selectively and irreversibly binds the cysteine that results from the KRAS c.34G>T (p.Gly12Cys) mutation (noted as KRAS G12C). Adagrasib is designed to covalently bind to the mutant cysteine (via the sulfur atom) at codon 12 in KRAS G12C and thereby lock mutant KRAS in its inactive conformation, blocking KRAS-dependent signal transduction and compromising cancer cell viability and tumor growth.

Primary and Secondary pharmacology

No quantitative PD or biomarker data have been generated and the time course of PD or biomarker response and PK/PD relationships are therefore not known. No special studies related to the primary pharmacology have been undertaken.

The effect of adagrasib on QT was evaluated in the patient study 001. Based on the concentration-QTc model, the predicted mean (90% CI) ΔQTcP (population-corrected QT) was 18.8 (16.4, 21.1) ms at the population geometric mean C_{max},ss (2240 ng/mL) in patients after administration of adagrasib 600 mg twice daily. The predicted ΔQTcF is also similar to ΔQTcP, with the predicted mean (90% CI) ΔQTcF of 17.93 (15.13, 20.73) ms.

Exposure-response analyses

Exposure-response (E-R) analyses were performed to explore the relationship between plasma exposure of adagrasib and efficacy and safety in patients with KRAS G12C-mutated solid tumors, including NSCLC in Study 849-001 (Phase 1/1b and Phase 2 Cohort A). Adagrasib exposure parameters were derived from the population PK model using the actual dose information (including dose reductions and/or interruptions). Logistic regression analysis and Kaplan-Meier plots were used to investigate the exposure-efficacy relationships. Logistic regression analysis was used to investigate the exposure-safety relationships.

Exposure-efficacy relationships

The endpoints of interest for inclusion in the E-R analyses were ORR, OS, and PFS for efficacy. A total of 118 patients with both efficacy and adagrasib PK data were included in the E-R analysis of efficacy. The following MRTX849 primary exposure metrics were used to explore the exposure-efficacy relationship:

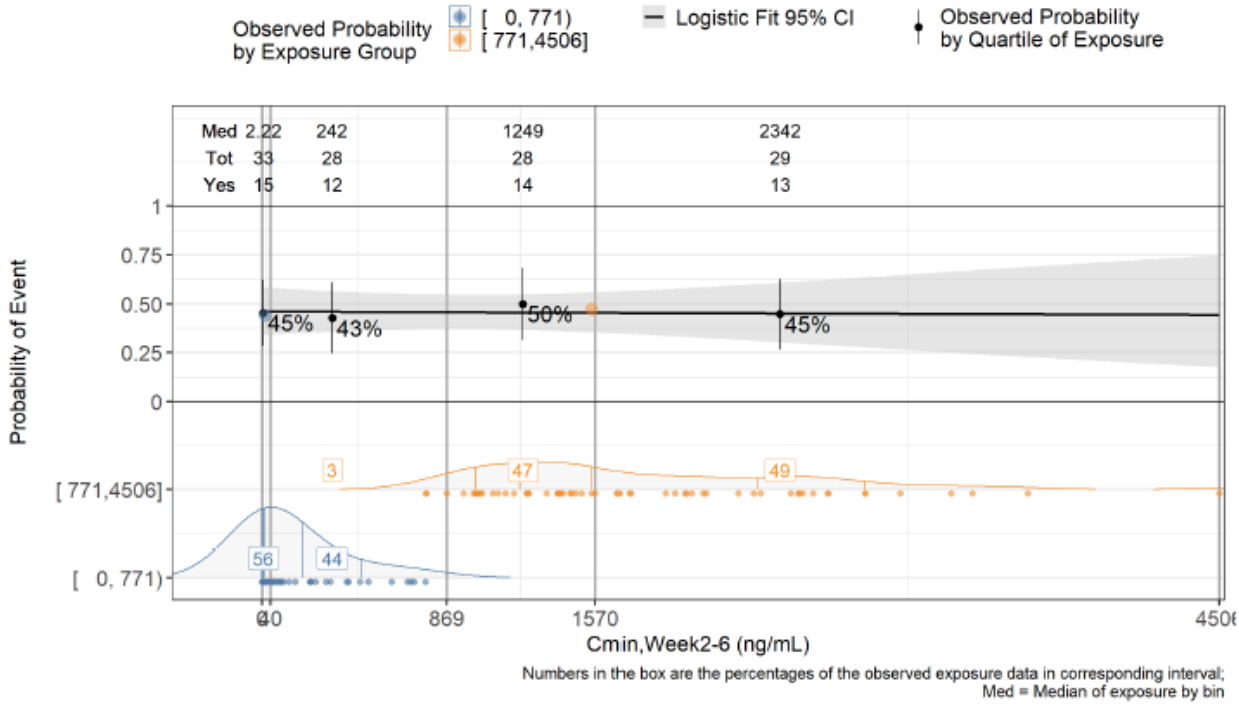
• Minimum concentration from Weeks 2 to 6 ($C_{min,Week2-6}$): The minimum value of all simulated concentrations from Weeks 2 to 6 was selected.

• Average concentration from Weeks 2 to 6 ($C_{ave,Week2-6}$): The average of all simulated concentrations from Weeks 2 to 6 was selected.

Objective response rate (ORR)

For ORR, the relationship between MRTX849 exposure and the probability of response (binary response: 0 = non-responder and 1 = responder) was modeled using a logistic regression model. The effects of baseline ECOG, age, sex, and race were formally evaluated as part of the logistic regression model. The probability of ORR as a function of $C_{min,Week2-6}$ is presented in Figure 13 . The effect of $C_{min,Week2-6}$ was not statistically significant (p-value = 0.933) in the base logistic regression model. Similarly, the effect of $C_{ave,Week2-6}$ in the base logistic regression model was also not statistically significant (p-value = 0.277).

Figure 13: Probability of ORR as a function of adagrasib $C_{min,Week2-6}$

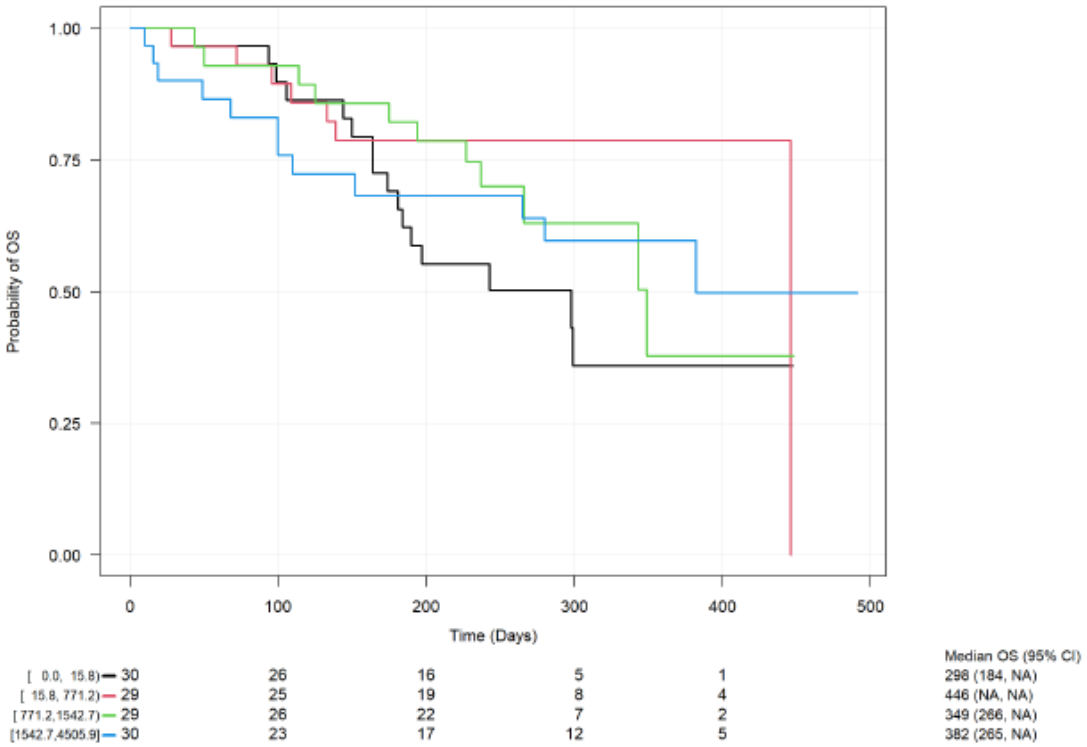


Source: Certara Report MIRA-PMX-MRTX849-2058, Figure 1
CI = confidence interval; $C_{min,Week2-6}$ = minimum concentration from Weeks 2 to 6; ORR = objective response rate.

Overall survival (OS)

For OS, a Kaplan-Meier plot for the probability of OS as a function of adagrasib $C_{min,Week2-6}$ was derived for exposure quartiles (Figure 14). The probability of OS as a function of adagrasib $C_{ave,Week2-6}$ by exposure quartiles showed similar results.

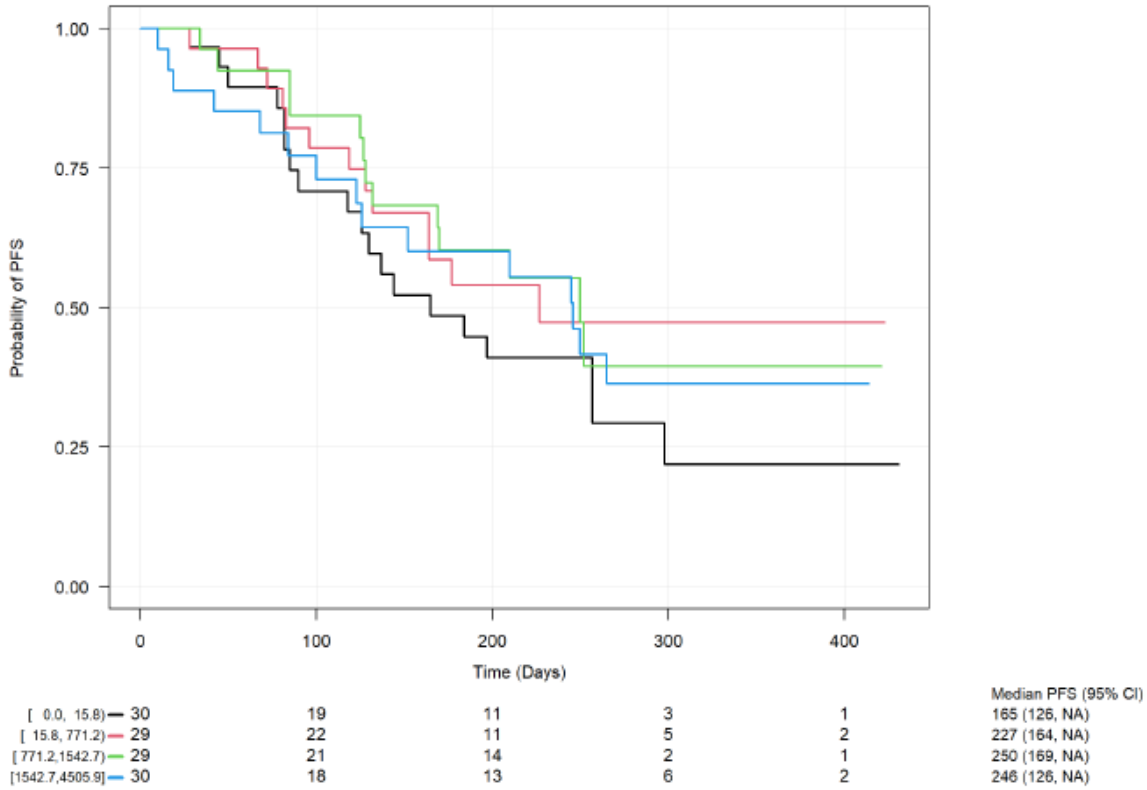
Figure 14: Probability of overall survival as a function of adagrasib $C_{min,Week2-6}$ by exposure quartiles



Source: Certara Report MIRA-PMX-MRTX849-2058, Appendix 2, Section 13.1
CI = confidence interval; $C_{min,Week2-6}$ = minimum concentration from Weeks 2 to 6; NA = not applicable; OS = overall survival.
Black curve = 1st quartile (lowest exposure); Red curve = 2nd quartile; Green curve = 3rd quartile; Blue curve = 4th quartile (highest exposure).

For PFS, a Kaplan-Meier plot for the probability of PFS as a function of adagrasib C_{min},Week2-6 was derived for exposure quartiles (Figure 15). No clear trend for the probability of PFS as a function of MRTX849 C_{min},Week2-6 by exposure quartiles was observed. The probability of PFS as a function of adagrasib $C_{ave,Week2-6}$ by exposure quartiles showed similar results.

Figure 15: Probability of progression-free survival as a function of $C_{min,Week2-6}$ by exposure quartiles



Source: Certara Report MIRA-PMX-MRTX849-2058, Appendix 3, Section 14.1
CI = confidence interval; $C_{min,Week2-6}$ = minimum concentration from Weeks 2 to 6; NA = not applicable; PFS = progression-free survival.
Black curve = 1st quartile (lowest exposure); Red curve = 2nd quartile; Green curve = 3rd quartile; Blue curve = 4th quartile (highest exposure).

Exposure-safety relationships

The endpoints of interest for inclusion in the E-R analyses were any TEAEs with Grade ≥ 3, diarrhea, nausea, vomiting, increase in AST, ALT and lipase, and hyponatremia for safety. A total of 132 patients in Study 849-001 (Phase 1/1b and Phase 2 Cohort A) with both safety and adagrasib PK data were included in the exposure-safety analysis. Of these 132 patients, 125 (94.7%) were NSCLC patients and 127 (96.2%) patients started treatment at the planned MRTX849 600 mg twice daily regimen.

The following MRTX849 primary exposure metrics were used to explore exposure-safety relationship (except for AST and ALT elevations):

• Maximum concentration at steady state ($C_{max,ss}$): The maximum concentration of MRTX849 was derived after each dose from Week 2 until the final dose and averaged in each patient.

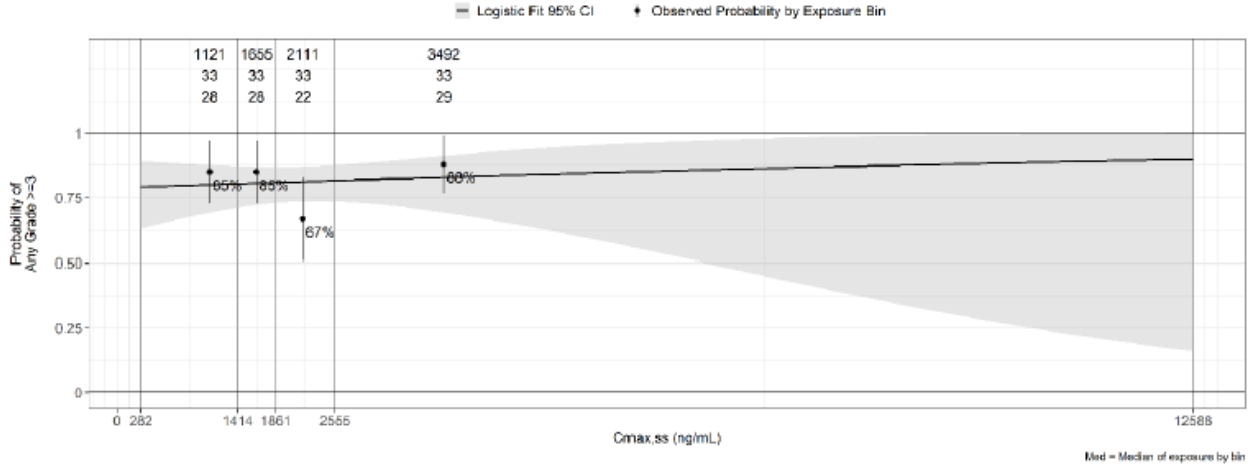
• Average concentration at steady state ($C_{ave,ss}$): The average concentration of MRTX849 was derived after each dose from Week 2 until the final dose and averaged in each patient.

For E-R analysis of AST and ALT elevations, adagrasib maximum and average concentrations from Weeks 1 to 3 ($C_{max,Week1-3}$ and $C_{ave,Week1-3}$, respectively) were used.

The result for **Any Grade ≥ 3 TEAE** is the only one presented here. The probability of any Grade ≥ 3 TEAEs as a function of adagrasib $C_{max,ss}$ is presented in Figure 16. No statistically significant E-R

relationship between $C_{max,ss}$ and the probability of any Grade ≥ 3 TEAEs was observed (p-value of exposure = 0.706). Similar results were observed for $C_{ave,ss}$ (p-value of exposure = 0.715).

Figure 16: Probability of any Grade ≥3 TEAE as a function of adagrasib $C_{max,ss}$



Source: Certara Report MIRA-PMX-MRTX849-2058, Figure 4
CI = confidence interval; $C_{max,ss}$ = maximum concentration at steady state..

According to the statistical analyses, no relationship between exposure quartiles and any of the safety endpoints was demonstrated.

2.6.3. Discussion on clinical pharmacology

Adagrasib (MRTX849) is a small molecule that elicits antitumor activity through selective, high affinity, covalent binding to and inhibition of the KRAS G12C mutant variant. Adagrasib is intended for monotherapeutic treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with KRAS G12C mutation. The clinical pharmacology of adagrasib has been characterized in the Phase 1/2 study in patients with advanced solid tumors with KRAS G12C mutation (study 849-001) and 6 Phase 1 clinical pharmacology studies: 4 in healthy subjects, 1 in subjects with hepatic impairment, and 1 in subjects with renal impairment. In addition, the PK of adagrasib was evaluated in popPK and PBPK models. The recommended dose of adagrasib is 600 mg orally twice daily. The dose modifications in the SmPC, however, cover only two dose modifications, i.e. until 600 mg QD. In 12.1% patients, the dose was reduced to 400 mg QD or 200 mg BID. The applicant has compared steady state average plasma concentration of adagrasib 600mg BID and steady state trough concentration of 400 mg QD. Average concentration and trough concentration are not comparable, as are not BID and QD. The applicant is recommended to evaluate the safety and efficacy of a lower dose regimen (400 mg BID) post-approval (study 849-021). During the clinical development of adagrasib, different drug formulations have been used with varying content of Form 1 and 2 adagrasib. The relative BA and the BE of different formulations of adagrasib were explored in studies 011 and 015. The intended formulation for marketing is a tablet containing up to 19% of Form 1 adagrasib.

In study 015, BE was shown for AUC but not C_{max} between Form 2 tablets (<4% Form 1 adagrasib) and the mixed form capsules used in the clinical studies. However, since Krazati 600 mg BID in steady state displays a flat PK profile with a peak to trough ratio of only 1.07, the impact of any slight difference in C_{max} between administration of the commercial tablet formulation and the capsules used in the clinical studies, is considered of no importance.

LC-MS/MS based methods were validated for the quantification of adagrasib (MRTX849) in human plasma and in human urine. Carry-over >20% of LLOQ was observed in 9.8% of analytical runs and

the impact on plasma concentrations assessed per SOP. A structural analogue was used as internal standard. Use of an isotope-labelled internal standard will be expected for future applications.

The population PK could be described by a two-compartment model with first-order absorption, linear elimination with a time-dependent decrease of CL which saturated after 3.5 days of 600 mg BID, caused by auto-inhibition of CYP3A4. Effect of weight, which was the only covariate with influence on MRTX849 exposure, was allometrically scaled with estimated exponents determined to 0.661 (CL) and 1.3 (V). The PK analysis set included data from 3049 samples collected in 353 subjects of which 252 were patients with advanced malignancies from Study 849-001. About 50% of the patients had NSCLC and 13.6% had CRC. The final model parameters were estimated with adequate precision. The final model was evaluated by bootstrap (904 converged runs of 1000), GoF plots and pcVPCs which indicated that the PK data could be captured across all 4 studies included.

Logistic regression models, Kaplan-Meier plots and log-rank tests were used to explore the E-R relations for safety and efficacy. Weight was a significant covariate that influenced exposure. The target exposure of 1544 ng/mL determined in a non-clinical xenograft model was met and maintained for the majority of patients during treatment. Some patients had exposures below the target at steady state. Weight was not evaluated as a covariate in the E-R analyses. A steeper drop in the Kaplan-Meier curves of PFS and of OS was observed for the 4th quartile of exposure which could not be explained by prognostic factors or reasons for censoring.

A linear mixed effect model with time effect was used to characterise the QTc concentration relation for adagrasib. A total of 1038 paired plasma concentrations and ECG measurements from 229 patients enrolled in Study 849-001, were taken post-dose and used for the analysis. Most patients received 600 mg BID. Hysteresis was evaluated in Study 849-006, Cohort 4 where 19 healthy subjects received a reduced dose of 400 mg BID on Days 6 to 9. Time-matched ECG and PK samples were collected up to 12 hours post-dose at Day 9. The ΔQTcP was largest at the pre-dose timepoint in most subjects and seemed to decline across tau of 12 hours, independently of adagrasib concentration. This variation was suggested to relate to a circadian pattern with lower values during night-time and a distinct peak in morning hours shortly after waking.

A PBPK model for adagrasib was developed in SimCyp for prediction of potential DDI in support of a clinical DDI study (Study 849-006). Initially, only CYP3A4 mediated metabolism was incorporated in the PBPK model but it was subsequently refined via inclusion of a non-CYP3A4 pathway (CYP2C8). Contributions of GSH conjugation (concluded to be minor) was not included in the model. Sensitivity analyses were performed to explore the sensitivity to some of the key model parameters (fmCYP3A4, CYP3A4 Ki, mechanism-based inhibition parameters, and fmCYP2C8). The PBPK model was used to extrapolate the effects of 400 mg to 600 mg adagrasib treatment on midazolam (CYP3A4) and dextromethorphan (CYP2D6) in cancer patients, which is accepted. Inhibition of these CYPs were investigated in vivo in healthy subjects following 400 mg adagrasib. However, the PBPK model is not considered qualified for quantitative predictions of untested scenarios. Especially the situation with strong autoinhibition of adagrasib and different contribution of different enzymes after a single dose and at steady-state appears too complex to qualify the SimCyp platform for such use at present.

The applicant was recommended to conduct and submit the results of a clinical DDI study with substrates of CYP2B6, MATE1 and MATE-2K. In addition, the applicant was recommended to conduct a clinical study to verify interactions of strong CYP3A4 inhibitors/inducers after multiple doses of adagrasib 600 mg in patients and finally, the applicant was recommended to repeat the in vivo study with digoxin and warfarin with adequate wash out, and to perform an in vivo study with gemfibrozil for adequate characterisation of interactions with CYP2C9, P-gp and CYP2C8.

In patients with KRAS G12C mutation, the median T_{max} is 6 hours. With the intended dose regimen of 600 mg BID, steady state is reached within day 8 and the accumulation of AUC is reported to be

approximately 6-fold. At steady state, the geometric mean AUC, C_{max}, and C_{min} was 31600 h x ng/mL (n=4), 3253 ng/mL (n=8), and 2693 ng/mL (n=8), respectively. Food intake increased adagrasib tablet C_{max} and AUC by approximately 20% and 38%, respectively, which are not considered clinically meaningful. The apparent volume of distribution of adagrasib is 942 L, indicating a high degree of tissue distribution. The protein binding is reported to be 99% in healthy subjects. Based on popPK analyses, the mean terminal elimination half-life ($t_{1/2}$) in patients is 29 hours, the geometric mean apparent oral clearance (CL/F) is 25.8 L/h, and the variability in exposure and disposition parameters was 51%-65%.

In the ADME study in healthy subjects, 79.2% of total radioactivity was accounted for with 74.7% of the radioactive dose recovered in feces and 4.5% (1.8% unchanged) recovered in urine. CYP3A4 mediates the majority of oxidative metabolism accounting for 72% of the activity based on nonclinical studies using. No major active metabolites are formed.

Non-linear PK is observed in both single and multiple dosing. In patients from Study 849-001, geometric mean CL/F at steady state was 30.1% lower than the CL/F after a single dose.

As for special populations, the Applicant has conducted dedicated studies in subjects with renal and hepatic impairment and covariates have been analysed in population PK analyses.

In the dedicated renal impairment study, renal impairment did not affect apparent adagrasib clearance (CL/F). Based on popPK analysis, geometric mean $AUC_{tau,ss}$ of adagrasib in patients with mild and moderate renal impairment were approximately 6% and 8% lower, respectively, than in patients with normal renal function. Together, these results reflect the low renal excretion (1.8% unchanged adagrasib) and no dose adjustment based on renal function is required (see section 4.2 of the SmPC).

In the hepatic impairment study, a comparable exposure ($C_{max,u}$ and $AUC_{\infty,u}$) in unbound adagrasib was observed between subjects with mild and moderate impairment and subjects with normal hepatic function. Subjects with severe hepatic impairment had comparable C_{max} but 66% higher AUC_{∞} of unbound adagrasib. The applicant performed PBPK simulations on patients with severe hepatic impairment and based on these, no change in dose for this special population is suggested. The applicant performed sensitivity analyses on the impact of fraction absorbed, fmCYP2C8, CYP3A4 abundance, additional HLM Clint values and the adagrasib mediated CYP3A4 time dependent inhibition. The sensitivity analyses presented, indicated that there is little difference in predicted exposure whether CYP2C8 is responsible for between 20% and 80% of the non-CYP3A4 metabolism. A similar lack of sensitivity was predicted for CYP3A4 abundance values from 15 to 135 pmol/mg and additional HLM CLint values between 24 and 108 µl/min/mg. The sensitivity analysis exploring the effect of CYP3A4 MBI parameters indicated that these parameters are less sensitive in the CP-C population compared to the HV population. This reduced effect is due to the lower CYP3A4 abundance in the CP-C population. All steady-state sensitivity analyses were repeated assuming the lower dosing regimen of 400 mg BID for CP-C subjects and all results followed the same pattern of sensitivity as observed for the 600 mg BID dose. Based on the ratios of unbound exposure (CP-C to HV) falling within 1.25-fold for the sensitivity analyses of fmCYP2C8, CYP3A4 abundance, and HLM CLint, it is acknowledged that no dose adjustment may be required for patients with severe hepatic impairment (Child-Pugh class C).

The impact of age (19 to 89 years), sex, race (White, Black, Asian), tumor burden, and ECOG performance status on adagrasib PK was evaluated in popPK analyses and these factors explained less than 5% of the variability in PK parameters of adagrasib and were therefore not included in the population PK model.

The posology of adagrasib includes the use of a fixed dose. Based on an analysis of weight quartiles, the exposure to adagrasib decreased from Q1 to Q4, as expected, but overall the exposures were comparable. In weight extreme patients (below the 5th and above the 95th percentiles), the predicted

steady state exposure is within the predicted natural variation in exposure parameters (approximately 50%) in the full population. Apart from patients with severe hepatic impairment, no dose adjustments for adagrasib are required in the investigated special populations.

With regard to drug-drug interactions, a clinical study and PBPK simulations have been conducted in order to evaluate the potential of adagrasib as victim or perpetrator in PK DDIs. It should be noted, though, that the qualification of the PBPK model for predictions of drug-drug interactions is questioned. The applicant planned to conduct a post-marketing interaction study to evaluate the effect of gemfibrozil (strong CYP2C8 inhibitor) on the PK of adagrasib (Recommendation). This should be conducted with adagrasib at steady state.

Overall, the PK data obtained in the target population are sparse with data from only 20 patients receiving the proposed dose regimen.

No pharmacodynamic endpoints have been determined and investigated. Accordingly, no PD biomarkers are proposed for monitoring of effect.

According to the QTc analyses, adagrasib has an effect on QT. The predicted mean (90% CI) ΔQTcF is 17.93 (15.13, 20.73) ms. Information on QT prolongation is found in section 4.2, 4.4, 4.5, and 4.8 of the SmPC. The risk of QT prolongation and precautionary measures are sufficiently described in section 4.4.

As for exposure-response analyses, the primary popPK derived adagrasib exposure metrics used to explore the exposure-efficacy relationship were $C_{min,week2\text{-}6}$ and $C_{ave,week2\text{-}6}$. According to the statistical analyses, no relationship between exposure (exposure quartiles or below/above median) and efficacy endpoints was demonstrated. However, for PFS the median for the lowest quartile (165 days) seems to be significantly lower compared with the other quartiles.

The primary popPK derived adagrasib exposure metrics used to explore the exposure-safety relationship were $C_{max,ss}$ and $C_{ave,ss}$. According to the statistical analyses, no relationship between exposure quartiles and safety endpoints was demonstrated. It is noted that the average adagrasib concentration may be more predictive (borderline significant P-value) for the risk of ALT elevations than the maximum concentration.

2.6.4. Conclusions on clinical pharmacology

The clinical pharmacology package is limited but acceptable for approval. The SmPC reflects the current knowledge on adagrasib PKPD. The proposed dose is considered appropriate in both the target population and in special populations.

2.6.5. Clinical efficacy

The main clinical studies that constitute the efficacy data package supporting the initial MAA of adagrasib (MRTX849) as monotherapy in previously treated patients with advanced NSCLC harboring the *KRAS* G12C mutation are briefly summarised in Table 14. Cohort A from registrational phase II Study 849-001 (KRYSTAL-1) is considered pivotal for initial approval of MRTX849 in NSCLC, while data from NSCLC patients from Cohorts B as well as the completed Phase 1/1b dose finding sub study are considered supportive.

Table 14: Design features of phase 1/2 dose-escalation and multiple expansion cohort Study 849-001 (KRYSTAL-1).

Segment CSR Status **Start Date**[1] **SCE Data Cutoff Date**	Study Drug Starting Dose, Route & Regimen	Study Objective	No. Pts[2] in Efficacy Evaluation	Diagnosis Inclusion Criteria
Phase 1/1b (dose finding) Final 26 Dec 2018 CSR: 27 Nov 2020	MRTX849 Oral/ Escalating doses	Safety, tolerability, PK, MTD/RP2D, clinical activity	25	Solid tumor with *KRAS* G12C mutation in tumor tissue, no available curative/standard-of-care treatment, or patient was ineligible or declined treatment. 16 patients with NSCLC were treated at 600 mg BID
Phase 2 Cohort A Final 17 Jan 2020 CSR: 15 Jun 2021	MRTX849 Oral/ 600 mg BID	Efficacy, safety, tolerability, PK	116	Squamous or nonsquamous NSCLC with *KRAS* G12C mutation in tumor tissue, prior treatment with at least a platinum-containing regimen and CIT
Phase 2 Cohort B Interim 17 Jan 2020 CSR: 29 Jan 2021 ISE: 15 Jun 2021	MRTX849 Oral/ 600 mg BID	Clinical activity, safety, tolerability, PK	56[3]	Squamous or nonsquamous NSCLC with *KRAS* G12C mutation in ctDNA, prior treatment with at least a platinum-containing regimen and CIT

BID = twice daily; CIT = checkpoint inhibitor therapy; CSR = clinical study report; ctDNA = circulating tumor DNA; ISE = Integrated Summary of Efficacy; MTD = maximum tolerated dose; NA = not applicable; No. = number; NSCLC = non-small cell lung cancer; PK = pharmacokinetic(s); Pts = patients; RP2D = recommended Phase 2 dose; SCE = Summary of Clinical Efficacy; tx = treatment.
[1] Date of first informed consent.
[2] As of the data cutoff date for the SCE (27 Nov 2020 for Phase 1/1b, 15 Jun 2021 for Phase 2 Cohorts A and B).
[3] In a posthoc sensitivity analysis included in, 4 additional patients who had enrolled in Cohort B at the time of the data cutoff date of 15 Jun 2021 were included, for a total of 60 patients in Cohort B.

The primary completion date for Cohort A was selected as 15 June 2021 to ensure that the last patient enrolled could be followed for at least 6 months after start of study treatment. Updated efficacy from data cut-off 15-OCT-2021 were provided during the procedure.

Additional cohorts:

Cohort C (phase II segment) will recruit patients with adenocarcinoma of the colon or rectum with KRAS G12C mutation, no available curative/standard-of-care treatment, or patient was ineligible or declined treatment.

Cohort D (phase II segment) will recruit patients with solid tumours with KRAS G12C mutation, no available curative/standard-of-care treatment, or patient was ineligible or declined treatment.

As of Protocol Amendment 6 (Version 7.0, 23-12-2020) 2 additional phase 1B cohorts were added (up to n=12 each):

- Phase 1b cohort to include patients with advanced, unresectable NSCLC with KRAS G12C mutation who decline currently available first-line systemic therapies (i.e., treatment naïve); and
- Phase 1b cohort to include patients with NSCLC with KRAS G12C mutation who were previously treated with a therapy targeting KRAS G12C mutation.

In the same Protocol Amendment, cohort E (phase II segment) for patients with NSCLC with KRAS G12C and STK11 mutations in the first line treatment setting was added.

As of Protocol Amendment 7 (Version 8.0, 12-APR-2021), Cohort F (phase II segment) for patients with colorectal cancer with KRAS G12C mutation (detected in tumor tissue) who have previously received each of the following agents: a fluoropyrimidine, oxaliplatin, irinotecan, and a VEGF/VEGFR inhibitor was added.

2.6.5.1. Dose response study(ies)

See section 2.6.2.2.

2.6.5.2. Main study

Study 849-001: A Phase 1/2 Multiple Expansion Cohort Trial of MRTX849 in Patients with Advanced Solid Tumors with KRAS G12C Mutation (KRYSTAL-1)

Methods

- **Study Participants**

Inclusion Criteria

1. Histologically confirmed diagnosis of a solid tumor malignancy with *KRAS* G12C mutation*:

   a. In Phase 2 Cohorts A and B, squamous or nonsquamous NSCLC.

   b. In Phase 2 Cohort C, adenocarcinoma of the colon or rectum.

* The presence of KRAS G12C mutation for the purpose of patient eligibility was established using Sponsor-approved local laboratory testing. Acceptable methods used for detection of KRAS G12C mutation included polymerase chain reaction (PCR), next-generation sequencing (NGS), and Sanger sequencing.

2. Unresectable or metastatic disease.

3. Available and prior therapy:

   a. No available treatment with curative intent.

   b. No available standard-of-care treatment or patient was ineligible or declined treatment, except

   c. In Phase 2 NSCLC (Cohorts A and B), patients had to have previously received treatment with at least a platinum-containing chemotherapy regimen and checkpoint inhibitor therapy (CIT).

4. Presence of tumor lesions to be evaluated per RECIST 1.1:

   a. In Phase 2 cohorts, patients must have measurable disease.

5. Age ≥18 years.

6. Life expectancy of at least 3 months.

7. Most recent prior systemic therapy (e.g., chemotherapy, immunotherapy, or investigational agent) and radiation therapy discontinued at least 2 weeks before first dose date.

8. Recovered from the adverse effects of prior therapy at the time of enrollment to Grade ≤1 (excluding alopecia).

9. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.

10. Laboratory values within the Screening period:

   a. Absolute neutrophil count (ANC) ≥1000/mm3 ≥1.0×109/L.

   b. Platelet count ≥100,000/mm3 (≥100×109/L).

   c. Hemoglobin ≥9 g/dL, in the absence of transfusions for at least 2 weeks.

d. Total bilirubin ≤1.5×upper limit of normal (ULN) (if associated with liver metastases or Gilbert's disease, ≤3×ULN).

e. Aspartate transaminase and alanine transaminase ≤3.0×ULN (if associated with liver metastases, ≤5×ULN).

f. Creatinine clearance ≥60 mL/min.

11. Women of childbearing potential (WOCBP) or men whose partner was a WOCBP had to agree to use contraception while participating in this study and for a period of 6 months following termination of IP.

12. Completed informed consent process, including signing IRB-approved ICF.

13. Willing to comply with clinical trial instructions and requirements.

Exclusion Criteria

1. Active brain metastases. Patients were eligible if brain metastases were adequately treated and patients were neurologically stable for at least 2 weeks prior to enrollment without the use of corticosteroids or were on a stable or decreasing dose of ≤10 mg daily prednisone (or equivalent).

2. Patients with carcinomatous meningitis.

3. History of significant hemoptysis or hemorrhage within 4 weeks of the first dose date.

4. Undergone major surgery within 4 weeks of first dose date.

5. History of intestinal disease or major gastric surgery likely to alter absorption of study treatment or inability to swallow oral medications.

6. Any of the following cardiac abnormalities within the previous 6 months:

a. Unstable angina pectoris.

b. Congestive heart failure New York Heart Association Class ≥3.

c. QT corrected (QTc) ≥480 milliseconds or family history of long QT syndrome.

7. History of stroke or transient ischemic attack within the previous 6 months.

8. Ongoing need for a medication with a known risk of Torsades de Pointes (TdP) that could not be switched to alternative treatment prior to study entry.

9. Known or suspected presence of another malignancy that could have been mistaken for the malignancy under study during disease assessments.

10. Known human immunodeficiency virus seropositivity or active hepatitis B or C. Patients treated for hepatitis C with no detectable viral load were permitted.

11. Pregnancy.

12. Breastfeeding or planning to breastfeed during the study or within 6 months after study treatment.

13. Any serious illness, uncontrolled intercurrent illness, psychiatric illness, active or uncontrolled infection, or other medical history, including laboratory results, which, in the Investigator's opinion, would have been likely to interfere with the patient's participation in the study or with the interpretation of the results.

14. Prior treatment with a therapy targeting *KRAS* G12C mutation.

- **Treatments**

Based on the safety and tolerability of adagrasib demonstrated in the Phase 1 component of the study, the dose of **600 mg twice daily** was selected as the starting dose for Phase 2, with each dose typically consisting of three 200-mg capsules taken with a cup of water and without food.

Duration of treatment: Patients received continuous treatment with adagrasib expressed as 3-week cycles at the discretion of the Investigator until disease progression, unacceptable adverse events, patient refusal, or death. Patients whose disease assessments met criteria for disease progression in accordance with RECIST 1.1, as assessed by the Investigator, could continue study participation if the Investigator both assessed that there was ongoing clinical benefit and recommended continuation.

Treatment with adagrasib beyond progression was allowed at the discretion of the investigator.

Dose reductions: For patients in phase 2 treated at the 600 mg twice daily starting dose level at the time of the data cutoff for the CSR (12-OCT-2021), doses could be sequentially decreased to 400 mg twice daily, 600 mg once daily, 400 mg once daily, and 200 mg twice daily.

- **Objectives**

The objectives of Cohort A of study 849-001 of the Phase 2 segment were the following:

- To evaluate the clinical activity/efficacy of adagrasib in cohort of patients having selected solid tumor malignancies with *KRAS* G12C mutation and Baseline characteristics.
- To characterize the safety and tolerability of adagrasib in patients having advanced solid tumor malignancies with *KRAS* G12C mutation.
- To evaluate the pharmacokinetics (PK) of adagrasib.

- **Outcomes/endpoints**

- The primary endpoint for evaluation of efficacy is overall response rate (ORR) by blinded independent central review (BICR) in the full analysis set (FAS), i.e., patients who received at least 1 dose of MRTX849 on this study and had measurable disease at Baseline.
    - Objective response was categorized in accordance with RECIST v1.1 criteria. ORR is defined as the percent of patients documented to have a confirmed complete response (CR) or partial response (PR). Best Overall Response (BOR) is defined as the best response among all the responses [(in the order CR, PR, stable disease (SD), progressive disease (PD) and not evaluable (NE)] recorded from the start of study drug treatment until disease progression/recurrence, end of treatment visit date or start of new anti-cancer therapy, whichever comes first. A Best Overall Response of CR or PR cannot be assessed unless it is confirmed, no earlier than four (4) weeks (28 days) from the time a response of CR or PR is first suspected (SD does not require confirmation).
- Secondary efficacy endpoints for efficacy included Duration of Response (DOR), Progression Free Survival (PFS), Overall Survival (OS).
    - DOR in months is defined as the time from date of the first documentation of objective response (CR or PR) to the first documentation of Progression of Disease (PD) or to death due to any cause in the absence of documented PD (i.e., min (PD date, death date) – date of the first observation of response +1)/30.4375. DOR will only be calculated for the subgroup of patients achieving a confirmed CR or PR. DOR will be evaluated based on response assessments by the independent central review and Investigator.

- PFS is defined as the time from the date of first study treatment to the date of first PD or death due to any cause in the absence of documented PD, whichever occurs first. PFS (in months) will be calculated as (first event date – first dose date +1)/30.4375.
- OS is defined as the time from the date of first study treatment to the date of death due to any cause. OS (in months) is calculated as (date of death − date of first dose of study drug +1)/30.4375. OS analysis will be based on the enrolled population.

• Safety endpoints outlined the type, incidence, severity, timing, seriousness, and relationship to adagrasib of adverse events and laboratory abnormalities.

Efficacy assessments: All patients enrolled in the study were to be evaluated for disease activity at Screening (28-day window allowed) and every 6 weeks from Cycle 1 Day 1 (±10-day window for all other assessments except Screening) until Week 49 (~12 months) and then every 12 weeks. At Screening/Baseline, assessments included computed tomography (CT) with contrast of the chest, contrasted CT or magnetic resonance imaging (MRI) of the abdomen and pelvis, and evaluation of any superficial lesions. At Baseline, if brain and/or bone lesions were known or suspected, respective Baseline scans were obtained. Brain imaging could include either brain MRI with and without gadolinium or brain CT with contrast. Bone imaging included whole-body bone scan (or positron-emission tomography [PET] or PET/CT if local standard for clinical trials). Subsequent disease assessments included all sites of disease identified at Baseline or suspected to have developed; bone scans could be performed half as often (every 12 weeks) as other radiology evaluations and performed during assessment for confirmation of disease response.

Follow-up: Patients who discontinued treatment without having experienced disease progression were to continue to have disease assessments every 6 weeks, and following disease progression, all patients were to be followed every 2 months for survival status and poststudy cancer treatments.

- **Sample size**

The primary endpoint for evaluation of efficacy for Cohort A was ORR. The standard of care for patients treated in this setting is docetaxel with or without ramucirumab, which is associated with ORR of up to 23%. The design for Cohort A utilized a 95% CI to exclude an ORR of 23% (Garon-2014). Assuming adagrasib would result in an ORR of at least 35% in this treatment setting, a sample size of approximately 105 evaluable patients would be sufficient for the lower bound of a 2-sided 95% CI (Clopper-Pearson method) to exclude an ORR of 23%.

- **Randomisation and Blinding (masking)**

Random assignment is not being used in this study. Blinding was not applicable. An IDMC oversaw the conduct of the study as outlined in the IDMC Charter. The IDMC was to have access to study data to review the conduct of the study and accruing safety and efficacy data at approximately 6-month intervals, at the time of interim futility analyses for the Phase 2 cohorts, and on an ad hoc basis as study questions arose.

- **Statistical methods**

Study populations

Enrolled Population: The enrolled population is defined as all patients who sign the main study informed consent form and determined by the Investigator to meet all eligibility criteria during screening assessments.

Full Analysis Set (FAS): The FAS is defined as all patients who receive at least one dose of adagrasib on this study and had measurable disease at baseline assessed by investigator using RECIST 1.1 (or similarly defined for response assessment by independent radiology).

For Cohort A, 2 FAS populations were defined. The FAS-BICR, for the primary analysis of radiographic endpoints, included all patients who had measurable disease at baseline determined by the BICR and received at least one dose of study medication, and the FAS-Investigator included all patients who had measurable disease at baseline determined by the Investigator and received at least one dose of study medication. The FAS-BICR comprised 112 patients, and the FAS-Investigator comprised 116 patients and included 4 patients assessed by BICR as having only non-measurable disease at baseline. The FAS-BICR will be used in the primary analyses for ORR and DOR. The FAS-Investigator will be used in the supportive analyses for ORR and DOR.

Clinical Activity Evaluable (CAE) Population: Patients included in the CAE population were patients who received at least one dose of adagrasib and had an evaluable baseline tumour assessment and at least one postbaseline tumour assessment.

Safety Population: Defines as all patients who received at least 1 dose of adagrasib.

ORR, DOR, and PFS summaries will be performed on the FAS for both investigator and independent central review. OS summaries will be summarized on the enrolled population.

Endpoints

Objective response rate (ORR)

Descriptive statistics (frequency and percentage) for ORR, and of best overall response (CR, PR, SD, PD) based on the response assessments by the Independent Central Review and Investigator, and the exact 95% Clopper-Pearson confidence interval for the ORR will be presented.

Patients who cannot be assessed for response will be counted as not evaluable.

In addition, the concordance of tumour response assessment between central review and investigator will be summarized in a table.

Duration of response (DOR)

DOR will only be calculated for the subgroup of patients achieving a confirmed CR or PR. DOR will be summarized descriptively, using the Kaplan-Meier estimate. Kaplan-Meier plot will be provided for DOR.

Sensitivity analysis using the investigator’s assessment will also be presented.

DOR will be evaluated based on response assessments by the independent central review and Investigator.

Progression-Free Survival (PFS)

PFS will be summarized descriptively, using the Kaplan-Meier estimate. Kaplan-Meier plot will be provided.

To assess the impact on PFS analysis due to COVID-19, a sensitivity analysis will be performed to treat those patients who have missing 2 or more consecutive tumour assessments due to COVID-19, and had PD or death not related to COVID-19 after the missed tumour assessment as event in PFS analysis. No patients qualified for this analysis.

Additionally, a sensitivity analysis may be performed for PFS excluding the important protocol deviations. Sensitivity analyses will only be performed for PFS by Independent Central Review.

PFS will be calculated based on both Independent Central Review results and Investigator assessments using the FAS.

Censoring Rules for Time-To-Event Endpoints Based on Radiographic Evaluations (DOR and PFS)

- Endpoints will be censored on the date of the first dose of study treatment with duration of 1 day under the following scenarios (apply to PFS only):
    - baseline disease assessment inadequate to apply RECIST1.1;
    - no disease assessments are performed during study treatment, except in the event of early death (see below for death as an event); or
    - all disease assessments performed during study treatment result in the conclusion of NE.
- Endpoints will be censored on the date of the last evaluable disease assessment under the following scenarios (apply to PFS and DOR):
    - PD or death occur after ≥2 consecutive tumor assessments that are missed or result in the conclusion of NE (i.e., > 12 weeks ± 14-day assessment window);
    - patient administered alternative cancer treatment prior to documented PD;
    - patient lost to follow-up;
    - patient withdrawal of consent for follow-up; or
    - patient continues on study treatment without PD at the time of data cutoff or End of Study.
- Date of death will be considered an event for DOR and PFS under the following scenarios:
    - death occurs prior to PD and ≤ 12weeks + 14-day window after the first dose of study treatment;
    - death occurs ≤ 12 weeks + 14-day window after the last evaluable disease assessment; and
    - death in the absence of receiving subsequent anti-cancer therapy.

Analysis for patients with PD or death occur after ≥2 consecutive tumor assessments that are missed or result in the conclusion of NE (i.e., > 12 weeks ± 14-day assessment window) considered as events will also be performed.

Overall Survival

OS will be summarized descriptively, using the Kaplan-Meier estimate. Kaplan-Meier plot will be provided.

OS analysis will be based on the enrolled population.

A sensitivity analysis on OS will be performed on the impact of COVID-19. Patients who died due to COVID-19 will be censored at patients' last on study follow-up.

Censoring Rules for OS

For patients who are continuing study at the time of data cutoff, who are lost to follow-up or who withdraw consent for follow-up, the OS endpoint will be censored on the last date that patients were known to be alive. For patients who did not receive study treatment, OS will be censored at Day 1. For patients with no follow-up after first dose of study drug, OS will be censored at the date of first dose.

Interim analyses

The design for Cohort A will include a non-binding stopping rule for futility derived using East® software v6.5 to control the Type 2 error rate of 0.2. The Type 2 error spending function is based on the Rho family with parameter 2.0. The futility analysis will be conducted when approximately 32 evaluable patients (approximately 30% of the total number of patients) are available for the response assessment. The futility bound will be 6 or fewer observed responses among the first 32 patients.

Subgroup analyses

Subgroup analyses were performed on the Cohort A efficacy analyses for the following patient demographic and disease characteristics:

- Gender.
- Age (< 65 versus ≥ 65 years).
- Number of prior systemic therapies (1 versus > 1).
- Concurrent versus sequential platinum and CIT.
- Smoking history.
- Baseline ECOG status.
- Liver metastases at baseline.
- Brain metastases at baseline.
- Bone metastases at baseline.
- Adrenal metastases at baseline.

Analyses are presented descriptively for each subgroup. Subgroup analyses of ORR and DOR were based on response as assessed by BICR.

To further examine the effect of key subgroups, subgroup analyses of ORR were performed on all NSCLC 600 mg twice daily groups (Cohorts A and B and Phase 1/1b) for subgroups defined by age (< 65 versus ≥ 65 years), number of prior systemic therapies (1 versus > 1), and concurrent versus sequential prior treatment with platinum and CIT.

SAP versions and changes to the planned analyses

SAP2.0 describes the statistical methods to be used during the analysis and reporting of data collected in the Phase 2 Cohort A segment for monotherapy treatment.

SAP2.0 should be read in conjunction with the study protocol and case report forms (CRF). This version of the plan has been developed using protocol version 6.0 dated 18 May 2020 and CRF version 6.0 dated 20 November 2020. Any further changes to the protocol or CRF may necessitate updates to the SAP2.0.

An initial SAP2.0 will be finalized based on the current protocol and CRF so that programming may be created. Changes to the protocol (e.g. protocol amendment) following approval of the SAP2.0 will be tracked in the SAP2.0 Change Log. An amended SAP2.0 will be finalized prior to database lock.

Changes to the Planned Analyses

The following deviations from the protocol planned analyses were documented in the SAP prior to database lock:

- The modified intent-to-treat population definition as defined in the protocol was renamed as the

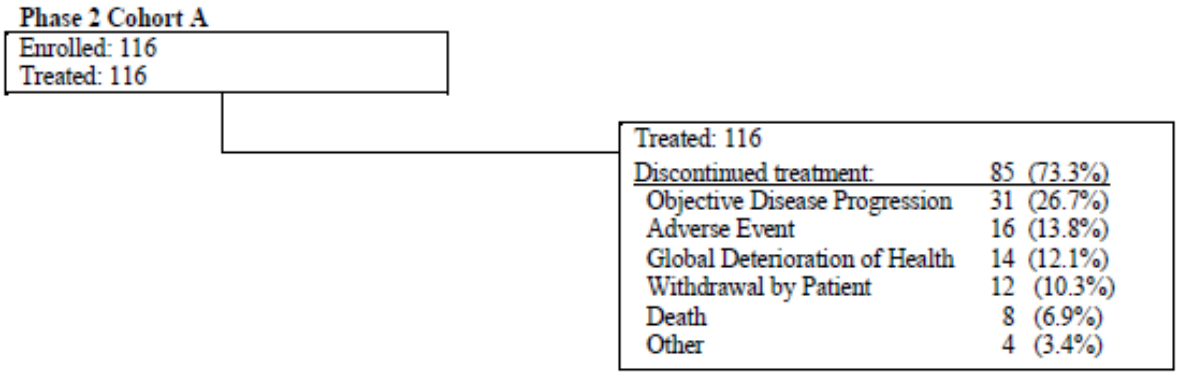
FAS in the SAP.

- The CAE population was modified to add a requirement for an evaluable Baseline tumour assessment to the initial criteria of receipt of at least 1 dose of study medication and at least 1 postbaseline tumour assessment.

Results

- **Participant flow**

Figure 17: Patient disposition/study participant flow – Study 849-001 Cohort A (15 Oct 2021)



"Global deterioration of health" characterizes scenarios where there is general decline in functional or performance status. For example, patients with cancer may develop disease-related increase in fatigue, decrease in appetite, decrease in exercise tolerance, depression, and/or adverse events related to disease location. Investigators report global deterioration of health for the cause of treatment discontinuation as none of the adverse events by themselves (which may be of low severity) results in treatment discontinuation, but rather the overall decline in health status is responsible.

Table 15: Summary of screen failures for Cohort A of Study KRYSTAL-1

Variable Reason [n]	Phase 2 Cohort A Total (N=215)
Patients Screened	215
Patients Pre-Screened for KRAS	39
Screen Failure Reason	99
Does not Meet Eligibility Criteria	81
Withdrawn Consent	8
Adverse Event	0
Death	6
Other	4

Note: Reasons for screen failure are based on the Screen Failure CRF pages.

- **Recruitment**

All patients from Cohort A were recruited across 30 study sites in the United States of America.

Date of first patient enrolled for Protocol 849-001: 26-DEC-2018.

Enrolment into Cohort A was completed in approximately 1 year from January 17, 2020 to November 24, 2020. Dates of first dose occurred between February 4, 2020 and December 9, 2020.

Date of last patient enrolled for Protocol 849-001: Although enrolment for Cohort A is completed, recruitment is still ongoing for other cohorts of this study.

At time of data cut-off (15-JUN-2021), the median follow-up in of patients from Cohort A (n=116) was 9.0 months (95% CI: 8.0 to 9.7 months). The primary analysis of ORR was performed once all treated

patients had enough follow-up to assess response (at least 6 months after the last patient enrolled started treatment).

- **Conduct of the study**

There are 8 versions of the protocol. The methods, procedures and submitted data are based on protocol version 6, the version used to develop the study SAP. Protocol version 7 and 8 were issued before the database cutoff date for this CSR; therefore, some limited data from patients who were treated under these versions are included in this report. A summary of changes of the protocol along study conduct follows.

Table 16: Summary of changes along protocol versions of Study KRYSTAL-1

Document	Version Date	Summary of Changes
Original Protocol, Version 1.0	29 October 2018	NA

Amendment 1, Version 2.0	29 November 2018	At the request of FDA during IND review –
		• Updated DLT definition to include:
		  ○ Any Grade 4 neutropenia
		  ○ AEs not clearly related to disease progression or intercurrent illness
		  ○ Any Grade 4 electrolyte decrease
		• Added on-study MUGA or ECHO Day 1 every other cycle (i.e., Cycles 3, 5, 7, etc.).
		• Removed a pilot phase 1 combination sub-study previously described in the study objectives, study design and an appendix. Any future combination pilot sub-studies will be implemented by protocol amendment after adequate safety data are available for MRTX849 administered as a single agent.
		• Additional administrative changes have been made to align footnotes in Table 2, Table 3 and Table 4.

Amendment 2, Version 3.0	01 July 2019	• In accordance with the communication plan described in Section 9.9.3 and Section 13.2:
		  ○ Summarized study results to date, including safety and PK data.
		  ○ Added Phase 1 evaluation of twice daily MRTX849 administration.
		  ○ Described the Phase 1b cohort to expand the safety and PK experience at 600 mg QD as the dose escalation study continues.
		  ○ Added an initial food effect evaluation to mitigate pill burden and observed mild gastrointestinal adverse events.
		• Added the possibility of intra-patient dose escalation to a dose level intermediate to the next higher dose in the escalation scheme and from the once daily to twice daily dose regimen.

Amendment 3, Version 4.0	14 November 2019	• In accordance with the communication plan described in Section 9.9.3 and Section 13.2:
		  ○ Summarized study results to date, including safety and PK data.
		  ○ Updated the plan for dose reduction steps in Phase 1/1b to be implemented to manage treatment-related AEs (Section 5.3.1.1, Table 13).

		○ Added the MRTX849 dosing regimen to be used in the Phase 2 single agent evaluation (Section 5.2.3), including dose reduction steps to be implemented to manage treatment-related AEs (Section 5.3.1.2, Table 14). • Added sub-study pilot Phase 1 evaluations of MRTX849 administered in combination with selected cancer therapeutic agents pembrolizumab (Appendix 7) or cetuximab (Appendix 8). Rationale and information supporting selection of the therapeutic agents for investigation in combination with MRTX849 added to background sections (Section 1.3.1, Section 1.3.2.1, and Section 1.5.5). • Clarified that tumor tissue samples for PD evaluation should be collected unless medically unsafe or infeasible. • Added flexibility to the schedule for LVEF assessment (increased window from ±2 days to -7/+2 days) and for on-treatment tumor tissue collection for PD evaluation. • Revised the collection of baseline ECG such that a single (rather than 2) triplicate is sufficient unless there is a 15 msec or more difference in QT between any two baseline ECGs. Corrected minor editing and typographical errors.
Amendment 4, Version 5.0	20 February 2020	Based on the observation of clinical activity in Phase 1 study participants, and discussions with the FDA, the design for Phase 2 evaluation of MRTX849 in patients with NSCLC with *KRAS* G12C mutation detected in tumor tissue (Cohort A) was updated to conduct a more extensive evaluation of efficacy. Changes that apply to Cohort A specifically include: • implementation of central radiology review for evaluation of disease response and progression; • requirement for evaluation for brain metastases to confirm objective disease response; • increased sample size; • stopping rule for futility constructed using the error spending function based on the Rho family with parameter 2.0; and • use of the 95% confidence interval approach for the final analysis for efficacy. Based on discussions with the FDA, the following sub-studies were redesigned: • the evaluation of new MRTX849 oral formulations described in Appendix 5 was updated from a pharmacokinetic evaluation to a relative bioavailability evaluation; and

		• the definitive evaluation of the effect of food on the PK of MRTX849 described in Appendix 6 was updated from a parallel evaluation of PK in the fed state to a randomized 2-way crossover design. Added collection of CSF in selected patients for correlation with circulating concentrations of MRTX849. Updated chemical name of MRTX849. Added eligible histological subtypes for NSCLC and CRC to the entry criteria. Revised eligibility requirement for creatinine clearance (CrCl) to include measured CrCl and other acceptable calculation methods. In the sub-study of MRTX849 administered in combination with cetuximab (Appendix 8): • added eligibility of patients initially treated in Phase 2 Cohort C of the main study, i.e., patients having advanced CRC, and • limited detailed collection of samples for MRTX849 PK to 12 patients evaluable for PK. In accordance with the communication plan described in Section 9.9.3 and Section 13.2: • Added sub-study pilot Phase 1 evaluation of MRTX849 administered in combination with the cancer therapeutic agent afatinib (Appendix 9). Rationale and information supporting selection of the therapeutic agent for investigation in combination with MRTX849 added to background sections (Section 1.3.1, Section 1.3.2.2, and Section 1.5.5).
Amendment 5, Version 6.0	18 May 2020	• In accordance with FDA guidance concerning study conduct during the COVID-19 public health emergency, added Appendix 10 to reiterate permitted study conduct adaptations, including those announced to study sites in a recent Administrative Letter to Investigator. • Added a Phase 1b cohort to evaluate the safety and clinical activity of MRTX849 in patients with limited brain metastases. • Limited the requirement for regularly scheduled bone imaging (bone scan or PET scan) and brain imaging in Phase 2 cohorts to patients with NSCLC or cancer of unknown primary. Removed requirement for patients with other tumor types for which these assessments are not standard. • Added description of an MRTX849 tablet formulation to be evaluated in the formulation sub-study (Appendix 5). • Clarified timing of addition triplicate ECGs to be performed in the formulation sub-study (Appendix 5) and food effect sub-study (Appendix 6).

		• Added minor clarifications to existing text in the document.
Amendment 6, Version 7.0	23 December 2020	Incorporated information and guidance previously distributed to study sites in Administrative Letters to Investigators: • Revised background information and guidance on use of concomitant medications: o recent in vitro studies indicate that MRTX849 is a substrate for P-gp and BCRP and has the potential to inhibit P-gp and BCRP; o preliminary results from an ongoing clinical drug-drug interaction study (data not available at the time of the Administrative Letter to Investigators) indicate restrictions for concomitant medications that are BCRP substrates are not required, however, medications with low therapeutic index that are P-gp efflux substrates should continue to be used with caution; o added guidance on use of gastric acid reducing medications and anti-emetics. • Updated the summary of clinical safety experience in the background section. • Updated AE management guidelines in Section 5.3.2. • Added potential to submit fresh frozen tumor samples for pharmacodynamic assessment. • In the cetuximab combination sub-study described in Appendix 8: o allowed crossover from the main study for patients with CRC who experience SD compared to baseline measurements (as opposed to nadir measurements), o allowed for use of cetuximab in the Q2W regimen. • In the afatinib combination sub-study described in Appendix 9, allowed prior receipt of treatment with inhibitors of KRAS. Updated MRTX849 clinical background sections in accordance with communication plan described in Section 9.9.3 and Section 13.2: • Updated summary of clinical pharmacokinetics. Included guidance for use of concomitant medications based on preliminary results from an ongoing clinical drug-drug interaction study that indicate that CYP3A4 substrates with low therapeutic index should be avoided during study participation. • Updated summary of clinical activity. Added two Phase 1b cohorts (up to n=12 each): • Phase 1b cohort to include patients with advanced, unresectable NSCLC with *KRAS* G12C mutation who

		decline currently available first-line systemic therapies (i.e., treatment naïve); and • Phase 1b cohort to include patients with NSCLC with *KRAS* G12C mutation who were previously treated with a therapy targeting KRAS G12C mutation. Revised the statistical design for Phase 2 Cohort B in patients with NSCLC with KRAS G12C mutation detected in blood (e.g., ctDNA) to lower the Type I error. Added Phase 2 Cohort E for patients with NSCLC with *KRAS* G12C and *STK11* mutations in the first line treatment setting: • Added background information supporting the hypothesis for Cohort E. • Added statistical design for Cohort E. • Added collection of available data during prescreening or screening assessments on PD-L1 in tumor tissue. In addition: • Added collection of data for ECG PR and QRS intervals beginning with patients enrolled under protocol V7.0 and higher. • Deleted specifics concerning MRTX849 clinical trial material bottle size and capsule and tablet unit strength in favor of inclusion of this information in the Pharmacy Manual. • Added Neogenomics to the list of sponsor approved laboratories for eligibility testing. • Updated template language concerning confidentiality and privacy protection in Section 10.5. • Updated recommendations for use of concomitant medications in Appendix 3 based on new information included in the protocol background. • Corrected scheduling of ECGs from C2D8 to C1D15 in the evaluation of food effect described in Appendix 6.
Amendment 7, Version 8.0	12 April 2021	Added Phase 2 Cohort F for patients with CRC with *KRAS* G12C mutation (detected in tumor tissue) who have previously received each of the following agents: a fluoropyrimidine, oxaliplatin, irinotecan, and a VEGF/VEGFR inhibitor: • Added background information supporting the hypothesis for Cohort F. • Added the statistical design for Cohort F. Increased the size of the Phase 1b cohort enrolling patients with brain metastases from 12 to 25 patients and revised the applicable eligibility criteria. Changed the name of the population for the Phase 2 efficacy analysis from modified Intent-to-Treat population to Full Analysis Set.

		Updated MRTX849 clinical background sections in accordance with communication plan described in Section 9.9.3 and Section 13.2: • Updated nonclinical toxicology background to include 13-week studies and additional genotoxicity studies. • Updated MRTX849 clinical safety background section. • Updated guidance on use of concomitant medications based on preliminary clinical pharmacokinetic data. • Provided guidance on the use of COVID-19 vaccines. • Updated the address of the study sponsor, Mirati Therapeutics, Inc., in San Diego, CA, USA. Updated minor errors in the text of the document.

Protocol deviations:

Table 17: Important protocol deviations from Cohort A, Study KRYSTAL-1

Category Deviation [n (%)]	Phase 2 Cohort A (N=116)
Any Important Deviation	6 (5.2)
Eligibility	2 (1.7)
Inclusion/Exclusion Criteria	1 (0.9)
Other Protocol Violations	1 (0.9)
Lab	1 (0.9)
Study Procedure/Assessments	1 (0.9)
Safety	1 (0.9)
Other Protocol Violations	1 (0.9)
Study Procedures	2 (1.7)
Study Procedure/Assessments	2 (1.7)

Note: For each category and deviation, subjects are included only once, even if they experienced multiple events in a category or deviation.

Eight important protocol deviations occurred in 7 patients (5.2%), as follows:

- There were 3 important eligibility deviations:
  - one patient had not received prior treatment with CIT (Listing 16.2.2.1)
  - one patient had not received prior treatment with CIT (Listing 16.2.4.6)
  - one patient had received a packed red blood cell transfusion 2 days before the Screening hemoglobin assessment
- There were 2 important study procedure deviations:
  - one patient did not have predose electrocardiogram assessment or a predose PK sample collected on Cycle 5 Day 1.
  - one patient had PK blood draw on Cycle 1 Day 8 performed before the electrocardiogram at Cycle 1 Day 8.
- There was 1 important laboratory deviation: one patient did not have a predose PK sample collected on Cycle 3 Day 1.
- One patient had 2 important safety deviations: the patient experienced 2 SAEs (hypoxemic respiratory failure and gastritis) after signing the informed consent but before beginning adagrasib that were not initially reported.

There were no important protocol deviations related to the informed consent process.

- **Baseline data**

Table 18: Demographic Characteristics of patients from Cohort A, Study KRYSTAL-1

Characteristic	Cohort A (N=116)
Sex [n (%)]	
Male	51 (44.0)
Female	65 (56.0)
Child-bearing Potential[2]	3 (4.6)
Postmenopausal[2]	49 (75.4)
Surgically Sterile[2]	13 (20.0)
Race [n (%)]	
White	97 (83.6)
Black or African American	9 (7.8)
Asian	5 (4.3)
American Indian or Alaska Native	1 (0.9)
Native Hawaiian or Other Pacific Islander	0
Other	4 (3.4)
Ethnicity [n (%)]	
Hispanic or Latino	3 (2.6)
Not Hispanic or Latino	107 (92.2)
Missing	6 (5.2)
Age (years)	
n	116
Mean (std)	64.4 (9.64)
Median	64.0
Q1, Q3	60.0, 70.0
Min, Max	25, 89
Age (years)	
< 65	59 (50.9)
≥ 65	57 (49.1)
Weight (kg)	
n	116
Mean (std)	72.233 (19.0035)
Median	69.510
Q1, Q3	59.260, 82.730
Min, Max	36.80, 138.60
Height (m)	
n	111
Mean (std)	1.676 (0.0957)
Median	1.664
Q1, Q3	1.600, 1.753
Min, Max	1.45, 1.88
ECOG Performance Status	
0	18 (15.5)
1	97 (83.6)
2	0
3	0
4	0
Missing	1 (0.9)
Smoking History	
Current Smoker	11 (9.5)
Former Smoker	100 (86.2)
Lifetime Nonsmoker	5 (4.3)

Table 19: Summary of KRAS G12C mutation diagnostic methods in tumour tissue from patients in Cohort A, Study KRYSTAL-1

Method Laboratory Name [n (%)]	Phase 2 Cohort A N=116
Next-Generation Sequencing	109 (94.0)
Foundation One	25 (21.6)
Impact	14 (12.1)
Profile	9 (7.8)
Caris Life Science	7 (6.0)
University of Colorado	5 (4.3)
Tempus	2 (1.7)
Other	47 (40.5)
Polymerase Chain Reaction	4 (3.4)
Other	3 (2.6)

Sponsor-coded local laboratory tests and methods establishing patient eligibility based on *KRAS* G12C mutation in tumor tissue, with information integrated from source documents (pathology and tumor genetic reports) and data entered into the case report form.
Source: Table 14.1.13 and Listing 16.2.8.10.2

Table 20: Primary Disease Characteristics (Enrolled Population)

Characteristic	Phase 2 Cohort A (N=116)
Diagnosis	
NSCLC	116 (100)
Histology	
Adenocarcinoma	113 (97.4)
Large Cell Carcinoma	0
Unclassified/Undifferentiated Carcinoma	0
Squamous	3 (2.6)
Other	0
Disease Stage	
Locally Advanced	13 (11.2)
Metastatic	103 (88.8)
Sites of Disease	
Lung	100 (86.2)
Lymph Node	68 (58.6)
Bone	50 (43.1)
Brain	34 (29.3)
Liver	24 (20.7)
Adrenal Gland	23 (19.8)
Other	35 (30.2)

Table 21: PD-L1 Tumour Proportion Score (Enrolled Population)

Characteristic	Phase 2 Cohort A (N=116)
PD-L1 Assay Used Central (22C3 pharmDx)	90*
PD-L1 Status (TPS) <1%	49 (42.2)
1-49%	27 (23.3)
≥50%	14 (12.1)
Unknown	26 (22.4)

*Includes the number of patients with a central test result; excludes 11 patients with an inadequate sample and 15 without an available sample for central PD-L1 testing.

Table 22: Prior treatments of patients from Cohort A, Study KRYSTAL-1

Variable	Phase 2 Cohort A (N=116)
Systemic Therapy	
Total Number of Prior Systemic Regimens	
0	0
1	50 (43.1)
2	40 (34.5)
3	12 (10.3)
4+	14 (12.1)
Mean	2.0
Median	2.0
Min, Max	1, 7
Prior systemic therapies [ATC2 \ Preferred term]	
Antineoplastic Agents	116 (100)
Carboplatin	108 (93.1)
Pemetrexed	108 (93.1)
Pembrolizumab	93 (80.2)
Cisplatin	20 (17.2)
Paclitaxel	20 (17.2)
Docetaxel	17 (14.7)
Gemcitabine	13 (11.2)
Atezolizumab	10 (8.6)
Bevacizumab	8 (6.9)
Nivolumab	8 (6.9)
Durvalumab	7 (6.0)
Ramucirumab	7 (6.0)
Paclitaxel albumin	4 (3.4)
Etoposide	3 (2.6)
Vinorelbine	3 (2.6)
Olaparib	2 (1.7)
Avelumab	1 (0.9)
Cediranib	1 (0.9)
Cobimetinib	1 (0.9)
Enfortumab vedotin	1 (0.9)
Ipilimumab	1 (0.9)
Oxaliplatin	1 (0.9)
Pevonedistat	1 (0.9)
PF 04518600	1 (0.9)
Ponatinib	1 (0.9)
Trametinib	1 (0.9)

Investigational Drug	8 (6.9)
Investigational drug	7 (6.0)
Sitravatinib	1 (0.9)
Immunostimulants	1 (0.9)
Interleukin-2	1 (0.9)
Regimen component	
Platinum therapy	116 (100)
CIT	114 (98.3)
Other	116 (100)
Systemic therapy	
Any Prior Systemic Therapy [n (%)]	
n	116
Neo-adjuvant or Adjuvant	17 (14.7)
Advanced Disease Treatment Regimen	108 (93.1)
Other	1 (0.9)
Prior Platinum Agent [n (%)]	
Cisplatin	20 (17.2)
Carboplatin	108 (93.1)
Other	1 (0.9)
Received Platinum Agent Only [n (%)]	2 (1.7)
Received Checkpoint Inhibitor Only [n (%)]	0
Received Both [n (%)]	114 (98.3)
Prior Checkpoint Inhibitor [n (%)]	
Nivolumab	8 (6.9)
Pembrolizumab	93 (80.2)
Durvalumab	7 (6.0)
Atezolizumab	10 (8.6)
Avelumab	1 (0.9)

Variable	**Phase 2 Cohort A (N=116)**
Concurrent prior platinum and CIT	82 (70.7)
Sequential prior platinum and CIT	32 (27.6)
Any Other Therapies [n (%)]	116 (100)

Best Overall Response to Latest Prior Therapy in Advanced Setting [n (%)]	
Complete Response (CR)	1 (0.9)
Partial Response (PR)	12 (10.3)
Stable Disease (SD)	32 (27.6)
Progressive Disease (PD)	48 (41.4)
Unknown	15 (12.9)
Duration of Prior Therapy (months)	
n	116
Mean (std)	12.76 (13.785)
Median	9.53
Q1, Q3	4.96, 17.66
Min, Max	0.7, 124.6
Radiotherapy	
Any Prior Radiotherapy [n (%)]	
Yes	80 (69.0)
Duration of Therapy (months)	
n	80
Mean (std)	1.19 (1.917)
Median	0.69
Q1, Q3	0.23, 1.41
Min, Max	0.03, 13.21
Location Radiated[a] [n (%)]	
n	80
Brain	39 (48.8)
Lung	34 (42.5)
Bone	30 (37.5)
Other	19 (23.8)
Surgery	
Any Prior Surgery [n (%)]	
No	40 (34.5)
Yes	76 (65.5)
Location[a]	
Lung	65 (85.5)
Liver	7 (9.2)
Lymph Node	16 (21.1)
Adrenal	4 (5.3)
Brain	6 (7.9)
Other	18 (23.7)
Time Since Surgery (months)	
n	76
Mean (std)	18.90 (23.751)
Median	10.73
Q1, Q3	3.86, 25.97
Min, Max	-0.3, 136.7

ATC2=anatomic therapeutic chemical Classification Level 2; CIT=checkpoint inhibitor therapy; max=maximum; min=minimum; Q1=first quartile; Q3=third quartile; std=standard deviation
Note: Patients can be included in multiple regimen types. Prior systemic therapies are coded using WHO Drug Dictionary version DDE-HD B3 2018MAR.
If a subject received both platinum therapy and CIT and any of the treatment periods overlap, the therapies are concurrent; else sequential.
a Percentage based on number of subjects under with prior treatment.
Source: Table 14.1.9.1, Table 14.1.9.2, Table 14.1.9.3, Table 14.1.9.4

KRAS G12C mutations in tumour tissue were identified in almost all cases (94%) with NGS; PCR or Sanger sequencing was used in the rest. Among the 11 cases where *KRAS* p.G12C was identified in the clinical trial assay (CTA) but not companion diagnostic (CD) assay, the testing methodology for the clinical trial assay was NGS for 10 cases and PCR for 1 case.

All patients received concomitant medications, including proton pump inhibitors (PPI, 53.4%) and glucocorticoids (49.1%), which use has been restricted in the study protocol.

- **Numbers analysed**

Table 23: Population datasets from Cohort A, Study KRYSTAL-1

Analysis Population	Phase 2 Cohort A
Enrolled Population [n]	116
Safety Population [n (%)]	116 (100)
Full Analysis Set - Investigator [n (%)]	116 (100)
Full Analysis Set - Independent Central Review [n (%)]	112 (96.6)
Pharmacokinetic Evaluable Population [n (%)]	111 (95.7)

Percentage is calculated using a denominator of all enrolled patients per cohort assignment.
Note: Enrolled population is defined as all patients who sign the main study informed consent form and determined by the investigator to meet all eligibility criteria during screening assessments.
Two patients with eligibility violations are included in the enrolled population because the eligibility violations were identified after enrollment.

- **Outcomes and estimation**

Primary endpoint, overall response rate:

The primary efficacy dataset of Cohort A from Study KRYSTAL-1 is constituted by the 116 patients that were treated with adagrasib. Patients who were considered non-evaluable or with absence-of-measurable-disease-at-baseline by the BICR were considered non-responders in the ORR analysis.

Table 24: Analysis of Tumor Response as per BICR (Study 849-001 Cohort A; ITT Population)

	Phase 2 Cohort A 15 Oct 2021 (N=116)	**Phase 2 Cohort A 15 Jun 2021 (N=116)**
Best overall response:		
Complete Response (CR)	1 (0.9)	1 (0.9)
Partial Response (PR)	47 (40.5)	47 (40.5)
Stable disease (SD)	44 (37.9)	44 (37.9)
Progressive disease (PD)	6 (5.2)	6 (5.2)
Not Evaluable (NE)	18 (15.5)	18 (15.5)
Objective response rate (ORR)		
n (%)	48 (41.4)	48 (41.4)
95% CI	32.3, 50.9	32.3, 50.9

BICR = blinded, independent central review; CI = confidence interval; CR = complete response; ITT = Intent-to-Treat Population (defined as enrolled population); NE = not evaluable; PR = partial response

Secondary endpoint, duration of response:

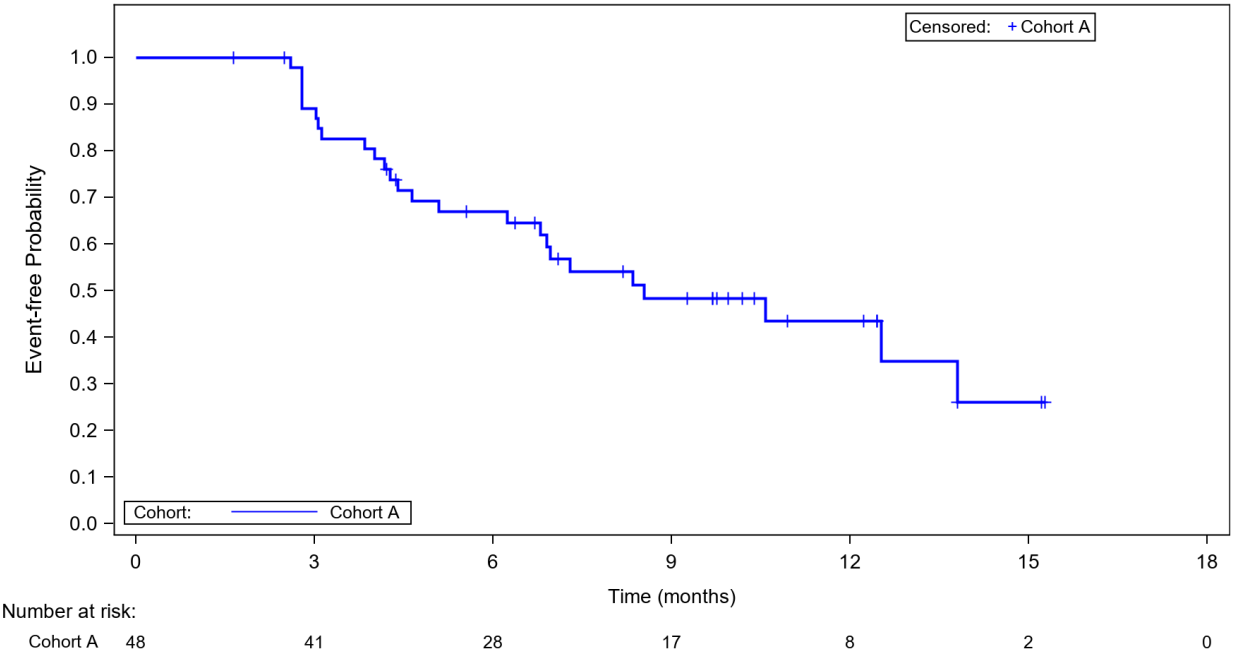
Table 25: Analysis of Duration of Response (DOR) – Independent Central Review (Study 849-001 Cohort A; ITT – Patients with Response Only)

	Phase 2 Cohort A 15 Oct 2021 (N=48)	**Phase 2 Cohort A 15 Jun 2021 (N=48)**
Status [n (%)]		
Events Observed	25 (52.1)	19 (39.6)
Censored	23 (47.9)	29 (60.4)
Duration of Response (months)[a]		
Percentile (95% CI)[b]		
25%	4.3 (3.0, 6.8)	4.3 (3.0, 6.8)
Median	8.5 (6.2, 13.8)	7.3 (5.1, NE)
75%	NR (12.5, NE)	NR (NE, NE)
Range	1.64 – 15.28+	1.41+ - 12.45+
Event-free Rate (95% CI)[c]		
3-month	89.1 (75.8, 95.3)	88.9 (75.3, 95.2)
6-month	66.9 (51.2, 78.6)	64.6 (48.1, 77.0)

	Phase 2 Cohort A 15 Oct 2021 (N=48)	Phase 2 Cohort A 15 Jun 2021 (N=48)
9-month	48.4 (32.5, 62.6)	48.4 (30.0, 64.5)
12-month	43.6 (26.9, 59.1)	48.4 (30.0, 64.5)
Response duration ≥ 6 months [n (%)]	28 (58.3)	17 (35.4%)

BICR = blinded, independent central review; CI = confidence interval; CR = complete response; FAS = Full Analysis Set; NE = not estimable; NR = not reached; PR = partial response
[a]Duration of Response (months) is calculated as (date of the first documentation of objective progression of disease or to death due to any cause in the absence of documented progression of disease – date of the first documentation of objective response (CR or PR) + 1)/ 30.4375. [b]Obtained via Kaplan-Meier estimation, Brookmeyer and Crowley (1982). [c]Obtained via Kaplan-Meier estimation, Greenwood's formula, Kalbfleisch and Prentice (1980).

Figure 18: Updated Analysis of Duration of Response (DOR) – BICR (ITT Patients with Response Only [15 Oct 2021])



BICR = blinded independent central review; FAS = full analysis set.

Secondary endpoint, progression free survival:

Table 26: Initial and Updated Analysis of Progression-free Survival (PFS) – Independent Central Review (Study 849-001 Cohort A; ITT)

	Phase 2 Cohort A 15 Oct 2021 (N=116)	Phase 2 Cohort A 15 Jun 2021 (N=116)
Status [n (%)]		
Events Observed	69 (59.5)	61 (52.6)
Censored	47 (40.5)	55 (47.4)
Progression-free Survival (months)[a]		
Percentile (95% CI)[b]		
25%	3.3 (2.7, 4.2)	3.3 (2.7, 4.2)
Median	6.0 (4.7, 8.4)	6.0 (4.7, 8.2)
75%	16.9 (9.9, NE)	NR (8.4, NE)
Range	0.03+ - 19.78	0.03+ - 14.16+

	Phase 2 Cohort A 15 Oct 2021 (N=116)	Phase 2 Cohort A 15 Jun 2021 (N=116)
Event-free Rate (95% CI)[c]		
3-month	76.8 (67.5, 83.8)	76.8 (67.5, 83.8)
6-month	50.5 (40.2, 59.9)	50.4 (40.0, 59.8)
9-month	36.8 (27.1, 46.5)	31.8 (21.2, 42.9)
12-month	29.1 (19.6, 39.3)	29.1 (18.5, 40.6)

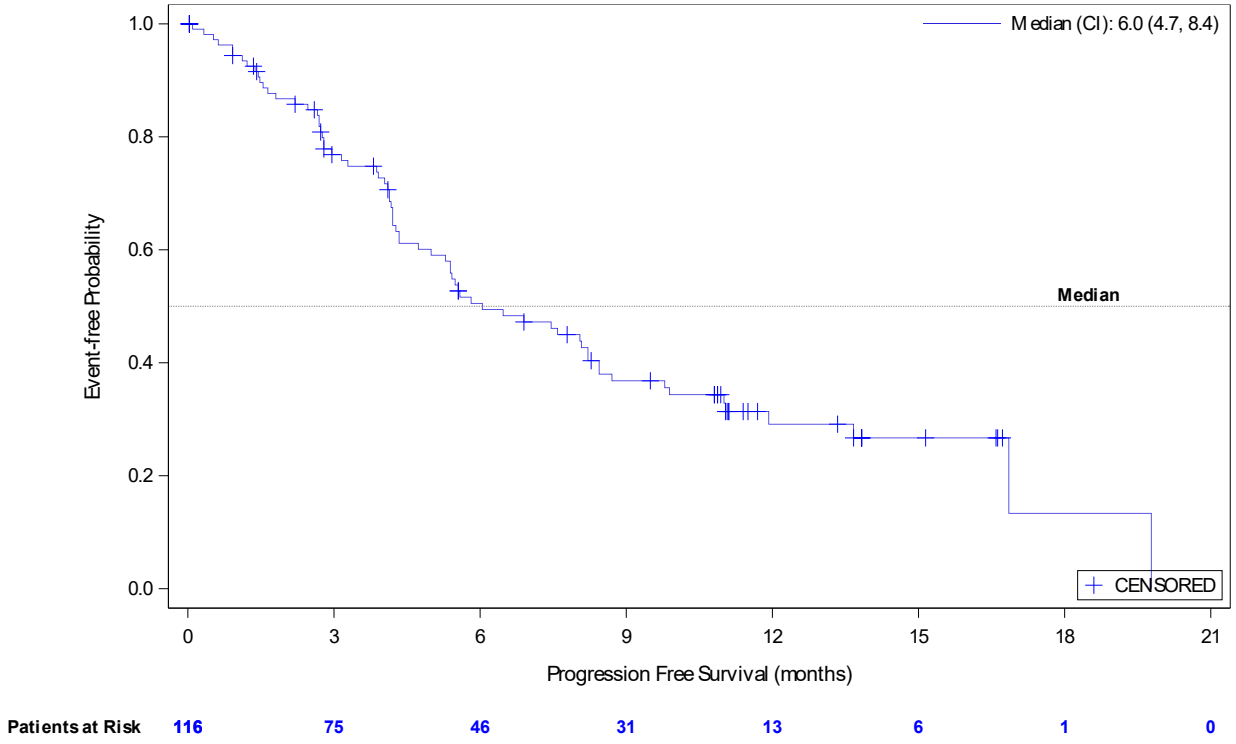
BICR = blinded independent central review; CI = confidence interval; FAS = full analysis set; NE = not estimable; NR = not reached; PD = progressive disease

[a]Progression-free Survival (months) is calculated as (date of the first documentation of objective progression of disease or death due to any cause in the absence of PD – date of the first dose of study treatment + 1) / 30.4375.

[b]Obtained via Kaplan-Meier estimation, Brookmeyer and Crowley (1982) method.

[c]Obtained via Kaplan-Meier estimation, Greenwood's formula, Kalbfleisch and Prentice (1980).

Figure 19: Updated Analysis of Progression-free Survival – BICR (ITT Population [15 Oct 2021])



Secondary endpoint, overall survival:

Table 27: Initial and Updated Analysis of Overall Survival (OS) (Study 849-001 Cohort A; Enrolled Population)

	Phase 2 Cohort A 15 Jan 2022 (N=116)	**Phase 2 Cohort A 15 Oct 2021 (N=116)**	**Phase 2 Cohort A 15 Jun 2021 (N=116)**
Status [n (%)]			
Events Observed	61 (52.6)	57 (49.1)	48 (41.4)
Censored	55 (47.4)	59 (50.9)	68 (58.6)
Overall Survival (months)[a]			
Percentile (95% CI)[b]			
25%	5.0 (3.6, 6.5)	5.0 (3.6, 6.5)	5.0 (3.6, 6.5)
Median	12.6 (9.2, 19.2)	11.7 (9.2, NE)	11.3 (8.7, NE)
75%	NR (19.2, NE)	19.3 (19.3, NE)	NR (14.7, NE)
Range	0.1+ - 21.6+	0.07+ - 19.81+	0.07+ - 16.13+
Event-free Rate (95% CI)[c]			
3-month	88.5 (81.0, 93.2)	88.5 (81.0, 93.2)	88.5 (81.0, 93.2)
6-month	70.6 (61.1, 78.3)	70.6 (61.1, 78.3)	70.6 (61.1, 78.3)
9-month	60.0 (50.1, 68.6)	60.0 (50.0, 68.6)	59.8 (49.2, 68.9)
12-month	50.8 (40.9, 60.0)	49.7 (39.5, 59.1)	45.6 (31.5, 58.6)

CI = confidence interval; NE = not estimable; NR = not reached

[a] Overall Survival (months) is calculated as (date of death due to any cause – date of the first dose of study treatment +1)/ 30.4375.

[b] Obtained via Kaplan-Meier estimation, Brookmeyer and Crowley (1982).

[c] Obtained via Kaplan-Meier estimation, Greenwood's formula, Kalbfleisch and Prentice (1980).

Figure 20: Updated Analysis of Overall Survival (Enrolled Population [15 Oct 2021])

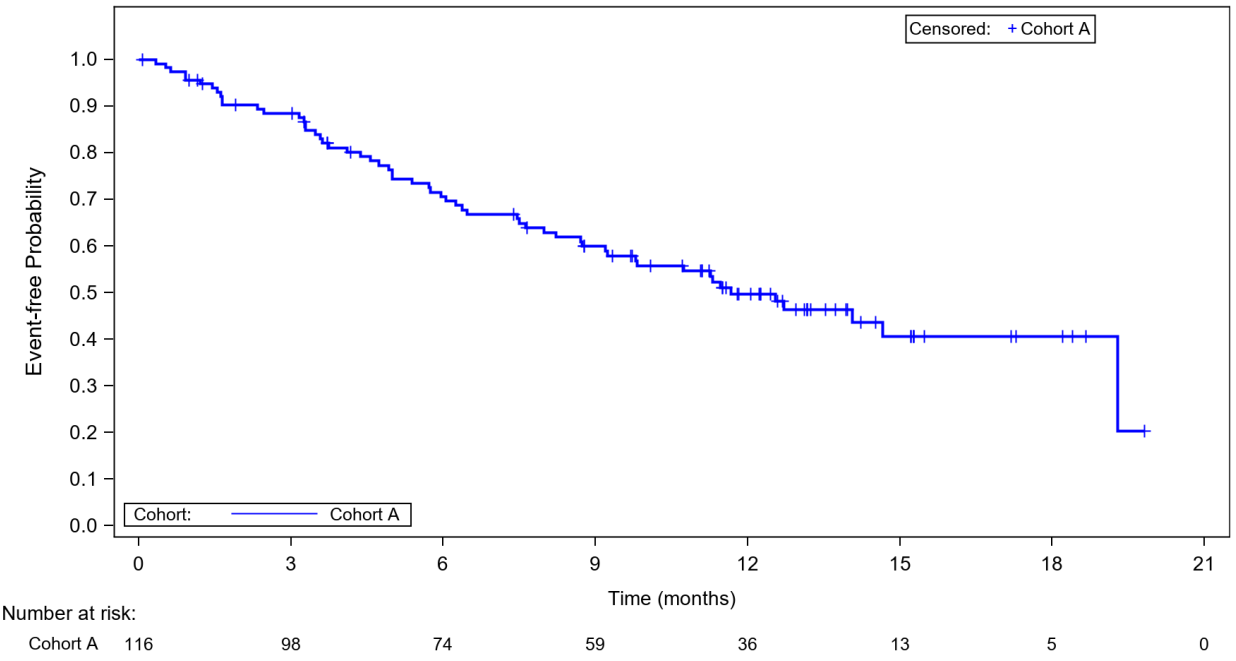
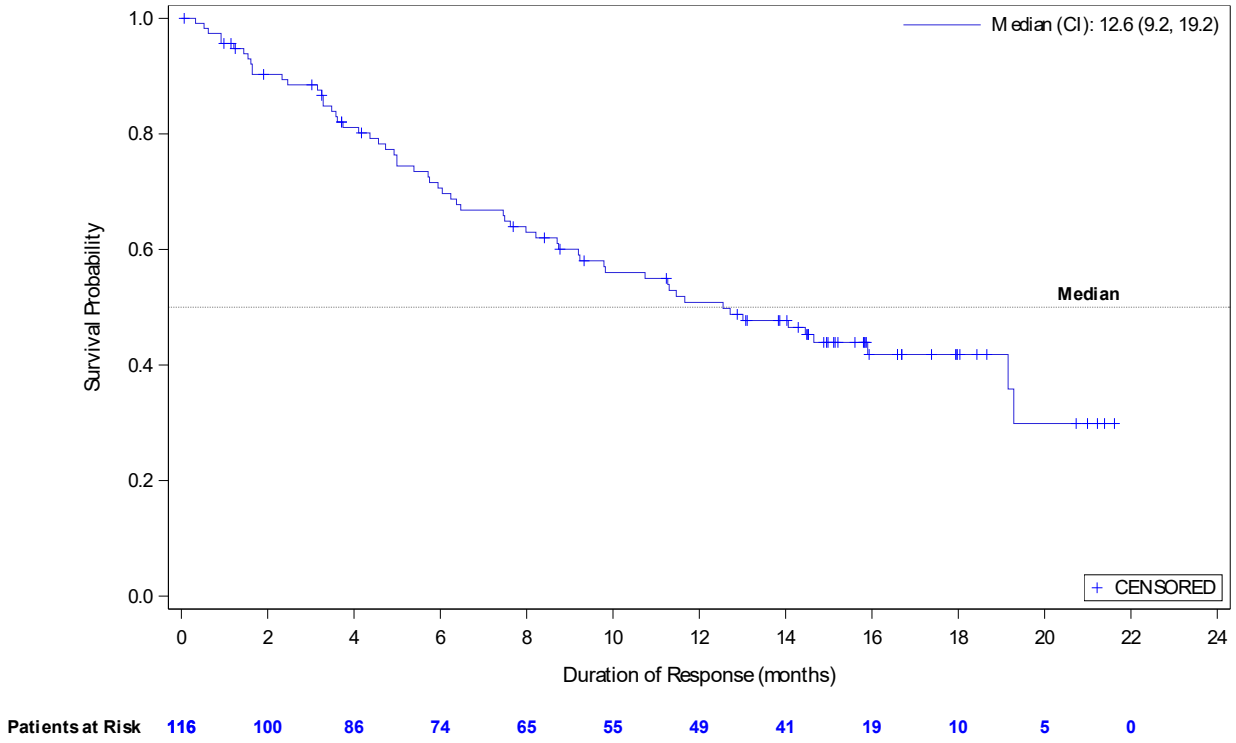


Figure 21: Updated Analysis of Overall Survival (Enrolled Population [15 Jan 2022])



A summary of primary and secondary initial (DCO 15 JUN 2012) and updated (DCO 15 OCT 2021) efficacy results is provided in the following tables.

Table 28: Overview of Primary and Secondary Initial and Updated Efficacy Endpoints by Data Cutoff (Study 849-001 Cohort A)

	Phase 2 Cohort A (15 Oct 2021)	Phase 2 Cohort A (15 Jun 2021)	Phase 2 Cohort A (15 Jan 2022)
Objective Response Rate (ORR) by BICR ITT (n=116)			
n (%)	41.4	41.4	
95% CI	32.3, 50.9	32.3, 50.9	
Duration of Response (DOR) by BICR ITT, Patients with Response Only (n=48)			
Median (months)	8.5	7.3	
95% CI	6.2, 13.8	5.1, NE	
Progression-free Survival (PFS) by BICR ITT (n=116)			
Median (months)	6.0	6.0	
95% CI	4.7, 8.4	4.7, 8.2	
Overall Survival (OS) Enrolled Population (n=116)			
Median (months)	11.7	11.3	12.6
95% CI	9.2, NE	8.7, NE	9.2,19.2

BICR: radiographic assessment performed by blinded independent central review; INV: radiographic assessment performed by investigators; ORR: objective response rate; mDOR: median duration of response; mPFS: median progression-free survival; mOS: median overall survival; NA: not applicable; N=112 refers to the FAS-BICR population; N=116 refers to the ITT population (which were de facto the same as the enrolled and FAS-INV population). Dates refer to the data cutoff dates. CI = confidence interval; FAS = Full Analysis Set; NE = not estimable; NR = not reached.

- **Ancillary analyses**

Not evaluable patients:

The reasons for categorising 18 patients as non-evaluable, including 4 patients with absent-measurable-disease-at-baseline-by-BICR are described in the table below. The reasons for discontinuation (14 patients) prior to the first scheduled imaging response assessment were withdrawal of consent (n=5), adverse event (n=3), death (n=2), global deterioration of health (n=3), and investigator decision (patient non-compliance, n=1).

Table 29: Reasons for assessment of NE (not evaluable)

Reason for NE Status	Cohort A (FAS, BICR) (N=112)	Cohort A Excluded from FAS (N=4)	Total (N=116)
No On-Study Scans	14	0	14
One On-Study Imaging Time Point Insufficient for Response Assessment	2	0	2
Single Time Point Response of NE	1	1	2
Total	17	1	18

Concordance of best overall response (BOR)

Concordance rate between BICR and investigator: The concordance rate between central review and investigator's review for ORR was 78.6%. A concordance analysis between investigator assessed and BICR assessed BOR for the ITT population is presented below (n=116).

Table 30: Objective Response Assessments

	Phase 2 Cohort A (N=116) Independent Central Review				
Investigator Assessment	**CR**	**PR**	**SD**	**PD**	**NE**
Complete Response (CR)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Partial Response (PR)	1 (100)	34 (72.3)	8 (18.2)	0 (0.0)	0 (0.0)
Stable Disease (SD)	0 (0.0)	11 (23.4)	35 (79.5)	2 (33.3)	0 (0.0)
Progressive Disease (PD)	0 (0.0)	1 (2.1)	1 (2.3)	4 (66.7)	0 (0.0)
Not Evaluable (NE)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	18 (100)

The greatest part of discrepancy lies within PR/SD while minor incongruences exist between CR/PR and SD/PD.

It was stated that BOR of CR/PR required a confirmatory assessment at least 4 weeks (28 days or more) since the first CR/PR response. The 7 patients for whom response was not confirmed in a confirmatory assessment, where not included as responders in the efficacy assessment. RECIST 1.1 was applied for tumour response assessment.

Sensitivity analyses:

Table 31: Updated Sensitivity Analyses of Progression-free Survival by Investigator and by BICR (Study 849-001 Cohort A; [15 Oct 2021])

	Phase 2 Cohort A – Investigator (N=116)	**Phase 2 Cohort A – BICR (FAS) (N=112)**
Status [n (%)]		
Events Observed	68 (58.6)	66 (58.9)
Censored	48 (41.4)	46 (41.1)
Progression-free Survival (months)[a]		
Percentile (95% CI)[b]		
25%	3.2 (2.1, 3.9)	3.3 (2.7, 4.2)
Median	5.9 (4.4, 8.7)	6.5 (4.7, 8.4)
75%	NR (10.0, NE)	16.9 (9.9, NE)
Range	0.03+ - 16.72+	0.03+ - 19.78
Event-free Rate (95% CI)[c]		
3-month	75.7 (66.2, 82.9)	76.9 (67.3, 84.0)
6-month	49.5 (39.2, 58.9)	51.6 (41.1, 61.2)
9-month	38.4 (28.7, 48.1)	37.3 (27.3, 47.2)
12-month	28.6 (19.3, 38.7)	29.3 (19.6, 39.7)

BICR = blinded independent central review; ITT = intent-to-treat population (defined as the enrolled population); CI = confidence interval;; NE = not estimable; NR = not reached; PD = progressive disease

[a] Progression-free Survival (months) is calculated as (date of the first documentation of objective progression of disease or death due to any cause in the absence of PD – date of the first dose of study treatment + 1) / 30.4375.

[b] Obtained via Kaplan-Meier estimation, Brookmeyer and Crowley (1982) method.

[c] Obtained via Kaplan-Meier estimation, Greenwood's formula, Kalbfleisch and Prentice (1980).

The applicant also performed additional sensitivity analyses for **DOR and PFS**. In these analyses, patients who discontinued the study drug and/or the study, switched to another anti-cancer therapy before progression/death, or who missed more than 2 consecutive assessments, were considered as DOR/PFS events. The analyses were performed for both BICR and Investigator's evaluations.

Table 32: Results of the Sensitivity Analyses

	Investigator Assessment	**BICR**
mDOR [mos(95% CI))	8.31 (6.47, NE)	6.90 (4.60, 10.58)
mPFS [mos(95% CI))	4.34 (3.45, 5.82)	4.31 (3.84, 5.59)

When PFS definition is widened to include starting other anti-cancer treatment or discontinuing study medication before progression is stated or missed more than 2 consecutive assessments, then mPFS and mDoR are slightly reduced.

Subgroup analyses:

The applicant performed subgroup analysis of ORR by BICR in Cohort A (n=116) in the most updated efficacy analysis.

Figure 22: Subgroup Analysis of Cohort A Assessed for Response by BICR – Part 1

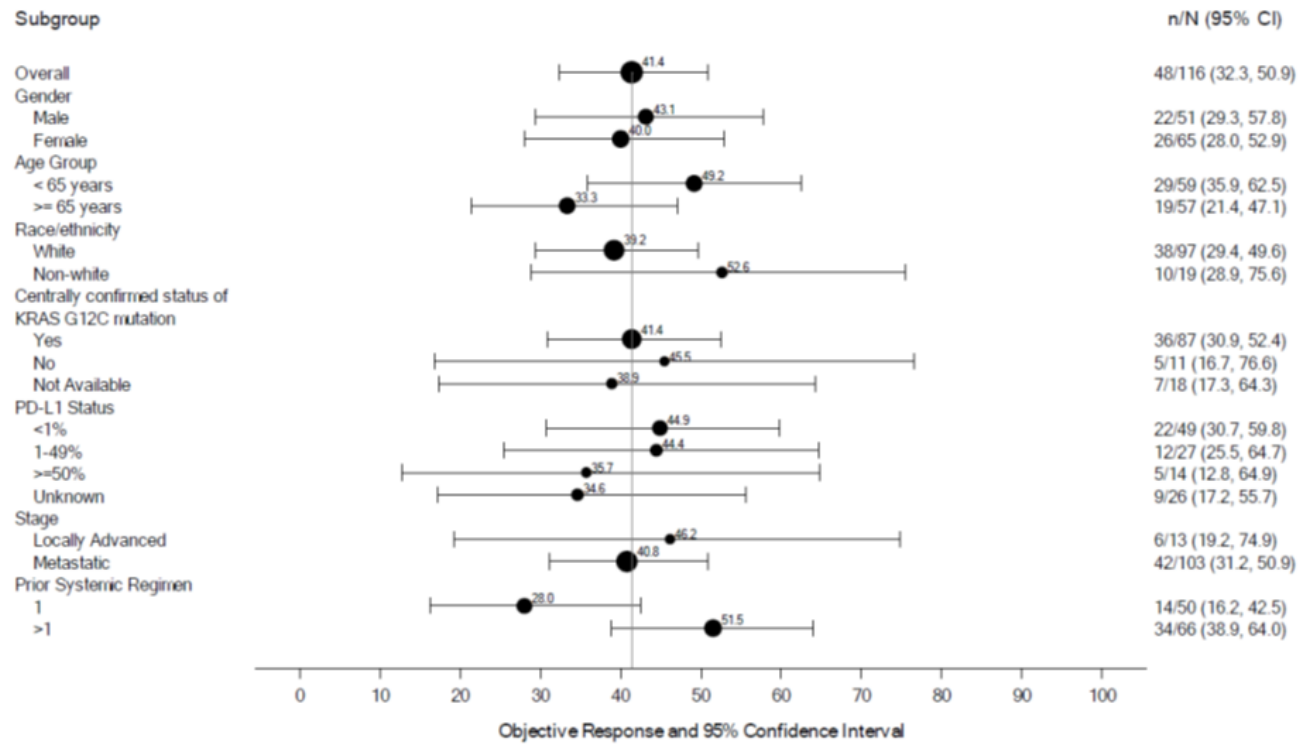
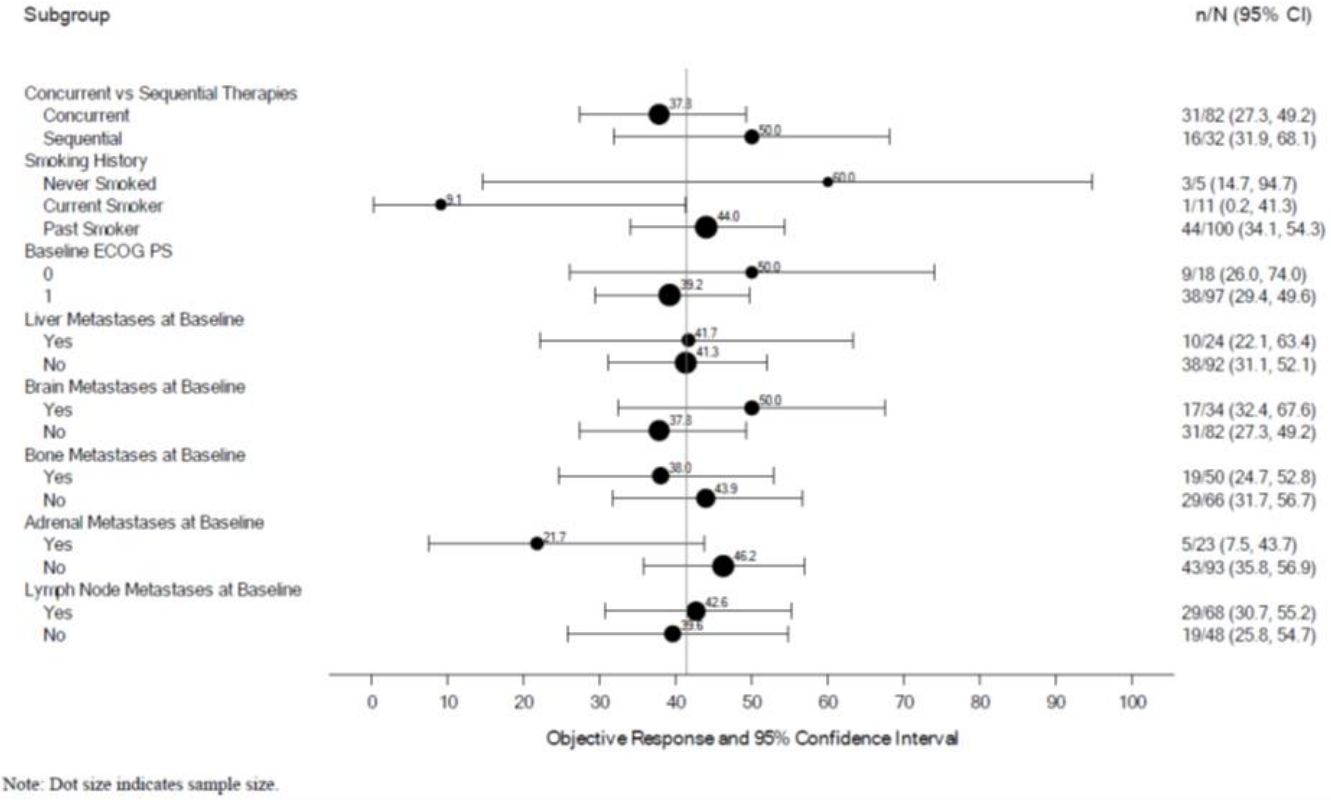


Figure 23: Subgroup Analysis of Cohort A Assessed for Response by BICR – Part 2



Note: Dot size indicates sample size.

As the study population included patients with both metastatic and locally advanced disease, the Applicant provided subgroup analysis in both patients with metastatic and locally advanced disease.

11.2% of patient had locally advanced disease and 88.8% had metastatic disease. Among these subgroups, the ORR was 46.2% (95% CI: 19.2, 74.9) and 40.8% (95% CI:31.2, 50.9), respectively.

In addition, subgroup analyses were conducted in order to explore the effect of different confounding factors on the primary endpoint ORR. Patients who had more than one prior systemic regimen, had a higher response rate (ORR 49.2; 95% CI 35.9 to 62.5), compared to those who had only one prior systemic therapy (ORR 35.8; 95% CI 23.1 to 50.2).

- **Summary of main efficacy results**

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

Table 33: Summary of efficacy for trial KRYSTAL-1

Title: A phase 1/2 multiple expansion cohort trial of MRTX849 (adagrasib) in patients with advanced solid tumours with KRAS G12C mutation			
Study identifier	KRYSTAL-1; study 849-001 (version 6) Phase 2 Segment, Cohort A; NCT03785249		
Design	Multicentre, single-country (US), multi-cohort, single arm, open-label, study consisting of dose-escalation and expansion parts (Phase 1) and clinical activity evaluation (Phase 2). Cohort A (patients with NSCLC and KRAS mutation in tumour tissue) is considered pivotal for efficacy in this setting.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Not applicable Not applicable Not applicable
Hypothesis	The design for Cohort A utilised a 95% confidence interval to exclude an ORR of 23%. Assuming MRTX849 will result in an ORR of at least 35% in this treatment setting, a sample size of approximately 105 evaluable patients would be sufficient for the lower bound of a 2-sided 95% confidence interval (Clopper-Pearson method) to exclude an ORR of 23%		
Treatment groups	Patients with advanced KRAS 12C mutant NSCLC		Adagrasib 600 mg orally twice daily n=116
Endpoints and definitions	Primary efficacy endpoint	ORR-BICR	Percentage of patients documented to have a confirmed complete response (CR) or partial response (PR) per RECIST v1.1 by blinded independent central review (BICR)
	Secondary efficacy endpoints	DOR-BICR	Time from first documentation of response per RECIST v1.1 by BICR until progressive disease (PD) or death
		PFS-BICR	Time from first study treatment until PD per RECIST v1.1 by BICR or death of any cause
		OS	Time from first study treatment until death of any cause
Clinical cut-off	15-OCT-2021		
Database lock	15-OCT-2021		
Results and Analysis			
Analysis description	Primary analysis of ORR-BICR.		
Analysis population and time point description	Patients from Cohort A: Advanced NSCLC with KRAS G12C mutation detected in tumour tissue. Clinical cut-off 15-OCT-2021 ensured that the last patient enrolled could be followed for at least 6 months after start of study treatment.		
Descriptive statistics and estimate variability	Treatment group		Cohort A
	Number of subjects		116
	ORR-BICR (%) N		41.4 48
	95% CI [a]		32.3, 50.9

	Median DOR-BICR, months [b]	8.5
	95% CI	6.2, 13.8
	Median PFS, months [b]	6.0
	95% CI	4.7, 8.4
	Median OS, months [b]	11.7
	95% CI	9.2, not estimable
Effect estimate per comparison	Not applicable, single arm trial	
Notes	[a] 95% CI based on exact binomial method (Clopper-Pearson). [b] Obtained via Kaplan-Meier estimation (Brookmeyer and Crowl	

2.6.5.3. Clinical studies in special populations

Table 34: Patients 65 Years or Older Tabulated

	Age 65-74 (Older subject number /total number)	**Age 75-84 (Older subject number /total number)**	**Age 85+ (Older subject number /total number)**
Controlled Trials	0	0	0
Non Controlled Trials	86 / 260	29 / 260	2 / 260

2.6.5.4. In vitro biomarker test for patient selection for efficacy

For the purpose of patient eligibility, the presence of KRAS G12C was established through local testing (PCR, NGS or Sanger sequencing) at recruitment sites, although for the cohort of interest, confirmatory KRAS 12C mutation testing of tumour tissue was performed centrally using a CE-marked commercially available companion diagnostic test (Qiagen therascreen ® KRAS mutation test). The applicant provided a bridging study that reports an acceptable concordance rate of local and central testing, with positive and negative agreement values of 100% and 91%, respectively, when using the central companion test as reference method.

Only 101 samples from pivotal Cohort A (n=116) were evaluable for central testing: 12 patients had insufficient tumour samples for further testing and samples submitted from other 3 patients were deemed non-evaluable.

From the 101 samples submitted, 3 were deemed not evaluable at time of testing. 87 out of 101 samples were confirmed positive and there were 11 discordant samples (KRAS G12C not present). The bridging report also presents ORR (unknown if by BICR or investigator) according to the testing subgroups: 41% (36 out of 87) for the confirmed KRAS+ patients and 50% (7 out of 14) for the not-confirmed/non-evaluable patients. The ORR for the overall tested (n=101) cohort is 43% (43 out of 101), which is comparable to the overall outcome of the totality of patients from Cohort A (n=116). Considering that central testing was not a requirement for recruitment, it is reassuring that efficacy in terms of ORR is comparable across the centrally and not-centrally confirmed patients.

It is to note that if the local test is used as reference, positive and negative agreement values are 86% and 97%, respectively.

2.6.5.5. Analysis performed across cohorts of study 849-001

In addition to pivotal data from Phase 2 Cohort A from the KRYSTAL-1 trial (N=116), efficacy results from patients with NSCLC and G12C KRAS mutations from other cohorts of the pivotal trial have been submitted:

- **Phase 1/1b** cohort includes 25 enrolled patients with solid tumours with KRAS G12C mutation treated with escalating doses of MRTX849 (Phase 1/1b CSR); of these, there were 16 patients with NSCLC with KRAS G12C mutation treated with MRTX849 at a starting dose 600 mg twice daily (the Phase 2 dose). The data cutoff for Phase 1/1b was 27-NOV-2020.
- **Phase 2 Cohort B** includes 60 enrolled patients with NSCLC with KRAS G12C mutation detected in blood (i.e., circulating tumour DNA [ctDNA]). The data cutoff for Phase 2 Cohort B is 15-JUN-2021.

Efficacy in terms of ORR/DOR/PFS across patients from Phase 1/1b and Cohort B was assessed by Investigator, and not by BICR, as for pivotal Cohort A.

Data from 192 patients with NSCLC and G12C KRAS mutations treated with adagrasib 600 mg BID are presented. The applicant has provided pooled efficacy results from Cohort A, Phase 1/1b and Cohort B (n=183). Scans of patients from Cohort B and Phase 1/1b were evaluated by the investigator. Also, BICR assessment and data on DoR for patients enrolled into Phase 1/1b and Cohort B were provided.

Table 35: Duration of Response by BICR in ITT Population with Data Lock Point of 15 January 2022

	Cohort A (N = 48)	**Phase 1/1b NSCLC/600 mg BID (N = 7)**	**Cohort B (N = 23)**	**Total (N = 78)**
Status [n (%)]				
Events Observed	26 (54.2)	3 (42.9)	15 (65.2)	44 (56.4)
Censored	22 (45.8)	4 (57.1)	8 (34.8)	34 (43.6)
Duration of Response (Months)				
Percentile (95% CI)				
25%	4.27 (3.02, 6.80)	10.81 (9.63, NE)	3.06 (2.30, 5.52)	4.27 (3.06, 5.55)
Median	8.54 (6.24, NE)	NR (9.63, NE)	5.59 (4.17, 12.71)	10.58 (6.24, 13.80)
75%	NR (12.52, NE)	NR (15.08, NE)	12.71 (5.59, NE)	NR (13.80, NE)
Range	1.64, 18.17	9.63, 23.69	2.30, 17.91	1.64, 23.69
Event-free Rate (95% CI)				
3-month	89.13 (75.84, 95.33)	100.00 (100.00, 100.00)	82.61 (60.06, 93.09)	88.19 (78.53, 93.67)
6-month	66.93 (51.20, 78.59)	100.00 (100.00, 100.00)	40.37 (20.01, 59.97)	62.43 (50.37, 72.35)
9-month	49.71 (34.05, 63.54)	100.00 (100.00, 100.00)	40.37 (20.01, 59.97)	52.10 (39.98, 62.89)
12-month	46.78 (31.19, 60.94)	71.43 (25.82, 91.98)	30.28 (10.30, 53.37)	44.74 (32.54, 56.21)
Duration of Response				
>= 6 months	29 (60.4)	7 (100.0)	8 (34.8)	44 (56.4)

BID = twice daily; CI = confidence interval; NSCLC = non-small cell lung cancer; NE = not estimable; NR = not reached
Source: Table Q49.1.
BID = twice daily; CI = confidence interval; NSCLC = non-small cell lung cancer; NE = not estimable; NR = not reached

Table 36: Analysis of Tumor Response (Independent Central Review – ITT population)

	Phase 1/1b			
Efficacy Outcomes, n(%)	**Cohort A (N=116)**	**NSCLC/600mg BID (N=16)**	**Cohort B (N=60)**	**Total (N=192)**
Best Overall Response [a]				
Complete Response (CR)	1 (0.9)	2 (12.5)	1 (1.7)	4 (2.1)
Partial Response (PR)	47 (40.5)	5 (31.3)	22 (36.7)	74 (38.5)
Stable Disease (SD)	44 (37.9)	7 (43.8)	27 (45.0)	78 (40.6)
Progressive Disease (PD)	6 (5.2)	1 (6.3)	4 (6.7)	11 (5.7)
Not Evaluable (NE)	18 (15.5)	1 (6.3)	6 (10.0)	25 (13.0)
Objective Response Rate (ORR) [b]				
n (%)	48 (41.4)	7 (43.8)	23 (38.3)	78 (40.6)
95% CI [c]	32.3, 50.9	19.8, 70.1	26.1, 51.8	33.6, 47.9

[a] A Best Overall Response (BOR) of CR/PR confirmed requires a confirmatory assessment at least 4 weeks (28 days or more) since the first CR/PR response. For a BOR of SD, an SD assessment must be at least 32 days from the date of first dose, otherwise it will be summarized as NE.
[b] ORR is defined as the proportion of patients documented to have a confirmed CR or PR according to RECIST v1.1 as the best response.
[c] 95% CI is calculated using the exact binomial method (Clopper-Pearson).

Table 37: Analysis of Progression-free Survival (Independent Central Review – ITT population)

	Phase 1/1b			
	Cohort A (N=116)	**NSCLC/600mg BID (N=16)**	**Cohort B (N=60)**	**Total (N=192)**
Status [n (%)]				
Events Observed	69 (59.5)	9 (56.3)	35 (58.3)	113 (58.9)
Censored	47 (40.5)	7 (43.8)	25 (41.7)	79 (41.1)
Progression Free Survival (Months)[a]				
Percentile (95% CI)[b]				
25%	3.29 (2.69, 4.21)	2.79 (1.22, 12.42)	3.25 (2.53, 4.63)	3.29 (2.73, 4.17)
Median	6.05 (4.73, 8.44)	16.85 (2.37, NE)	6.60 (4.37, 6.93)	6.60 (5.42, 8.08)
75%	16.85 (9.89, NE)	NR (12.42, NE)	NR (6.93, NE)	16.85 (11.93, NE)
Range	0.03, 19.78	0.03, 24.94	0.03, 16.53	0.03, 24.94

[a] Progression-free Survival (months) is calculated as (date of the first documentation of objective progression of disease or death due to any cause in the absence of PD - date of the first dose of study treatment) + 1 / 30.4375.
[b] Obtained via Kaplan-Meier estimation, Brookmeyer and Crowley (1982) method. Source: t-pfs-ind-itt-pooled

Table 38: Analysis of ORR in patients with NSCLC treated at 600 mg BID (by Investigator)

Statistics	Cohort A (BICR) (N=116)	Phase 1/1b NSCLC/600 mg BID (Investigator) (N=16)	Cohort B (Investigator) (N=60)	Total (N=192)
Best Overall Response[1]				
Complete Response (CR)	1 (0.9)	0	0	1 (0.5)
Partial Response (PR)	47 (40.5)	6 (37.5)	24 (40.0)	77 (40.1)
Stable Disease (SD)	44 (37.9)	9 (56.3)	24 (40.0)	77 (40.1)
Progressive Disease (PD)	6 (5.2)	0	3 (5.0)	9 (4.7)
Not Evaluable (NE)	18 (15.5)	1 (6.3)	9 (15.0)	28 (14.6)
Objective Response Rate (ORR)[2]				
n (%)	48 (41.4)	6 (37.5)	24 (40.0)	78 (40.6)
95% CI[3]	32.3, 50.9	15.2, 64.6	27.6, 53.5	33.6, 47.9

Table 39: Analysis of PFS in patients with NSCLC treated at 600 mg BID (by Investigator)

Statistics	Cohort A (BICR) (N=116)	Phase 1/1b NSCLC/600 mg BID (Investigator) (N=16)	Cohort B (Investigator) (N=60)	Total (N=192)
Status [n (%)]				
Events Observed	61 (52.6)	7 (43.8)	28 (46.7)	96 (50.0)
Censored	55 (47.4)	9 (56.3)	32 (53.3)	96 (50.0)
Progression-free Survival (months)[1]				
Percentile (95% CI)[2]				
25%	3.3 (2.7, 4.2)	2.8 (2.2, 8.3)	4.2 (2.6, 5.5)	3.9 (2.8, 4.2)
Median	6.0 (4.7, 8.2)	NR (2.6, NE)	5.8 (5.4, 6.9)	6.5 (5.5, 8.1)
75%	NR (8.4, NE)	NR (8.3, NE)	8.3 (6.1, NE)	NR (8.7, NE)
Range	0.03+ - 14.16+	0.03+ - 13.90+	0.03+ - 10.97+	0.03+ - 14.16+
Event-free Rate (95% CI)[3]				
3-month	76.8 (67.5, 83.8)	71.4 (40.6, 88.2)	84.6 (71.5, 92.0)	78.8 (71.8, 84.2)
6-month	50.4 (40.0, 59.8)	64.3 (34.3, 83.3)	48.2 (30.5, 63.9)	52.1 (43.8, 59.8)
9-month	31.8 (21.2, 42.9)	50.0 (22.9, 72.2)	21.4 (7.4, 40.3)	33.2 (24.6, 42.0)
12-month	29.1 (18.5, 40.6)	50.0 (22.9, 72.2)	NR (NE, NE)	28.0 (19.2, 37.5)

The applicant has provided pooled efficacy data by investigator assessment for Cohort A, Phase 1/1b (NSCLC at 600 mg BID dose level), and Cohort B as of data cut-off date of 15 October 2021.

Table 40: Efficacy Outcomes by Investigator Assessment

	Cohort A (N = 116)	Phase 1/1b (N = 16)	Cohort B (N = 60)	Total (N = 192)
BOR				
CR	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.5)
PR	43 (37.1)	8 (50.0)	28 (46.7)	79 (41.1)
SD	48 (41.4)	7 (43.8)	22 (36.7)	77 (40.1)
PD	6 (5.2)	0 (0.0)	3 (5.0)	9 (4.7)
NE	18 (15.5)	1 (6.3)	7 (11.7)	26 (13.5)
ORR				
n (%)	44 (37.9)	8 (50.0)	28 (46.7)	80 (41.7)
95% CI	29.1, 47.4	24.7, 75.3	33.7, 60.0	34.6, 49.0
mDOR (mos)	9.92 (6.97, NR)	16.43 (3.06, NR)	5.59 (4.17, NR)	8.31 (5.78, 16.43)
mPFS (mos)	5.95 (4.37, 8.71)	11.07 (2.56, NR)	6.08 (5.39, 7.98)	6.74 (5.49, 8.21)
mOS (mos)	11.66 (8.74, NR)	NR (3.09, NR)	10.68 (7.62, NR)	12.55 (9.23, 16.33)

BOR=best overall response; CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; NE=not evaluable; ORR=objective response rate; CI=confidence interval; mDOR=median duration of response, based on patients with a response (n=44, 8, 28, 80, respectively); mPFS=median progression-free survival; OS=overall survival; NR=not reached.

Table 41: Analysis of ORR in patients with NSCLC treated at 600 mg BID

Statistics	Cohort A (BICR) (N=116)	Phase 1/1b NSCLC/600 mg BID (Investigator) (N=16)	Cohort B (Investigator) (N=60)	Total (N=192)
Best Overall Response[1]				
Complete Response (CR)	1 (0.9)	0	0	1 (0.5)
Partial Response (PR)	47 (40.5)	6 (37.5)	24 (40.0)	77 (40.1)
Stable Disease (SD)	44 (37.9)	9 (56.3)	24 (40.0)	77 (40.1)
Progressive Disease (PD)	6 (5.2)	0	3 (5.0)	9 (4.7)
Not Evaluable (NE)	18 (15.5)	1 (6.3)	9 (15.0)	28 (14.6)
Objective Response Rate (ORR)[2]				
n (%)	48 (41.4)	6 (37.5)	24 (40.0)	78 (40.6)
95% CI[3]	32.3, 50.9	15.2, 64.6	27.6, 53.5	33.6, 47.9

2.6.5.6. Supportive study(ies)

The following table summarises efficacy across the NSCLC cohorts from pivotal KRYSTAL-1 trial and also includes efficacy data from cohort C (CRC with KRAS G12C mutations) and cohort D (solid tumours with KRAS G12C mutations).

Table 42: Overall summary of efficacy results across different cohorts from KRYSTAL-1

Cohort/ Phase	Description	No. Treated/ No. Discon. Tx/ No. Ongoing	ORR [n (%)] (95% CI)1,2	DOR (months) (95% CI)2.3,4 (No. Events)	PFS (months) (95% CI)2,3 (No. Events)	OS (months) (95% CI)2.3 (No. Events)
A[5]	NSCLC with *KRAS* G12C mutation detected in tumor tissue	116/ 76/ 40	48 (42.9%)[6] (33.5% to 52.6%)	7.3 (5.1 to NE) (19)	6.5 (4.7 to 8.2) (58)	11.3 (8.7 to NE) (48)
B, C, D[7]	B: NSCLC with *KRAS* G12C mutation detected in blood	54/ 20/ 34	9 (16.7%)[8] (7.9% to 29.3%)	4.7 (3.5 to NE) (4)	5.5 (3.2 to 8.3) (16)	7.3 (6.1 to NE) (9)
	C: CRC with *KRAS* G12C mutation detected in blood or tumor tissue	44/ 17/ 27[9]	6 (13.6%) (5.2% to 27.4%)	4.2 (2.3 to NE) (6)	5.6 (3.4 to 7.3) (21)	Not reached (10.1 to NE) (5)
	D: Solid tumor with *KRAS* G12C mutation detected in blood or tissue	22/ 3/ 19	4 (18.2%) (5.2% to 40.3%)	Not reached (5.6 to NE) (1)	Not reached (4.1 to NE) (5)	Not reached (5.4 to NE) (2)
1/1b[10]	Solid tumor harboring *KRAS* G12C mutation detected in blood or tissue	25/ 16/ 9	6 (37.5%) (15.2% to 64.4%)	Not reached (3.1 to NE) (2)	Not reached (2.6 to NE) (7)	Not reached (3.1 to NE) (5)

Source: Cohort A CSR, Cohort B/C/D CSR, Phase 1/1b CSR
BICR = blinded independent central review; BID = twice daily; CI = confidence interval; CRC = colorectal cancer; CSR = clinical study report; Discon. = discontinued; DOR = duration of response; NE = not evaluable; No. = number; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; Tx = treatment.
[1] 95% Clopper-Pearson CI.
[2] For Cohort A, response is based on the ORR analysis; for Cohorts B, C, and D and Phase 1/1b, response is based on the Investigator's assessment.
[3] Median from the Kaplan-Meier estimate; 95% CI of Brookmeyer and Crowley (Brookmeyer, 1982).
[4] Only patients with a response (partial or complete) were included for DOR.
[5] The population for the primary efficacy analysis included 112 patients with measurable disease at baseline by the BICR for ORR, DOR, and PFS, and 116 patients for OS.
[6] Based on the BICR analysis; 95% CI excludes prespecified benchmark ORR for standard-of-care (docetaxel with or without ramucirumab) of 23% (Garon, 2014).
[7] Interim analysis, as of the CSR data cutoff date of 29 Jan 2021; at that time, 80 patients (all cohorts) were continuing on treatment and 9, 1, and 1 patient on Cohorts B, C, and D, respectively, had unconfirmed PR at the time of the data cutoff without any time point assessments of PD.
[8] Updated results, with a cutoff date of 15 Jun 2021 are presented in Section 3.
[9] Includes 5 patients who crossed over to combination therapy with MRTX849+cetuximab.
[10] As of the CSR data cutoff date of 27 Nov 2020; only 16 patients with NSCLC who began treatment at 600 mg BID are included in the activity analyses.

In Phase 2 Cohort B, patients with NSCLC who had previously received treatment with at least a platinum-containing chemotherapy regimen and checkpoint inhibitor therapy and had KRAS G12C mutation identified in ctDNA, were recruited. 54 patients out of 56 received adagrasib 600 mg BID. The applicant has provided interim efficacy results, as treatment with IP was ongoing for 34 (63.0%) patients, survival follow-up continuing for 45 (83.3%) patients, and enrollment continuing.

The updated efficacy results are comparable between Cohort A and B.

Table 43: Analysis of Tumour Response

Statistics	Cohort A (FAS[a], BICR) (N=112)	Cohort B (FAS[a], Investigator) (N=56)
Best Overall Response [b]		
Complete Response (CR)	1 (0.9)	0
Partial Response (PR)	47 (42.0)	24 (42.9)
Stable Disease (SD)	41 (36.6)	22 (39.3)
Progressive Disease (PD)	6 (5.4)	3 (5.4)
Not Evaluable (NE)	17 (15.2)	7 (12.5)
Objective Response Rate (ORR) [c]		
n (%)	48 (42.9)	24 (42.9)
95% CI[d]	33.5, 52.6	29.7, 56.8

BICR = Blinded Independent Central Review; CI = Confidence Interval; FAS=Full Analysis Set

[a] The Full Analysis Set is defined as all patients who receive at least one dose of MRTX849 (and had measurable disease at baseline by BICR for Cohort A only).

[b] A Best Overall Response (BOR) of CR/PR confirmed requires a confirmatory assessment at least 4 weeks (28 days or more) since the first CR/PR response. For a BOR of SD, an SD assessment must be at least 32 days from the date of first dose, otherwise it will be summarized as NE.

[c] ORR is defined as the proportion of patients documented to have a confirmed CR or PR according to RECIST v1.1 as the best response.

[d] 95% CI is calculated using the exact binomial method (Clopper-Pearson).

2.6.6. Discussion on clinical efficacy

A conditional marketing authorisation (CMA) is sought for Krazati (adagrasib), a KRAS G12C oral inhibitor, intended for the treatment of patients with advanced NSCLC whose tumours bear a KRAS G12C mutation and who have progressed after therapy with a platinum-containing regimen agent and an immune checkpoint inhibitor (concurrently or sequentially).

The main efficacy dataset to support this application is constituted by primary analysis results of Cohort A (n=116) from the phase 2 segment of KRYSTAL-1 (Study 849-001), a phase 1/2, open-label, multi-cohort, single-arm trial conducted in the US. ORR, as assessed by BICR, is the primary endpoint of efficacy to support this application, whereas DOR, PFS and OS are secondary endpoints.

Supportive efficacy data come from other NSCLC cohorts from the same trial: 60 patients from phase 2 Cohort B (advanced NSCLC and KRAS G12C mutation diagnosed with ctDNA in blood) and 16 patients from the phase 1/1b segment with similar clinical characteristics to patients of Cohort A. Confirmatory data in a similar population is expected in Q3 2024 from the ongoing phase 3, open-label, randomised controlled Study 849-012.

Design and conduct of clinical studies

No interactions were held with the European authorities through the initial clinical development of adagrasib nor the design of KRYSTAL-1. After appointment of Rapporteurs in 2021, the applicant held a national scientific advice with the Danish Medicines Agency to present a series of amendments of the confirmatory phase 3 Study 849-012, since recruitment challenges rose upon the imminent introduction of sotorasib (another KRAS G12C inhibitor intended for the same clinical setting) in the US and Europe. The need for these changes was acknowledged, and the applicant has expanded the clinical trial footprint to attempt completion within timelines, adopting Protocol Version 5 in October 2021, which allowed cross-over. As of 12 April 2023, 259 patients have been randomised into the trial. With the current conduct of the study, it is regarded feasible to reach the aim of 450 included patients by Q4 2023 and subsequent submission of the results (CSR) by Q3 2024. Additional clarifications on this trial are presented in section 3.7.3.

Study participants: Inclusion/exclusion criteria for the main efficacy dataset (Cohort A of Study KRYSTAL-1) did not suffer major amendments during conduct of the trial and appropriately reflect the

targeted population intended for treatment with adagrasib. Documentation of progression was not required for eligibility, but as expected in the studied clinical setting, very few patients (4/116 = 3%) did not have radiographic disease progression. As such, overall results are attributable to patients with established progressive disease, and the proposed therapeutic indication is reflective of the recruited population.

The presence of a KRAS G12C mutation was established through local testing of tumour tissue (NGS in 94% of cases; PCR or Sanger sequencing in the rest), and centrally confirmed in 87 out of 101 available samples.

Treatments: Adagrasib was administered at 600 mg twice daily and the SmPC describes two dose reduction levels. As is the usual case in Oncology, treatment was to be maintained until disease progression or unacceptable toxicity, although treatment beyond progression was allowed at the discretion of the investigator. Nevertheless, any statements that could encourage off-label post-progression treatment at the SmPC are inappropriate and have been removed.

Outcomes/endpoints: At the time of data cut-off (15-OCT-2021), about two thirds of patients from Cohort A had discontinued adagrasib and the rest were still on treatment. As expected, about a third (31 out of 85) of discontinuations were due to progressive disease, while ~20% (16 out of 85) were due to adverse events. Upon limited interpretability of time-to-event endpoints in an uncontrolled setting, a significant proportion of responders is considered a clinically relevant indicator of treatment effect in single-arm trials. Prolonged durability of such responses is considered paramount support for claimed ORR benefits. The fact that response/duration were assessed by BICR is expected to reduce investigator bias, and concordance with investigator evaluation was shown.

Statistical methods: Target sample size of n=105 in Cohort A was based on excluding 23% (ORR for the docetaxel + ramucirumab arm in advanced NSCLC after platinum-based therapy at the REVEL study, Garon et al 2014) from the lower bound of the two-sided 95% CI of the expected ORR from adagrasib. Although the calculations are followed, the referenced ORR cannot be contextualised in the current approach to patients with advanced KRAS-G12C-mutant NSCLC: patients from the REVEL study were unselected and checkpoint immunotherapy was not yet established in first or second lines.

The primary analysis of ORR was performed once all treated patients had enough follow-up to assess response (at least 6 months after the last patient enrolled started treatment).

The primary efficacy dataset of Cohort A from Study KRYSTAL-1 is constituted by the 116 patients that were treated with adagrasib. The ORR-BICR results, including all treated patients from Cohort A (n= 116), are reflected in Section 5.1 of the SmPC. Patients who were considered non-evaluable or with absence-of-measurable-disease-at-baseline by the BICR were considered non-responders in the ORR analysis. The statistical methods used to analyse the primary endpoint are endorsed. Upon concerns from the censoring rules, sensitivity analyses of DOR and PFS were provided and considered supportive of the outcome.

Baseline characteristics: 116 patients were recruited and started adagrasib in Cohort A between January and November 2020. 84% were white, 56% female, 84% had ECOG PS 1, median age was 64. A minority of patients had never smoked (4%), and the rest were former (86%) or current (10%) smokers; almost all patients had adenocarcinomas (97%) and the disease stage was metastatic in the majority (89%). All patients had received prior platinum-based chemotherapy and all but two patients had received immune checkpoint inhibitors: ~70% concurrent chemo-immunotherapy and the rest sequential treatment.

Overall, patient baseline and disease characteristics are as expected from a population with advanced KRAS-mutant NSCLC in the 2L+ setting, noting the absence of patients with ECOG PS ≥ 2. No concomitant actionable oncogenic aberrations (including: EGFR exon 19 deletion, p.L858R, p.T790M, or

exon 20 insertion, ALK rearrangements, ROS1 fusions, MET exon 14 skipping mutations, RET fusions, NTRK1, NTRK2, or NTRK3 fusions, and BRAF p.V600E). PD-L1 status was available for 90 of the 116 included patients. The majority of patients were PD-L1 negative <1% (42.2%), fewer were 1-49% positive (23.3%) and even less were ≥50% positive (12.1%). Although this distribution slightly differs from the general population of patients with NSCLC (approximately a third in each category), this is not deemed of importance considering the mechanism of action of adagrasib.

Efficacy data and additional analyses

At initial data cut-off (DCO) 15-JUN-2021, 48 patients out of 116 were considered confirmed responders by retrospective BICR, accounting for an ORR of 41.4% (95% 32.3, 50.9). The inferior limit of the 95% CI excludes the 23% specified benchmark used in sample size calculations, rendering the primary analysis successful. Analysis of ORR by investigator (37.1%) is concordant. Subgroup analysis suggested that the ORR benefit from adagrasib is consistent across the main predefined categories. Of note, the biomarker bridging study reports a similar response rate (43%) in the centrally-tested subpopulation (n=101: 87 confirmed G12C KRAS mutant samples, 3 non-evaluable and 11 discordant). At DCO 15-Jun-2021, ~40% of progression events in responders had occurred and mDOR was estimated at 7.3 months.

Initial DCO was contingent on allowing the last patient from Cohort A enough time to evaluate and confirm tumour response, but since recruitment took place in ~1 year, median follow-up (9 months) of the main efficacy dataset was considered limited, entailing the request for updated efficacy. The updated dataset has 4 additional months of follow-up with a cut-off date of 15-OCT-2021, with a median follow-up of 12.9 months. Addition of 4 months of follow-up is considered limited but acceptable within the current procedure. The applicant has also provided OS data with a longer follow-up of 7 additional months with a cut-off date of 15 Jan. 2022 and a median follow-up of 15.6 months.

At the updated DCO, no new objective responses were reported between the two data cutoffs, and ORR by BICR remained at 41.4%. ORR by investigator was 37.9%. Median duration of response (mDOR) by BICR had increased to 8.5 (95% CI: 6.2-13.8) months, mPFS was stable at 6.0 (95% CI: 4.7-8.4) months and mOS had increased to 11.7 (95% CI: 9.2-NE) months. Maturity of the OS data at the DCO on 15 Oct 2021 was ~50%. The additional update of OS with DCO 15-JAN-2022 reported median OS of 12.6 months (95% CI: 9.2, 19.2). At this timepoint, and compared to previous analyses, an upper boundary of the CI for mOS was reached. At updated DCO of 15 Oct. 2021, there had been no new objective responses and maturity of OS was 52.6%.

Further updates on data from study KRYSTAL-1 are currently not required. With 4 months of additional FU, all efficacy endpoints are either stable (ORR 41.4/41.4%, mPFS 6/6 months) or show a minor trend for improvement (mDOR 7.3/8.5 months, mOS 11.3/11.7 months).

Noting limited interpretability of time-to-event endpoints in the uncontrolled open-label nature of the data provided, median PFS (6.0 months at 59.5% of events) and median OS (12.6 months at 52.6% of events) endorse the ORR/DOR benefit from adagrasib in the 2L+ setting of this KRAS-selected population.

Overall efficacy results from adagrasib in KRYSTAL-1 are indirectly supported by similar outcomes in an akin population (n=124) treated with sotorasib in the CodeBreak 100 Study (Lumykras EPAR): ORR 37.1%, mDOR 11.1 months, mPFS 6.8 months and mOS 12.5 months.

Supportive data: Response rates –as assessed by Investigator– across the other cohorts of NSCLC with KRAS G12C mutations in pivotal Study KRYSTAL-1 (37.5% in 16 patients from phase 1/1b and 40% in 60 patients identified via ctDNA in blood, i.e., Cohort B) are overall consistent with those from pivotal Cohort A. Results from time-to-event endpoints also hold similar trends across NSCLC cohorts.

Although data are promising, there is not sufficient evidence to recommend the use of adagrasib in patients with KRAS mutations identified via ctDNA.

Additional efficacy data needed in the context of a conditional MA

Evidence for efficacy of adagrasib in the targeted population is limited and comes from an uncontrolled single-arm trial (849-001, KRYSTAL-1). Comprehensive data are not yet available and the applicant requested a conditional marketing authorisation in the initial submission based on response rate, while committing to provide results from the phase III trial 849-012 as confirmatory evidence.

Efficacy results from the single-arm trial KRYSTAL-1 provide preliminary evidence for a promising treatment effect from Krazati in the targeted population. Data from response-related endpoints appear comparable to Lumykras, the other conditionally approved product in this setting.

However, emerging data from the randomised controlled CodeBreak 200 trial comparing sotorasib to docetaxel (de Langen et al. Lancet. 2023), give reason to question whether the magnitude of effect observed with adagrasib is likely to translate into a major therapeutic advantage over docetaxel. This is due to the similar mechanism of action of adagrasib and sotorasib.

The applicant addressed this issue in an oral explanation focusing on the unmet medical need of the targeted population (poor prognosis, limited treated options), and reiterated major therapeutic advantage over docetaxel, while addressing the unmet medical need to a similar extent as sotorasib. Additionally, emerging data on activity of adagrasib in brain metastases from KRYSTAL-1, showing 42% of intracranial response rate in 25 patients with untreated brain metastases were presented (Negrao, JCO 2023).

The CHMP considered that the applicant was unable to demonstrate any specific pharmacological differences, that would support an anticipation of more favorable effects on time dependent endpoint (PFS; OS) than what was seen with sotorasib.

It is also noted that Krazati is orally administered and has a different safety profile than docetaxel. However, these attributes alone are not considered sufficient to address the unmet medical need. Therefore in the absence of an established major therapeutic advantage and in view of the non-comprehensive data on efficacy and safety, it is considered that the benefits to public health of the immediate availability of Krazati do not outweigh the risks inherent in the fact that additional data are still required.

2.6.7. Conclusions on the clinical efficacy

Evidence for efficacy of Krazati in the treatment of adult patients with advanced NSCLC with KRAS G12C mutation who have received at least one prior systemic therapy is limited and comes from an uncontrolled single-arm trial (849-001, KRYSTAL-1). At the latest data cut-off (DCO) of 15 October 2021, 48 out of 116 patients treated were considered confirmed responders by retrospective BICR, leading to an ORR of 41.4% (95% 32.3; 50.9). The median duration of response (mDOR) was estimated at 8.5 months (95% 6.2; 13.8). The long-term benefit of Krazati is unclear since its impact on time-to-event endpoints, i.e., PFS and OS, cannot be reliably estimated in the context of an uncontrolled trial.

2.6.8. Clinical safety

The data were generated primarily in the ongoing Study 849-001 (KRYSTAL-1), a multicenter, Phase 1/2, multiple expansion cohort study evaluating the safety, pharmacokinetics (PK), and clinical activity/efficacy of MRTX849 (adagrasib) as monotherapy in patients with advanced solid tumours with

KRAS G12C mutation (Table 44). The Safety population was defined as all patients who received at least 1 dose of study medication.

Table 44: Main cohorts from Phase 1/1b and 2 of pivotal trial KRYSTAL-1

Portion CSR Status **Start Date[1]** **SCS Data Cutoff Date**	Study Drug Starting Dose, Route & Regimen	Study Objective	No. Pts in Safety Evaluation	Diagnosis Inclusion Criteria
Phase 1/1b (dose-finding) Final 26 Dec 2018 15 Oct 2021	MRTX849 Escalating doses, Oral	Safety, tolerability, PK, MTD/RP2D, clinical activity	25	Solid tumor with *KRAS* G12C mutation in tumor tissue, no available curative/standard-of-care treatment, or patient was ineligible or declined treatment 16 patients with NSCLC were treated at 600 mg BID
Phase 2, Cohort A Final 17 Jan 2020 15 Oct 2021	MRTX849 600 mg, Oral BID	Efficacy, safety, tolerability, PK	116	Squamous or nonsquamous NSCLC with *KRAS* G12C mutation in tumor tissue, prior treatment with at least a platinum-containing regimen and CIT
Phase 2, Cohort B Interim 17 Jan 2020 15 Oct 2021	MRTX849 600 mg, Oral, BID	Clinical activity, safety, tolerability, PK	56[2]	Squamous or nonsquamous NSCLC with *KRAS* G12C mutation in ctDNA, prior treatment with at least a platinum-containing regimen and CIT
Phase 2, Cohort C Interim 22 Jan 2020 15 Oct 2021	MRTX849 600 mg, Oral BID	Clinical activity, safety, tolerability, PK	44	Adenocarcinoma of the colon or rectum with *KRAS* G12C mutation, no available curative/standard-of-care treatment, or patient was ineligible or declined treatment
Phase 2, Cohort D Interim 27 Feb 2020 15 Oct 2021	MRTX849 600 mg, Oral BID	Clinical activity, safety, tolerability, PK	24	Solid tumor with *KRAS* G12C mutation, no available curative/standard-of-care treatment, or patient was ineligible or declined treatment

BID = twice daily; CIT = checkpoint inhibitor therapy; ctDNA = circulating tumor DNA; MTD = maximum tolerated dose; No. = number; NSCLC = non-small cell lung cancer; Pts = patients; PK = pharmacokinetic(s); RP2D = recommended Phase 2 dose; SCS = Summary of Clinical Safety.
[1] Date of informed consent.
[2] Includes patients enrolled as of 29 Jan 2021. Four additional patients who enrolled in Cohort B as of 15 Jun 2021 (for a total of 60 patients in Cohort B) are included in an additional sensitivity analysis of efficacy.

Safety data from the current dataset of 265 patients administered adagrasib monotherapy are summarized in the following groups:

- Adagrasib using the 600 mg twice daily regimen (dose intended for marketing):
  - Phase 2 Cohort A (n = 116 patients).
  - All NSCLC patients (n = 188 patients with NSCLC treated in Cohorts A [n = 116] and B [n = 56], and in Phase 1/1b [n = 16]).
  - Other (n = 72 patients with other diagnoses treated in Cohorts C and D [n = 68] and in Phase 1/1b [n = 4]).
  - Total (n = 260 patients).
- Adagrasib using other dosing regimens in Phase 1/1b (n = 5 patients).

The overall safety database of adagrasib is constituted by 260 patients across multiple cohorts from pivotal phase 1/2 Study KRYSTAL-1. The main safety datasets, in which patients received adagrasib at the dose intended for marketing, i.e., 600 mg BID (Cohort A, n=116; NSCLC pool, n=188; other tumours, n=72; and total, n=260).

The cut-off date for the safety database (15-OCT-2021) differs from the one used for the efficacy data (15-JUN-2021). The median follow-up period for safety across the 4 submitted datasets was ~12 months in all of the 4 groups.

For the 4 groups used to summarise safety, the median follow-up times as of the data cutoff date of 15 October 2021 are shown in Table 45 below.

Table 45: Median Follow-Up Times

	Cohort A (N=116)	**NSCLC (N=188)**	**Other (N=72)**	**Total (N=260)**
Median Follow-up in Months (95% CI)[a]	12.5 (11.8, 13.2)	12.3 (11.5, 13.2)	11.8 (10.8, 14.6)	12.2 (11.5, 13.1)

[a] Obtained via reverse Kaplan-Meier estimation.

2.6.8.1. Patient exposure

Table 46: Summary of exposure of adagrasib, Study KRYSTAL-1 (DCO 15-OCT-2021)

	MRTX849 Monotherapy				
	600 mg BID				
Variable	**Cohort A (N=116)**	**NSCLC (N=188)**	**Other (N=72)**	**Total (N=260)**	**Other Doses (N=5)**
Study Treatment Duration[1] (months)					
n	116	188	72	260	5
Mean (std)	7.0003 (5.3729)	7.286 (5.7124)	7.196 (5.1437)	7.262 (5.5511)	8.903 (13.5757)
Median	5.700	6.390	6.111	6.177	2.563
Q1, Q3	2.136, 12.025	2.218, 11.433	3.302, 10.152	2.727, 11.039	2.070, 6.735
Min, Max	0.03, 19.55	0.03, 25.40	0.59, 28.65	0.03, 28.65	0.33, 32.82
Study Treatment Duration[1] [n (%)]					
≤ 3 months	39 (33.6)	60 (31.9)	15 (20.8)	75 (28.8)	3 (60.0)
> 3-6 months	23 (19.8)	33 (17.6)	21 (29.2)	54 (20.8)	0
> 6-12 months	24 (20.7)	53 (28.2)	26 (36.1)	79 (30.4)	1 (20.0)
> 12-18 months	28 (24.1)	35 (18.6)	7 (9.7)	42 (16.2)	0
> 18-24 months	2 (1.7)	5 (2.7)	2 (2.8)	7 (2.7)	0
> 24 months	0	2 (1.1)	1 (1.4)	3 (1.2)	1 (20.0)
Total Number of Cycles Initiated					
n	116	188	72	260	5
Mean (std)	10.2 (7.64)	10.6 (8.15)	10.5 (7.45)	10.6 (7.95)	11.8 (17.80)
Median	9.0	9.0	9.0	9.0	3.0
Q1, Q3	3.0, 17.0	3.5, 16.0	5.0, 15.0	4.0, 16.0	2.0, 10.0
Min, Max	1, 27	1, 37	1, 42	1, 42	1, 43
Total Number of Cycles Initiated [n (%)]					
1	14 (12.1)	20 (10.6)	2 (2.8)	22 (8.5)	1 (20.0)
2	11 (9.5)	17 (9.0)	6 (8.3)	23 (8.8)	1 (20.0)
3	5 (4.3)	10 (5.3)	3 (4.2)	13 (5.0)	1 (20.0)
4	9 (7.8)	13 (6.9)	4 (5.6)	17 (6.5)	0
5	6 (5.2)	7 (3.7)	7 (9.7)	14 (5.4)	0
6	3 (2.6)	8 (4.3)	3 (4.2)	11 (4.2)	0
7	6 (5.2)	9 (4.8)	2 (2.8)	11 (4.2)	0

Variable	MRTX849 Monotherapy 600 mg BID Cohort A (N=116)	NSCLC (N=188)	Other (N=72)	Total (N=260)	Other Doses (N=5)
8	3 (2.6)	4 (2.1)	7 (9.7)	11 (4.2)	0
9	5 (4.3)	7 (3.7)	6 (8.3)	13 (5.0)	0
10	3 (2.6)	9 (4.8)	2 (2.8)	11 (4.2)	1 (20.0)
11-20	37 (31.9)	60 (31.9)	23 (31.9)	83 (31.9)	0
21-30	14 (12.1)	20 (10.6)	6 (8.3)	26 (10.0)	0
31+	0	4 (2.1)	1 (1.4)	5 (1.9)	1 (20.0)
Relative Dose Intensity (%)[2]					
n	116	188	72	260	5
Mean (std)	75.13 (21.888)	75.62 (21.199)	83.77 (19.183)	77.88 (20.946)	157.59 (134.456)
Median	78.15	77.30	93.99	82.10	96.83
Q1, Q3	58.11, 97.15	60.84, 97.01	68.59, 99.81	62.76, 98.94	90.00, 225.85
Min, Max	24.8, 100.0	24.8, 104.3	33.2, 102.8	24.8, 104.3	17.9, 357.3
Dose Compliance (%)[3]					
n	116	188	72	260	5
Mean (std)	85.58 (16.810)	85.79 (16.046)	88.70 (14.861)	86.60 (15.753)	161.23 (87.695)
Median	94.52	92.74	98.66	94.50	100.0
Q1, Q3	71.62, 100.00	72.32, 99.88	79.36, 99.89	74.41, 99.88	100.0, 225.85
Min, Max	38.1, 100.0	38.1, 100.0	45.3, 100.0	38.1, 100.0	96.8, 283.5
Dose Compliance (%)[3]					
> 90%	65 (56.0)	104 (55.3)	46 (63.9)	150 (57.7)	5 (100)
> 80%-90%	10 (8.6)	18 (9.6)	6 (8.3)	24 (9.2)	0
> 70%-80%	17 (14.7)	28 (14.9)	9 (12.5)	37 (14.2)	0
≤ 70%	24 (20.7)	38 (20.2)	11 (15.3)	49 (18.8)	0

Source: ISS MAA Table 14.3.1.1
BID = twice daily; Max = maximum; Min = minimum; NSCLC = non-small-cell lung cancer; Q1 = first quartile; Q3 = third quartile; std = standard deviation.
Six patients in Cohort C who crossed over from MRTX849 monotherapy to MRTX849+cetuximab treatment are included in the MRTX849 Monotherapy 600 mg BID other group. Only the safety data occurring during the MRTX849 monotherapy period are included.
[1] Study treatment duration (months) is calculated as (last dose date - first dose date + 1)/30.4375.
[2] Relative dose intensity (%) is calculated as the cumulative dose received (mg)/cumulative planned dose (mg)* 100, where planned cumulative dose is calculated as the starting daily dose multiplied by the number of days between the actual date of first dose and the actual date of last dose + 1, ie, study treatment duration.
[3] Compliance (%) is calculated as cumulative dose received (mg)/[cumulative dose received (mg) + number of days of missed doses * preceding dose] *100. Missed doses only refers to missed doses and does not encompass planned dose interruptions or reductions.

Table 47: Summary of dose reductions and dose interruptions, Study KRYSTAL-1 (DCO 15-OCT-2021)

Variable [n (%)]	MRTX849 Monotherapy 600 mg BID Cohort A (N=116)	NSCLC (N=188)	Other (N=72)	Total (N=260)	Other Doses (N=5)
Patients with at Least 1 Dose Reduction	68 (58.6)	111 (59.0)	28 (38.9)	139 (53.5)	3 (60.0)
Reason for Dose Reduction					
Adverse Event	67 (57.8)	108 (57.4)	28 (38.9)	136 (52.3)	3 (60.0)
Other	5 (4.3)	10 (5.3)	3 (4.2)	13 (5.0)	0
Number of Dose Reductions					
0	48 (41.4)	77 (41.0)	44 (61.1)	121 (46.5)	2 (40.0)

Variable [n (%)]	MRTX849 Monotherapy 600 mg BID Cohort A (N=116)	MRTX849 Monotherapy 600 mg BID NSCLC (N=188)	MRTX849 Monotherapy 600 mg BID Other (N=72)	MRTX849 Monotherapy 600 mg BID Total (N=260)	Other Doses (N=5)
1	37 (31.9)	62 (33.0)	19 (26.4)	81 (31.2)	2 (40.0)
2	23 (19.8)	34 (18.1)	5 (6.9)	39 (15.0)	1 (20.0)
3	8 (6.9)	14 (7.4)	3 (4.2)	17 (6.5)	0
4	0	1 (<1)	0	1 (<1)	0
5+	0	0	1 (1.4)	1 (<1)	0
Patients with at Least 1 Dose Interrupted	108 (93.1)	177 (94.1)	61 (84.7)	238 (91.5)	4 (80.0)
Reason for Dose Interruption					
Adverse Event	90 (77.6)	146 (77.7)	40 (55.6)	186 (71.5)	2 (40.0)
Patient Non-compliance	22 (19.0)	36 (19.1)	8 (11.1)	44 (16.9)	1 (20.0)
Patient Discontinued Treatment	66 (56.9)	100 (53.2)	30 (41.7)	130 (50.0)	1 (20.0)
Missed Dose	56 (48.3)	87 (46.3)	31 (43.1)	118 (45.4)	1 (20.0)
Other	30 (25.9)	51 (27.1)	16 (22.2)	67 (25.8)	0
Number of Dose Interruptions					
0	8 (6.9)	11 (5.9)	11 (15.3)	22 (8.5)	1 (20.0)
1	11 (9.5)	25 (13.3)	12 (16.7)	37 (14.2)	1 (20.0)
2	25 (21.6)	35 (18.6)	10 (13.9)	45 (17.3)	1 (20.0)
3	5 (4.3)	12 (6.4)	9 (12.5)	21 (8.1)	1 (20.0)
4	10 (8.6)	12 (6.4)	7 (9.7)	19 (7.3)	0
5	12 (10.3)	18 (9.6)	3 (4.2)	21 (8.1)	0
6	8 (6.9)	15 (8.0)	7 (9.7)	22 (8.5)	0
7+	37 (31.9)	60 (31.9)	13 (18.1)	73 (28.1)	1 (20.0)

Source: ISS MAA Table 14.3.1.2
BID = twice daily; NSCLC = non-small cell lung cancer; SCS = Summary of clinical Safety.
Six patients in Cohort C who crossed over from MRTX849 monotherapy to MRTX849+cetuximab treatment are included in the MRTX849 Monotherapy 600 mg BID other group. Only the safety data occurring during the MRTX849 monotherapy period are included.

Table 48: Summary of patients with dose reductions due to AEs, Study KRYSTAL-1 (DCO 15-OCT-2021)

	MRTX849 Monotherapy 600 mg BID Cohort A (N=116)	MRTX849 Monotherapy 600 mg BID NSCLC (N=188)	MRTX849 Monotherapy 600 mg BID Other (N=72)	MRTX849 Monotherapy 600 mg BID Total (N=260)
Number of Patients with Dose Reduction [n (%)]	67 (57.8)	108 (57.4)	28 (38.9)	136 (52.3)
MRTX849 400 mg BID	37 (31.9)	57 (30.3)	17 (23.6)	74 (28.5)
MRTX849 600 mg QD	14 (12.1)	22 (11.7)	7 (9.7)	29 (11.2)
MRTX849 400 mg QD/200 mg BID	15 (12.9)	26 (13.8)	3 (4.2)	29 (11.2)
MRTX849 200 mg QD	1 (<1)	1 (<1)	1 (1.4)	2 (<1)
MRTX849 Other	0	2 (1.1)	0	2 (<1)

Source: ISS MAA Table 14.3.1.3
BID = twice daily; NSCLC = non-small cell lung cancer; QD = once daily; SCS = Summary of Clinical Safety.
Six patients in Cohort C who crossed over from MRTX849 monotherapy to MRTX849+cetuximab treatment are included in the MRTX849 Monotherapy 600 mg BID other group. Only the safety data occurring during the MRTX849 monotherapy period are included.
Patients are counted in the lowest administered dose group.

2.6.8.2. Adverse events

Overview of AEs:

Table 49: Overview of Adverse Events

	MRTX849 Monotherapy 600 mg BID			
	Cohort A	**NSCLC**	**Other**	**Total**
n (%)	**(N=116)**	**(N=188)**	**(N=72)**	**(N=260)**
Any Treatment-emergent Adverse Events	116 (100)	188 (100)	72 (100)	260 (100)
Any Grade 3 or Greater TEAEs	95 (81.9)	153 (81.4)	37 (51.4)	190 (73.1)
Any MRTX849-related TEAE	113 (97.4)	182 (96.8)	67 (93.1)	249 (95.8)
Any Grade 3 or Greater MRTX849-related TEAE	52 (44.8)	88 (46.8)	20 (27.8)	108 (41.5)
Any TEAE Leading to Discontinuation of Study	7 (6.0)	10 (5.3)	0	10 (3.8)
Any MRTX849-related TEAE Leading to Discontinuation of Study	4 (3.4)	6 (3.2)	0	6 (2.3)
Any TEAE Leading to Discontinuation of Study Treatment	18 (15.5)	26 (13.8)	3 (4.2)	29 (11.2)
Any MRTX849-related TEAE Leading to Discontinuation of Study Treatment	8 (6.9)	11 (5.9)	0	11 (4.2)
Any TEAE Leading to Dose Reduction or Interruption	96 (82.8)	158 (84.0)	43 (59.7)	201 (77.3)
Any MRTX849-related TEAE Leading to Dose Reduction or Interruption	80 (69.0)	129 (68.6)	36 (50.0)	165 (63.5)
Any SAE	72 (62.1)	111 (59.0)	22 (30.6)	133 (51.2)
Any MRTX849-related SAE	20 (17.2)	37 (19.7)	6 (8.3)	43 (16.5)
Any SAE Leading to Discontinuation of Study Treatment	17 (14.7)	23 (12.2)	2 (2.8)	25 (9.6)
Any TEAE with Outcome of Death within 28 days of Last Dose	20 (17.2)	33 (17.6)	5 (6.9)	38 (14.6)
Any MRTX849-related TEAE with Outcome of Death within 28 days of Last Dose	2 (1.7)	4 (2.1)	0	4 (1.5)
Any SAE with Outcome of Death within 28 days of Last Dose	20 (17.2)	33 (17.6)	5 (6.9)	38 (14.6)
Any MRTX849-related SAE with Outcome of Death within 28 days of Last Dose	2 (1.7)	4 (2.1)	0	4 (1.5)
GI adverse reactions [a]	103 (88.8)	169 (89.9)	65 (90.3)	234 (90.0)
Hepatotoxicity[b]	43 (37.1)	81 (43.1)	21 (29.2)	102 (39.2)

[a] includes nausea, vomiting, diarrhoea, and retching.

[b] includes increased AST, increased ALT, increased alkaline phosphatase, increased bilirubin, mixed liver injury, liver function test increased, transaminases increased, hepatic enzyme increased, gamma-glutamyltransferase increased, hepatitis, drug-induced liver injury, hepatocellular injury, hepatitis acute, hepatitis toxic, hepatotoxicity, liver disorder, hepatic failure, hepatic steatosis, and hepatic lesion.

Common AEs:

Table 50: Adverse events reported in ≥10% NSCLC patients

	MRTX849 Monotherapy 600 mg BID			
Group/Preferred Term [n (%)]	Cohort A (N=116)	NSCLC (N=188)	Other (N=72)	Total (N=260)
Patients with at Least 1 TEAE	116 (100)	188 (100)	72 (100)	260 (100)
Nausea [1]	92 (79.3)	151 (80.3)	55 (76.4)	206 (79.2)
Diarrhoea	82 (70.7)	133 (70.7)	53 (73.6)	186 (71.5)
Fatigue [2]	69 (59.5)	108 (57.4)	41 (56.9)	149 (57.3)
Musculoskeletal Pain [3]	54 (46.6)	84 (44.7)	25 (34.7)	109 (41.9)
Liver Disorder [4]	43 (37.1)	81 (43.1)	21 (29.2)	102 (39.2)
Renal Insufficiency [5]	46 (39.7)	72 (38.3)	20 (27.8)	92 (35.4)
Decreased appetite	37 (31.9)	66 (35.1)	12 (16.7)	78 (30.0)
Anaemia	42 (36.2)	65 (34.6)	22 (30.6)	87 (33.5)
Dyspnoea	41 (35.3)	65 (34.6)	13 (18.1)	78 (30.0)
Oedema [6]	39 (33.6)	63 (33.5)	24 (33.3)	87 (33.5)
Dizziness [7]	27 (23.3)	46 (24.5)	13 (18.1)	59 (22.7)
Abdominal pain [8]	25 (21.6)	44 (23.4)	21 (29.2)	65 (25.0)
Constipation	27 (23.3)	43 (22.9)	14 (19.4)	57 (21.9)
Hyponatraemia	27 (23.3)	43 (22.9)	12 (16.7)	55 (21.2)
Pancreatic Enzyme Increase [9]	25 (21.6)	41 (21.8)	4 (5.6)	45 (17.3)
Cough	24 (20.7)	37 (19.7)	5 (6.9)	42 (16.2)
Lung Infection [10]	29 (25.0)	37 (19.7)	4 (5.6)	41 (15.8)
QT Prolongation [11]	23 (19.8)	36 (19.1)	10 (13.9)	46 (17.7)
Weight decreased	18 (15.5)	35 (18.6)	10 (13.9)	45 (17.3)
Hypoalbuminaemia	20 (17.2)	33 (17.6)	6 (8.3)	39 (15.0)
Rash [12]	21 (18.1)	33 (17.6)	12 (16.7)	45 (17.3)
Hypokalaemia	16 (13.8)	31 (16.5)	9 (12.5)	40 (15.4)
Headache	17 (14.7)	27 (14.4)	6 (8.3)	33 (12.7)
Hypotension	13 (11.2)	27 (14.4)	3 (4.2)	30 (11.5)
Insomnia	15 (12.9)	27 (14.4)	6 (8.3)	33 (12.7)
Dehydration	14 (12.1)	26 (13.8)	8 (11.1)	34 (13.1)
Dysgeusia	14 (12.1)	26 (13.8)	9 (12.5)	35 (13.5)
Peripheral Neuropathy [13]	14 (12.1)	23 (12.2)	9 (12.5)	32 (12.3)
Pyrexia	12 (10.3)	23 (12.2)	8 (11.1)	31 (11.9)
Skin discolouration [14]	14 (12.1)	23 (12.2)	5 (6.9)	28 (10.8)
Fall	12 (10.3)	21 (11.2)	4 (5.6)	25 (9.6)
Pleural effusion	17 (14.7)	21 (11.2)	2 (2.8)	23 (8.8)
Muscular weakness	13 (11.2)	19 (10.1)	5 (6.9)	24 (9.2)

Note: Adverse events were coded using MedDRA version 21.0. For each preferred term, patients are included only once, even if they experienced multiple events in that preferred term.
Source: Listing 16.2.7.2, Dataset: ADAE, Program: t_q163_1.sas, Output: t_q163_1.rtf, Generated on: 2022-12-12T14:53, Datacutoff: 2021-10-15
Source: t_q163_1
[1] Includes nausea, vomiting, retching; [2]Includes fatigue, asthenia; [3]Includes arthralgia, back pain, pain in extremity, muscle spasms, myalgia, musculoskeletal chest pain, musculoskeletal pain, neck pain; [4] Includes ALT increased, AST increased, blook alkaline phosphatase increased, blood bilirubin increased, bilirubin conjugated increased, gamma-glutamyltransferase increased, hepatic enzyme increased, liver function test increased, mixed liver injury, ammonia increased, jaundice cholestatic; [5] Includes blood creatinine increased, acute kidney injury, blood urea increased, chronic kidney disease, renal failure; [6] Includes oedema peripheral, face oedema, peripheral swelling, localised oedema, oedema, oedema genital, periorbital oedema; [7] Includes dizziness, vertigo, dizziness postural, vestibular disorder; [8] Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort; [9] Includes amylase increased, lipase increased, pancreatitis, amylase; [10] Includes pneumonia, lung infection, pneumonia streptococcal, respiratory tract infection; [11] Includes electrocardiogram QT prolonged, electrocardiogram abnormal; [12] Includes rash, rash maculo-papular, rash macular, dermatitis, dermatitis acneiform, eczema, rash pruritic, dermatitis contact, stasis dermatitis; [13] Includes paraesthesia, neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, peroneal nerve palsy; [14] Includes skin hyperpigmentation, skin discolouration, pigmentation disorder.

Table 51: Treatment-related adverse events reported in ≥5% NSCLC patients

	MRTX849 Monotherapy 600 mg BID			
Group/Preferred Term [n (%)]	**Cohort A (N=116)**	**NSCLC (N=188)**	**Other (N=72)**	**Total (N=260)**
Patients with at least 1 MRTX849-related TEAE	113 (97.4)	182 (96.8)	67 (93.1)	249 (95.8)
Nausea [1]	82 (70.7)	139 (73.9)	44 (61.1)	183 (70.4)
Diarrhoea	73 (62.9)	121 (64.4)	42 (58.3)	163 (62.7)
Fatigue [2]	47 (40.5)	71 (37.8)	30 (41.7)	101 (38.8)
Liver Disorder [4]	36 (31.0)	70 (37.2)	13 (18.1)	83 (31.9)
Renal Insufficiency [5]	32 (27.6)	51 (27.1)	10 (13.9)	61 (23.5)
Decreased appetite	28 (24.1)	48 (25.5)	8 (11.1)	56 (21.5)
Pancreatic Enzyme Increase [9]	23 (19.8)	37 (19.7)	2 (2.8)	39 (15.0)
Anaemia	21 (18.1)	32 (17.0)	8 (11.1)	40 (15.4)
QT Prolongation [11]	19 (16.4)	32 (17.0)	8 (11.1)	40 (15.4)
Oedema [6]	13 (11.2)	23 (12.2)	11 (15.3)	34 (13.1)
Dysgeusia	12 (10.3)	22 (11.7)	8 (11.1)	30 (11.5)
Hyponatraemia	12 (10.3)	22 (11.7)	1 (1.4)	23 (8.8)
Abdominal pain [8]	13 (11.2)	21 (11.2)	6 (8.3)	27 (10.4)
Weight decreased	10 (8.6)	21 (11.2)	5 (6.9)	26 (10.0)
Rash [12]	12 (10.3)	20 (10.6)	8 (11.1)	28 (10.8)
Musculoskeletal Pain [3]	12 (10.3)	19 (10.1)	7 (9.7)	26 (10.0)
Dizziness [7]	12 (10.3)	18 (9.6)	4 (5.6)	22 (8.5)
Skin discolouration [14]	10 (8.6)	18 (9.6)	4 (5.6)	22 (8.5)
Dehydration	6 (5.2)	13 (6.9)	3 (4.2)	16 (6.2)
Blood creatine phosphokinase increased	8 (6.9)	12 (6.4)	1 (1.4)	13 (5.0)
Hypokalaemia	3 (2.6)	12 (6.4)	1 (1.4)	13 (5.0)
Pneumonitis [18]	6 (5.2)	11 (5.9)	0	11 (4.2)
Decreased Ejection Fraction [16]	6 (5.2)	10 (5.3)	2 (2.8)	12 (4.6)

Note: Adverse events were coded using MedDRA version 21.0. For each preferred term, patients are included only once, even if they experienced multiple events in that preferred term.
Source: Listing 16.2.7.2, Dataset: ADAE, Program: t_q163_2.sas, Output: t_q163_2.rtf, Generated on: 2022-12-12T14:54, Datacutoff: 2021-10-15
Source: t_q163_2
[1] Includes nausea, vomiting, retching; [2] Includes fatigue, asthenia; [3] Includes arthralgia, back pain, pain in extremity, muscle spasms, myalgia, musculoskeletal chest pain, musculoskeletal pain, neck pain; [4] Includes ALT increased, AST increased, blook alkaline phosphatase increased, blood bilirubin increased, bilirubin conjugated increased, gamma-glutamyltransferase increased, hepatic enzyme increased, liver function test increased, mixed liver injury, ammonia increased, jaundice cholestatic; [5] Includes blood creatinine increased, acute kidney injury, blood urea increased, chronic kidney disease, renal failure; [6] Includes oedema peripheral, face oedema, peripheral swelling, localised oedema, oedema, oedema genital, periorbital oedema; [7] Includes dizziness, vertigo, dizziness postural, vestibular disorder; [8] Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort; [9] Includes amylase increased, lipase increased, pancreatitis, amylase; [11] Includes electrocardiogram QT prolonged, electrocardiogram abnormal; [12] Includes rash, rash maculo-papular, rash macular, dermatitis, dermatitis acneiform, eczema, rash pruritic, dermatitis contact, stasis dermatitis; [14] Includes skin hyperpigmentation, skin discolouration, pigmentation disorder; [16] Includes ejection fraction decreased, cardiac failure, cardiac failure congestive, cardiomyopathy; [18] Includes pneumonitis, interstitial lung disease.

High-grade (≥G3) AEs:

Table 52: Grade 3 or higher adverse events reported in ≥2% NSCLC patients

	MRTX849 Monotherapy 600 mg BID			
Group/Preferred Term [n (%)]	**Cohort A (N=116)**	**NSCLC (N=188)**	**Other (N=72)**	**Total (N=260)**
Patients with at least 1 CTCAE Grade 3 or Greater TEAE	95 (81.9)	153 (81.4)	37 (51.4)	190 (73.1)
Lung Infection [10]	23 (19.8)	28 (14.9)	0	28 (10.8)
Anaemia	17 (14.7)	22 (11.7)	7 (9.7)	29 (11.2)
Dyspnoea	12 (10.3)	22 (11.7)	1 (1.4)	23 (8.8)
Fatigue [2]	8 (6.9)	18 (9.6)	5 (6.9)	23 (8.8)
Liver Disorder [4]	12 (10.3)	17 (9.0)	4 (5.6)	21 (8.1)
Hypoxia	9 (7.8)	14 (7.4)	2 (2.8)	16 (6.2)
Pancreatic Enzyme Increase [9]	9 (7.8)	14 (7.4)	2 (2.8)	16 (6.2)
Hyponatraemia	10 (8.6)	13 (6.9)	3 (4.2)	16 (6.2)
Malignant neoplasm progression	8 (6.9)	13 (6.9)	3 (4.2)	16 (6.2)
Lymphocyte count decreased	7 (6.0)	11 (5.9)	2 (2.8)	13 (5.0)
Musculoskeletal Pain [3]	8 (6.9)	11 (5.9)	2 (2.8)	13 (5.0)
QT Prolongation [11]	7 (6.0)	10 (5.3)	3 (4.2)	13 (5.0)
Hypotension	5 (4.3)	9 (4.8)	0	9 (3.5)
Nausea [1]	5 (4.3)	9 (4.8)	2 (2.8)	11 (4.2)
Pericardial effusion	3 (2.6)	9 (4.8)	1 (1.4)	10 (3.8)
Renal Insufficiency [5]	8 (6.9)	9 (4.8)	3 (4.2)	12 (4.6)
Respiratory failure	5 (4.3)	9 (4.8)	0	9 (3.5)
Diarrhoea	1 (<1)	8 (4.3)	4 (5.6)	12 (4.6)
Sepsis	6 (5.2)	8 (4.3)	1 (1.4)	9 (3.5)
Altered Mental Status [15]	5 (4.3)	7 (3.7)	0	7 (2.7)
Decreased Ejection Fraction [16]	5 (4.3)	7 (3.7)	0	7 (2.7)
Thrombosis [17]	6 (5.2)	7 (3.7)	2 (2.8)	9 (3.5)
Decreased appetite	5 (4.3)	6 (3.2)	0	6 (2.3)
Dehydration	3 (2.6)	6 (3.2)	0	6 (2.3)
Muscular weakness	5 (4.3)	6 (3.2)	0	6 (2.3)
Pleural effusion	5 (4.3)	5 (2.7)	0	5 (1.9)
Pneumonitis [18]	3 (2.6)	5 (2.7)	0	5 (1.9)
Atrial fibrillation	2 (1.7)	4 (2.1)	1 (1.4)	5 (1.9)
Hypokalaemia	3 (2.6)	4 (2.1)	3 (4.2)	7 (2.7)
Neutrophil count decreased	3 (2.6)	4 (2.1)	2 (2.8)	6 (2.3)

Note: Adverse events were coded using MedDRA version 21.0. For each preferred term, patients are included only once, even if they experienced multiple events in that preferred term.
Source: Listing 16.2.7.2, Dataset: ADAE, Program: t_q163_3.sas, Output: t_q163_3.rtf, Generated on: 2022-12-12T14:54, Datacutoff: 2021-10-15
Source: t_q163_3

[1] Includes nausea, vomiting, retching; [2] Includes fatigue, asthenia; [3] Includes arthralgia, back pain, pain in extremity, muscle spasms, myalgia, musculoskeletal chest pain, musculoskeletal pain, neck pain; [4] Includes ALT increased, AST increased, blook alkaline phosphatase increased, blood bilirubin increased, bilirubin conjugated increased, gamma-glutamyltransferase increased, hepatic enzyme increased, liver function test increased, mixed liver injury, ammonia increased, jaundice cholestatic; [5] Includes blood creatinine increased, acute kidney injury, blood urea increased, chronic kidney disease, renal failure; [9] Includes amylase increased, lipase increased, pancreatitis, amylase; [10] Includes pneumonia, lung infection, pneumonia streptococcal, respiratory tract infection; [11] Includes electrocardiogram QT prolonged, electrocardiogram abnormal; [15] Includes confusional state, mental status changes; [16] Includes ejection fraction decreased, cardiac failure, cardiac failure congestive, cardiomyopathy; [17] Includes embolism, deep vein thrombosis, pulmonary embolism, jugular vein thrombosis; [18] Includes pneumonitis, interstitial lung disease.

Table 53: Grade 3 or higher treatment-related adverse events reported in ≥2% NSCLC patients

	MRTX849 Monotherapy 600 mg BID			
Group/Preferred Term [n (%)]	**Cohort A (N=116)**	**NSCLC (N=188)**	**Other (N=72)**	**Total (N=260)**
Patients with at least 1 CTCAE Severity Grade 3 or Greater MRTX849-related TEAE	52 (44.8)	88 (46.8)	20 (27.8)	108 (41.5)
Liver Disorder [4]	10 (8.6)	14 (7.4)	3 (4.2)	17 (6.5)
Fatigue [2]	5 (4.3)	13 (6.9)	4 (5.6)	17 (6.5)
Pancreatic Enzyme Increase [9]	7 (6.0)	11 (5.9)	0	11 (4.2)
Nausea [1]	5 (4.3)	8 (4.3)	1 (1.4)	9 (3.5)
QT Prolongation [11]	5 (4.3)	8 (4.3)	3 (4.2)	11 (4.2)
Anaemia	6 (5.2)	7 (3.7)	4 (5.6)	11 (4.2)
Diarrhoea	1 (<1)	7 (3.7)	3 (4.2)	10 (3.8)
Hyponatraemia	5 (4.3)	7 (3.7)	0	7 (2.7)
Decreased Ejection Fraction [16]	5 (4.3)	6 (3.2)	0	6 (2.3)
Decreased appetite	4 (3.4)	5 (2.7)	0	5 (1.9)
Lymphocyte count decreased	2 (1.7)	4 (2.1)	0	4 (1.5)

Note: Adverse events were coded using MedDRA version 21.0. For each preferred term, patients are included only once, even if they experienced multiple events in that preferred term.
Source: Listing 16.2.7.2, Dataset: ADAE, Program: t_q163_4.sas, Output: t_q163_4.rtf, Generated on: 2022-12-12T14:55, Datacutoff: 2021-10-15
Source: t_q163_4
[1] Includes nausea, vomiting, retching; [2] Includes fatigue, asthenia; [4] Includes ALT increased, AST increased, blook alkaline phosphatase increased, blood bilirubin increased, bilirubin conjugated increased, gamma-glutamyltransferase increased, hepatic enzyme increased, liver function test increased, mixed liver injury, ammonia increased, jaundice cholestatic; [9] Includes amylase increased, lipase increased, pancreatitis, amylase; [11] Includes electrocardiogram QT prolonged, electrocardiogram abnormal; [16] Includes ejection fraction decreased, cardiac failure, cardiac failure congestive, cardiomyopathy.

An overview AEs table with standard categories: any-grade, high-grade (≥G3), SAEs, AEs leading to death, AEs leading to dose reductions/interruptions, AEs leading to discontinuations has been provided for the 4 safety datasets from KRYSTAL-1, which also pools gastrointestinal side events nausea/vomiting/diarrhoea (and all related PTs) and hepatotoxicity (and all related PTs, e.g., increased AST, increased ALT, increased alkaline phosphatase, increased bilirubin, hepatitis, drug-induced liver injury, hepatocellular injury, hepatitis acute, hepatitis toxic, hepatotoxicity, liver disorder, hepatic failure, hepatic steatosis, hepatic lesion).

2.6.8.3. Serious adverse event/deaths/other significant events

SAEs:

Table 54: Serious adverse events reported in ≥2% of NSCLC patients

	MRTX849 Monotherapy 600 mg BID			
Group/Preferred Term [n (%)]	**Cohort A (N=116)**	**NSCLC (N=188)**	**Other (N=72)**	**Total (N=260)**
Patients with at Least 1 SAE	72 (62.1)	111 (59.0)	22 (30.6)	133 (51.2)
Lung Infection [10]	21 (18.1)	26 (13.8)	0	26 (10.0)
Dyspnoea	11 (9.5)	16 (8.5)	0	16 (6.2)
Malignant neoplasm progression	8 (6.9)	13 (6.9)	3 (4.2)	16 (6.2)
Renal Insufficiency [5]	10 (8.6)	12 (6.4)	1 (1.4)	13 (5.0)
Decreased Ejection Fraction [16]	7 (6.0)	9 (4.8)	1 (1.4)	10 (3.8)
Pericardial effusion	2 (1.7)	7 (3.7)	1 (1.4)	8 (3.1)
Respiratory failure	4 (3.4)	7 (3.7)	0	7 (2.7)
Sepsis	6 (5.2)	7 (3.7)	1 (1.4)	8 (3.1)
Thrombosis [17]	5 (4.3)	7 (3.7)	1 (1.4)	8 (3.1)
Altered Mental Status [15]	4 (3.4)	6 (3.2)	0	6 (2.3)
Dehydration	3 (2.6)	6 (3.2)	0	6 (2.3)
Hyponatraemia	4 (3.4)	6 (3.2)	1 (1.4)	7 (2.7)
Hypotension	4 (3.4)	6 (3.2)	0	6 (2.3)
Hypoxia	5 (4.3)	6 (3.2)	0	6 (2.3)
Pleural effusion	6 (5.2)	6 (3.2)	1 (1.4)	7 (2.7)
Muscular weakness	4 (3.4)	5 (2.7)	0	5 (1.9)
Nausea [1]	3 (2.6)	5 (2.7)	2 (2.8)	7 (2.7)
Pyrexia	4 (3.4)	5 (2.7)	1 (1.4)	6 (2.3)
Anaemia	4 (3.4)	4 (2.1)	1 (1.4)	5 (1.9)
Atrial fibrillation	2 (1.7)	4 (2.1)	1 (1.4)	5 (1.9)
Diarrhoea	3 (2.6)	4 (2.1)	0	4 (1.5)
Myocardial infarction	2 (1.7)	4 (2.1)	0	4 (1.5)
Pneumonitis [18]	2 (1.7)	4 (2.1)	0	4 (1.5)

Note: Adverse events were coded using MedDRA version 21.0. For each preferred term, patients are included only once, even if they experienced multiple events in that preferred term.
Source: Listing 16.2.7.2, Dataset: ADAE, Program: t_q163_5.sas, Output: t_q163_5.rtf, Generated on: 2022-12-12T14:55, Datacutoff: 2021-10-15
Source: t_q163_5
[1] Includes nausea, vomiting, retching; [5] Includes blood creatinine increased, acute kidney injury, blood urea increased, chronic kidney disease, renal failure; [10] Includes pneumonia, lung infection, pneumonia streptococcal, respiratory tract infection; [15] Includes confusional state, mental status changes; [16] Includes ejection fraction decreased, cardiac failure, cardiac failure congestive, cardiomyopathy; [17] Includes embolism, deep vein thrombosis, pulmonary embolism, jugular vein thrombosis; [18] Includes pneumonitis, interstitial lung disease.

Table 55: Treatment-related serious adverse events

	MRTX849 Monotherapy 600 mg BID			
Group/Preferred Term [n (%)]	**Cohort A (N=116)**	**NSCLC (N=188)**	**Other (N=72)**	**Total (N=260)**
Patients with at Least 1 MRTX849-related SAE	20 (17.2)	37 (19.7)	6 (8.3)	43 (16.5)
Decreased Ejection Fraction [1]	5 (4.3)	6 (3.2)	1 (1.4)	7 (2.7)
Renal Insufficiency [2]	4 (3.4)	6 (3.2)	0	6 (2.3)
Diarrhoea	3 (2.6)	4 (2.1)	0	4 (1.5)
Hyponatraemia	3 (2.6)	4 (2.1)	0	4 (1.5)
Nausea [3]	2 (1.7)	4 (2.1)	1 (1.4)	5 (1.9)
Dehydration	1 (<1)	3 (1.6)	0	3 (1.2)
Hypotension	2 (1.7)	3 (1.6)	0	3 (1.2)
Muscular weakness	2 (1.7)	3 (1.6)	0	3 (1.2)
Pancreatic Enzyme Increase [4]	1 (<1)	3 (1.6)	0	3 (1.2)
Anaemia	2 (1.7)	2 (1.1)	1 (1.4)	3 (1.2)
Liver Disorder [5]	2 (1.7)	2 (1.1)	0	2 (<1)
Pneumonitis [6]	1 (<1)	2 (1.1)	0	2 (<1)
Pyrexia	1 (<1)	2 (1.1)	0	2 (<1)
QT Prolongation [7]	1 (<1)	2 (1.1)	0	2 (<1)
Rash [8]	0	2 (1.1)	0	2 (<1)
Acute respiratory failure	0	1 (<1)	0	1 (<1)
Aphasia	1 (<1)	1 (<1)	0	1 (<1)
Atrial fibrillation	0	1 (<1)	1 (1.4)	2 (<1)
Dizziness [9]	0	1 (<1)	2 (2.8)	3 (1.2)
Drug hypersensitivity	1 (<1)	1 (<1)	0	1 (<1)
Dyspnoea	0	1 (<1)	0	1 (<1)
Encephalitis	1 (<1)	1 (<1)	0	1 (<1)
Fatigue [10]	0	1 (<1)	0	1 (<1)
Febrile neutropenia	1 (<1)	1 (<1)	0	1 (<1)
Hyperglycaemia	0	1 (<1)	0	1 (<1)
Lung Infection [11]	1 (<1)	1 (<1)	0	1 (<1)
Myocardial infarction	0	1 (<1)	0	1 (<1)
Oesophagitis	0	1 (<1)	0	1 (<1)
Pericardial effusion	0	1 (<1)	1 (1.4)	2 (<1)
Pulmonary haemorrhage	1 (<1)	1 (<1)	0	1 (<1)
Pulmonary oedema	0	1 (<1)	0	1 (<1)
Rhabdomyolysis	0	1 (<1)	0	1 (<1)
Seizure	0	1 (<1)	0	1 (<1)
Sepsis	0	1 (<1)	0	1 (<1)
Splenomegaly	1 (<1)	1 (<1)	0	1 (<1)
Thrombosis [12]	0	1 (<1)	0	1 (<1)
Ventricular fibrillation	0	1 (<1)	0	1 (<1)
Ventricular tachycardia	0	1 (<1)	0	1 (<1)
White blood cell count decreased	1 (<1)	1 (<1)	0	1 (<1)
Dysarthria	0	0	1 (1.4)	1 (<1)

Note: Adverse events were coded using MedDRA version 21.0. For each preferred term, patients are included only once, even if they experienced multiple events in that preferred term.
Source: Listing 16.2.7.2, Dataset: ADAE, Program: t_q163_6.sas, Output: t_q163_6.rtf, Generated on: 2022-12-12T14:55, Datacutoff: 2021-10-15
Source: t_q163_6
[1] Includes ejection fraction decreased, cardiac failure, cardiac failure congestive, cardiomyopathy; [2] Includes blood creatinine increased, acute kidney injury, blood urea increased, chronic kidney disease, renal failure; [3] Includes nausea, vomiting, retching; [4] Includes amylase increased, lipase increased, pancreatitis, amylase; [5] Includes ALT increased, AST increased, blook alkaline phosphatase increased, blood bilirubin increased, bilirubin conjugated increased, gamma-glutamyltransferase increased, hepatic enzyme increased, liver function test increased, mixed liver injury, ammonia increased, jaundice cholestatic; [6] Includes pneumonitis, interstitial lung disease; [7] Includes electrocardiogram QT prolonged, electrocardiogram abnormal; [8] Includes rash, rash maculo-papular, rash macular, dermatitis, dermatitis acneiform, eczema, rash pruritic, dermatitis contact, stasis dermatitis; [9] Includes dizziness, vertigo, dizziness postural, vestibular disorder; [10] Includes fatigue, asthenia; [11] Includes pneumonia, lung infection, pneumonia streptococcal, respiratory tract infection; [12] Includes embolism, deep vein thrombosis, pulmonary embolism, jugular vein thrombosis.

The majority of SAEs were attributed to progressive disease.

AEs with outcome of death:

Table 56: Adverse events with outcome of death within 28 days of last dose

	MRTX849 Monotherapy 600 mg BID			
Group/Preferred Term [n (%)]	**Cohort A (N=116)**	**NSCLC (N=188)**	**Other (N=72)**	**Total (N=260)**
Patients with at least 1 TEAE with Outcome of Death	20 (17.2)	33 (17.6)	5 (6.9)	38 (14.6)
Malignant neoplasm progression	8 (6.9)	12 (6.4)	3 (4.2)	15 (5.8)
Respiratory failure	3 (2.6)	6 (3.2)	0	6 (2.3)
Acute respiratory failure	1 (<1)	2 (1.1)	0	2 (<1)
Lung Infection [1]	2 (1.7)	2 (1.1)	0	2 (<1)
Altered Mental Status [2]	1 (<1)	1 (<1)	0	1 (<1)
Cerebrovascular accident	1 (<1)	1 (<1)	0	1 (<1)
Chronic obstructive pulmonary disease	0	1 (<1)	0	1 (<1)
Chronic respiratory failure	0	1 (<1)	0	1 (<1)
Death	1 (<1)	1 (<1)	0	1 (<1)
Decreased Ejection Fraction [3]	1 (<1)	1 (<1)	0	1 (<1)
Dyspnoea	0	1 (<1)	0	1 (<1)
Enterocolitis infectious	0	1 (<1)	0	1 (<1)
Pneumonitis [4]	0	1 (<1)	0	1 (<1)
Pulmonary haemorrhage	1 (<1)	1 (<1)	0	1 (<1)
Thrombosis [5]	1 (<1)	1 (<1)	0	1 (<1)
Cardiac arrest	0	0	1 (1.4)	1 (<1)
Cardio-respiratory arrest	0	0	1 (1.4)	1 (<1)

Note: Adverse events were coded using MedDRA version 21.0. For each preferred term, patients are included only once, even if they experienced multiple events in that preferred term.
Source: Listing 16.2.7.2, Dataset: ADAE, Program: t_q163_7.sas, Output: t_q163_7.rtf, Generated on: 2022-12-12T14:56, Datacutoff: 2021-10-15
Source: t_q163_7
[1] Includes pneumonia, lung infection, pneumonia streptococcal, respiratory tract infection; [2] Includes confusional state, mental status changes; [3] Includes ejection fraction decreased, cardiac failure, cardiac failure congestive, cardiomyopathy; [4] Includes pneumonitis, interstitial lung disease; [5] Includes embolism, deep vein thrombosis, pulmonary embolism, jugular vein thrombosis.

Table 57: Treatment-related adverse events with outcome of death within 28 days of last dose

	MRTX849 Monotherapy 600 mg BID			
Group/Preferred Term [n (%)]	**Cohort A (N=116)**	**NSCLC (N=188)**	**Other (N=72)**	**Total (N=260)**
Patients with at least 1 MRTX849-related TEAE with Outcome of Death	2 (1.7)	4 (2.1)	0	4 (1.5)
Acute respiratory failure	0	1 (<1)	0	1 (<1)
Decreased Ejection Fraction [1]	1 (<1)	1 (<1)	0	1 (<1)
Pneumonitis [2]	0	1 (<1)	0	1 (<1)
Pulmonary haemorrhage	1 (<1)	1 (<1)	0	1 (<1)

Note: Adverse events were coded using MedDRA version 21.0. For each preferred term, patients are included only once, even if they experienced multiple events in that preferred term.
Source: Listing 16.2.7.2, Dataset: ADAE, Program: t_q163_8.sas, Output: t_q163_8.rtf, Generated on: 2022-12-12T14:56, Datacutoff: 2021-10-15
Source: t_q163_8
[1] Includes ejection fraction decreased, cardiac failure, cardiac failure congestive, cardiomyopathy; [2] Includes pneumonitis, interstitial lung disease.

Adverse drug reactions (ADRs):

The applicant reviewed all safety data through the data cutoff date (15 Oct 2021) in order to determine which AEs warrant inclusion in labeling as adverse drug reactions (ADRs). The ISS pooled database was the primary safety database used for the determination of ADRs. The frequencies of the ADRs used for the label are based on the pivotal study MRTX849-001 Cohort A.

To provide a robust dataset at the intended dose and to maximize the potential for identifying AEs that were related to MRTX849 use, ADRs were evaluated in all patients with NSCLC who were treated with MRTX849 monotherapy at a starting dose of 600 mg twice daily (ie, the All NSCLC 600 mg Twice Daily group; 188 patients).

Based on this review, ADRs for MRTX849 were initially selected by evaluating AEs that occurred with a > 10% overall incidence rate, Grade ≥ 3 AEs with a ≥ 2% overall incidence rate, or SAEs with ≥ 2% overall incidence rate. An assessment was also performed on AEs not meeting any of these thresholds that could represent potentially serious toxicities (eg, cardiac and neurological events), or those commonly associated with drug use (eg, rash). Additional considerations such as temporal association, biological plausibility, and medical judgment were then applied for a probable causal drug event association to determine the final ADRs.

Table 58: Adverse drug reactions in patients who received adagrasib 600 mg BID in KRYSTAL 1

	Cohort A (N=116)		MRTX849 600mg BID NSCLC (N=188)	
Adverse Reaction	**All Grades n(%)**	**Grades 3/4 n(%)**	**All Grades n(%)**	**Grades 3/4 n(%)**
Patients experienced any adverse reaction	115 (99.1)	58 (50.0)	186 (98.9)	94 (50.0)
Diarrhoea	82 (70.7)	1 (0.9)	133 (70.7)	8 (4.3)
Nausea	81 (69.8)	5 (4.3)	132 (70.2)	9 (4.8)
Fatigue (group)	69 (59.5)	8 (6.9)	108 (57.4)	18 (9.6)
Vomiting	66 (56.9)	1 (0.9)	108 (57.4)	4 (2.1)
Hepatotoxicity (group)	43 (37.1)	12 (10.3)	81 (43.1)	17 (9.0)
Decreased appetite	37 (31.9)	5 (4.3)	66 (35.1)	6 (3.2)
Anaemia	42 (36.2)	17 (14.7)	65 (34.6)	22 (11.7)
Blood creatinine increased	40 (34.5)	1 (0.9)	64 (34.0)	2 (1.1)
Alanine aminotransferase increased	33 (28.4)	6 (5.2)	61 (32.4)	10 (5.3)
Aspartate aminotransferase increased	31 (26.7)	6 (5.2)	61 (32.4)	10 (5.3)
Oedema peripheral	33 (28.4)	0	55 (29.3)	1 (0.5)
Dizziness (group)	25 (21.6)	1 (0.9)	44 (23.4)	3 (1.6)
Hyponatraemia	27 (23.3)	10 (8.6)	43 (22.9)	13 (6.9)
Blood alkaline phosphatase increased	23 (19.8)	5 (4.3)	41 (21.8)	7 (3.7)
Electrocardiogram QT prolonged	23 (19.8)	7 (6.0)	36 (19.1)	10 (5.3)
Amylase increased	21 (18.1)	1 (0.9)	30 (16.0)	2 (1.1)
Lipase increased	18 (15.5)	9 (7.8)	30 (16.0)	13 (6.9)
Lymphocyte count decreased	9 (7.8)	7 (6.0)	17 (9.0)	11 (5.9)

Note: Adverse events were coded using MedDRA version 21.0. NCI CTCAE grading v5.0 applied.
Fatigue (group) includes preferred terms: fatigue and asthenia. Dizziness (group) includes preferred terms: dizziness and vertigo.
Hepatotoxicity (group) includes preferred terms: 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.

Table 59: Onset and outcome of adverse drug reactions in Cohort A (Part 1)

	Diarrhoea	Nausea	Vomiting	Decreased Appetite	AST Increased	ALT Increased	ALP Increased	Amylase Increased	Lipase Increased
Time (days) to First Onset									
n	82	81	66	37	31	33	23	21	18
Median	8	7	8	15	22	22	22	36	22
Min, Max	1, 365	1, 130	1, 302	1, 410	1, 65	1, 64	1, 306	1, 378	1, 378
Duration (days) of First Onset									
KM Median (95% CI)	20.0 (12.00, 43.00)	56.0 (29.00, 141.00)	5.5 (3.00, 13.00)	33.0 (15.00, 92.00)	14.0 (8.00, 21.00)	17.0 (12.00, 22.00)	14.0 (8.00, 22.00)	20.0 (8.00, 42.00)	14.0 (8.00, 21.00)
First Onset, n (%)									
Grade 1	70 (60.3)	60 (51.7)	49 (42.2)	19 (16.4)	24 (20.7)	19 (16.4)	15 (12.9)	15 (12.9)	4 (3.4)
Ongoing	22 (19.0)	20 (17.2)	5 (4.3)	6 (5.2)	3 (2.6)	5 (4.3)	2 (1.7)	3 (2.6)	1 (0.9)
Resolved and no recurrence	27 (23.3)	20 (17.2)	25 (21.6)	9 (7.8)	10 (8.6)	8 (6.9)	7 (6.0)	7 (6.0)	1 (0.9)
Recurrence with grade 1	15 (12.9)	8 (6.9)	17 (14.7)	2 (1.7)	3 (2.6)	3 (2.6)	1 (0.9)	2 (1.7)	1 (0.9)
Recurrence with grade 2	5 (4.3)	10 (8.6)	2 (1.7)	2 (1.7)	5 (4.3)	2 (1.7)	2 (1.7)	3 (2.6)	1 (0.9)
Recurrence with grade 3	1 (0.9)	2 (1.7)	0	0	3 (2.6)	1 (0.9)	3 (2.6)	0	0
Grade 2	12 (10.3)	20 (17.2)	17 (14.7)	17 (14.7)	5 (4.3)	12 (10.3)	7 (6.0)	5 (4.3)	8 (6.9)
Ongoing	0	7 (6.0)	3 (2.6)	5 (4.3)	0	0	3 (2.6)	0	1 (0.9)
Resolved and no recurrence	1 (0.9)	5 (4.3)	10 (8.6)	4 (3.4)	2 (1.7)	5 (4.3)	2 (1.7)	1 (0.9)	1 (0.9)
Recurrence with grade 1	8 (6.9)	3 (2.6)	3 (2.6)	4 (3.4)	1 (0.9)	4 (3.4)	0	2 (1.7)	3 (2.6)
Recurrence with grade 2	3 (2.6)	3 (2.6)	0	0	1 (0.9)	0	1 (0.9)	2 (1.7)	0
Recurrence with grade 3	0	2 (1.7)	1 (0.9)	4 (3.4)	1 (0.9)	3 (2.6)	1 (0.9)	0	3 (2.6)
Grade 3	0	1 (0.9)	0	1 (0.9)	2 (1.7)	1 (0.9)	1 (0.9)	1 (0.9)	6 (5.2)
Ongoing	0	0	0	0	0	0	0	0	0
Resolved and no recurrence	0	0	0	1 (0.9)	1 (0.9)	0	0	0	1 (0.9)
Recurrence with grade 1	0	0	0	0	0	1 (0.9)	1 (0.9)	0	0
Recurrence with grade 2	0	1 (0.9)	0	0	1 (0.9)	0	0	1 (0.9)	3 (2.6)
Recurrence with grade 3	0	0	0	0	0	0	0	0	2 (1.7)
Grade 4	0	0	0	0	0	1 (0.9)	0	0	0
Ongoing	0	0	0	0	0	1 (0.9)	0	0	0

Table 60: Onset and outcome of adverse drug reactions in Cohort A (Part 2)

	Fatigue	Anaemia	Oedema Peripheral	Dizziness	QT Prolongation	Blood creatinine increased	Hyponatraemia	Lymphocyte Count Decreased
Time (days) to First Onset								
n	69	42	33	24	23	40	27	9
Median	15	22	29	21.5	8	12	22	15
Min, Max	1, 379	1, 463	1, 402	1, 213	1, 85	1, 467	1, 377	1, 62
Duration (days) of First Onset								
KM Median (95% CI)	91.0 (51.00, 171.00)	22.0 (14.00, 42.00)	71.0 (29.00, NA)	29.0 (8.00, 82.00)	28.0 (14.00, 64.00)	22.0 (15.00, 39.00)	14.0 (4.00, 18.00)	23.0 (2.00, 64.00)
First Onset, n (%)								
Grade 1	36 (31.0)	16 (13.8)	28 (24.1)	21 (18.1)	13 (11.2)	31 (26.7)	14 (12.1)	0
Ongoing	17 (14.7)	5 (4.3)	12 (10.3)	5 (4.3)	4 (3.4)	10 (8.6)	3 (2.6)	0
Resolved and no recurrence	5 (4.3)	5 (4.3)	9 (7.8)	14 (12.1)	6 (5.2)	8 (6.9)	7 (6.0)	0
Recurrence with grade 1	4 (3.4)	1 (0.9)	6 (5.2)	0	1 (0.9)	7 (6.0)	2 (1.7)	0
Recurrence with grade 2	8 (6.9)	4 (3.4)	1 (0.9)	1 (0.9)	1 (0.9)	5 (4.3)	2 (1.7)	0
Recurrence with grade 3	2 (1.7)	1 (0.9)	0	1 (0.9)	1 (0.9)	1 (0.9)	0	0
Grade 2	28 (24.1)	17 (14.7)	5 (4.3)	3 (2.6)	4 (3.4)	9 (7.8)	5 (4.3)	4 (3.4)
Ongoing	11 (9.5)	5 (4.3)	2 (1.7)	1 (0.9)	1 (0.9)	0	0	0
Resolved and no recurrence	5 (4.3)	5 (4.3)	2 (1.7)	2 (1.7)	0	1 (0.9)	1 (0.9)	2 (1.7)
Recurrence with grade 1	5 (4.3)	0	1 (0.9)	0	3 (2.6)	3 (2.6)	1 (0.9)	0
Recurrence with grade 2	6 (5.2)	0	0	0	0	5 (4.3)	1 (0.9)	0
Recurrence with grade 3	1 (0.9)	7 (6.0)	0	0	0	0	2 (1.7)	2 (1.7)
Grade 3	5 (4.3)	9 (7.8)	0	0	6 (5.2)	0	8 (6.9)	5 (4.3)
Ongoing	2 (1.7)	1 (0.9)	0	0	0	0	1 (0.9)	1 (0.9)
Resolved and no recurrence	0	2 (1.7)	0	0	4 (3.4)	0	3 (2.6)	0
Recurrence with grade 1	1 (0.9)	0	0	0	2 (1.7)	0	0	0
Recurrence with grade 2	1 (0.9)	2 (1.7)	0	0	0	0	3 (2.6)	1 (0.9)
Recurrence with grade 3	1 (0.9)	4 (3.4)	0	0	0	0	1 (0.9)	2 (1.7)
Recurrence with grade 4	0	0	0	0	0	0	0	1 (0.9)

Adverse events of special interest (AESIs):

Nausea/Vomiting/retching

In the all 600 mg BID group (n=260), nausea was reported in 68.1% and vomiting in 57.7% of patients. In the All NSCLC 600 mg BID group (n=188), treatment-emergent nausea (including nausea, vomiting, retching) from any cause was reported in 80.3% patients. Most events were reported as Grade 1 or 2; Grade ≥3 nausea (nausea, vomiting, retching) was reported for 4.8% of patients. During Investigator calls conducted during the Phase 1/1b portion of the study, Investigators stated that nausea typically occurred soon after dosing (approximately 30 minutes to 1 hour), suggesting a local effect. Antiemetics were prescribed for 86.7% patients as either prophylaxis or treatment. In addition, for patients with vomiting, more frequent monitoring of electrolytes that include potassium and magnesium should be considered as well as oral and/or IV supplementation for levels below the lower limit of normal.

Diarrhea

Treatment-emergent diarrhoea from any cause was reported in 71.5% of patients in the all 600 mg BID group (n=260), in 70.7% of patients in the All NSCLC 600 mg BID group (n=188) and 70.7% of patients in Cohort A (n=116); most events were reported as Grade 1 or 2, with Grade ≥ 3 diarrhoea reported for 4.3% of patients in the All NSCLC 600 mg BID group and < 1% in Cohort A. Antidiarrheals were prescribed for 52.7% patients in the All NSCLC 600 mg BID group, and 49.1% patients in Cohort A as either prophylaxis or treatment.

Hepatotoxicity

In the All NSCLC 600 mg BID group, 95.1% had normal baseline values for alanine aminotransferase, and 4.9% had values up to 3 × ULN. The maximum on-study values were normal in 48.1% patients with elevations of Grade 1 for 38.3%, Grade 2 for 8.2%, and Grade 3 for 5.5%.

For the same group, 89.6% had normal baseline values for aspartate aminotransferase, and 9.8% had values up to 3 × ULN. The maximum on-study values were normal in 36.6% of patients, with elevations of Grade 1 for 48.1%, Grade 2 for 9.3%, and Grade 3 for 6.0%.

Alkaline phosphatase was normal in 77.0% patients at baseline and elevated up to 2.5 × ULN for 20.8% patients, > 2.5 to 5 × ULN for 1.6% patients, and > 5 to 20 × ULN for < 1% patients. The maximum on-study values were normal in 39.3% patients, elevated up to 2.5 × ULN for 44.3%, > 2.5 to 5.0 × ULN for 11.5%, > 5.0 to 20.0 × ULN for 4.4%, and > 20 × ULN for < 1%.

A medical search for liver disorders was performed combining 4 SMQ searches that included cholestasis and jaundice of hepatic origin SMQ (narrow search), hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ (narrow search), hepatitis, non-infectious SMQ (narrow search), and liver related investigations, signs and symptoms SMQ (broad search). In the All NSCLC 600 mg BID group, 47.9% patients had at least one TEAE in this search, which included aspartate aminotransferase increased and alanine aminotransferase increased (each 32.4%), blood alkaline phosphatase increased (21.8%), hypoalbuminemia (17.6%), blood bilirubin increased (3.7%), and bilirubin conjugated increased, gamma-glutamyl transferase increased, hepatic enzyme increased, liver function test increased, and mixed liver injury (each < 1%). Maximum severity was Grade 4 for 1 patient with alanine aminotransferase increased, and Grade 3 for 9.6% patients, which included aspartate aminotransferase increased (5.3%), alanine aminotransferase increased (4.8%), blood alkaline phosphatase increased (3.7%), blood bilirubin increased (1.6%), hypoalbuminemia (1.1%), and gamma-glutamyl transferase increased and mixed liver injury (each < 1%).

Management for Grade 1/2 events was left at the discretion of the Investigator, which included continuation of treatment with close monitoring; management of Grade 3 or 4 events included evaluation of potential etiologic factors as well as dose interruption and reduction.

Hy's law: Five patients (3 from Cohort A and 2 from Cohort B) had total bilirubin >2 × ULN and aspartate aminotransferase/alanine aminotransferase >3 × ULN. From these, 4 patients also presented significant increases in alkaline phosphatase, and therefore do not meet criteria for Hy's law. One patient did meet the criteria for Hy's law, but in this case the liver injury was most likely due to new metastases/disease progression in the liver.

When pooled together in preferred terms, liver disorders (includes: ALT increased, AST increased, blook alkaline phosphatase increased, blood bilirubin increased, bilirubin conjugated increased, gamma-glutamyltransferase increased, hepatic enzyme increased, liver function test increased, mixed liver injury, ammonia increased, jaundice cholestatic) were observed in 43.1% of the NSCLC pool (n=188) and grade ≥3 was observed in 9%.

QT Prolongation

Table 61: QTcF Results by Maximum ICH E14 Category (Safety Population)

	MRTX849 Monotherapy				
	600 mg BID				
QTc Category ICH E14 Category [n (%)]	**Cohort A (N=116)**	**NSCLC (N=188)**	**Other (N=72)**	**Total (N=260)**	**Other Doses (N=5)**
Maximum On-treatment Value[1] (QTcF) (N1)	114	185	72	257	5
≤ 450 msec	48 (42.1)	86 (46.5)	35 (48.6)	121 (47.1)	2 (40.0)
> 450 to ≤ 480 msec	44 (38.6)	69 (37.3)	25 (34.7)	94 (36.6)	2 (40.0)
> 480 to ≤ 500 msec	12 (10.5)	17 (9.2)	8 (11.1)	25 (9.7)	0
> 500 msec	10 (8.8)	13 (7.0)	4 (5.6)	17 (6.6)	1 (20.0)
Maximum Change from Baseline[1] (QTcF)					
≤ 30 msec	42 (36.8)	79 (42.7)	25 (34.7)	104 (40.5)	1 (20.0)
> 30 to ≤ 60 msec	55 (48.2)	84 (45.4)	35 (48.6)	119 (46.3)	4 (80.0)
> 60 msec	17 (14.9)	22 (11.9)	12 (16.7)	34 (13.2)	0

Source: ISS MAA Table 14.3.6.2
BID = twice daily; ICH = International Council on Harmonisation; NSCLC = non-small cell lung cancer; QTcF = QT interval corrected using Fridericia's formula.
Six patients in cohort C who crossed over from MRTX849 monotherapy to MRTX849+cetuximab treatment are included in the MRTX849 Monotherapy 600 mg BID other group. Only the safety data occurring during the MRTX849 monotherapy period are included.
[1] Based on the highest observed on-treatment value (or highest value of on-treatment average of triplicate, where applicable) which was an increase from baseline or the greatest observed shift from baseline. Percentages are based on the number of patients with nonmissing results for each QTc category (N1).

In Study 849-001, electrocardiograms were collected in triplicate predose at baseline (on Cycle 1 Day 1, or where applicable, on PK Lead-In Period Day 1), 4 hours after the first dose; then predose and 4 hours postdose on Cycle 1 Day 8 and Cycle 2 Day 1; then predose on Day 1 of Cycles 3 and 5. Among the NSCLC patients treated with 600 mg twice daily with electrocardiograms, 173/185 (93.5%) had Grade 0 QTcF prolongation at baseline, while 12/185 (6.5%) had Grade 1 baseline QTcF prolongation. The mean changes from baseline are presented by timepoint in Table 62.

Table 62: Mean Change in QTcF from Baseline in Cohort A and the All NSCLC 600 mg Twice Daily Group

Timepoint	Mean Predose ΔQTcF in msec		Mean Postdose ΔQTcF in msec	
	Cohort A	All NSCLC 600 mg BID	Cohort A	All NSCLC 600 mg BID
Day 1 (Cycle 1 or PK Lead-In)	NA	NA	2.7	1.3
Cycle 1 Day 8	26.7	24.0	25.0	22.2
Cycle 2 Day 1	18.5	16.8	20.7	17.7
Cycle 3 Day 1	16.4	13.0	NA	NA
Cycle 5 Day 1	18.4	16.9	NA	NA

Source: ISS MAA Table 14.3.6.1

BID = twice daily; NA = not applicable; NSCLC = non-small cell lung cancer; PK = pharmacokinetic; ΔQTcF = change in QT corrected using Fridericia's formula.

The maximum QTcF on-study (among all time points including unscheduled assessments, using the mean of triplicate where available), met criteria thresholds for Grade 3 severity in 24/185 (13.0%) patients in the All NSCLC 600 mg BID group, and 18/114 (15.8%) patients in Cohort A. ICH thresholds included QTcF > 500 msec in 13/185 (7.0%) patients in the All NSCLC 600 mg BID group and 10/114 (8.8%) patients in Cohort A.

Increases from baseline in QTcF > 60 msec were observed in 22/185 (11.9%) patients in the All NSCLC 600 mg BID group, and 17/114 (14.9%) patients in Cohort A.

A medical search using the Torsade de pointes/QT prolongation SMQ (broad search) was performed, excluding preferred term of multiple organ dysfunction syndrome (this term was removed from the Torsade de pointes/QT prolongation SMQ in MedDRA version 23.0, but Study 849-001 used version 21.0). Among the All NSCLC 600 mg BID group, 20.2% had ≥ 1 TEAE in this search, which included electrocardiogram QT prolonged (19.1%), syncope (1.1%), and ventricular fibrillation and ventricular tachycardia (each < 1%). Severity of the AEs was assessed as Grade 3 for electrocardiogram QT prolonged in 5.9% patients, Grade 3 for syncope in < 1% patients, and Grade 4 for ventricular tachycardia and ventricular fibrillation in < 1% patients (reported in same patient).

The following table summarises time to the first TEAE of Grade 3 or higher electrocardiogram QT prolonged and the duration of Grade 3 or higher electrocardiogram QT prolonged in Cohort A and the All NSCLC 600 mg BID group. The median time to Grade 3 electrocardiogram prolonged was 8.0 days, and the maximum was 22 days (approximately Cycle 2 Day 1) for both Cohort A and the All NSCLC 600 mg Twice Daily group. Median durations of Grade 3 electrocardiogram prolonged events were 4 days (range: 2 to 23 days) for both Cohort A and the All NSCLC 600 mg Twice Daily group.

Table 63: Summary of ≥G3 ECG QT prolonged AEs in NSCLC patients

	Cohort A (N=116)	MRTX849 600 mg BID NSCLC (N=188)
Time to 1st Grade ≥3 Electrocardiogram QT prolonged (days)		
n	7	10
Mean (Std)	11.9 (7.63)	11.9 (7.46)
Median	8.0	8.0
Q1, Q3	8.0, 20.0	8.0, 20.0
Min, Max	1, 22	1, 22
Duration of Grade ≥3 Electrocardiogram QT prolonged (days)		
n	7	10
Mean (Std)	8.0 (8.41)	7.8 (7.27)
Median	4.0	4.0
Q1, Q3	3.0, 17.0	3.0, 12.0
Min, Max	2, 23	2, 23

Management of patients treated with adagrasib includes mitigating risk of Torsade de pointes, including limiting use in patients with other risk factors, avoiding concomitant use with drugs known to prolong QT, and supplementing potassium and magnesium if levels are low. Dose interruption and/or reduction should be included in the management of patients who develop QTc > 500 msec.

When pooled together in preferred terms, QT prolongation (includes: electrocardiogram QT prolonged, electrocardiogram abnormal) was observed in 19.1% og the NSCLC pool (n=188) and grade ≥3 was observed in 5.3%.

Cardiac Failure

LVEF was assessed in patients every other cycle using MUGA or ECHO. Maximum decrease in LVEF for the All NSCLC 600 mg BID group was 10 percentage points or more in 20.2%, including 18.6% patients whose LVEF remained at least 40% and 1.6% patients whose LVEF decreased to below 40%. Decrease by 20 percentage points or more was reported for 1.6% patients, including 1.1% patients whose LVEF decreased below 40%.

A narrow search SMQ for cardiac failure was conducted and showed that cardiac failure events were reported for 8.0% of the All NSCLC 600 mg BID group, and included ejection fraction decreased (4.8%), cardiac failure (3.2%), pulmonary edema (1.6%), and cardiac failure congestive (< 1%). AE severity was Grade 1/2 for 4.3%, Grade 3 for 3.2%, and Grade 5 for 1 patient (< 1%; cardiac failure).

Some patients with AEs in this group were admitted to the hospital with some components of nausea, vomiting, dehydration, and creatinine increased, with cardiac failure events diagnosed after a few days of hospital care. Decreases in scheduled LVEFs were not typical presenting manifestations. Management is supportive with permanent discontinuation recommended for symptomatic left ventricular systolic dysfunction or decreased in LVEF by 20 percentage points or more to an abnormal LVEF.

Renal toxicity

In the All NSCLC 600 mg BID group and with available laboratory data, the 92.9% patients who had normal baseline values for creatinine, included 34.4% patients with on-study values increased up to 1.5 × ULN and 13.1% with on-study values 1.5 to 3 × ULN ; the 6.6% who had increased baseline values for creatinine up to 1.5 × ULN included 3.3% patients with on-study values remaining increased up to 1.5 × ULN, 2.7% with on-study values 1.5 to 3 × ULN, and < 1% with normal on-study values. Mean and median creatinine values were 74.8 and 72.0 µmol/L, respectively, at baseline, and 96.8 and 90.2 µmol/L, respectively on Cycle 1 Day 8. Subsequently, the mean and median ranges were 92.5 to 111.1 µmol/L and 88.4 to 107.8 µmol/L, respectively, through Cycle 23, after which there were < 15 patients with reported values.

A broad search SMQ for acute renal failure was conducted and showed TEAEs were reported for 27.1% of the All NSCLC 600 mg BID group, and included blood creatinine increased (25.5%), acute kidney injury (2.1%), proteinuria (1.6%), and renal failure and blood urea increased (each < 1%). AE severity was Grade 1/2 for 25.5% and Grade 3 for 1.6%. There were no Grade 4 or 5 events.

In some cases, patients increased creatinine may have been associated with dehydration, and treatment with fluids may be considered, although the overall incidences of vomiting, diarrhea, and dehydration were similar among patients with and without increased creatinine and patients with or without acute kidney injury. Guidelines for management of increased creatinine in Study 849 001 included dose reduction for Grade 2 increases and dose interruption and reduction for Grade ≥ 3 events.

Renal toxicity was identified as an event of interest. Increased creatinine TEAEs were reported for 64 of 188 subjects (34.0%) with NSCLC (0% grade ≥ 3). A total of 14 subjects in the monotherapy any tumour/any dose population had acute kidney injury. Most of the 14 patients had an underlying condition that may have increased the risk of developing this event.

When pooled together in preferred terms, Renal Insufficiency (includes: blood creatinine increased, acute kidney injury, blood urea increased, chronic kidney disease, renal failure) was observed in 38.3% og the NSCLC pool (n=188) and grade ≥3 was observed in 4.8%.

Among patients with NSCLC initiating adagrasib at 600 mg twice daily, the mean and median creatinine values were 74.8 and 72.0 µmol/L, respectively, at baseline, and 96.8 and 90.2 µmol/L, respectively on Cycle 1 Day 8. Subsequently, the mean and median ranges were 92.5 to 111.1 µmol/L and 88.4 to 107.8 µmol/L, respectively, through Cycle 23, after which there were < 15 patients with reported values. Though increased from baseline, the posttreatment means and medians remained within the normal textbook range.
Nonclinical data show that adagrasib inhibits human MATE1 and MATE2-K with IC50 values of 0.342 µM and 3.91 µM. The calculated 50*C_{max},u/Ki values (EMA, 2012) for adagrasib inhibition of the MATE1 and MATE2-K transporters are 10.29 and 0.90 (assuming Ki=IC50), respectively, and indicate that adagrasib may inhibit MATE1 in vivo. Because creatinine is a substrate of MATE1, inhibition of MATE1 may lead to an artifactual increase in serum creatinine that is not indicative of an effect on glomerular filtration rate.

2.6.8.4. Laboratory findings

*Most relevant parameters only.

Haematology:

	Maximum On-treatment Grade						
Lab Parameter [n (%)]	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Missing
Hemoglobin (g/L) - Anemia							
MRTX849 Monotherapy Cohort A	18 (15.9)	39 (34.5)	46 (40.7)	10 (8.8)	0	113	3
MRTX849 600 mg BID NSCLC	28 (15.3)	70 (38.3)	69 (37.7)	16 (8.7)	0	183	5
MRTX849 600 mg BID Other	11 (15.3)	32 (44.4)	23 (31.9)	6 (8.3)	0	72	0
MRTX849 600 mg BID Total	39 (15.3)	102 (40.0)	92 (36.1)	22 (8.6)	0	255	5
MRTX849 Monotherapy Other Dose	0	4 (80.0)	1 (20.0)	0	0	5	0
Lymphocyte (10^9/L) count decreased							
MRTX849 Monotherapy Cohort A	20 (18.0)	13 (11.7)	46 (41.4)	28 (25.2)	4 (3.6)	111	5
MRTX849 600 mg BID NSCLC	34 (18.8)	21 (11.6)	68 (37.6)	52 (28.7)	6 (3.3)	181	7
MRTX849 600 mg BID Other	18 (25.0)	8 (11.1)	31 (43.1)	14 (19.4)	1 (1.4)	72	0
MRTX849 600 mg BID Total	52 (20.6)	29 (11.5)	99 (39.1)	66 (26.1)	7 (2.8)	253	7
MRTX849 Monotherapy Other Dose	3 (60.0)	2 (40.0)	0	0	0	5	0

Neutrophils (10^9/L) count decreased							
MRTX849 Monotherapy Cohort A	99 (89.2)	4 (3.6)	5 (4.5)	0	3 (2.7)	111	5
MRTX849 600 mg BID NSCLC	159 (87.8)	7 (3.9)	10 (5.5)	1 (<1)	4 (2.2)	181	7
MRTX849 600 mg BID Other	68 (94.4)	1 (1.4)	1 (1.4)	0	2 (2.8)	72	0
MRTX849 600 mg BID Total	227 (89.7)	8 (3.2)	11 (4.3)	1 (<1)	6 (2.4)	253	7
MRTX849 Monotherapy Other Dose	5 (100)	0	0	0	0	5	0
Platelets (10^9/L) count decreased							
MRTX849 Monotherapy Cohort A	80 (70.8)	31 (27.4)	2 (1.8)	0	0	113	3
MRTX849 600 mg BID NSCLC	131 (71.6)	47 (25.7)	4 (2.2)	1 (<1)	0	183	5
MRTX849 600 mg BID Other	54 (75.0)	13 (18.1)	4 (5.6)	1 (1.4)	0	72	0
MRTX849 600 mg BID Total	185 (72.5)	60 (23.5)	8 (3.1)	2 (<1)	0	255	5
MRTX849 Monotherapy Other Dose	5 (100)	0	0	0	0	5	0

Blood chemistry:

	Maximum On-treatment Grade						
Lab Parameter [n (%)]	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Missing
Alanine Aminotransferase (U/L) increased							
MRTX849 Monotherapy Cohort A	58 (51.3)	40 (35.4)	10 (8.8)	5 (4.4)	0	113	3
MRTX849 600 mg BID NSCLC	88 (48.1)	70 (38.3)	15 (8.2)	10 (5.5)	0	183	5
MRTX849 600 mg BID Other	45 (62.5)	21 (29.2)	4 (5.6)	1 (1.4)	1 (1.4)	72	0
MRTX849 600 mg BID Total	133 (52.2)	91 (35.7)	19 (7.5)	11 (4.3)	1 (<1)	255	5
MRTX849 Monotherapy Other Dose	4 (80.0)	1 (20.0)	0	0	0	5	0
Aspartate Aminotransferase (U/L) increased							
MRTX849 Monotherapy Cohort A	47 (41.6)	49 (43.4)	10 (8.8)	7 (6.2)	0	113	3
MRTX849 600 mg BID NSCLC	67 (36.6)	88 (48.1)	17 (9.3)	11 (6.0)	0	183	5
MRTX849 600 mg BID Other	34 (47.2)	35 (48.6)	0	3 (4.2)	0	72	0
MRTX849 600 mg BID Total	101 (39.6)	123 (48.2)	17 (6.7)	14 (5.5)	0	255	5
MRTX849 Monotherapy Other Dose	3 (60.0)	2 (40.0)	0	0	0	5	0
Creatinine (umol/L) increased							
MRTX849 Monotherapy Cohort A	50 (44.2)	45 (39.8)	18 (15.9)	0	0	113	3
MRTX849 600 mg BID NSCLC	84 (45.9)	69 (37.7)	30 (16.4)	0	0	183	5
MRTX849 600 mg BID Other	35 (48.6)	30 (41.7)	6 (8.3)	1 (1.4)	0	72	0
MRTX849 600 mg BID Total	119 (46.7)	99 (38.8)	36 (14.1)	1 (<1)	0	255	5
MRTX849 Monotherapy Other Dose	1 (20.0)	2 (40.0)	2 (40.0)	0	0	5	0
Sodium (mmol/L) - Hyponatremia							
MRTX849 Monotherapy Cohort A	43 (38.1)	49 (43.4)	12 (10.6)	9 (8.0)	0	113	3
MRTX849 600 mg BID NSCLC	63 (34.4)	85 (46.4)	24 (13.1)	10 (5.5)	1 (<1)	183	5
MRTX849 600 mg BID Other	36 (50.0)	29 (40.3)	6 (8.3)	1 (1.4)	0	72	0
MRTX849 600 mg BID Total	99 (38.8)	114 (44.7)	30 (11.8)	11 (4.3)	1 (<1)	255	5
MRTX849 Monotherapy Other Dose	4 (80.0)	1 (20.0)	0	0	0	5	0

Thyroid parameters:

	MRTX849 Monotherapy				
	Cohort A	600 mg BID			Other Dose
		NSCLC	Other	Total	
	(N=116)	(N=188)	(N=72)	(N=260)	(N=5)
Thyrotropin >= 20 mIU/L	1 (<1)	2 (1.1)	5 (6.9)	7 (2.7)	0
Baseline [n (%)]	1 (<1)	2 (1.1)	3 (4.2)	5 (1.9)	0
Cycle 2 Day 1 [n (%)]	0	1 (<1)	0	1 (<1)	0
Cycle 3 Day 1 [n (%)]	0	1 (<1)	0	1 (<1)	0
Cycle 22 Day 1 [n (%)]	0	0	1 (1.4)	1 (<1)	0
End of Treatment [n (%)]	0	0	2 (2.8)	2 (<1)	0

ECG parameters:

Table 64: QTcF Results by maximum ICH E14 Category, Study KRYSTAL-1 (DCO 15-OCT-2021)

	MRTX849 Monotherapy				
		600 mg BID			
QTc Category ICH E14 Category [n (%)]	**Cohort A (N=116)**	**NSCLC (N=188)**	**Other (N=72)**	**Total (N=260)**	**Other Doses (N=5)**
Maximum On-treatment Value[1] (QTcF) (N1)	114	185	72	257	5
≤ 450 msec	48 (42.1)	86 (46.5)	35 (48.6)	121 (47.1)	2 (40.0)
> 450 to ≤ 480 msec	44 (38.6)	69 (37.3)	25 (34.7)	94 (36.6)	2 (40.0)
> 480 to ≤ 500 msec	12 (10.5)	17 (9.2)	8 (11.1)	25 (9.7)	0

QTc Category ICH E14 Category [n (%)]	MRTX849 Monotherapy 600 mg BID Cohort A (N=116)	NSCLC (N=188)	Other (N=72)	Total (N=260)	Other Doses (N=5)
> 500 msec	10 (8.8)	13 (7.0)	4 (5.6)	17 (6.6)	1 (20.0)
Maximum Change from Baseline[1] (QTcF)					
≤ 30 msec	42 (36.8)	79 (42.7)	25 (34.7)	104 (40.5)	1 (20.0)
> 30 to ≤ 60 msec	55 (48.2)	84 (45.4)	35 (48.6)	119 (46.3)	4 (80.0)
> 60 msec	17 (14.9)	22 (11.9)	12 (16.7)	34 (13.2)	0

Source: ISS MAA Table 14.3.6.2
BID = twice daily; ICH = International Council on Harmonisation; NSCLC = non-small cell lung cancer; QTcF = QT interval corrected using Fridericia's formula.
Six patients in cohort C who crossed over from MRTX849 monotherapy to MRTX849+cetuximab treatment are included in the MRTX849 Monotherapy 600 mg BID other group. Only the safety data occurring during the MRTX849 monotherapy period are included.
[1] Based on the highest observed on-treatment value (or highest value of on-treatment average of triplicate, where applicable) which was an increase from baseline or the greatest observed shift from baseline. Percentages are based on the number of patients with nonmissing results for each QTc category (N1).

Ejection fraction by multigated acquisition scan (MUGA):

MUGA/Echocardiogram Parameter (unit) TimePoint	MRTX849 Monotherapy 600 mg BID Cohort A (N=116)	NSCLC (N=188)	Other (N=72)	Total (N=260)	Other Doses (N=5)
End of Treatment					
n	22	43	29	72	2
Mean (std)	64.6 (7.48)	63.7 (7.92)	62.6 (4.87)	63.2 (6.84)	68.5 (12.02)
Median	62.5	62.0	62.0	62.0	68.5
Q1, Q3	60.0, 68.0	58.0, 70.0	60.0, 65.0	60.0, 66.5	60.0, 77.0
Min, Max	55, 80	49, 80	54, 74	49, 80	60, 77
Change from Baseline to End of Treatment					
n	22	43	29	72	2
Mean (std)	1.9 (13.52)	0.0 (10.71)	0.6 (5.56)	0.3 (8.95)	-4.0 (1.41)
Median	1.0	0.0	0.0	0.0	-4.0
Q1, Q3	-4.0, 3.0	-7.0, 3.0	-2.0, 5.0	-4.5, 4.5	-5.0, -3.0
Min, Max	-13, 55	-15, 55	-11, 10	-15, 55	-5, -3
LVEF (%)					
Decrease from Baseline of >=10% and Absolute on-treatment Value >=40%	20 (17.2)	35 (18.6)	9 (12.5)	44 (16.9)	0
Decrease from Baseline of >=10% and Absolute on-treatment Value <40%	2 (1.7)	3 (1.6)	1 (1.4)	4 (1.5)	0
Decrease from Baseline of >=20% and Absolute on-treatment Value >=40%	1 (<1)	1 (<1)	1 (1.4)	2 (<1)	0
Decrease from Baseline of >=20% and Absolute on-treatment Value <40%	1 (<1)	2 (1.1)	0	2 (<1)	0

Table 65: Maximum on-treatment chemistry CTCAE grade for alkaline phosphatase, blood bilirubin (total), amylase, lipase (Safety population)

Lab Parameter [n (%)]	Maximum On-treatment Grade Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total	Missing
Alkaline Phosphatase (U/L) increased							
MRTX849 Monotherapy Cohort A	57 (50.4)	45 (39.8)	6 (5.3)	5 (4.4)	0	113	3
MRTX849 600 mg BID NSCLC	83 (45.4)	78 (42.6)	16 (8.7)	6 (3.3)	0	183	5
MRTX849 600 mg BID Other	27 (37.5)	41 (56.9)	3 (4.2)	1 (1.4)	0	72	0
MRTX849 600 mg BID Total	110 (43.1)	119 (46.7)	19 (7.5)	7 (2.7)	0	255	5
MRTX849 Monotherapy Other Dose	2 (40.0)	2 (40.0)	1 (20.0)	0	0	5	0
Amylase (U/L) increased							
MRTX849 Monotherapy Cohort A	83 (73.5)	23 (20.4)	7 (6.2)	0	0	113	3
MRTX849 600 mg BID NSCLC	135 (73.8)	36 (19.7)	12 (6.6)	0	0	183	5
MRTX849 600 mg BID Other	59 (81.9)	12 (16.7)	1 (1.4)	0	0	72	0
MRTX849 600 mg BID Total	194 (76.1)	48 (18.8)	13 (5.1)	0	0	255	5
MRTX849 Monotherapy Other Dose	4 (80.0)	1 (20.0)	0	0	0	5	0
Bilirubin (umol/L) increased							
MRTX849 Monotherapy Cohort A	105 (92.9)	3 (2.7)	3 (2.7)	2 (1.8)	0	113	3
MRTX849 600 mg BID NSCLC	167 (91.3)	4 (2.2)	8 (4.4)	4 (2.2)	0	183	5
MRTX849 600 mg BID Other	63 (87.5)	5 (6.9)	4 (5.6)	0	0	72	0
MRTX849 600 mg BID Total	230 (90.2)	9 (3.5)	12 (4.7)	4 (1.6)	0	255	5
MRTX849 Monotherapy Other Dose	5 (100)	0	0	0	0	5	0

Lipase (U/L) increased							
MRTX849 Monotherapy Cohort A	72 (63.7)	22 (19.5)	17 (15.0)	2 (1.8)	0	113	3
MRTX849 600 mg BID NSCLC	115 (62.8)	37 (20.2)	25 (13.7)	6 (3.3)	0	183	5
MRTX849 600 mg BID Other	59 (81.9)	6 (8.3)	6 (8.3)	1 (1.4)	0	72	0
MRTX849 600 mg BID Total	174 (68.2)	43 (16.9)	31 (12.2)	7 (2.7)	0	255	5
MRTX849 Monotherapy Other Dose	4 (80.0)	0	0	1 (20.0)	0	5	0

Note: For each laboratory parameter, patients are included only once, in the maximum CTCAE grade, for that laboratory parameter.
Percentages are based on the number of patients with at least 1 on-treatment result. NCI CTC grading v5.0 applied.
Dataset: ADLB, Program: t_q58.sas, Output: t_q58.rtf, Generated on: 2022-09-28T09:46, Datacutoff: 2021-10-15

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Table 66: Safety in special populations

MedDRA Terms	Age <65 number (percentage)	Age 65-74 number (percentage)	Age 75-84 number (percentage)	Age 85+ number (percentage)
Total AEs	143 (100%)	86 (100%)	29 (100%)	2 (100%)
Serious AEs – Total	70 (49.0%)	39 (45.3%)	23 (79.3%)	1 (50.0%)
- Fatal	19 (13.3%)	12 (14.0%)	7 (24.1%)	0 (0%)
- Hospitalization/prolong existing hospitalization	63 (44.1%)	33 (38.4%)	17 (58.6%)	1 (50.0%)
- Life-threatening	3 (2.1%)	4 (4.7%)	2 (6.9%)	0 (0%)
- Disability/incapacity	0 (0%)	1 (1.2%)	0 (0%)	0 (0%)
- Other (medically significant)	2 (1.4%)	3 (3.5%)	4 (13.8%)	0 (0%)
AE leading to drop-out	4 (2.8%)	4 (4.7%)	2 (6.9%)	0 (0%)
Psychiatric disorders	42 (29.4%)	24 (27.9%)	12 (41.4%)	0 (0%)
Nervous system disorders	72 (50.3%)	43 (50.0%)	16 (55.2%)	0 (0%)
Accidents and injuries*	6 (4.2%)	5 (5.8%)	2 (6.9%)	0 (0%)
Cardiac disorders	34 (23.8%)	14 (16.3%)	5 (17.2%)	0 (0%)
Vascular disorders	38 (26.6%)	20 (23.3%)	8 (27.6%)	0 (0%)
Cerebrovascular disorders**	1 (0.7%)	0 (0%)	2 (6.9%)	0 (0%)
Infections and infestations	64 (44.8%)	37 (43.0%)	15 (51.7%)	2 (100%)
Anticholinergic syndrome	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Quality of life decreased	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures***	36 (25.2%)	35 (40.7%)	15 (51.7%)	0 (0%)
Fatigue	74 (51.7%)	54 (62.8%)	18 (62.1%)	1 (50.0%)
Decreased appetite	34 (23.8%)	30 (34.9%)	14 (48.3%)	0 (0%)
Dizziness	22 (15.4%)	20 (23.3%)	12 (41.4%)	0 (0%)

* Accidents and injuries includes preferred terms: Contusion, Head injury, Ligament sprain, Skin abrasion, Skin laceration.
** Cerebrovascular disorders includes preferred terms: Cerebrovascular accident, Hemiparesis.
*** Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures includes preferred terms: Ankle fracture, Ataxia, Balance disorder, Dizziness, Dizziness postural, Fall, Fracture, Humerus fracture, Orthostatic hypotension, Presyncope, Rib fracture, Spinal compression fracture, Spinal fracture, Syncope, Upper limb fracture.

Patients of 75 years or older experienced overall a higher degree of toxicity than patients of less than 75 years.

Data on safety by intrinsic factors (gender, age, race, tumour type, ECOG PS) are presented for the total dataset (n=260). There are no unexpected findings or tendencies in the presented safety data by intrinsic factors.

Table 67: Overview summary of treatment-emergent adverse event by gender (male, female) (Safety population)

	MRTX849 Monotherapy 600 mg BID		
n (%)	Female (N=148)	Male (N=112)	Total (N=260)
Any Treatment-emergent Adverse Events	148 (100)	112 (100)	260 (100)
Any Grade 3 or Greater TEAEs	109 (73.6)	81 (72.3)	190 (73.1)
Any MRTX849-related TEAE	143 (96.6)	106 (94.6)	249 (95.8)
Any Grade 3 or Greater MRTX849-related TEAE	63 (42.6)	45 (40.2)	108 (41.5)
Any TEAE Leading to Discontinuation of Study	5 (3.4)	5 (4.5)	10 (3.8)
Any MRTX849-related TEAE Leading to Discontinuation of Study	4 (2.7)	2 (1.8)	6 (2.3)
Any TEAE Leading to Discontinuation of Study Treatment	19 (12.8)	10 (8.9)	29 (11.2)
Any MRTX849-related TEAE Leading to Discontinuation of Study Treatment	9 (6.1)	2 (1.8)	11 (4.2)
Any TEAE Leading to Dose Reduction or Interruption	117 (79.1)	84 (75.0)	201 (77.3)
Any MRTX849-related TEAE Leading to Dose Reduction or Interruption	101 (68.2)	64 (57.1)	165 (63.5)
Any SAE	73 (49.3)	60 (53.6)	133 (51.2)
Any MRTX849-related SAE	29 (19.6)	14 (12.5)	43 (16.5)
Any SAE Leading to Discontinuation of Study Treatment	17 (11.5)	8 (7.1)	25 (9.6)
Any TEAE with Outcome of Death within 28 days of Last Dose	19 (12.8)	19 (17.0)	38 (14.6)
Any MRTX849-related TEAE with Outcome of Death within 28 days of Last Dose	4 (2.7)	0	4 (1.5)
Any SAE with Outcome of Death within 28 days of Last Dose	19 (12.8)	19 (17.0)	38 (14.6)
Any MRTX849-related SAE with Outcome of Death within 28 days of Last Dose	4 (2.7)	0	4 (1.5)
GI toxicity[a]	139 (93.9)	95 (84.8)	234 (90.0)
Hepatotoxicity[b]	57 (38.5)	45 (40.2)	102 (39.2)

Note: Adverse events were coded using MedDRA version 21.0. For each preferred term, patients are included only once, even if they experienced multiple events in that preferred term.
a. includes nausea, vomiting, diarrhoea, and retching.
b. includes increased AST, increased ALT, increased alkaline phosphatase, increased bilirubin, mixed liver injury, liver function test increased, transaminases increased, hepatic enzyme increased, hepatitis, drug-induced liver injury, hepatocellular injury, hepatitis acute, hepatitis toxic, hepatotoxicity, liver disorder, hepatic failure, hepatic steatosis, hepatic lesion, and gamma-glutamyltransferase increased.
Source: Listing 16.2.7.2, Dataset: ADAE, Program: t q60 1.sas, Output: t q60 1.rtf, Generated on: 2022-11-23T12:42, Datacutoff: 2021-10-15

Table 68: Overview summary of treatment-emergent adverse event by age (<65, ≥65) (Safety population)

	MRTX849 Monotherapy 600 mg BID		
n (%)	Age < 65 years (N=143)	Age >= 65 years (N=117)	Total (N=260)
Any Treatment-emergent Adverse Events	143 (100)	117 (100)	260 (100)
Any Grade 3 or Greater TEAEs	101 (70.6)	89 (76.1)	190 (73.1)
Any MRTX849-related TEAE	138 (96.5)	111 (94.9)	249 (95.8)
Any Grade 3 or Greater MRTX849-related TEAE	54 (37.8)	54 (46.2)	108 (41.5)
Any TEAE Leading to Discontinuation of Study	4 (2.8)	6 (5.1)	10 (3.8)
Any MRTX849-related TEAE Leading to Discontinuation of Study	4 (2.8)	2 (1.7)	6 (2.3)
Any TEAE Leading to Discontinuation of Study Treatment	15 (10.5)	14 (12.0)	29 (11.2)
Any MRTX849-related TEAE Leading to Discontinuation of Study Treatment	6 (4.2)	5 (4.3)	11 (4.2)
Any TEAE Leading to Dose Reduction or Interruption	104 (72.7)	97 (82.9)	201 (77.3)
Any MRTX849-related TEAE Leading to Dose Reduction or Interruption	85 (59.4)	80 (68.4)	165 (63.5)
Any SAE	70 (49.0)	63 (53.8)	133 (51.2)
Any MRTX849-related SAE	26 (18.2)	17 (14.5)	43 (16.5)
Any SAE Leading to Discontinuation of Study Treatment	12 (8.4)	13 (11.1)	25 (9.6)
Any TEAE with Outcome of Death within 28 days of Last Dose	19 (13.3)	19 (16.2)	38 (14.6)
Any MRTX849-related TEAE with Outcome of Death within 28 days of Last Dose	4 (2.8)	0	4 (1.5)
Any SAE with Outcome of Death within 28 days of Last Dose	19 (13.3)	19 (16.2)	38 (14.6)
Any MRTX849-related SAE with Outcome of Death within 28 days of Last Dose	4 (2.8)	0	4 (1.5)
GI toxicity[a]	127 (88.8)	107 (91.5)	234 (90.0)
Hepatotoxicity[b]	52 (36.4)	50 (42.7)	102 (39.2)

Note: Adverse events were coded using MedDRA version 21.0. For each preferred term, patients are included only once, even if they experienced multiple events in that preferred term.
a. includes nausea, vomiting, diarrhoea, and retching.
b. includes increased AST, increased ALT, increased alkaline phosphatase, increased bilirubin, mixed liver injury, liver function test increased, transaminases increased, hepatic enzyme increased, hepatitis, drug-induced liver injury, hepatocellular injury, hepatitis acute, hepatitis toxic, hepatotoxicity, liver disorder, hepatic failure, hepatic steatosis, hepatic lesion, and gamma-glutamyltransferase increased.
Source: Listing 16.2.7.2, Dataset: ADAE, Program: t q60 2.sas, Output: t q60 2.rtf, Generated on: 2022-11-23T12:43, Datacutoff: 2021-10-15

Table 69: Overview summary of treatment-emergent adverse event by race (white, non-white) (Safety population)

	MRTX849 Monotherapy 600 mg BID		
n (%)	White (N=216)	Non-White (N=44)	Total (N=260)
Any Treatment-emergent Adverse Events	216 (100)	44 (100)	260 (100)
Any Grade 3 or Greater TEAEs	156 (72.2)	34 (77.3)	190 (73.1)
Any MRTX849-related TEAE	207 (95.8)	42 (95.5)	249 (95.8)
Any Grade 3 or Greater MRTX849-related TEAE	92 (42.6)	16 (36.4)	108 (41.5)
Any TEAE Leading to Discontinuation of Study	10 (4.6)	0	10 (3.8)
Any MRTX849-related TEAE Leading to Discontinuation of Study	6 (2.8)	0	6 (2.3)
Any TEAE Leading to Discontinuation of Study Treatment	28 (13.0)	1 (2.3)	29 (11.2)
Any MRTX849-related TEAE Leading to Discontinuation of Study Treatment	11 (5.1)	0	11 (4.2)
Any TEAE Leading to Dose Reduction or Interruption	168 (77.8)	33 (75.0)	201 (77.3)
Any MRTX849-related TEAE Leading to Dose Reduction or Interruption	139 (64.4)	26 (59.1)	165 (63.5)
Any SAE	107 (49.5)	26 (59.1)	133 (51.2)
Any MRTX849-related SAE	37 (17.1)	6 (13.6)	43 (16.5)
Any SAE Leading to Discontinuation of Study Treatment	24 (11.1)	1 (2.3)	25 (9.6)
Any TEAE with Outcome of Death within 28 days of Last Dose	30 (13.9)	8 (18.2)	38 (14.6)
Any MRTX849-related TEAE with Outcome of Death within 28 days of Last Dose	4 (1.9)	0	4 (1.5)
Any SAE with Outcome of Death within 28 days of Last Dose	30 (13.9)	8 (18.2)	38 (14.6)
Any MRTX849-related SAE with Outcome of Death within 28 days of Last Dose	4 (1.9)	0	4 (1.5)
GI toxicity[a]	193 (89.4)	41 (93.2)	234 (90.0)
Hepatotoxicity[b]	87 (40.3)	15 (34.1)	102 (39.2)

Note: Adverse events were coded using MedDRA version 21.0. For each preferred term, patients are included only once, even if they experienced multiple events in that preferred term.
a. includes nausea, vomiting, diarrhoea, and retching.
b. includes increased AST, increased ALT, increased alkaline phosphatase, increased bilirubin, mixed liver injury, liver function test increased, transaminases increased, hepatic enzyme increased, hepatitis, drug-induced liver injury, hepatocellular injury, hepatitis acute, hepatitis toxic, hepatotoxicity, liver disorder, hepatic failure, hepatic steatosis, hepatic lesion, and gamma-glutamyltransferase increased.
Source: Listing 16.2.7.2, Dataset: ADAE, Program: t q60 4.sas, Output: t q60 4.rtf, Generated on: 2022-11-23T12:44, Datacutoff: 2021-10-15

Table 70: Overview summary of treatment-emergent adverse event by tumour type (NSCLC, CRC) (Safety population)

	MRTX849 Monotherapy 600 mg BID		
n (%)	NSCLC (N=188)	CRC (N=46)	Total (N=260)
Any Treatment-emergent Adverse Events	188 (100)	46 (100)	260 (100)
Any Grade 3 or Greater TEAEs	153 (81.4)	24 (52.2)	190 (73.1)
Any MRTX849-related TEAE	182 (96.8)	42 (91.3)	249 (95.8)
Any Grade 3 or Greater MRTX849-related TEAE	88 (46.8)	15 (32.6)	108 (41.5)
Any TEAE Leading to Discontinuation of Study	10 (5.3)	0	10 (3.8)
Any MRTX849-related TEAE Leading to Discontinuation of Study	6 (3.2)	0	6 (2.3)
Any TEAE Leading to Discontinuation of Study Treatment	26 (13.8)	1 (2.2)	29 (11.2)
Any MRTX849-related TEAE Leading to Discontinuation of Study Treatment	11 (5.9)	0	11 (4.2)
Any TEAE Leading to Dose Reduction or Interruption	158 (84.0)	26 (56.5)	201 (77.3)
Any MRTX849-related TEAE Leading to Dose Reduction or Interruption	129 (68.6)	22 (47.8)	165 (63.5)
Any SAE	111 (59.0)	14 (30.4)	133 (51.2)
Any MRTX849-related SAE	37 (19.7)	3 (6.5)	43 (16.5)
Any SAE Leading to Discontinuation of Study Treatment	23 (12.2)	1 (2.2)	25 (9.6)
Any TEAE with Outcome of Death within 28 days of Last Dose	33 (17.6)	2 (4.3)	38 (14.6)
Any MRTX849-related TEAE with Outcome of Death within 28 days of Last Dose	4 (2.1)	0	4 (1.5)
Any SAE with Outcome of Death within 28 days of Last Dose	33 (17.6)	2 (4.3)	38 (14.6)
Any MRTX849-related SAE with Outcome of Death within 28 days of Last Dose	4 (2.1)	0	4 (1.5)
GI toxicity[a]	169 (89.9)	44 (95.7)	234 (90.0)
Hepatotoxicity[b]	81 (43.1)	10 (21.7)	102 (39.2)

Note: Adverse events were coded using MedDRA version 21.0. For each preferred term, patients are included only once, even if they experienced multiple events in that preferred term.
a. includes nausea, vomiting, diarrhoea, and retching.
b. includes increased AST, increased ALT, increased alkaline phosphatase, increased bilirubin, mixed liver injury, liver function test increased, transaminases increased, hepatic enzyme increased, hepatitis, drug-induced liver injury, hepatocellular injury, hepatitis acute, hepatitis toxic, hepatotoxicity, liver disorder, hepatic failure, hepatic steatosis, hepatic lesion, and gamma-glutamyltransferase increased.
26 patients had tumor types other than NSCLC and CRC.
Source: Listing 16.2.7.2, Dataset: ADAE, Program: t q60 5.sas, Output: t q60 5.rtf, Generated on: 2022-11-23T12:44, Datacutoff: 2021-10-15

Table 71: Overview summary of treatment-emergent adverse event by ECOG performance status (0, 1) (Safety population)

	MRTX849 Monotherapy 600 mg BID		
n (%)	ECOG Status: 0 (N=67)	ECOG Status: 1 (N=192)	Total (N=260)
Any Treatment-emergent Adverse Events	67 (100)	192 (100)	260 (100)
Any Grade 3 or Greater TEAEs	40 (59.7)	149 (77.6)	190 (73.1)
Any MRTX849-related TEAE	65 (97.0)	183 (95.3)	249 (95.8)
Any Grade 3 or Greater MRTX849-related TEAE	25 (37.3)	82 (42.7)	108 (41.5)
Any TEAE Leading to Discontinuation of Study	0	10 (5.2)	10 (3.8)
Any MRTX849-related TEAE Leading to Discontinuation of Study	0	6 (3.1)	6 (2.3)
Any TEAE Leading to Discontinuation of Study Treatment	5 (7.5)	24 (12.5)	29 (11.2)
Any MRTX849-related TEAE Leading to Discontinuation of Study Treatment	3 (4.5)	8 (4.2)	11 (4.2)
Any TEAE Leading to Dose Reduction or Interruption	44 (65.7)	156 (81.3)	201 (77.3)
Any MRTX849-related TEAE Leading to Dose Reduction or Interruption	34 (50.7)	130 (67.7)	165 (63.5)
Any SAE	25 (37.3)	108 (56.3)	133 (51.2)
Any MRTX849-related SAE	8 (11.9)	35 (18.2)	43 (16.5)
Any SAE Leading to Discontinuation of Study Treatment	4 (6.0)	21 (10.9)	25 (9.6)
Any TEAE with Outcome of Death within 28 days of Last Dose	7 (10.4)	31 (16.1)	38 (14.6)
Any MRTX849-related TEAE with Outcome of Death within 28 days of Last Dose	0	4 (2.1)	4 (1.5)
Any SAE with Outcome of Death within 28 days of Last Dose	7 (10.4)	31 (16.1)	38 (14.6)
Any MRTX849-related SAE with Outcome of Death within 28 days of Last Dose	0	4 (2.1)	4 (1.5)
GI toxicity[a]	63 (94.0)	170 (88.5)	234 (90.0)
Hepatotoxicity[b]	24 (35.8)	77 (40.1)	102 (39.2)

Note: Adverse events were coded using MedDRA version 21.0. For each preferred term, patients are included only once, even if they experienced multiple events in that preferred term.
a. includes nausea, vomiting, diarrhoea, and retching.
b. includes increased AST, increased ALT, increased alkaline phosphatase, increased bilirubin, mixed liver injury, liver function test increased, transaminases increased, hepatic enzyme increased, hepatitis, drug-induced liver injury, hepatocellular injury, hepatitis acute, hepatitis toxic, hepatotoxicity, liver disorder, hepatic failure, hepatic steatosis, hepatic lesion, and gamma-glutamyltransferase increased.
One patient had missing ECOG status at baseline.
Source: Listing 16.2.7.2, Dataset: ADAE, Program: t q60 6.sas, Output: t q60 6.rtf, Generated on: 2022-11-23T12:44, Datacutoff: 2021-10-15

Table 72: Adverse Events by Age Groups

	< 65 years (N=143)	65 - <75 years (N=86)	≥75 years (N=31)
GI Toxicity	127 (88.8)	78 (90.7)	29 (93.5)
Diarrhoea	105 (73.4)	59 (68.6)	22 (71.0)
Nausea	98 (68.5)	57 (66.3)	22 (71.0)
Vomiting	86 (60.1)	48 (55.8)	16 (51.6)
Hepatotoxicity	52 (36.4)	35 (40.7)	15 (48.4)
ECG QT prolonged	26 (18.2)	12 (14.0)	7 (22.6)

2.6.8.7. Immunological events

Not applicable

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

See section 2.6.2.1. Pharmacokinetics.

2.6.8.9. Discontinuation due to adverse events

AEs leading to dose reductions or dose interruptions:

Table 73: Adverse Events Leading to Dose Reductions or Interruptions for ≥5% of NSCLC Patients

	MRTX849 Monotherapy 600 mg BID NSCLC (N=188)			
Group/Preferred Term [n (%)]	**Grade 1/2**	**Grade 3/4**	**Grade 5**	**All grades**
Patients with at least 1 TEAE Leading to Dose Reduction or Interruption	44 (23.4)	113 (60.1)	1 (<1)	158 (84.0)
Nausea [1]	50 (26.6)	6 (3.2)	0	56 (29.8)
Liver Disorder [4]	21 (11.2)	13 (6.9)	0	34 (18.1)
Diarrhoea	25 (13.3)	4 (2.1)	0	29 (15.4)
Fatigue [2]	17 (9.0)	11 (5.9)	0	28 (14.9)
Lung Infection [10]	1 (<1)	14 (7.4)	0	15 (8.0)
Dyspnoea	7 (3.7)	7 (3.7)	0	14 (7.4)
Renal Insufficiency [5]	10 (5.3)	4 (2.1)	0	14 (7.4)
Decreased appetite	9 (4.8)	3 (1.6)	0	12 (6.4)
Pancreatic Enzyme Increase [9]	3 (1.6)	9 (4.8)	0	12 (6.4)
Anaemia	2 (1.1)	9 (4.8)	0	11 (5.9)
QT Prolongation [11]	1 (<1)	10 (5.3)	0	11 (5.9)

Note: Adverse events were coded using MedDRA version 21.0. For each preferred term, patients are included only once, even if they experienced multiple events in that preferred term.
Source: Listing 16.2.7.2, Dataset: ADAE, Program: t_q163_11.sas, Output: t_q163_11.rtf, Generated on: 2022-12-12T14:54, Datacutoff: 2021-10-15
Source: t_q163_11
[1] Includes nausea, vomiting, retching; [2] Includes fatigue, asthenia; [4] Includes ALT increased, AST increased, blook alkaline phosphatase increased, blood bilirubin increased, bilirubin conjugated increased, gamma-glutamyltransferase increased, hepatic enzyme increased, liver function test increased, mixed liver injury, ammonia increased, jaundice cholestatic; [5] Includes blood creatinine increased, acute kidney injury, blood urea increased, chronic kidney disease, renal failure; [9] Includes amylase increased, lipase increased, pancreatitis, amylase; [10] Includes pneumonia, lung infection, pneumonia streptococcal, respiratory tract infection; [11] Includes electrocardiogram QT prolonged, electrocardiogram abnormal.

Table 74: AEs leading to treatment discontinuation of adagrasib

	MRTX849 Monotherapy 600 mg BID			
Group/Preferred Term [n (%)]	**Cohort A (N=116)**	**NSCLC (N=188)**	**Other (N=72)**	**Total (N=260)**
Patients with at least 1 TEAE Leading to Discontinuation of Study Treatment	18 (15.5)	26 (13.8)	3 (4.2)	29 (11.2)
Lung Infection [10]	2 (1.7)	4 (2.1)	0	4 (1.5)
Decreased Ejection Fraction [16]	2 (1.7)	2 (1.1)	0	2 (<1)
Malignant neoplasm progression	2 (1.7)	2 (1.1)	1 (1.4)	3 (1.2)
Pneumonitis [18]	1 (<1)	2 (1.1)	0	2 (<1)
Respiratory failure	1 (<1)	2 (1.1)	0	2 (<1)
Cerebrovascular accident	1 (<1)	1 (<1)	0	1 (<1)
Dyspnoea	1 (<1)	1 (<1)	0	1 (<1)
Encephalitis	1 (<1)	1 (<1)	0	1 (<1)
Failure to thrive	0	1 (<1)	0	1 (<1)
Fatigue [2]	0	1 (<1)	1 (1.4)	2 (<1)
Hypotension	1 (<1)	1 (<1)	0	1 (<1)
Liver Disorder [4]	1 (<1)	1 (<1)	0	1 (<1)
Muscular weakness	1 (<1)	1 (<1)	0	1 (<1)
Nausea [1]	0	1 (<1)	0	1 (<1)
Pulmonary haemorrhage	1 (<1)	1 (<1)	0	1 (<1)
Pyrexia	1 (<1)	1 (<1)	0	1 (<1)
Sepsis	1 (<1)	1 (<1)	0	1 (<1)
Small intestinal obstruction	1 (<1)	1 (<1)	0	1 (<1)
Thrombosis [17]	1 (<1)	1 (<1)	0	1 (<1)
Wound infection	0	1 (<1)	0	1 (<1)
Cardiac arrest	0	0	1 (1.4)	1 (<1)

Note: Adverse events were coded using MedDRA version 21.0. For each preferred term, patients are included only once, even if they experienced multiple events in that preferred term.
Source: Listing 16.2.7.2, Dataset: ADAE, Program: t_q163_9.sas, Output: t_q163_9.rtf, Generated on: 2022-12-12T14:56, Datacutoff: 2021-10-15
Source: t_q163_9
[1] Includes nausea, vomiting, retching; [2] Includes fatigue, asthenia; [4] Includes ALT increased, AST increased, blook alkaline phosphatase increased, blood bilirubin increased, bilirubin conjugated increased, gamma-glutamyltransferase increased, hepatic enzyme increased, liver function test increased, mixed liver injury, ammonia increased, jaundice cholestatic; [10] Includes pneumonia, lung infection, pneumonia streptococcal, respiratory tract infection; [15] Includes confusional state, mental status changes; [16] Includes ejection fraction decreased, cardiac failure, cardiac failure congestive, cardiomyopathy; [17] Includes embolism, deep vein thrombosis, pulmonary embolism, jugular vein thrombosis; [18] Includes pneumonitis, interstitial lung disease.

Table 75: TRAEs leading to treatment discontinuation of adagrasib

	MRTX849 Monotherapy 600 mg BID			
Group/Preferred Term [n (%)]	**Cohort A (N=116)**	**NSCLC (N=188)**	**Other (N=72)**	**Total (N=260)**
Patients with at least 1 MRTX849-related TEAE Leading to Discontinuation of Study Treatment	8 (6.9)	11 (5.9)	0	11 (4.2)
Decreased Ejection Fraction [16]	2 (1.7)	2 (1.1)	0	2 (<1)
Pneumonitis [18]	1 (<1)	2 (1.1)	0	2 (<1)
Encephalitis	1 (<1)	1 (<1)	0	1 (<1)
Fatigue [2]	0	1 (<1)	0	1 (<1)
Hypotension	1 (<1)	1 (<1)	0	1 (<1)
Liver Disorder [4]	1 (<1)	1 (<1)	0	1 (<1)
Muscular weakness	1 (<1)	1 (<1)	0	1 (<1)
Nausea [1]	0	1 (<1)	0	1 (<1)
Pulmonary haemorrhage	1 (<1)	1 (<1)	0	1 (<1)
Pyrexia	1 (<1)	1 (<1)	0	1 (<1)

Note: Adverse events were coded using MedDRA version 21.0. For each preferred term, patients are included only once, even if they experienced multiple events in that preferred term.
Source: Listing 16.2.7.2, Dataset: ADAE, Program: t_q163_10.sas, Output: t_q163_10.rtf, Generated on: 2022-12-12T14:53, Datacutoff: 2021-10-15
Source: t_q163_10
[1] Includes nausea, vomiting, retching; [2] Includes fatigue, asthenia; [4] Includes ALT increased, AST increased, blook alkaline phosphatase increased, blood bilirubin increased, bilirubin conjugated increased, gamma-glutamyltransferase increased, hepatic enzyme increased, liver function test increased, mixed liver injury, ammonia increased, jaundice cholestatic; [16] Includes ejection fraction decreased, cardiac failure, cardiac failure congestive, cardiomyopathy; [18] Includes pneumonitis, interstitial lung disease.

2.6.8.10. Post marketing experience

Adagrasib received approval from the FDA on 12-DEC-2022, but post marketing data are not available yet.

2.6.9. Discussion on clinical safety

The overall safety database of adagrasib is constituted by 260 patients across multiple cohorts from pivotal phase 1/2 Study KRYSTAL-1. The safety data cut-off date is the same (15-OCT-2021) as the one used for the updated efficacy analysis.

The main safety datasets, in which patients received adagrasib at the dose intended for marketing, i.e., 600 mg BID are: Cohort A, n=116; NSCLC pool, n=188; other tumours, n=72; and total, n=260. The NSCLC safety dataset (n=188) contains the highest number of patients with similar clinical characteristics and background as the targeted population for treatment with adagrasib in 4.1 (strictly represented by Cohort A), but the total population (n=260), which includes 72 patients with other tumour types, is considered to provide more comprehensive data. Subsequently, section 4.8 was reformulated using the total dataset (n=260). Results from patients treated with adagrasib at other dosages during the dose escalation phase (n=5) were provided for completeness.

Exposure: Median treatment duration approaches ~6 months in the NSCLC pool, which is consistent with median PFS in the main efficacy dataset (Cohort A). Of note, nearly a quarter of patients from such cohort had received treatment for more than a year at safety data cut-off. However, the median duration of exposure of about 6 months could also be considered limited - with only 50.6% and 22.4% of subjects receiving treatment for ≥6 and ≥12 months, respectively, long-term safety data are not available. Thus, it cannot be assumed that cumulative toxicity, rare adverse events nor delayed toxic events will not occur. Median dose compliance approaches 95% and median dose intensity 80% across all safety datasets. About 60% of patients across the NSCLC pool required at least one dose reduction,

in nearly all cases due to adverse events. Importantly, about half of those patients required one dose level reduction, whereas the rest required two or even three level reductions. In the same line, the majority of patients (~94%) across the NSCLC pool experimented dose interruptions, frequently due to adverse events. Overall, exposure is deemed as expected for the 2L+ advanced NSCLC setting in which adagrasib was evaluated (Cohort A and NSCLC pool), noting a substantial proportion of patients who required dose interruptions and/or reductions on account of adverse events. The pattern of exposure is very similar across the 4 safety datasets of pivotal Study 849-001 KRYSTAL-1.

PK data indicate no dose- or exposure-dependency in efficacy between patients who received the assigned 600 mg BID regimen and patients with dose interruptions/reduction. In addition, the selection of the dose of adagrasib at 600 mg BID is based on the determination of the maximum tolerated dose in the dose-finding component of Study 849-001 and based on early evidence of clinical activity in the Phase 1 setting. The applicant is recommended to evaluate the safety and efficacy of a lower dosing regimen (400 mg BID) post approval (study 849-021).

Adverse events: All patients that started treatment with adagrasib experienced adverse events. Concerning the NSCLC pool, ~80% of patients presented high-grade (≥G3) AEs, ~60% SAEs, 18% AEs with outcome of death, 14% AEs leading to treatment discontinuation and 84% AEs leading to dose reduction/interruption. The proportions of AE categories are somewhat lower in the other tumours (n=72) dataset, which slightly reduces the percentages in the total (n=260) dataset. As expected from causality attribution, the percentages of patients with adagrasib-related AEs across categories are lower. The number of patients with NSCLC is limited (188 patients) and the single-cohort design of the phase I/II study 849-001 precludes a causality assessment for many TEAEs.

Any-grade AEs: For eased interpretability, all AEs tables have been reformulated. Preferred terms that belong to a single clinical entity have been pooled to avoid dilution of the true incidence of a specific AE.

The 10 most common AEs in the NSCLC pool were, nausea (80%), diarrhoea (71%), fatigue (57%), Musculoskeletal Pain (45%), Liver Disorder (43%), Renal Insufficiency (38%), anaemia (35%), Oedema (34%), dyspnoea (35%), decreased appetite (35%). Other AEs of clinical relevance with significant incidence were dizziness (25%), constipation (23%), abdominal pain (23%), Hyponatraemia (23%), Pancreatic Enzyme Increase (22%) and QT prolonged (19%). The proportions of these AEs in the total (n=260) dataset were similar. Pooled together as Gastrointestinal AEs, including nausea, vomiting, diarrhoea, and retching, 90% of the included patients experienced these events.

High-grade (≥G3) AEs: Lung infection (14.9%), anaemia (11.7%), dyspnoea (11.7%), fatigue (9.6%), liver disorders (9.0%), hypoxia (7.4%), pancreatic enzyme increase (7.4%), hyponatremia (6.9%), and lymphocyte count decreased (5.9%) were the most common high-grade AEs in the NSCLC pool.

SAEs: SAEs occurred in ~60% of patients from the NSCLC pool but were much less frequent in the other tumours pool (~30%). As is the usual case in patients with advanced (lung) cancer, lung infection (13.8%), dyspnoea (9.5%), malignant neoplasm progression (6.9%), Renal Insufficiency (6.4%) and decreased Ejection Fraction (4.8%) were the most common types of SAEs. Expectedly, lung infection was the first cause for hospitalisation across the NSCLC pool. Despite the very high rates of any-grade haematological or gastrointestinal AEs, these toxicities were not amongst the main causes of SAEs, although upon review of narratives, concerns for underreporting are pending clarification: it appears that a substantial number of patients with SAEs of dehydration and/or hyponatremia presented underlying severe nausea/vomiting and/or diarrhoea, known adverse events from adagrasib. Accumulated SAE frequencies of diarrhoea, nausea (includes nausea, vomiting and retching), hyponatremia, and dehydration were 9.1% in the NSCLC pool (n=188) and 9.2% in the total population (n=260). Overall, most of the SAEs seem to be related to the clinical context of patients (advanced 2L+ lung cancer), rather than toxic effects from adagrasib. However, a significant

proportion of patients (6%) from the NSCLC pool presented serious adagrasib-related laboratory and ECG abnormalities, notably elevated liver enzymes and QT prolongations, respectively.

AEs with outcome of death occurred in 33 patients (~18%) from the NSCLC pool, out of which 12 deaths were declared as AE of "malignant neoplasm progression". As expected in this clinical setting, AEs with outcome of death were related to respiratory/thoracic/ mediastinal disorders in the majority of cases, while few patients died from heart-related or infectious causes. According to the applicant, adagrasib-related deaths are reported in only 4 patients (2%) from the NSCLC pool.

Adverse drug reactions (ADRs): The table on ADRs presented in section 4.8 of the SmPC has been reformulated according to specific guidance. Anaemia (33.5%) and peripheral oedema (33.5%) are AEs that are assessed as ADRs under the appropriate SOC, and thus included in the table.

Adverse events of special interest (AESIs): The applicant claims that no AESIs from adagrasib have been identified to date. This is not agreed, since a number of specific AEs seem to have a clear relationship with adagrasib upon biological plausibility (mechanism of action and non-clinical data) and similar class-drug precedents. Overall, it is considered that gastrointestinal toxicity in the spectrum of nausea/vomiting/diarrhoea, hepatotoxicity and QTc prolongation are AESIs from adagrasib.

-Gastrointestinal toxicity (nausea/vomiting/diarrhoea) is of highest clinical concern, not only because it occurred in about two thirds of patients and was the commonest type of event leading to dose reductions/interruptions, but particularly since this array of symptoms seems to have led to more serious clinical consequences such as dehydration, hyponatremia (and other electrolyte disturbances), acute renal failure and hypovolemic cardiac failure –among others– in a significant proportion of patients across the different safety datasets of Study KRYSTAL-1. Patients should be monitored and managed using supportive care, including anti -diarrhoeals, antiemetics, or fluid replacement, as indicated. Based on the severity of the adverse reaction, the dose of adagrasib should either be reduced, temporarily withheld until a return to ≤ Grade 1 or return to baseline then resumed at a reduced dose (see sections 4.2, 4.4 and 4.8 of the SmPC).

-Hepatotoxicity, mostly in the form of elevation of liver enzymes, occurred in nearly a half of patients, but it was mostly of low-grade and overall manageable through dose reductions and interruptions. Liver laboratory tests, including AST, ALT, alkaline phosphatase, and blood bilirubin should be monitored prior to the start of treatment and monthly for 3 months after starting treatment with adagrasib and as clinically indicated, with more frequent testing in patients who develop transaminase and/or alkaline phosphate elevations. Based on the severity of the adverse reaction, the adagrasib dose should either be reduced, temporarily withheld until a return to ≤ Grade 1 or return to baseline then resumed at a reduced dose or permanently discontinued (see sections 4.2 and 4.4 of the SmPC).

-QT prolongations were also frequent (~ a third of patients), but in rare instances led to clinical events of importance. It is recommended that a baseline electrocardiogram (ECG) prior to treatment initiation be performed in all patients and repeated during treatment. When possible, the use of adagrasib should be avoided in patients with congenital long QT syndrome, in patients with concurrent QTc prolongation and in patients who have experienced torsades de pointes arrhythmia in the past. Periodic monitoring with electrocardiograms and electrolytes should be considered in patients with congestive heart failure, electrolyte abnormalities, or those who are taking medicinal products that are known to prolong the QTc interval. Based on the severity of the adverse reaction, and after correction of any possible electrolyte disturbances, treatment with adagrasib can be continued with a reduced dose or temporarily discontinued followed by resumption at a reduced dose after a return to ≤ Grade 1 or return to baseline. In patients who develop QTc interval prolongation with signs or symptoms of life threatening arrhythmia, adagrasib should be permanently discontinued. The use of medicinal products known to prolong the QTc interval should be avoided (see sections 4.2, 4.5 and 4.8 of the SmPC).

- Based on case-analysis, there is not enough evidence to indicate that MRTX849 has a causal association with the event acute kidney injury. Thus, acute kidney injury is not considered as an Adverse Drug Reaction (ADR) at this time. In a review of the 5 SAEs, all patients experienced nausea/vomiting, diarrhea, and reduced oral intake which can be managed by medications or fluid hydration. This indicates that the acute kidney injury is potentially preventable.

- Food effect: In relation to the tolerability issue, the Applicant has hypothesized that a tablet formulation and food effect may decrease the issues related to GI toxicity. All patients in Study 849-001 included in this summary received MRTX849 in a capsule presentation. A tablet presentation and food effect evaluation have recently demonstrated similar exposures to support commercial dosing of a tablet with or without food. Additionally, during the conduct of the bioavailability study (Study 849-011 CSR food effect, part 3), the frequency of gastrointestinal disorders, particularly diarrhea, nausea, abdominal pain, and vomiting, appeared to be lower when tablets were taken with food as compared to fasted conditions.

The effect of food on adagrasib tolerability in patients, is being investigated further in the dose-optimization Study 849-021 (recommendation). Tolerability is an important aspect of adagrasib, as a large proportion of patients seem to have gastrointestinal side-effects and reducing these effects is of interest. The tablet formulation is to be further explored in study 849-012 (Phase 3).

Safety on special populations: Patients of 75 years or older experienced overall a higher degree of toxicity than patients of less than 75 years, which is as expected. There are no unexpected findings or tendencies in the presented safety data by intrinsic factors (gender, age, race, tumour type, ECOG PS). Treatment with adagrasib was better tolerated in patients with PS 0 vs 1.

Interactions, particularly with proton pump inhibitors (quite commonly used in Oncology) are well described in Section 4.5 of the SmPC.

Dose reductions and interruptions: The three most frequent AEs leading to reductions or interruptions were nausea (29.8%), liver disorders (18.1%) and diarrhoea (15.4%). Fatigue was the following category leading to reductions and interruptions (14.9%), then lung infections (8%) and dyspnoea (7.4%).

Treatment discontinuations: As was the case with SAEs, the main categories of AEs leading to permanent discontinuations in the NSCLC pool (26 out of 188 patients, 14%) were lung infections (4 patients), pneumonitis/respiratory failure/dyspnoea (5 patients) and decreased ejection fraction (2 patients).

Additional safety data needed in the context of a conditional MA

Additional safety data, including comparative results in a population similar to that intended in the indication, were expected as part of the confirmatory study 849-012 intended to fulfil a CMA.

2.6.10. Conclusions on the clinical safety

The safety profile of Krazati is characterised by gastrointestinal toxicity in the form of nausea/vomiting/diarrhoea, hepatotoxicity and risk for QT prolongation. The first is of particular concern, as it creates an additional symptomatic burden and may lead to dehydration, hyponatremia and/or acute renal failure. Hepatotoxicity and QT prolongation require close monitoring but can be managed with dose reductions or temporary interruptions. The uncontrolled design of the pivotal trial 849-001 hampers assessment of the causality of reported adverse events. In addition, there is no direct comparison of the Krazati safety profile with currently authorised alternatives (sotorasib,

chemotherapy and immunotherapy). In the absence of long-term safety data, the risks for patients of cumulative toxicity, rare adverse events or delayed toxicity cannot be assessed.

The CHMP considered the following measures necessary to address the limitations in the safety data submitted in the context of a conditional MA:

In order to further confirm the efficacy and safety of adagrasib in the treatment of patients with KRAS G12C-mutated NSCLC, the MAH was recommended to submit the clinical study report for the phase 3 clinical study KRYSTAL-12, comparing efficacy of adagrasib versus docetaxel in patients with NSCLC with KRAS G12C mutation and who have received prior therapy. The clinical study report was planned to be submitted by 30 September 2024.

2.7. Risk Management Plan

2.7.1. Safety concerns

None

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

None

2.7.4. Conclusion

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

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

2.8.2. Periodic Safety Update Reports submission requirements

Not applicable.

2.9. Product information

2.9.1. User consultation

In light of the negative recommendation, a satisfactory package leaflet cannot be agreed at this stage.

2.9.2. Additional monitoring

Not applicable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The sought indication is: *KRAZATI as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with KRAS G12C mutation and disease progression after at least one prior systemic therapy.*

3.1.2. Available therapies and unmet medical need

In the absence of a targeted treatment option, the preferred initial treatment of advanced/metastatic NSCLC is a combination of platinum-based chemotherapy and immune checkpoint inhibitor therapy. Upon disease progression to these treatments, however, the scarce remaining options provide limited benefits. In non-selected (tumours without targetable genomic aberrations) patients previously treated with platinum-based chemotherapy and a checkpoint inhibitor, docetaxel alone or in combination with ramucirumab or nintedanib, or pemetrexed (if not used in 1L) remain approved chemotherapy options. For patients who did not receive immunochemotherapy upfront, immune checkpoint inhibitors in monotherapy (nivolumab, pembrolizumab, atezolizumab) are also acceptable choices (D. Planchard et al, ESMO 2019). Regarding patients with advanced NSCLC and KRAS mutations, Lumykras (sotorasib) was the first targeted treatment to receive a CMA by the European Commission, in January 2022 (Lumykras EPAR). This product was approved for the treatment of patients with advanced NSCLC with KRAS G12C mutation and who have progressed after at least one prior line of systemic therapy, based on pharmacological, efficacy and safety data from the CodeBreak 100 study, which showed favourable results from sotorasib in the intended population, with an ORR of 37.1% (95% CI: 28.6, 46.2) and a median DOR of 11.1 months (95% CI: 6.9, 15.0). It is to note that updated results from CodeBreak 200 (the confirmatory trial for such initial conditional approval) are already available and outline a statistically positive –albeit clinically marginal– PFS benefit from sotorasib over docetaxel: median PFS 5·6 months [95% CI 4·3–7·8] vs 4·5 months [3·0–5·7]; hazard ratio 0·66 [0·51–0·86]; p=0·0017 (de Langen et al, Lancet 2023). Overall survival in this trial is difficult to interpret due to cross-over.

Despite therapeutic advances, treatment for patients with advanced NSCLC and KRAS G12C mutation remains palliative, and there remains an unmet medical need with additional treatment options warranted.

3.1.3. Main clinical studies

Efficacy results to support this application come from the primary analysis of Cohort A (n=116) from the phase 2 segment of KRYSTAL-1 (Study 849-001), a phase 1/2, open-label, multi-cohort, single-arm trial conducted in the US.

ORR as assessed by BICR is the primary endpoint of efficacy, whereas DOR, PFS and OS are secondary endpoints.

3.2. Favourable effects

At data cut-off (DCO) 15-JUN-2021, 48 patients out of 116 were considered confirmed responders by retrospective BICR, accounting for an ORR of 41.4% (95% 32.3, 50.9). Analysis of ORR by investigator (37.1%) was concordant. Subgroup analysis suggest that the ORR benefit from adagrasib was consistent across the main predefined categories. At the updated DCO 15 October 2021, no new objective responses were reported between the two data cutoffs, and ORR by BICR remained at 41.4%.

With ~40% of progression events in responders at data cut-off 15 June 2021, median duration of response (mDOR) was estimated at 7.3 months. At the updated DCO 15 October 2021, mDOR had slightly improved to 8.5 (95% CI: 6.2-13.8) months.

At DCO 15 October 2021, mPFS was 6.0 (95% CI: 4.7-8.4) months and mOS was 11.7 (95% CI: 9.2-NE) months. Maturity of PFS was 59.5% and of OS was 49.1%. The additional update of OS with DCO 15 January 2022 reported median OS of 12.6 months (95% CI: 9.2, 19.2) with a maturity of 53%.

3.3. Uncertainties and limitations about favourable effects

Long-term treatment benefits remain to be proven when the results from confirmatory trial 849-012 become available.

Emerging data from the randomised controlled CodeBreak 200 trial comparing sotorasib to docetaxel (de Langen et al. Lancet. 2023), give reason to question whether the magnitude of effect observed with adagrasib is likely to translate into a major therapeutic advantage over docetaxel.

3.4. Unfavourable effects

The overall safety database of adagrasib is constituted by 260 patients across multiple cohorts from pivotal phase 1/2 Study KRYSTAL-1. The NSCLC safety pool (n=188) contains the highest number of patients with similar clinical characteristics and background as the targeted population in the proposed indication for treatment with adagrasib (strictly represented by Cohort A).

All patients that started treatment with adagrasib experienced adverse events. In the NSCLC pool, ~80% of patients presented high-grade (≥G3) AEs, ~60% SAEs, 18% AEs with outcome of death, 14% AEs leading to treatment discontinuation and 84% AEs leading to dose reduction/interruption.

The **most common AEs** in the NSCLC pool were diarrhoea (71%), nausea (70%), vomiting (57%), fatigue (57%), anaemia (35%), dyspnoea (35%), decreased appetite (35%), increased creatinine (34%), increased aspartate aminotransferase (32%), increased alanine aminotransferase (32%), peripheral oedema (29%), constipation (23%), alkaline phosphatase increased (22%) and QT prolonged (19%).

Anaemia (11.7%), dyspnoea (11.7%), fatigue (9.0%), pneumonia (8.5%), hypoxia (7.4%), lipase increased (6.9%), hyponatremia (6.9%), and lymphocyte count decreased (5.9%) were the most common **high-grade (≥G3) AEs** in the NSCLC pool.

Respiratory/thoracic/mediastinal disorders (21%) and infections (19%) were the most common types of **SAEs**. Expectedly, pneumonia was the first cause for hospitalisation across the NSCLC pool.

AEs with outcome of death occurred in 33 patients (~18%) from the NSCLC pool, out of which 12 deaths were declared as AE of "malignant neoplasm progression". As expected in this clinical setting, AEs with outcome of death were related to respiratory/thoracic/ mediastinal disorders in the majority

of cases, while few patients died from heart-related or infectious causes. Four (2%) of the deaths were adagrasib-related.

It is considered that gastrointestinal toxicity in the spectrum of nausea/vomiting/diarrhoea, hepatotoxicity and QTc prolongation are the main **AESIs** from adagrasib.

Nausea (26%), vomiting (16%) diarrhoea (15%) and hepatotoxicity (14% ALT increased and 11% AST increased) were the most frequent **AEs leading to dose reductions or interruptions**.

As was the case with SAEs, the main categories of **AEs leading to permanent discontinuation** of adagrasib in the NSCLC pool (26 out of 188 patients, 14%) were infections (7 patients) and respiratory/thoracic/mediastinal disorders (7 patients).

3.5. Uncertainties and limitations about unfavourable effects

The uncontrolled design of the pivotal trial 849-001 phase precludes a causality assessment. Also there is no direct comparison of the adagrasib safety profile with currently authorised alternatives (sotorasib, chemotherapy and immunotherapy).

Long-term safety data are not available, and it thus cannot be assumed that cumulative toxicity, rare adverse events nor delayed toxic events do not occur. This could be addressed by the confirmatory study 849-012.

3.6. Effects Table

Table 76: Effects Table for adagrasib in the treatment of patients with advanced NSCLC with KRAS G12C mutation, who have received platinum-based chemotherapy and immunotherapy. Data cut-off for efficacy 15-OCT-2021 and for safety 15-OCT-2021.

Effect	Short Description	Unit	Adagrasib, N=116	Uncertainties/ Strength of evidence	References
Favourable Effects					
ORR-BICR	Overall response rate by BICR	% (95% CI)	41.4 (32.3, 50.9)	Single-arm trial	KRYSTAL-1 CSR
mDOR-BICR	Median duration of response by BICR	Months (95% CI)	8.5 (6.2, 13.8)	Single-arm trial	KRYSTAL-1 CSR
Unfavourable Effects in the total safety dataset, N=260					
High-grade (≥G3) AEs		%	42		SCS
SAEs		%	51		SCS
AEs outcome of death		%	15		SCS
AEs leading to discontinuation		%	11		SCS
AEs leading reductions or interruptions		%	77		SCS

Effect	Short Description	Unit	Adagrasib, N=116	Uncertainties/ Strength of evidence	References
Nausea/vomiting/diarrhoea		%	90		SCS
Hepatotoxicity		%	39		SCS
QT prolonged		%	19		SCS

Abbreviations: BICR=blinded independent central review; NE=not estimable
Notes: The safety dataset includes the NSCLC pool (N=188: 116 patients from cohort A, 56 patients from cohort B, 16 patients from Phase 1/1b) and 72 patients with other tumours.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

KRAS is the most common oncogene driver in human cancer and has been the subject of extensive drug development efforts along the last 40 years. Most of these approaches have not proved successful in clinical studies, but the recent discovery of a vulnerable GTP/GDP binding pocket in the KRAS protein has shown encouraging clinical developments. Sotorasib being the first in the class has been conditionally approved for the treatment of patients with advanced NSCLC with KRAS G12C mutations who have progressed after prior systemic therapy.

Efficacy results from KRYSTAL-1, an uncontrolled single-arm trial, provide preliminary evidence for a relevant treatment effect from adagrasib in the target population. Data from response-related endpoints are improved in comparison to fully marketed choices and appear comparable to the other conditionally approved product, sotorasib. However, emerging data from the randomised controlled CodeBreak 200 trial comparing sotorasib to docetaxel (de Langen et al. Lancet. 2023), give reason to question whether the magnitude of effect observed with adagrasib is likely to translate into a major therapeutic advantage over docetaxel. In addition, there is no direct comparison of the Krazati efficacy profile with currently authorised alternatives (sotorasib, chemotherapy and immunotherapy). Furthermore, the long-term benefit of Krazati is unclear since its impact on time-to-event endpoints, i.e., PFS and OS, cannot be reliably estimated in the context of an uncontrolled trial.

The safety profile of adagrasib is characterised by gastrointestinal toxicity in the form of nausea/vomiting/diarrhoea, hepatotoxicity and a significant risk for QT prolongation. Of especial concern is the first, because it creates an additional symptomatic burden and may lead to dehydration, hyponatremia and/or acute renal failure, among others. Hepatotoxicity and QT prolongation require close monitoring but can be more easily controlled with dose reductions or temporary interruptions. The uncontrolled design of the pivotal trial 849-001 hampers assessment of the causality of reported adverse events. In addition, there is no direct comparison of the Krazati safety profile with currently authorised alternatives (sotorasib, chemotherapy and immunotherapy). In the absence of long-term safety data, the risks for patients of cumulative toxicity, rare adverse events or delayed toxicity cannot be assessed.

3.7.2. Balance of benefits and risks

In view of the limitations of the submitted non-comprehensive data package and considering that a major therapeutic advantage over existing therapies has not been established, the CHMP considers that the benefits to public health of the immediate availability of Krazati do not outweigh the risks

inherent in the fact that additional data are still required in the context of a conditional marketing authorisation.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

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

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

In the context of the conditional marketing authorisation (CMA) application, and to provide comprehensive data post approval, the applicant proposed to provide the results from the randomised controlled phase III trial 849-012 as a specific obligation (SOB).

Efficacy results from the single-arm trial KRYSTAL-1 provide preliminary evidence for a promising treatment effect from Krazati in the targeted population. Data from response-related endpoints appear comparable to Lumykras, the other conditionally approved product in this setting.

However, emerging data from the randomised controlled CodeBreak 200 trial comparing sotorasib to docetaxel (de Langen et al. Lancet. 2023), give reason to question whether the magnitude of effect observed with adagrasib is likely to translate into a major therapeutic advantage over docetaxel. This is due to the similar mechanism of action of adagrasib and sotorasib, along with the fact that the applicant was unable to demonstrate any specific pharmacological differences, that would support an anticipation of more favorable effects on time dependent endpoint (PFS; OS) than what was seen with sotorasib.

It is noted that Krazati is orally administered and has a different safety profile than docetaxel. However, these attributes alone are not considered sufficient to address the unmet medical need. Therefore in the absence of an established major therapeutic advantage and in view of the non-comprehensive data on efficacy and safety, it is considered that the benefits to public health of the immediate availability of Krazati do not outweigh the risks inherent in the fact that additional data are still required.

3.8. Conclusions

In the context of the conditional marketing authorisation, the CHMP considers that the efficacy and safety of Krazati is not properly or sufficiently demonstrated in view of the limitations of the submitted non-comprehensive data package and considering that the requirements laid down in Article 4 of Commission Regulation (EC) No 507/2006 are not met.

Divergent position is appended to this report.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Krazati as monotherapy in the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with KRAS G12C mutation and disease progression after at least one prior systemic therapy, the CHMP considers by

majority decision that the requirements laid down in Article 4 of Regulation (EC) No 507/2006 are not met and pursuant to Article 12 of Regulation (EC) No 726/2004, the safety and efficacy of the above-mentioned medicinal product is not properly or sufficiently demonstrated in the context of a conditional MA application and therefore recommends the refusal of the granting of the conditional marketing authorisation for the above-mentioned medicinal product.

The CHMP considers that:

- In view of the limitations of the submitted non-comprehensive data package and considering that a major therapeutic advantage over existing therapies has not been established, the CHMP considers that the benefits to public health of the immediate availability of Krazati do not outweigh the risks inherent in the fact that additional data are still required in the context of a conditional marketing authorisation.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and post-authorisation measures cannot be agreed at this stage.

Divergent position

Divergent position to the majority recommendation is appended to this report.

New active substance

Furthermore, following review of the available data in the context of the applicant's claim of new active substance status, the CHMP position at the time of this report is that adagrasib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union. The CHMP position at the time of this report is reflected in Appendix 5.1. This is without prejudice to the CHMP's recommendation to refuse the granting of the conditional marketing authorisation for Krazati on the above-mentioned grounds.

5. Re-examination of the CHMP opinion of 20 July 2023

Following the CHMP conclusion that Krazati was not approvable based on insufficient justification of an unmet medical need and of the benefits to public health of the immediate availability outweighing the risks inherent in the fact that additional data are still required, as per conditional MA criteria, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Detailed grounds for re-examination submitted by the applicant

The applicant presented in writing and at an oral explanation the following detailed grounds for re-examination.

A summary of the applicant's grounds for re-examination is presented below

Ground for re-examination #1

CMA Requirement (c): Unmet Medical Need

CHMP's main objection states that adagrasib does not fulfill an unmet medical need as a major therapeutic advantage over existing therapies has not been established. According to the CHMP, the data from the randomised controlled CodeBreaK 200 trial comparing sotorasib to docetaxel, gave

reason to question whether the magnitude of effect observed with adagrasib is likely to translate into a major therapeutic advantage over docetaxel. This was due to the similar mechanism of action of adagrasib and sotorasib, along with the fact that the applicant was unable to demonstrate any specific pharmacological differences, that would support an anticipation of more favourable effects on time dependent endpoint (PFS; OS) than what was seen with sotorasib.

The applicant respectfully disagrees with the above scientific assessment and provides a detailed discussion of adagrasib fulfilling the unmet medical need and concludes that:

i. despite CodeBreaK 200 data, adagrasib brings a major therapeutic advantage over fully authorised docetaxel (Section 1); and

ii. adagrasib addresses the unmet medical needs to a similar or greater extent compared to conditionally approved sotorasib (Section 4).

1. Definition of Major Therapeutic Advantage

When determining fulfilment of the unmet medical need, the assessment of a major therapeutic advantage is a key point for this re-examination and the CHMP assessment. Commission Regulation (EC) No 507/2006 ("CMA Regulation") and CHMP ''Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004' are the key frameworks when assessing whether adagrasib fulfils an unmet medical need.

It is important to highlight that the CMA Guidance does recognise different bases to conclude that a medicinal product provides a major therapeutic advantage, and it is also important to note that each of these criteria alone is sufficient for recognising a major therapeutic advantage.

Therefore, a claim of major therapeutic advantage can be supported either by (1) meaningful improvements of efficacy, or (2) by meaningful improvements of clinical safety, or (3) by major improvements to patients care (or by a combination thereof).

Moreover, Art. 4 (2) of the CMA Regulation requires that the new product shows a **major therapeutic advantage against a treatment with a full marketing authorisation**. The CMA Guideline clarifies that major therapeutic advantage should be shown over "***existing methods used in clinical practice*** *using robust evidence, normally from well conducted randomised controlled trials (evidence-based demonstration of benefit).*"

Below, the Applicant addresses each of the above requirements individually as the Applicant believes that the CHMP has not all of them sufficiently considered in its assessment, also summarised in Section 5.

2. Docetaxel

Adagrasib has to demonstrate a major therapeutic advantage over the fully authorised medicinal product used in clinical practice for patients with advanced NSCLC with a KRAS G12C mutation. Docetaxel is the fully approved existing agent used in clinical practice for patients with advanced NSCLC with KRAS G12C mutation. It constitutes the fully approved SOC treatment method used in clinical practice after failure with chemoimmunotherapy. The applicant holds that adagrasib is of major therapeutic advantage over docetaxel for the following reasons:

2.1. Efficacy

Study 849-001 Cohort A shows significantly improved efficacy for adagrasib over docetaxel. Study 849 001, Cohort A, was designed to demonstrate the safety and efficacy of adagrasib in a Single-Arm-Trial

(SAT). Consistent with the draft EMA Guidance "Reflection paper on establishing efficacy based on single arm trials submitted as pivotal evidence in a marketing authorisation," several key steps were taken within the context of this trial to limit uncertainty and facilitate interpretation of study results:

- Selection of the patient population that had received key treatments – platinum-based chemotherapy and a checkpoint inhibitor – enabled optimal assessment of benefit-risk.
- The primary study endpoint of ORR was chosen not only because responses by RECIST 1.1 indicate a direct tumour effect that does not occur spontaneously for the indicated population, but it is also clinically meaningful when accompanied by durable responses and manageable safety.
- An a priori definition of success that reflects clinical benefit relative to available treatment options, including docetaxel, was specified: An ORR for which the lower bound of the 95% CI excludes 23%, the highest ORR reported for a docetaxel-based regimen in a Phase 3 study.

The activity of docetaxel in NSCLC after treatment with platinum-based chemotherapy (with or without other subsequent treatment) has been reported for several Phase 3 trials, demonstrating the consistency of the estimates for ORR, PFS, and OS. Initial studies demonstrated an ORR that was typically <10% and a median PFS of approximately 3 months. More recently, clinical trials that included a treatment arm with docetaxel consistently show an ORR of approximately 12-13% and a PFS of approximately 4 months. The highest ORR reported among these trials was 23% (95% CI: 19.7, 26.4), which was reported for the combination of docetaxel and ramucirumab administered after a maximum of one prior treatment regimen for advanced disease; the results of this study was an outlier compared to other trials. The use of ORR from this trial represents a very conservative approach, particularly when this regimen is only infrequently used.

Table 77: Efficacy Estimates for Docetaxel Regimens in Phase 3 Clinical Trials

		ORR (95% CI)	**Median PFS (95% CI), months**	**Median OS (95% CI), months**	**Reference**
Docetaxel Monotherapy: Early Experience		7.1%	NR	7.5	Shepherd, 2000
		6.7% (3.1, 13.1)	NR	5.7	Fossella, 2000
		8.8%	2.9	7.9	Hanna, 2004
		14%	3.0 (2.8, 3.9)	9.1 (8.4, 10.0)	Garon, 2014
		3.6%*	2.8*	10.3*	Vargatef EPAR, 2015
Combinations	Ramucirumab	23% (19.7, 26.4)	4.5 (4.2, 5.4)	10.5 (9.5, 11.2)	Garon, 2014
	Nintedanib	4.7%* (2.6, 7.6)	4.2* (3.2, 4.4)	12.6* (10.6, 15.1)	Vargatef EPAR, 2015
Docetaxel Monotherapy in the Era of Immunotherapy Trials		12% (9, 17)	4.2 (3.5, 4.9)	9.4 (8.1 to 10.7)	Borghaei, 2015

	ORR (95% CI)	Median PFS (95% CI), months	Median OS (95% CI), months	Reference
	8%†	4.0 (3.1, 4.2) †	8.5 (7.5, 9.8) †	Herbst, 2016
	13%	4.0 (3.3, 4.2)	9.6 (8.6, 11.2)	Rittmeyer, 2017
	13.7%‡	2.8‡	7.9‡	Jänne, 2017
	12%	4.1 (3.0, 5.3)	10.3 (8.5, 13.0)	Barlesi, 2018
Docetaxel Monotherapy in the Era of Immunotherapy‖	14%	4.2	11.3	Paz-Ares, 2021
	13.3%	4.0 (3.1, 4.4)	10.5 (8.6, 13.0)	Neal, 2023
	13.2%§ (8.6, 19.2)	4.5§ (3.0, 5.7)	11.3§ (9.0, 14.9)	de Langen, 2023

* adenocarcinoma only; †PD-L1≥1% only; ‡KRAS mutant only; §KRAS G12C mutant only; ‖available only after start of pivotal Study 849-001

With respect to these considerations, the benchmark for ORR for the control treatment was intentionally set to be the highest ORR reported in a Phase 3 study for a docetaxel-based regimen in heavily pre-treated NSCLC: 23% (95% CI: 19.7, 26.4) for the combination of docetaxel and ramucirumab. Cohort A was designed such that the lower limit of the 2-sided 95% CI (Clopper-Pearson method) of the ORR would exclude this benchmark ORR of 23%. Imaging frequency scheduled every 6 weeks was typical of reference trials to mitigate ascertainment bias, and blinded, independent central review was performed for the primary analysis to limit assessment bias.

Based on the aforesaid and by comparing data side by side for docetaxel, specifically in KRAS G12C-mutant advanced NSCLC, with the results from adagrasib, it is evident that adagrasib shows benefits including, but not limited to (i) 3x more patients responding to adagrasib versus docetaxel (ORR 41.4% vs. 13.2%), and (ii) a significant rate of durable responses, with 4x more patients experiencing a response lasting ≥6 months versus docetaxel (24.1% vs. 5.3%). At the latest DCO of 15 October 2021, 48 out of 116 patients treated achieved confirmed responses as assessed by BICR, leading to an ORR of 41.4% (95% CI: 32.3, 50.9), with the lower bound of the 95% CI excluding the benchmark ORR of 23%. The median duration of response (mDOR) was 8.5 months (95% CI: 6.2, 13.8).

The clinically meaningful ORR and DOR are key parameters supporting CMA applications for oncology treatments. An ORR of approximately 40% or more, when combined with meaningful DOR and acceptable safety profile, has conventionally supported a CMA. It is worthwhile noting that CHMP drew its conclusion for sotorasib based on ORR and DOR alone without commenting on the magnitude of effect on PFS, and Applicant presumes that the design of CodeBreaK 200 was agreed by CHMP, including the target magnitude of effect used for the sample size calculation. Completed confirmatory trials have shown that this level of activity on ORR translates into significant improvement in PFS over standard therapy (e.g., docetaxel) in NSCLC. The CHMP assessment of sotorasib underlines the aforesaid by stating that "*…the observed ORR of 37% is considered clinically meaningful in the patient population with advanced NSCLC carrying G12C mutation, and it is also higher than the ORRs observed with non-targeted treatments and docetaxel …the current response rate is considered relevant …* [and] *supports clinically relevant response duration and clinical benefit.*"

As CHMP considered the sotorasib ORR of 37% clinically meaningful and hence addresses an unmet medical need versus docetaxel, then the adagrasib ORR of 41.4% versus docetaxel should be assessed similarly. CHMP considered that the sotorasib DOR of 11.1 months supports clinically relevant response duration and clinical benefit. The same applies for the DOR of 8.5 months of adagrasib in 849-001 Cohort A, in which the patient population was more heavily pretreated and had a poorer ECOG performance status. Thus, an ORR of 41.4% with durable responses meets the scientific thresholds of CMA for this indication and the proportion of patients achieving a durable response further supports the efficacy of adagrasib.

Table 78 further illustrates the significant improvement of efficacy that adagrasib has demonstrated over docetaxel.

Table 78: Adagrasib Major Therapeutic Advantage Over Docetaxel

Treatment	**ORR (95% CI)**	**Median DOR, Months (95% CI)**	**Treated Patients with Response ≥ 6.0 Months (95% CI)**
Adagrasib (600 mg BID)	41.4% (32.3, 50.9)	8.5 (6.2, 13.8)	24.1% (28/116) (16.7, 33.0)
Approved SOC for Second-Line NSCLC			
Docetaxel (75 mg/m^2)[1] (estimates shown for *KRAS*^{G12C} mutant NSCLC)	13.2% (8.6, 19.2)	6.8 (4.3, 8.3)	5.3% (8/151) (2.3, 10.2)

[1]de Langen, 2023

The efficacy of adagrasib observed in 849-001 is highly relevant to clinical practice when treating patients with advanced NSCLC with KRAS G12C mutation. The 3-fold increase in ORR with adagrasib over published data on docetaxel represents greater tumour shrinkage and better disease control with adagrasib. Importantly the lower bound of the 95% CI for adagrasib ORR excluded the benchmark ORR of 23%. Furthermore, a meta-analysis of 15 comparative trials indicates that the 3-fold increase in ORR observed with adagrasib, in hard-to-treat patients, is expected to translate into improved PFS. The meta-analysis found a strong correlation between ORR and PFS (correlation coefficient -0.78). This is not surprising given that both ORR and PFS are tumour-based endpoints, hence it is reasonable to assume that high ORR will be associated with longer PFS.

Docetaxel achieves DOR of approximately 6.8 months (median), but response is observed in only approximately 13% of treated patients. Adagrasib on the other hand, not only achieves a longer median DOR of 8.5 months, but also achieves objective responses in over 40% of patients. Increasing both the proportion of responding patients and the durability of the response in patients who are particularly hard-to-treat due to extensive prior therapies and poor ECOG status underscores the relevance of the therapeutic effect.

In addition, the nearly fivefold increase in patients with responses beyond 6 months, compared to published data on docetaxel, underscores that the benefits of adagrasib are durable. In daily practice, response assessment along with other indicators of patient's condition guides decision-making, and the results observed with adagrasib will further improve outcomes for patients with advanced KRAS G12C-mutant NSCLC.

Moreover, 849-001 Cohort A, ORR was selected as the surrogate endpoint in support of a potential CMA, which is in accordance with EU guidance. Although ORR may be considered a clinically meaningful endpoint on its own when sufficiently high, improvement in OS remains a more readily

accepted endpoint to demonstrate efficacy in oncology trials. The applicant claimed that response has been associated with OS in published patient-level analyses. These data suggest an ORR of 40% in the second-line treatment of NSCLC will translate into a clinically meaningful impact on OS, which is further supported when the observed responses are durable; these observations support the use of ORR as a surrogate endpoint in NSCLC.

Through the CMA procedure, the EMA supports the development of medicines that address unmet medical needs. For applications for agents intended for the treatment of cancer, trial endpoints of ORR and DOR are commonly used for demonstration of efficacy. Specifically for targeted agents intended for the treatment of 2L+ NSCLC, ORR of approximately 40% along with durable responses and an acceptable safety profile have supported CMA approvals. Recent examples are shown in **Table 79** below, along with data for adagrasib. The recent CMA approvals demonstrate that adagrasib has demonstrated the effectiveness with an ORR and DOR that have sufficiently limited uncertainty for CMA.

Table 79: Targeted NSCLC Therapies Granted a CMA on the Basis of a SAT

Agent	Line of Therapy	ORR	DOR
adagrasib	2L+	41.4%	8.5 mos
ceritinib	2L	56.4%	8.3 mos
alectinib	2L	44.8%	15 mos
lorlatinib	2L, 3L	42.9%, 38.7%	5.6, 9.9 mos
amivantamab-vmjw	2L+	37%	12.5 mos
capmatinib	2L+	44%	9.72 mos
tepotinib	2L+	44%	11.1 mos

Fully approved treatment options for patients with KRAS G12C mutation who have received first line treatment with platinum chemotherapy and/or a checkpoint inhibitor are almost exclusively limited to docetaxel, either alone or in combination with either nintedanib or ramucirumab. The highest ORR reported with a second-line docetaxel regimen is 23% (95% CI: 19.7, 26.4). The pivotal cohort of adagrasib was designed to demonstrate a greater ORR relative to this benchmark. This study demonstrated an ORR of 41.4% (95% CI: 32.3, 50.9) with the lower bound of the 95% CI excluding the benchmark ORR of 23%, representing a major therapeutic advantage over a regimen with a full marketing authorisation in the EU.

2.2. Brain Metastases

Effective treatment of brain metastases is of paramount importance. During the sotorasib assessment, CHMP has stated that there is "*historical evidence of poor outcomes in patients with brain metastases compared to patients without" and that "ongoing study in subjects with NSCLC and brain metastases should further inform the effect in this population*".

Another key differentiation versus docetaxel is the clinically significant level of intracranial activity observed for adagrasib. Analyses from study 849-001 have demonstrated an ORR of 33.3% using m-RANO-BM in treated, stable brain metastasis and more importantly, an ORR of 42% with CNS RECIST v1.1 in untreated, active brain metastasis. In addition, Negrao et al demonstrated the high concordance (79%) between systemic and intracranial disease control. The key results from the 849-

001 study summarising the impact of adagrasib on brain metastases is shown in Table 80. The level of intracranial brain response represents another point of positive differentiation for adagrasib compared to docetaxel, for which the systemic response rate is estimated at 13.2%.

In support of the high intracranial response rate, adagrasib has significant cerebrospinal fluid penetration as shown by the unbound brain to unbound plasma concentration ratio (Kp,uu) of 0.47 in subjects with brain metastases. This ratio is consistent with the ratio for other well documented CNS penetrant targeted therapies which have shown meaningful intercranial objective response rates in patients with brain metastases: for example, osimertinib (Kp,uu = 0.39), alectinib (Kp,uu = 0.63-0.94), and lorlatinib (Kp,uu = 0.75).

Table 80: Intracranial Activity Observed in Study 849-001

	Retrospective Cohort A Treated Brain Metastasis (95% CI)	**Prospective Phase 1b Untreated Brain Metastasis[c] (95% CI)**
No. with Brain Metastases	42[a]	25
No. Evaluable[b]	33	19
Median F/U	15.4 months	13.7 months
ORR[a,c]	33% (18.0, 51.8	42% (20.3,66.5)
Median icDOR[a,c]	11.2 months (3.0, NE)	12.7 months (3.9, NE)
Median icPFS[a,c]	5.4 months (3.3, 11.6)	5.4 months (2.7, NE)

[a] Centrally-assessed using mRANO-BM, b Includes patients who underwent brain imaging at baseline and at least once on-study, c Preliminary results provided in Response to Day 120 List of Questions are updated here using a DCO of 01Aug2022.
Kp,uu = 0.47
Phase 1b cohort evaluated using CNS RECISTv1.1
Treated = Spira, 2022; Untreated = Negrao, 2023

2.3. Clinical Safety and Patient Care

The possibility to grant a CMA is provided in the interest of patients, to ensure that their medical needs can be addressed. The assessment of the criteria needs to be based on a detailed and objective scientific assessment of all relevant elements. Applicant holds that additional benefits of adagrasib that would establish a major therapeutic advantage over docetaxel were not fully considered, most notably, adagrasib's improved safety profile over docetaxel and the major improvements in patient care.

2.3.1. Meaningful Improvement of Clinical Safety

Considering the incurable nature of advanced NSCLC, decisions on treatment methods should also prioritise patients' quality of life. The severe peripheral neuropathy and alopecia caused by docetaxel have detrimental effects on activities of daily living and emotional well-being.

In addition, unlike docetaxel, life-threatening and resource intense febrile neutropenia is not seen with adagrasib due to its distinct mechanism of action. Grade 4 neutropenia is common with docetaxel treatment, affecting 54.2% of NSCLC patients. This degree of neutropenia increases the risk for febrile neutropenia (FN), a medically important adverse event that often necessitates hospitalisation and

antibiotic treatment. FN rates were evaluated in advanced NSCLC patients treated with docetaxel as 2L therapy in routine clinical practice; the study reported that 17.4% of NSCLC patients encountered at least one episode of FN, resulting in an average hospital stay of 9.2 days. This finding is important when deciding on optimal choices for 2nd line treatment.

2.3.2. Major Improvement to Patient Care

CMA Guidance states that major improvements to patient care could also provide a major therapeutic advantage and explicitly refers to a new treatment allowing ambulatory treatment instead of treatment in hospital. It has been dismissed that adagrasib is administered orally by the patient at home, whereas docetaxel requires an infusion to be carried out in specialised units under the supervision of physician.

Adagrasib's oral administration also reduces healthcare resource use compared to docetaxel by eliminating the need for intravenous administration, thus improving patient care. According to the Taxotere® prescribing information, the administration of docetaxel necessitates premedication with dexamethasone at a dosage of 16 mg per day for 3 days and administration of docetaxel only in specialised units under the supervision of physician. Again, treatment with adagrasib, an oral oncolytic, is initiated by physician and subsequently taken home, thus removing the demand for healthcare resource use entailed with docetaxel administration.

Additionally, in palliative settings, both doctors and patients show a preference for oral administration of anticancer treatments over intravenous regimens. A study conducted in France that assessed physicians' preferences for prescribing oral versus intravenous anticancer drugs highlighted that, particularly in a palliative setting, oral administration route was a significant factor influencing treatment selection. Similarly, many cancer patients also prefer oral anticancer therapy over intravenous treatments for their convenience and perceived benefits in coping with the disease. This preference is further illustrated in the CodeBreak 200 trial, where 13% of patients in the docetaxel arm withdrew from the trial before receiving the treatment.

3. CodeBreaK 200 Does Not Give Reason to Question adagrasib's Major Therapeutic Advantage over Docetaxel

Applicant acknowledges that the CHMP's main concern appears to be CodeBreaK 200 comparing sotorasib to docetaxel, as CHMP believes "*…CodeBreaK 200 give reason to question whether the magnitude of effect observed with adagrasib is likely to translate into a major therapeutic advantage over docetaxel…" and that "…the applicant was unable to demonstrate any specific pharmacological differences, that would support an anticipation of more favorable effects on time dependent endpoint (PFS; OS) than what was seen with sotorasib…*" .

The applicant appreciates CHMP's approach in considering all available scientific data it deems relevant for the assessment of adagrasib's CMA application and understands CHMP applies a scientific judgment in assessing for a major therapeutic advantage over docetaxel by balancing the strength of 849-001 data against the uncertainty due to the pending status of adagrasib's phase 3 study 849-012, and due to the recent results of CodeBreaK 200,. However, the Applicant respectively disagrees with this scientific judgement for the following reasons:

3.1. Extrapolation of the Effect in CodeBreaK 200 not Justified as adagrasib and sotorasib are Pharmacologically Distinct Different Compounds (no "class effect")

The applicant holds that results from CodeBreaK 200 cannot be applied to the adagrasib efficacy data and that adagrasib should be assessed on its own merits. The CHMP Assessment Report offers no scientific evidence to support a conclusion of pharmacological similarity or extrapolation of estimated

magnitude of treatment effects from CodeBreaK 200. The applicant will provide evidence to show pharmacological differences of putative importance for clinical efficacy.

It is scientifically unsubstantiated when CHMP concludes in the final assessment report that "… *emerging data from the randomised controlled CodeBreaK 200 trial comparing sotorasib to docetaxel give reason to question whether the magnitude of effect observed with adagrasib…This is due to the similar mechanism of action of adagrasib and sotorasib.*" A similar mechanism of action cannot justify the extrapolation of CodeBreaK 200 to adagrasib. Although adagrasib and sotorasib belong to the same drug ATC class , they are pharmacologically distinct compounds, as pointed out in the Divergent Position

"…*Pharmacological differences between drugs may result in differences in efficacy and safety, despite having the same primary mechanism of action. These include, e.g., inhibitory potency and binding kinetics to the primary target; target selectivity at relevant exposures; the exposure reached with the proposed dosing regimen; the pattern of exposure over time; tissue distribution, including the extent of CNS penetration; and tolerability at the relevant dose. Data to characterize adagrasib and sotorasib with respect to their pharmacological similarity are incomplete.*"

The available pharmacological data on adagrasib and sotorasib show distinct differences, with multiple properties that suggest positive differentiation of adagrasib over sotorasib and against a "class effect" for magnitude of drug activity; these differences are shown in Table 81 and described in more detail.

Table 81: Adagrasib Medicinal Chemistry and Pharmacokinetics

	Adagrasib	**Sotorasib**	**Potential Implications**
Dosing	600 mg BID	960 mg QD	
Terminal elimination half-life	23 hours	5	Longer half-life provides sustained target inhibition
Peak to Trough Ratio (PTR)	1.07	~40	Low PTR results in sustained drug level which may be advantageous for clinical response and tolerability
Dose-dependent exposure	Yes	No (CYP3A4 autoinduction at 180 to 960 mg QD)	Dose-dependent exposure facilitates management of adverse events
Polar Surface Area (PSA)	87 $Å^2$	102 $Å^2$	Lower PSA correlates with increased permeability, with PSA < 90 $Å^2$ needed for BBB penetration
k_{inact}/K_I	35,000 $M^{-1}S^{-1}$	9,900 $M^{-1}S^{-1}$	Efficiency of covalent bond formation limits off-target toxicity
GSH reactivity (5nM) $t_{1/2}$	2637 mins	200 mins	Longer GSH stability correlates with lower reactivity to thiols and decreased risk of hepatotoxicity
$K_{p,uu}$	0.47	unknown	$K_{p,uu}$ for adagrasib is comparable to other CNS-penetrant targeted

			therapies (osimertinib, 0.39; lorlatinib, 0.75)

Source: Drug Hunter, 2023

The differing k_{inact}/K_I ratios for adagrasib and sotorasib reflect the favourable binding potency and efficiency of covalent bond formation with the Cys12 residue for adagrasib relative to sotorasib. This difference, along with the relative stability when incubated with glutathione (GSH) for adagrasib when compared to sotorasib, are favourable and differentiating attributes for adagrasib that may limit off-target toxicity and decrease the risk of hepatotoxicity. The lower Polar Surface Area (PSA) for adagrasib relative to sotorasib is a factor leading to favourable CNS exposure for adagrasib that may be predictive of the efficacy described in Section 'Brain metastases'.

Adagrasib also exhibits unique and favourable pharmacokinetic (PK) properties in patients compared to sotorasib, which are expected to result in differences in clinical efficacy and safety. Adagrasib exposure increases with increasing dose over the dose range of 150 mg QD to 600 mg BID (Table 82). In contrast, sotorasib exposure did not increase with increasing dose over the dose range of 180 mg QD to 960 mg QD (Table 83), indicating that there are no benefits for patients to receive the approved dose of 960 mg QD compared to lower doses. Furthermore, management of sotorasib-related adverse events is difficult as dose reduction from 960 mg QD to 180 mg QD does not result in reduced drug exposure.

At steady-state, adagrasib concentrations for 600 mg BID show a very low fluctuation during the dosing interval (ie, peak-to-trough ratio of 1.07) with sustained drug concentrations above the target thresholds for durable KRAS inhibition throughout the dosing interval (Figure 24). In contrast, sotorasib concentrations for 960 mg QD exhibit a large fluctuation during the dosing interval (ie, peak-to-trough ratio of approximately 8) with mean concentrations reaching the in vitro IC90 at the end of the dosing interval (Figure 25), indicating no durable KRAS inhibition throughout the dosing interval for most patients. These data suggest that adagrasib 600 mg BID is expected to result in a different and improved efficacy and safety profile over sotorasib 960 mg QD.

Table 82 : Adagrasib Steady-State PK Parameters in Patients

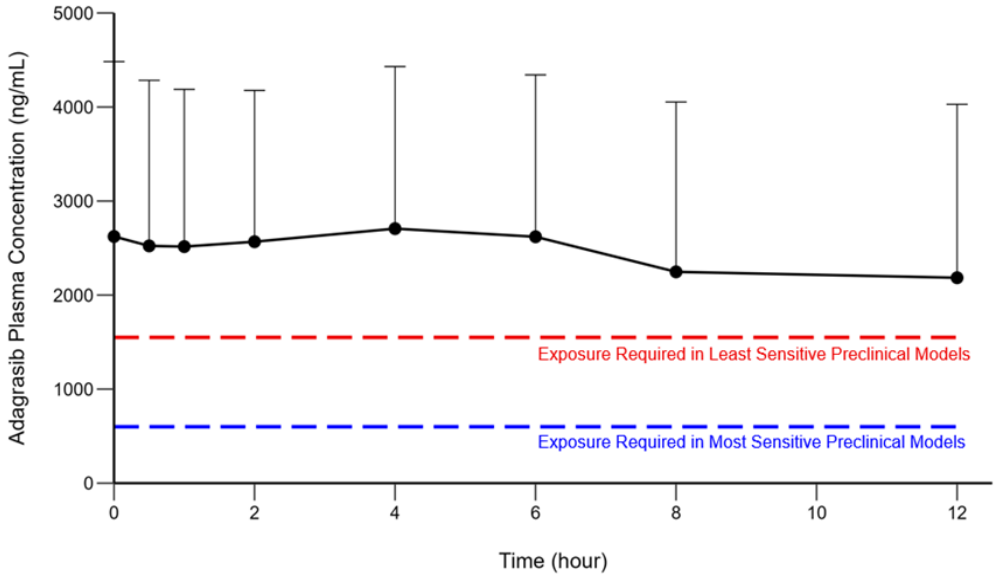
Dose (mg)	**$C_{max,ss}$ (µg/mL)**	**$AUC_{□,ss}$ (µg*h/mL)**
150 mg QD	0.270	3.72
300 mg QD	0.397	6.52
400 mg BID	1.77	18.5
600 mg BID	3.25	31.6

Table 83: Sotorasib Steady-State PK Parameters in Patients

Dose (mg)	**$C_{max,ss}$ (µg/mL)**	**$AUC_{□,ss}$ (µg*h/mL)**
180 mg QD	6.44	31.7
360 mg QD	6.31	38.9
720 mg QD	5.45	42.1
960 mg QD	5.39	32.4

Source: CDER Multi-disciplinary Review, 2020

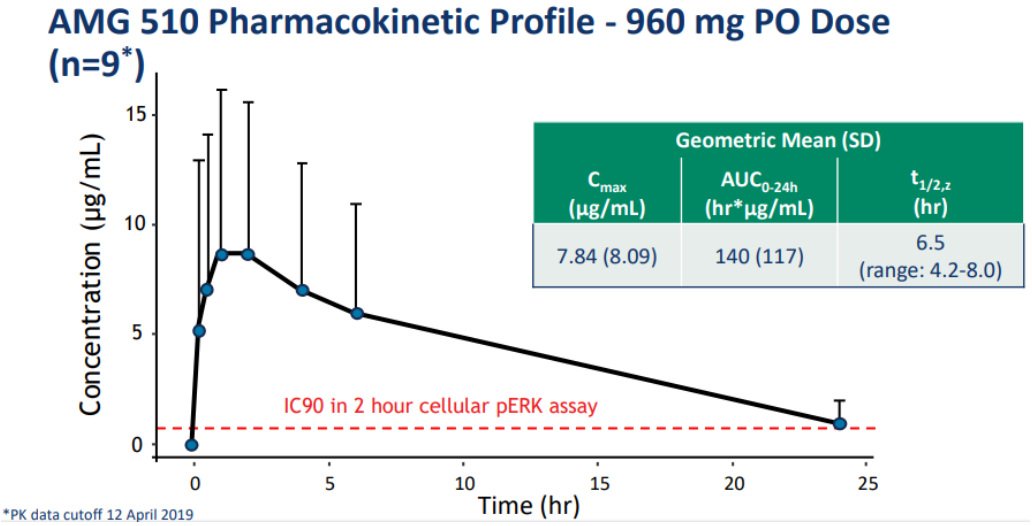
Figure 24: Adagrasib 600 mg BID Steady-State PK Profile



PK Parameter	Geometric Mean (GeoCV%)
$C_{max,ss}$ (ng/mL)	3253 (36.9)
$C_{min,ss}$ (ng/mL)	2693 (39.1)
$AUC_{t,ss}$ (ng*h/mL)	31600 (44.0)
PTR	1.07 (12.9)
$t_{1/2,z}$(h)[a]	23 (16)

[a] Arithmetic mean (CV%)

Figure 25 : Sotorasib 960 mg QD Steady-State PK Profile



Applicant holds that the CHMP should also take into account that, unlike sotorasib, adagrasib has shown significant CNS activity in patients with untreated brain metastases. The $K_{p,uu}$ for adagrasib is 0.47, which is consistent with other well documented CNS penetrant targeted therapies that have shown meaningful intercranial objective response rates in patients with brain metastases, for example, osimertinib ($K_{p,uu}$ = 0.39), alectinib ($K_{p,uu}$ = 0.63-0.94), and lorlatinib ($K_{p,uu}$ = 0.75). CNS exposure is unknown for sotorasib, and for adagrasib this difference presents another important characteristic with the potential for pharmacological and clinical difference from sotorasib.

These differences provide evidence that adagrasib and sotorasib are distinct molecular entities with different pharmacological and clinical characteristics, and that direct extrapolation of the treatment effect of CodeBreaK 200 as a "class effect" is not appropriate.

3.2. Available Evidence Supports the Likelihood That Pharmacological Differences have an Impact on Clinical Outcomes

A more extensive comparison of the available evidence for adagrasib and sotorasib is presented when establishing that adagrasib fulfills an unmet medical need for patients with advanced NSCLC characterised by a KRAS G12C mutation to a similar or greater extent when compared with sotorasib in Section 4. Here, the clinical data are used to provide further evidence that adagrasib and sotorasib are different and hence the magnitude of treatment effect for sotorasib in CodeBreaK 200 cannot be applied to adagrasib.

In a side-by side comparison of results of the full analysis between the adagrasib 849-001 Cohort A and the sotorasib CodeBreaK 100 study, it is evident that the ORR and DOR are numerically comparable:

- adagrasib (n = 116): ORR 41.4% (95% CI: 32.3, 50.9), percentage of subjects with response ≥ 6 months 24.1% (95% CI: 16.7, 33.0)
- sotorasib (n = 126): ORR 37.1% (95% CI: 28.6, 46.2), percentage of subjects with response ≥ 6 months 23.0% (95% CI: 16.0, 31.4)

It is important to note that CodeBreaK 100 included subjects treated with prior platinum-based chemotherapy and/or checkpoint inhibitor therapy (CIT), with only 81.0% receiving both treatments. In contrast, both the adagrasib Phase 2 study (849-001 Cohort A) and the sotorasib Phase 3 study (CodeBreaK 200) had inclusion criteria that required subjects to be previously treated with both platinum and CIT therapy. Thus, the top-line comparison presented above is biased against adagrasib. When focusing on sotorasib subjects who received both treatments, adagrasib demonstrates a different (higher) efficacy with a higher percentage of durable responses (≥ 6 months). See Figure 26.

In a separate, indirect treatment comparison between adagrasib and sotorasib, the data were adjusted for key patient characteristics such as demographics, performance status, histology, and disease extent. A statistically significant 2-fold increase in ORR was observed with adagrasib compared to sotorasib, Odds Ratio (OR)=2.22 (95% CI: 1.25-3.96). Additionally, numerically favourable trends for PFS (HR 0.79 [95% CI: 0.55, 1.12]) and OS (0.81 [0.55, 1.17]) in favour of adagrasib were also observed (Table 84). Applicant is aware of the potential biases inherent in such a comparison even when best statistical epidemiological approaches are applied and a claim of superiority is not the intention behind presenting these data here. Applicant does however consider this strong supportive evidence. Despite use of very different, alternative approaches to compare sotorasib to adagrasib (ie, subset analysis by types of prior treatment versus matching of other baseline features), greater comparative activity was observed for adagrasib, which provides strong evidence to support the

hypothesis that the pharmacological differences (e.g., half-life and predicted sustained target inhibition) lead to differences in clinical efficacy.

Table 84: Adjusted Cross-Trial Comparison

Endpoint	Adagrasib*	Docetaxel		Sotorasib	
		Estimate	HR (95% CI)	Estimate	HR (95% CI)
ORR	46.4%	13.2%	NA**	28.1%	NA**
Median PFS	8.0 months	4.4 months	0.55 (0.38, 0.80)	5.6 months	0.79 (0.55, 1.12)
Median OS	14.7 months	11.2 months	0.83 (0.57, 1.20)	10.2 months	0.81 (0.55, 1.17)

* Adagrasib efficacy outcomes after adjustment for age, sex, ECOG, smoking status, disease extent, and histology
** Odds ratio (OR) for adagrasib vs docetaxel 5.692 (95% CI: 2.99, 10.83); OR for adagrasib vs sotorasib 2.222 (95% CI: 1.25, 3.96)

As stated above, cerebrospinal fluid penetration has been quantified for adagrasib and is consistent with other well documented CNS penetrant targeted therapies which have shown meaningful intercranial objective response rates in patients with brain metastases. To the applicant knowledge, the same has not been quantified for sotorasib and this presents another important characteristic of the two compounds with the potential for pharmacological and clinical differences.

In respect of safety, a key risk for sotorasib is hepatotoxicity, particularly after IO therapy. In a side-by side comparison of the results of the 849-001 Cohort A and the sotorasib CodeBreaK 100 study, it is evident that for hepatic events in patients who previously underwent CIT, distinct differences emerge between adagrasib and sotorasib. Notably, the use of sotorasib after CIT is linked to a greater risk of hepatic events compared to adagrasib. Among adagrasib-treated patients, a smaller proportion experienced Grade ≥ 3 hepatic events after CIT (7.4%), contrasting with the higher rates observed with sotorasib (16.5-21.6%) (Figure 27).

Applicant is aware of the potential biases inherent in cross-study comparisons of safety data and a claim of superiority is not the intention behind presenting these data here. However, Applicant again holds that the data provide strong supportive evidence that the pharmacological differences in GSH reactivity are likely to lead to differences in clinical safety, i.e. hepatotoxicity in favour of adagrasib.

3.3. Consistency of Scientific Assessments

The above conclusion would also be in line with the fundamental principle for CHMP scientific assessments, which is to ensure consistency of the opinion and the statement of reasons. CHMP has made its statement of reasons on the fulfilment of an unmet medical need in the CHMP final assessment report for adagrasib without offering scientific evidence to support a conclusion of pharmacological similarity or extrapolation of estimated treatment effects from CodeBreaK 200. It has assumed a similar treatment effect (i.e. "class effect") by applying the CodeBreaK 200 data to adagrasib without providing scientific statement of reason and despite the fact that there is significant scientific evidence that adagrasib and sotorasib have distinctly different pharmacological properties. This assessment has also been recognised in the Divergent Position. Under Article 20 EU Charter of Fundamental Rights of the European Union (EU Charter) CHMP is required to apply equality to its scientific assessments of comparable cases, which is also derived from Article 41 EU Charter ensuring applicants the right to good administration. However, where cases are scientifically different, CHMP is also required under Article 20 and 41 EU Charter to assess the cases separately and on their own

merits; unlike comparing and extrapolating CodeBreaK 200 data from the sotorasib CMA process to the adagrasib CMA application.

Thus, Applicant holds that CHMP has not been consistent with previous CMA assessments, in particular the CMA assessment for sotorasib. If CHMP considers the sotorasib Phase II CodeBreaK 100 data, for example ORR of 37%, clinically meaningful and addressing an unmet medical need versus docetaxel justifying a CMA approval, the adagrasib ORR of 41.4% versus docetaxel as demonstrated in the Phase II Study 849-001 Cohort A cannot be assessed differently and should be assessed on these merits; given the distinct characteristics of sotorasib and adagrasib. This conclusion is also in line with the objective and intent of the CMA Regulation, which aims to "facilitating access to medicines for patients with unmet medical needs", in this case patients with advanced non-small cell lung cancer (NSCLC) with KRAS G12C mutation.

3.4. Discussion of CodeBreaK 200

Despite the distinct characteristics of sotorasib and adagrasib, even if the Applicant follows CHMP's scientific assessment to directly apply CodeBreaK 200 to the adagrasib CMA application, the Applicant disagrees with CHMP's conclusion that "…*emerging data from the randomised controlled CodeBreaK 200 trial comparing sotorasib to docetaxel (de Langen, 2023), give reason to question whether the magnitude of effect observed with adagrasib is likely to translate into a major therapeutic advantage over docetaxel…*".

CodeBreaK 200 demonstrated a statistically significant increase in PFS with a HR of 0.66. This result represents a 34% decrease in the risk of progression or death. Applicant recognises the perceptions of the topline report for sotorasib may be focused on the difference of 1.1 months in the point estimates of the medians for PFS. A difference of the medians, however, does not provide a comprehensive summary of the magnitude of a treatment effect. A focus on point estimates of the difference in medians in this case obscures the overall efficacy of sotorasib and the importance of this potential treatment option for patients. Landmark analyses are also presented in the publication of CodeBreaK 200 and show an associated increase in 1-year PFS rate from 10.1% for docetaxel to 24.8% for sotorasib. To our interpretation, such an increase in patients surviving to one year without progression of disease or death is of clear clinical relevance and of a magnitude that substantiates a major therapeutic advantage.

Applicant also recognises that the reported HR for OS of 1.01 is disappointing. However, interpretation of OS in targeted agents for NSCLC is confounded by crossover. As shown in Table 85, other targeted therapies for NSCLC similarly show statistically significant improvement in PFS without statistically significant improvement in OS, including studies where the HR for OS was close to unity and agents that were granted CMA. While the crossover rate in CodeBreaK 200 was reported at 33.9%, the crossover rate is likely higher when taking into account that 30 patients assigned to the docetaxel arm withdrew consent (20 prior to dosing, 10 after dosing). The authors report that patients who withdrew before receiving docetaxel tended to have worse baseline prognostic features, including history of CNS involvement (10 [44%] vs 50 [33%]), disease refractory to previous therapy (10 [44%] vs 47 [31%]), ECOG performance status of 1 (17 [74%] vs 98 [65%]), and liver metastases (7 [30%] vs 28 [19%]). The prognostic profile of these patients, and the approaches taken to statistical analysis, to which Applicant does not have access, may have introduced bias in favour of docetaxel into the treatment comparisons for PFS and OS. In addition, the K-M curve for overall survival showed favourable outcomes for sotorasib through the first ~5 months (near the median PFS for docetaxel), further supporting the interpretation that crossover confounded the survival result.

Table 85: Targeted NSCLC Therapy Treatment Outcome

Agent	Treatment Setting and Treatment Arms	PFS Results and Estimate of Medians (95% CI)	OS Results and Estimate of Medians (95% CI)
Gefitinib	No prior chemotherapy Gefitinib versus chemotherapy (carboplatin + paclitaxel)	HR 0.48 (0.36, 0.64) p<0.001 9.5 mos vs 6.3 mos	HR 1.00 (0.76, 1.33) p=0.99 21.6 mos vs 21.9 mos
Erlotinib	No prior chemotherapy Erlotinib versus chemotherapy (platinum + [docetaxel or gemcitabine])	HR 0.37 (0.25, 0.54) p<0.0001 9.7 mos vs 5.2 mos	HR 1.04 (0.65, 1.68) p=0.87 19.3 mos vs 19.5 mos
Crizotinib	Prior chemotherapy Crizotinib versus chemotherapy (docetaxel or pemetrexed)	HR 0.49 (0.37, 0.64) p<0.001 7.7 mos vs 3.0 mos	HR 1.02 (0.68, 1.54) p=0.54 20.3 mos vs 22.8 mos
Crizotinib	No prior chemotherapy Crizotinib versus chemotherapy (platinum + pemetrexed)	HR 0.45 (0.35, 0.60) p<0.001 10.9 mos vs 7.0 mos	HR 0.82 (0.54, 1.26) p=0.36 NR vs NR
Ceritinib	Prior chemotherapy and crizotinib Ceritinib versus chemotherapy (docetaxel or pemetrexed)	HR 0.49 (0.36, 0.67) p<0.0001 5.4 mos vs 1.6 mos	HR 1.0 (0.67, 1.49) p=0.50 18.1 mos vs 20.1 mos
Alectinib	Prior chemotherapy and crizotinib Ceritinib versus chemotherapy (docetaxel or pemetrexed)	HR 0.32 (0.17, 0.59) p<0.001 7.1 mos vs 1.6 mos	HR 0.89 (0.35, 2.24) p=0.50 12.6 mos vs NR
Lorlatinib	Treatment naïve Lorlatinib versus crizotinib	HR 0.28 (0.19, 0.41) p<0.0001 NE mos vs 9 mos	HR 0.72 (0.41, 1.25) p=N.S. NR vs NR
Amivantamab-vmjw	Treatment-naïve Chemotherapy + amivantamab-vmjw versus Chemotherapy	Positive topline results reported in a press release	NA

Applicant holds that the overall results from sotorasib CodeBreaK 200 are favourable. Applicant also holds that it is not appropriate to assume that adagrasib 849-012 confirmatory will show the same magnitude of treatment effect. This assessment is made because adagrasib has favourable physicochemical and pharmacokinetic properties compared to sotorasib (see Section 3), and there is evidence that these distinct properties translate into better clinical outcomes for patients treated with adagrasib (see Section 4). It is critical to account for differences in inclusion/exclusion criteria in CB100 and 849-001, as well as overall differences in patient populations that occur with cross-trial comparisons. For these reasons, Applicant holds that the results from CodeBreaK 200 do not increase uncertainty for adagrasib in 849-012, but rather increase the likelihood that 849-012 will confirm the clinical benefit demonstrated in study 849 001.

4. Sotorasib

For assessing whether adagrasib fulfills an unmet medical need for patients with advanced NSCLC with a KRAS G12C mutation, a comparison against sotorasib is also provided.

If comparator treatment is approved under a CMA, here sotorasib, it is sufficient if adagrasib addresses the unmet medical need to a similar or greater extent compared to the conditionally authorised medicine. This is confirmed by the CMA Guidance which clarifies that a new "*medicinal product could potentially address the same unmet medical needs, provided it is expected, based on appropriate scientific data, that such a product addresses the unmet medical needs to a similar or greater extent than what is understood for the already conditionally authorised product. A second (or subsequent) medicinal product could in such case be recommended for a conditional marketing authorisation*". Thus, despite sotorasib having a CMA, adagrasib can still address the same unmet medical need vis-à-vis sotorasib, here the treatment of patients with advanced NSCLC with KRAS G12C mutation. This should be demonstrated and supported by "appropriate scientific data" and there is no requirement for direct comparative data to be provided.

CHMP did not dispute in its scientific assessment that adagrasib addresses the unmet medical need for patients with advanced NSCLC with a KRAS G12C mutation to a similar or greater extent when compared with sotorasib, with which Applicant agrees for the following reasons:

4.1. Efficacy

In a side-by side comparison of results of the full analysis between the adagrasib 849-001 Cohort A and the sotorasib CodeBreaK 100 study, it is evident that the ORR and median PFS are numerically comparable:

- adagrasib (n = 116): ORR 41.4% (95% CI: 32.3, 50.9), percentage of subjects with response ≥ 6 months 24.1% (95% CI: 16.7, 33.0)
- sotorasib (n = 126): ORR 37.1% (95% CI: 28.6, 46.2), percentage of subjects with response ≥ 6 months 23.0% (95% CI: 16.0, 31.4)

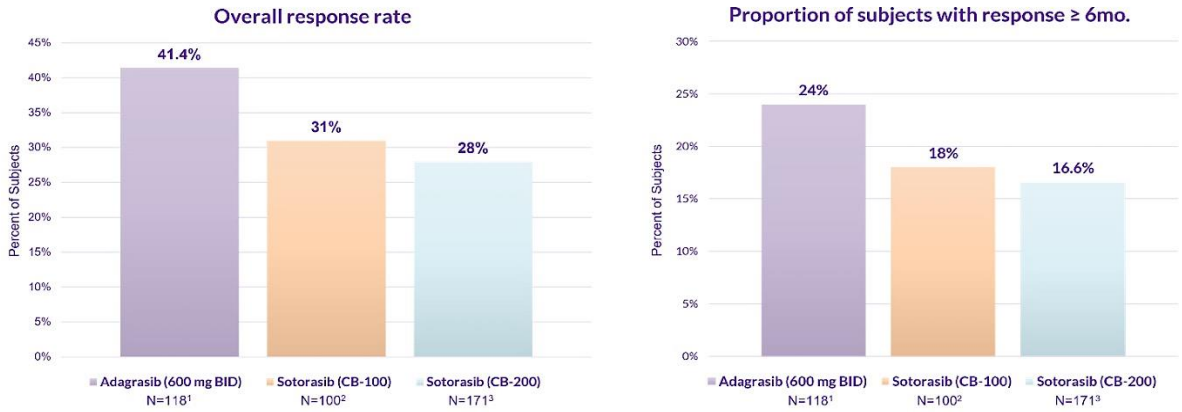
Thus, a side-by-side comparison of top-line results of adagrasib and sotorasib demonstrates that adagrasib addresses the unmet medical need of patients with advanced NSCLC with KRAS G12C mutation to a similar or greater extent when compared to sotorasib.

It is important to note that CodeBreaK 100 included subjects treated with prior platinum-based chemotherapy and/or checkpoint inhibitor therapy (CIT), with only 81.0% receiving both treatments. In contrast, both the adagrasib Phase 2 study (849-001 Cohort A) and the sotorasib Phase 3 study (CodeBreaK 200) had inclusion criteria that required subjects to be previously treated with both platinum and CIT therapy. Notably, the ORR for sotorasib was 31% (95% CI: 22, 41) among patients who had received both platinum-based chemotherapy and a PD-1/PD-L1 inhibitor versus 58.3% (95% CI: 36.6, 77.9) among those who had not, and 69.2% (95% CI: 38.6, 90.9) among those who had not

received prior platinum-based chemotherapy. When focusing on sotorasib subjects who received both treatments, adagrasib demonstrates an advantage over sotorasib with more favorable response with a higher percentage of durable responses (≥ 6 months). See Figure 26.

- adagrasib 849-001 Cohort A (n = 116): ORR 41.4% (95% CI: 32.3, 50.9), percentage of subjects with response ≥ 6 months 24.1% (95% CI: 16.7, 33.0)
- sotorasib CodeBreaK 100 (n = 100): ORR 31.0% (95% CI: 22.0, 41.0), percentage of subjects with response ≥ 6 months 18.0% (95% CI: 11.0, 26.9)
- sotorasib CodeBreaK 200 (n = 171): ORR 28.1% (95% CI: 21.5, 35.4), percentage of subjects with response ≥ 6 months 16.6% (95% CI: 11.3, 23.1)

Figure 26: Efficacy Outcomes in Subjects Who Received Prior CIT and Platinum- based Chemotherapy.



[1] adagrasib SmPC 2 FDA, Lumakras NDA MultiDisciplinary Review, 2021, 3 de Langen, 2023

In an indirect treatment comparison between adagrasib and sotorasib as described in Section 3.2, the data were adjusted for key patient characteristics such as demographics, performance status, histology, and disease extent. A statistically significant 2-fold increase in ORR was observed with adagrasib compared to sotorasib (OR=2.22; 95% CI: 1.25-3.96) . Additionally, numerically favourable trends for PFS (HR 0.79 [95% CI: 0.55, 1.12]) and OS (0.81 [0.55, 1.17]) in favour of adagrasib were also observed.

Adagrasib also has the potential to address the existing medical need for patients with brain metastases, due to its enhanced ability to penetrate the CNS. With an unbound brain to unbound plasma concentration ratio (Kp,uu) of 0.47 in humans, cerebrospinal fluid penetration is expected with adagrasib. Notably, adagrasib demonstrates unique intracranial activity in patients with untreated brain metastases among KRAS G12C inhibitors. This distinction has led to its endorsement as the preferred KRAS G12C inhibitor in the NCCN CNS guidelines, providing a viable treatment option for patients with central nervous system involvement.

Table 86: Clinical Response in Patients with Intracranial Metastases

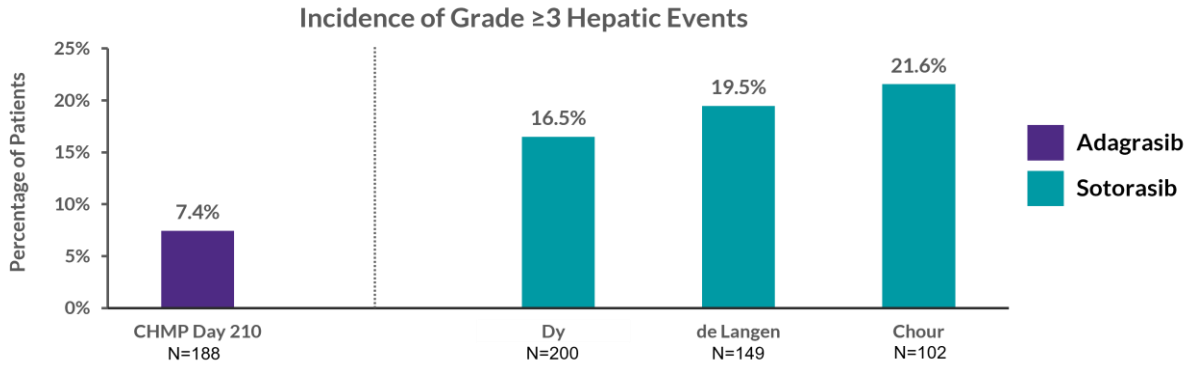
Intracranial Metastases	adagrasib	Sotorasib
Untreated % (n)*[1]	ORR: 42% (8/19) DCR: 90% mDOR: 12.7 months mPFS: 5.4 months mOS: 11.4 months	N/A
Previously treated, stable % (n)** [2, 3]	ORR: 33% (11/33) DCR: 85% mDOR: 11.2 months mPFS: 5.4 months	ORR: 33% (6/18)[a] DCR: 83%[a] mDOR: N/A mPFS: 9.6 months

[1] Negrao, 2023; 2 Jänne, 2022; 3 Dingemans, ASCO 2023 poster
** = modified RANO-BM by BICR;
* = CNS RECIST v1.1 by BICR
a Patients with measurable lesions at baseline per BICR

4.2. Safety

Moreover, adagrasib addresses the unmet medical need in regard to the safety of the treatment to a similar or greater extent when compared with CMA approved sotorasib due to adagrasib's manageable safety profile. While Applicant appreciates that both products are generally well-tolerated, CHMP has concluded for sotorasib that "…*the key risk with sotorasib is hepatotoxicity with laboratory abnormalities for serum transaminases, mostly mild-moderate, but require monitoring and resulted in dose modification, or temporary interruption or use of steroids until resolution*…". In a side-by side comparison of the results of the 849-001 Cohort A and the sotorasib CodeBreaK 100 study, it is evident that for hepatic events in patients who previously underwent CIT, distinct differences emerge between adagrasib and sotorasib. Notably, the use of sotorasib after CIT is linked to a greater risk of hepatic events compared to adagrasib. Among adagrasib-treated patients, a smaller proportion experienced Grade ≥3 hepatic events after CIT (7.4%), contrasting with the higher rates observed with sotorasib (16.5-21.6%) (**Figure 27**).

Figure 27: Adagrasib has a Lower Reported Frequency of Grade ≥ 3 Hepatic Events following CIT.



Dy, 2023; de Langen, 2023; Chour, 2023

The timing of KRAS G12C inhibitor treatment appears to play a role in the occurrence of hepatic events. For instance, in CodeBreaK 200, 33.3% of patients who received sotorasib within 1.6 months following prior CIT encountered Grade ≥3 hepatic events. To explore potential associations between adagrasib administration timing and hepatic event frequency, a comparable analysis was conducted using data from study 849-001 cohort A. Results showed that adagrasib led to significantly fewer Grade ≥3 hepatic events in contrast to sotorasib (Table 87). In the 849 001 cohort A, 41.6% of adagrasib-treated patients experienced hepatic events, with only 9.1% reaching Grade ≥3 severity. Conversely, among sotorasib-treated patients with hepatic events (25.5%), a majority (19.5%) experienced Grade ≥3 severity. Given that most patients with advanced KRAS G12C-mutant NSCLC receive a combination of CIT and chemotherapy, and frequently present with stage IV metastatic disease, the immediate use of sotorasib after failure of the initial combination treatments could present a medical challenge. These findings underscore the need for therapies that can be administered immediately, as delays could adversely affect patients with advanced KRAS G12C-mutant NSCLC.

Table 87: Incidence of Hepatoxicity TRAE with KRAS G12C Inhibitors by Timing Since Prior CIT

Subgroup by Gap Time Distribution	**N**	**Hepatotox. n (%)**	**Hepatotox. (Grade≥3) n (%)**	**N**	**Hepatotox. n (%)**	**Hepatotox. (Grade≥3) n (%)**
	Adagrasib (849-001 Cohort A)			Sotorasib (CodeBreaK 200)		
All patients	116	36 (31.0)	7 (6.0)	169	41 (24.3)	32 (18.9)
All patients who received prior IO	77	32 (41.6)	7 (9.1)	149	38 (25.5)	29 (19.5)
< 1.58m	30	16 (53.3)	4 (13.3)	36	12 (33.3)	12 (33.3)
1.58m – 2.6m	21	8 (38.1)	1 (4.8)	38	13 (34.2)	9 (23.7)
2.6m – 6.21m	14	4 (28.6)	2 (14.3)	36	8 (22.2)	5 (13.9)
6.21m – 48.39m	12	4 (33.3)	0	39	5 (12.8)	3 (7.7)

Applicant Therapeutics, Data on file (data cutoff date = 15Oct2021, cohort A.); Jänne, 2022, de Langen, 2023

5. CMA Requirement (c) – Conclusion

Adagrasib does fulfill an unmet medical need given the established major therapeutic advantage over docetaxel as follows:

- **3x more patients responding to adagrasib versus docetaxel (ORR 41.4% vs. 13.2%)**, a significant rate of durable responses with **4x more patients experiencing a response lasting ≥6 months versus docetaxel (24.1% vs. 5.3%)** and a median duration of response (**mDOR**) of **8.5 months** (95% CI: 6.2, 13.8). This is highly relevant to clinical practice as the 3-fold increase in ORR compared to docetaxel is likely to translate into improved PFS. There is a strong correlation between ORR and PFS (correlation coefficient 0.78) which is not surprising as both ORR and PFS are tumor-based endpoints, and it is reasonable to assume that high ORR will be associated with longer PFS.

- Docetaxel achieves DOR of approximately 6.8 months (median), but response is observed in only approximately 13% of treated patients. Adagrasib on the other hand, not only achieves a longer median DOR of 8.5 months, but also achieves **objective responses in over 40% of patients**.
- Having demonstrated an **ORR of 33.3% per mRANO-BM in treated, stable brain metastasis and an ORR of 42% with CNS RECIST v1.1 in untreated, active brain metastasis**. In addition, Negrao et al demonstrated the high concordance (79%) between systemic and intercranial disease control. Currently, efficacy data for treatment-naïve patients with active brain metastasis is only available for adagrasib.
- Providing a meaningful **improvement of clinical safety** over docetaxel in terms of decreased life-threatening and resource intense febrile neutropenia. Grade 4 neutropenia is common with docetaxel treatment, affecting 54.2% of NSCLC patients often necessitating hospitalisation and antibiotic treatment.
- Contributing to a **major improvement to patient care** as adagrasib is administered orally by the patient at home, whereas docetaxel requires an infusion to be carried out in specialised units under the supervision of physician; i.e. the new treatment allowing ambulatory treatment instead of treatment in hospital as outlined in the CMA Guideline.

CodeBreaK 200 data for sotorasib cannot contradict adagrasib's demonstrated major therapeutic advantage over docetaxel due to the following:

- It is scientifically **unjustified to directly apply the CodeBreaK 200 data to adagrasib's CMA** assessment and assume a similar magnitude of treatment effect. Data show that there are distinct differences between sotorasib and adagrasib with respect to physicochemical characteristics, pharmacokinetics, activity in brain metastases, post-IO hepatotoxicity, and clinical activity, none of which supports a claim of "class effect". This has also been noted in the Divergent Position.
- The overall results from sotorasib CodeBreaK 200 are favourable. **It is not appropriate to assume that adagrasib 849-012 confirmatory study will show the same magnitude of treatment effect**. The results from CodeBreaK 200 do not increase uncertainty for adagrasib in 849-012, but rather increase the likelihood that 849-012 will confirm the clinical benefit demonstrated in study 849 001.

Adagrasib also addresses the unmet medical need to a similar or greater extent compared to conditionally approved sotorasib:

- In a side-by side comparison of results of the full analysis between the adagrasib 849 001 Cohort A and the sotorasib CodeBreaK 100 study that the ORR and DOR are similar:
    - adagrasib (n = 116): ORR 41.4% (95% CI: 32.3-50.9), percentage of subjects with response ≥ 6 months 24.1% (95% CI: 16.7, 33.0)
    - sotorasib (n = 126): ORR 37.1% (95% CI: 28.6-46.2), percentage of subjects with response ≥ 6 months 23.0% (95% CI: 16.0, 31.4)
- When focusing on sotorasib patients treated with both prior platinum-based chemotherapy and checkpoint inhibitor therapy (CIT), adagrasib demonstrates an advantage over sotorasib with more favorable response with a higher percentage of durable responses (≥ 6 months):
    - adagrasib 849-001 Cohort A (n = 116): ORR 41.4% (95% CI: 32.3, 50.9), percentage of subjects with response ≥ 6 months 24.1% (95% CI: 16.7, 33.0)
    - sotorasib CodeBreaK 100 (n = 100): ORR 31.0% (95% CI: 22.0, 41.0), percentage of subjects with response ≥ 6 months 18.0% (95% CI: 11.0, 26.9)

    - sotorasib CodeBreaK 200 (n = 171): ORR 28.1% (95% CI: 21.5, 35.4), percentage of subjects with response ≥ 6 months 16.6% (95% CI: 11.3, 23.1)

- In a separate, indirect treatment comparison between adagrasib and sotorasib, the data were adjusted for key patient characteristics such as demographics, performance status, histology, and disease extent. A statistically significant 2-fold increase in ORR was estimated with adagrasib compared to sotorasib, OR=2.22 (95% CI: 1.25-3.96) and a numerically favorable trend for PFS (HR 0.79 [95% CI: 0.55, 1.12]) and OS (0.81 [0.55, 1.17]) in favor of adagrasib .
- Use of sotorasib after CIT is linked to a greater risk of hepatic events compared to adagrasib. Among adagrasib-treated patients, a smaller proportion experienced Grade ≥3 hepatic events after CIT (7.4%), contrasting with the higher rates observed with sotorasib (16.5-21.6%).
- Adagrasib demonstrates unique intracranial activity in patients with untreated brain metastases among KRAS G12C inhibitors.

In summary, adagrasib therefore fulfils CMA requirement (c).

CHMP position on the first ground for re-examination

On brain metastases

The conclusion from the original assessment stands, that the magnitude of efficacy results presented from the post-hoc analyses of treated patients with brain metastases is uncertain, and information is lacking for a complete review of the results.

For the sotorasib approval, efficacy on brain metastases was not discussed in detail. ORR in the subpopulation with metastases (n=26) was 15.4 (95% CI 4.4, 34.9) based on (Lumykras EPAR Figure 14 p. 83). Notably, this is not intracranial ORR. The lower ORR in this subgroup was attributed to prognostic differences according to the efficacy discussion. In addition, post hoc analysis of CodeBreak 100 of efficacy in stable brain metastases has been conducted (Ramalingam et al. poster presentation p52.03) and intracranial efficacy has been assessed post-hoc in the phase 3 RCT of sotorasib vs. docetaxel (Dingemans et al. poster session LBA9016).

Based on available evidence presented in the grounds for re-examination, sotorasib is not devoid of intracranial activity. However, there is more evidence for the intracranial activity for adagrasib.

On clinical safety

In accordance with CMA Regulation, the applicant argues for major therapeutic advantage against docetaxel in terms of advantageous safety profile.

According to the ESMO guidelines for patients with advanced NSCLC with PS 0-2 and contraindication for ICI, comparable options as second-line and beyond therapy consist of pemetrexed, or docetaxel (all histologies), nintedanib-docetaxel in patients with adenocarcinoma progressing after previous chemotherapy, or ramucirumab-docetaxel in patients with NSCLC progressing after first-line chemotherapy.

For patients without Immune Checkpoint Inhibitor (ICI) contraindication, the second line choice depends on the agents used in the first line, as well as on the response and tolerability. Hence, the option for second line for patients with PS 0-2 might consist of rechallenge with anti-PD-(L)1 or chemotherapy in case of previously substantial clinical benefit from chemotherapy +/-ICI, or of monotherapy with PD-(L)1 inhibitors (nivolumab, pembrolizumab and atezolizumab) for patients not treated in the first line with ICI.

Considering the relevant regulatory precedents in granting CMA for major therapeutic advantage evaluation in case of a new treatment option, a new mechanism of action, oral administration and different safety profile can be considered advantages.

A different, advantageous safety profile over docetaxel in terms of neutropenia, febrile neutropenia and peripheral neuropathy that are observed only for docetaxel can be agreed.

On the other hand, the safety profile of adagrasib is characterized by hepatotoxicity and QT prolongation, that are not reported for docetaxel. Hepatotoxicity and QT prolongation require close monitoring; however, these are manageable with dose reductions or temporary interruptions.

There is no available direct comparison between adagrasib and docetaxel in a RCT so far and thus it is difficult to ascertain the difference in gastrointestinal toxicity usually reported for both, although stomatitis and esophagitis seems to be specific for docetaxel.

In addition, there is no available direct comparison of the adagrasib safety profile with currently authorised alternatives and existing methods used in clinical practice (sotorasib, chemotherapy other than docetaxel and immunotherapy).

However, a different safety profile for adagrasib from these well-known of immunotherapy dominated by immune-related adverse reactions, or of chemotherapeutics such pemetrexed, or docetaxel and combinations of docetaxel with ramucirumab, or nintedanib can be of advantage in the clinical praxis when deciding the individualized approach.

An indirect comparison with sotorasib has been provided by the applicant. In the context of major therapeutic advantage over sotorasib authorized in the same line of therapy, the applicant argues for a similar or better safety profile for adagrasib mostly in terms of hepatotoxicity.

Differences in safety profile between sotorasib and adagrasib suggest existing pharmacological differences. The impact of these on overall clinical performance remains to be explored.

On major improvement to patient care

According to CMA regulation, major improvements to patient care are can also be considered to provide a major therapeutic advantage. It is agreed that oral administration of an anticancer product that can replace an intravenous regimen represents an advantage for patients with advanced NSCLC, allowing ambulatory treatment and improving treatment compliance.

On PK/PD differences

The PK properties of the two compounds are different.

Sotorasib has a substantially less than dose proportional increase in exposure, with similar exposure observed after a 180 mg and 960 mg dose. In addition to the dose dependency in bioavailability, sotorasib is a moderate inducer and appears to induce its own metabolism, leading to lower exposure at steady state than after a single dose. The half-life is around 5 hours and the multiple dose PK data available from patients at day 8 support that drug concentrations at the end of the dosing interval are low (Lumykras EPAR).

Sotorasib metabolism appears to be both non-enzymatic and oxidative, and a contribution of CYP3A4 and/or Pgp was confirmed in a DDI-study with the strong 3A4/Pgp inhibitor itraconazol with a single dose sotorasib, which increased sotorasib AUC by around 30%. Sotorasib is a moderate CYP3A4 inducer, and an inhibitor of both BCRP and Pgp.

Adagrasib, on the other hand shows a more than dose proportional increase in exposure after single doses of 200 mg to 600 mg, and has also a time dependent PK with decreased clearance with time due

to auto-inhibition of the metabolising enzyme CYP3A4. The auto-inhibition is proposed to contribute to the observed large accumulation.

Adagrasib is a strong CYP3A4 inhibitor inhibiting not only its own metabolism but also that of other CYP3A4 substrates, 400 mg BID increased the exposure of midazolam 21-fold. Adagrasib also inhibits CYP2C9, CYP2D6 as well as Pgp.

To summarize, sotorasib and adagrasib have different pharmacokinetic characteristics. Sotorasib has larger fluctuations at steady state than adagrasib. The potential clinical impact of the differences in PK on the clinical efficacy of these compounds is unknown.

Grounds for re-examination #2:

CMA requirement (d) - Benefit to Public Health of the Immediate Availability Outweighs the Risk Inherent in the Fact that Additional Data are still Required

For the scientific assessment of adagrasib, Applicant respectfully submits that the CHMP has not sufficiently entered into a scientific discussion of CMA requirement (d), but draw the conclusion that CMA requirement (c) was not met and applied this to CMA requirement (d) accordingly without full consideration of separate, independent basis establishing a benefit to public health of immediate availability.

Under Article 4(1)(d), the CMA Regulation acknowledges that there will be a need for additional data when granting the CMA, and thus it requires a specific additional benefit-risk-assessment. For this criterion, the applicable law and the CMA Guidance requires an explicit assessment and balancing of the benefits of the immediate availability of the medicinal product to the public health against the risks resulting from the fact that additional data are still required. According to the CMA Guidelines the impact of immediate availability on public health, based as far as possible on objective and quantifiable epidemiological information, as opposed to the risks inherent in the fact that additional data are still required, taking into account CMA requirement (a).

Consideration of this criterion for adagrasib shows that in this case there is a clear benefit to public health of the immediate availability on the market of adagrasib and that the benefit outweighs the risk inherent in the fact that additional data are still required. The Divergent Position also underscores that the benefits to public health of the immediate availability of adagrasib outweigh the risks inherent in the fact that additional data are still required in the context of a CMA.

1. Benefits to Public Health of Immediate Availability

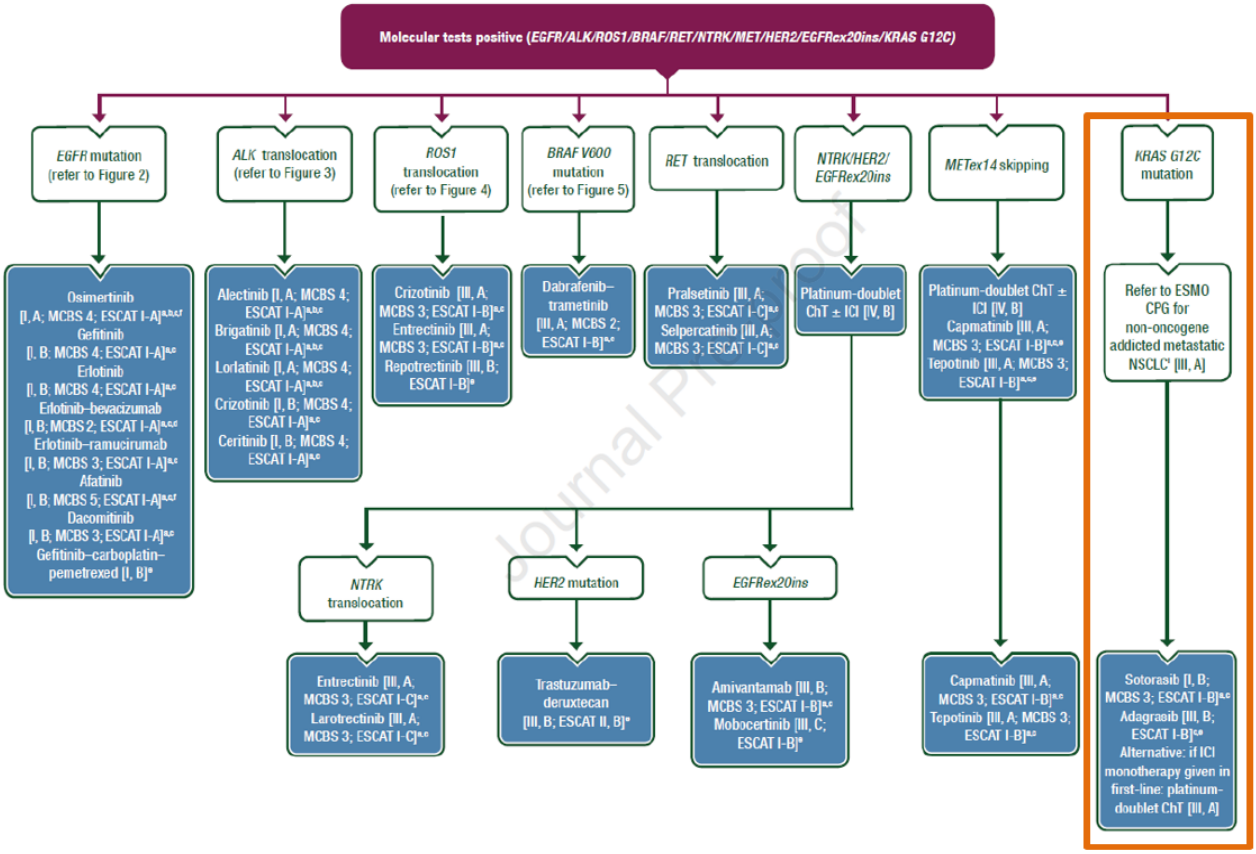
As described above, there are limited treatment options for patients with advanced NSCLC with KRAS G12C mutation and disease progression after at least one prior systemic therapy. NSCLC with a KRAS G12C mutation has been undruggable for over 40 years. The current clinical practice offers as the second-line treatments for advanced KRAS G12C-mutated NSCLC palliative care due to poor survival, highlighting the urgent need for treatment options to effectively address this unmet medical need. The 2L therapy options are primarily regimens based on docetaxel as the SOC. However, although an option, docetaxel use has significant safety concerns, including severe neutropenia, febrile neutropenia, alopecia, and severe peripheral neuropathy. Patients are reluctant to use docetaxel treatment. In the CodeBreaK 200 trial, 13% of patients allocated to the docetaxel arm opted out before receiving the treatment. Additionally, a recent 2023 study by Gray revealed that real-world outcomes for 2L+ docetaxel-treated advanced KRAS G12C-mutated NSCLC patients remain poor, with a median OS of 5.8 months and median PFS of 3.4 months. In advanced KRAS G12C-mutant NSCLC, a

little over 40% of patients develop brain metastasis, a drug with CNS activity would be highly valuable for patients and clinicians underscoring the need for effective therapies for these patients.

Public health is an important factor to consider in regards to the benefit of immediate availability of adagrasib. It would be served by making adagrasib available for patients immediately given the demonstrated benefits and the clinical context. Prolonged progression-free survival (e.g. at 12 months) and durable responses in this setting represent a clinical benefit, for which adagrasib is also more effective than docetaxel. Waiting for the phase 3 study results delays availability, and with regulatory and access procedures taking 2-3 or more years, the delay in availability means many missed treatment opportunities for patients. Thus, making adagrasib immediately available, based on its positive risk-benefit and the evidence available for its superior efficacy and safety to docetaxel, would provide substantial benefit to public health, notably to patients with advanced NSCLC with KRAS G12C mutation. This can be further supported by the following:

1.1. Adagrasib Included in Medical Guidelines

Adagrasib has already been included in several medical guidelines including (i) the NCCN Clinical practice guideline for NSCLC, (ii) Pancreatic Adenocarcinoma, and (iii) Central Nervous System Cancers. The inclusion demonstrates that the clinical practice conclusion of the benefit adagrasib can bring to address the unmet medical need for advanced NSCLC patients with a KRAS G12C mutation. In regards to Europe, ESMO guidelines for Oncogene-Addicted NSCLC includes adagrasib, as shown below.



1.2. Adagrasib to Provide Benefit for Patients with Brain Metastases

As indicated, adagrasib has the potential to address the existing medical need for advanced NSCLC patients with brain metastases, due to its enhanced ability to penetrate the CNS. With an unbound

brain to unbound plasma concentration ratio ($K_{p,uu}$) of 0.47, exceptional intracranial activity is expected with adagrasib. Notably, adagrasib demonstrates unique intracranial activity in untreated brain metastases among KRAS G12C inhibitors. This distinction has led to its endorsement as the preferred KRAS G12C inhibitor in the NCCN CNS guidelines, providing a viable treatment option for patients with central nervous system involvement. Analyses from study 849-001 has demonstrated ORR of 33.3% per mRANO-BM in treated, stable brain metastasis and 42% with CNS RECIST v1.1 in untreated, active brain metastasis.

1.3. Adagrasib Early Access use and the Current Clinical Need

Adagrasib has been available since February 2023 via early access with 147 patients with 2L+ NSCLC and 239 patients currently treated overall (total number of requests totaling over 300 as of 10th September 2023). Currently, patients are treated with adagrasib in a broad number of the European Union Member States: Belgium, Finland, France, Germany, Hungary, Italy, Ireland, Netherlands, Poland, and Spain. On a weekly basis, Applicant has received an average of 10 treatment requests from physicians within the European Union and beyond. This demand clearly supports the immediate needs for an alternative treatment option, which adagrasib provides. In addition, per the national requirements for early access via the named patient process, regulatory and/or ethical approval has been obtained in 7 countries (namely Finland, France, Hungary, Italy, Netherlands, Poland, Spain). In France, the Agence nationale de sécurité du médicament et des produits de santé (ASNM) has also provided guidance on their website confirming the authorisation of an Autorisation d'accès compassionnel (AAC) for both advanced NSCLC and mCRC.

These outcomes serve as evidence from physicians, ethics committees and national health authorities that the benefit-risk of adagrasib is understood and that adagrasib has a meaningful impact on public health, which supports immediate availability under a CMA approval, namely for advanced NSCLC patients with a KRAS G12C mutation.

1.4. Opinion of Expert Lung Cancer Physician

Applicant submits a statement as Annex 1 following discussions with expert lung cancer physicians experienced in treating patients with KRAS G12C-mutant, advanced NSLCC with docetaxel, sotorasib and adagrasib in routine clinical practice, clinical trials, and for KRAS G12C inhibitors, early access measures. This statement outlines the need for adagrasib's immediate availability, to address the following major points:

i. the limitations in the efficacy of docetaxel treatment for patients with the KRAS G12C mutation

ii. the significant safety concerns of the docetaxel treatment, including severe neutropenia, febrile neutropenia, and severe peripheral neuropathy,

iii. the need to have treatments available with CNS activity in this population with a high incidence of lesions in the brain,

iv. the need to have options to allow patients the best chance of achieving a durable response and having a manageable treatment safety profile to ensure the best possible quality of life for patients with this serious and life-threatening disease.

2. Risks Inherent in the Fact that Additional Data are Still Required

The final CHMP Assessment Report does not specify or quantify the risk. The CHMP did not conduct an scientific assessment on such risks but stated in the CHMP final assessment report that "*…in view of the limitations of the submitted non-comprehensive data package and considering that a major therapeutic advantage over existing therapies has not been established, the CHMP considers that the*

benefits to public health of the immediate availability of adagrasib do not outweigh the risks inherent in the fact that additional data are still required in the context of a conditional marketing authorisation…".

This conclusion does not fully address the intent and provisions of the CMA Regulation. According to recital (5) of the CMA Regulation, CMAs are distinct and authorisation is granted before all data are available. Thus, it is inherent to a CMA application that the data for adagrasib is non-comprehensive and cannot be held against the Applicant. The fact that additional data for adagrasib is required is not disputed by Applicant. However, Applicant holds that CHMP should take into consideration the following:

"…*the fulfilment of an unmet medical need is a major feature of products suitable for conditional marketing authorisation and indicates the particular value that the product is expected to bring, outweighing not only the risks clearly identified at the time of authorisation, but also the risks related to less comprehensive data than would be normally the case.*" .

2.1. Mitigated Risk of Negative Reproducibility of adagrasib 849-001 Results with 849-012

Applicant has demonstrated above that adagrasib represents a major therapeutic advantage over docetaxel and also shown that adagrasib addressed unmet medical need at least as much as sotorasib. In fact, adagrasib has favourable physicochemical and pharmacokinetic properties compared to sotorasib (see Section 3), and there is evidence that these distinct properties translate into better clinical outcomes for patients treated with adagrasib (see Section 4). This demonstrates that we have mitigated the risk of negative reproducibility of 849-001 Cohort A.

In addition, Applicant further mitigated this risk related to less comprehensive data and the associated "residual uncertainty" by implementing a scientifically sound and robust design and execution of the adagrasib Phase 3 study 849-012.

For the current application, the Applicant has chosen a primary endpoint of ORR in recognition of the low inherent risk of patient selection bias in documenting objective tumour response (no spontaneous responses). Additionally, BICR was used to mitigate assessment bias, and we leveraged a standard statistical approach to demonstrate superiority (lower bound of 95% confidence interval excluding benchmark ORR). Furthermore, the reproducibility of the ORR across study cohorts reduces the uncertainty in the estimate of the reported magnitude of treatment effect, and the observed ORR met the pre-defined study threshold with a margin of difference that reduces uncertainty. Namely, the ORR of 41.4% (95% CI: 32.3, 50.9) for adagrasib from 849-001 Cohort A far exceeds the ORR for docetaxel in combination with ramucirumab of 23% (95% CI: 19.7, 26.4). Furthermore, this ORR also exceeds that reported in CodeBreaK 200 for both docetaxel [13.2% (95% CI: 8.6, 19.2)] and for sotorasib [28.1% (95% CI: 21.5, 35.4)]. In addition, the 1 year PFS rate of 29.1% (95% CI: 19.6, 39.3) for adagrasib exceeds the 1 year PFS rate of 25% for sotorasib. As also substantiated in Section 'Reproducibility of adagrasib Results Across Cohorts', the Applicant has demonstrated reproducibility of the PFS results across separate patient cohorts, in addition to supplemental analyses that demonstrate an improvement in PFS. Cohort A, as well as the totality of the data reduce uncertainty and demonstrate an improvement in PFS.

As confirmed by the CHMP, study 849-012 is adequately designed to fulfill the requirements of full marketing authorisation.

2.1.1. Inclusion/Exclusion Criteria

The 849-001 cohort A and 849-012 have the same inclusion/exclusion criteria in relation to key factors that affect patient outcomes:

849-001 Cohort A	**849-012**
Histologically confirmed diagnosis of a solid tumor malignancy with *KRAS* G12C mutation (squamous or non-squamous NSCLC)	Histologically or cytologically confirmed diagnosis of NSCLC with *KRAS* G12C mutation.
Unresectable or metastatic disease	Unresectable, locally advanced or metastatic disease
Patients must have previously received treatment with at least a platinum-containing chemotherapy regimen and checkpoint inhibitor therapy	Receipt of prior treatment with a platinum (cisplatin or carboplatin)-containing regimen and an immune checkpoint inhibitor (ie, anti-PD-1/PD-L1 inhibitor) concurrently or sequentially for advanced or metastatic disease with the outcome of objective disease progression on or after treatment.
Treated, stable CNS metastases were allowed	Active brain metastases. Patients are eligible if brain metastases are treated and patients are neurologically stable for at least 2 weeks prior to randomization.
ECOG performance status of 0 or 1	ECOG performance status of 0 or 1

The nearly identical patient populations in the adagrasib 849-001 cohort A Phase 2 and 849-012 Phase 3 trials increase the likelihood of confirming the clinical activity seen in 849 001 cohort A.

2.1.2. Study Design of 849-012

In addition, 849-012 will enroll 450 subjects to ensure the relevant number of events required for the final PFS analysis are reached (power 90%, HR 0.645). In addition, this sample size allows for 334 events for the final analysis of OS which is also powered at 80% (HR 0.72).

Study Design		**849-012 (adagrasib), Protocol V 7.0**	
	Randomization Ratio	2:1	
	Sample Size	450	
	Testing procedure	Fixed testing sequence procedure on endpoints PFS and OS	
PFS	Endpoint	Primary	
	Median Estimates	Experimental: 6.2 months	Control: 4 months
	HR	0.645	
	Alpha	0.05 (2-sided)	
	Power	90%	
	Events for Final Analysis	246	
OS	Endpoint	Secondary	
	Median Estimates	Experimental: 13.9 months	Control: 10 months

	HR	0.72
	Alpha	0.05 (2-sided)
	Power	80%
	Events for Final Analysis	334
	Events for IA	~167 (50% of total required events)
PFS2[a]	Endpoint	Exploratory

[a] Time from randomization to disease progression on the next-line of therapy, or death from any cause, whichever is first.

2.1.3. Reproducibility of adagrasib Results Across Cohorts

In pivotal Cohort A of Study 849-001, a total of 116 patients enrolled and received at least one dose of adagrasib. All patients had tumour that were KRAS G12C-positive, and 114 (98.3%) patients had received prior treatment with both a platinum-based regimen and a checkpoint inhibitor therapy. All patients had measurable disease as assessed by the investigator. The primary endpoint of ORR was assessed by blinded, independent central review (BICR) in accordance with RECIST 1.1. Measurable disease at baseline was reported for 112 patients by BICR, which was defined as the full analysis set. The ORR by this analysis was 42.9% (95% CI: 33.5, 52.6) and included 1 complete response (CR) and 47 partial responses (PRs) for a DCO of 15 June 2021. A supplemental pooled analysis by BICR for the enrolled population (ITT) for Cohort A, Phase 1/1b, and Cohort B (which was enrolled based on KRAS G12C mutation identified by ctDNA rather than tumour tissue) was also conducted and demonstrated the consistency of the ORR across cohorts using DCO of 15 October 2021.

Table 88: Analysis of Tumour Response by BICR in the ITT Population

Efficacy Outcomes, n(%)	**Cohort A (N=116)**	**Phase 1/1b NSCLC/600mg BID (N=16)**	**Cohort B (N=60)**	**Total (N=192)**
Best Overall Response [a]				
Complete Response (CR)	1 (0.9)	2 (12.5)	1 (1.7)	4 (2.1)
Partial Response (PR)	47 (40.5)	5 (31.3)	22 (36.7)	74 (38.5)
Stable Disease (SD)	44 (37.9)	7 (43.8)	27 (45.0)	78 (40.6)
Progressive Disease (PD)	6 (5.2)	1 (6.3)	4 (6.7)	11 (5.7)
Not Evaluable (NE)	18 (15.5)	1 (6.3)	6 (10.0)	25 (13.0)
Objective Response Rate (ORR)[b]				
n (%)	48 (41.4)	7 (43.8)	23 (38.3)	78 (40.6)
95% CI [c]	32.3, 50.9	19.8, 70.1	26.1, 51.8	33.6, 47.9

a A Best Overall Response (BOR) of CR/PR confirmed requires a confirmatory assessment at least 4 weeks (28 days or more) since the first CR/PR response. For a BOR of SD, an SD assessment must be at least 32 days from the date of first dose, otherwise it will be summarized as NE.
b ORR is defined as the proportion of patients documented to have a confirmed CR or PR according to RECIST v1.1 as the best response.
c 95% CI is calculated using the exact binomial method (Clopper-Pearson).

Similarly, the median PFS for Cohort A based on disease assessments by BICR was 6.5 months (95% CI: 4.7, 8.2) for the 112 patients in the FAS as of the DCO of 15 June 2021. A supplemental pooled analysis demonstrated consistent results for PFS using a DCO of 15 October 2021 (Table 89).

Table 89: Pooled Analysis of Progression-free Survival by BICR in the ITT Population

	Cohort A (N=116)	**Phase 1/1b NSCLC/600mg BID (N=16)**	**Cohort B (N=60)**	**Total (N=192)**
Status [n (%)]				
Events Observed	69 (59.5)	9 (56.3)	35 (58.3)	113 (58.9)
Censored	47 (40.5)	7 (43.8)	25 (41.7)	79 (41.1)
Progression Free Survival (Months)[a]				
Percentile (95% CI)[b]				
25%	3.29 (2.69, 4.21)	2.79 (1.22, 12.42)	3.25 (2.53, 4.63)	3.29 (2.73, 4.17)
Median	6.05 (4.73, 8.44)	16.85 (2.37, NE)	6.60 (4.37, 6.93)	6.60 (5.42, 8.08)
75%	16.85 (9.89, NE)	NR (12.42, NE)	NR (6.93, NE)	16.85 (11.93, NE)
Range	0.03, 19.78	0.03, 24.94	0.03, 16.53	0.03, 24.94

a Progression-free Survival (months) is calculated as (date of the first documentation of objective progression of disease or death due to any cause in the absence of PD - date of the first dose of study treatment) + 1 / 30.4375.
b Obtained via Kaplan-Meier estimation,

Brookmeyer, 1982,

The reproducibility of the results in Cohort A, Phase 1/1b, and Cohort B supports the robustness of the results and reduces the probability of false positive conclusions.

Thus, the risk for a false positive result for ORR has been controlled. Furthermore, the reproducibility of the ORR across study cohorts reduces the uncertainty in the estimate of the magnitude of the treatment effect, and the observed ORR met the pre-defined study threshold with a margin of difference that reduces the uncertainty relating to whether an effect on PFS will be shown in 849-012. The 849-001 data shows reproducibility of the PFS results across separate patient cohorts.

3. CMA Requirement (d) - Conclusion

The applicant concludes that Adagrasib meets requirement of Article 4(1)(d) of the CMA Regulation and the benefits to public health of the immediate availability of adagrasib substantially outweighs the risk inherent in the fact that additional data are still required.

This conclusion is consistent with EU pharmaceutical laws, under which the CMA is a regulatory instrument to handle a state of limited information about a medicinal product and to bridge a period of uncertainty. The law acknowledges that there will be incomplete data and uncertainty about the respective medicinal product. Hence, limited information and uncertainty do not per se preclude the granting of a CMA. Instead, the CHMP has to specifically and holistically review all available information

and balance the scope and impact of the uncertainty for the CMA application in light of the purposes of the law and the criteria of the specific CMA Regulation.

Given adagrasib's inclusion in various medical guidelines at this stage, combined with the benefit the product can provide to patients with brain metastases demonstrates the substantial benefit to public health in case of immediate availability. This determination is further supported by the extensive use of adagrasib in the European Union and beyond via early access. Patients with advanced NSCLC characterised by a KRAS G12C mutation are in clear need of alternative treatment options to docetaxel. Adagrasib can address this need. This conclusion is consistent with CMA Regulation, which aims to safeguard "the interests of public health" (Recital 2) and the availability of critical medicines for patients with severe diseases.

The risk related to less comprehensive data and the associated "residual uncertainty" are mitigated as Applicant will be in a position to provide comprehensive clinical data for adagrasib confirming that the benefit-risk balance is positive with the ongoing phase 3 study 849-012. The CHMP also confirmed that Applicant will be in a position to provide this data, which by stating that CMA requirement (b) has been fulfilled by conduct and endpoints of 849-012, under which it is likely that comprehensive data will be provided for adagrasib.

CHMP position on the second ground for re-examination

The arguments provided to support conditional approval based on the criterion (d) are appropriate. In the population with advanced NSCLC progressing after first-line, considering the activity within the range of other oncogene-directed therapies that have been approved for NSCLC, and a manageable safety profile, the benefit/risk of adagrasib is considered to be positive.

Report from the SAG-Oncology
Following a request from the applicant at the time of the re-examination, the CHMP convened a Scientific Advisory Group (SAG) inviting the experts to provide their views on the CHMP grounds for refusal, taking into account the applicant's response. The SAG took place on the 25th of October 2023.

1) The SAG should comment on the CHMP grounds for negative opinion in view of the grounds for re-examination submitted by the applicant.

The SAG discussed the CHMP grounds for negative opinion, especially in terms of the existing data to support a conditional approval for adagrasib, and the impact of what is known about sotorasib, including the outcomes of CodebreaK200 trial. The different views are summarised as follows (see answer to question 2).

2) Considering the reported outcomes of Codebreak200, and that adagrasib has a similar mechanism of action as does sotorasib, does the SAG consider it relevant to grant early patient access to adagrasib based on single arm trial KRYSTAL-1, or should the results of randomised controlled trial KRYSTAL-12 be awaited?

The SAG had split views:

- Based on high activity observed in the KRYSTAL-1 trial, despite limitations in the design and the small sample size, the majority considered that adagrasib can be assumed to be associated with a major therapeutic advantage. The activity against intracranial lesions is also worth considering as a potential therapeutic advantage, even if based on small numbers.

  Awaiting the results of the KRYSTAL-12 trial is not required prior to a conditional marketing authorisation, which is considered appropriate in this setting based on high unmet medical

need and limited treatment options with standard approval (e.g., docetaxel).

The CodebreaK200 trial of sotorasib against docetaxel, regardless of any apparent limitations of this trial, does not invalidate the assumption of a major therapeutic advantage for adagrasib. The majority of the SAG agrees that comparison between different drugs is not necessarily valid in this setting despite similarities in mode of action. Different resistance mechanisms and different pharmacology support that findings in sotorasib cannot necessarily be extrapolated to the adagrasib.

The confirmatory phase 3 trial KRYSTAL-12 is well under way and is expected to address remaining uncertainties on the importance of the activity observed post-approval.

The toxicity associated with adagrasib, especially GI toxicity, is significant but manageable with dose reduction.

- A minority of the SAG members noted the high toxicity and was not convinced about a positive benefit-risk balance or major therapeutic advantage for adagrasib, regardless of the outcome of CodebreaK200.

  The results of CodebreaK200 bear some relevance as to the expected effect of adagrasib since the two drugs appear to have similar activity for ORR, PFS, and OS in indirect comparisons. This further weakens the assumption that adagrasib might be associated with a major therapeutic advantage.

  According to this view, it is important to await the results of the confirmatory trial KRYSTAL-12 before approval of adagrasib. Major therapeutic advantage cannot be assumed.

The SAG agreed on the importance to collect data to confirm the preliminary intracranial activity observed in Krystal-1. Regrettably, patients with active brain metastases were excluded from the confirmatory trial.

Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the Scientific Advisory Group.

During the re-examination, CHMP focused its review on the fulfilment of the requirements for a conditional marketing authorisation, and especially on the criteria of unmet medical need and major therapeutic advantage of Krazati over docetaxel and on the criteria that the benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

The CHMP concluded that the grounds for refusal have been resolved by the Applicant and that a positive opinion can be granted for Krazati in the context of a conditional approval.

5.1. Risk Management Plan

5.1.1. Safety concerns

No safety concerns have been identified for this product.

5.1.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

5.1.3. Risk minimisation measures

None.

5.1.4. Conclusion

The CHMP considered that the risk management plan version 0.4 is acceptable.

The applicant is reminded that in case of a positive opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

5.2. Pharmacovigilance

5.2.1. Pharmacovigilance system

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

5.2.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 12.12.2022. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

5.3. Product information

5.3.1. User consultation

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

5.3.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Krazati (adagrasib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

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

6. Benefit-risk balance following re-examination

6.1. Therapeutic Context

6.1.1. Disease or condition

The applicant seeks a conditional marketing authorisation (CMA) for the medicinal product Krazati (adagrasib) with the following therapeutic indication:

"*Krazati as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with KRAS G12C mutation and disease progression after at least one prior systemic therapy.*".

The natural history of lung cancer is one of progressive disease that is generally fatal, and despite the significant advances of chemotherapy and immunotherapy for NSCLC, most patients ultimately develop progressive disease. The 5-year survival of metastatic NSCLC remains at approximately 6%, indicating that NSCLC is a serious and life-threatening condition with an unmet medical need.

KRAS-mutant cancers have generally been associated with poorer overall survival (OS) compared to KRAS wild type tumours, especially in the advanced stages.

Mutations in KRAS occur in approximately one-third of cases and represent the most frequent driver mutation in lung adenocarcinoma, with the KRAS G12C variant comprising nearly half of all KRAS mutations. KRAS has been the subject of extensive drug development efforts along the last 40 years. Most of these approaches have not proven successful in clinical studies, but the recent approach to target the cysteine residue present only in the mutant form of KRAS G12C, along with the subsequent discovery of a vulnerable GTP/GDP binding pocket in the KRAS protein, has allowed for clinical development of KRAS G12C inhibitors sotorasib and adagrasib.

6.1.2. Available therapies and unmet medical need

In the absence of a targeted first line treatment option, the preferred initial treatment of advanced/metastatic NSCLC is a combination of platinum-based chemotherapy and immune checkpoint inhibitor therapy. Immune checkpoint inhibitors (ICIs), including nivolumab, pembrolizumab, and atezolizumab, were first proven to be effective in the treatment of advanced NSCLC in the second-line setting (Borghaei, 2015; Garon, 2015; Herbst, 2016; Rittmeyer, 2017), followed by studies in the first-line setting demonstrating a survival advantage as monotherapy in patients with untreated, advanced NSCLC characterized by ≥ 50% tumour PD-L1 expression (Reck, 2016; Herbst, 2020), and in combination with a platinum-based chemotherapy regimen in the first-line, advanced disease treatment setting for patients with NSCLC regardless of PD L1 status (Gandhi, 2018; Socinski, 2018).

Docetaxel, alone or in combination with ramucirumab or nintedanib, and pemetrexed are approved chemotherapy options in patients previously treated with platinum-based chemotherapy and a checkpoint inhibitor. Pemetrexed is much less common as an option in this setting due to earlier administration as part of first-line or maintenance settings (Gandhi, 2018; Planchard, 2018) and histology (Planchard, 2018).

In January 2022, the European Commission granted a Conditional Marketing Authorisation (CMA) to Lumykras (sotorasib) for the treatment of patients with previously treated NSCLC harbouring the KRAS G12C mutation. Such approval was based on pharmacological, efficacy and safety data from the CodeBreak 100 study, which showed favourable results from sotorasib in the overall population, with

an ORR of 37.1% (95% CI: 28.6, 46.2) and a median DOR of 11.1 months (95% CI: 6.9, 15.0). Top line results from the confirmatory trial for such CMA (CodeBreak 200) are already available. These show a median PFS of 5.6 months for sotorasib vs 4.5 months for docetaxel; hazard ratio 0.66 [0.51–0.86]; p=0.0017 (de Langen, 2023). Overall survival is similar between arms. The study allowed cross-over.

Despite therapeutic advances, treatment for patients with advanced NSCLC and KRAS G12C mutation remains palliative, and there remains an unmet medical need with additional treatment options warranted.

6.1.3. Main clinical studies

Efficacy results to support this application come from the primary analysis of Cohort A (n=116) from the phase 2 segment of KRYSTAL-1 (Study 849-001), a phase 1/2, open-label, multi-cohort, single-arm trial conducted in the US.

ORR as assessed by BICR is the primary endpoint of efficacy, whereas DOR, PFS and OS are secondary endpoints.

6.2. Favourable effects

At data cut-off (DCO) 15 June 2021 with a median follow-up of 9.0 months, 48 patients out of 116 were considered confirmed responders by retrospective BICR, accounting for an ORR of 41.4% (95% 32.3, 50.9). Analysis of ORR by investigator (37.1%) was concordant. Subgroup analysis suggest that the ORR benefit from adagrasib was consistent across the main pre-defined categories. At the updated 15 October 2021 DCO with a median follow-up of 12.9 months, no new objective responses had been reported and ORR by BICR thus remained 41.4%.

With ~40% of progression events in responders at the 15 June 2021 DCO, median duration of response (mDOR) was estimated at 7.3 months (95% CI: 5.1, NE). At the updated 15 October 2021 DCO , mDOR had slightly improved to 8.5 months (95% CI: 6.2, 13.8).

At the 15 October 2021 DCO, mPFS was 6.0 months (95% CI: 4.7, 8.4) and mOS was 11.7 months (95% CI: 9.2, NE). Maturity of PFS was 59.5% and of OS was 49.1%. The additional OS update with a 15 January 2022 DCO reported a mOS of 12.6 months (95% CI: 9.2, 19.2) with a maturity of 53%.

In terms of intracranial activity, analyses from study 849-001 have shown an ORR of 33.3% using m-RANO-BM in treated, stable brain metastasis and an ORR of 42% with CNS RECIST v1.1 in untreated, active brain metastases.

6.3. Uncertainties and limitations about favourable effects

The pivotal study has an uncontrolled/single-arm design which introduces inherent limitations as the therapeutic effect might be subject to various sources of bias and efficacy may be overestimated. In addition, the results of the time-to-event endpoints PFS and OS cannot be interpreted.

The sample size is rather small and the duration of follow-up limited.

The intracranial ORR rate may to an unknown extent be impacted by prior radiotherapy.

KRYSTAL-12, an on-going phase 3 open label, randomised controlled study comparing efficacy of adagrasib versus docetaxel in patients with NSCLC with KRAS G12C mutation should address the uncertainties and limitations identified and confirm the benefits of adagrasib.

6.4. Unfavourable effects

The overall safety database of adagrasib is constituted by 260 patients across multiple cohorts from the pivotal phase 1/2 Study KRYSTAL-1. The NSCLC safety pool (n=188) contains the highest number of patients with similar clinical characteristics and background as the targeted population in the proposed indication for treatment with adagrasib (strictly represented by Cohort A).

All patients that started treatment with adagrasib experienced adverse events. In the NSCLC pool, ~80% of patients presented high-grade (≥G3) AEs, ~60% SAEs, 18% AEs with outcome of death, 14% AEs leading to treatment discontinuation and 84% AEs leading to dose reduction/interruption.

The **most common AEs** in the NSCLC pool were diarrhoea (71%), nausea (70%), vomiting (57%), fatigue (57%), anaemia (35%), dyspnoea (35%), decreased appetite (35%), increased creatinine (34%), increased aspartate aminotransferase (32%), increased alanine aminotransferase (32%), peripheral oedema (29%), constipation (23%), alkaline phosphatase increased (22%) and QT prolonged (19%).

Anaemia (11.7%), dyspnoea (11.7%), fatigue (9.0%), pneumonia (8.5%), hypoxia (7.4%), lipase increased (6.9%), hyponatremia (6.9%), and lymphocyte count decreased (5.9%) were the most common **high-grade (≥G3) AEs** in the NSCLC pool.

Respiratory/thoracic/mediastinal disorders (21%) and infections (19%) were the most common types of **SAEs**. Pneumonia was the leading cause for hospitalisation across the NSCLC pool.

AEs with outcome of death occurred in 33 patients (~18%) from the NSCLC pool, out of which 12 deaths were declared as AE of "malignant neoplasm progression". AEs with outcome of death were related to respiratory/thoracic/mediastinal disorders in the majority of cases, while few patients died from heart-related or infectious causes. Four (2%) of the deaths were adagrasib-related.

It is considered that gastrointestinal toxicity in the spectrum of nausea/vomiting/diarrhoea, hepatotoxicity and QTc prolongation are the main **AESIs** for adagrasib.

Nausea (26%), vomiting (16%) diarrhoea (15%) and hepatotoxicity (14% ALT increased and 11% AST increased) were the most frequent **AEs leading to dose reductions or interruptions**.

As was the case with SAEs, the main categories of **AEs leading to permanent discontinuation** of adagrasib in the NSCLC pool (26 out of 188 patients, 14%) were infections (7 patients) and respiratory/thoracic/mediastinal disorders (7 patients).

Hepatotoxicity and QT prolongation require close monitoring. However, these are generally manageable with dose reductions or temporary interruptions.

6.5. Uncertainties and limitations about unfavourable effects

The uncontrolled design of the pivotal trial precludes the causality assessment of many adverse events. The uncertainties related to the limited safety database and the absence of long-term safety data will be addressed by the confirmatory study KRYSTAL-12.

6.6. Effects Table

Table 90: Effects Table for adagrasib in the treatment of patients with advanced NSCLC with KRAS G12C mutation, who have received platinum-based chemotherapy and immunotherapy. Data cut-off for efficacy and safety 15-OCT-2021.

Effect	Short Description	Unit	Adagrasib, N=116	Uncertainties/ Strength of evidence	References
Favourable Effects					
ORR-BICR	Overall response rate by BICR	% (95% CI)	41.4 (32.3, 50.9)	Single-arm trial	KRYSTAL-1 CSR
mDOR-BICR	Median duration of response by BICR	Months (95% CI)	8.5 (6.2, 13.8)	Single-arm trial, short median follow-up	KRYSTAL-1 CSR
Unfavourable Effects in the total safety dataset, N=260					
High-grade (≥G3) AEs		%	42	Single-arm trial short median follow-up	SCS
SAEs		%	51		SCS
AEs outcome of death		%	15		SCS
AEs leading to discontinuation		%	11		SCS
AEs leading reductions or interruptions		%	77		SCS
Nausea/vomiting/diarrhoea		%	90		SCS
Hepatotoxicity		%	39		SCS
QT prolonged		%	19		SCS

Abbreviations: BICR=blinded independent central review; CSR=clinical study report; NE=not estimable; SCS=summary of clinical safety
Notes: The safety dataset includes the NSCLC pool (N=188: 116 patients from cohort A, 56 patients from cohort B, 16 patients from Phase 1/1b) and 72 patients with other tumours.

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

Efficacy results from KRYSTAL-1, an uncontrolled single-arm trial, provide evidence for a meaningful activity of adagrasib in the target population. Data from response-related endpoints are improved in comparison to fully marketed choices such as docetaxel and appear comparable to the other conditionally approved product, Lumykras (sotorasib).

However, the long-term benefit of Krazati is unclear since its impact on time-to-event endpoints, i.e., PFS and OS, cannot be reliably estimated in the context of an uncontrolled trial. However, additional

analyses from the single-arm trial have shown promising intracranial activity of adagrasib in patients with brain metastases.

The safety profile of adagrasib is characterised by gastrointestinal toxicity in the form of nausea/vomiting/diarrhoea, hepatotoxicity and QT prolongation.

Uncertainties on efficacy and safety, essentially due to the non-comprehensive nature of the data in the sense of a conditional marketing authorisation, will be addressed by the confirmatory trial, an on-going phase 3 open label, randomised controlled study comparing adagrasib versus docetaxel in a similar population to cohort A from KRYSTAL-1.

The applicant has the obligation to provide the result of this trial by Q3 2024.

6.7.2. Balance of benefits and risks

The benefit-risk balance of adagrasib is considered positive. The available evidence demonstrates a meaningful activity of adagrasib for the second line treatment setting and beyond (2L+) of patients with KRAS G12C-mutated locally advanced or metastatic NSCLC. The toxicity profile is considered acceptable.

Results from KRYSTAL-1 support a conditional marketing authorisation and the SOB will provide comprehensive data on the impact on time-dependent endpoint, as well as comparative safety.

6.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

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

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

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

- **The benefit-risk balance of the product is positive**

In the context of a CMA as applied for, the efficacy results on response-related endpoints provide preliminary evidence for a promising treatment effect from Krazati in the targeted population. The magnitude of this treatment effect is considered to outweigh the risks related to the safety profile of Krazati.

- **It is likely that the Applicant will be able to provide comprehensive data**

The proposed confirmatory trial Krystal-12, comparing Krazati to docetaxel in previously treated patients with KRAS C12G mutated NSCLC, is an on-going phase 3 open label, randomised controlled study comparing adagrasib versus docetaxel in a similar population to cohort A from KRYSTAL-1, with a sample size of 450 patients. The clinical study results will be submitted by the applicant by Q3 2024. The primary endpoint is PFS and OS is one of the secondary endpoints. This study, for which the results are expected soon, is considered appropriate in design to address remaining uncertainties on the importance of the activity observed post-approval and to confirm a positive benefit risk.

- **Unmet medical needs will be addressed**

The unmet medical need in previously treated, metastatic NSCLC is indubitable, as this is a seriously debilitating and lethal condition, notwithstanding available therapies.

A major therapeutic advantage of Krazati over existing, fully approved therapies can be concluded and Krazati addresses the unmet medical need at least to a similar extent as sotorasib.

Since Lumykras (sotorasib) is approved under a conditional marketing authorisation, it is sufficient that Krazati addresses the unmet medical need to a similar extent as this product (as per Commission Regulation (EC) No 507/2006 "CMA Regulation" and CHMP 'Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004'). Considering the overall similarities in the efficacy and safety data provided, Krazati addresses the unmet medical need to a similar extent as Lumykras.

A major therapeutic advantage can be concluded over existing therapies with a full marketing authorisation; these include afatinib, docetaxel, erlotinib, nintedanib/docetaxel, pemetrexed ramucirumab/docetaxel, atezolizumab, nivolumab, and pembrolizumab.

The activity of Adagrasib in terms of ORR and DoR are of a magnitude that has previously been considered sufficient to infer a likely major therapeutic advantage on efficacy over existing therapies for the 2nd line treatment of NSCLC. In addition compared to fully approved therapies, adagrasib provides a novel mechanism of action and consequently a different safety profile.

Finally, adagrasib provides an oral therapeutic option for this patient population which can be considered a major improvement to patient care.

Therefore in the original assessment justification for major therapeutic advantage over available treatment options in 2nd line setting was considered to be sufficient by the CHMP, except for docetaxel due to the results of Codebreak 200, a phase 3 trial comparing sotorasib to docetaxel (de Langen et al. Lancet. 2023).

Emerging data from CodeBreaK 200 questioned whether the magnitude of effect observed with adagrasib would translate into a major therapeutic advantage over docetaxel considering the similar mechanism of action between Lumykras and Krazati. However, while adagrasib and sotorasib share the same primary pharmacological target, the substances display differences with regards to secondary pharmacology (e.g., affinity to hERG channels) and pharmacokinetics. Their PK profile is substantially different, adagrasib having a considerably longer half-life than sotorasib, providing more stable exposure over the dosing interval. Adagrasib exposure is dose-dependent (linear pharmacokinetics), whereas sotorasib exposure is not.

Intracranial activity also seems to differ between sotorsaib and adagrasib.

While the most common adverse effects (gastrointestinal, hepatic) are qualitatively similar, QT prolongation is relevant for adagrasib but not sotorasib, whereas pneumonitis has been reported for sotorasib but not for adagrasib.

Therefore, it is not evident that the clinical performance of Krazati in relation to docetaxel will be similar to what was seen for Lumykras.

The majority of the expert of the SAG, convened during the re-examination procedure, was also of the opinion that comparison between sotorasib and adagrasib is not necessarily valid in this setting despite similarities in mode of action. Different resistance mechanisms and different pharmacology indeed support that findings in sotorasib, namely results of CodeBreak 200, cannot necessarily be extrapolated to adagrasib. They reiterated the high unmet medical need and limited treatment options

with standard approval (e.g., docetaxel), as well as the high activity observed in the KRYSTAL-1 trial, despite limitations in the design and the small sample size. The activity against intracranial lesions is also worth considering as a potential therapeutic advantage, even if based on small numbers.

Taking the above into account, the emerging data from the confirmatory study of Lumykras, Codebreak200, are not incompatible with a major therapeutic advantage for Krazati over docetaxel.

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

In the population with advanced NSCLC progressing after first-line, with activity within the range of other oncogene-directed therapies that have been approved for NSCLC, and a manageable safety profile the benefit/risk of adagrasib is considered to be positive.

The level of activity of adagrasib, together with a differential safety profile compared to docetaxel, as well as the oral rather than i.v. administration are considered sufficient benefits to public health to support the immediate availability of adagrasib in view of the risks inherent in the fact that additional data are still required.

6.8. Conclusions

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

Divergent position(s) are appended to this report.

7. Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that the benefit-risk balance of Krazati is favourable in the following indication(s):

KRAZATI as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with KRAS G12C mutation and disease progression after at least one prior systemic therapy.

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

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

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

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

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

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

Description	Due date
In order to further confirm the efficacy and safety of adagrasib in the treatment of patients with KRAS G12C-mutated NSCLC, the MAH should submit the clinical study report for the phase 3 clinical study KRYSTAL-12, comparing adagrasib versus docetaxel for the treatment of previously treated patients with KRAS G12C mutated NSCLC. The clinical study report will be submitted by:	Q3/2024

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

Not applicable.

New active substance status

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

Please refer to Appendix on NAS.

Divergent position(s)

Divergent position(s) to the majority recommendation are appended to this report.

8. Appendices

- Divergent position to the majority recommendation dated 9 November 2023

APPENDIX

DIVERGENT POSITION DATED 09 November 2023

DIVERGENT POSITION DATED 09 November 2023

Krazati EMEA/H/C/006013/0000

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

KRAZATI as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with KRAS G12C mutation and disease progression after at least one prior systemic therapy.

The reasons for the divergent opinion were the following:

Efficacy results from KRYSTAL-1, an uncontrolled single-arm trial, provide preliminary evidence for activity of adagrasib in the target population. The long-term benefit of adagrasib is unclear, however, since its impact on time-to-event endpoints, i.e., PFS and OS, cannot be reliably estimated in the context of an uncontrolled pivotal trial.

Emerging data from the randomised controlled CodeBreaK 200 trial comparing sotorasib (another KRAS G12C inhibitor approved for use in the same clinical setting) to docetaxel give reason to question whether the magnitude of activity observed with adagrasib in KRYSTAL-1 is likely to translate into a clinical benefit for patients such as prolonged PFS and OS*. Although, differences are observed between the pharmacological profiles of sotorasib compared to adagrasib, cross study comparisons do not show relevant differences in clinical efficacy and safety parameters, including data on intracranial activity.

Overall, considering the uncertainty on the beneficial effect of Krazati we cannot conclude on a positive B/R at this stage and, in the context of the applied for conditional marketing authorisation (CMA), also not whether the available results provide a major therapeutic advantage over existing therapies including docetaxel (as laid down in EMA/CHMP/509951/2006, Rev.1). As requirements for a CMA are thus not met, this renders the application not approvable.

CHMP Members expressing a divergent opinion:

Peter Mol

Martina Weise

Robert Porszasz

Jan Muller-Berghaus

* De Langen AJ and all; Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with KRASG12C mutation: a randomised, open-label, phase 3 trial. Lancet. 2023 Mar 4;401(10378):733-746