CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216340Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	NDA
Application Number(s)	NDA 216340
Priority or Standard	Standard
Submit Date(s)	October 29, 2021; November 24, 2021; December 14, 2021
Received Date(s)	October 29, 2021; November 24, 2021; December 14, 2021
PDUFA Goal Date	December 14, 2022
Division/Office	Division of Oncology 2/Office of Oncologic Diseases
Review Completion Date	Electronic stamp date
Established Name	Adagrasib
(Proposed) Trade Name	KRAZATI
Pharmacologic Class	Inhibitor of the RAS GTPase family
Code name	MRTX849
Applicant	Mirati Therapeutics, Inc.
Formulation(s)	Tablets, 200 mg
Dosing Regimen	600 mg orally twice daily, with or without food
Applicant Proposed Indication(s)/Population(s)	MRTX849 is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with KRAS G12C mutation as determined by an FDA approved test, and who have received at least one prior systemic therapy.
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	KRAZATI is indicated for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy.

Table of Contents

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Table of Tables

Table of Figures

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

3D	three dimension
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AT	accelerated titration
AUC	area under the concentration-time curve
BCRP	breast cancer resistance protein
BID	twice daily
BICR	blinded, independent central review
BLA	biologics license application
BTDR	breakthrough therapy designation request
C_{ave}	average plasma concentration
$C_{ave,ss}$	average plasma concentration at steady state
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	confidence interval
CIT	checkpoint inhibitor therapy
CL_{CR}	creatinine clearance
CL/F	apparent oral clearance
CL_R	renal clearance
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
C_{min}	minimum plasma concentration
CNS	central nervous system
C-QTc	concentration-corrected QT interval
CR	complete response
CRF	case report form
CSR	clinical study report
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DDI	drug-drug interaction
DLT	dose limiting toxicity
DOR	duration of response
DMF	drug master file
ECG	electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document

eGFR	estimated glomerular filtration rate
E-R	exposure-response
ERK	extracellular signal-regulated kinase
FAS	Full Analysis Set
FDA	Food and Drug Administration
FF adj AUC_{24}	free fraction adjusted area under the plasma concentration-time curve from time 0 to 24 hours
FIH	first-in-human
GCP	good clinical practice
GLP	good laboratory practice
HER2	human epidermal growth factor receptor 2
hERG	human ether-a-go-go related gene
H	Hour
IC_{50}	half-maximal inhibitory concentration
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IND	Investigational New Drug
CL_{int}	intrinsic clearance
IRB	Institutional Review Board
hERG	human ether-a-go-go related gene
IC_{50}	half-maximal inhibitory concentration
ISS	integrated summary of safety
kg	kilogram
K_i	inhibitory constant
K_{inact}	inactivation rate constant
KRAS	Kirsten rat sarcoma viral oncogene homolog protein
KRAS	Kirsten rat sarcoma viral oncogene homolog DNA
KRAS G12C	KRAS protein with a G12C amino acid substitution
KRAS G12C	*KRAS* gene with a mutation resulting in a G12C amino acid substitution at the protein level
LVEF	left ventricular ejection fraction
MATE	multi-antimicrobial extrusion protein
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
µg	microgram
mL	milliliter
µM	micromolar
msec	millisecond
mTPI	modified toxicity probability interval
MUGA	multigated acquisition scan
NA	not applicable
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NCI-ODWG	National Cancer Institute-Organ Dysfunction Working Group
NDA	new drug application
NE	not estimated
ng	nanogram
nM	nanomolar
NME	new molecular entity
NOAEL	no-observed-adverse-effect-level
NSCLC	non-small cell lung cancer
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBPK	physiologically-based pharmacokinetic
PD	pharmacodynamic
PD-1	programmed death receptor-1
PD-L1	programmed cell death ligand 1
PDX	patient-derived xenograft
PFS	progression-free survival
P-gp	P-glycoprotein
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPD	Predictive Probability Design
PPI	patient package insert
PR	partial response
PRO	patient reported outcome
PS	Performance Status
PTR	peak-to-trough ratio
QD	once daily
QTc	corrected QT interval
QTcF	corrected QT interval Fridericia
QTcP	population-corrected QT
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	risk evaluation and mitigation strategy
RTOR	Real Time Oncology Review
SAE	serious adverse event
TEAE	treatment emergent adverse event
$t_{1/2}$	terminal elimination half-life
TK	toxicokinetic

t_{max}	time to maximum plasma concentration
ULA	ultra-low attachment
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
Vz/F	apparent volume of distribution
WT	wildtype

1 Executive Summary

1.1. Product Introduction

Adagrasib (also known as MRTX849) is a small molecule, covalent inhibitor of the RAS GTPase family that binds irreversibly to Kirsten rat sarcoma proto-oncogene (KRAS) G12C, thereby locking the kinase receptor in an inactive conformation. Adagrasib is not currently approved in the United Sates (U.S.) or any other part of the world. The proposed dosage regimen for adagrasib is 600 mg orally by mouth twice daily (BID) with or without food until disease progression or unacceptable toxicity. Mirati's proposed indication for adagrasib is "for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with *KRAS G12C* mutation as determined by an FDA approved test, and who have received at least one prior systemic therapy".

1.2. Conclusions on the Substantial Evidence of Effectiveness

The submitted evidence meets the statutory evidentiary standard for accelerated approval. The recommendation for accelerated approval of adagrasib according to 21 CFR 314.510, is based on results from a single arm, multicenter, expansion cohort clinical trial, Study 849-001 (also known as KRYSTAL-1) in patients with *KRAS G12C* mutated locally advanced or metastatic NSCLC who received adagrasib 600 mg orally BID. The efficacy population for this application included 112 patients with *KRAS G12C* mutated locally advanced or metastatic NSCLC and had at least one site of measurable disease at baseline as assessed by blinded independent central review (BICR). The demonstrated overall response rate (ORR) by BICR per RECIST v1.1 of 43% (95% CI: 34, 53) with a median duration of response (DOR) of 8.5 months (95% CI: 6.2, 13.8) is considered clinically meaningful when considering the intended patient population of adult patients with *KRAS G12C* mutated locally advanced or metastatic NSCLC who have received at least one prior systemic therapy.

For NSCLC, ORR may be considered an endpoint reasonably likely to predict clinical benefit when the treatment effect size is large and the responses are durable (Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics). Based on the findings in Study 849-001, FDA expects that adagrasib will have, as described in section 505(d) of the Food, Drug, and Cosmetic Act, "the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof".

This is the second accelerated approval of an oral targeted therapy for patients with *KRAS G12C* mutated NSCLC. The ORR and durable responses observed with adagrasib are reasonably likely to predict clinical benefit and provide a meaningful advantage over available treatments for this

disease and, in the context of an acceptable safety profile, are consistent with a favorable risk:benefit profile.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Lung cancer is the leading cause of cancer deaths in the U.S., accounting for almost 25% of all cancer deaths in 2021 (Siegel 2021). Population-level mortality from NSCLC has declined over the past 10 years, with the reductions in mortality surpassing the reductions in incidence (Sigel 2021, Howlader 2020). Analysis of SEER data suggests that the reduction in mortality from NSCLC accelerated starting in 2013, coinciding with the recommendations for routine testing for EGFR and ALK molecular alterations, with improvements in survival likely related to the identification of oncogenic driver mutations and the development and approval of therapies targeting these mutations (Howlader 2019). Despite these advances, metastatic NSCLC remains a fatal, incurable disease, with a 5-year survival rate of <10%.

Locally advanced or metastatic NSCLC with *KRAS G12C* mutation is a genetically distinct form of lung cancer that is not curable with available therapy and is found in 13.8% of advanced NSCLC cases, affecting approximately 15,760 patients in the U.S. per year (Nassar 2021, Siegel 2021). Kirsten rat sarcoma proto-oncogene (KRAS) has been recognized as an oncogenic driver mutation in NSCLC and is associated with a history of smoking. Patients harboring this mutation traditionally have had a poor prognosis compared to patients with epidermal growth factor receptor (EGFR) mutated NSCLC (Fan 2017). Furthermore, until recently with the accelerated approval on May 28, 2021 of sotorasib, another oral KRAS G12C inhibitor, KRAS G12C has been refractory to drug targeting resulting in a substantial unmet need for this patient population. The clinical benefit of sotorasib has not been verified and no targeted therapy for the treatment of patients with KRAS G12C-mutated NSCLC has been granted traditional approval.

Adagrasib is a small molecule inhibitor that binds KRAS G12C, locking the protein in its inactive conformation. The proposed dosing regimen is 600 mg orally twice daily with or without food, and adagrasib is not approved for any other indication in the U.S. or globally.

The pivotal trial supporting this NDA is Study 849-001 (also known as KRYSTAL-1), a multicenter, multicohort, dose escalation and dose expansion trial in the U.S. which included patients in Cohort A with *KRAS G12C* mutated locally advanced or metastatic NSCLC who received adagrasib 600 mg orally BID. The primary efficacy population for this application included 112 patients from Cohort A who had at least one site of measurable disease at baseline as assessed by blinded independent central review (BICR). All 112 of these patients had received prior treatment with platinum-based chemotherapy and anti-PD-(L)1 based therapy. The overall response rate (ORR) by BICR per RECIST v1.1 was

43% (95% CI: 34, 53). The median duration of response (DOR) was 8.5 months (95% CI: 6.2, 13.8) with 58% of patients experiencing a DOR of at least 6 months.

Adagrasib has an acceptable safety profile when assessed in the context of a life-threatening condition. The primary safety review focused on the population of 116 patients with *KRAS G12C* mutated NSCLC who received adagrasib 600 mg orally twice daily in Study 849-001. In the primary safety population, the most common treatment-emergent adverse reactions (≥20%) were diarrhea (70%), nausea (69%), fatigue (59%), vomiting (56%), musculoskeletal pain (41%), hepatotoxicity (37%), renal impairment (36%), dyspnea (35%), edema (32%), decreased appetite (30%), cough (24%), pneumonia (24%), dizziness (23%), constipation (22%), abdominal pain (21%), and QTc interval prolongation (20%). Permanent discontinuation of adagrasib due to adverse reactions occurred in 13% of patients; adverse reactions leading to permanent discontinuation occurring in two patients each (1.7%) were pneumonia and pneumonitis, and occurring in one patient each (0.9%) were cerebrovascular accident, dyspnea, decreased ejection fraction, encephalitis, gastrointestinal obstruction, hemorrhage, hepatotoxicity, hypotension, muscular weakness, pulmonary embolism, pyrexia, respiratory failure and sepsis. Fatal adverse reactions occurred in 11% of patients, including pneumonia (3.4%), respiratory failure (1.7%), sudden death (1.7%), cardiac failure (0.9%), cerebrovascular accident (0.9%), mental status change (0.9%), pulmonary embolism (0.9%), and pulmonary hemorrhage (0.9%).

Safety issues identified as significant and serious during the NDA review, in the pooled safety population of 366 patients with NSCLC and other solid tumors who received adagrasib as a single agent at 600 mg BID, were gastrointestinal adverse reactions, QTc interval prolongation, hepatotoxicity, and interstitial lung disease (ILD)/pneumonitis. Gastrointestinal adverse reactions of diarrhea, nausea, and vomiting occurred in 89% of patients including 9% Grade 3. Serious gastrointestinal adverse reactions were gastrointestinal bleeding (3.8%), gastrointestinal obstruction (1.6%), colitis (0.5%), ileus (0.5%), and gastrointestinal stenosis (0.3%). QTc interval prolongation, which can increase the risk for ventricular tachyarrhythmias (e.g., Torsades de Pointes) or sudden death, also occurred in patients who received adagrasib. In patients with at least one post-baseline electrocardiogram (ECG) assessment, 6% had an average QTc ≥501 ms and 11% had an increase from baseline of QTc ≥ 60 msec. Hepatotoxicity occurred in 37% of patients and 7% were Grade 3 or 4. ILD/pneumonitis occurred in 4.1% of patients, of which 1.4% of cases were Grade 3 or 4, and one case was fatal. These safety concerns are adequately addressed by information in the Warnings and Precautions section of the U.S. Prescribing Information (USPI) and the dose modification recommendations included in the adagrasib product labeling. There were no significant safety concerns identified during NDA review requiring risk management beyond labeling or warranting consideration for Risk Evaluation and Mitigation Strategy (REMS). Adagrasib appears to have an acceptable safety profile when assessed in the context of a life-threatening disease.

A supplemental premarket application (sPMA) for a tissue-based companion diagnostic test (QIAGEN *therascreen* KRAS RGQ PCR Kit CDx) was submitted by Qiagen and a PMA for a plasma-based companion diagnostic test (RESOLUTION ctDX FIRST assay CDx) was submitted by Resolution Biosciences for contemporaneous review and approval with this NDA. Given that concordance analysis revealed a positive percent agreement (PPA) of only approximately 63% for the plasma test compared to the tissue test, suggesting that 37% of tissue positive samples will be missed by the plasma test, (b) (4).

The submitted evidence meets the statutory evidentiary standard for accelerated approval of adagrasib. The durable response rate, which exceeds that of available second-line therapies, and favorable safety profile observed with adagrasib in a patient population with a significant unmet need support approval. However, while the benefit-risk profile in the indicated population is favorable , the 600 mg BID dosage may not be optimized from a PK, safety, and efficacy standpoint as there was limited evaluation of adagrasib at other dosage levels. Adagrasib shows a high toxicity profile with 82% of patients experiencing TEAEs leading to dose reduction or interruption and high incidences of gastrointestinal adverse reactions. Therefore, a dose optimization postmarketing requirement (PMR) will be issued for the Applicant to evaluate an alternative dosage that may provide similar efficacy with improved safety as compared to the 600 mg BID dosage.

Therefore, based on a favorable risk:benefit assessment, adagrasib was granted accelerated approval for the following indication:
"*Adagrasib is indicated for the treatment of adult patients with KRAS G12C mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy*."

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Lung cancer is the leading cause of cancer deaths accounting for almost 25% of all cancer deaths in the U.S. in 2021. (Siegel 2021) • KRAS G12C mutated NSCLC represents 13.8% of all metastatic NSCLC. This mutation is associated with a history of smoking tobacco and higher programmed death-ligand 1 (PD-L1) expression and tumor mutational burden than observed in KRAS wild-type NSCLC. • The median overall survival observed in patients with KRAS G12C NSCLC treated with immunotherapy is approximately 21-28 months compared to 10-20 months with chemotherapy alone (Herbst 2019, Gadgeel 2019). There are no approved targeted therapies for patients with KRASG12C NSCLC. KRAS G12C has been refractory to drug-targeting. • The 5-year survival rate for patients with metastatic NSCLC is <10%. There are no randomized trial data available regarding survival specifically for patients with KRAS G12C mutated NSCLC.	Advanced NSCLC (metastatic or locally advanced not amenable to curative intent therapy) is a life threatening condition with poor survival.
Current Treatment Options	• No therapy has received regular approval specifically for the treatment of patients with KRAS G12C mutated NSCLC. • Standard of care for patients with metastatic KRAS G12C mutated NSCLC includes the same therapies for treatment of metastatic NSCLC that does not harbor a targetable mutation, although the effectiveness of these treatments has not specifically been studied in this subpopulation. • For patients with progression of disease following platinum-based chemotherapy with or without an immune checkpoint inhibitor, treatment options include sotorasib, a RAS GTPase family inhibitor, which received accelerated approval on May 28, 2021, chemotherapy (e.g., docetaxel as a single agent or in combination with	There remains an unmet medical need for patients with advanced KRAS G12C mutated NSCLC who have received at least one prior systemic therapy. This conclusion is based on the observed ORR, DOR, and overall survival (OS) reported for the limited therapies currently used in clinical practice for the treatment of this patient population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	ramucirumab), and single agent anti-PD-(L)1 antibody if not received in the first-line setting.	
Benefit	• The primary trial supporting this NDA is Study 849-001 (KYRSTAL-1), an open-label, single-arm, multicohort dose escalation and dose expansion study for patients with advanced/metastatic solid tumors harboring a KRAS G12C mutation. Patients with KRAS G12C mutated NSCLC who have received at least one prior systemic therapy enrolled in Cohort A (n=116). • The ORR observed in the primary efficacy population (n=112) of patients with KRAS G12C mutated NSCLC was 43% (95% CI: 34, 53) who received adagrasib 600 mg orally twice daily and had at least one site of measurable disease at baseline per RECIST v1.1. • The median duration of response (DOR) was 8.5 months (95% CI:6.2, 13.8). • 58% of the responders had a duration of response ≥6 months. • The limitation of single arm trials is the potential for known and unknown patient selection bias.	The submitted evidence from clinical trial Study 849-001 meets the statutory evidentiary standard for accelerated approval. The observed improvement in ORR of 43% (95% CI: 34, 53) and median DOR of 8.5 months (95% CI: 6.2, 13.8) are clinically meaningful in the context of the poor prognosis of the disease and the limited available FDA-approved therapies. The trial was conducted in the U.S., and although there were some inspectional findings related to under reporting of adverse events and concomitant medication at one site, the OSI inspection of the remaining clinical sites revealed no significant finding regarding the conduct of the trial.
Risk and Risk Management	• The primary safety population for the assessment of safety and tolerability of adagrasib in patients with KRAS G12C mutated NSCLC included 116 patients who received at least one dose of adagrasib 600 mg orally twice daily. The pooled safety population included 366 patients with KRAS G12C mutated solid tumors who received at least one dose of adagrasib 600 mg orally twice daily. The data in this NDA	Although adagrasib can cause serious toxicities, information in the Warnings and Precautions and Dosage and Administration sections of the U.S. product labeling address these safety issues adequately. In addition, the observed safety profile is acceptable when

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	are adequate to assess the safety of adagrasib in the targeted U.S. population of patients with KRAS G12C mutated NSCLC. • The most common (≥20%) treatment emergent adverse reactions in the primary safety population were diarrhea, nausea, fatigue, vomiting, musculoskeletal pain, hepatoxicity, renal impairment, dyspnea, edema, decreased appetite, cough, pneumonia, dizziness, constipation, abdominal pain, and QTc interval prolongation. • Serious adverse reactions (SARs) occurred in 57% of patients in the primary safety population. SARs occurring in ≥2% of patients were pneumonia, dyspnea, renal impairment, sepsis, hypoxia, pleural effusion,respiratory failure, anemia, cardiac failure, hyponatremia, hypotension, muscular weakness, pyrexia, dehydration, diarrhea, mental status changes, pulmonary embolism, and pulmonary hemorrhage. • Fatal adverse reactions occurred in 11% of patients who received adagrasib due to pneumonia (3.4%), respiratory failure (1.7%), sudden death (1.7%), cardiac failure (0.9%), cerebrovascular accident (0.9%), mental status change (0.9%), pulmonary embolism (0.9%), and pulmonary hemorrhage (0.9%). • Permanent discontinuations of adagrasib occurred in 13% of patients. • Adverse reactions that were included in the Warnings and Precautions section of the USPI for adagrasib are gastrointestinal adverse reactions, QTc interval prolongation, hepatoxicity, and interstitial lung disease (ILD)/pneumonitis. • Study treatment interruptions or dose reduction of adagrasib occurred in 82% of patients. • In a non-randomized, non-comparative clinical trial such as Study 849-	assessed in the context of a life-threatening disease. There were no significant safety concerns identified during the NDA review requiring risk management beyond labeling or warranting consideration for Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use of adagrasib.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	001, a direct comparison of adagrasib-associated toxicity versus toxicity associated with current standard of care therapy is not possible.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as			
			□	Patient reported outcome (PRO)	
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	x	Other: (Please specify)			No patient experience data were submitted.
□	Patient experience data that was not submitted in the application, but was considered in this review.				

x

Paz Vellanki, MD, PhD
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Lung cancer remains the leading cause of cancer-related death in the United States (US). Approximately 235,760 new cases of lung cancer are expected to be diagnosed in the US in 2021, and approximately 131,880 deaths will be attributed to lung cancer (American Cancer Society 2021). Non-small cell lung cancer (NSCLC) accounts for approximately 84% of lung cancer cases (Noone et al. 2018), of which approximately half are classified as adenocarcinoma of the lung, approximately one-quarter as squamous cell carcinoma, while large cell carcinoma is infrequently diagnosed.

Mutation of glycine specifically to cysteine, noted as *KRAS* [p.G12C] (also noted as *KRAS* G12C), occurs in approximately 14% of lung adenocarcinomas, and results from a DNA transversion mutation (guanine to thymine in KRAS gene) that has been attributed to carcinogens in tobacco smoke, particularly polycyclic aromatic hydrocarbons (Pfeifer et al. 2002, Riely et al. 2008). The incidence of NSCLC with *KRAS G12C* mutation is estimated to be approximately 15,000 cases per year in the US. These patients and are currently treated using NSCLC paradigms.

The natural history of lung cancer is one of progressive disease that is rapidly fatal (Detterbeck et al. 2008), and despite the significant advances of chemotherapy and immunotherapy for NSCLC, patients ultimately develop progressive disease. The 5-year survival of metastatic NSCLC remains at approximately 6% (Howlader et al. 2019), indicating that NSCLC is a serious and life-threatening condition with an unmet medical need.

Recent studies have indicated that targeting the KRAS G12C mutant variant may be feasible through irreversible targeting of the mutated cysteine with covalent small molecule inhibitors (Ostrem et al. 2013, Lito et al. 2016). This work led to the development of adagrasib for the treatment of patients with NSCLC characterized by a *KRAS* G12C mutation.

The FDA's Assessment:

FDA agrees with the Applicant's position.

2.2. Analysis of Current Treatment Options

Functional genomics studies have demonstrated that NSCLC cell lines exhibiting *KRAS* mutations are highly dependent on KRAS function for cell growth and survival (McDonald et al. 2017). As observed in large genomic studies, *KRAS* mutations are mutually exclusive with other known oncogenic driver mutations in NSCLC, including *EGFR*, *ALK*, *ROS1*, *RET*, and *BRAF*, indicating that *KRAS* mutations define a unique segment of lung cancer (Campbell et al. 2016).

In the absence of a targeted treatment option, standard, initial treatment of advanced/ metastatic NSCLC includes platinum-based chemotherapy and immune checkpoint (programmed death receptor-1 [PD-1] or programmed cell death ligand 1 [PD-L1]) inhibitor therapy (CIT) administered concurrently or sequentially.

Until recently, platinum-based chemotherapy doublets, with or without bevacizumab in selected patients, represented the standard of care for most patients with advanced NSCLC in the first-line treatment setting (Schiller et al. 2002, Sandler et al. 2006, Scagliotti et al. 2008). Subsequently, immune checkpoint inhibitor therapies (CITs), including nivolumab, pembrolizumab, and atezolizumab, were proven to be effective in the treatment of advanced NSCLC in the second-line setting (Borghaei et al. 2015, Garon et al. 2015, Herbst et al. 2016, Rittmeyer et al. 2017). In addition, studies in the first-line setting demonstrated a survival advantage as monotherapy in patients with untreated, advanced NSCLC characterized by ≥ 50% tumor PD-L1 expression (Reck et al. 2016, Herbst et al. 2020), and in combination with a platinum-based therapy in the first-line, advanced disease treatment setting for patients with NSCLC regardless of PD-L1 status (Gandhi et al. 2018, Socinski et al. 2018).

Second-line chemotherapy remains a standard after failure of a platinum-based chemotherapy and CIT. Docetaxel, alone or in combination with ramucirumab, and pemetrexed remain approved chemotherapy options in patients previously treated with platinum-based chemotherapy. Median overall survival (OS) reported in randomized clinical trials using these regimens as experimental or comparator therapies has varied between approximately 5.7 and 9.5 months, while median progression-free survival (PFS) and objective response rate (ORR) have ranged from 2.3 to 4.5 months and 5.5% to 12%, respectively (Shepherd et al. 2000, Hanna et al. 2004, Krzakowski et al. 2010, Scagliotti et al. 2009, Tomasini et al. 2016). With combination therapy, an ORR of 23% (95% confidence interval [CI]: 20% to 26%) has been observed in patients receiving docetaxel with ramucirumab (Garon et al. 2014). Efficacy results for traditional second-line treatment options are summarized in Applicant Table 1.

Applicant Table 1: Efficacy Endpoints with Traditional Second-Line Treatment Options Mutation

Treatment	Response Rate	DOR (months)	PFS (months)	OS (months)
Docetaxel (75 mg/m^2)	6.7-14%[1-4]	5.3-9.1[2-4]	2.9-3.0[1,4]	5.7-9.1[1-4]
Docetaxel (75 mg/m^2) (254 patients with *KRAS*-mutant NSCLC)[5]	13.7%	4.5	2.8	7.9
Pemetrexed[4]	9.1%	4.6	2.9	8.3
Docetaxel + Ramucirumab[1]	23%	NR	4.5	10.5

Abbreviations: DOR = duration of response; NR = not reported; PFS = progression-free survival; OS = overall survival.
[1] Garon et al. 2014, [2] Shepherd et al. 2000, [3] Fossella et al. 2000, [4] Hanna et al. 2004, [5] Jänne et al. 2017.

In addition, on 28 May 2021 the US Food and Drug Administration (FDA) granted accelerated approval to sotorasib for *KRAS* G12C mutated NSCLC after at least one prior systemic therapy based on an ORR of 36% (95% CI: 28%, 45%) and a median response duration of 10.0 months (range 1.3+, 11.1) (LUMAKRAS USPI 2021). Among the 100 subjects who had prior treatment with both platinum-based chemotherapy and anti-PD-1 or anti-PD-L1, ORR was 31% (95% CI: 22, 41) and median duration of response was 10 months (95% CI: 6.9, not estimable) (Center for Drug Evaluation and Research 2021).

In the second-line setting, treatment remains palliative, and docetaxel-based regimens are associated with significant myelosuppression and consequent risk of infection as well as other adverse events (AEs) that could limit its use (Shepherd et al. 2000, Fossella et al. 2000, Scagliotti et al. 2009, Krzakowski et al. 2010, Al-Saleh et al. 2012, Tomasini et al. 2016). Thus, there remains an unmet medical need for patients with *KRAS*-mutant NSCLC after failure of treatment with both a platinum-based chemotherapy and a PD-1/PD-L1 inhibitor.

Second-line treatment options applicable to patients with advanced NSCLC with *KRAS* G12C mutation are presented in Applicant Table 2.

Applicant Table 2: Summary of Second-line Treatment Options for Patients with NSCLC with *KRAS* Mutation

Product (s) Name	Year and Type of Approval for Second-line NSCLC	Dosing Regimen	Efficacy Information	Warnings and Precautions
Docetaxel	1999 Full	Intravenous: 75 mg/m^2 every 3 weeks	ORR: 6.7-14%[1-4] mDOR: 5.3-9.1 months[2-4] mPFS: 2.9-3.0 months[1,4] mOS: 5.7-9.1 months[1-4]	Toxic deaths, hepatotoxicity, neutropenia, hypersensitivity reactions, fluid retention, secondary primary malignancies, cutaneous reactions, neurologic reactions, eye disorders, asthenia, embryo-fetal toxicity, alcohol content, tumor lysis syndrome
Ramucirumab plus Docetaxel	2014 Supplemental Full	Ramucirumab Intravenous: 10 mg/kg every 3 weeks Docetaxel Intravenous: 75 mg/m^2 every 3 weeks	REVEL (NCT01168973) ORR: 23%[1] mDOR: NR mPFS: 4.5 months[1] mOS; 10.5 months[1]	Hemorrhage, gastrointestinal perforations, impaired wound healing, arterial thromboembolic events, hypertension, infusion-related reactions, worsening of pre-existing hepatic impairment, posterior reversible encephalopathy syndrome, proteinuria including nephrotic syndrome, thyroid dysfunction, embryo-fetal toxicity
Pemetrexed	2004 Accelerated 2008 Full	Intravenous: 500 mg/ m^2 every 3 weeks	Study JMEI (NCT00004881) ORR: 9.1% mDOR: 4.6 months[4] mPFS: 2.9 months[4] mOS; 8.3 months[4]	Myelosuppression, renal failure, bullous and exfoliative skin toxicity, interstitial pneumonitis, and radiation recall, embryo-fetal toxicity
Sotorasib	2021 Accelerated	Oral: 960 mg once daily	CodeBreaK 100 (NCT03600883) ORR: 36% mDOR: 10.0 months	Hepatotoxicity, interstitial lung disease/pneumonitis
Nivolumab	2015 Full	Intravenous: 240 mg every 2 weeks or 480 mg every 4 weeks	Study CHECKMATE-017 (NCT01642004) vs docetaxel mOS: 9.2 vs 6.0 months	Immune-mediated reactions (pneumonitis, colitis, hepatitis and hepatotoxicity, endocrinopathies, dermatologic adverse reactions, and nephritis and renal dysfunction),

Product (s) Name	Year and Type of Approval for Second-line NSCLC	Dosing Regimen	Efficacy Information	Warnings and Precautions
			ORR: 20% vs 9% mPFS: 3.5 vs 2.8 months	infusion reactions, complications of allogeneic HSCT, embryo-fetal toxicity
Pembrolizu-mab	2015 Accelerated 2016 Full	Intravenous: 200 mg every 3 weeks or 400 mg every 6 weeks	Study KEYNOTE-010 (NCT01905657) vs docetaxel TPS ≥ 50% mOS: 14.9 vs 8.2 months mDOR: NR v 8.1 months ORR: 30% vs 8% TPS ≥ 1% mOS: 10.4 vs 8.5 months mDOR: NR vs 6.2 months ORR: 18% vs 9%	Immune-mediated reactions (including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, dermatologic adverse reactions, solid organ transplant rejection), infusion-related reactions, complications of allogeneic HSCT, embryo-fetal toxicity
Atezolizumab	2016 Full	Intravenous 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks	Study OAK (NCT02008227) vs docetaxel mOS: 13.8 vs 9.6 months mPFS: 2.8 vs 4.0 months x ORR: 14% vs 13%	Immune-related events (including pneumonitis, colitis, hepatitis, endocrinopathies, dermatologic adverse reactions, nephritis and renal dysfunction, solid organ transplant rejection); infusion related reactions, complications of allogeneic HSCT, embryo-fetal toxicity

Abbreviations: NR = not reached; NSCLC = non-small lung cancer; ORR = objective response rate; mDOR = median duration of response; mOS = median overall survival; mPFS = median progression-free survival; TPS = tumor proportion score Source: Product prescribing information

[1] Garon et al. 2014, [2] Shepherd et al. 2000, [3] Fossella et al. 2000, [4] Hanna et al. 2004.

The Applicant's Position:

The treatment options for patients with NSCLC without an actionable mutation have evolved and now typically include chemotherapy with checkpoint (PD-1 or PD-L1) inhibitor administered either concurrently or sequentially. For patients with lung adenocarcinoma, chemotherapy

typically includes a platinum agent and pemetrexed, with pemetrexed also an approved option for maintenance therapy. With *KRAS* G12C mutation in NSCLC occurring almost exclusively in lung adenocarcinoma, approved treatment options after a platinum regimen and a checkpoint inhibitor are largely limited to docetaxel with or without ramucirumab and recently, sotorasib. However, treatment remains palliative and can be associated with significant toxicity; thus, there remains an unmet medical need for additional treatment options for patients with NSCLC with *KRAS* G12C mutation after failure for chemotherapy and immunotherapy.

The FDA's Assessment:
FDA agrees with the Applicant's position.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position

Adagrasib is not currently registered or approved in the US or other regions.

The FDA's Assessment:
FDA agrees with the Applicant's position.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

A summary of the key regulatory interactions with the FDA concerning adagrasib for the proposed indication in patients with advanced NSCLC with *KRAS* G12C mutation is presented in Applicant Table 3.

Applicant Table 3: Key Regulatory Interactions with FDA Concerning Adagrasib

Date	Type	Outcomes
29-October-2018	Initial IND	IND 138735 (containing Study 849-001) Study May Proceed received 28-Nov-2018
03-February-2020	B - End of Phase 1	Proposed patient population for Cohort A in Study 849-001 is considered acceptable. Primary endpoint of ORR with DOR is acceptable as a surrogate endpoint for accelerated approval.

Date	Type	Outcomes
20-May-2020		Fast Track Designation granted
31-July-2020	B - Pre-Phase 3	Mirati intends to submit Study 849-012, an open-label, randomized trial to verify the clinical benefit of adagrasib for the proposed indication, under a new IND dedicated to the development of adagrasib monotherapy for the treatment of NSCLC.
10-May-2021		Agreed on NSCLC initial Pediatric Study Plan (iPSP)
07-June-2021		Orphan Drug Designation granted for treatment for *KRAS* G12C positive non-small cell lung cancer.
24-June-2021		Breakthrough Therapy Designation granted.
28-October-2021		Participation in RTOR Pilot program granted.
17-November-2021	B - Pre-NDA	Agreement reached on finalization, submission and label consideration for completed hepatic impairment study. Agreement reached on evaluation of alternate dosing. Two pre-submission requests were submitted to CDRH from two diagnostic partners to enable contemporaneous approval of companion diagnostics at the time of drug approval. Agreement on approach (timing and format) for 120-day safety update. Agreement on supplemental safety data presentation 30-45 days post submission of original NDA. Agreement on submission of updated efficacy data with the 120-day safety update. NDA, will support a full waiver from requirements of PREA. FDA agreed that the proposal for Priority Review designation will be made upon initial review of the NDA.

The FDA's Assessment:

FDA agrees with the Applicant's timeline of regulatory interactions but notes there are several caveats to the outcomes described by the Applicant. FDA provided feedback and recommendations during the meetings; however, FDA does not agree with the Applicant's characterization that agreements were reached when describing FDA feedback and advice provided at meetings. The only bullet points listed which may be characterized as agreements are those points related to the content and format of the NDA at pre-NDA meetings. While FDA agreed during the February 3, 2020, meeting that a primary endpoint of ORR with DOR may be acceptable in the KRYSTAL-1 trial to support a marketing application for accelerated approval, FDA did not indicate that ORR and DOR are validated surrogate endpoints for longer-term clinical outcomes such as overall survival.

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4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The review division (DO2) and OSI selected four clinical investigators (Drs. Pasi Janne [Site #808], Gregory Riely [Site #806], Igor Rybkin/Shirish Gadgeel [Site #811], and Alexander Spira [Site #814], as well as the central imagining contract research organization (CRO), (b) (4) for inspection using a risk-based approach taking into consideration the total number of patients enrolled and safety and efficacy parameters.

Although there were some inspectional findings related to under reporting of adverse events and concomitant medications not documented as protocol violations at Dr Igor Rybkin/Shirish Gadgeel site, the inspections revealed no significant findings at the remaining clinical investigator sites or the CRO. Based on the results of these inspections, the Study 849-001 overall appears to have been conducted adequately and the data generated by the inspected clinical investigators and the CRO appear acceptable in support of the indication in the NDA.

Dr. Pasi Janne enrolled a total of 22 patients. Protocol violations in 2 patients who received the medication ondansetron while on adagrasib therapy were identified. In these instances, administration of ondansetron was reported to the NDA but not reported as protocol deviations. Ondansetron was listed as medication to be avoided (protocol version 1.0 to 6.0) due to the known risk of QT prolongation and Torsade de Pointes. The protocol was amended (version 7.0, 12/23/2020) to allow for oral ondansetron at doses up to 4 mg every 6 hours, with a maximum total daily dose of 16 mg for patients without underlying bradycardia, CHF, or congenital long QT syndrome. Use of intravenous ondansetron was to be avoided during the study. In addition, review of the medical records indicated that two additional patients were prescribed ondansetron.

Dr. Igor Rybkin/Dr. Shirish Gadgeel enrolled a total of 9 patients. At the inspection preannouncement, FDA was informed that Dr Igor Rybkin had left the institution and Dr. Shirish Gadgeel was the responsible individual for Study 849-001. Two issues were observed during the inspection. Three unreported adverse events (i.e., sepsis, deep venous thrombosis [DVT], and seizure) and one unreported concomitant medication (intrahepatic radiation beads) were identified during the inspection. After identification of these three unreported adverse events, DO2 included these events for the safety analysis of this NDA. In addition, three patients were not re-consented using the revised informed consent form associated with the amendment to protocol 849-001 on 12/23/2020 (protocol version 7.0) which included numerous revisions, including updates on the clinical safety experience, adverse event management guidelines, and guidance on use of concomitant medications. Following a Full Board Meeting on 02/09/2021,

the IRB approved the implementation of the protocol and did not consider the risk of patients increased and recommended against reconsenting patients who were currently active in the trial. However, OSI indicated in their review that it is the responsibility of the clinical investigators and research staff to ensure that trial participants are informed of any changes or new information that may influence their decision to continue to participate in a research protocol. Therefore, the three patients who were receiving adagrasib at the time of the consent form amendment should have been reconsented for the trial.

Based on OSI findings at this site (i.e., Site #811), an FDA information request was sent to the Applicant to update the protocol violations dataset and to evaluate if other patients enrolled in the study may have received intrahepatic radiation bead administration while on adagrasib therapy. Refer to FDA Table 14 for the protocol violations. Additionally, refer to Section 8.1.2 regarding the impact of intrahepatic radiation bead administration on the efficacy analysis for this NDA.

Dr. Gregory Riely enrolled a total of 15 patients and Dr. Alexander Spira enrolled a total of 11 patients. The inspections found no regulatory violations at these two sites.

For additional details, refer to the Clinical Inspection Summary by Lee Pai-Scherf, MD.

4.2. Product Quality

See the FDA's Assessment of impurities in Section 5.5.5 Other Toxicology Studies, subsection Studies on Impurities.

4.3. Clinical Microbiology

See the CMC review from the current NDA submission; no clinical microbiology concerns were identified.

4.4. Devices and Companion Diagnostic Issues

Refer to the Center for Devices and Radiological Health (CDRH) review memos by Drs. Timothy Schaefer, Rama Kamesh Bikkavilli, Soma Ghosh, Francisca Reyes Turcu, Wendy Rubinstein, and Donna Roscoe for full details. Please refer to the Summary of Safety and Effectiveness Data (SSED) for P210040 and the labeling documents for P110027/S013 for additional details.

The applicant partnered with QIAGEN Manchester Ltd. to submit a PMA for the *therascreen* KRAS RGQ PCR Kit (P110027/S013) for the qualitative detection of KRAS G12C mutations in formalin-fixed, paraffin-embedded (FFPE) tumor tissue from patients with NSCLC who may benefit from treatment with adagrasib. There was another PMA (P210040) for the RESOLUTION ctDx FIRST for the detection of KRAS G12C mutations in circulating cell-free DNA (cfDNA) from

plasma from patients with NSCLC who may benefit from treatment with adagrasib. Patients with NSCLC whose FFPE tissue or plasma sample produce a positive test result for the presence of KRAS G12C mutations are eligible for treatment with adagrasib.

There were 112 patients with baseline scans that identified measurable disease per RECIST v1.1 enrolled in the KRYSTAL-1 (NCT03785249) clinical study using tumor tissue detected by clinical trial assays (CTAs) with KRAS G12C mutations. The KRYSTAL-1 clinical study did not include patients negative for KRAS G12C mutations. A clinical bridging study was performed to demonstrate the concordance/agreement (PPA, Positive Percent Agreement and, NPA, Negative Percent Agreement) between the CTAs and the *therascreen* KRAS RGQ PCR Test as well as to establish the clinical validity of the *therascreen* KRAS RGQ PCR Test. Of the 112 patients with KRAS G12C mutated NSCLC from the KRYSTAL-1 clinical trial, 98 patients had valid *therascreen* KRAS RGQ PCR Test results available (87 patients were CTA+, therascreen KRAS RGQ PCR Test+, while 11 samples were CTA+, therascreen KRAS RGQ PCR Test negative). Thus, clinical effectiveness was based on a bridging study using 98 patient samples that were evaluable by the *therascreen* KRAS RGQ PCR Test companion diagnostic (CDx). The 98 CDx evaluable samples that were CTA+ were retested using the *therascreen* KRAS RGQ PCR Test resulting in a PPA of 88.7% (87/98). The NPA was estimated to be 100% (111/111) between the CTAs and *therascreen* KRAS RGQ PCR Test by testing biomarker-negative samples that were commercially procured. Clinical efficacy of adagrasib for the KRAS G12C mutation positive population (ORR = 41% [36/87], 95% CI: 31% - 52%) identified by the *therascreen* KRAS RGQ PCR Test was similar to the clinical efficacy in the KRYSTAL-1 Cohort A (ORR = 43% [48/112]; 95% CI: 34% - 53%).

A clinical bridging study was also performed to demonstrate the concordance between the CTAs and the RESOLUTION ctDx FIRST assay to establish the clinical validity of the RESOLUTION ctDx FIRST assay. Of the 112 patients with KRAS G12C mutated NSCLC, only 71 patients had valid RESOLUTION ctDx FIRST plasma test results. The PPA between the CDx and the CTAs, when patients were re-tested from the efficacy population, was estimated to be 65% (47/73). The lower PPA may be in part attributed to variables such as low tumor shedding. The NPA between the RESOLUTION ctDx FIRST assay and the CTAs obtained by testing commercially procured samples was found to be 100% (116/116). The observed ORR for RESOLUTION ctDx FIRST positive samples was 51% (95% CI 36% - 66%) which is similar to that for the full primary population from the KRYSTAL-1 study (ORR 43% [48/112]; 95% CI: 34% - 53%).

Since the PPA of the plasma test when compared to tissue results is 63%, it is possible that a subset of patients that test negative by plasma may have a tissue positive result. For this reason, patients whose plasma sample produces a negative result using the RESOLUTION ctDx FIRST assay should be reflexed to testing for the presence of KRAS G12C mutations with FFPE tumor tissue.

The data support a reasonable assurance of safety and effectiveness of the devices when used in accordance with the indications for use. The use of these devices to aid clinicians in identifying patients with NSCLC who may be eligible for treatment with adagrasib based on detection of the KRAS G12C mutation is expected to provide a benefit in ORR of about 41% for the *therascreen* KRAS RGQ PCR Test and 51% for the RESOLUTION ctDx FIRST assay which is similar to the benefit observed in the full primary efficacy population from the KRYSTAL-1 study (ORR 43% [48/112]). For the RESOLUTION ctDx FIRST assay, there is some uncertainty to this assessment based primarily on analytical performance factors of the RESOLUTION ctDx FIRST device. Accordingly, condition of approval studies in the postmarket setting with respect to some analytical validation studies, including frozen plasma stability and blood collection tube studies, will be required.

In summary, considering all factors including conditions of approval (postmarket study requirements), the benefits of the use of the *therascreen* KRAS RGQ PCR Test and RESOLUTION ctDx FIRST assay in patients with NSCLC containing KRAS G12C mutations are judged to outweigh the risks.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The FDA's Assessment:

The *KRAS* (Kirsten rat sarcoma viral oncogene homolog) oncogene encodes the guanosine 5'-triphosphate hydrolase (GTPase) protein KRAS, a family member of the RAS/MAPK signal transduction pathway. GTPases are membrane-bound enzymes that function as molecular on/off switches involved in cell growth, migration, adhesion, survival, and differentiation in response to extracellular stimuli. GTPases convert from active and inactive states via conformational change induced by hydrolyzation of GTP to GDP (inactive state). A reverse reaction then catalyzes hydrolysis of GDP to GTP (active state). Genetic mutations, including chromosomal rearrangements or point mutations, can lead to constitutive activation of GTPases, resulting in the development of human cancers. *KRAS* gene mutations promote tumor pathogenesis; in particular, the KRAS G12C mutation is frequently found in lung, colorectal, and pancreatic cancers (Drosten and Barbacid 2020).

Adagrasib (MRTX849) is an oral small molecule drug with an established pharmacological class of inhibitor of the RAS GTPase family. A mass spectrometry-based modification assay employing a KRAS G12C recombinant protein in which all native cysteines were mutated to serine or leucine demonstrated that adagrasib irreversibly and covalently modified the specific cysteine at codon 12, with an inhibitory constant (K_i) of 1.43 µM. Another mass spectrometry-based assay employed NCI-H358 lung cancer cells harboring a KRAS G12C mutation to determine the selectivity of adagrasib toward cysteine amino acid 12 of KRAS G12C compared to 2490 other proteins in the cell line's proteome. Following incubation with 1 or 10 µM adagrasib, the cysteine amino acid of KRAS G12C demonstrated peptide ratios of 0.029 or 0.008, which were the lowest ratios observed of 5702 surface-exposed cysteine residues, indicating near-complete engagement of the KRAS G12C target. Together, these results demonstrate that adagrasib binds to KRAS G12C mutant protein.

Functional assays demonstrated that adagrasib inhibited the growth of lung cancer cell lines harboring KRAS G12C mutation (IC_{50} = 0.2 to 55.5 nM) but did not affect cells harboring alternate KRAS mutations (G12S, G13D) or wild type cells (IC_{50} >3000 nM). Mass spectrometry analysis of tumors isolated at various time points from KRAS G12C lung tumor xenografts exposed to a single dose of adagrasib over a range of dose levels demonstrated a dose-dependent increase in irreversible covalent KRAS cysteine G12C modification (i.e., adagrasib binding) that correlated with increases of adagrasib plasma exposure in these animals. In biochemical activity assays, adagrasib inhibited phosphorylation of a KRAS downstream signaling protein, extracellular signal-regulated kinase (ERK) 1/2 (IC_{50} = 17 nM). Adagrasib

exhibited in vivo anti-tumor efficacy in an NCI-H358 KRAS G12C lung cancer xenograft model. Significant dose-dependent tumor regression occurred in mice administered ≥ 30 mg/kg/day. One of four mice had complete tumor regression by Day 33 of the study at 100 mg/kg/day. In a panel of KRAS G12C-mutant and KRAS G12C-negative tumor xenograft models, adagrasib had anti-tumor activity in 14 of 17 KRAS G12C-mutant lung xenograft models. In contrast, adagrasib did not exhibit anti-tumor activity in KRAS G12C-negative tumor models.

In secondary pharmacology screening studies, adagrasib showed >50% inhibition of 18 off-target receptors, including >90% inhibitory activity in 4 off-target kinases or enzymes at 10 μM concentration (≥81 times the human free steady-state C_{max} at the recommended dose of 600 mg twice daily, referred as recommended dose in Section 5). A follow-up experiment showed that the IC_{50} values for these top 4 kinase receptors, alpha 1A adrenergic antagonist (310 nM), muscarinic M2 antagonist (420 nM), serotonin 5HT1A agonist (350 nM), and serotonin 5HT1B (230 nM), were approximately ≥ 3-fold higher than the human free steady-state C_{max} (0.08 μM based on ~98% protein-binding) at the recommended dose.

Adagrasib inhibited hERG potassium channel currents with an IC_{50} of 3.8 μM in a safety pharmacology assessment, which is approximately 48-fold higher than the human free steady-state C_{max} of ~0.08 μM based on ~98% protein-binding at the recommended dose. While the in vitro finding would suggest a low risk of QTc prolongation through this pathway in humans, QTc prolongation was one of the most common adverse reactions (≥ 20%) observed in clinical trials in patients treated with adagrasib. The label contains a warning and precaution for QTc prolongation. Additional safety pharmacology assessments incorporated into repeat-dose toxicology studies revealed normal assessment of ECG cardiovascular parameters, but moderate subacute myocardial necrosis was observed in one dog exposed to daily adagrasib at 25 mg/kg. Toxicology studies also revealed mortality in rats attributed to heart and lung findings at 300 mg/kg (approximately 1.5 times the human AUC at the recommended dose). Heart findings were characterized as diffuse myocardium microvesicular vacuolation. Clinical signs of abnormal respiratory sounds in rats during the 4-week repeat-dose toxicology study correlated with histopathology findings of protein and foamy macrophage infiltration in the alveoli and epithelial vacuolation in the lung at 300 mg/kg adagrasib. Rats administered adagrasib at 150 mg/kg up to 13 weeks also had similar histopathology findings but lacked respiratory clinical signs. Dogs exposed to adagrasib had similar pathologic lung findings in the absence of respiratory clinical signs. Findings of foamy macrophage infiltration are often consistent with lysosomal phospholipid accumulation (i.e., phospholipidosis); however, this diagnosis could not be made under the conditions of the histopathology analysis.

There were 37 proposed or identified human metabolites of adagrasib. There were no unique human metabolites. Two circulating metabolites, M11 and M68, were further evaluated as they accounted for >10% of adagrasib-related material in human plasma. Metabolite M11 was also found following incubation of adagrasib with microsomes and/or hepatocytes from rats and

dogs. Metabolites M68 and M11 were also present in rat and dog plasma, although M68 was higher in human plasma. In vitro studies suggest that only M11 inhibited KRAS-dependent downstream phosphorylation of ERK1/2 but at concentrations approximately 89-fold higher than adagrasib; and both metabolites did not inhibit in vitro hERG potassium currents at relevant concentrations. The Applicant did not conduct definitive GLP genotoxicity assays with M68 and M11. The bacterial reverse mutation screening assay using strains TA100 and TA98 suggests both metabolites are not mutagenic. Results from an in vitro screening micronucleus assay using TK6 cells were equivocal due to observed increases in percent of micronuclei induced up to the limit of cytotoxicity or solubility, that at high concentrations were above the historical control but did not reach statistical significance. Given that adagrasib, was not genotoxic in in vitro and in vivo GLP genotoxicity assays (see discussion below) and that metabolites M11 and M68 are structurally related to adagrasib, the totality of the data suggests that there is low risk of genotoxicity with the metabolites.

Following single oral administration to rats, ^{14}C-adagrasib-derived radioactivity distributed to nearly all tissues by 8 hours post-dose. Adagrasib demonstrated affinity for melanin-pigmented tissues. Radioactivity was also detected in male reproductive tissues. In rats and dogs, adagrasib accumulated approximately 2- to 3-fold over time. In consultation with the FDA clinical pharmacology team, animal to human exposure multiples were calculated using human steady-state PK parameters of C_{max} and area under the curve (AUC) values of 2500 ng/mL and 28,100 ng*hr/mL. Additionally, because rats at 300 mg/kg in the 28-day GLP repeat-dose toxicology study were terminated early, animal to human exposure multiples for the 300 mg/kg group were calculated using Day 1 exposure data.

The Applicant evaluated the safety of adagrasib in GLP-compliant 28-day and 13-week repeat-dose toxicology studies in Sprague-Dawley rats and Beagle dogs, using the intended oral route of administration. In the 28-day toxicology study in rats, unexpected mortalities at the 300 mg/kg daily dose (approximately 1.5 times the human AUC at the recommended dose) resulted in early termination of dosing on Day 22. Consistent with clinical experience, dogs exposed to ≥10 mg/kg daily experienced vomiting and decreased appetite. In the 13-week toxicology study, significant weight loss in the canine 25 mg/kg group led to a dose holiday on Day 20, with dose reduction beginning on Day 24 at 15 mg/kg daily. In both rats and dogs, the target organs were heart, lungs, adrenal gland, kidney, and liver. Toxicology studies of up to 13 weeks duration in both species revealed microscopic findings of macrophage infiltration and vacuolation in several tissues, suggestive of phospholipidosis, which was considered adverse in the 28-day study in rats at the 300 mg/kg dose (approximately 1.5 times the human AUC at the recommended dose) due to deaths. Conversely, phospholipidosis was not considered adverse in rats at lower dose levels (≤150 mg/kg, approximately 2.2 times the human AUC at the recommended dose), even following the extended exposure time of 13 weeks (approximately 4.8 times the human AUC at the recommended dose) due to the absence of correlative adverse findings. Most of the findings in each toxicology study were reversible. Although the

significance of phospholipidosis in humans is unknown, animal findings of phospholipidosis were included in the label in Section 13.2.

Dedicated carcinogenicity studies were not conducted with adagrasib, as they are not needed to support the use of a drug intended to treat patients with advanced cancer. In the standard genotoxicity battery, adagrasib was not mutagenic in a bacterial reverse mutation (Ames) assay nor clastogenic in an in vitro micronucleus assay. However, it is noted that following a 3-hour incubation of cells with adagrasib in the presence of S9, there was increased endoreduplication by almost 4% at 9 µg/mL. An in vivo bone marrow micronucleus study in rats was unremarkable. Taken together, adagrasib is not genotoxic. Adagrasib did not exhibit phototoxicity potential in an in vitro phototoxicity assay employing murine fibroblast cells.

To assess the potential developmental and reproductive toxicity of adagrasib, the Applicant conducted embryo-fetal development studies of oral adagrasib administered once daily during the period of organogenesis to Wistar Han rats (Gestation Day 6-17) and New Zealand White rabbits (Gestation Day 7-20). At 270 mg/kg adagrasib (approximately 2 times the recommended dose based on body surface area [BSA]), three pregnant rats were euthanized in extremis due to body weight loss, decreased food consumption and clinical observations of thinness, decreased activity, weakness, hunched posture and/or piloerection. Observations of decreased fetal body weight and increased frequency of skeletal malformations and variations were noted in the 270 mg/kg group; however, these findings are thought to be related to maternal toxicity. In rabbits, there was maternal toxicity at 30 mg/kg (approximately 0.11 times the human AUC at the recommended dose), indicated by decreased mean body weight gain and reduced food consumption. Adagrasib did not have a significant adverse effect on embryo-fetal survival or on development in rabbits. The FDA recommends describing the animal data in the label but a warning for embryo-fetal toxicity was not included since adagrasib did not induce a clear significant adverse effect in embryo-fetal development studies. Additionally, adagrasib showed specificity to KRASG12C, and lacked genotoxic activity. No studies were conducted nor necessary to investigate the presence of adagrasib or its metabolites in milk. As many drugs are secreted in breastmilk, the label includes a warning not to breastfeed during treatment or for 1 week after the last dose.

The Applicant did not conduct fertility studies and these studies are not needed to support an advanced cancer indication. Studies in animals indicated that male and female fertility may be impaired by treatment with adagrasib. In the 4-week repeat-dose toxicology study conducted in rats, males exposed to 300 mg/kg of adagrasib (approximately 1.6 times the human AUC at the recommended dose) exhibited marked atrophy of the prostate and seminal vesicles and moderate epithelial vacuolation of seminal vesicles. Similar findings of mild bilateral vacuolation in the epididymides and seminiferous tubules in the testes of the single male dog that received 100 mg/kg of adagrasib once daily for two weeks (approximately 1.6 times the human AUC at the recommended dose) were described in the non-GLP 14-day dose range-

finding study (not reviewed). These toxicities may result from the 2 to 3-fold bioaccumulation of adagrasib in the male reproductive tissues of rats and dogs, as characterized in the ADME studies. Prostate and seminal vesicle findings were not present in the 13-week toxicology studies with lower doses of adagrasib, in which rats received 150 mg/kg of adagrasib once daily (approximately 5 times the human AUC at the recommended dose) or dogs that received 25 mg/kg for 23 days and 15 mg/kg from Days 24-91 (approximately 0.7 times the human AUC at the recommended dose). Although the exposure multiple from rats in the 13-week study at the 150 mg/kg dose appears higher than that from male rats in the 28-day study at the 300 mg/kg dose (5 versus 1.6 times the human AUC at the recommended dose), the latter is based on animal exposure data from Day 1, and therefore likely represents an underestimate of the actual exposure multiple.

Female reproductive toxicities were also observed in toxicology studies. In a repeat-dose toxicology study of up to 13 weeks in duration conducted in rats, adagrasib induced mild ovarian macrophage vacuolation in female rats at 150 mg/kg (approximately 5 times the human AUC at the recommended dose), which resolved upon recovery. Female reproductive toxicities observed in the 28-day toxicology study included moderate microvesicular vacuolation of the uterus and vagina at 300 mg/kg (approximately 1.3 times the human AUC at the recommended dose), and mild mucification and mucosal atrophy of the vagina at dose levels ≥ 150 mg/kg (approximately 1.1 times the human AUC at the recommended dose). The Day 1 AUC from the 300 mg/kg group was used for exposure comparison in the absence of available AUC data from the high-dose group on Day 28. Exposure margins provide an estimate in context of safety, so the exposure multiple reflects the worst-case scenario here. Altogether, the totality of the animal data indicates that adagrasib may potentially impair fertility, and this information was included in Section 8.3 and 13.1 of the label.

Recommendation:
There are no outstanding issues from a pharmacology/ toxicology perspective that would prevent the approval of adagrasib.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

There are no referenced new drug applications (NDAs), biologics license applications (BLAs), or drug master files (DMFs) related to nonclinical pharmacology or toxicology for adagrasib.

5.3. Pharmacology

Primary pharmacology

The Applicant's Position:

Adagrasib demonstrated 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 inhibitory constant (K_i) of 1.43 µM (PH-MRTX849-001).

The selectivity of adagrasib toward cysteine 12 of KRAS G12C, versus other surface-exposed cysteine residues present in other proteins, was evaluated in adagrasib-treated NCI-H358 cells utilizing mass spectrometry-based methods (PH-MRTX849-003). The peptide containing cysteine 12 of KRAS G12C demonstrated the lowest peptide ratio following treatment with adagrasib. The peptide ratios for 1 µM and 10 µM adagrasib treated for 3 hours were 0.029 and 0.008, respectively, indicating near complete engagement of the intended target. Overall, adagrasib demonstrated a high degree of selectivity toward cysteine 12 of KRAS G12C, versus other surface-exposed cysteines in the NCI-H358 proteome.

Additional studies were conducted to confirm that modification of recombinant protein translated into inhibition of KRAS activity and KRAS-dependent signal transduction pathways in cells harboring a *KRAS* G12C mutation (PH-MRTX849-002). Adagrasib was evaluated in an NCI-H358 cell-based assay and inhibited the phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2), after a 3-hour incubation with a half-maximal inhibitor concentration (IC_{50}) value of 17 nM (0.017 µM, 0.0103 µg/mL).

Adagrasib was evaluated in a series of three-dimension (3D) ultra-low attachment (ULA) viability assays across a panel of *KRAS* G12C-mutated and nonmutated cancer cell lines in vitro (PH-MRTX849-005). Using these assay conditions, adagrasib inhibited the growth of all 17 *KRAS* G12C-mutant cell lines with IC_{50} values ranging from 0.2 to 1042 nM and all but one cell line exhibiting an IC_{50} value of less than 100 nM (Applicant Table 4). In contrast, all 3 non-*KRAS* G12C-mutant cell lines tested demonstrated IC_{50} values greater than 3000 nM.

Applicant Table 4: Activity of Adagrasib in KRAS G12C-mutant and Non-KRAS G12C-mutant Cell Line Models

Cell Line (Tumor Type)	*KRAS* Mutation Status	3D Viability Assay IC_{50} (nM)[1]
NCI-H2030 (lung)	G12C	0.2
NCI-H358 (lung)	G12C	2.5
IALM (lung)	G12C	3.8
NCI-H1792 (lung)	G12C	8.6
HCC44 (lung)	G12C	8.7
NCI-H1373 (lung)	G12C	12.9

Cell Line (Tumor Type)	*KRAS* Mutation Status	3D Viability Assay IC_{50} (nM)[1]
SW1573 (lung)	G12C	15.7
UM-UC-3 (urinary)	G12C	16.4
Calu-1 (lung)	G12C	19.3
MIA PaCa-2 (pancreas)	G12C	29.6
NCI-H23 (lung)	G12C	32.3
LU99 (lung)	G12C	38.7
LU65 (lung)	G12C	44.5
NCI-H2122 (lung)	G12C	55.5
SW837 (rectum)	G12C	77.5
SW756 (cervix)	G12C	83.7
KYSE-410 (esophagus)	G12C	1042.0
A549 (lung)	G12S	> 3000
HCT 116 (colon)	G13D	> 3000
NCI-H1299 (lung)	WT	> 3000

PH-MRTX849-005

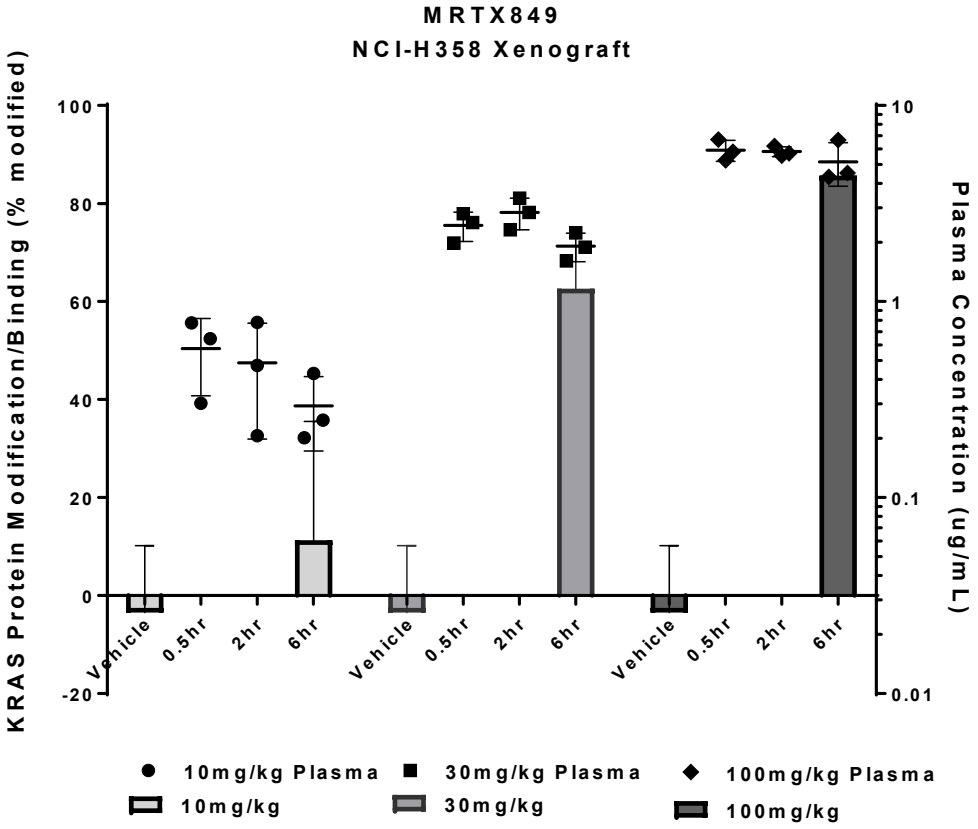
Abbreviations: 3D = three-dimensional; IC_{50} = half-maximal inhibitor concentration; WT = wildtype

[1] A CellTiter-Glo (Promega) assay to evaluate cell viability was performed on cells grown in 3D conditions using 96-well, ULA plates. Cells were treated for 12 days with adagrasib using a 9-point concentration-response, 3 µM top dose and a 3-fold dilution series. > 3000 indicates IC_{50} values were outside of the range of the assay.

To evaluate the effect of 2 circulating human metabolites of adagrasib, M11 and M68, on KRAS-dependent downstream signal transduction, phosphorylation of ERK1/2 was evaluated over a range of concentrations (PH-MRTX849-015, PH-MRTX849-024). Metabolite M68 was not active and M11 was > 80-fold less active compared to adagrasib.

To evaluate the pharmacodynamic (PD) effects of adagrasib in vivo and to correlate drug exposure with target inhibition, adagrasib was administered as a single dose over a range of dose levels to NCI-H358 xenograft-bearing mice and plasma and tumors were collected at defined time points (PH-MRTX849-006). Plasma concentrations of adagrasib were measured at 0.5, 2, and 6 hours postdose, and tumors were harvested 6 hours postdose and analyzed for covalent KRAS cysteine 12 modification utilizing mass spectrometry-based methods. A dose-dependent increase in plasma levels of adagrasib was observed, and it correlated with a dose- and concentration-dependent increase in the fraction of covalently modified KRAS G12C-mutant protein (Hallin et al. 2020) (Applicant Figure 1). The fraction of KRAS G12C covalently modified by adagrasib was measured at 11%, 63%, and 86% of total evaluable KRAS G12C protein at the 10, 30, and 100 mg/kg doses, respectively.

Applicant Figure 1: Dose-dependent Increase in Adagrasib Plasma Concentrations and KRAS G12C Protein Modification in NCI-H358 Tumor Xenografts Implanted in Immunocompromised Mice

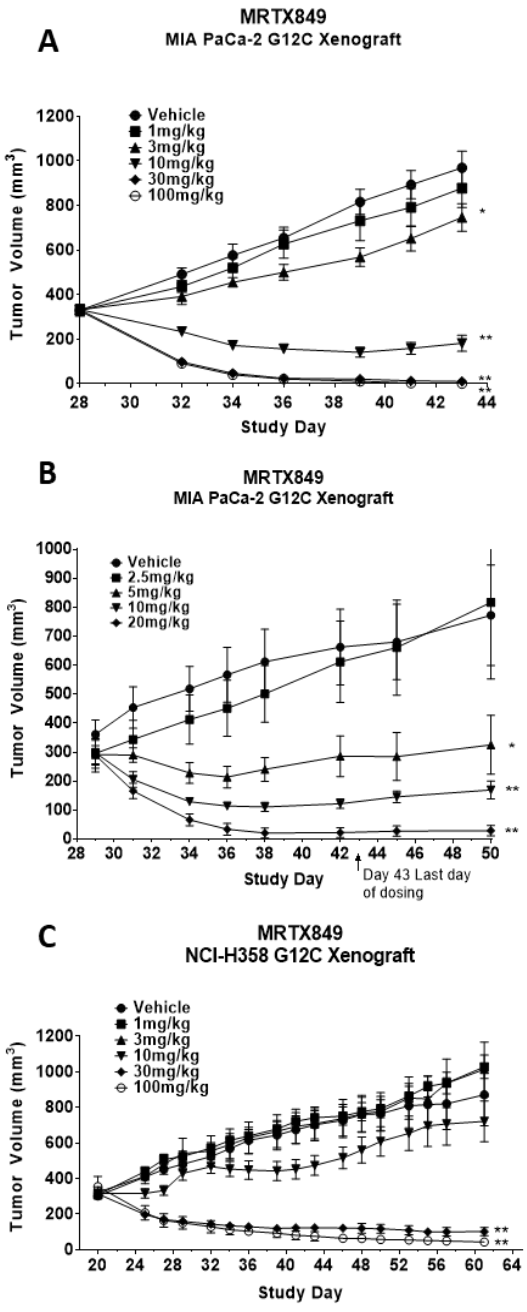


PH-MRTX849-006
Adagrasib was administered orally as a single dose to mice bearing established NCI-H358 xenografts at 10, 30, and 100 mg/kg. Plasma was collected 0.5, 2, and 6 hours postdose and tumors were collected 6 hours postdose. KRAS modification and adagrasib plasma concentration data are shown as mean ± standard deviation.

The anti-tumor efficacy of adagrasib was evaluated over a range of dose levels administered by oral gavage utilizing the *KRAS* G12C-mutant MIA PaCa-2 (pancreatic ductal adenocarcinoma) model implanted in immunocompromised mice (PH-MRTX849-006). Significant, dose-dependent anti-tumor activity was observed at the 3, 10, 30, and 100 mg/kg/day dose levels (Applicant Figure 2). Evidence of rapid tumor regression was observed at the earliest tumor measurement after initiation of dosing at each of the 30 and 100 mg/kg/day dose levels, including the observation of complete tumor regression at Study Day 15 (Applicant Table 5). To further evaluate dose-dependence for anti-tumor activity, additional dose levels were evaluated in a follow-up experiment using the MIA PaCa-2 model. Dose-dependent anti-tumor efficacy was observed at the 5, 10, and 20 mg/kg/day dose levels in this study (Applicant Figure

2) and 2 of 5 mice at the 20 mg/kg/day dose level exhibited complete tumor regression (Applicant Table 5).

Applicant Figure 2: Dose-dependent Anti-tumor Activity of Adagrasib in Human Tumor Xenograft Models Implanted in Immunocompromised Mice



PH-MRTX849-006

Adagrasib was administered once daily by oral gavage at the dose levels indicated to mice bearing established MIA PaCa-2 (A & B) or NCI-H358 (C) cell line-derived xenografts. For the MIA PaCa-2 studies (A and B), adagrasib was administered to mice daily until Day 43 and for the NCI-H358 study (C), all groups were treated until Day 55. Tumor volumes after 12 or 13 days of treatment were determined to be statistically significant versus vehicle control using the two-tailed Student's *t* test. "*" indicates $p < 0.05$; "**" indicates $p < 0.01$.

Applicant Table 5: Dose-dependent Anti-tumor Activity of Adagrasib in Human Xenograft Models Grown in Immunodeficient Mice

Model (Tumor Type)	*KRAS* Status	Dose (mg/kg/day)	% Growth Inhibition[1] / Regression[2] (Day)	CR[3] (Day)
MIA PaCa-2 (pancreas)	G12C	1	18 (13)	NA
		3	43* (13)	NA
		10	-52* (13)	NA
		30	-96* (13)	4/7 (15)
		100	-99* (13)	4/4 (19)
MIA PaCa-2 (pancreas)	G12C	2.5	17 (13)	NA
		5	-2* (13)	NA
		10	-59* (13)	NA
		20	-92* (13)	2/5 (13)
NCI-H358 (lung)	G12C	1	0 (12)	NA
		3	0 (12)	NA
		10	26 (12)	NA
		30	-54* (12)	NA
		100	-63* (12)	1/4 (33)

PH-MRTX849-006

Abbreviations: NA = Not Applicable

Adagrasib was administered daily via oral gavage to mice bearing established cell line xenografts indicated. Tumor volumes after 12 or 13 days of treatment were determined to be statistically significant versus vehicle control using the two-tailed Student's *t* test. "*" indicates $p < 0.05$.

[1] Tumor growth inhibition was calculated when average final treated tumor volume was greater than initial treated tumor volume using the following equation: 100%*((Final vehicle tumor volume) – (Final treated tumor volume))/((Final vehicle tumor volume) – (Initial vehicle tumor volume)).

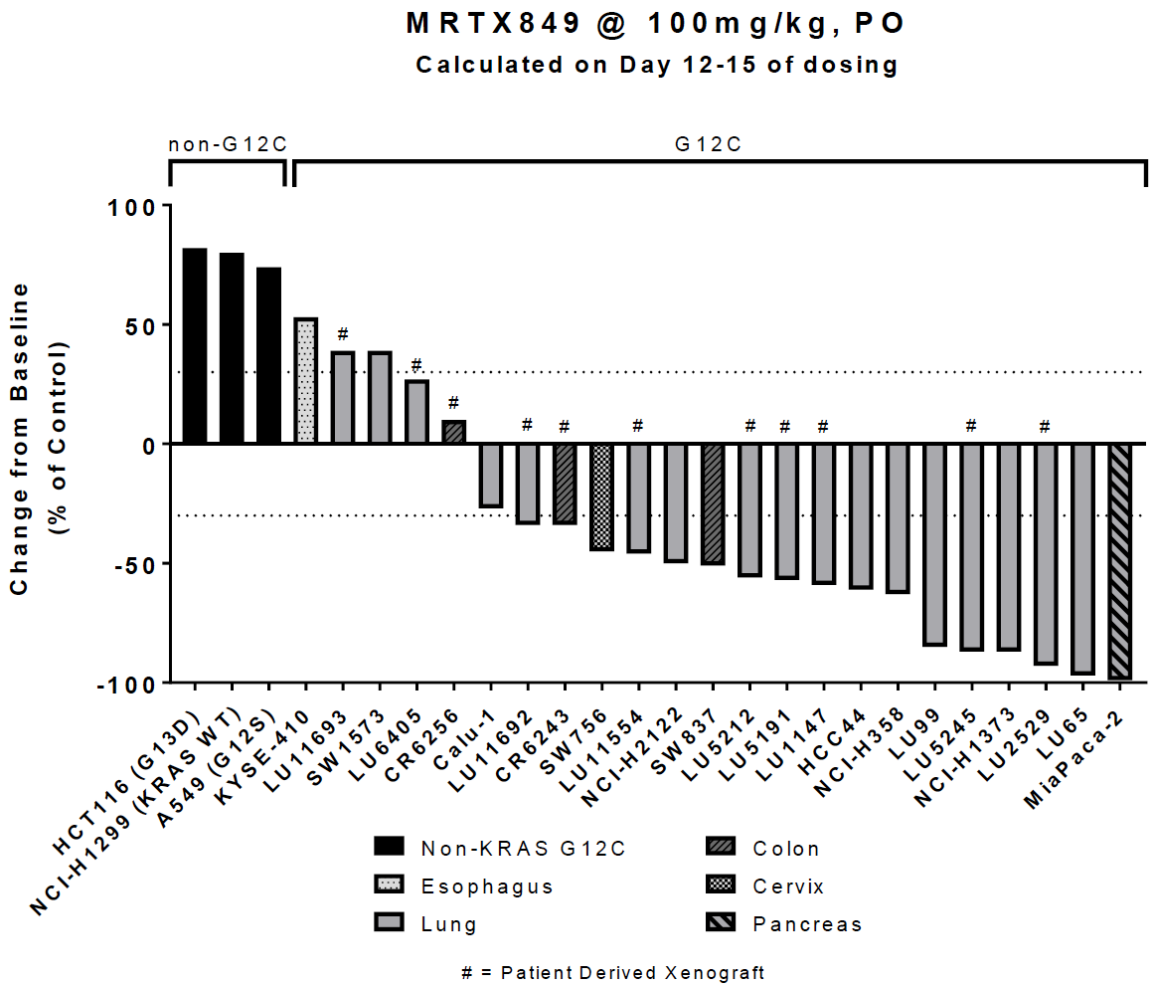
[2] Tumor regression was calculated when the average tumor volume of final treated tumors was less than initial treated tumor volume using the following equation: (-100%)*(1 – ((Final treated tumor volume)/(Initial treated tumor volume)).

[3] CR - Complete response indicates number of animals that did not have a palpable tumor on the indicated day.

The anti-tumor efficacy of adagrasib was evaluated at a fixed dose of 100 mg/kg/day administered daily in a panel of human *KRAS* G12C-mutant xenograft models (PH-MRTX849-

012, PH-MRTX849-013). The 100 mg/kg/day dose was selected based on the maximal or near maximal degree of KRAS modification and anti-tumor activity observed at this dose in multiple models. This study included 12 cell line-derived and 11 patient-derived xenograft (PDX) models. In addition, 3 G12C-negative tumors, 1 *KRAS* wild type (WT) xenograft model (H1299) and 2 xenograft models harboring alternative *KRAS* mutations, HCT 116 (*KRAS* G13D) and A549 (*KRAS* G12S), were also evaluated. Adagrasib demonstrated significant tumor regression in 18 of the 23 *KRAS* G12C-mutant models evaluated and did not exhibit significant anti-tumor activity in the 3 *KRAS* G12C-negative tumors models (Applicant Figure 3).

Applicant Figure 3: Anti-tumor Activity of Adagrasib in *KRAS* G12C-Mutant and Non *KRAS* G12C-Mutant Human Tumor Xenograft Models



PH-MRTX849-012, PH-MRTX849-013

Adagrasib was administered once daily via oral gavage at 100 mg/kg/day to mice bearing the cell line xenograft or PDX models indicated. The % change from control was calculated at Day 12-15.

The relationship of plasma concentration of adagrasib to anti-tumor efficacy over a variety of dose levels and administration schedules was evaluated with particular emphasis on determining plasma exposure and pharmacokinetic (PK) parameters that correlated with the observed anti-tumor efficacy. The analysis of time-plasma concentration curves and associated anti-tumor efficacy indicated that AUC and average plasma concentration (C_{ave}) were closely correlated with the extent of anti-tumor efficacy compared with maximum plasma concentration (C_{max}) or minimum plasma concentration (C_{min}). This determination was based on the mean plasma concentrations measured in efficacy studies where adagrasib was delivered subcutaneously via osmotic pump resulting in constant plasma concentration at steady state, as well as the evaluation of PK parameters determined from efficacy studies dosed orally daily (QD) and twice daily (BID). These studies demonstrated that the mean plasma concentrations associated with moderate tumor regression in the drug pump studies were most closely correlated to the area under the concentration-time curve (AUC) and C_{ave} for dose levels that resulted in the same degree of anti-tumor activity in the orally dosed efficacy studies (PH-MRTX849-011, PH-MRTX849-022). C_{ave} values from efficacy studies using QD and BID schedules at the same daily total dose also demonstrated good correlation with efficacy (PH-MRTX849-022). Based on this analysis, the following PK results were selected to aid in modeling of human efficacious target plasma exposure levels and to understand therapeutic index across nonclinical species: (1) the lowest AUC_{24} or C_{ave} values observed with significant tumor regression at the end of compound administration, (2) the AUC_{24} or C_{ave} observed with maximal tumor regression in the most sensitive pharmacology xenograft model and/or, (3) the AUC_{24} or C_{ave} required to maximally inhibit the least sensitive xenograft model in the cohort tested. In this analysis, 10 mg/kg QD was the lowest dose level that elicited regression in all animals treated at the end of the dosing period in the MIA PaCa-2 model. At 10 mg/kg QD, the calculated AUC_{24} was 6970 ng*h/mL and an estimated human C_{ave} of 171 ng/mL, which therefore represents the minimum exposure required to achieve significant regression in nonclinical models (PH-MRTX849-011) (Applicant Table 6). The 30 mg/kg QD dose level demonstrated maximum regression in the MIA PaCa-2 model and exhibited an AUC_{24} of 24300 ng*h/mL and an estimated human C_{ave} of 596 ng/mL (PH-MRTX849-011). The 100 mg/kg QD dose level demonstrated a maximum response in the HCC44 xenograft model and was associated with an AUC_{24} of 63000 ng*h/mL and an estimated human C_{ave} of 1544 ng/mL (PH-MRTX849-014). Plasma AUC_{24} values across this range were roughly dose proportional and dose-normalized AUC_{24} values were within ~20%.

It is notable that some models exhibited complete responses to adagrasib administration at the 30 mg/kg dose level and that other models exhibited maximal responses at the 100 mg/kg dose level (consistent with a human projected C_{ave} of 1544 ng/mL) and that these models exhibited a submaximal response at the 30 mg/kg dose level (consistent with defining a human target C_{ave} exceeding 1544 ng/mL). In addition, some nonclinical models (e.g., KYSE410) did not exhibit a maximal response at 100 mg/kg QD and increased antitumor activity was observed at a 200 mg/kg dose level. The differences in dose levels and plasma exposures required to elicit a

maximal response across preclinical models is likely due, at least in part, to the observation that adagrasib only binds to KRAS G12C in its inactivated state and that the expression or genetic alteration of upstream receptor tyrosine kinases result in an increased proportion of mutant KRAS proteins existing in the active conformation of KRAS resulting in higher concentrations of adagrasib required to demonstrate maximal KRAS binding and PD target inhibition. For example, KYSE410 exhibits high level focal amplification of the human epidermal growth factor receptor 2 (HER2) gene locus resulting in persistent KRAS activation and higher adagrasib concentrations and dose levels required for maximal inhibition of KRAS. For these reasons, the Applicant has developed a hypothesis that it is important to exceed the target plasma concentration of at least 1544 ng/mL in patients harboring *KRAS* G12C mutated tumors to maximize the target inhibition and clinical activity in the largest population of patients possible.

Applicant Table 6: Relationship Between Dose, AUC_{24}, and Anti-tumor Efficacy in Nonclinical Human Xenograft Models

Model	Dose (mg/kg QD)	AUC_{24} (ng*h/mL)	FF adj AUC_{24} (ng*h/mL)[1]	% Regression (Day)	Dose Normalized AUC_{24} (ng*h/mL)/(mg/kg)	Estimated Human C_{ave} Target Concentration (ng/mL)[2]
MIA PaCa-2	10	6970	69.7	-52% (13)	697	171
MIA PaCA-2	30	24300	243	-96% (13)	810	596
HCC44	100	63000	630	-61% (13)	630	1544

10 and 30 mg/kg: PH-MRTX849-011; 100 mg/kg: PH-MRTX849-014

Abbreviations: AUC_{24} = Area under the plasma concentration-time curve from time 0 to 24 hours; C_{ave} = Average plasma concentration; FF adj AUC_{24} = free fraction adjusted area under the plasma concentration-time curve from time 0 to 24 hours

[1] Free-fraction adjusted AUC_{24} (FF adj AUC_{24}) calculated utilizing mouse plasma protein binding of 99.0% and formula (1–0.99)*AUC_{24}.

[2] Human C_{ave} target concentration calculated using mouse FF adj AUC_{24}/((fraction unbound human plasma = 1.7% = 0.017)*(24 h)).

The FDA's Assessment:

The FDA generally agrees with the Applicant's conclusion for primary pharmacology. The FDA did not review the relationship of plasma concentration of adagrasib to anti-tumor efficacy because some of these experiment (e.g., osmotic drug pump studies; pharmacokinetic and anti-tumor and pharmacodynamic effect studies) were conducted with pancreatic MIA PaCA-2 xenograft models that are not relevant to the proposed indication. Thus, the FDA will not comment on the Applicant's proposed hypothesis and conclusions.

Secondary Pharmacology

The Applicant's Position:

Selectivity of adagrasib was profiled against a broad panel of 44 receptors, ion channels, and enzymes. The initial screen at 10 µM resulted in 50% inhibition against 18 targets (PH-MRTX849-007). The follow-up assay to determine K_i and IC_{50} values for selected receptors identified 4 receptors with K_i values less than 1 µM (PH-MRTX849-008). The receptors included alpha 1A adrenergic antagonist, muscarinic M2 antagonist, serotonin 5HT1A agonist, and serotonin 5HT1B antagonist activity, with K_i values of 0.15 µM, 0.30 µM, 0.17 µM, and 0.14 µM, respectively. These K_i values are ≥ 2-fold above the observed free steady-state human C_{max} of 0.07 µM after administration of an adagrasib dose of 600 mg twice daily in patients.

The FDA's Assessment:

The FDA generally agrees with the Applicant's conclusion; however, the FDA calculated the fold-difference based on IC50 values. Study # PH-MRTX849-008 showed adagrasib inhibited alpha 1A adrenergic antagonist, muscarinic M2 antagonist, serotonin 5HT1A agonist, and serotonin 5HT1B antagonist activity, with IC50 values of 0.31 µM, 0.42 µM, 0.35 µM, and 0.23 µM, respectively. These IC50 values were approximately ≥ 3-fold higher than the human free steady-state Cmax (0.08 µM based on ~98% protein-binding) at the recommended dose, suggesting a low risk for off-target activity. The Applicant did not evaluate the off-target activity of metabolites M68 and M11.

Safety Pharmacology

The Applicant's Position:

The safety pharmacology of adagrasib was evaluated in vitro and in vivo (Applicant Table 7). In vitro, adagrasib and 2 human metabolites were assessed for binding to the human ether-à-go-go related gene (hERG) to assess the risk of QT prolongation. For the in vivo studies, a stand-alone cardiovascular study was conducted in telemetered dogs.

Applicant Table 7: Cardiovascular Safety Pharmacology Studies Evaluating Adagrasib

Organ Systems Evaluated	Species / Strain	Method of Admin.	Dose or Concentration	Gender and No. per Group	Noteworthy Findings	GLP Compliance	Study Number
Cardiovascular (hERG)	CHO cells	In vitro	0.37–30 µM	NA	hERG IC_{50} = 4.8 µM	non-GLP	PH-MRTX849-009
Cardiovascular (hERG)	HEK cells	In vitro	0.1–10 µM	NA	Adagrasib IC_{50} = 3.8 µM Metabolite MRTX2359 (M11) IC_{50} > 10 µM Metabolite MRTX4928 (M68) IC_{50} > 10 µM	GLP	PH-MRTX849-025
Cardiovascular	Guinea pig	In vitro	0.25–5 µM	3 males/group	Increased QTc by 8.4%, increased PR interval by 34.8% compared to baseline, and decreased left ventricular developed pressure by 44% at 5 µM	non-GLP	PH-MRTX849-010
Cardiovascular	Dog/Beagle	Oral	0, 5, 10, 25 mg/kg/day QD	5 male dogs	No adverse findings in blood pressure, heart rate, or ECG parameters	GLP	TX-MRTX849-009

Abbreviations: CHO = Chinese hamster ovary; ECG = electrocardiogram; GLP = good laboratory practice; HEK = human embryonic kidney; hERG = human ether-a-go-go-related gene; IC_{50} = concentration resulting in 50% inhibition; NA = not applicable; PR interval = measure of time between the start of the P wave to the start of the QRS complex; µM = micromolar; QTc = corrected QT interval

In addition to the cardiovascular safety pharmacology study discussed in Applicant Table 7, there were no remarkable electrocardiogram (ECG) changes in the 28-day (TX-MRTX849-005) or the 13-week (TX-MRTX849-013) repeat dose toxicology studies in dogs.

Separate respiratory, central nervous system (CNS), and renal safety pharmacology studies were not conducted; however, these parameters were incorporated into the rat and dog 28-day (TX-MRTX849-004, TX-MRTX849-005) and 13-week (TX-MRTX849-012, TX-MRTX849-013) repeat dose toxicology studies. In the 28-day study in rats, 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, and in the rat 13-week study, 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 dogs. There were no remarkable clinical signs suggestive of CNS effects, nor were there microscopic changes in neuronal tissues. There were no remarkable clinical pathology changes suggestive of renal injury in the dog; however, in the rat, renal injury is possibly related to the morbidity seen in the 28-day rat study at dose levels of 300 mg/kg/day. There was no evidence of kidney injury in the 13-week rat study at doses up to 150 mg/kg/day.

The FDA's Assessment:

The FDA generally agrees with the Applicant's conclusions and expands with additional detail discussed below.

The IC50 value of 3.8 μM for adagrasib in the GLP-compliant in vitro hERG channel study (PH-MRTX849-025), is approximately 48-fold higher than the human free steady-state Cmax (~0.08 μM) based on ~98% protein-binding at the recommended dose. Although the hERG channel study predicted low risk of QTc prolongation in humans treated with adagrasib, QTc prolongation was one of the most common adverse events observed in the clinic (20% of patients). A GLP-compliant 28-day repeat-dose toxicology study conducted in dogs (Study # TX-MRTX849-005) did not reveal dose-dependent effects in ECG parameters; however, other aberrant cardiac toxicities were observed in animal studies. In the 28-day toxicology study conducted in rats (TX-MRTX849-004, reviewed by Dr. Elizabeth Spehalski), one male from the 300 mg/kg group was found dead on Day 21, with the cause of death attributed to mild vacuolation of the myocardium. One female in the 300 mg/kg group was euthanized on Day 22 due to moribundity; this animal was found to have heart vacuolation. Additionally, in the 28-day toxicology study in dogs, moderate subacute myocardial necrosis occurred in the papillary muscle with mild vacuolation of myofibers present in an individual male dog at the highest dose tested, 25 mg/kg (approximately equal to the human AUC at the recommended dose). Additionally, one male dog in the 25 mg/kg recovery cohort also exhibited moderate myocardial fibrosis in the left papillary muscle, the study report indicates that this resulted from necrotic myocardial repair. Per the study report, in dogs, papillary muscle necrosis in the heart often results from ischemia caused by hemodynamic alterations. Even though there is often great inter-animal variability in the incidence of this finding in dogs, the investigators considered this heart finding adverse as it is not a common background finding.

In the 28-day GLP-compliant repeat-dose toxicology study conducted in rats (Study # TX-MRTX849-004), clinical signs in the 300 mg/kg group included abnormal respiratory sounds. One male was euthanized on Day 15 due to moribundity in the 300 mg/kg/day group, corresponding to approximately 1.5 times the human AUC at the recommended dose (exposure

margin is based on Day 1 toxicokinetics results because the high-dose group was prematurely discontinued due to toxicity). In addition to phospholipidosis observed in multiple tissues of all of the main study animals, necropsy of the euthanized male and the female euthanized on Day 22 (mentioned above) revealed both had alveolar foamy macrophage infiltration. Consistent with lung findings in the 28-day repeat-dose toxicology study in rats, results of the GLP-compliant 13-week repeat-dose toxicology study in rats (Study # TX-MRTX849-12) revealed marked macrophage alveolar aggregates and marked accumulation of alveolar eosinophilic extracellular material in the lungs of all rats exposed to 150 mg/kg of adagrasib (approximately 4.8 times the human AUC at the recommended dose), but lacked clinical respiratory signs. Additionally, the GLP-compliant 13-week repeat-dose toxicology study in dogs (Study # TX-MRTX849-13) revealed minimal findings of focal alveolar hyperplasia and infiltrate in the lung following exposure to 10 or 25 mg/kg, in the absence of aberrant clinical respiratory findings.

One dog in the 25 mg/kg recovery group (N = 2) from the 13-week toxicology study had mild infiltrates in the optic nerve and brain, with correlating neurologic observations of abnormal gait and incoordination.

5.4. ADME/PK

The Applicant's Position:

The absorption, distribution, metabolism, excretion (ADME) properties and PK characteristics of adagrasib were evaluated in CD-1 mice, Sprague-Dawley rats, Beagle dogs, and cynomolgus monkeys. Several in vitro and in vivo studies were performed to evaluate the metabolism of adagrasib in pre-clinical species and human. The toxicokinetics of adagrasib was characterized in non-GLP and GLP toxicology studies in Wistar Han rat, New Zealand White rabbits, and Beagle dogs. The potential for drug-drug interaction (DDI) with adagrasib was investigated by evaluating the inhibition or induction of selected CYP enzymes, along with the evaluation of adagrasib as a substrate or inhibitor of selected human drug transporters.

Absorption
Following single oral administration at 30 mg/kg, t_{max} was reached at approximately 1 to 4 hours across species PK-MRTX849-001, PK-MRTX849-003, and PK-MRTX849-026). The absolute oral bioavailability was approximately 25 to 65% and [^{14}C]-MRTX849-derived radioactivity was partially (~ 50%) absorbed after a single 100 mg/kg (200-µCi/kg) oral dose of [^{14}C]-adagrasib to rats (PK-MRTX849-029). After multiple days of QD oral dosing, adagrasib exposure increased more than dose-proportionally (from 10 to 150 mg/kg/day in rats, from 6 to 30 mg/kg/day in pregnant rabbits, and from 5 and 10 mg/kg/day in dogs). Adagrasib demonstrated dose-dependent accumulation after repeated oral QD dosing in these species (TX-MRTX849-004, TX-MRTX849-012, TX-MRTX849-015, TX-MRTX849-021, TX-MRTX849-005, and TX-MRTX849-013).
Distribution
Adagrasib reversible protein binding ranged from 97% to 99% across species (PK-MRTX849-016). Adagrasib binding to HSA and human AGP was 93.7% and 98.4%, respectively, at 1µM concentration (PK-MRTX849-036). The in vitro measured blood-to-plasma ratios for adagrasib indicate greater partitioning of adagrasib to red

blood cells in preclinical species (1.1 to 1.7) compared to human (0.7) (PK-MRTX849-018). In vivo in rats, the mean blood-to-plasma concentration ratio of [^{14}C]-MRTX849-related radioactivity was approximately 1 up to 24 hours post-dose but increased to greater than 2 after 24 hours, suggesting radioactivity had a slower rate of elimination from the cellular fraction of blood compared with that in plasma (PK-MRTX849-029). The V_{ss} ranged from 2 to 21 L/kg across species, indicating that adagrasib was extensively distributed to tissues (PK-MRTX849-001, PK-MRTX849-026, PK-MRTX849-003, and PK-MRTX849-038). Organ distribution data from the [^{14}C]-adagrasib study in rats indicate that [^{14}C]-MRTX849-derived radioactivity was extensively distributed to most tissues. Test article-derived radioactivity had an affinity for melanin in the pigmented rat, especially ocular melanin (PK-MRTX849-029). Distribution to the brain was evaluated in mice and CSF concentration data indicate adagrasib CNS exposure after a single oral dose of 100 mg/kg and 200 mg/kg adagrasib to mice (PK-MRTX849-037).
Metabolism
Adagrasib was subjected to extensive metabolism in animals and humans. There were no unique human metabolites. The 2 circulating human metabolites, M68 and M11, which each accounted for >10% of drug-related materials, were present in rat and dog species used for safety testing (PK-MRTX849-039). Both M68 and M11 do not contribute significantly to the pharmacological activity of adagrasib (PH-MRTX849-015 and PH-MRTX849-024). CYP3A4 mediated the majority of oxidative metabolism, with calculated fraction metabolized 72% (PK-MRTX849-008), however, other CYP enzymes such as CYP2C8, CYP2D6, CYP2J2, and CYP3A5 are also involved in the formation of human oxidative metabolites PK-MRTX849-039).
Excretion
Adagrasib clearance after IV dosing ranged from low to high across pre-clinical species (approximately 20, 44, 30, and 37 mL/min/kg in mice, rats, dogs, and monkeys, respectively. The half-life was moderate (1.5 to 8 hours) (PK-MRTX849-001, PK-MRTX849-026, PK-MRTX849-003, and PK-MRTX849-038). Elimination of adagrasib was primarily by hepatic metabolism and fecal excretion in rats and the urinary and biliary excretion of adagrasib were low (PK-MRTX849-024 and PK-MRTX849-029). The preponderance of metabolites in bile and the attenuated excretion of metabolites in feces in BDC rats compared with intact rats indicates that the majority of [^{14}C]-MRTX849-derived metabolites were eliminated by biliary secretion (PK-MRTX849-029).
Drug-Drug Interactions
In vitro evaluations of adagrasib as substrate of drug transporters indicate that adagrasib is a substrate of P-gp and BCRP (PK-MRTX849-012, PK-MRTX849-015, and PK-MRTX849-040). The DDI risk assessments for adagrasib as an inhibitor or inducer of CYP enzymes or drug transporters were performed using in vitro DDI data (PK-MRTX849-013, PK-MRTX849-014, PK-MRTX849-021, PK-MRTX849-030, and PK-MRTX849-035) and anticipated adagrasib clinical dose and steady-state exposure and the current regulatory guidance (FDA, 2020). Adagrasib clinical dose of 600 mg BID has the potential to inhibit CYP2B6, CYP2C9, CYP2D6, and CYP3A4 and to induce CYP3A4. Adagrasib is also a time-dependent inhibitor of CYP3A4. Adagrasib also has the potential to inhibit drug transporters P-gp, BCRP, and MATE1.

Abbreviations: AGP = α1-acid glycoprotein; BCRP = breast cancer resistance protein; BDC = bile duct annulated; BID = twice daily; CNS = central nervous system; CSF = cerebrospinal fluid; CYP = cytochrome P450; DDI = drug-drug interaction; HSA = human serum albumin; IV = intravenous; MATE1 = multi-antimicrobial extrusion protein-1; P-gp = P-glycoprotein; QD = once daily; tmax = time to maximum plasma concentration; Vss = apparent volume of distribution at steady state

The FDA's Assessment:

The FDA generally agrees with the Applicant's summaries of the nonclinical ADME/PK data. See the FDA's additional noteworthy results and comments below. Dr. Elizabeth Spehalski reviewed some of the pharmacokinetics studies for adagrasib under the original IND submission. See

Section 6 for the FDA's assessment of in vitro PK drug interaction studies (e.g., cytochrome P450 metabolism and transporter studies).

Type of Study	Major Findings
Distribution	
Absorption, Distribution, Metabolism, and Excretion of ^{14}C-MRTX849 After a Single Oral Dose to Rats/ PK-MRTX849-029	Sprague Dawley (SD) albino rats and Long Evans (LE) rats received a single oral dose of 100 mg/kg (200 µCi/kg) of ^{14}C-adagrasib. ^{14}C-adagrasib-derived radioactivity was detected in whole blood and plasma. At time points up to 24 hours, the quantity of ^{14}C-adagrasib was comparable between blood and plasma. From 24 to 48 hours, the blood: plasma concentration ratios increased, suggesting there was a greater elimination rate in the blood compared with that in plasma. Radioactivity distributed to nearly all tissues in both rat models by 8 hours post-dose, with affinity for melanin-pigmented tissues in LE rats observed as the principal difference between models. In pigmented LE rats, ^{14}C-adagrasib distribution was highest in the pituitary gland, Harderian gland, meninges, eye, and eye uveal tract. Radioactivity was detected in the uveal tract and meninges through 672 hours post-dose, and in skin at 168 hours post-dose. In contrast to the affinity to melanin-pigmented tissues in LE rats, ^{14}C-adagrasib distribution in SD non-pigmented rats was highest in the intra-orbital and exorbital lacrimal glands, adrenal and Harderian glands, spleen, lungs, and liver. Tissues with the lowest exposure were central nervous system (CNS) tissues surrounded by the blood-brain barrier (i.e., spinal cord, brain cerebellum, cerebrum, medulla, olfactory lobe), testes, and eye. Radioactivity in reproductive tissues was detected in the bulbo-urethral gland, epididymis, preputial gland, prostate, seminal vesicles, and testes (3290 to 64,400 ng eqiv./g) in SD rats.
Metabolism	
Absorption, Distribution, Metabolism, and Excretion of ^{14}C-MRTX849 After a Single Oral Dose to Rats/ PK-MRTX849-029	• There were 54 trace – minor metabolites quantified; 37 were identified or proposed. • The primary metabolism was mediated by oxidation and glutathione conjugation. • M10 (N-Desmethyl-MRTX849) metabolite was found exclusively in male rat plasma.
MRTX849 In Vivo Metabolism in Rat, Dog, and Human Plasma and In Vitro CYP Mapping/ PK-MRTX849-039	See the Clinical Pharmacology Section 6.3.1 *Elimination*, subsection Metabolism, for a description of a human mass balance study, including identification of metabolites. Toxicokinetic analyses of plasma isolated from Wistar Han rats (TX-MRTX849-012) and Beagle dogs (TX-MRTX849-013) following adagrasib exposure to the highest tolerated dose of 150 mg/kg/day for 89 days in rats or 15 mg/kg/day for 90 days in dogs revealed the presence of metabolites M68 and M11 by mass

<table>
<tr><td></td><td>spectrometry in both species. M68 was less abundant in rats and dogs than in humans. While it was detected by mass spectroscopy analysis in rats and dogs, it was not in sufficient abundance to be detected by ultraviolet (UV) analysis. Conversely, the abundance of M11 was nearly identical in rat and steady-state human plasma, with UV areas of 2.88 and 2.66 absorbance units, respectively.

Based on the proposed metabolic scheme for adagrasib in humans:
• Metabolite M11 is formed via oxidation and dehydrogenation of adagrasib
• Metabolite M57 is formed via amide hydrolysis or oxidative N-dealkylation of adagrasib
• Metabolite M68 is formed via amide hydrolysis or oxidative N-dealkylation of M11 or oxidation and dehydrogenation of M57</td></tr>
<tr><td>Excretion</td><td></td></tr>
<tr><td>Absorption, Distribution, Metabolism, and Excretion of ^{14}C-MRTX849 After a Single Oral Dose to Rats/ PK-MRTX849-029</td><td>• Most radioactivity from ^{14}C-adagrasib study was eliminated by 72 hours post-dose in rats.</td></tr>
<tr><td>TK data from general toxicology studies
A 13-Week Study of MRTX849 by Oral Gavage in Rats with a 28-Day Recovery Period (Study # TX-MRTX849-12)</td><td>Rat
T1/2: Not calculated; T_{max}:1-8 hours
Dose proportionality: C_{max} and AUC_{tlast} increased greater than dose-proportionately at doses ≥ 10 mg/kg on Days 1 and 91 in males and females.
Accumulation: ~3-fold in males and up to 3.5-fold in females.
Sex differences: Generally comparable at doses ≥ 30 mg/kg but ~2 to 3-fold higher in females at 10 mg/kg on Days 1 and 91.

<table>
<tr><th rowspan="2">Day</th><th rowspan="2">Dose (mg/kg)</th><th colspan="2">C_{max} (ng/mL)</th><th colspan="2">AUC_{tlast}* (ng·hr/mL)</th><th colspan="2">T_{max} (hr)</th></tr>
<tr><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td rowspan="3">1</td><td>10</td><td>70.5</td><td>101</td><td>385</td><td>1240</td><td>4</td><td>4</td></tr>
<tr><td>30</td><td>257</td><td>443</td><td>2990</td><td>4580</td><td>4</td><td>1</td></tr>
<tr><td>150</td><td>2460</td><td>2460</td><td>40200</td><td>40400</td><td>8</td><td>8</td></tr>
<tr><td rowspan="3">91</td><td>10</td><td>105</td><td>147</td><td>1050</td><td>1760</td><td>4</td><td>2</td></tr>
<tr><td>30</td><td>725</td><td>783</td><td>8460</td><td>9820</td><td>2</td><td>2</td></tr>
<tr><td>150</td><td>5590</td><td>7100</td><td>128000</td><td>141000</td><td>8</td><td>4</td></tr>
</table>
Hr = hours; *AUC_{tlast} = summation under the curve generated by plasma analyte concentration versus sampling time of last plasma analyte concentration (24 hours).</td></tr>
<tr><td>A 13-Week Study of MRTX849 by Oral Gavage in Dogs with a 28-Day Recovery Period (Study # TX-MRTX849-13)</td><td>Dog
$T_{1/2}$: Not calculated; T_{max}: 2-4 hours
Dose proportionality: On Day 1, exposures increased mostly dose-proportionately. On Day 89, exposure increased greater than dose-proportionately from 5 to 10 mg/kg, dose-proportionately in males but less than dose-proportionately in females.
Accumulation: Observed 2 to 3.5-fold in males and females at 5 and 10 mg/kg on Day 89 compared to Day 1.</td></tr>
</table>

Sex differences: Females exhibited <2-fold lower exposures at the 15 mg/kg dose on Day 89.

Day	Dose (mg/kg)	C_{max} (ng/mL)		AUC_{tlast}* (ng·hr/mL)		T_{max} (hr)	
		M	F	M	F	M	F
1	5	119	126	1720	1950	4	2.5
	10	290	296	4140	4150	2	4
	25/15[a]	570	546	8500	8940	2	3
89	5	241	305	3840	4360	3	3
	10	740	830	13000	12500	4	3
	25/15[a]	1140	894	20400	15000	4	2

Hr = hours; a, Dose was reduced from 25 to 15 mg/kg on Day 24, following a 3-day dosing holiday due to toxicity; *AUC_{tlast} = summation under the curve generated by plasma analyte concentration versus sampling time of last plasma analyte concentration (24 hours).

TK data from reproductive toxicology studies
An Oral (Gavage) Study of the Effects of MRTX849 on Embryo/Fetal Development in Rabbits (Study # TX-MRTX849-021)

Rabbit
$T_{1/2}$: Not calculated; *T_{max}:* 1-4 hours
Dose proportionality: C_{max} and AUC_{tlast} increased 30- and 16-fold or 31- and 25-fold greater, respectively, than dose proportionately between 6 and 30 mg/kg on GD 7 and 21
Accumulation: 3 to 4-fold at all dose levels on GD 21 compared to GD 7

Plasma concentrations in all samples from vehicle animals or from treated groups prior to dose administration on GD 7 were below the limit of quantitation

Gestation Day	Dose (mg/kg)	C_{max} (ng/mL)	AUC_{tlast}* (ng·hr/mL)	T_{max} (hr)
7	6	6.34	35.0	4
	15	27.7	157	4
	30	189	1080	4
20	6	22.5	127	1
	15	99.5	649	1
	30	351	3210	4

Hr = hours; *AUC_{tlast} = summation under the curve generated by plasma analyte concentration versus sampling time of last plasma analyte concentration (24 hours).

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:

Adagrasib was assessed in a series of nonclinical toxicology studies in alignment with International Council for Harmonisation (ICH) M3(R2), ICH S9, and other applicable ICH guidance documents. The rat and dog were chosen as the species for toxicology based on their suitable PK properties and similar in vitro metabolite profile compared to humans. The oral route of exposure was selected for these studies as this is the intended route of administration in humans. The definitive studies were performed in accordance with US Code of Federal Regulations, Title 21, Part 58: Good Laboratory Practices for Nonclinical Laboratory Studies.

Adagrasib was administered once daily by oral gavage to rats and dogs in toxicity studies for up to 13-weeks in duration. The no-observed-adverse-effect-level (NOAEL) in the rat 28-day and 13-week studies was 150 mg/kg/day. After 28-days of adagrasib administration to dogs, the NOAEL was 10 mg/kg/day. In the 13-week repeat dose dog study, the NOAEL was 15 mg/kg/day.

Adagrasib was well tolerated in repeat dose studies in rats at doses up to 150 mg/kg/day in the 28-day study, while early deaths at 300 mg/kg/day were noted. In the 13-week study in rats, there were no treatment related early deaths or any adverse clinical signs. In the 13-week toxicology study in dogs at 25 mg/kg/day, one animal was euthanized on Day 11 due to decreased activity, thin, and uncoordinated. The cause of death of this animal was undetermined. The clinical signs in the remaining dogs administered 25 mg/kg/day included emesis, along with decreased body weight and food consumption that required reducing the dose to 15 mg/kg/day on Day 24. After dose reduction, reduced body weights and food consumption resolved. In both rat and dog repeat-dose studies, multiple organs exhibited microscopic evidence of vacuolation consistent with phospholipidosis. However, these changes were non-adverse as they did not appear to lead to evidence of tissue injury or altered organ function and demonstrated reversibility.

Repeat-Dose Toxicity: Pivotal Studies

<table>
<tr><td colspan="2">Study Number: TX-MRTX849-004
Study Title: 28-Day Repeated Oral Gavage Toxicity and Toxicokinetics Study in Rats with a 14-Day Recovery Period
eCTD Location: 4.2.3.2
Key Drug-related Adverse Findings:
• Early deaths and adverse clinical signs in the high-dose group resulted in early sacrifice and necropsy of remaining main study animals on Day 23
• No Observed Adverse Effect Level: 150 mg/kg/day
GLP compliance: Yes</td></tr>
<tr><td>Dose and frequency of dosing:</td><td>0, 30, 150, 300 mg/kg/day once daily for 28 days</td></tr>
<tr><td>Route of administration:</td><td>Oral</td></tr>
<tr><td>Formulation/Vehicle:</td><td>10% (w/v) vitamin E TPGS in purified water/suspension</td></tr>
</table>

Species/Strain:	Rat/Wistar Han							
Number/Sex/Group:	10 in main study, 5 in postdose recovery evaluation							
Age:	6-8 weeks							
Satellite groups:	Toxicokinetic group							
Toxicokinetics								
Daily Dose (mg/kg)	0 (Control)		30		150		300	
Number of TK Animals	M:3	F:3	M:4	M:4	M:4	M:4	M:4	M:4
C_{max} (ng/mL)								
Day 1	NA	NA	214	302	1920	1810	2370	1880
Day 28	NA	NA	320	339	3060	3970	NA	NA
AUC_{0-24h} (ng*h/mL)								
Day 1	NA	NA	1980	2780	27600	31600	45800	37100
Day 28	NA	NA	2880	3020	49000	76100	NA	NA

Findings:	
Died or Sacrificed Moribund	Due to early deaths beginning on Day 15, remaining rats in the 300 mg/kg/day group were necropsied on Day 23 and recovery animals placed into recovery on Day 22.
Body Weight and Food Consumption	Body weight and body weight gain were decreased in rats treated with 300 mg/kg/day corresponding to a decrease in food consumption. The effect on body weight was more pronounced in male rats.
No Noteworthy Findings	Ophthalmology and Urinalysis
Clinical Observations	Prior to early deaths and morbidity in rats administered 300 mg/kg/day, clinical signs included cold to touch, prostration, hunched posture, thinness, decreased activity, piloerection, skin discoloration (ears and/or feet, white/pale), ocular discharge (red/brown), unkempt appearance, and abnormal respiratory sounds.
Hematology	Hematology changes were predominately at 300 mg/kg/day in rats that were sacrificed in extremis on Day 23. Slight increases in white blood cell count, neutrophils, and monocytes were possibly related to inflammation in regions of splenic and skeletal muscle necrosis.
Serum Chemistry	Clinical chemistry changes in females at 300 mg/kg/day included decreased albumin and increased cholesterol. In male rats in the 300 mg/kg/day group, there were no changes in cholesterol, while albumin was slightly decreased. In both males and females at 300 mg/kg/day, AST was elevated most likely due to degeneration and necrosis in multiple tissues including the skeletal muscle and spleen.
Coagulation	Coagulation parameters demonstrated a decrease in activated partial thromboplastin time in males at ≥ 150 mg/kg/day and a slight increase in fibrinogen in females at ≥ 150 mg/kg/day.

Organ Weight	Organ weight changes included increased spleen to body weight ratios at ≥ 150 mg/kg/day, increased liver to body weight ratios at ≥ 150 mg/kg/day, and increased adrenal to body weight ratios at 300 mg/kg/day. Thymic weights were also decreased at ≥ 150 mg/kg/day in male rats but was not significant.

Gross Necropsy Observations and Histopathology	• Vacuolization due to phospholipidosis across multiple tissues with the severity increasing with dose.
	• At 300 mg/kg/day
	  • Gross findings in the of enlarged adrenals, discolored spleens, and small thymus.
	  • Accumulations of foamy macrophages and protein within alveoli in the lung observed, considered adverse due to association with respiratory sounds in the male rats euthanized due to morbidity.
	  • In the trachea of one male, moderate metaplasia of the epithelium was considered adverse.
	  • In the heart of rats, mild vacuolation of the myocardium in one male considered potentially adverse because this finding was considered the cause of death for one male found dead on Day 21.
	  • In the skeletal muscle of animals, minimal degeneration in one female and mild degeneration in three males and one female was considered test article-related due to the association of this change with minimal vacuolation of myocytes in affected animals. Mild degeneration was considered an adverse change due to the magnitude of the change and the corresponding increases in serum AST.
	  • In the spleen, mild to marked necrosis was observed and less severe effects consisted of mild to marked infiltration by foamy macrophages and mild to moderate decreased lymphocytes.
	  • Increases in spleen weight correlated with necrosis and/or foamy macrophage infiltration and macroscopic discoloration.
	  • In pancreas of 2 males, focal necrosis of the superficial pancreas occurred, considered secondary to necrosis in the spleen, anatomically adjacent to the pancreas.
	  • In the female reproductive tract, several changes occurred that were considered adverse due to the expected effect on reproduction, consisted of mildly increased vacuolation in the corpora lutea in the ovaries, mild to moderate vacuolation of the glandular epithelium in the uterus, and mild atrophy with mucification of the vaginal mucosa.

Postdose Evaluation	• Clinical signs of morbidity not observed in high dose postdose recovery rats. • Body weight in the high dose group was comparable to controls. • Changes in clinical pathology parameters completely reversed. • Histopathology indicated a number of tissues with macrophage infiltrates and vacuolation; however, these effects were less severe, while in some tissues there was no evidence of vacuolation. Recovery from these changes occurred but did not completely reverse.

Study Number: TX-MRTX849-012
Study Title: A 13-Week Study of MRTX849 by Oral Gavage in Rats with a 28-Day Recovery Period
eCTD Location: 4.2.3.2
Key Drug-related Adverse Findings:

- No Observed Adverse Effect Level: 150 mg/kg/day

GLP compliance: Yes

Dose and frequency of dosing:	0, 10, 30, 150 mg/kg/day once daily for 13 weeks
Route of administration:	Oral
Formulation/Vehicle:	10% (w/v) vitamin E TPGS in purified water/suspension
Species/Strain:	Rat/Wistar Han
Number/Sex/Group:	10 in main study, 5 in postdose recovery evaluation of control and high-dose groups
Age:	9 weeks
Satellite groups:	Toxicokinetics group

Toxicokinetics

Daily Dose (mg/kg)	0 (Control)		10		30		150	
Number of TK Animals	M:3	F:3	M:6	M:6	M:6	M:6	M:6	M:6
C_{max} (ng/mL)								
Day 1	NA	NA	70.5	101	257	443	2460	2460
Day 91	NA	NA	105	147	725	783	5590	7100
AUC_{tlast} (ng*h/mL)								
Day 1	NA	NA	385	1240	2990	4580	40200	40400
Day 91	NA	NA	1050	1760	8460	9820	128000	141000

Findings

Died or Sacrificed Moribund	None
Body Weight and Food Consumption	Decrease body weight and body weight gain in males at 150 mg/kg/day, and decreased food consumption in males and females at 150 mg/kg/day compared to vehicle controls.
No Noteworthy Findings	Clinical Observations, ophthalmology, and urinalysis.
Hematology, Serum Chemistry	At 150 mg/kg/day, mild to moderate and non-adverse increased white blood cells, neutrophils, lymphocytes, and monocytes; increased AST; and decreased albumin/globulin ratio.
Organ Weight	Increased organ weight (adrenal, kidney, liver, spleen) at 150 mg/kg/day.

Histopathology	• Test article-related findings considered non-adverse due to a lack of correlating histologic findings suggestive of injury or altered organ functionality. • Findings consistent with phospholipidosis. • Mottled/pale discoloration of lungs at 150 mg/kg/day. • Microscopic findings of aggregation of foamy macrophages and eosinophilic material in alveolar spaces.
Postdose Evaluation	• Changes in clinical pathology parameters completely reversed. • Histopathology findings completely or partially reversed, except for the gross discoloration in the lungs.

Study Number: TX-MRTX849-005
Study Title: 28-Day Repeated Oral Gavage Toxicity and Toxicokinetics Study in Beagle Dogs with 14-Day Recovery
eCTD Location: 4.2.3.2
Key Drug-related Adverse Findings:

- Highest Non-Severely Toxic Dose: 25 mg/kg/day
- No Observed Adverse Effect Level: 10 mg/kg/day

GLP compliance: Yes

Dose and frequency of dosing:	0, 5, 10, 25 mg/kg/day x 28 days
Route of administration:	Oral
Formulation/Vehicle:	10% (w/v) vitamin E TPGS in purified water/suspension
Species/Strain:	Dog/Beagle
Number/Sex/Group:	3 in main study, 2 in postdose recovery evaluation
Age:	11-12 months

Toxicokinetics

Daily Dose (mg/kg)	0 (Control)		5		10		25	
Number of Main Study Animals	M:3	F:3	M:3	F:3	M:3	F:3	M:3	F:3
C_{max} (ng/mL)								
Day 1	NA	NA	120	111	336	373	1120	874
Day 28	NA	NA	213	176	634	635	1770	1300
AUC_{tlast} (ng*h/mL)								
Day 1	NA	NA	1500	1480	5100	5910	16300	13100
Day 28	NA	NA	3330	2650	10900	11100	33700	24200

Findings	
Died or Sacrificed Moribund	None
No Noteworthy Findings	Ophthalmology examinations, blood pressure, electrocardiogram parameters, clinical chemistry, coagulation, urinalysis, organ weights, or macroscopic findings.
Clinical Observations	Intermittent emesis at ≥ 10 mg/kg/day.
Body Weight and Food Consumption	Decreased body weight, body weight gain and food consumption in male dogs administered 25 mg/kg/day.
Serum Chemistry	Slight decreased total protein and albumin at the end of the 28 day treatment period.
Histopathology	Adverse findings limited to the bone marrow, heart, lungs, and spleen of dogs administered 25 mg/kg/day. • Bone marrow - moderate to marked decrease in erythropoiesis for males and a minimal to mild decrease in females, correlating with decrease in reticulocyte counts and red blood cell parameters. • Heart - one high-dose male dog, subacute myocardial necrosis in the papillary muscle along with mild vacuolation. • Lungs – in two males and one female given 25 mg/kg/day, minimal to mild increases in alveolar macrophages with vacuolated cytoplasm. This finding is possibly associated with phospholipidosis, not considered adverse given the minor nature of the change. • Spleen - non-adverse lymphoid depletion in males given ≥ 5 mg/kg/day.
Postdose Evaluation	• Histopathology changes appeared to reverse or partially reverse at the end of the 14-day recovery period. One high-dose male had moderate myocardial fibrosis in a left papillary muscle.

Study Number: TX-MRTX849-013
Study Title: A 13-Week Study of MRTX849 by Oral Gavage in Dogs with a 28-Day Recovery Period
eCTD Location: 4.2.3.2
Key Drug-related Adverse Findings:

- No Observed Adverse Effect Level: 15 mg/kg/day
- Emesis and decreased body weight and food consumption led to the discontinuation of dosing at 25 mg/kg/day on Day 20. Dosing resumed on Day 24 at 15 mg/kg/day.

GLP compliance: Yes

Dose and frequency of dosing:	0, 5, 10, 25/15 mg/kg/day x 13 weeks
Route of administration:	Oral
Formulation/Vehicle:	10% (w/v) vitamin E TPGS in purified water/suspension
Species/Strain:	Dog/Beagle
Number/Sex/Group:	4 in main study, 2 in in the control and high-dose group for postdose recovery evaluation

Age:	6 months							
Toxicokinetics								
Daily Dose (mg/kg)	**0 (Control)**		**5**		**10**		**25/15**	
Number of Main Study Animals	M:4	F:4	M:4	F:4	M:4	F:4	M:4	F:4
C_{max} (ng/mL)								
Day 1	NA	NA	119	126	290	296	570	546
Day 89	NA	NA	241	305	740	830	1140	894
AUC_{tlast} (ng*h/mL)								
Day 1	NA	NA	1720	1950	4140	4150	8500	8940
Day 89	NA	NA	3840	4360	13000	12500	20400	15000

Findings	
Died or Sacrificed Moribund	One 25 mg/kg/day female was euthanized moribund on Day 11 due to clinical observations of abnormal gait, decreased activity, abnormal consistency of feces, thin appearance, and incoordination. The cause of death was undetermined.
No Noteworthy Findings	Ophthalmology, electrocardiogram, clinical chemistry, urinalysis, gross necropsy findings, organ weight changes, or microscopic findings.
Clinical Observations	Emesis, body weight loss and decreased food consumption in the high-dose group lead to dose reduction for the group from 25 mg/kg/day to 15 mg/kg/day.
Hematology	At the end of the treatment period, decreased hemoglobin, hematocrit, and mean cell volume were considered non-adverse.
Postdose Evaluation	All effects demonstrated reversibility.

Abbreviations: F = female; M = male; NA = not applicable; TPGS = Tocopherol polyethylene glycol succinate.

The FDA's Assessment:

The findings that the Applicant described were generally present in both species. Most aberrant findings at least partially resolved upon recovery. While the FDA generally agrees with the Applicant's summary of the 28-day and 13-week repeat-dose toxicology studies, we do not agree with the Applicant's position that development of phospholipidosis in multiple organs of rats and dogs is considered non-adverse. The FDA considers that at the high dose groups of 300 mg/kg in rats (28-day toxicology study) and 25 mg/kg in dogs (28-day and 13-week toxicology studies), phospholipidosis may be considered adverse for several reasons: 1) mild vacuolation of the myocardium in one male rat was considered its cause of death, 2) findings of foamy macrophages infiltration in the alveoli and vacuolation in lung, correlating with respiratory impairment were considered the cause of death in some rats, 3) mild to marked infiltration of foamy macrophages in the spleen of rats correlated with mild to moderate decrease in lymphocytes, increase in splenic weight relative to body weight, macroscopic discoloration of the spleen, and focal necrosis of the neighboring pancreas; 4) vacuolation was associated with

necrosis and atrophy of male and female reproductive tracts, with adverse effects likely to impede reproduction. At the remaining doses of the toxicology studies, phospholipidosis did not alter organ function, cause tissue injury, or lead to death and FDA therefore does not consider that adverse.

Additional noteworthy data is presented below. We also note that the Applicant mislabeled females (F) as males (M) for adagrasib treatment groups in the toxicokinetic tables for both repeat-dose studies conducted in rats.

Study Title/ number: A 13-Week Study of MRTX849 by Oral Gavage in Rats with a 28-Day Recovery Period/ TX-MRTX849-012

Key Study Findings:

- Target organs included lungs, liver, adrenal gland, and kidney.
- Females had increased fibrinogen and alkaline phosphatase levels, which improved upon recovery.

Parameters	Major findings
Body Weights and Feed Consumption	Males in the 150 mg/kg group had lower body weight gain across the dosing period (-26%), resulting in lower body weight (-12%). Weight loss in the 150 mg/kg group likely occurred due to ~11% decrease in food consumption from Day 29 to Day 50.
Coagulation	Females in the 150 mg/kg group had increased fibrinogen on Day 92, which mostly resolved upon recovery.

Coagulation: % Change from Concurrent Control (13-week Study; Rats)

Test	Study Day	Male			Female		
		10 mg/kg	30 mg/kg	150 mg/kg	10 mg/kg	30 mg/kg	150 mg/kg
Fibrinogen	92	-10.51%	-10.41%	8.54%	-10.91%	-6.37%	60.87%
	120			6.21%			21.15%*

Hematology	There were significant increases in WBC and myeloid-lineage cell populations in rats in the 150 mg/kg group. Most elevated hematologic parameters resolved upon recovery.

Parameters	Major findings

Clinical Hematology: % Change from Concurrent Control on Days 92 and 120 (13-week study; Rats)

Test	Day	Male			Female		
		10 mg/kg	30 mg/kg	150 mg/kg	10 mg/kg	30 mg/kg	150 mg/kg
LYMPH	92	-11.13%	-4.18%	42.99%**	5.03%	0.79%	83.62%**
	100			0.33%			0.67%
MONO	92	-29.51%	-3.28%	76.23%**	-5.33%	-13.33%	**201.33%****
	120			5.00%			33.33%
NEUT	92	-3.27%	-3.62%	69.86%**	8.74%	4.88%	**221.85%****
	120			8.74%			16.59%
WBC	92	-10.02%	-4.00%	50.28%**	5.47%	1.34%	**108.42%****
	100			2.88%			5.19%
RETIC	92	-4.89%	-5.40%	8.50%	1.16%	1.51%	16.67%*
	100			26.63%*			30.37%

Values ≥100% are bold; *p<0.5; **p<0.01

Clinical Chemistry	Females in the 150 mg/kg group exhibited reversible elevated alkaline phosphatase (ALP) and non-reversible decrease in albumin/globulin ration (ALB/GLOB); and males had slightly elevated alanine aminotransferase (ALT), which resolved upon recovery.

Clinical Chemistry: % Change from Concurrent Control on Days 92 and 120 (13-week study; Rats)

Test	Study Day	Male			Female		
		10 mg/kg	30 mg/kg	150 mg/kg	10 mg/kg	30 mg/kg	150 mg/kg
ALT	92	7.79%	14.29%	34.74%	13.00%	22.00%	18.00%
	120			2.45%			-5.43%
ALP	92	-5.63%	10.80%	-9.86%	-13.87%	7.30%	56.57%
	120			8.28%			-2.05%
ALB/GLOB	92	2.18%	-7.86%	-10.48%	-9.39%	-23.03%*	-43.94%**
	120			-22.31%**			-33.99%**

*p<0.5; **p<0.01

Urinalysis	There was an increase in urine volume in the 150 mg/kg group.

Urinalysis: % Change from Concurrent Control on Days 92 and 120 (13-week Study; Rats)

Test	Study Day	Male			Female		
		10 mg/kg	30 mg/kg	150 mg/kg	10 mg/kg	30 mg/kg	150 mg/kg
Volume	92	65.83%	91.65%	**138.06%**	80.57%	76.57%	**366.29%****
	120			-25.73%			17.14%

Values ≥100% are bold; ** p≤0.01

Organ Weights	Animals in the 150 mg/kg group demonstrated increased organ-to-body weight ratio of adrenal gland; males had increased ratio of kidney. Adrenal gland and kidney organ-to-body weight ratios mostly resolved upon recovery.

Organ to Body Weight Ratio: % Difference from Concurrent Control on Days 92 and 120 (13-week Study; Rats)

Organ/ Tissue	Study Day	Male			Female		
		10 mg/kg	30 mg/kg	150 mg/kg	10 mg/kg	30 mg/kg	150 mg/kg
	92	10.98%	-3.26%	88.79%**	6.87%	4.22%	54.40%**

Parameters		Major findings					
Gland, Adrenal[a]	120			22.43%			25.68%
Kidney[a]	92	1.62%	0.46%	41.28%*	-5.25%	-6.53%	12.33%
	120			16.70%**			14.96%**
Liver	92	-3.04%	0.94%	27.52%*	2.96%	3.92%	29.32%*
	120			19.16%*			11.72%*
Spleen	92	6.89%	-4.30%	40.36%*	2.70%	2.69%	38.26%*
	120			28.74%			19.88%

a: Bilateral specimens examined; * p≤0.05; ** p≤0.01

Histopathology Adequate battery: Yes	See Table below. There were no significant findings in groups receiving 10 or 30 mg/kg, so these groups were excluded from the table. Macrophage vacuolation in multiple tissues were described as phospholipidosis.

Histopathology Findings on Days 92 and 120 (13-week Study; Rats)

Organ/ Tissue	Finding	Severity	Male		Female	
			0 mg/kg	150 mg/kg	0 mg/kg	150 mg/kg
		N =	10	10, 5R	10	10, 5R
Lung	accumulation, eosinophilic extracellular material; alveolar*	marked		10		10
	aggregate, alveolar; macrophage*	mild		2R		2R
		marked		10		10
Liver	vacuolation, biliary; epithelial*	mild		10		10
Kidney	vacuolation, tubular*	mild		10		10
Lymph Node, Mesenteric	vacuolation, macrophage*	mild		7		6
	vacuolation, macrophage*	mod		2		3
Gland, Adrenal	vacuolation, cortical*	mild		10		10
Ovary	vacuolation, macrophage*	mild				10
		N =	10, 0R	10	10, 0R	10, 0R
Spleen	vacuolation, macrophage*	mild		10		10

*Non-neoplastic; R: recovery

Study Title/ number: A 13-Week Study of MRTX849 by Oral Gavage in Dogs with a 28-Day Recovery Period/ TX-MRTX849-013

Key Study Findings:

- Adagrasib decreased body weight and food intake, leading to a 4-day dosing holiday and dose reduction in high dose groups from 25 mg/kg to 15 mg/kg.
- Adagrasib caused dose-dependent decreases in reticulocytes, which did not resolve upon recovery.

Parameters	Major findings
Body Weights and Feed Consumption	Dogs in the 25 mg/kg group exhibited significant decrease in body weight gain from Days 8 to 15 (males) or Days 1 to 8 (females).
Clinical Observations	Dogs in the 25 mg/kg group experienced vomiting and had partially digested food and/or other mucoid material present in their cage.

Clinical Signs (13-week Study; Dogs)

Sign	Male				Female			
	N = 4/2R	4	4	4/2R	N = 4/2R	4	4	4/2R
	0 mg/kg	5 mg/kg	10 mg/kg	25/15 mg/kg	0 mg/kg	5 mg/kg	10 mg/kg	25/15 mg/kg
Eye Discharge,			1	1		1		
Food Partly Digested		2	4	5		1	4	6
Material Present in Cage	1	3	4	6		2	4	5
Salivation				6			2	2
Vocalization								2
Vomitus		1	1	5			1	4

R = Recovery group

Hematology	Dogs exposed to adagrasib had reduced reticulocytes (RETIC), which did not resolve upon recovery.

Clinical Hematology: % Change from Concurrent Control on Days 92 and 120 (13-week study; Dogs)

Test	Study Day	Male			Female		
		5 mg/kg	10 mg/kg	25/15 mg/kg	5 mg/kg	10 mg/kg	25/15 mg/kg
RETIC	92	-26.40%	-47.75%	-39.41%	-12.29%	-26.10%	-33.56%
	120			-59.12%			-43.53%

Clinical Chemistry	Unremarkable

Parameters	Major findings
Urinalysis	There was a significant increase in urine volume in the 25/15 mg/kg group during recovery, indicating dehydration during treatment.

Urinalysis: % Change from Concurrent Control on Days 92 and 120 (13-week Study; Dogs)

Test	Study Day	Male			Female		
		5 mg/kg	10 mg/kg	25/15 mg/kg	5 mg/kg	10 mg/kg	25/15 mg/kg
Volume	92	-46.17%	-14.80%	10.69%	7.19%	-0.70%	11.50%
	120			**364.83%***			**128.84%**

Values ≥100% are bold; * represents 3-fold increase from pre-dose volume

Organ Weights	There was dose-dependent increase in female dog ovary weight, which partially resolved upon recovery.

Organ to Body Weight Ratio: % Difference from Concurrent Control on Days 92 and 120 (13-week Study; Dogs)

Organ/ Tissue	Female		
	5 mg/kg	10 mg/kg	25/15 mg/kg
Ovary*	-14.86%	46.71%	89.81%
Recovery*			23.77%

*Bilateral specimens examined

Histopathology Adequate battery: Yes	There were minimal findings of lung alveolar infiltrate, salivary gland acinar infiltrate, and esophageal periglandular tunica muscularis infiltrate in dogs treated with 25/15 mg/kg of adagrasib.

Dr. Elizabeth Spehalski conducted the review of the 28-day, repeat-dose toxicology studies, which supported findings consistent with those of the 13-week studies. One difference in the 28-day study is the finding of toxicity in male reproductive organs of rats at the 300 mg/kg dose (approximately 1.6 times the human AUC at the recommended dose), including mild to marked prostate gland atrophy and minimal to mild prostate gland epithelial vacuolation; and moderate to marked seminal vesicle atrophy and moderate seminal vesicle epithelial vacuolation. These findings resolved upon recovery. In a 14-day dose range-finding study, exposure of a single male dog to 100 mg/kg (approximately 1.6 times the human AUC at the recommended dose) resulted in a similar finding of mild bilateral vacuolation in the epididymides and seminiferous tubules in the testes (not reviewed). Adagrasib exposure also caused female reproductive tract toxicity. In the 13-week toxicology study conducted in rats, exposure to 150 mg/kg adagrasib (approximately 5 times the human AUC at the recommended dose) resulted in mild ovarian macrophage vacuolation, which resolved during the recovery period. In the 28-day toxicology study conducted in rats, exposure to 300 mg/kg (approximately 1.3 times the human AUC at the recommended dose) caused moderate microvesicular vacuolation of the uterus, mild vacuolation in the corpus luteum of the ovary; and moderate microvesicular vacuolation, mild mucosal atrophy, and mild mucification of the vagina. Overall, based on histological findings in reproductive organs in males and females, adagrasib may impair male and female fertility.

5.5.2. Genetic Toxicology

The Applicant's Position:

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 MTD 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 (Applicant Table 8).

Applicant Table 8: Genotoxicity Studies Conducted with Adagrasib

Type of Test	Test System	Dose/ Concentration	Results
Microbial reverse mutation assay	*Salmonella typhimurium and Escherichia coli*	1.5–1000 µg/well	(–)
Definitive Bacterial Mutation Assay	*Salmonella typhimurium and Escherichia coli*	2.5 – 2000 µg/well	(–)
In Vitro Cytogenetics	CHO cells (in vitro) 3-hour without S9 24-hour without S9 3-hour with S9	 1.0–8 µg/mL 0.5–6.0 µg/mL 2-14 µg/mL	 (–) (–) (–)
Definitive Chromosomal Aberration Assay	CHO cells (in vitro) 3-hour without S9 22-hour without S9 3-hour with S9	 2–9 µg/mL 0.5–4 µg/mL 5-18 µg/mL	 (–) (–) (–)
In Vivo Micronucleus	Wistar Han rats	250, 500, 1000 mg/kg/day	(–)

Abbreviations: CHO = Chinese hamster ovary.

Applicant's Position:

The genotoxic potential of adagrasib was adequately assessed in a series of in vitro and an in vivo study, and negative in all genotoxicity studies.

The FDA's Assessment:

The FDA confirmed the Applicant's presentation of the results of the submitted genotoxicity studies and agrees with the conclusions for the active pharmaceutical ingredient, adagrasib. FDA additionally notes that in the definitive in vitro chromosomal aberration assay (Study # MRTX849-11), a 3-hour incubation of CHO cells with adagrasib in the absence of S9 resulted in increased endo-reduplication (indicative of disruption of cell-cycle progression or cell division) between 1.7 and 3.7% at 7 and 9 µg/mL, which was higher than the concurrent negative control and the historical control data range. Standard positive controls confirmed the sensitivity and validity of each assay. See Other Toxicology Studies section for discussion of genotoxic potential of metabolites.

5.5.3. Carcinogenicity

The Applicant's Position:

In alignment with ICH S9 guidance, carcinogenicity studies have not been conducted with adagrasib.

The FDA's Assessment:

The FDA agrees that carcinogenicity studies are not needed to support the use of adagrasib in the currently proposed indication per ICH S9.

5.5.4. Reproductive and Developmental Toxicology

Applicant's Position:

The embryo-fetal toxicity of adagrasib was assessed in pregnant rats (TX-MRTX849-001) and rabbits (TX-MRTX849-021), demonstrating no teratogenic effects.

In the rat study, higher mean litter proportions of skeletal malformations (bent limb bones) and developmental variations (bent scapula in conjunction with bent limb bones, wavy ribs), and supernumerary (short cervical ribs) occurred in the 270 mg/kg/day group. These findings were noted in the presence of test article-related maternal toxicity. No test article-related fetal malformations or developmental variations were noted at 30 and 90 mg/kg/day. Based on maternal body weight loss, lower mean body weight gain, and food consumption at 270 mg/kg/day, a dose level of 90 mg/kg/day was considered to be the NOAEL for maternal and developmental toxicity for adagrasib in this study.

Study Number: TX-MRTX849-001
Study Title: An Oral (Gavage) Study of the Effects of MRTX849 on Embryo/Fetal Development in Rats
eCTD Location: 4.2.3.5.2
Key Drug-related Adverse Findings:

- No Observed Adverse Effect Level: F_0 Females: 90 mg/kg/day, F_1 Litters: 90 mg/kg/day

GLP compliance: Yes

Dose and frequency of dosing:	Control, 30, 90, 270 mg/kg/day
Route of administration:	Oral
Formulation/Vehicle:	10% (w/v) Vitamin E TPGS in water
Species/Strain:	Rat/Wistar Han
Number/Group:	22F
Age:	12-13 weeks
Schedule:	Duration of Dosing: Gestation Days 6-17 Day of C-Section: Gestation Day 21

Findings	
Died or Sacrificed Moribund	3 females in the 270 mg/kg/day group euthanized in extremis on Gestation Days 16, 17, and 20, due to body weight loss, low food consumption, clinical observations (including abnormal breathing or animal thin) and/or veterinary observations (including decreased activity, general weakness, hunched posture, and/or piloerection).
Clinical Observations, Body Weight, and Food Consumption	Red staining of the fur on the nostril, nose, and/or muzzle at 270 mg/kg/day beginning after the first dose and continuing through study. Thinness association with reduced food consumption and body weight loss and considered adverse noted in 3 surviving females in this group.

Necropsy Observations	• 270 mg/kg/day group
	  • 1 female sacrificed in extremis, enlarged adrenal glands and pale foci on the liver.
	  • 3 females had focal or multifocal pale tan areas in the liver at the scheduled necropsy. Another female had masses and multifocal tan nodules in the liver. These findings were considered test article-related, but adversity could not be determined due to the lack of microscopic evaluation.
	  • Mean gravid uterine weight lower than the control group.
	  • Mean fetal body weights approximately 19.3% to 20.0% lower than the control group.
	  • Higher mean litter proportions of skeletal malformations (bent limb bones) and developmental variations (bent scapula in conjunction with bent limb bones, wavy ribs, and supernumerary short cervical ribs), due to maternal body weight loss.

Abbreviations: F = female; TPGS = Tocopherol polyethylene glycol succinate.

In the rabbit study, there were no test article-related fetal malformations. A higher mean litter proportion of unossified sternebra was noted in the 30 mg/kg/day group compared to the

concurrent control group. This finding was considered secondary to the lower mean fetal body weights and was not considered adverse. Based on the lack of adverse effects on dams and fetuses, a dose level of 30 mg/kg/day was considered to be the NOAEL for maternal toxicity and developmental toxicity when adagrasib was administered orally by gavage to time-mated New Zealand White rabbits. At 30 mg/kg/day, the maternal Gestation Day 20 AUC_{tlast} and C_{max} were 3210 ng*h/mL and 351 ng/mL, respectively.

Study Number: TX-MRTX849-021
Study Title: An Oral (Gavage) Study of the Effects of MRTX849 on Embryo/Fetal Development in Rabbits
eCTD Location: 4.2.3.5.2
Key Drug-related Adverse Findings:

- No Observed Adverse Effect Level: F_0 Females: 30 mg/kg/day, F_1 Litters: 30 mg/kg/day

GLP compliance: Yes

Dose and frequency of dosing:	Control, 6, 15, 30, mg/kg/day
Route of administration:	Oral
Formulation/Vehicle:	10% (w/v) Vitamin E TPGS in water
Species/Strain:	Rabbit/New Zealand White
Number/Group:	22F
Age:	7 months
Schedule:	Duration of Dosing: Gestation Days 7-20 Day of C-Section: Gestation Day 29

Toxicokinetics

Daily Dose (mg/kg)	**0 (Control)**	**6**	**15**	**30**
Number of Animals	F:22	F:22	F:22	F:22
C_{max} (ng/mL)				
Gestation Day 7	NA	6.34	27.7	189
Gestation Day 20	NA	22.5	99.5	351
AUC_{tlast} (ng*h/mL)				
Gestation Day 7	NA	35.0	157	1080
Gestation Day 20	NA	127	649	3210

Findings

Died or Sacrificed Moribund	1 female in the 30 mg/kg/day group found dead on Gestation Day 20 within 4 minutes of dosing following an episode of non-sustained convulsions; no macroscopic findings at necropsy noted. Death was attributed to procedure during dosing.
No Noteworthy Findings	Clinical observations, body weight, food consumption, necropsy observations

Abbreviations: F = female; TPGS = Tocopherol polyethylene glycol succinate.

The FDA's Assessment:

The FDA generally agrees with the Applicant's conclusion, with additional pertinent details and comments about NOAEL added below. Overall, these studies showed that adagrasib causes maternal toxicity in rats and rabbits, which led to secondary fetal effects. Other fetal developmental findings observed with adagrasib lacked a clear dose-response.

In rats dosed at 270 mg/kg (approximately 2 times the recommended dose based on body surface area [BSA]), decreases in fetal body weight and skeletal malformations and variations were associated with maternal toxicity. At 90 mg/kg (approximately 0.72 times the recommended dose based on BSA), where no maternal toxicity was observed, 4(3) fetuses (litters) had external and skeletal malformations and skeletal variations. These findings were not considered adagrasib-related since findings were not observed at the high dose.

In rabbits, there was maternal toxicity at 30 mg/kg (approximately 0.11 times the human AUC at the recommended dose) characterized by reduced dam mean body weight gain and food consumption. Adagrasib did not have significant adverse embryo-fetal survival effects or developmental effects; however, adagrasib at 30 mg/kg resulted in decreased mean fetal body weight (not statistically significant but below historical control), and increased litter frequency of unossified sternebra. The changes in sternebra are most likely related to the decreased fetal body weight.

Based on the overall findings, the FDA determined that the NOAEL in rats was 90 mg/kg for maternal toxicity as well as developmental toxicity. The NOAEL for developmental toxicity was established at the mid-dose level because the effects observed were not dose-dependent. In rabbits, the FDA determined the NOAEL was 15 mg/kg for maternal toxicity. FDA recommends describing animal data in the label but a warning for embryo-fetal toxicity does not seem warranted since adagrasib 1) did not induce a clear significant adverse effect, 2) showed specificity to KRASG12C in primary pharmacology studies, and 3) lacked genotoxic activity.

Findings in the repeat-dose toxicology study in rats and dogs suggest that adagrasib may affect male and female fertility. Results from these studies will be included in Section 13.1 of the label.

Data (presented by FDA):

Embryo-Fetal Development:

Study title/ number: An Oral (Gavage) Study of the Effects of MRTX849 on Embryo/Fetal Development in Rats/ # TX-MRTX849-001

Key Study Findings

- Adagrasib exposure led to significant, dose-dependent reductions in body weight (-68%), food consumption (-20%), and gravid uterus weight (-28%) in the 270 mg/kg group on GD 21 compared to controls.
- Adagrasib induced skeletal malformations, such as bent limb bones, and developmental variations (bent scapula, wavy ribs, and supernumerary short cervical ribs) at 270 mg/kg. These abnormalities were associated with maternal toxicity and reduced fetal body weights.

Methods

Study design:	Toxicokinetics analyses were not conducted.
Deviation from study protocol affecting interpretation of results:	None

Observations and Results

Parameters	Major findings
Body Weights	Dams in the 270 mg/kg group exhibited -68% (p≤0.01) difference in weight gain throughout the study, compared to the control group. There were several days throughout the study in which adagrasib exposure led to significant (p≤0.001), dose-dependent decrease in food intake. Starting on GD 6 and 7 and up to GD 21, dams in the 270 mg/kg group consumed 18% to 57% less food than the control group.
Gravid Uterine Weights	**270 mg/kg:** There was a statistically significant decrease (-28%) in gravid uterus weight.

Cesarean Section Findings (Embryo-fetal Development Study; Rats)

Dose	0 mg/kg	30 mg/kg	90 mg/kg	270 mg/kg
# Mated females	22	22	22	22
# Pregnant (%)	22 (100%)	22 (100%)	21 (100%)	18[a,b] (100%)
# Dams with live fetuses	22 (100%)	22 (100%)	21 (100%)	18[a,b] (100%)
Mean # corpora lutea	13	12.8	12.7	12.8
Mean # implantation sites	10.7	11.1	10.9	10.3
Mean % pre-implantation loss	18.08%	12.57%	13.64%	19.30%
Mean % post-implantation loss	6.79%	8.13%	6.03%	14.07%
Mean # early resorption (%)	0.8 (3.6%)	0.8 (3.6%)	0.7 (3.3%)	1.3 (7.2%)
Mean # late resorptions (%)	0 (0%)	0 (0%)	0 (0%)	0.1 (0.6%)
Mean total resorptions (%)	0.8 (3.6%)	0.8 (3.6%)	0.7 (3.3%)	1.4 (7.8%)
Mean # dead fetuses	0	0	0	0
Mean # live fetuses	9.9	10.3	10.2	8.9
Mean fetal body weight (g)	5.230	5.352	5.139	4.274**
Mean fetal sex ratio (% males)	49.49%	51.46%	49.02%	47.19%

a, 1 female in the 270 mg/kg group was nongravid; b, early decedents (n = 3) were excluded; **, P ≤ 0.01 vs. controls; Mean % pre- and post-implantation loss were calculated by Applicant [% pre-implantation loss = (# of corpora lutea - # implants / # of corpora lutea x 100; % post-

implantation loss = (# of implants - # of live fetuses) / # of implants x 100]; Other mean % was calculated on a litter basis = (Total # of litters with malformation or variation / Total # of litters) x 100

Study title/ number: An Oral (Gavage) Study of the Effects of MRTX849 on Embryo/Fetal Development in Rabbits/ # TX-MRTX849-021

Key Study Findings

- Adagrasib exposure led to 7% lower mean fetal weight (not statistically significant relative to control but below historical control) and increased litter frequency of unossified sternebra at 30 mg/kg (approximately 0.11 times the human AUC at the recommended dose), which correlated with 33% reduction in dam mean body weight gain, reduced food consumption, and reduced fecal output during the treatment period.

Observations and Results

Parameters	Major findings
Clinical Signs	Dams receiving ≥6 mg/kg adagrasib had dose-dependent findings of decreased fecal output, soft feces, and brown staining of fur on anus and paws. Findings were mild.
Body Weights	Compared to controls, dams in the 30 mg/kg group exhibited an up to a 4% decrease in mean body weight but had a 33% decrease in mean body weight gain over the course of the study (GD 0 to GD 29). These changes correlated with decreased food consumption (significantly lower GD 19-20) and decreased fecal output throughout the treatment period.
Gravid Uterine Weights	There were no dose-dependent differences in uterine weights between groups.
Necropsy findings Cesarean Section Data	There were dose-dependent findings of abnormal-appearing spleen. Two dams in the 30 mg/kg had abnormal accumulation of material in the uterus.

Cesarean Section Findings (Embryo-fetal development Study; Rabbits)

Dose	0 mg/kg	6 mg/kg	15 mg/kg	30 mg/kg
# Mated females	22	22	22	22
# Pregnant (%)	22 (100%)	21 (95.5%)	21 (95.5%)	22 (100%)
# Dams with live fetuses	21	21	21	20
Mean # corpora lutea	10.0	11.3	11.5*	10.3
Mean # implantation sites	9.0	9.3	8.4	9.2
Mean % pre-implantation loss	10.4%	17.0%	25.8%**	10.0%
Mean % post-implantation loss	7.38%	6.7%	3.08%	10.96%)
Mean # early resorption (%)	0.67 (3.2%)	0.33 (1.6%)	0.24 (1.2%)	0.29 (1.5%)
Mean # late resorptions (%)	0.10 (0.48%)	0.29 (1.4%)	0.05 (0.24%)	0.76 (3.8%)
Mean total resorptions (%)	0.76 (3.6%)	0.68 (3.2%)	0.29 (1.3%)	1.1 (5.5%)
Mean # dead fetuses	0	0	0	0

Dose	0 mg/kg	6 mg/kg	15 mg/kg	30 mg/kg
Mean # live fetuses	8.2	8.7	8.1	8.2
Mean fetal body weight (g)	41.13	41.33	42.73	38.23
Mean fetal sex ratio (% males)	51.45	53.77	54.43	49.23

*, P ≤ 0.05 vs. controls; **, P ≤ 0.01 vs. controls; Mean % pre- and post-implantation loss were calculated by Applicant [% pre-implantation loss = (# of corpora lutea - # implants / # of corpora lutea x 100; % post-implantation loss = (# of implants - # of live fetuses) / # of implants x 100]; Other mean % was calculated on a litter basis = (Total # of litters with malformation or variation / Total # of litters) x 100

Necropsy findings Offspring	There was a slight decrease in fetal body weight (not statistically significant) noted at 30 mg/kg that was mainly driven by 2/20 litters. Statistically significant changes in unossified sternebra and short thoracolumbar supernumerary ribs were observed in 30 mg/kg groups, which are most likely secondary to decreased fetal body weight.

5.5.5. Other Toxicology Studies

Phototoxicity

Applicant's Position:

Adagrasib was not phototoxic in an in vitro Good Laboratory Practice (GLP) assay using 3T3 fibroblasts.

The FDA's Assessment:
The FDA agrees with the Applicant's conclusions regarding phototoxicity. In a GLP-compliant phototoxicity study (TX-MRTX849-014), the Applicant evaluated the phototoxic potential of adagrasib by comparing the viability of BALB/c 3T3 murine fibroblast cells in the presence or absence of ultraviolet radiation (5 J/cm2 UVA and 24 or 25 mJ/cm2 UVB). The photoirritancy factor (PIF) was calculated as ~1.93 using the reduced cell viability IC50 value of cells exposed to adagrasib in the absence of UV radiation divided by the IC50 value determined in the presence of UV radiation. As the PIF is <5.000, this supports a conclusion that adagrasib has low phototoxic potential under the conditions of this assay. A mean photo effect (MPE) of 0.04, also supports a conclusion that adagrasib is not phototoxic under the conditions of this assay, as the criterion for a phototoxic agent is a MPE ≥0.15.

Metabolites
The FDA's Assessment:

In vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/number: Non-GLP Bacterial Reverse Mutation Screen/TX-MRTX849-025

Key Study Findings:

- Metabolites M11 and M68 were not mutagenic up to precipitating concentrations in strains TA98 or TA100 in the presence or absence of S9.

GLP compliance: No
Test system: Salmonella typhimurium strains TA98 and TA100; up to 5000 μg/plate; +/- S9
Study is valid: Yes

In vitro Assays in Mammalian Cells

Study title/number: In vitro Micronucleus Screen in TK6 Cells/TX-MRTX849-026

Key Study Findings:

- Results with metabolites M11 or M68 were considered equivocal due to observed increases in percent of micronuclei (%MN) induced up to the limit of cytotoxicity or solubility, without reaching statistical significance.

GLP compliance: No
Test system: TK6 lymphocyte cells; up to 500 μg/mL (~ 1mM); +/- S9
Study is valid: Yes

Treatment	Cytotoxicity (% of control)	% Micronuclei
Without metabolic activation (-S9) – 4 hr incubation		
DMSO, 1%	0	0.43
M11, 3.91 μg/mL	<0	0.52
M11, 7.81 μg/mL	1	0.44
M11, 15.6 μg/mL	10	0.33
M11, 31.3 μg/mL	15	0.35
M11, 62.5 μg/mL†	21	0.40
M68, 3.91 μg/mL	<0	0.46
M68, 7.81 μg/mL	3	0.63
M68, 15.6 μg/mL	21	0.39
Mitomycin-C, 0.0625 μg/ml	14	2.83*
Mitomycin-C, 0.125 μg/ml	27	7.24*
With metabolic activation (+S9) – 4 hr incubation		
DMSO, 1%	0	0.51
M11, 3.91 μg/mL	3	0.56
M11, 7.81 μg/mL	5	0.64
M11, 15.6 μg/mL	20	0.52
M11, 31.3 μg/mL	23	0.54
M11, 62.5 μg/mL	26	0.39
M68, 3.91 μg/mL	<0	0.51
M68, 7.81 μg/mL	4	0.78
M68, 15.6 μg/mL	13	0.58
Cyclophosphamide, 4.7 μg/ml	20	4.88*
Without metabolic activation (-S9) – 27 hr incubation		
DMSO, 1%	0	0.51
M11, 3.91 μg/mL	8	0.35
M11, 7.81 μg/mL	8	0.82
M68, 3.91 μg/mL	4	0.45
M68, 7.81 μg/mL	13	0.64
M68, 15.6 μg/mL	49	1.52
Vinblastine sulfate, 0.0025 μg/ml	29	7.97*
Vinblastine sulfate, 0.003 μg/ml	32	8.45*

* $z' \geq 0.6$

† = precipitate was observed

The genotoxic potential of metabolites M68 and M11 was investigated in screening assays only. While the screening assays with metabolites are not definitive, in an ADME study, we note that metabolite M11 was present following incubation of adagrasib with microsomes and/or hepatocytes from rats and dogs. The ADME study did not include information on metabolite M68. Metabolites M68 and M11 were also present in rat and dog plasma, although M68 was higher in human plasma. Additionally, it appears that metabolites M11 and M68 are structurally

similar to adagrasib, which was not genotoxic in in vitro and in vivo assays. The totality of the data with the active pharmaceutical ingredient and metabolites (genotoxicity, ADME and structure), suggests a low risk of genotoxicity with metabolites.

Studies on Impurities

The FDA's Assessment:

The CMC drug product and substance reviewers requested qualification levels of ten impurities exceeding the ICH Q3A/B qualification threshold (Table 1). The proposed acceptance criteria in the drug substance, specific to each impurity, was ≤ (b) (4)% to ≤ (b) (4)%. The proposed acceptance criteria in the drug product for impurities (b) (4) was (b) (4)%. Impurities were qualified by general toxicology studies and dedicated repeat-dose toxicology studies with impurities conducted in rats or with levels of impurities in clinical batches. The dose of 150 mg/kg in rat (the human equivalent dose of 900 mg/m^2 based on BSA) was selected to qualify impurities because it is the NOAEL in the 28-day and 13-week toxicology studies conducted in rats. Although there were microscopic findings of phospholipidosis in multiple tissues observed in the 28-day study at this dose, the findings were not associated with aberrant clinical signs nor deaths and at least partially resolved upon recovery. As shown in the Table below, impurities (b) (4) were all qualified based on levels investigated in the general toxicology study TX-MRTX849-004 conducted with adagrasib in rats or in humans.

Table 9: Summary of Adagrasib Drug Impurities

Impurity	Acceptance Criteria (%) DS or DP	Levels in Toxicology Batch	Levels in rat based on toxicology batches: (b) (4) mg/kg (900 mg/m^2)	Levels in humans based on acceptance criteria at the human daily dose, (b) (4) mg/m^2	Safety margin[1]
(b) (4)					

Human daily dose: 1200 mg/ 60 kg x (b) (4) Km = (b) (4) mg/m^2

DS = Drug Substance; DP = Drug Product

1, Safety margins are calculated by comparing level in animals (toxicology batch) divided by level in humans based on acceptance criteria level.

Three separate toxicology studies were also conducted to assess the potential toxicity of specific adagrasib impurities following daily administration of (b) (4) for 28 days

via oral gavage. The human equivalent dose of (b) (4) based on a 60 kg body weight. Wistar Han rats received (b) (4) daily oral administration of (b) (4) (TX-MRTX849-022), or (b) (4) (TX-MRTX849-019), or (b) (4) (TX-MRTX849-024) for 28 days, followed by a 2-week recovery. The results of the impurity studies revealed that there were no changes in body weight, food and water consumption, eye toxicity, clinical signs, or necropsy findings, compared to controls following daily exposure to each impurity. As such, all impurities tested in these studies ((b) (4)) were qualified, with safety margins ranging from (b) (4)-fold to (b) (4)-fold compared to the recommended dose.

Impurity MR84926 is an enantiomer of adagrasib. It was not detected in toxicology studies or most clinical batches. In drug substance batches (b) (4), CPo124587-03-06-01-75-01 and CPo124587-02-06-01-75-01, MR84926 was detected at (b) (4)% and (b) (4)%, respectively; however, these values are high because of co-elution with (b) (4). CPo124587-03-06-01-75-01 batch was used for bulk drug product used in clinical studies, suggesting that humans have been exposed to MR84926. The Applicant proposes to (b) (4) for commercial process, and batches manufactured under this process have MR84926 levels at < (b) (4)%. Per the Applicant, MR84926 would result if (b) (4) , the Applicant states that formation of MR84926 is highly unlikely as it would require a (b) (4)

<u>In Silico Genotoxicity Assessment</u>

According to ICH S9 Question and Answer guidance, genotoxicity assessment of impurities should be conducted if the active pharmaceutical ingredient is not genotoxic, and the impurity exceeds the ICH Q3A/B qualification threshold. At the recommended adagrasib daily dose of 1200 mg (600 mg, twice daily), the proposed criteria exceed the qualification thresholds of ICH Q3A and ICH Q3B(R2) for impurities.

The bacterial mutagenic potential of up to 17 impurities, intermediates, and degradants of adagrasib was further assessed in quantitative structure activity relationship [(Q)SAR] studies (TX-MRTX849-008, TX-MRTX849-028). Both *in silico* studies employed complementary rule-base (DEREK and GT_Expert) and statistical-based (Model Applier, TEST, Case Ultra) software programs to identify potential for mutagenic structures.

In silico assessments did not identify structural alerts for genotoxicity for most impurities ((b) (4)) that exceeded the qualification thresholds, but (b) (4) showed mutagenic potential in the rule-based GT_Expert based on (b) (4) moiety. The potential positive result was overruled, as the (b) (4) moiety was negative in DEREK and is also present in several impurities that predicted negative

for genotoxic structural alerts. Moreover, (b) (4) , which demonstrated negative results in the standard genotoxicity battery. Given the totality of the evidence, the impurities present in clinical batches are negative for mutagenic potential.

In conclusion, the acceptance criteria levels are acceptable and there are no safety concerns with levels from a pharmacology/ toxicology perspective.

X	X
Amy M. Skinner, PhD	Claudia P. Miller, PhD
Primary Reviewer	Acting Supervisor

6 Clinical Pharmacology

APPEARS THIS WAY ON ORIGINAL

6.1. Executive Summary

The FDA's Assessment:

Adagrasib is an irreversible inhibitor of KRAS G12C that covalently binds to the mutant cysteine in KRAS G12C. The proposed indication is for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA approved test, who have received at least one prior systemic therapy. The proposed dosage is 600 mg taken orally twice daily (BID) without regard to food.

The evidence of efficacy of adagrasib for the proposed indication is derived from the Applicant's pivotal Study **849-001** (Phase 2 Cohort A). An objective response rate (ORR = CR + PR, BICR-assessed) of 43% (95% CI: 34, 53) was observed in 112 patients in the target population who received adagrasib treatment at the proposed dosage. In the pivotal safety cohort of 116 patients, the safety evaluation showed that adagrasib at the proposed dosage resulted in a Grade ≥3 TEAE rate of 79%, a serious TEAE rate of 57%, a TEAE leading to dose reduction or interruption rate of 82%, and a TEAE leading to discontinuation rate of 13%. The most common adverse reactions (≥ 20% incidence) were diarrhea (70%), nausea (69%), fatigue (59%), vomiting (56%), musculoskeletal pain (41%), hepatotoxicity (37%), renal impairment (36%), dyspnea (35%), edema (32%), decreased appetite (30%), cough (24%), pneumonia (24%), dizziness (23%), constipation (22%), abdominal pain (21%), and QT prolongation (20%).

The clinical pharmacology review focused on the evaluations of the proposed dosage, formulation bridging (capsules to tablets), food effect, drug-drug interactions, and organ impairment. Population PK (PPK), exposure-response (E-R), and physiologically-based PK (PBPK) modeling analyses were also conducted and reviewed.

The proposed dosage of 600 mg BID has demonstrated acceptable efficacy, however it has not been determined whether 600 mg BID represents an optimal dose from PK, safety, and efficacy perspectives as there was limited evaluation of adagrasib at dose levels other than 600 mg BID. Adagrasib shows a high toxicity profile, with 79% of patients experiencing Grade 3 or greater TEAEs, 57% of patients experiencing serious TEAEs, and 82% of patients experiencing TEAEs leading to dose reduction or interrupton. There were also high incidences of gastrointestinal (GI) adverse reactions including 70% diarrhea. A dose optimization PMR will therefore be issued for the Applicant to evaluate an alternative adagrasib dosage that may provide similar efficacy with improved safety as compared to the 600 mg BID dosage.

Recommendations

The Office of Clinical Pharmacology has reviewed the information and data contained in NDA 216340. This NDA is approvable from a Clinical Pharmacology perspective, with the PMRs listed in the PMR/PMC section (below).

The key review issues with specific recommendations / comments are summarized below:

REVIEW ISSUE	RECOMMENDATIONS / COMMENTS
Pivotal or supportive evidence of effectiveness	See Executive Summary (above).
General dosing instructions	600 mg BID without regard to food.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The following dosing recommendations should be followed: ▪ **Strong CYP3A4 inducers:** avoid use ▪ **Strong CYP3A4 inhibitors:** avoid use until adagrasib concentrations have reached steady-state ▪ **Sensitive CYP3A4 substrates:** avoid use ▪ **Sensitive CYP2C9 substrates:** avoid use where minimal concentration changes may lead to serious adverse reactions ▪ **Sensitive 2D6 substrates:** avoid use where minimal concentration changes may lead to serious adverse reactions ▪ **P-gp substrates:** avoid use where minimal concentrations may lead to serious adverse reactions ▪ **QT/QTc prolonging drugs:** avoid use
Labeling	Overall, the proposed labeling recommendations are acceptable upon Applicant's agreement to FDA's revisions.
Bridge between the clinical trial and to-be-marketed formulations	Applicant's clinical development, including their pivotal Study **849-001**, used a capsule formulation. The to-be-marketed formulation has since been evaluated in Applicant's currently ongoing confirmatory Study **849-012**, which showed comparable systemic exposures in patients who received 600 mg BID tablets (n=40) vs. those who received 600 mg BID capsules (n=139).

Post-Marketing Requirement (PMR) or Commitment (PMC)

The following issues should be addressed as PMRs. See Section 13 of the Assessment Aid:

1. Dose optimization study to evaluate an alternative adagrasib dosage that may provide comparable efficacy with improved safety (especially GI tolerability) as compared to the 600 mg BID dosage.
2. Effect of a strong CYP2C8 inhibitor on the steady-state PK of adagrasib.
3. Effect of a BCRP inhibitor on the single-dose PK of adagrasib.
4. Effect of adagrasib on the PK of a CYP2B6 substrate.
5. Effect of adagrasib on the PK of a MATE-1/-2K substrate.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

Presented data are based on the adagrasib capsules (unless otherwise stated).

Clinical pharmacokinetics: Adagrasib exposure increased more than proportionally with single oral doses from 150 mg to 600 mg in patients and healthy subjects (Studies 849-001, 849-006). Following repeat dosing of 600 twice daily in patients, adagrasib steady-state was reached within 8 days of dosing and adagrasib accumulated approximately 6-fold relative to a single dose. Daily fluctuations in adagrasib plasma concentrations are low, with a mean peak-to-trough ratio (PTR) at steady state of 1.07.

Absorption: Following oral administration, the median time to maximum plasma concentration (t_{max}) of adagrasib was approximately 6 to 8 hours (Studies 849-001, 849-006, 849-011, 849-015). Food (high-fat, high-calorie) intake had no clinically meaningful effect on the exposure of the tablet formulation (Module 2.7.1).

Distribution: Adagrasib is highly bound to human plasma proteins with estimated percentage bound of approximately 98-99%. The blood-to-plasma ratio is approximately 0.877 (Study 849-005). The geometric mean apparent volume of distribution (Vz/F) is 942 L (Study 849-006), suggesting extensive tissue distribution.

Elimination: The arithmetic mean terminal elimination half-life ($t_{1/2}$) in patients is 23 hours (Study 849-001). The geometric mean apparent oral clearance (CL/F) is 36.5 L/h (849-006).

Metabolism: Adagrasib is extensively metabolized in humans and does not form any major active metabolites. CYP3A4 mediates the majority of oxidative metabolism, with the estimated fraction of drug metabolized between 72% and 83%.

Excretion: Following a single oral dose of [^{14}C]-adagrasib in healthy subjects (Study 849-005), the mean cumulative recovery of total radioactivity was approximately 79.2%. Fecal excretion was the predominant route of elimination, accounting for 74.7% of the administered [^{14}C]-adagrasib, with urine accounting for 4.5%. Only 1.8% of the administered dose was excreted in urine as unchanged adagrasib, indicating negligible renal clearance (CL_R) for adagrasib.

The Applicant's Position:
Adagrasib PK properties have been adequately characterized in patients and healthy subjects. The recommended dosing regimen of 600 mg twice daily resulted in a low PTR at steady state.

The FDA's Assessment:

FDA generally agrees with the Applicant's position, with the following clarifications:

- **Dose proportionality:** Based on updated patient data from Study **849-001** (evaluating a lower dose cohort of 400 mg BID monotherapy), adagrasib exposures appear to increase dose-proportionally from 400 to 600 mg BID.
- **Metabolism:** Adagrasib is primarily metabolized by CYP3A4 following single-dose administration. However, adagrasib inhibits its own CYP3A4 metabolism (autoinhibitor of CYP3A4) following multiple-dosing which permits other CYP enzymes (CYP2C8, CYP1A2, CYP2B6, CYP2C9, CYP2D6) to contribute to adagrasib metabolism at steady-state.
- **Excretion:** Based on mass balance Study **849-005**, 75% of [^{14}C]-adagrasib radioactivity was recovered in the feces (14% as unchanged) while 4.5% was recovered in the urine (1.8% as unchanged).

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

The 600 mg twice daily dose level was selected as the proposed dose for the intended patient population based on the totality of evidence available for adagrasib efficacy and safety data and supporting clinical pharmacology data.

The Phase 2 starting dose was established in the Phase 1/1b segment of Study 849-001 using the accelerated titration (AT) and the modified toxicity probability interval (mTPI) designs. Among 18 patients treated at 600 mg twice daily and evaluable for dose limiting toxicity (DLT), a DLT was observed in 3 patients for a probability of DLT estimated at 17%, and this dose level was selected as the starting dose for the Phase 2 cohorts.

As summarized in Module 2.7.3 and Module 2.7.4, the efficacy and safety results from Study 849-001 Phase 2 Cohort A support the selection of 600 mg twice daily as an effective and safe dose in this patient population. From a clinical efficacy perspective, the 600 mg twice daily dose level resulted in durable clinical benefit with an ORR per BICR of 42.9% (95% CI: 33.5%, 52.6%), median duration of response 7.3 months (95% CI: 5.1, not estimated [NE]), median PFS 6.5 months (95% CI: 4.7, 8.2), and median OS of 11.3 months (95% CI: 8.7, NE) in patients with advanced NSCLC with *KRAS* G12C mutation who have previously received treatment with a platinum-based regimen and CIT. The 600 mg twice daily dose level had an acceptable risk/benefit profile.

From a clinical pharmacology perspective, exposure-response (E-R) analyses were performed for efficacy endpoints (i.e., ORR, OS, and PFS) and safety endpoints (i.e., any treatment emergent adverse events [TEAEs] with Grade ≥ 3, diarrhea, nausea, vomiting, increase in alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lipase, and

hyponatremia) (Module 2.7.2). Overall, no E-R relationships were observed between adagrasib plasma exposure and efficacy or safety endpoints in NSCLC patients with *KRAS* G12C mutation. The absence of E-R relationship between adagrasib plasma exposure and efficacy/safety endpoints may be due to 1 or more of the following reasons: 1) in the E-R analyses ~95% (for safety) and 100% (for efficacy) of patients started treatment at the planned 600 mg twice daily regimen; 2) the 600 mg twice daily regimen may have already represented a plateau of the dose-response relationship; and 3) the 600 mg twice daily regimen achieved steady-state average plasma concentration ($C_{ave,ss}$) in patients (2100 ng/mL) above the target efficacious C_{ave} derived from the least sensitive preclinical xenograft model (1544 ng/mL) and therefore it is expected to provide optimal pharmacological exposure.

The Applicant's Position:
The proposed dose of 600 mg twice daily is effective with a manageable safety profile in patients with locally advanced or metastatic NSCLC with *KRAS G12C* mutation. The proposed dosing regimen is supported by the observed efficacy and safety data and demonstrates a favorable benefit-risk profile.

The FDA's Assessment:
FDA generally agrees with the Applicant's position that the proposed dosage of 600 mg BID demonstrated acceptable efficacy, however it has not been determined whether 600 mg BID represents an optimal dose from PK, safety, and efficacy perspectives as there was limited evaluation of adagrasib at dose levels other than 600 mg BID. At the proposed dosage, Adagrasib shows a high rate of toxicity. The summary of treatment emergent adverse events (TEAEs) in the safety population from trial 849-001 (Cohort A, N=116) at the proposed dosage indicates that 79% of patients experienced Grade 3 or greater TEAEs, 82% of patients experienced TEAEs leading to dose reduction or interruption, and 13% of patients experienced TEAEs leading to dose discontinuation. The most common adverse reactions occurring in ≥ 20% of patients were diarrhea (70%), nausea (69%), fatigue (59%), vomiting (56%), musculoskeletal pain (41%), hepatotoxicity (37%), renal impairment (36%), dyspnea (35%), edema (32%), decreased appetite (30%), cough (24%), pneumonia (24%), dizziness (23%), constipation (22%), abdominal pain (21%), and QT prolongation (20%). A dose optimization PMR will therefore be issued for the Applicant to evaluate an alternative adagrasib dosage that may provide similar efficacy with improved safety as compared to the 600 mg BID dosage. In addition, the dose optimization PMR will also determine if the incidence of GI-related AEs, which were also the common AEs leading to dose modifications, may be alleviated if adagrasib is administered with food.

6.2.2.2. Therapeutic Individualization

Data:

Following a single oral dose of adagrasib 600 mg in healthy and non-cancer subjects, no clinically meaningful difference in adagrasib exposure was observed between subjects with normal renal function (creatinine clearance [CL_{CR}] ≥ 90 mL/min) and subjects with mild (CL_{CR} 60 to < 90 mL/min), moderate (CL_{CR} 30 to < 60 mL/min), or severe (CL_{CR} < 30 mL/min) renal impairment (Study 849-004).

The influence of demographic and clinical characteristic factors on the PK of adagrasib were investigated using population PK (Module 2.7.2). No clinically meaningful differences in the PK of adagrasib were observed based on age (19 to 89 years), sex, race (White, Black and Asian), body weight (36 to 139 kg), Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) (0, 1), baseline tumor burden, mild and moderate renal impairment (CL_{CR} or estimated glomerular filtration rate [eGFR] ≥30 mL/min), or mild hepatic impairment (National Cancer Institute-Organ Dysfunction Working Group [NCI-ODWG] criteria).

A high-fat and high-calorie meal increased adagrasib C_{max} and AUC using the planned tablet commercial formulation by approximately 20% and 38%, respectively, compared to fasted conditions following a single 600 mg oral dose of adagrasib in healthy subjects (Study 849-011). The increase in exposure to adagrasib in the fed state is not considered clinically significant (Module 2.7.1).

Results from the clinical DDI Study 849-006, physiologically-based PK (PBPK) modeling, and population PK analysis (Module 2.7.2) show the following:

- Co-administration of multiple doses of pantoprazole, a proton-pump inhibitor, with a single 600 mg dose of adagrasib decreased adagrasib C_{max} and AUC by approximately 38% and 32%, respectively, in healthy subjects (Study 849-006). Population PK analysis showed that H_2 receptor antagonists and antacids (with staggered dosing) were not the covariates, suggesting that these agents did not have a significant effect on adagrasib PK (Module 2.7.2).

- Co-administration of multiple doses of itraconazole 200 mg QD (a strong cytochrome P450 (CYP) 3A4 inhibitor) with a single 200 mg dose of adagrasib increased adagrasib C_{max} and AUC by approximately 2.4-fold and 4-fold, respectively in healthy subjects (Study 849-006). However, co-administration of multiple doses of itraconazole 200 mg once daily with multiple doses of adagrasib (600 mg twice daily) in patients is predicted to have a negligible effect on adagrasib steady-state exposure (Module 2.7.2). The lack of itraconazole effect on adagrasib steady-state exposure is due to the extent of auto-inhibition by adagrasib at 600 mg twice daily steady state, thus the majority of CYP3A4-mediated intrinsic clearance (CL_{int}) is already inhibited by adagrasib (Module 2.7.2).

- Co-administration of multiple doses of rifampin 600 mg QD (a strong CYP3A4 inducer) with a single 600 mg dose of adagrasib decreased adagrasib C_{max} by 88% and AUC by

95% in healthy subjects (849-006). Co-administration of multiple doses of rifampin (600 mg QD) with multiple doses of adagrasib (600 mg twice daily) in patients is predicted to decreased adagrasib C_{max} by 61% and AUC by 66%. A moderate CYP3A4 inducer (efavirenz 600 mg QD) is predicted to decrease adagrasib (600 mg twice daily) steady-state C_{max} and AUC by 23% and 25%, respectively, in patients.

The Applicant's Position:

- Adagrasib tablet formulation can be administered with or without food.
- (b) (4)
- No dose adjustment of adagrasib is needed when adagrasib is co-administered with CYP3A4/P-glycoprotein (P-gp) inhibitors.
- Co-administration of adagrasib with strong CYP3A4 inducers should be avoided.
- No dosage adjustments for adagrasib are warranted based on age, sex, race, body weight, disease status at screening, mild, moderate, and severe renal impairment, or mild hepatic impairment.

The FDA's Assessment:

FDA generally agrees with the Applicant's position, with the following clarifications:

- **Proton pump inhibitors (PPIs):** No restrictions are needed. This is based on updated data from Study **849-001** that is evaluating a lower dose cohort of 400 mg BID monotherapy in patients with NSCLC. Initial efficacy has been observed in patients who received 400 mg BID (preliminary ORR rate = 67% (4/6, all PRs); confirmed ORR = 50% (2/4, all PRs)), which indicate that lower exposures following 400 mg BID did not appear to compromise the efficacy of adagrasib. The observed decreased exposures of 32-38% following adagrasib administration with concomitant PPIs are similar to the decreased exposures following 400 mg BID compared to 600 mg BID.
- **Antacids / H2 receptor antagonists:** No restrictions are needed, which follows no restrictions needed for PPIs.
- **Strong CYP3A4 inhibitors:** Avoid use until adagrasib concentrations have reached steady-state. This is due to observed 2.4 to 4.0-fold increases in adagrasib 600 mg single-dose exposures following co-administration of multiple doses of itraconazole (a strong CYP3A4 inhibitor). As noted by the Applicant above, co-administration of adagrasib 600 mg BID with multiple doses of itraconazole is not predicted to have a clinically meaningful effect on adagrasib steady-state exposures.

- **P-gp substrates:** Avoid use where minimal concentrations may lead to serious adverse reactions. This is based on predicted 50 to 90% increases in digoxin (a P-gp substrate) exposures following co-administration with adagrasib 600 mg BID.
- **Sensitive CYP3A4 substrates:** Avoid use (b) (4) due to very potent CYP3A4 inhibition effect of adagrasib on midazolam exposures (a sensitive CYP3A4 substrate).
- **Sensitive CYP2D6 and CYP2C9 substrates:** Agree with avoiding use with substrates where minimal concentration changes may lead to serious adverse reactions.

Refer to the PBPK modeling review for details regarding DDI predictions.

Refer to the Pharmacometrics review for details regarding population PK analysis.

6.2.2.3. Outstanding Issues

Data:

None.

The Applicant's Position:
There are no outstanding clinical pharmacology issues.

The FDA's Assessment:
Five PMRs will be issued, as presented in the PMR/PMC Section (above). There are no other outstanding issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

Pharmacokinetics

Based on comprehensive clinical pharmacology evaluations in healthy subjects and in patients with *KRAS* G12C-mutated solid tumors, including NSCLC, adagrasib capsules (unless stated otherwise) can be described with the following characteristics:

- Adagrasib exposure increased more than proportionally with single oral doses from 150 mg to 600 mg (Study 849-001 Phase 1/1b, 849-006).

- Following repeat dosing of 600 mg twice daily in patients, adagrasib steady-state was reached within 8 days of dosing and adagrasib accumulated approximately 6-fold

relative to a single dose. Daily fluctuations in adagrasib plasma concentrations are low, with a mean PTR at steady state of 1.07 (Study 849-001 Phase 1/1b).

- Adagrasib exhibits moderate between-subject PK variability. The between-subject variability in healthy subjects were estimated at 29% to 58% for AUC and C_{max} (Studies 849-006, 849-011, 849-015). The between-subject variability in patients were estimated at approximately 51% to 52% for $AUC_{tau,ss}$ and $C_{max,ss}$ for 600 mg twice daily (Module 2.7.2).

Absorption

Following oral administration, the median t_{max} of adagrasib was approximately 6 to 8 hours.

Food (high-fat, high-calorie meal) intake increased adagrasib tablet C_{max} and AUC by approximately 20% and 38%, respectively, compared to fasting conditions (Study 849-011). The effect of food on the systemic exposure of adagrasib tablet is not considered clinically meaningful in consideration of the relative bioavailability of the tablet formulation (the tablet formulation under fed conditions is expected to result in a similar C_{max} and 22% higher AUC compared to the capsule formulation under fasted conditions), and a lower between-subject variability in adagrasib tablet exposure under fed conditions (~24% to 30%) compared to fasted conditions (~45% to 57%), indicating that food did not increase PK variability of the tablet formulation.

Distribution

- Adagrasib is highly bound to human plasma proteins with estimated percentage bound of approximately 98% to 99% (PK-MRTX849-016, Study 849-004).

- The geometric mean Vz/F is 942 L (Study 849-006), suggesting extensive tissue distribution.

- There is 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 [^{14}C]-MRTX849, the geometric mean whole blood/plasma AUC_{∞} ratio for total radioactivity was approximately 0.877 (Study 849-005).

Elimination

- The arithmetic mean $t_{1/2}$ in patients is 23 hours (Study 849-001, Phase 1/1b). The geometric mean CL/F is 36.5 L/h (Study 849-006).

- Metabolism: Adagrasib is extensively metabolized in humans and does not form any major active metabolite. CYP3A4 mediates the majority of oxidative metabolism based

on nonclinical studies using human biomaterials, with the calculated fraction metabolized of 72%; however, other CYP enzymes such as CYP2C8, CYP2D6, CYP2J2, and CYP3A5 have been shown to form human oxidative metabolites. Following a single dose administration of [^{14}C]-adagrasib in healthy subjects, adagrasib (parent), M55a, M11, and M68 were major plasma components which accounted for 38.33%, 13.58%, 13.40%, and 10.96% of total plasma radioactivity exposure, respectively (Study 849-005). However, M55a was not detected in human plasma at steady state after multiple dosing of 600 mg twice daily in patients (PK-MRTX849-039). Both M68 and M11 are not human specific metabolites (i.e., were formed in nonclinical regulatory toxicology species) and do not contribute significantly to the pharmacological activity of adagrasib.

- Excretion: Following a single dose administration of [^{14}C]-adagrasib in healthy subjects, the mean cumulative recovery of total radioactivity over the collection period (0 to 504 hours) was approximately 79.2%. Fecal excretion was the predominant route of elimination, accounting for 74.7% of the administered [^{14}C]-MRTX849, with urine accounting for 4.5%. Only 1.8% of the administered dose was excreted in urine as unchanged adagrasib, indicating negligible renal clearance for adagrasib (Study 849-005).

Specific Populations

Renal impairment:

Following a single oral dose of adagrasib 600 mg in healthy and non-cancer subjects, no clinically meaningful difference in adagrasib exposure was observed between subjects with normal renal function (CL_{CR} ≥ 90 mL/min) and subjects with mild (CL_{CR} 60 to < 90 mL/min), moderate (CL_{CR} 30 to < 60 mL/min), or severe (CL_{CR} < 30 mL/min) renal impairment (Study 849-004).

Population PK analysis also showed that mild and moderate renal impairment (CL_{CR} or eGFR ≥30 mL/min) had no effect on adagrasib PK in patients. There were no data on patients with severe renal impairment to be included in population PK analysis (Module 2.7.2).

Hepatic impairment:

Population PK analysis showed that mild hepatic impairment had no effect on adagrasib PK in patients. There are no or limited data for patients with moderate and severe hepatic impairment to be included in the population PK analysis (Module 2.7.2).

Pediatrics:

No investigations have been conducted with adagrasib in pediatric populations. As the drug is intended for use in NSCLC, adagrasib is not indicated for use in children.

Elderly:

Population PK analysis showed no clinically meaningful differences in the PK of adagrasib based on age (19 to 89 years). Approximately half of the subjects who received adagrasib at the recommended dose of 600 mg twice daily were aged 65 years and older. No overall differences were observed in the safety or efficacy of adagrasib between elderly and non-elderly subjects. No dosage adjustments of adagrasib are recommended for elderly patients.

Gender:

Population PK analysis showed no clinically meaningful differences in the PK of adagrasib based on gender. Approximately 43% of the subjects who received adagrasib at the recommended dose of 600 mg twice daily were male. No overall differences were observed in the safety or efficacy of adagrasib between male and female subjects. No dosage adjustments of adagrasib are recommended based on the gender of the patient.

Drug-Drug Interactions

Results from the clinical DDI Study 849-006 and PBPK modeling are summarized in Applicant Table 9 and Applicant Table 10. Additionally, population PK analysis showed that H_2 receptor antagonists and antacids (with staggered dosing) were not the covariates, suggesting that these agents did not have any effect on adagrasib PK.

Applicant Table 10: Effects of Other Drugs on The Single-Dose and Steady-State Exposure of Adagrasib

Perpetrators	Adagrasib dose	N	Source	Effect on Adagrasib	
				C_{max}	AUC_∞ or AUC_t
Acid-reducing agents					
Pantoprazole 40 mg QD – proton-pump inhibitor	600 mg single dose	11	Observed	38% reduction	32% reduction
CYP3A4 inhibitors					
Itraconazole 200 mg QD – Strong CYP3A4 inhibitor	200 mg single dose	14	Observed	2.43-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

Perpetrators	Adagrasib dose	N	Source	Effect on Adagrasib	
				C_{max}	AUC_{∞} or AUC_t
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
CYP3A4 inducers					
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

Abbreviations: BID = twice daily; CYP = cytochrome P450; PBPK = physiologically-based pharmacokinetic; QD = once daily; TID = three times daily
Source: Observed (Study 849-006 Clinical Study Report [CSR]); PBPK modeling (Module 2.7.2)

Applicant Table 11: Effect of Adagrasib on Exposure of The Oral Probe Substrates of CYPs and Drug Transporters

Oral probe substrate	Adagrasib 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

Oral probe substrate	Adagrasib Dose	N	Source	Effect on oral probe substrate	
				C_{max}	AUC_{last} or AUC_{∞}
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	(b) (4)	
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	(b) (4)	

Abbreviations: BCRP = breast cancer resistance protein; BID = twice daily; CYP = cytochrome P450; PBPK = physiologically-based pharmacokinetic; MATE = multi-antimicrobial extrusion protein; P-gp = P-glycoprotein
Source: Observed (Study 849-006 CSR); PBPK modeling (Module 2.7.2)

Pharmacodynamics

Biomarkers: The time course of PD or biomarker response and PK/PD relationship are not known.

Cardiac Electrophysiology: Based on the concentration-corrected QT interval (C-QTc) linear mixed effect model, the predicted mean (90% CI) population-corrected QT (QTcP) change from baseline (ΔQTcP) and corrected QT interval Fridericia (QTcF) change from baseline (ΔQTcF) were 18.8 (16.4, 21.1) msec and 17.93 (15.13, 20.73) msec, respectively, at the population geometric mean $C_{max,ss}$ in patients after administration of adagrasib 600 mg twice daily (Module 2.7.2).

Exposure-Response

Exposure-response analyses were performed to explore the relationship between plasma exposure of adagrasib and efficacy and safety in patients with *KRAS* G12C-mutated solid tumors in Study 849-001 (Phase 1/1b and Phase 2 Cohort A). In 118 patients with NSCLC with *KRAS* G12C mutation included in exposure-efficacy analysis who started treatment at the planned 600 mg twice daily regimen, no relationship between adagrasib exposure and efficacy endpoints (i.e., ORR, OS, and PFS) was observed. In 132 patients included in the exposure-safety analysis with 127 (96.2%) patients who started treatment at the planned 600 mg twice daily regimen and 125 (94.7%) patients with NSCLC, no relationship between adagrasib exposure and safety endpoints (i.e., any TEAEs with Grade ≥ 3, diarrhea, nausea, vomiting, increase in AST, ALT and lipase, and hyponatremia) was observed (Module 2.7.2).

The Applicant's Position:

The comprehensive clinical pharmacology evaluations in healthy subjects and in patients with *KRAS* G12C-mutated solid tumors, including NSCLC, support the proposed therapeutic dose of 600 mg twice daily. Adagrasib tablet formulation can be administered with or without food. No dosing adjustments are necessary based on sex, body weight, race, or age, and no dosing adjustments are necessary for mild, moderate, and severe renal impairment or mild hepatic impairment.

The FDA's Assessment:

FDA generally agrees with the Applicant's position, with the following clarifications:

- **Proton pump inhibitors (PPIs):** No restrictions are needed. This is based on updated data from Study **849-001** that is evaluating a lower dose cohort of 400 mg BID monotherapy in patients with NSCLC. Initial efficacy has been observed in patients who received 400 mg BID (preliminary ORR rate = 67% (4/6, all PRs); confirmed ORR = 50% (2/4, all PRs)), which indicate that lower exposures following 400 mg BID did not appear to compromise the efficacy of adagrasib. The observed decreased exposures of 32-38% following adagrasib administration with concomitant PPIs are similar to the decreased exposures following 400 mg BID compared to 600 mg BID.
- **Antacids / H2 receptor antagonists:** No restrictions are needed, which follows no restrictions needed for PPIs.
- **Strong CYP3A4 inhibitors:** Avoid use until adagrasib concentrations have reached steady-state. This is due to observed 2.4 to 4.0-fold increases in adagrasib 600 mg single-dose

exposures following co-administration of multiple doses of itraconazole (a strong CYP3A4 inhibitor). As noted by the Applicant above, co-administration of adagrasib 600 mg BID with multiple doses of itraconazole is not predicted to have a clinically meaningful effect on adagrasib steady-state exposures.

- **P-gp substrates:** Avoid use where minimal concentrations may lead to serious adverse reactions. This is based on predicted 50 to 90% increases in digoxin (a P-gp substrate) exposures following co-administration with adagrasib 600 mg BID.
- **Sensitive CYP3A4 substrates:** Avoid use (b) (4) due to very potent CYP3A4 inhibition effect of adagrasib on midazolam exposures (a sensitive CYP3A4 substrate).
- **Sensitive CYP2D6 and CYP2C9 substrates:** Agree with avoid use with substrates where minimal concentration changes may lead to serious adverse reactions.
- **QT/QTc prolonging drugs:** Avoid use, due to known clinical QT/QTc prolongation risk of adagrasib.
- **Hepatic impairment (HI):** Based on Applicant's updated PBPK modeling analyses to evaluate the effect of hepatic impairment on the steady-state exposures of adagrasib, no dose adjustment is needed in patients with HI (mild, moderate, or severe HI). Refer to FDA's PBPK modeling review for details.
- **Renal impairment (RI):** Since adagrasib is minimally excreted in the urine (< 5%) and based on negative findings of the predicted effect of severe HI on the steady-state exposures of adagrasib, no dose adjustment is needed in patients with RI (mild, moderate, or severe RI).

Refer to the PBPK modeling review for details regarding DDI and HI predictions.

Refer to the Pharmacometrics review for details regarding population PK and exposure-response analyses.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

E-R analyses were performed for efficacy endpoints (i.e., ORR, OS, and PFS). Overall, no E-R relationships were observed between adagrasib plasma exposure and efficacy endpoints in NSCLC patients with *KRAS* G12C mutation. The absence of E-R relationship between adagrasib plasma exposure and efficacy endpoints may be due to 1 or more of the following reasons: 1) 100% of patients started treatment at the planned 600 mg twice daily regimen; 2) the 600 mg twice daily regimen may have already represented a plateau of the dose-response relationship; and 3) the 600 mg twice daily regimen achieved $C_{ave,ss}$ in patients (2100 ng/mL) above the target efficacious C_{ave} derived from the least sensitive preclinical xenograft model (1544 ng/mL) and therefore it is expected to provide optimal pharmacological exposure.rosuvastatin

The Applicant's Position:
The observed primary outcome (ORR of 42.9%) for adagrasib treatment at 600 mg twice daily represents a clinically meaningful benefit when considering the intended patient population with life-threatening disease and limited available therapies.

The FDA's Assessment:
FDA generally agrees with the Applicant's position that the proposed dosage of 600 mg BID has demonstrated acceptable efficacy, however it has not been determined whether 600 mg BID represents an optimal dose from PK, safety, and efficacy perspectives as there was limited evaluation of adagrasib at dose levels other than 600 mg BID. Meaningful inference of the E-R relationships for both efficacy and safety cannot be made for adagrasib at dose levels other than 600 mg BID due to the narrow PK exposures mainly from 600 mg BID. A dose optimization PMR will therefore be issued for the Applicant to evaluate an alternative adagrasib dosage that may provide similar efficacy with improved safety as compared to the 600 mg BID dosage.

Refer to the Pharmacometrics review for details regarding exposure-response analyses.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

See Section 6.2.2.1, General Dosing.

The Applicant's Position:

The proposed dose of adagrasib 600 mg twice daily is effective and with a manageable safety profile in subjects with *KRAS* G12C-mutated locally advanced or metastatic NSCLC. The proposed dosing regimen is supported by the available efficacy and safety data and demonstrates a favorable benefit-risk profile. Exposure-safety analyses showed no relationship between adagrasib exposure and safety endpoints (i.e., any TEAEs with Grade ≥ 3, diarrhea, nausea, vomiting, increase in AST, ALT and lipase, and hyponatremia).

The FDA's Assessment:

FDA generally agrees with the Applicant's position that the proposed dosage of 600 mg BID has demonstrated acceptable efficacy, however it has not been determined whether 600 mg BID represents an optimal dose from PK, safety, and efficacy perspectives as there was limited evaluation of adagrasib at dose levels other than 600 mg BID. Meaningful inference of the E-R relationships for both efficacy and safety cannot be made for adagrasib at dose levels other than 600 mg BID due to the narrow PK exposures mainly from 600 mg BID. A dose optimization PMR will therefore be issued for the Applicant to evaluate an alternative adagrasib dosage that may provide similar efficacy with improved safety as compared to the 600 mg BID dosage.

Refer to the Pharmacometrics review for details regarding exposure-response analyses.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Data:

See Section 6.2.2.2, Therapeutic Individualization.

The Applicant's Position:

Intrinsic covariates of age, body weight, sex, race, ECOG PS (0, 1), tumor burden, mild, moderate and severe renal impairment, and mild hepatic impairment did not show clinically meaningful effects on adagrasib PK, suggesting no dose adjustments are required for these intrinsic factors.

The FDA's Assessment:

FDA agrees with the Applicant's position that no dose adjustments are needed in patients for the intrinsic factors described above.

Refer to the Pharmacometrics review for details regarding population PK analyses.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:

See Section 6.2.2.2, Therapeutic Individualization and Section 6.3.1, General Pharmacology and Pharmacokinetic Characteristics.

The Applicant's Position:

- Adagrasib tablet formulation can be administered with or without food**.**
- (b) (4)
- No dose adjustment of adagrasib is needed when adagrasib is co-administered with CYP3A4 inhibitors**.**
- Co-administration of adagrasib with strong CYP3A inducers should be avoided.
- (b) (4)
- Adagrasib is a moderate inhibitor of CYP2C9 and CYP2D6. Patients are advised to avoid co-administration of adagrasib with substrates of CYP2C9 or CYP2D6 with a narrow therapeutic index. If alternative treatments cannot be used, consider a dose reduction of the concomitant CYP2C9 or CYP2D6 substrate drug.
- Adagrasib is a weak inhibitor of CYP2B6, P-gp, and breast cancer resistance protein (BCRP). No dose adjustments for CYP2B6, P-gp, or BCRP substrates are needed during co-administration with adagrasib.
- Adagrasib has no effect on multi-antimicrobial extrusion protein (MATE). No dosage adjustments for MATE substrates are needed during co-administration with adagrasib.

The FDA's Assessment:

FDA generally agrees with the Applicant's position, with the following clarifications:

- **Proton pump inhibitors (PPIs):** No restrictions are needed. This is based on updated data from Study **849-001** that is evaluating a lower dose cohort of 400 mg BID monotherapy in patients with NSCLC. Initial efficacy has been observed in patients who received 400 mg BID (preliminary ORR rate = 67% (4/6, all PRs); confirmed ORR = 50% (2/4, all PRs)), which indicate that lower exposures following 400 mg BID did not appear to compromise the efficacy of adagrasib. The observed decreased exposures of 32-38% following adagrasib administration with concomitant PPIs are similar to the decreased exposures following 400 mg BID compared to 600 mg BID.
- **Antacids / H2 receptor antagonists:** No restrictions are needed, which follows no restrictions needed for PPIs.
- **Strong CYP3A4 inhibitors:** Avoid use until adagrasib concentrations have reached steady-state. This is due to observed 2.4 to 4.0-fold increases in adagrasib 600 mg single-dose exposures following co-administration of multiple doses of itraconazole (a strong CYP3A4 inhibitor). As noted by the Applicant above, co-administration of adagrasib 600 mg BID with multiple doses of itraconazole is not predicted to have a clinically meaningful effect on adagrasib steady-state exposures.
- **P-gp substrates:** Avoid use where minimal concentrations may lead to serious adverse reactions. This is based on predicted 50 to 90% increases in digoxin (a P-gp substrate) exposures following co-administration with adagrasib 600 mg BID.
- **Sensitive CYP3A4 substrates:** Avoid use (b) (4) due to very potent CYP3A4 inhibition effect of adagrasib on midazolam exposures (a sensitive CYP3A4 substrate).
- **Sensitive CYP2D6 and CYP2C9 substrates:** Agree with avoiding use with substrates where minimal concentration changes may lead to serious adverse reactions.
- **QT/QTc prolonging drugs:** Avoid use, due to known clinical QT/QTc prolongation risk of adagrasib.

Refer to the PBPK modeling review for details regarding DDI predictions.

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Vicky Hsu
Primary Reviewer

Jeanne Fourie Zirkelbach
Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Applicant Table 12: Listing of Clinical Trials Relevant to this NDA

Trial Identity/ NCT No./ No. of Centers and Countries	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients/Subjects Treated	Study Population
Studies to Support Efficacy and Safety						
849-001 NCT No. 03785249	Phase 1/2 Dose-escalation and multiple expansion cohort study Single arm	All segments, adagrasib by oral administration	Safety, tolerability, PK, clinical activity/ efficacy	All segments, until disease progression or discontinuation Survival follow-up	NA	All segments, patients with advanced solid tumors with *KRAS* G12C mutation
Phase 1/1b Segment 9 centers in US	Phase 1 Dose-escalation and expansion FIH study	Adagrasib escalating doses Once and twice daily	Safety, tolerability, PK, MTD/RP2D, clinical activity		25	Patients with advanced solid tumors with *KRAS* G12C mutation
Phase 2 Cohort A 29 centers in US	Phase 2 Dose-expansion study	Adagrasib 600 mg twice daily	Efficacy, safety, tolerability, PK		116	Patients NSCLC with *KRAS* G12C mutation in tumor tissue, prior treatment with at least a platinum-containing regimen and checkpoint inhibitor therapy
Phase 2 Cohorts B, C, and D 42 centers in US	Phase 2 Dose-expansion studies	Adagrasib 600 mg twice daily	Clinical activity, safety, tolerability, PK		124	Patients with solid tumor with *KRAS* G12C mutation, NSCLC for Cohort B, colorectal carcinoma for Cohort C, other solid tumors for Cohort D

Trial Identity/ NCT No./ No. of Centers and Countries	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients/Subjects Treated	Study Population
Bioavailability Studies (Module 5.3.1.1)						
849-011 NCT No. NA 1 center in US	Phase 1, Open-label, Randomized, Crossover, Relative Bioavailability and Food Effect Study	Single oral doses of 600 mg capsule and tablet formulations under fasted conditions and tablet formulation under fed conditions	PK, safety, and tolerability	2 separate days/11 to 13 days after last dose	82	Healthy male and female subjects, between 18 and 60 years of age, inclusive
Comparative Bioavailability and Bioequivalence Studies (Module 5.3.1.2)						
849-015 NCT No. NA 1 center in US	Phase 1, Open-Label, Randomized, 2-Sequence, 4-Period, Fully-replicate, Crossover Bioequivalent Study	Single oral doses of 600 mg capsule and tablet formulations under fasted conditions	PK, safety, and tolerability	4 separate days/12 days after last dose	73	Healthy male and female subjects, between 18 and 60 years of age, inclusive
Healthy Subject PK and Initial Tolerability Study Reports (Module 5.3.3.1)						
849-005 NCT No. NA 1 center in US	Phase 1, Open-label, Mass Balance Study	Single oral dose of 600 mg adagrasib containing 1 µCi of [^{14}C]-adagrasib	Absorption, metabolism, and excretion, PK, safety, and tolerability	1 day/22 days	7	Healthy male subjects, between 30 and 65 years of age, inclusive

Trial Identity/ NCT No./ No. of Centers and Countries	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients/Subjects Treated	Study Population
Intrinsic Factor PK Study Reports (Module 5.3.3.3)						
849-004 NCT No. NA 5 centers in US	Phase 1, Open-label, Nonrandomized, Multi-center, Parallel-group	Single oral dose of 600 mg capsule	PK, safety, and tolerability	1 day/11 days	31	Males and females, with mild, moderate, or severe renal impairment or with normal renal function, between 18 and 75 years of age, inclusive
Extrinsic Factor PK Study Reports (Module 5.3.3.4)						
849-006 NCT No. NA 1 center in US	Phase 1, open-label, parallel, 4-cohort, fixed-sequence DDI study	Cohort 1: Adagrasib single oral dose of 200 mg capsule. Itraconazole 200 mg BID followed by 200 mg QD. Cohort 2: Adagrasib single oral dose of 600 mg capsule. Rifampin 600 mg QD. Cohort 3: Adagrasib single oral dose of 600 mg capsule. Pantoprazole 40 mg QD. Cohort 4: Adagrasib 600 mg QD followed by 400 mg BID	PK, safety, and tolerability	Cohort 1: 3 days (adagrasib) and 10 days (itraconazole) / 6-8 days after discharge. Cohort 2: 2 days (adagrasib) and 10 days (rifampin) / 6-8 days after discharge. Cohort 3: 2 days (adagrasib) and 7 days (pantoprazole)/ 6-8 days after discharge. Cohort 4: 3 days (probe drug cocktail) and 9 days (adagrasib)/	76	Healthy male and female subjects, between 18 and 60 years of age, inclusive

Trial Identity/ NCT No./ No. of Centers and Countries	Trial Design	Regimen/Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients/Subjects Treated	Study Population
		Probe drug cocktail (2 mg midazolam, 30 mg dextromethorphan, 10 mg warfarin, 0.25 mg digoxin, and 5 mg rosuvastatin).		6-8 days after discharge.		

Abbreviations: BID = twice daily; DDI = drug-drug interaction; FIH = first-in-human; MTD = maximum tolerated dose; NA = not applicable; NCT.= National Clinical Trials; No. = number; NSCLC = non-small cell lung cancer; PK = pharmacokinetic; QD = once daily; RP2D = recommended Phase 2 dose; US = United States.

The Applicant's Position:

All studies pertinent to the evaluation of efficacy and safety for the intended indication in NSCLC are summarized above in Applicant Table 11. The primary support for the efficacy of the proposed indication is based on the results from the subjects (Cohort A) with previously treated *KRAS* G12C-mutated advanced NSCLC enrolled in the pivotal Phase 2 portion of Study 849-001.

The FDA's Assessment:

FDA agrees with the description of the clinical studies included in the Applicant Table 11.

FDA also notes that 4 patients from Study 849-12 (KRYSTAL-12; NCT04685135) are additionally included in the FDA pooled safety population for FDA's review of this application. KRYSTAL-12 is an ongoing, randomized, multiregional clinical trial that is being conducted to verify the clinical benefit of adagrasib in patients with KRAS G12C-mutated NSCLC who have previously received platinum-based chemotherapy and an anti-PD-(L)1 antibody. Based on the original protocol, 340 patients will be randomized 2:1 to receive adagrasib 600 mg BID or docetaxel 75 mg/m^2 until disease progression or unacceptable toxicity. Patients on the docetaxel arm will crossover to receive adagrasib upon disease progression. The primary endpoint is PFS per BICR.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 849-001

Trial Design

The Applicant's Description:

Efficacy data supporting this NDA were generated in Study 849-001, an open-label, multi-center, first-in-human (FIH), Phase 1/2, multiple expansion cohort study of adagrasib in patients with advanced solid tumors malignancies with *KRAS* G12C mutation. Study 849-001 was designed and conducted in accordance with FDA draft guidance issued in August 2018 (FDA 2018) and conducted in the United States.

The dose-finding phase of the study used the AT design and an mTPI design. The study started with dose escalation using the AT design and converted to mTPI when the predefined degree of toxicity was observed, to further evaluate the potential Phase 2 dose regimen. Phase 1b cohorts evaluated specific questions in selected patient subsets. Pilot Phase 1 combination sub-studies were also undertaken.

In Phase 2, separate cohorts of patients assigned by histological diagnosis were evaluated for the clinical activity/efficacy of adagrasib in patients with *KRAS* G12C mutated disease. Diseases evaluated in Phase 2 cohorts included NSCLC, colorectal carcinoma, and a basket cohort for patients with other solid tumors.

Phase 2 Cohort A enrolled patients with advanced NSCLC with *KRAS* G12C mutation who had previously received treatment with at least a platinum-containing chemotherapy regimen and CIT. Objectives for Cohort A were to evaluate the clinical efficacy, safety and tolerability, and PK of adagrasib in patients with NSCLC with *KRAS* G12C mutation detected in tumor tissue.

Key eligibility criteria for Cohort A were histologically confirmed diagnosis of squamous or nonsquamous NSCLC with *KRAS* G12C mutation (documented by a Sponsor-approved laboratory); unresectable or metastatic disease; prior treatment with at least a platinum-containing chemotherapy regimen and CIT; presence of measurable tumor lesions per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1; ECOG PS 0 or 1; no active brain metastases or carcinomatous meningitis; and acceptable organ function as defined in the study protocol.

Patients enrolled in Cohort A initiated treatment with adagrasib at 600 mg twice daily administered in a continuous regimen. Adagrasib doses were taken at least 2 hours after the

previous meal and 1 hour before the next meal. The protocol provided guidelines for management of AEs, including dose modifications. Treatment continued until disease progression, unacceptable AEs, patient refusal, or death.

Disease assessments were performed every 6 weeks for 1 year, then every 3 months. Disease response and progression were assessed using RECIST 1.1 (Eisenhauer et al. 2009). The primary efficacy analysis of radiographic endpoints was based on blinded, independent central review (BICR). Disease assessment by the Investigator was used as sensitivity analyses.

The conduct of all phases and cohorts of Study 849-001 was overseen by an independent Data Monitoring Committee (IDMC).

The FDA's Assessment:
FDA generally agrees with the Applicant's description of the trial design for clinical trial 849-001. The adagrasib capsule formulation was administered to patients in the clinical trial; therefore, patients were instructed to take adagrasib capsule at least 2 hours after the previous meal or 1 hour before the next meal.

Refer to the Clinical Pharmacology Sections 6 and 19.4.2 for review of the adagrasib formulation bridging study of capsules to tablets.

Study Endpoints

The Applicant's Description:

The primary efficacy endpoint was ORR based on blinded, independent central review of imaging. Secondary endpoints included DOR, PFS, and OS. ORR may be considered a clinically meaningful endpoint on its own, as objective responses may improve disease-related symptoms; in addition, a strong linear correlation with OS has been described (Clarke, 2015). The use of ORR as the study endpoint was raised with the FDA as a Type B meeting item prior to initiation of Cohort A enrollment, and the use of ORR as well as the magnitude of the ORR estimate were agreed upon, in addition to agreement that response duration is an important review consideration. ORR and response duration have been used as the main outcome measures for other targeted agents for NSCLC to support approval by the FDA. Examples include full approval of entrectinib for *ROS1*-positive NSCLC, full supplemental approval of crizotinib for *ROS1*-positive NSCLC, accelerated approval of larotrectinib and entrectinib for NSCLC and other tumors with *NTRK* gene fusions, and accelerated approval of capmatinib and tepotinib for NSCLC with *MET* exon 14 skipping mutations. Thus, the use of ORR as the primary endpoint is appropriate and precedented.

The FDA's Assessment:
FDA agrees with the Applicant's description of the trial endpoints with the exception that FDA does not reach "agreements" with Sponsors or Applicants. FDA provides recommendations and

provides the current thinking on matters regarding the study endpoints in single arm trials. FDA clarified that at the End of Phase 1 meeting, the "primary endpoint of ORR with DOR is acceptable. Whether the data will support an accelerated approval will be based on the magnitude of ORR, DOR, and safety and tolerability profile. Patients should be followed for at least 6 months after first response in order to evaluate DOR. The ORR and DOR (including lower limit) will be considered in the context of available therapy."

Statistical Analysis Plan and Amendments

The Applicant's Description:

The design for Cohort A was noncomparative and used ORR as the primary endpoint. The sample size calculation for the pivotal study, Study 849-001 Cohort A, is based on the confidence interval (CI) approach to exclude the benchmark ORR associated with the standard of care of docetaxel with ramucirumab, where the associated ORR is 23% (Garon et al. 2014). Based on the assumption that treatment with 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%. The design for Cohort A included 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 was based on the Rho family with parameter 2.0. The futility analysis was to be conducted when approximately 32 evaluable patients (approximately 30% of the total number of patients) were available for the response assessment. The futility bound was 6 or fewer observed responses among the first 32 patients.

For Cohort A, 2 Full Analysis Set (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 adagrasib. The FAS-Investigator used in the sensitivity analysis included all patients who had measurable disease at baseline determined by the Investigator and received at least one dose of adagrasib.

Subgroup analyses planned for the primary efficacy endpoint in Cohort A included gender, age group, number of prior systemic cancer therapy regimens, concurrent versus sequential administration of required prior therapies, smoking history, baseline ECOG PS, and selected organ sites of disease involvement.

Missing data were not imputed. Missing observations in the time-to-event data were censored as described in the statistical analysis plan.

The FDA's Assessment:

FDA agrees with the Applicant's description of the statistical analysis plan. Although the

benchmark ORR rate was considered appropriate for sample size planning, ORR observed in the trial should be of sufficient magnitude and of adequate durability to support a favorable benefit-risk assessment.

For single-arm trials, FDA generally recommends all patients who were treated with at least one dose of investigational treatment be included in the efficacy population. This patient population was used for FDA's sensitivity analysis because the FAS-BICR excluded four patient who were treated who had no measurable disease at the baseline. Refer to Section 8.3 of the Assessment Aid for the results and assessment of the sensitivity analysis compared to the primary efficacy analysis.

Protocol Amendments

The Applicant's Description:

A summary of key changes to the protocol for Study 849-001 as of the data cutoff for this NDA is provided in Applicant Table 12. In addition, in accordance with application of the FIH multiple expansion cohort study design and as appropriate, emerging study and program data were summarized and updated guidance on management of AEs and use of concomitant medications were made in protocol amendments.

Applicant Table 13: Summary of Protocol Amendments for Study 849-001

Document	Summary of Changes
Amendment 1	• Responded to IND feedback on the definition for dose limiting toxicity during dose escalation and the schedule for selected safety assessments
Amendment 2	• Added Phase 1 evaluation of the twice daily adagrasib regimen
Amendment 3	• Implemented the Phase 2 dosing regimen • Added pilot Phase 1 combination regimen evaluations
Amendment 4	• Revised the statistical design and increased the sample size for Cohort A to enable the pivotal evaluation of clinical efficacy following EOP1 meeting • Added a pilot Phase 1 combination regimen evaluation
Amendment 5	• Added a Phase 1b evaluation in a selected patient population
Amendment 6	• Provided guidance for conduct of the study during the COVID-19 public health emergency, in accordance with FDA guidance • Expanded the design for a pilot Phase 1 combination sub-study • Added several Phase 1b evaluations in selected patient populations • Revised the statistical design for a Phase 2 Cohort • Added a Phase 2 evaluation
Amendment 7	• Added a Phase 2 evaluation • Expanded a Phase 1b cohort

Abbreviations: EOP1 = end of Phase 1; IND = Investigational New Drug.

The FDA's Assessment:

FDA agrees with the Applicant's above protocol amendment table, with the exception that amendments 8 and 9 were not included in the Applicant's table. The information for amendment 8 and 9 are provided below for completeness.

Amendment 8 (dated October 25, 2021): Major changes included adding a Phase 1b evaluation with the tablet formulation, expanding the Phase 2 cohort, and adding Phase 1b cohorts for combination therapies with adagrasib.

Amendment 9 (dated August 31, 2022): Major changes included increasingthe sample size for the Phase 1b and Phase 2 cohorts, and indicating that all newly enrolled patients will initiate treatment with the tablet formulation of adagrasib and all currently enrolled patients will switch to the tablet formulation (from capsule formulation) at the start of their next cycle.

8.1.2. Study Results

Compliance with Good Clinical Practices

Data:

Study 849-001 was conducted in accordance with International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (GCP) ICH 1996), ICH E6 (R2), Code of Federal Regulations (CFR) governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) and concepts that have their origin in the Declaration of Helsinki (World Medical Association 1996, 2008 & 2013). The original protocol and protocol amendments were approved by an independent Institutional Review Board (IRB) associated with each study center. Signed Informed consent was obtained from all participants prior to enrollment into the study. The study was conducted under IND 138735.

The Applicant's Position:
Study 849-001 was conducted in compliance with all applicable guidelines and regulations.

The FDA's Assessment:
FDA agrees with the Applicant's description of compliance with Good Clinical Practices.

Financial Disclosure

Data:

Financial disclosure information was collected from all investigators participating in Study 849-001.

The Applicant's Position:
Financial interests and arrangements were adequately disclosed. The use of a multi-center trial with enrollment distributed across several study sites and the use of blinded independent central review mitigate the risk of potential conflicts of interest and help ensure data integrity.

The FDA's Assessment:
FDA agrees with the Applicant's position and all the study sites were located in the United States. Refer to Financial Disclosure19.2 for additional details.

Patient Disposition

Data:

Cohort A enrolled 116 patients, all of whom received at least one dose of adagrasib. Patients enrolled in Cohort A were followed for at least 6 months from enrollment to the time of the data cutoff date for the primary analysis on 15 June 2021. Forty (34.5%) patients were ongoing on adagrasib treatment at the time of the data cutoff. The most frequent reasons for adagrasib discontinuation were objective disease progression (22.4%), AE (12.9%), and global deterioration of health (12.1%).

The Applicant's Position:

Pre-screening for genetic eligibility and study screening were conducted prior to cohort assignment. Patients meeting eligibility criteria for Cohort A were enrolled; all 116 enrolled patients were treated; and all 116 treated patients were included in the safety population and in the efficacy evaluation by investigator assessment. The primary analysis of ORR included all patients with measurable lesions identified by BICR at baseline (112 of 116 patients). Definitions for analysis populations were pre-specified, and analyses were conducted in accordance with the pre-specified statistical analysis plan.

The FDA's Assessment:

FDA's analysis was based on the primary efficacy population which included 112 patients with measurable disease at baseline identified by BICR and received at least one dose of adagrasib. As of a data cutoff date of June 15, 2021, a total of 53 of 112 patients (47%) were still on trial. Of the 59 (53%) patients who discontinued the trial, 45 (40%) died, 9 (8%) withdrew consent and 2 (1.8%) were lost to follow-up. A total of 74 patients (66%) discontinued adagrasib; reasons for discontinuation included progressive disease (26 patients [23%]), adverse events (14 patients [13%]), death (7 patients [6%]), withdrawal by patient (11 patients[10%]), and global deterioration of health (14 patients [13%]).

Protocol Violations/Deviations

Data:

In Cohort A, 2 patients had eligibility criteria violations due to no prior treatment with a CIT. The deviations were identified after each patient started study treatment; both patients were allowed to continue study participation. In addition, 1 patient had received a red blood cell transfusion 2 days before the screening hemoglobin assessment, and 2 patients had 1 instance each of deviations in scheduling for on-treatment ECG and PK blood sample collection.

The Applicant's Position:

The foregoing protocol deviations did not affect the overall interpretation of the results of the study.

The FDA's Assessment:

The Applicant documented protocol deviations by category (i.e., inclusion and exclusion criteria, investigational product [IP] administration, study procedures and assessments, study visit schedule, informed consent, and other). Important protocol deviations were defined as those potentially impacting safety or efficacy assessments and analyses.

COVID-19 specific protocol deviations were listed separately. The number of patients missing visits due to the COVID-19 pandemic was summarized.

The table below, summarizes major protocol deviations observed in Study 849-001. There were 3 patients who did not meet eligibility criteria for trial enrollment: two patients (# (b) (6) and (b) (6)) did not receive prior immune checkpoint inhibitors and one patient (# (b) (6)) had active brain metastases. Patient # (b) (6) discontinued adagrasib treatment on Day 25 due to general deterioration and died due to disease progression on Day 28. Patient # (b) (6) received adagrasib 600 mg orally twice daily prior to experiencing a serious adverse event of acute kidney injury on Day 13 which resolved on Day 18. The adagrasib dose was reduced to 400 mg orally twice daily.

Patient # (b) (6) was initially reported as not receiving prior immune checkpoint inhibitor, but this was later corrected to reflect that the patient had previously received pembrolizumab. Therefore, patient # (b) (6) was not included in the table under eligibility criteria. The patient received adagrasib for 87 days prior to a serious adverse event of Grade 3 pneumonitis.

The two patients (# (b) (6) and # (b) (6)) received TheraSphere, an intrahepatic radiation treatment while receiving adagrasib therapy in Study 849-001. Patient # (b) (6) received the TheraSphere treatment on Day 231 and adagrasib therapy was interrupted. On July 23, 2020, the ORR assessment by BICR was PD due to new liver lesions prior to receiving the TheraSphere. The exclusion of this patient in the efficacy analysis does not impact the ORR and DOR results for adagrasib. For Patient # (b) (6), the patient had received treatment with TheraSphere on (b) (6). The treatment does not impact the efficacy results for adagrasib as the data cutoff date of June 15, 2021 for the FDA efficacy analysis occurred prior to the patient's receipt of the TheraSphere treatment.

The protocol violations are not expected to impact the interpretability of the efficacy results for adagrasib.

As noted in Section 4.1, under reporting of concomitant medications were identified during the clinical site inspections. Upon re-evaluation of the concomitant medication list, eight patients (7%) received ondansetron, a medication know to prolong the QTc interval, while enrolled in the trial. Patients were to avoid medications known to prolong the QTc interval and pose a risk

of Torsades de Pointes. Patient # (b) (6) received adagrasib and ondansetron concurrently for 56 days at an outside rehabilitation facility; there were no reports of QTc prolongation despite concomitant use of adagrasib and ondansetron. For patient # (b) (6), Grade 1 QTc prolongationwas reported prior to starting ondansetron. The QTc interval was monitored at each visit.

FDA evaluated the unreported adverse events of sepsis, deep vein thrombosis, and seizure. Upon review of these unreported adverse events in the safety population, sepsis has already been reported in 5% of patients, deep vein thrombosis reported in 7% of patients, and seizure reported in 2.6% of patients. The addition of these reported events does not appear to impact the overall safety profile of adagrasib.

There were three patients who were not reconsented while enrolled in the trial after protocol amendments related to updated safety information were issued for Study 849-001. The patients were not reconsented due to recommendations from the IRB that this was not necessary. As it is the responsibility of the clinical investigators and research staff to ensure that trial participants are informed of any changes or new information that may influence their decision to continue to participate in a research protocol, the clinical investigators were instructed to make appropriate corrections to the procedures to ensure this is not repeated in any ongoing or future studies.

FDA agrees with the Applicant that the reported protocol deviations are not expected to impact the interpretability of the trial results. The Applicant has implemented a Corrective Action and Preventive Action (CAPA) to screen any unreported protocol violations due to the prohibited use of ondansetron in Study 849-001 and retrain study monitors to review source documents for any unreported prohibited concomitant medication use.

FDA Table 14: Important Protocol Deviations in Cohort A

	Adagrasib 600 mg BID	
Category **Deviation**	**Cohort A (N=116)[a]** **N (%)**	**Cohort A (N=116)[b]** **N (%)**
Any Important Deviation	6 (5.2)	13 (11)
Eligibility	2 (1.7)	3 (2.6)
Inclusion/Exclusion Criteria	1 (0.9)	2 (1.7)
Other Protocol Violations	1 (0.9)	1 (0.9)
Lab	1 (0.9)	1 (0.9)
Study Procedure/Assessments	1 (0.9)	1 (0.9)
Safety	1 (0.9)	11 (9)
Other Protocol Violations	1 (0.9)	8 (7)
Adverse Event reporting	NR	3 (2.6)
Study Procedures	2 (1.7)	5 (4.3)
Study Procedure/Assessments	2 (1.7)	2 (1.7)
Informed Consent	NR	3 (2.6)
Number of subjects missing at least one visit due to COVID-19	1 (0.9)	1 (0.9)
Number of visits missed	1 (0.9)	1 (0.9)
1	1 (0.9)	1 (0.9)
2	0	0
>2	0	0

Note: For each category and deviation, patients are included only once, even if they experienced multiple events in a category or deviation.
NR – not reported
[a] Protocol deviations reported with the ADDV dataset with a data cutoff date of June 15, 2021. One deviation (entry criteria for Patient (b) (6)) was not entered into the protocol deviation log in time for inclusion in the study database and is not included in the table.
[b] Updated ADDV dataset with a data cutoff date of October 15, 2021

Demographic Characteristics

Data:

All patients were enrolled and treated at sites in the US. In Cohort A, the mean age was 64.4 years (SD: 9.64 years), median age was 64.0 years (range: 25 to 89 years) and included 49.1% patients aged ≥ 65 years and 12.9% patients were aged ≥ 75 years. Additionally, 56.0% of patients were

female, and 44% were male. The racial composition included White, 83.6%; Black or African American, 7.8%; Asian, 4.3%; American Indian or Alaska Native, 0.9%; and Other, 3.4%. In terms of ethnicity, at least 2.6% of patients were Hispanic or Latino. The median weight was 69.5 kg (range: 36.8 to 138.6).

The Applicant's Position:

The demographics of patients enrolled in Cohort A were generally representative of the patient population in US and supportive of the proposed indication.

The FDA's Assessment:

The above information is also presented in the Applicant Table 21 based on 116 patients. FDA agrees with the Applicant with the exception that FDA has defined the efficacy population as the 112 patients who had measurable disease according to RECIST 1.1 at baseline identified by BICR and received at least one dose of adagrasib. The FDA's analysis of baseline characteristics was conducted using the primary efficacy population of 112 patients. Refer to FDA Table 15 for demographic and disease characteristics.

The median age of 64 years (range: 25 to 89) is similar to that reported in the literature for patients with KRAS G12C-mutated NSCLC (Sebastian 2021) as is the high prevalence of current or former smokers (86% of patients in efficacy population). The efficacy population appears representative of the population of patients with KRAS G12C-mutated NSCLC in the U.S., as the incidence of KRAS G12C mutation is approximately 11% in Black patients and 3.6% in Asian patients in the U.S. (Nassar 2021) and the efficacy population appears to have a similar distribution of patients based on race.

FDA Table 15. Demographic and disease characteristics

	Adagrasib 600 mg BID	
Characteristic	**Cohort A (N=116) N (%)**	**Cohort A (N=112) N (%)**
Sex		
Male	51 (44.0)	50 (45)
Female	65 (56.0)	62 (55)
Race		
White	97 (83.6)	93 (83)
Black or African American	9 (7.8)	9 (8)
Asian	5 (4.3)	5 (4.5)
American Indian or Alaska Native	1 (<1)	1 (0.9)
Other	4 (3.4)	4 (3.6)
Ethnicity		
Hispanic or Latino	3 (2.6)	3 (2.7)
Not Hispanic or Latino	107 (92.2)	103 (92)
Missing	6 (5.2)	6 (5)
Age Group		
< 65	59 (50.9)	59 (53)
≥ 65	57 (49.1)	53 (47)
≥ 65-< 75	42 (36.2)	39 (35)
≥ 75	15 (12.9)	14 (13)
ECOG PS		
0	18 (15.5)	18 (16)
1	97 (83.6)	93 (83)
Missing	1 (<1)	1 (0.9)
Histology		
Adenocarcinoma	113 (97)	109 (97)
Squamous	3 (2.6)	3 (2.7)
Disease Stage		
Locally Advanced	13 (11.2)	12 (11)
Metastatic	103 (88.8)	100 (89)

	Adagrasib 600 mg BID	
Characteristic	**Cohort A (N=116) N (%)**	**Cohort A (N=112) N (%)**
Total Number of Prior Systemic Regimens		
1	50 (43.1)	47 (42)
2	40 (34.5)	40 (36)
3	12 (10.3)	11 (10)
4+	14 (12.1)	14 (13)
Mean	2	2
Median	2	2
Min, Max	1, 7	
Smoking status		
Lifetime Non-smoker	5 (4.3)	5 (4.5)
Current Smoker	11 (9.5)	11 (10)
Former Smoker	100 (86.2)	96 (86)

Other Baseline Characteristics

Data:

In Cohort A, all 116 patients had been diagnosed with NSCLC, 97.4% had adenocarcinoma, and 2.6% patients had squamous histology. All patients presented with *KRAS* G12C-positive NSCLC as documented by a Sponsor-approved laboratory and had previously received treatment for their disease. Baseline ECOG PS was 1 in 83.6% of patient and 0 in 15.5% of patients (datum was missing for 1 patient). Most patients had previously smoked (86.2%) or were current smokers (9.5%). Metastatic disease was reported for 88.8% of patients; 11.2% of patients had locally advanced disease. Sites of metastatic disease at baseline as reported by BICR included bone (42.0%), brain (30.4%), liver (21.4%), and adrenal (20.5%). All patients had received prior treatment with a platinum-based therapy, including 93.1% who had received carboplatin and 17.2% who had received cisplatin. One hundred fourteen (98.3%) patients had also received CIT, including 80.2%, 8.6%, 6.9%, 6.0%, and 0.9% who had received pembrolizumab, atezolizumab, nivolumab, durvalumab, and avelumab, respectively. In total, 70.7% of patients received prior platinum and CIT concurrently, and 27.6% had received these treatments sequentially. Concurrent conditions included hypertension for 48.3%, and chronic obstructive pulmonary disease (COPD) for 33.6%. Symptoms at baseline included dyspnea, 47.4%; fatigue, 46.6%; and cough, 45.7%.

The Applicant's Position:

The baseline characteristics and prior treatment history of patients enrolled in Cohort A were considered to be representative of the patient population in US with locally advanced or metastatic, previously treated NSCLC, and supportive of the proposed indication.

The FDA's Assessment:
FDA generally agrees with the Applicant's position.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Patients enrolled in Cohort A initiated treatment with adagrasib at 600 mg twice daily administered in a continuous regimen. Median compliance was 95.22% (range: 38.1% to 100%), and most patients (65.5%) were >80% compliant.

Concomitant anticancer systemic therapy was prohibited. Concomitant cancer surgery or radiotherapy were discouraged but could be allowed if medically necessary.

Treatments for comorbidities, disease signs and symptoms, and AEs were to be provided as necessary in the judgment of the Investigator. All 116 patients treated in Cohort A received non–cancer-related concomitant medications. The most common (≥20% patients) non–cancer-related concomitant medications were antiemetics and antinauseants, analgesics, drugs for acid related disorders, psycholeptics, drugs for obstructive airway diseases, antianemic preparations, antithrombotic agents, corticosteroids for systemic use, antidiarrheals, intestinal anti-inflammatory/anti-infective agents, mineral supplements, antibacterials for systemic use, lipid modifying agents, drugs for constipation, psychoanaleptics, cough and cold preparations, vaccines, beta blocking agents, antiinflammatory and antirheumatic products, antihistamines for systemic use, agents acting on the renin-angiotensin system, diuretics, and thyroid therapy.

The Applicant's Position:

Median treatment compliance of 95.22% was high, with a wide range that may reflect the expected variation in comorbidities, memory, and AEs. Patients were included in the analysis of safety and efficacy regardless of compliance, mitigating the risk of informative censoring.

The concomitant treatments administered were representative of those commonly prescribed in the patient population under study and did not limit the generalizability of the study results.

The FDA's Assessment:
FDA generally agrees with the Applicant's position. Refer to FDA Table 14: Important Protocol Deviations in Cohort A regarding the use of concomitant anticancer treatments in two patients

who received TheraSphere (intrahepatic bead radiation therapy) while enrolled in Study 849-001.

No rescue medications were administered in Study 849-001.

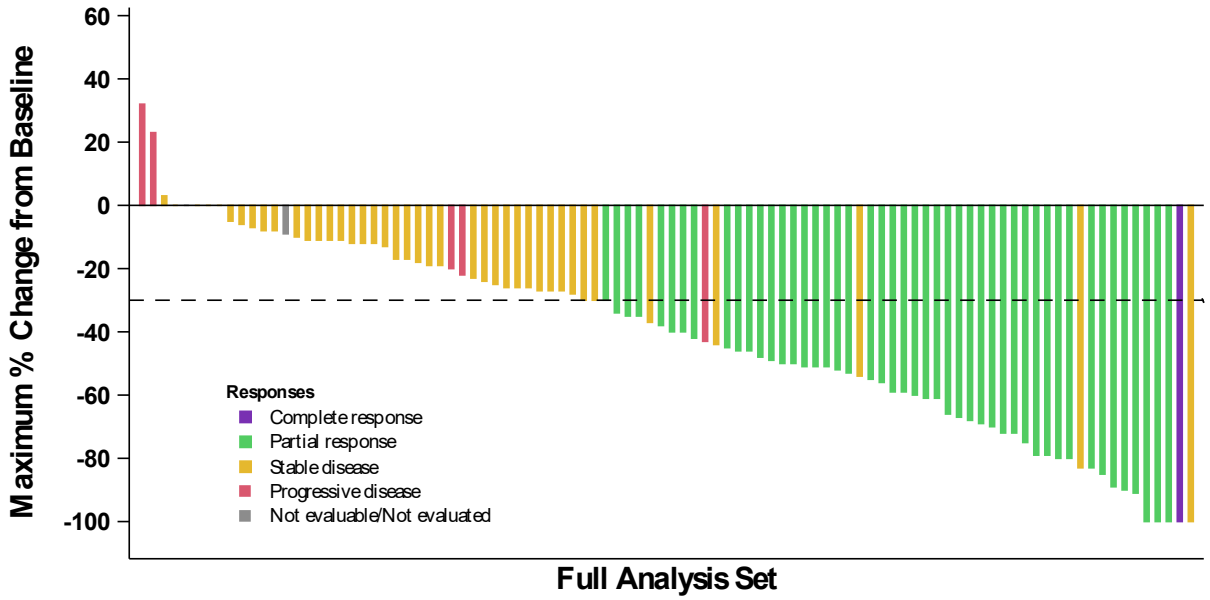
Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

As of the data cutoff date 15 Jun 2021, 116 patients with advanced or metastatic NSCLC with *KRAS* G12C mutation, and who had previously been treated with at least a platinum-containing regimen and a CIT, were enrolled and treated in Study 849-001 Cohort A. ORR assessed per RECIST 1.1 was the primary efficacy endpoint. The primary efficacy analysis was based on BICR assessment in the FAS-BICR population; 112 patients had measurable disease at baseline as determined by BICR.

The ORR in Cohort A was 42.9% (48 patients with response among 112 patients; 95% CI: 33.5% to 52.6%). The lower limit of the 95% CI excluded the prespecified benchmark ORR of 23%. Disease responses included 1 complete response (CR) and 47 partial responses (PRs). The tumor burden change from baseline is summarized in Applicant Figure 4. Most patients experienced a decrease in the sum of target lesion diameters, including those without an objective response.

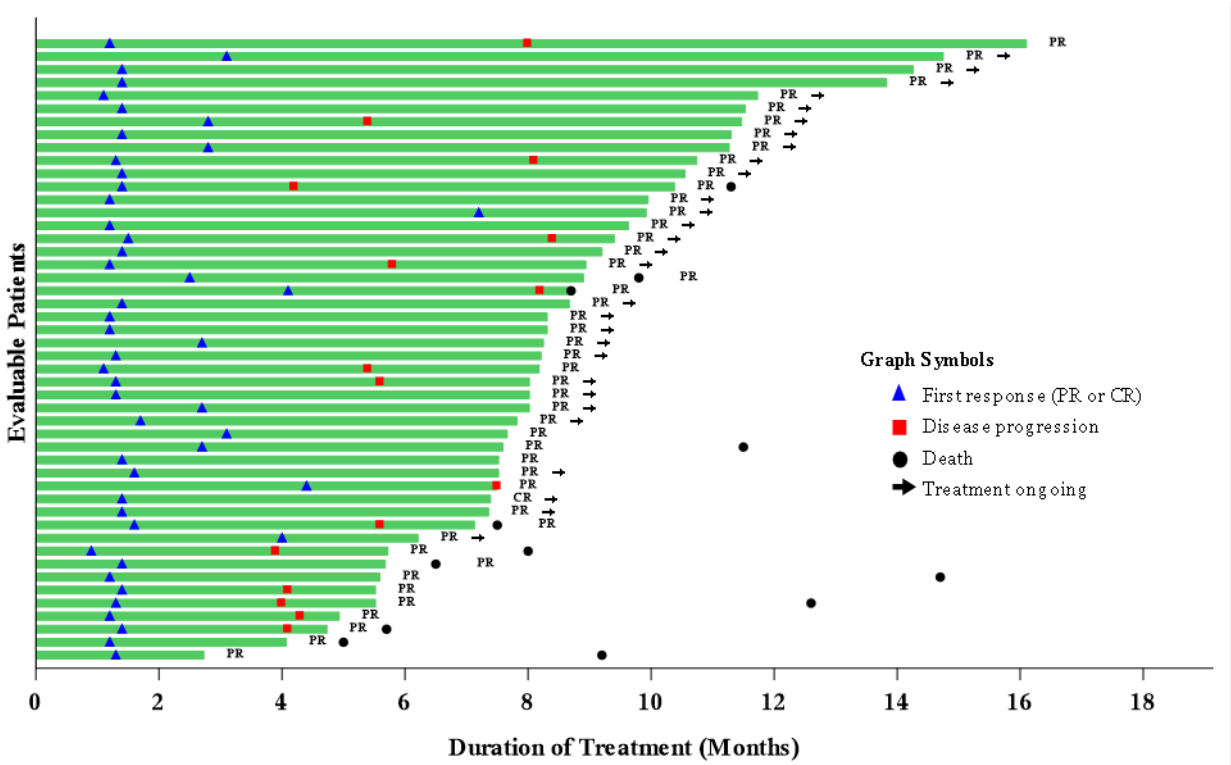
Applicant Figure 4: Best Tumor Response and Change in Tumor Burden From Baseline – Cohort A (FAS-BICR)



Abbreviations: BICR = blinded, independent central review; FAS = Full Analysis Set
Notes: Sixteen subjects had no change of baseline in tumor size, since no postbaseline measurements were available.
Five subjects had change from baseline of 0 showing as blank spot in the graph.
One patient had the target lesion disappear, but a new lesion appeared at Week 13.
Source: Module 2.7.3

The time course of response, including time to first complete or partial response and time to progression, is displayed for responders in a swimmer plot in Applicant Figure 5. Most responses appeared at about 6 weeks after starting treatment (the time of the first disease assessment per protocol). Among patients with objective disease response, 89.6% had initial response occurring at least 6 months prior to the data cutoff.

Applicant Figure 5: Time Course of Response - Cohort A (FAS-BICR)

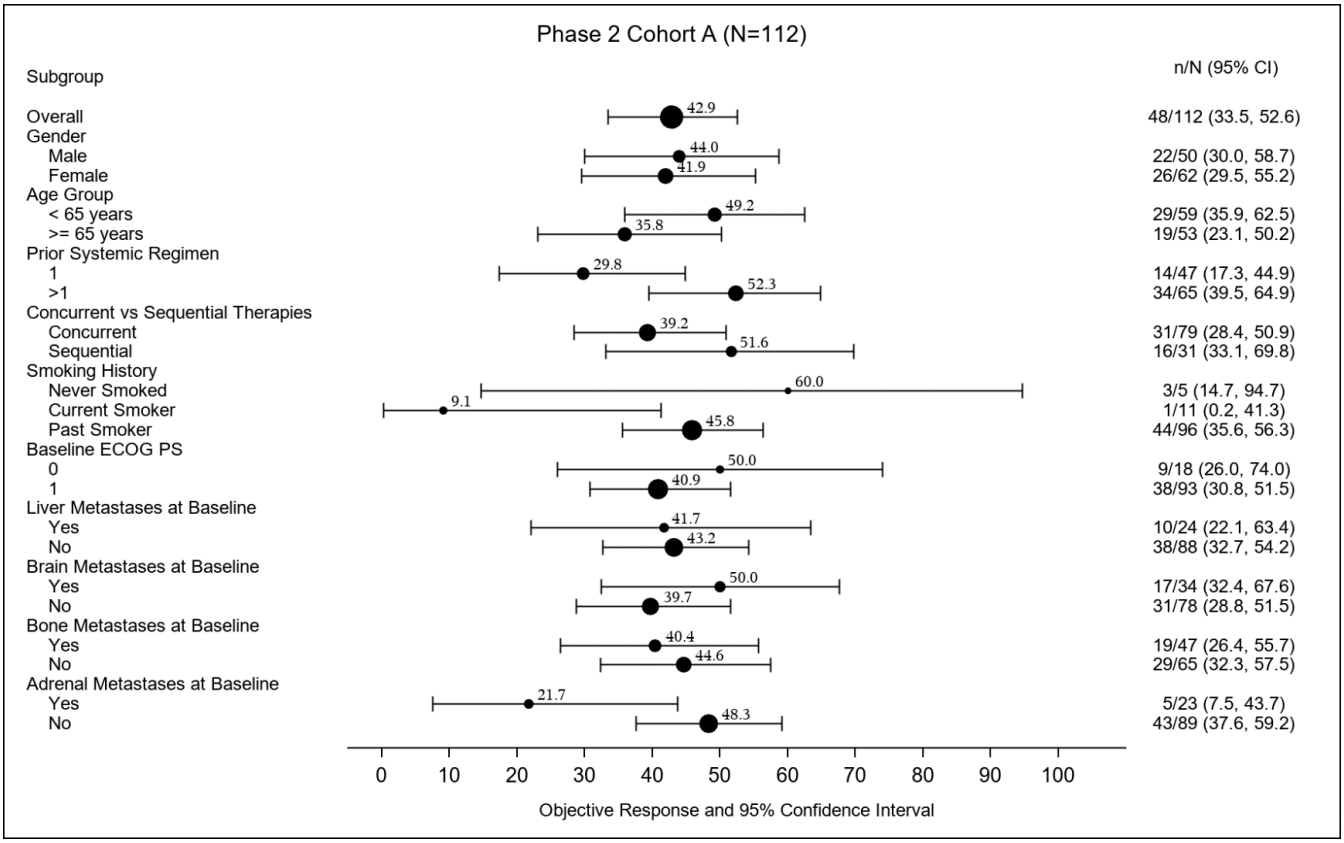


Abbreviations: BICR = blinded, independent central review; CR = complete response; FAS = Full Analysis Set; PR = partial response.
Note: Only subjects with CR or PR are displayed in the graph (48 of 112 patients in the FAS-BICR).
Source: Module 2.7.3

Results based on the Investigator's assessment of disease response in according with RECIST 1.1 were used in sensitivity analyses for Cohort A; all 116 patients had measurable disease at baseline assessed by Investigator and are included in the FAS-Investigator population. The ORR as assessed by Investigator was 37.1% (43 patients; 95% CI: 28.3% to 46.5%).

Subgroup analyses were performed using ORR as determined by BICR. A forest plot for all subgroup analyses is provided in Applicant Figure 6. For all subgroups, the 95% CI overlapped the overall ORR (42.9%), with the exception of current smokers (ORR = 9.1%, 95% CI = 0.2% to 41.3%, n = 11). Clinical efficacy, as demonstrated by ORR, was generally consistent in patient subgroups defined by baseline demographics, disease history, and prior therapy.

Applicant Figure 6: Subgroup Analysis of Objective Response Rate (Cohort A) (FAS-BICR)



Source: Module 2.7.3

The Applicant's Position:

Efficacy was demonstrated in Cohort A. The primary endpoint for Cohort A was ORR, and the study results met the pre-specified criterion that the lower limit of the 95% CI for ORR exclude the ORR of 23% observed with docetaxel plus ramucirumab. The ORR based on BICR was 42.9% (95% CI: 33.5% to 52.6%). Subgroup analyses for Cohort A generally showed consistent results for ORR. Additionally, supportive data for patients with NSCLC in Phase 1/1b and another Phase 2 NSCLC cohort (Cohort B) presented in the Summary of Clinical Efficacy (Module 2.7.3) show consistent results for ORR and increase the confidence in the point estimate.

The FDA's Assessment:

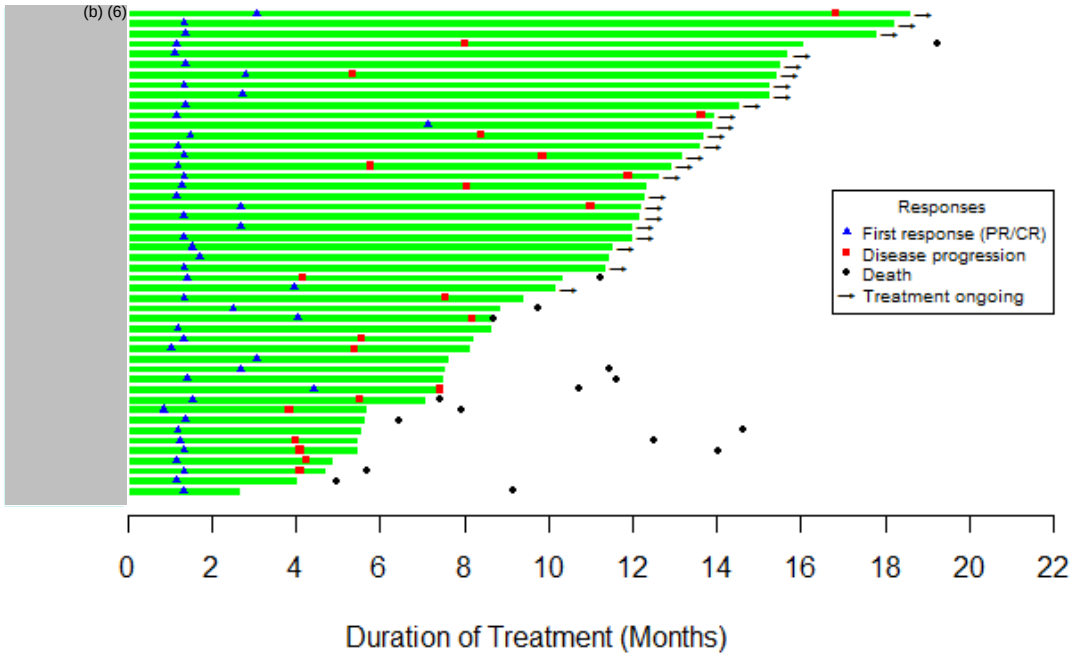
FDA agrees with the Applicant's efficacy results of the primary endpoint including sensitivity analyses, which are based on the data cutoff date of June 15, 2021. Of the 112 patients with measurable disease at baseline per the BICR assessment, 1 patient had a CR and 47 patients had PRs. The sensitivity analyses based on investigator assessed tumor response and based on BICR assessed tumor response including all patients who were treated with at least 1 dose of

adagrasib were supportive of the primary analysis. In the latter analysis, patients with no measurable disease at baseline were included as nonresponders, and resulted in an ORR of 41% (95% CI: 32% to 51%).

FDA considers pre-specified criterion on ORR to be useful for sample size planning, but does not necessarily use it as the benchmark to define trial success. An ORR of sufficient magnitude and of adequate durability in the context of available therapy is required for an overall favorable benefit:risk assessment.

FDA also analyzed data from the 120-day update based on a data cutoff date of October 15, 2021, and updated the swimmer plot as shown in FDA Figure 7.

FDA Figure 7: Time Course of Response – Cohort A (FAS-BICR) based on 120-day update with data cutoff date of October 15, 2021.



Data Quality and Integrity

Data:

Investigators were selected based on qualifications, experience, and having adequate personnel and facilities to conduct oncology clinical trials, and investigators underwent GCP and study-

specific training. Study data were captured on electronic case report forms (CRFs) in an electronic database with automated edit checks during data entry. Study monitoring was performed by a contract research organization trained in the conduct of the study. Study monitors were granted access to subject medical records for full source data verification of entries reported on CRFs for the pivotal cohort and were responsible for reviewing compliance with GCP, documentation of informed consent, adherence to the protocol, and the completeness and accuracy of the data. During study conduct, study data entries were reviewed by study monitors, data managers, a clinical scientist, and a medical monitor for generation and resolution of data queries to ensure accuracy and completeness.

The study was conducted in accordance with the clinical protocol submitted to and approved by the FDA, a central IRB, and independent IRBs associated with some study centers. Data analyses were conducted in accordance with the statistical analysis plan.

Radiographic efficacy endpoints, including the primary endpoint of ORR, were determined by BICR using standard, validated criteria for assessing study endpoints. Oversight for study conduct, including efficacy and safety analyses, was provided by the IDMC.

Changes were made to the study protocol in response to the COVID-19 health emergency and in accordance with FDA guidance (FDA 2020). Adherence to the altered protocol requirements was not considered deviation from the protocol. Protocol changes included the following:

- Broadening visit windows by several days around mandated study assessments.
- Allowing use of alternative radiographic imaging modalities after discussion with the study sponsor.
- Accepting, on a case-by-case basis, study procedures that could not be conducted due to institutional restrictions. Examples included baseline ophthalmology examination, assessment for bone lesions, PK sample collection and corresponding electrocardiograms at time points of 4 hours or more after dosing, and foregoing collection of tumor tissue samples at the time of disease progression.
- Allowance of remote visits with site staff by telephone or using video technology and/or with a visit by a home health care professional, if permitted by institutional guidelines.

The Applicant's Position:

No issues were identified with the data quality or integrity from Study 849-001 that could affect the interpretation of the efficacy results, and the sponsor guidance for study conduct during the COVID-19 health emergency was appropriate for ensuring the safety of study patients while maintaining rigorous evaluation of the key study endpoints.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of data quality and integrity. Protocol amendment 5 dated May 18, 2020, provided for adjustment to visit windows and study assessments, remote patient visits, shipment of adagrasib clinical trial materials to patients, study drug administration delay or interruption, and action and reporting in the event of documented or suspected COVID-19 infection due to the COVID-19 public health emergency.

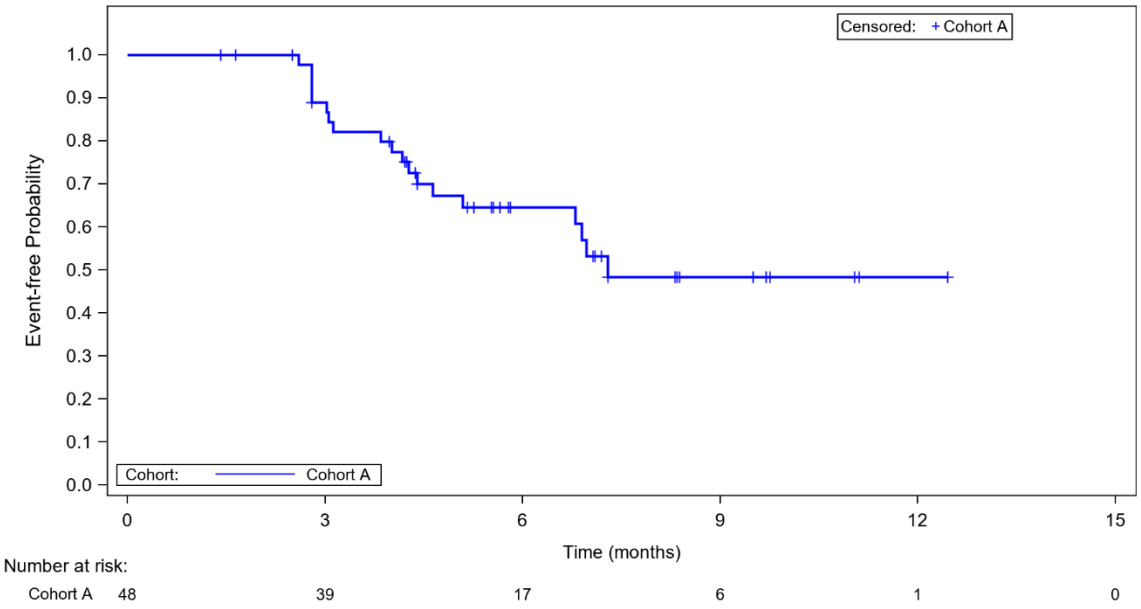
Efficacy Results – Secondary and other relevant endpoints

Data:

Duration of Response

As of the data cutoff of 15 June 2021, median duration of follow-up for response for Cohort A was 7.10 months. Among the 48 patients with objective disease response as assessed by BICR, 39.6% had a progression or death event, and 60.4% were censored. Based on disease assessments by BICR in the FAS-BICR, median DOR was 7.3 months (95% CI: 5.1 months to NE) (Applicant Figure 7). In the BICR analysis, the estimated event-free rate at 6 months was 64.6% (95% CI: 48.1% to 77.0%), and at 1 year it was 48.4% (95% CI: 30.0% to 64.5%). Seventeen patients (35.4% patients with a tumor response) had a response duration ≥ 6 months at the time of analysis. Based on disease assessments by Investigator in the FAS-Investigator, median DOR was 8.3 months (95% CI: 6.9 months to NE). Clinical efficacy, as demonstrated by DOR, was generally consistent in patient subgroups defined by baseline demographics, disease history, and prior therapy.

Applicant Figure 8: Analysis of Duration of Response (Cohort A) (Full Analysis Set-BICR)

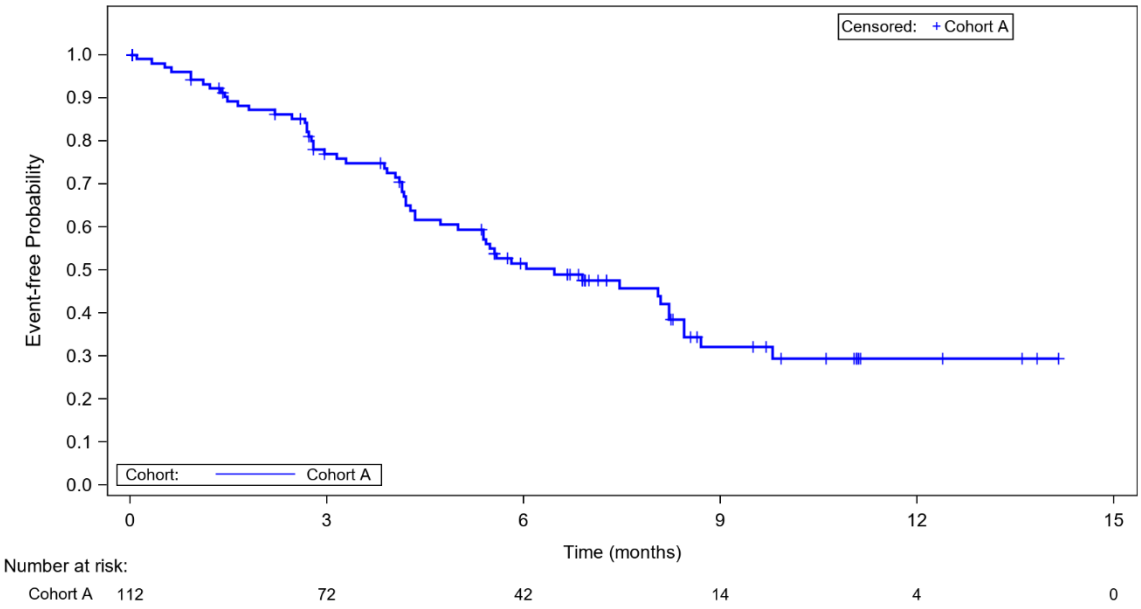


Abbreviation: BICR = blinded, independent central review
Source: Study 849-001 Cohort A CSR Figure 14.2.2.1

Progression-free Survival

Based on disease assessments by BICR in the FAS-BICR, median PFS was 6.5 months (95% CI: 4.7 to 8.2 months) (Applicant Figure 9). At the time of analysis (cutoff date 15 June 2021), observations for approximately 48% of the patients remained censored. The estimated event-free rate at 6 months was 51.5% (95% CI: 40.9% to 61.1%), and at 1 year it was 29.5% (95% CI: 18.6% to 41.2%). For disease assessments by Investigator in the FAS-Investigator, median PFS was 5.9 months (95% CI: 4.4 to 8.4 months).

Applicant Figure 9: Analysis of Progression-free Survival (Cohort A) (Full Analysis Set-BICR)

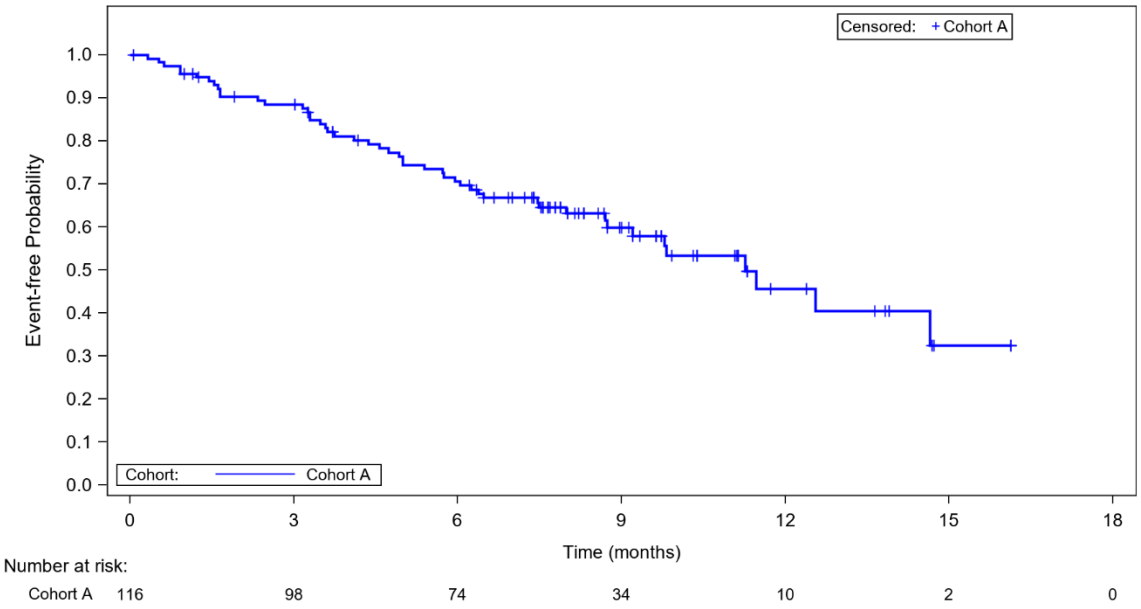


Source: Module 2.7.3

Overall Survival

In the Enrolled population, median OS was 11.3 months (95% CI: 8.7 months to NE). At the time of analysis (cutoff date 15 June 2021), median duration of follow-up for survival in Cohort A was 8.97 months (Applicant Figure 10), and approximately 59% of the patients were still alive. The estimated event-free rate at 6 months was 70.6% (95% CI: 61.1% to 78.3%), and at 1 year it was 45.6% (95% CI: 31.5% to 58.6%).

Applicant Figure 10: Analysis of Overall Survival (Cohort A) (Enrolled Population)



Source: Module 2.7.3

The Applicant's Position:

Efficacy results of the secondary endpoints in the pivotal study are consistent with clinically meaningful activity with adagrasib treatment. In particular, the median DOR of 7.3 months (95% CI: 5.1 months to NE) supports the durability of the observed responses.

The FDA's Assessment:

FDA agrees with the Applicant's analyses of duration of response based on a data cutoff date of June 15, 2021. Subgroup analyses results should be interpreted with caution due to small sample sizes.

FDA also analyzed the data submitted with the 120-day update with a data cutoff date of October 15, 2021 and the updated results are summarized below:

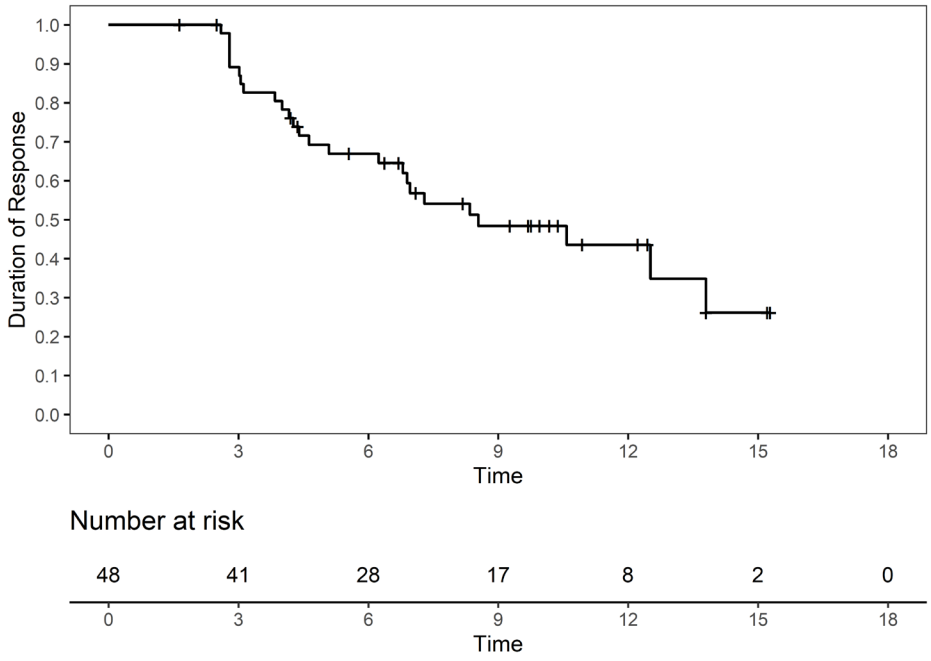
1. DOR per BICR assessment:
    a. Median duration of follow-up for response for Cohort A was 10.2 months based on the Kaplan-Meier method with censoring/event label inversed.
    b. Median DOR was 8.5 months (95% CI: 6.2 to 13.8 months) based on the Kaplan-Meier method (FDA Figure 11).
    c. Twenty-eight patients (58% patients with a tumor response) had a response

duration of at least 6 months.

2. Median DOR per investigator assessment was 9.9 months (95% CI: 7.1 months to NE).

FDA notes that the PFS and OS analyses in the single arm trial are uninterpretable for efficacy in the absence of a randomized comparator arm.

FDA Figure 11: Analysis of DOR per BICR in Cohort A based on 120-day update with data cutoff date of October 15, 2021



Dose/Dose Response

Data:

All patients included in the Phase 2 efficacy analyses initiated treatment at a dose of 600 mg twice daily.

The Applicant's Position:

The limited number of patients assigned to a starting dose other than 600 mg twice daily does not permit meaningful analysis of dose response. Further evaluation is ongoing.

The FDA's Assessment:

FDA agrees with the Applicant. In the dose escalation part of the clinical trial, there was one patient each dosed with adagrasib 150 mg QD, 300 mg QD, 600 mg QD and 1200 mg QD as the

dose escalation used an accelerated titration design. Dose optimization is undetermined due to very limited evaluation in dose levels other than 600 mg BID. The one patient in the 1200 mg QD cohort, experienced postdosing emesis possibly attributed to pill burden (12 x 100 mg adagrasib capsules QD) and this resulted in an adaptation of the adagrasib regimen to BID administration. The adagrasib 600 mg BID dose level was selected as the starting dose for Cohort A in the KRYSTAL-1 trial based on the accelerated titration and modified toxicity probability interval (mTPI) designs for the dose-escalation part of the trial. Refer to FDA's assessment in Section 6.2.2.1 for further details on the dose.

Durability of Response

Data:

See the section above for reporting of duration of response.

The Applicant's Position:

See section above.

The FDA's Assessment:
The FDA's analysis of DOR is based on the data cutoff date of October 15, 2021 with a median DOR of 8.5 months (95% CI: 6, 14).

Persistence of Effect

Data:

During study treatment, persistence of effect is demonstrated by duration of response and PFS. Based on disease assessments by BICR in the FAS-BICR for Cohort A (cutoff date 15 June 2021), median DOR was 7.3 months (95% CI: 5.1 months to NE) with a range of 1.41+ to 12.45+ months (+ indicates a censored observation). Median PFS was 6.5 months (95% CI: 4.7 to 8.2 months) with observations censored for approximately 48% of the patients.

There are no analyses that quantitatively assess persistence of effect after treatment interruption or discontinuation.

The Applicant's Position:

Based on assessment of duration of response and PFS, treatment effect is durable. Persistence of effect after treatment interruption or discontinuation is unknown.

The FDA's Assessment:
The Applicant's position on DOR and PFS is not applicable in this section. FDA agrees with the

Applicant's position that persistence of effect after treatment interruption or discontinuation is unknown.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

No other secondary or exploratory endpoints were undertaken.

The Applicant's Position:

Not applicable.

The FDA's Assessment:
Not applicable.

Additional Analyses Conducted on the Individual Trial

Data:

The sponsor did not conduct exploratory analyses for efficacy.

The Applicant's Position:

Not applicable.

The FDA's Assessment:
Not applicable.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

This application is supported by results from Study 849-001. Of the 116 patients enrolled in the trial, 112 patients had measurable disease at baseline as assessed by BICR. Among these 112 patients, there were 47 patients with PRs and one patient with a CR based on the assessment by BICR, which resulted in an ORR of 43% (95% CI: 34% to 53%). As of a data cutoff date of October 15, 2021, the median DOR was 8.5 months (95% CI: 6.2 to 13.8 months). The responses were durable with 28 responders (58% of responders) having a response duration of 6 months or longer. Sensitivity analyses demonstrated the robustness of the ORR and DOR results. Subgroup analyses demonstrated the consistency of the results across various prespecified subgroups, except current smokers where only one response was observed out of eleven patients. However, the subgroup analysis results should be interpreted with caution due to the

small sample sizes.

8.1.4. Assessment of Efficacy Across Trials

Primary Endpoints

Data:

Study 849-001 is the only study supporting the efficacy claim for this NDA.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

Secondary and Other Endpoints

Data:

Study 849-001 is the only study supporting the efficacy claim for this NDA.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

Subpopulations

Data:

Study 849-001 is the only study supporting the efficacy claim for this NDA.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

Additional Efficacy Considerations

The FDA's Assessment:

Not applicable.

8.1.5. Integrated Assessment of Effectiveness

Data:

Study 849-001 is the only study supporting the efficacy claim for this NDA.

The Applicant's Position:

Not applicable.

The FDA's Assessment:
Not applicable.

8.2. Review of Safety

Data:

The safety population summarized in the Integrated Safety Summary (ISS) includes 265 patients participating in Phase 1/1b and Phase 2 segments in Study 849-001 (Applicant Table 16).

Applicant Table 16: Safety Population Included in Integrated Safety Summary

Study 849-001 Segment	Adagrasib Starting Dose and Regimen	Number of Patients in Safety Evaluation	Diagnosis
Phase 1/1b dose escalation, expansion	150-1200 mg once daily	5	Solid tumor with *KRAS* G12C mutation in tumor tissue
Phase 1b dose expansion	600 mg twice daily	20	Solid tumor with *KRAS* G12C mutation in tumor tissue
Phase 2, Cohort A	600 mg twice daily	116	NSCLC with *KRAS* G12C mutation in tumor tissue
Phase 2, Cohort B	600 mg twice daily	56	NSCLC with *KRAS* G12C mutation in ctDNA
Phase 2, Cohort C	600 mg twice daily	44	Colorectal carcinoma with *KRAS* G12C mutation in tumor tissue or ctDNA
Phase 2, Cohort D	600 mg twice daily	24	Solid tumor with *KRAS* G12C mutation in tumor tissue or ctDNA

Abbreviations: ctDNA = circulating tumor DNA; NSCLC = non-small cell lung cancer.
Source: Module 2.7.4

With few exceptions, the focus for discussion in this safety section of the Assessment Aid is on the pivotal study, Cohort A (n = 116). Comment on the safety data for the total group of patients in Study 849-001 treated with adagrasib 600 mg twice daily (n = 260) is included where warranted. Data tables are presented with the following data columns:

1. Phase 2 Cohort A (n =116 patients)
2. Other patients treated with adagrasib 600 mg twice daily regimen (n = 144 patients)
3. Total 600 mg twice daily group (n = 260 patients)

The schedule of assessments for Study 849-001 is presented in Applicant Table 17. Adagrasib treatment was administered in 3-week cycles. A physical examination, including all major body systems, was mandated at screening and the end of treatment visit only. During study treatment, symptom directed physical examinations will be performed during each clinic visit. Vital signs to be assessed include weight, body temperature, blood pressure, pulse rate and respiratory rate. Laboratory safety assessments for which data were collected included hematology, coagulation, thyroid tests, urinalysis and chemistry parameters. Hematology parameters included hemoglobin, platelet, white blood cell, neutrophil, lymphocyte, eosinophil, basophil, monocyte, and red blood cell counts, as well as reticulocyte percent. Coagulation parameters assessed were international normalized ratio and partial thromboplastin time. Urinalysis was performed by dipstick and included blood, glucose and protein parameters. Thyroid stimulating hormone was assessed. Serum chemistry parameters included AST, ALT, alkaline phosphatase, lactate dehydrogenase, total bilirubin, creatinine, blood urea nitrogen, uric acid, total protein, albumin, glucose (non-fasted), sodium, potassium, chloride, bicarbonate, total calcium, phosphate, magnesium, lipase, amylase, and creatine kinase. Single and triplicate ECGs were performed as outlined in Applicant Table 17. It was preferable that the machine used had the capacity to calculate the standard intervals automatically with overreading by a cardiologist where warranted. In addition, QTc was derived programmatically using the Fridericia's formula. During study treatment, triplicate ECGs were to coincide with PK sample collection as indicated in Applicant Table 17 and as unscheduled assessments when warranted. A multigated acquisition scan (MUGA) (preferred) or echocardiogram (ECHO) was performed as outlined in the schedule of assessments; additional assessments of left ventricular ejection fraction (LVEF) were performed as clinically indicated. Ophthalmology examinations performed at screening and as clinically indicated included visual acuity test, physical examination, and ophthalmological examination of the anterior and posterior chambers, i.e., slit lamp and funduscopic examinations.

Applicant Table 17: Study 849-001 Abbreviated Assessment Schedule [1]

	Screen/ Baseline	Cycle 1			Cycles 2 and 3		Subsequent Cycles	End of Treatment
	Within 28 days	Day 1	Day 8	Day 15	Day 1	Day 15	Day 1	At least 28 Days After Last Dose
Physical Exam	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X
Coagulation	X	X			X			X
Serum Chemistry	X	X	X	X	X	X	X	X
Thyroid Function	X							X
Urinalysis (dip stick)	X	X						X
Single ECG	X							X
Triplicate ECG		Pre-dose and Peak	Pre-dose and Peak		Pre-dose and Peak		Pre-dose Cycle 5	
PK Sample		Pre-dose and Peak	Pre-dose and Peak		Pre-dose and Peak		Pre-dose Cycle 5	
MUGA or ECHO	Within 45 days				Day 1 every other cycle (Cycles 3, 5, 7, etc.)			X
Ophthalmology	X							
PK Sampling		Pre-dose and Peak	Pre-dose and Peak		Pre-dose and Peak Cycle 2 Pre-dose Cycle 5			
Disease Evaluation	X	Every 6 weeks						

Abbreviations: ECG = electrocardiogram; ECHO = echocardiogram; MUGA = multigated acquisition scan; PK = pharmacokinetic.

[1] The schedule of assessments presented applied after the initial dose escalation phase. During the dose escalation phase, additional assessments included physical examination with vital signs Cycle 1 Day 4, Cycle 2 Day 8, and Day 15 of subsequent cycles; hematology on Day 15 of Cycles 4 and subsequent; coagulation Day 1 of Cycle 4 and subsequent; thyroid function on Day 1 of each cycle; and additional PK sampling.

Source: Module 5.3.5.2

The Applicant's Position:

The safety population comprised 265 patients, including 260 patients treated at the Phase 2 starting dose, adagrasib 600 mg twice daily, with 116 patients in pivotal Cohort A. The safety profile of adagrasib was assessed through collection of safety data that included AEs, laboratory assessments, ECGs, and multigated acquisition scan/echocardiogram. Laboratory parameters

were assessed at scheduled intervals and included hematology and chemistry, as well as liver function tests, amylase, lipase, thyroid stimulating hormone, and creatine kinase. The size of the safety population, prospective collection of safety data, focus on data quality, and summary of safety data are sufficient to enable characterization of the safety profile of adagrasib.

The FDA's Assessment:

FDA agrees with the Applicant's position with the caveat that on March 17, 2022, the Applicant submitted the 120-day safety update which provided an updated number of patients as of the data cut-off (DCO) date of October 15, 2021; a breakdown of the patients is provided in FDA - Table 18. The safety analyses done by FDA was based upon the primary safety population consisting of patients from Phase 2 Cohort A (n = 116; DCO date of June 15, 2021; herein referred to as the "primary safety population") and the pooled safety population of all patients with solid tumors with *KRAS G12C* mutation dosed with adagrasib 600 mg twice daily (n = 366, DCO date of October 15, 2021; herein referred to as the "pooled safety population").

FDA - Table 18 Safety Populations

	Adagrasib Starting Dose and Regimen	**Number of Patients in Safety Evaluation**	**Diagnosis**
Study 849-001 (KRYSTAL-1)			
Phase 1/1b dose escalation, expansion	150-1200 mg QD	5	Solid tumor with *KRAS* G12C mutation in tumor tissue
Phase 1b dose expansion	600 mg BID	60	Solid tumor with *KRAS* G12C mutation in tumor tissue
Phase 2, Cohort A	600 mg BID	116	NSCLC with *KRAS* G12C mutation in tumor tissue
Phase 2, Cohort B	600 mg BID	60	NSCLC with *KRAS* G12C mutation in ctDNA
Phase 2, Cohort C	600 mg BID	44	Colorectal carcinoma with *KRAS* G12C mutation in tumor tissue or ctDNA
Phase 2, Cohort D	600 mg BID	43	Solid tumor with *KRAS* G12C mutation in tumor tissue or ctDNA
Phase 2, Cohort E	600 mg BID	16	NSCLC with *KRAS* G12C and *STK11* mutations
Phase 2, Cohort F	600 mg BID	23	Colorectal carcinoma with *KRAS* G12C mutation in tumor tissue
Study 849-012 (KRYSTAL-12)			
Adagrasib Arm	600 mg BID	4	NSCLC with *KRAS G12C* mutation in tumor tissue
Total		371	All patients dosed with at least one dose of adagrasib
Total Pooled Safety Population	**600 mg BID**	**366**	**Solid tumor with *KRAS G12C* mutation dosed with adagrasib 600 mg BID**

Abbreviations: ctDNA - circulating tumor DNA; NSCLC - non-small cell lung cancer.
Source: 120-Day Safety Update, Table 1

8.2.1. Safety Review Approach

Data:

During the conduct of the clinical study, regular safety reviews were performed to evaluate for emerging safety signals with added focus on AEs that could be consistent with nonclinical findings. Reviews of AEs included the type, frequency, severity, seriousness, and investigator-reported relatedness; laboratory and other safety assessments were reviewed for abnormalities. Adverse events that met criteria for seriousness were reviewed by a pharmacovigilance physician on a case basis during study conduct.

Initial characterization of the safety profile after database lock was based on summary and interpretation of safety assessments. Adverse events were summarized according to preferred term and MedDRA classification, and parameters reported included frequency, severity according to NCI CTCAE (version 5) criteria, seriousness, and relatedness. Additionally, AEs leading to dose discontinuation or dose modification (interruption and/or reduction) were summarized. Laboratory studies and other safety assessments were summarized for overall trends and for clinically significant abnormalities.

Based on 1) observations from regular review during the study conduct, 2) observations from review of AEs in MedDRA format for similar conditions reported with different preferred terms, and 3) AEs of potential regulatory interest, standardized MedDRA queries (SMQs) were selected and summarized. Evaluation of AEs included consideration of whether any AEs warranted designation as an AE of special interest.

To fully characterize and describe the safety profile, all safety data were reviewed, integrating reported summaries of AEs and SMQs, laboratory studies, and other safety assessments. Particular attention was paid to carefully review serious adverse events (SAEs) including deaths, any designated medical events, and any unusual events with high degree of unexpectedness. Frequencies of AEs were interpreted against estimated background rates. Supplemental analyses were performed for certain AEs to characterize timing and outcome after dose modification.

The Applicant's Position:

The sponsor's approach to safety review approach was comprehensive and enabled characterization of the safety profile, and the sponsor's description of the safety profile in Module 2.7.4 and summary tables are expected to enable quality Agency review of key safety data observed in patients treated with adagrasib.

The FDA's Assessment:

FDA generally agrees with the Applicant's position regarding the safety review approach. However, FDA has applied this approach to both the primary safety population and the pooled safety population. FDA combined analgous or closely related preferred terms (PTs) into custom grouped terms (GTs) for the analyses as indicated throughout the Assessment Aid.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

The extent of adagrasib exposure is summarized for the Safety Population, defined as all patients receiving at least one dose of study treatment. In Cohort A, the median duration of exposure at the time of the data cutoff was 5.70 months (range: 0.03 to 16.13 months), and the median number of cycles started was 9 (range: 1 to 23) (Applicant Table 19). In the total group of patients treated at 600 mg twice daily (n = 260), the median duration of exposure was 5.55 months. The duration of exposure exceeded 12 months for 5.2% of patients in Cohort A and 5.8% of the broader group of patients starting treatment at 600 mg twice daily.

Applicant Table 19: Summary of Adagrasib Exposure

	Adagrasib 600 mg Twice Daily		
Variable	**Cohort A (N=116)**	**Other (N=144)**	**Total (N=260)**
Study Treatment Duration (months)			
n	116	144	260
Mean (std)	5.798 (4.0153)	5.866 (3.8409)	5.836 (3.9122)
Median	5.700	5.520	5.552
Q1, Q3	2.136, 8.312	2.858, 7.901	2.710, 8.246
Min, Max	0.03, 16.13	0.16, 18.07	0.03, 18.07

	Adagrasib 600 mg Twice Daily		
Variable	**Cohort A (N=116)**	**Other (N=144)**	**Total (N=260)**
Study Treatment Duration n(%)			
≤ 3 months	39 (33.6)	37 (25.7)	76 (29.2)
> 3-6 months	23 (19.8)	43 (29.9)	66 (25.4)
> 6-12 months	48 (41.4)	54 (37.5)	102 (39.2)
> 12-18 months	6 (5.2)	9 (6.3)	15 (5.8)
> 18-24 months	0	1 (<1)	1 (<1)
Total Number of Cycles initiated			
n	116	144	260
Mean (std)	8.5 (5.74)	8.7 (5.57)	8.6 (5.64)
Median	9.0	8.0	8.0
Q1, Q3	3.0, 12.0	4.0, 11.5	4.0, 12.0
Min, Max	1, 23	1, 27	1, 27
Relative Dose Intensity (%) [a]			
n	116	144	260
Mean (std)	75.53 (22.167)	80.63 (19.653)	78.35 (20.925)
Median	79.61	84.93	82.62
Q1, Q3	58.44, 98.17	65.25, 99.71	62.51, 99.35
Min, Max	24.3, 100.0	33.0, 100.9	24.3, 100.9

Abbreviations: max = maximum; min = minimum; Q1 = first quartile; Q3 = third quartile; std = standard deviation
[a] Relative dose intensity calculated as the cumulative dose received (mg)/cumulative planned dose (mg)* 100.
Source: Module 2.7.4

The Applicant's Position:

The extent of exposure, based on 260 patients receiving the adagrasib 600 mg twice daily regimen, including 116 patients in Cohort A with a median duration of exposure of 5.70 months, and approximately 6% of patients treated over 1 year, is sufficiently broad to characterize the safety profile of adagrasib.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. FDA conducted exposure analysis for both the primary safety population and the updated pooled safety population as shown in FDA - Table 20. For the pooled safety population, the median duration of exposure is 4.9 months, with approximately 15% of patients being treated over one year.

FDA - Table 20: Summary of Adagrasib Exposure

	Adagrasib 600 mg Twice Daily	
Variable	**Cohort A [a] (N=116)**	**Total [b] (N=366)**
Study Treatment Duration (months)		
n	116	366
Mean (std)	5.8 (4.0)	6.1 (5.3)
Median	5.7	4.9
Q1, Q3	2.1, 8.3	1.7, 9.5
Min, Max	0.0, 16.1	0.0, 28.7
Study Treatment Duration n (%)		
≤ 3 months	39 (34)	132 (36)
> 3-6 months	23 (20)	86 (24)
> 6-12 months	48 (41)	94 (26)
> 12-18 months	6 (5)	44 (12)
> 18-24 months	0	7 (1.9)
> 24 months	0	3 (0.8)
Total Number of Cycles initiated		
n	116	366
Mean (std)	8.5 (5.7)	9.0 (7.5)
Median	9	7
Q1, Q3	3, 12	1, 13.3
Min, Max	1, 23	1, 42
Relative Dose Intensity (%) [c]		
n	116	366
Mean (std)	75.5 (22.2)	79.2 (21.3)
Median	79.6	85.1
Q1, Q3	58.3, 98.3	63.4, 99.4
Min, Max	24.3, 100.0	13.5, 112.7

Abbreviations: max = maximum; min = minimum; Q1 = first quartile; Q3 = third quartile; std = standard deviation
[a] Data-cut off date of June 15, 2021
[b] Data-cut off date of October 15, 2021
[c] Relative dose intensity calculated as the cumulative dose received (mg)/cumulative planned dose (mg)*100.
Source: ADEX and ADEXSUM datasets

Relevant characteristics of the safety population:

Data:

The Enrolled population included all patients who signed the main study informed consent form and were determined by the Investigator to meet all eligibility criteria during screening assessments. The eligibility criteria required ECOG PS 0 or 1, adequate blood counts, acceptable

liver function tests, creatinine clearance ≥ 60 mL/min, no active brain metastases, no unstable angina pectoris or congestive heart failure (of ≥ NYHA Class 3), no recent stroke, and no ongoing need of certain concomitant medications. The Enrolled population was used to describe demographics and baseline disease characteristics and could have included patients who did not receive treatment.

The Safety Population was defined as all patients who received at least 1 dose of study medication and was used to summarize safety assessments. The demographics and baseline characteristic of patients (n = 260) participating in Study 849-001 are listed in Applicant Table 21.

Applicant Table 21: Demographic and Baseline Characteristic

	Adagrasib 600 mg Twice Daily		
Characteristic	**Cohort A (N=116)**	**Other (N=144)**	**Total (N=260)**
Sex [n (%)]			
Male	51 (44.0)	61 (42.4)	112 (43.1)
Female	65 (56.0)	83 (57.6)	148 (56.9)
Race [n (%)]			
White	97 (83.6)	119 (82.6)	216 (83.1)
Black or African American	9 (7.8)	12 (8.3)	21 (8.1)
Asian	5 (4.3)	6 (4.2)	11 (4.2)
American Indian or Alaska Native	1 (<1)	1 (<1)	2 (<1)
Other	4 (3.4)	6 (4.2)	10 (3.8)
Ethnicity [n (%)]			
Hispanic or Latino	3 (2.6)	11 (7.6)	14 (5.4)
Not Hispanic or Latino	107 (92.2)	130 (90.3)	237 (91.2)
Missing	6 (5.2)	3 (2.1)	9 (3.5)
Age (years)			
n	116	144	260
Mean (std)	64.4 (9.64)	61.4 (11.92)	62.8 (11.04)
Median	64.0	62.5	64.0
Q1, Q3	60.0, 70.0	55.0, 70.5	57.0, 70.0
Min, Max	25, 89	21, 82	21, 89
Age (years)			
< 65	59 (50.9)	84 (58.3)	143 (55.0)
≥ 65	57 (49.1)	60 (41.7)	117 (45.0)
Age (years)			
< 65	59 (50.9)	84 (58.3)	143 (55.0)
≥ 65-< 75	42 (36.2)	44 (30.6)	86 (33.1)
≥ 75	15 (12.9)	16 (11.1)	31 (11.9)

	Adagrasib 600 mg Twice Daily		
Characteristic	**Cohort A (N=116)**	**Other (N=144)**	**Total (N=260)**
ECOG Performance Status			
0	18 (15.5)	49 (34.0)	67 (25.8)
1	97 (83.6)	95 (66.0)	192 (73.8)
Missing	1 (<1)	0	1 (<1)
Smoking History			
Lifetime Non-smoker	5 (4.3)	48 (33.3)	53 (20.4)
Current Smoker	11 (9.5)	16 (11.1)	27 (10.4)
Former Smoker	100 (86.2)	80 (55.6)	180 (69.2)

Abbreviations: EGOG = Eastern Cooperative Oncology Group; max = maximum; min = minimum; Q1 = first quartile; Q3 = third quartile; std = standard deviation.
[a] Percentages based on the number of female patients
Source: Module 2.7.4

In Cohort A, all 116 (100.0%) patients had been diagnosed with NSCLC, 113 (97.4%) had adenocarcinoma, and 3 (2.6%) patients had squamous histology. Metastatic disease was reported for 103 (88.8%) patients; 13 (11.2%) other patients had locally advanced disease. Sites of metastatic disease at baseline as reported by the BICR included bone (42.0%), brain (30.4%), liver (21.4%), and adrenal (20.5%).

In the 600 mg Twice Daily Total group, 188 patients had been diagnosed with NSCLC. Of these, 96.3% had adenocarcinoma, 3.2% had squamous histology, and 1 (< 1%) had adenosquamous carcinoma histology. Metastatic disease was reported for 90.4% NSCLC patients; 9.6% other patients had locally advanced disease. Forty-six patients had been diagnosed with CRC. Of these, 97.8% had adenocarcinoma, and 1 (2.2%) had other histology. Metastatic disease was reported for 97.8% and 1 (2.2%) patient had locally advanced disease. Twenty-six patients had been diagnosed with other cancers, including 6 with pancreatic cancer, 5 with mucinous appendiceal carcinoma, 4 with cholangiocarcinoma, 3 with ovarian/fallopian tube cancer, 2 with endometrial cancer, 2 with a gastroesophageal junction tumor, 2 with unknown primary tumors, and 2 with other diagnoses. Metastatic disease was reported for 92.3%; 7.7% patients had locally advanced disease.

The Applicant's Position:

The study population is expected to be generalizable in consideration of the representative demographic characteristics, although patients with certain characteristics excluded from the pivotal cohort may be treated in the postmarket setting, including patients with an estimated creatinine clearance below 60 mL/min (considering the advanced age of this patient population), with poorer performance status (e.g., ECOG PS 2), or with active brain metastases, noting

evolving paradigms for the treatment of patients with NSCLC with brain metastases. Additionally, due to individual patient circumstances, some patients may not receive treatment with both a platinum agent and a PD-1/PD-L1 inhibitor prior to treatment with adagrasib. The safety profile for these populations may reflect comorbid conditions, but there are no data to indicate that the safety profile would otherwise be different.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. The comparison of the demographics and baseline characteristics between the primary safety population and the updated pooled safety population is shown in the FDA - Table 23. The two populations are generally similar except that the pooled safety population has more patients with an ECOG performance status of 0 compared to the primary safety population (29% vs 16%) and the pooled safety population has more lifetime non-smokers compared to the primary safety population (20% vs 4.3%).

FDA - Table 22: Demographic and Baseline Characteristics

	Adagrasib 600 mg Twice Daily	
Characteristic0	**Cohort A (N=116)**	**Total (N=366)**
Sex [n (%)]		
Male	51 (44)	156 (43)
Female	65 (56)	210 (57)
Race [n (%)]		
White	97 (84)	301 (82)
Black or African American	9 (8)	33 (9)
Asian	5 (4.3)	14 (3.8)
American Indian or Alaska Native	1 (0.8)	2 (0.5)
Other	4 (3.4)	16 (4.4)
Ethnicity [n (%)]		
Hispanic or Latino	3 (2.6)	22 (6)
Not Hispanic or Latino	107 (92)	334 (91)
Missing	6 (5)	10 (2.7)
Age (years)		
n	116	366
Mean (std)	64.4 (9.6)	63.0 (11.2)
Median	64.0	64.0
Q1, Q3	60.0, 70.0	57.0, 70.0
Min, Max	25, 89	21, 89
Age (years)		
< 65	59 (51)	197 (54)
≥ 65-< 75	42 (36)	120 (33)
≥ 75	15 (13)	49 (13)
ECOG Performance Status		
0	18 (16)	106 (29)
1	97 (84)	259 (71)
Missing	1 (0.8)	1 (0.3)
Smoking History		
Lifetime Non-smoker	5 (4.3)	75 (20)
Current Smoker	11 (9)	46 (13)
Former Smoker	100 (86)	245 (67)

Abbreviations: EGOG = Eastern Cooperative Oncology Group; max = maximum; min = minimum; Q1 = first quartile; Q3 = third quartile; std = standard deviation.
Source: 120- Day Safety Update, Table 6

Adequacy of the safety database:

Data:

The safety database includes 116 patients with NSCLC in Cohort A and an additional 144 patients starting treatment at 600 mg twice daily, including 56 patients with NSCLC, 44 patients with CRC, 24 patients with other tumors. Among these 260 patients, there were a total of 188 patients with NSCLC. The median duration of exposure was 5.6 months, with patients starting up to 27 cycles of treatment.

The Applicant's Position:

In consideration of the number of patients treated, the number of patients with NSCLC, and the duration of treatment, the safety database is adequate to assess the safety of adagrasib in the intended population.

The FDA's Assessment:
FDA agrees with the Applicant's position on the adequacy of the safety database that includes the primary safety population (n = 116) and the updated pooled safety population based on data provided at the 120-day safety update (n = 366).

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

The type and schedule of safety assessments to be performed during study participation were outlined in the study protocol. Additional, unplanned assessments were performed as clinically indicated, including for the purpose of fully evaluating AEs. The clinical study protocol defined AEs, SAEs, and reporting procedures. Adverse events were reported from the first day of study treatment until at least 28 days after the last study treatment. In addition, SAEs were reported in the safety database from the time of informed consent until resolution. Serious adverse event reconciliation between the clinical and safety databases was performed in accordance with the 849-001 SAE reconciliation plan.

Physical examinations including vital signs were performed at each patient visit. Clinical laboratory safety assessments for which data were collected included hematology, coagulation, chemistry, thyroid tests, and urinalysis parameters. Electrocardiograms and evaluation of LVEF were performed as outlined in the protocol. Ophthalmology evaluation was performed at baseline and as clinically indicated.

Study sites were monitored by clinical research associates following study-specific monitoring plans. Direct access to patient medical and laboratory records was permitted to verify entries on the study-specific CRFs. Data were queried per study-specific data management plans, including automated database edit checks and internal data review by data management, clinical program management, and medical reviewers.

The Applicant's Position:

No issues were identified regarding data integrity or submission quality that had an effect on the safety content of the submission.

The FDA's Assessment:

FDA agrees with the Applicant's position. The data submitted was organized and adequate to perform a complete review of the safety of adagrasib. Overall, FDA agrees that there were no significant data quality or reporting issues identified during the review of this NDA. FDA did issue several information requests during the review cycle to obtain clarification and additional information regarding safety data included in the NDA. Additionally, refer to Section 4.1 regarding limited issues uncovered during the clinical site inspection process.

Categorization of Adverse Event

Data:

All observed or volunteered AEs were reported by the Investigator as verbatim terms in source documents and CRFs. Adverse events were graded for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 5.0) and coded according to Medical Dictionary for Regulatory Activities (MedDRA), version 21.0. Specific events were evaluated based on standardized MedDRA queries when applicable.

The best available medical terminology was used to describe AEs in source documents and CRFs. Terms describing the diagnosis were preferred over individual signs and symptoms of the diagnosis. If determination of the diagnosis was delayed, signs and symptoms were recorded and the diagnosis recorded as an additional AE when available. Any ongoing AE that changed in attribution or increased in severity was captured as a new AE. A TEAE was defined as an event that started or worsened on or after the first day of study treatment. Abnormal laboratory test results were reported as AEs only if assessed by the Investigator as clinically significant taking into account of the following: clinical symptoms; requirement for additional tests (beyond repeats), treatment, or intervention; resulted in change in study treatment dosing; requirement for discontinuation from study treatment; and/or considered by the Investigator or Sponsor to be an AE. The schedule of events included a specific visit to capture nonserious AEs occurring up to 28 days after the last dose, and serious SAEs were followed until resolution, stabilization,

or permanent impairment. Verbatim terms reflecting more than one preferred term were queried to split into different terms.

The Applicant's Position:

The protocols defined AEs and SAEs, as well as the reporting procedures. The collection of AEs in the clinical studies was appropriate. Recording, coding, and categorization of AEs were appropriate.

The FDA's Assessment:
FDA agrees with the Applicant's position. For purposes of the FDA review of safety, incidences of adverse events were analyzed without consideration of relatedness particularly given the safety data supporting this NDA is from a nonrandomized, non-comparative clinical trial. Additionally, as there may be heterogeneity between investigators and difficulty in accurately assigning attribution of adverse events to study therapy, FDA generally does not report drug-related adverse events.

Routine Clinical Tests

Data:

The protocol for Study 849-001 prespecified clinical laboratory parameters to be evaluated during study participation (see Section 8.2). Local laboratories were used for routine laboratory parameters, and reference ranges for each laboratory were collected and used in the analysis. Clinical significance of laboratory values that were out of range was determined and reported by the investigator; clinically significant abnormalities were reported as AEs.

The Applicant's Position:

Laboratory assessments were carried out as specified in Protocol 849-001 with adequate frequency and duration for a robust safety assessment.

The FDA's Assessment:
FDA agrees with the Applicant's position with regards to the adequacy of clinical laboratory monitoring.

8.2.4. Safety Results

Deaths

Data:

Among 116 patients enrolled in Study 849-001 Cohort A, 17.2% of patients experienced AEs with the outcome of death within 28 days after the last dose of adagrasib (Applicant Table 24). The causes of death were malignant neoplasm progression (6.9%); respiratory failure (2.6%); pneumonia (1.7%); and acute respiratory failure, pulmonary embolism, pulmonary hemorrhage, cardiac failure, death not otherwise specified, cerebrovascular accident, and mental status changes (each < 1%).

Applicant Table 23: Treatment-emergent Adverse Events with Outcome of Death within 28 days of Last Dose by System Organ Class and Preferred Term

	Adagrasib 600 mg Twice Daily		
System Organ Class Preferred Term [n (%)]	**Cohort A (N=116)**	**Other (N=144)**	**Total (N=260)**
Patients with at least 1 TEAE with Outcome of Death	20 (17.2)	13 (9.0)	33 (12.7)
Cardiac disorders	1 (<1)	1 (<1)	2 (<1)
Cardiac arrest	0	1 (<1)	1 (<1)
Cardiac failure	1 (<1)	0	1 (<1)
General disorders and administration site conditions	1 (<1)	0	1 (<1)
Death	1 (<1)	0	1 (<1)
Hepatobiliary disorders	0	1 (<1)	1 (<1)
Hepatic failure	0	1 (<1)	1 (<1)
Infections and infestations	2 (1.7)	1 (<1)	3 (1.2)
Pneumonia	2 (1.7)	0	2 (<1)
Enterocolitis infectious	0	1 (<1)	1 (<1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (6.9)	4 (2.8)	12 (4.6)
Malignant neoplasm progression	8 (6.9)	4 (2.8)	12 (4.6)
Nervous system disorders	1 (<1)	0	1 (<1)
Cerebrovascular accident	1 (<1)	0	1 (<1)
Psychiatric disorders	1 (<1)	0	1 (<1)
Mental status changes	1 (<1)	0	1 (<1)

System Organ Class Preferred Term [n (%)]	Adagrasib 600 mg Twice Daily Cohort A (N=116)	 Other (N=144)	 Total (N=260)
Respiratory, thoracic and mediastinal disorders	6 (5.2)	6 (4.2)	12 (4.6)
Respiratory failure	3 (2.6)	2 (1.4)	5 (1.9)
Acute respiratory failure	1 (<1)	2 (1.4)	3 (1.2)
Chronic obstructive pulmonary disease	0	1 (<1)	1 (<1)
Pneumonitis	0	1 (<1)	1 (<1)
Pulmonary embolism	1 (<1)	0	1 (<1)
Pulmonary haemorrhage	1 (<1)	0	1 (<1)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent AE.
Note: For each system organ class and preferred term, patients are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Module 2.7.4

The Applicant's Position:

Review of fatal AEs did not identify any findings that were assessed as adverse drug reactions (ADRs) that warrant inclusion in the US Prescribing Information (USPI). Two AEs with an outcome of death were assessed by the sponsor as treatment related. Cardiac failure was reported in a patient hospitalized for the nausea and increased creatinine who developed cardiac failure and pericardial effusion with cardiac tamponade 4 days after admission. Risk factors for development of myocardial or pericardial inflammation include prior treatment with pembrolizumab. In review of the totality of the data, cardiac failure was not assessed as an adverse drug reaction. Pulmonary hemorrhage was reported for a patient with baseline tumor involvement of the right pulmonary artery that resulted in hemorrhage, possibly precipitated by a rapid tumor response to treatment. Because tumor invasion into the vessel was the cause of the hemorrhage, this case is not included in the proposed USPI. Among the cases reported as unrelated to study drug, fatal malignant neoplasm progression was reported for 8 patients; 4 additional deaths were due to disease progression and reported as death, mental status changes, respiratory failure, and pulmonary embolism, which was coincident with disease progression. Additionally, pneumonia was the cause of death for 5 patients and assessed as unrelated to study treatment and included 4 cases in patients with COPD and significant corticosteroid use and 1 patient with pneumonia as a complication of urosepsis; these cases were reported using preferred terms of pneumonia, respiratory failure, and acute respiratory failure and represent expected events for this patient population. One additional case due to cerebrovascular accident in a patient with a history of transient ischemic attacks was reported following transiently decreased LVEF complicated by a watershed stroke and assessed as unrelated to study treatment.

The FDA's Assessment:

Below are FDA's results for treatment-emergent adverse events with outcome of death within 28 days of the last dose for both the primary safety population and the FDA pooled safety

population (n=366). Cases of "malignant neoplasm progression" were not included as fatal AEs; however, patient narratives for all cases of malignant neoplasm progression from Cohort A and the pooled safety population were reviewed to determine if additional information or readjudication of the cause of the fatal AE were necessary. In Cohort A there was one case of malignant neoplasm progression that was determined by FDA to be "sudden death" (patient ID# 849-001-(b) (6)). In the pooled safety population, there were 3 cases of maliganant neoplasm progression that were readjudicated to 2 cases of pneumonia and 1 case of sepsis.

FDA - Table 24: Treatment-emergent Adverse Events with Outcome of Death within 28 days of Last Dose by System Organ Class and Preferred Term

	Adagrasib 600 mg Twice Daily	
System Organ Class Preferred Term [n (%)]	**Cohort A (N=116)**	**Total (N=366)**
Patients with at least 1 TEAE with Outcome of Death	13 (11)	31 (8)
Cardiac disorders	1 (0.8)	4 (1.1)
Cardiac failure	1 (0.8)	2 (0.5)
Cardiac arrest	0	2 (0.5)
General disorders and administration site conditions	2 (1.7)	3 (0.8)
Sudden Death	2 (1.7)	3 (0.8)
Infections and infestations	4 (3.4)	10 (2.7)
Pneumonia	4 (3.4)	8 (2.2)
Infectious enterocolitis	0	1 (0.3)
Sepsis	0	1 (0.3)
Nervous system disorders	1 (0.8)	1 (0.3)
Cerebrovascular accident	1 (0.8)	1 (0.3)
Psychiatric disorders	1 (0.8)	1 (0.3)
Mental status changes	1 (0.8)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	4 (3.4)	12 (3.3)
Respiratory failure*	2 (1.7)	6 (1.6)
Pulmonary embolism	1 (0.8)	2 (0.5)
Pulmonary hemorrhage	1 (0.8)	1 (0.3)
Chronic obstructive pulmonary disease	0	1 (0.3)
Dyspnea	0	1 (0.3)
Pneumonitis	0	1 (0.3)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent AE.
* Grouped term.
Note: For each system organ class and preferred term, patients are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: ADSL and ADAE datasets

FDA reviewed all fatal adverse events that occurred in both the primary and pooled safety populations. In the primary safety population, deaths due to AEs that were not clearly related to disease progression or an alternative etiology according to patient narratives were reported in thirteen patients (11%). The fatal AEs for which adagrasib's involvement could not be ruled out include pneumonia (3.4%), respiratory failure (1.7%), sudden death (1.7%), cardiac failure (0.9%), cerebrovascular accident (0.9%), mental status change (0.9%), pulmonary embolism (0.9%), and pulmonary hemorrhage (0.9%). FDA - Table 26 below describes the fatal AEs and FDA's determination of death causality in greater detail.

FDA - Table 25: FDA Assessment of Causality for Fatal Adverse Events in Primary Safety Population

Patient ID	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality	Included in U.S. Prescribing Information
849-001-(b) (6)	68-year-old male who was found to have disease progression on Day 43 (last treatment on Day 42). Patient subsequently found unresponsive on Day 49 with EMS called and patient pronounced dead; no autopsy was done, and Grade 5 **malignant neoplasm progression** was reported.	Malignant Neoplasm Progression Given the patient's progressive disease and discontinuation of treatment prior to sudden death, FDA agrees that this death was likely due to disease progression.	No
849-001-(b) (6)	75-year-old male who was hospitalized on Day 12 due to sepsis and syncope. During work-up, imaging showed a malignant left pleural effusion. Patient was treated with antibiotics and discharged on Day 22. On Day 28, fatal **malignant neoplasm progression** was reported; no autopsy was done.	Malignant Neoplasm Progression Given the worsening disease noted on imaging (i.e., pleural effusion), FDA agrees that the patient's death was likely due to disease progression.	No
849-001-(b) (6)	61-year-old female who presented to the emergency department on Study Day 277 with lethargy, right hand weakness, and visual field deficit and was hospitalized with Grade 3 myocardial infarction, Grade 3 lung infection, Grade 2 cerebrovascular accident, and Grade 1 heart failure. On Study Day 271, MRI brain revealed multiple areas of stroke in a watershed distribution. ECG revealed ST elevation consistent with myocardial infarction attributed to takotsubo cardiomyopathy. Patient was treated with sacubitril/valsartan and metoprolol for heart	Cerebrovascular Accident FDA agrees with the investigators assessment of the cause of death of cerebrovascular accident.	Yes

Patient ID	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality	Included in U.S. Prescribing Information
	failure and transferred to a rehabilitation center on Study Day 282. On Study Day 294 the patient was admitted to an outside hospital due to a Grade 4 cerebrovascular accident and subsequently experienced Grade 5 **cerebrovascular accident** on Study Day 297.		
849-001-(b) (6)	70 year-old female with persistent right lower extremity weakness attributed to steroid myopathy and poor oral intake and was hospitalized on Study Day 135 for Grade 2 increased creatinine. CT chest showed left lung ground glass opacities consistent with inflammation and infection, new left lower lobe nodule, increased, small right pleural effusion, and new trace left pleural effusion. Patient underwent bronchoscopy with bronchoalveolar lavabe (BAL) revealing *Pneumocystis carinii* pneumonia, methicillin-resistant *Staphylococcus aureus*, *Pseudomonas*, and cytomegalovirus. The patient's condition worsened and she died of Grade 5 **acute respiratory failure** on Study Day 149.	Pneumonia Given the imaging, cultures, and signs and symptoms pointing towards pneumonia, FDA determined the patient's likely cause of death was pneumonia.	Yes
849-001-(b) (6)	64-year-old female hospitalized on Day 31 with dyspnea, hypoxia, tachycardia, leukocytosis, and electrolyte abnormalities. CT scan showed a collapsed right lung and right moderate to large pleural effusion, and ground glass opacities of lingula. The patient underwent a right thoracentesis, which improved symptoms. CT abdomen-pelvis was concerning for ileus and malignancy. The patient was noted to be anemic. A PleurX catheter was placed to drain the pleural effusion. However, the patient was found to be septic on Day 46. The following day, a "Do Not Resuscitate" (DNR) order was signed and on Day 50, the patient died due to Grade 5 **malignant neoplasm progression**.	Malignant Neoplasm Progression Given the patient's disease progression seen on imaging, with worsening pleural effusion and new disease noted on the CT abdomen-pelvis, FDA agrees that the patient's worsening condition and death were ultimately related to disease progression.	No
849-001-(b) (6)	70-year-old female who underwent bilateral, percutaneous nephrostomy tube placement for bilateral hydronephrosis most likely due to peritoneal/retroperitoneal involvement of	Respiratory Failure FDA agrees with the investigators assessment of the	Yes

Patient ID	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality	Included in U.S. Prescribing Information
	their cancer (the patient was found to have acute kidney injury during screening). She started treatment on adagrasib two weeks later. On Day 69 she was hospitalized for Grade 4 sepsis and Grade 4 respiratory failure. CT imaging revealed progressive disease, including interlobular septal thickening in the lung consistent with progression of lymphangitic spread and no evidence of pulmonary emboli. Urine and blood cultures yielded Pseudomonas aeruginosa. She was treated with pressors and antibiotics in the intensive care unit and subsequently transitioned to comfort care on Day 70 and died on Study Day 71 due to **respiratory failure**.	cause of death of respiratory failure.	
849-001-(b) (6)	43-year-old female experienced Grade 3 nausea and vomiting and Grade 1 diarrhea on Day 10. On Day 11, she developed Grade 3 serum creatinine elevation and was hospitalized. During the hospitalization, on Day 15, she developed Grade 4 cardiac failure, Grade 3 ejection fraction decreased, Grade 3 troponin T increased, and Grade 4 respiratory failure. On Day 16, she developed Grade 4 cardiac tamponade and pericardial effusion and Grade 3 seizures. She died on Day 19 from **cardiac failure**.	Cardiac Failure FDA agrees with the investigators assessment of the cause of death of cardiac failure.	Yes
849-001-(b) (6)	79-year-old male with history of chronic obstructive pulmonary disease, pneumonitis (with ongoing, limited respiratory reserve) was hospitalized on Day 32 for Grade 3 partial large bowel obstruction. The patient underwent exploratory laparotomy and lysis of adhesions on Day 33; hospital course was complicated by urinary tract infection and nosocomial pneumonia manifested by acute decompensation of respiratory function; he was treated with cefepime. The patient's oxygen requirement progressively increased, and he was transitioned to a "do not attempt resuscitation/do not intubate" status and died on Day 47 due to Grade 5 **pneumonia**.	Pneumonia FDA agrees with the investigators assessment of the cause of death of pneumonia.	Yes
849-001-(b) (6)	62-year-old female who developed symptoms associated with radiation induced cholecystitis (found on CT) on Day 237 and	Malignant Neoplasm Progression	No

Patient ID	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality	Included in U.S. Prescribing Information
	was admitted for management. Patient was treated with fluids and antibiotics, with symptom improvement and was discharged. She restarted treatment on Day 275. Patient was found to have disease progression on Day 316 (discontinued treatment). She subsequently died on Day 343 due to Grade 5 **malignant neoplasm progression**; no autopsy done.	Given the patient's progressive disease and discontinuation of treatment prior to death, FDA agrees that this death was likely due to disease progression.	
849-001 (b) (6)	67-year-old male, with history of COPD, DVT, and chronic pulmonary emboli, with increasing dyspnea on Day 71. CT images showed improvement of pulmonary emboli and new, patchy consolidation and ground glass opacities bilaterally, attributed to possible multifocal pneumonia and increasing bilateral pleural effusions. The patient was treated with antibiotics and with alteplase for possible pulmonary embolism. On Day 73, the patient developed worsening respiratory distress, small volume hemoptysis, and increasing oxygen requirement; he was subsequently to transitioned to hospice on Day 73. The patient died of pneumonia on Day 75 due to Grade 5 **pneumonia**.	Pneumonia Given the imaging findings and treatment with antibiotics, FDA agrees with the investigator's assessment that death was likely due to pneumonia.	Yes
849-001- (b) (6)	61-year-old male with history of pneumonitis, pulmonary embolism, COPD, found to have disease progression on Day 204, with treatment discontinued on Day 212. The patient then presented on Day 219 with dyspnea and cough and was hospitalized for interstitial pneumonitis. Chest X-ray showed multifocal pneumonia, and CT showed disease progression in the lung and interlobular septal thickening concerning for lymphangitic spread. He was treated with antibiotics, inhaled bronchodilators, and corticosteroids and discharged after 3 days. On Day 225, the patient was hospitalized for Grade 3 worsening dyspnea and productive cough. CT chest was negative for pulmonary embolism and revealed extensive disease in the lungs. Treatment included antibiotics, inhaled bronchodilators, and corticosteroids. The patient was discharged to hospice care on	Pneumonia While the etiology of the patient's death involved multiple factors, given the imaging findings and the interventions used, FDA determined the cause of death to be pneumonia.	Yes

Patient ID	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality	Included in U.S. Prescribing Information
	Day 227. The patient died due to Grade 5 **respiratory failure** on Day 228.		
849-001-(b) (6)	78-year-old female with a history of brain metastasis (from lung primary) in the right precentral gyrus, intracerebral hemorrhage, left-sided weakness, seizure (with ongoing treatment with levetiracetam), breast cancer, hemifacial spasm, hypertension, diabetes, and hypothyroidism was hospitalized on Day 21 for Grade 3 left-sided weakness. She had discontinued apixaban 2 days prior. Noncontrasted head CT, CT angiography of the head and neck with contrast, and CT cerebral perfusion analysis revealed no evidence of acute intracranial abnormality. On Day 28, left-sided weakness spontaneously resolved. On Day 120, she presented with slurred speech, difficulty walking, and altered mental status and was admitted for further evaluation. CT of the head revealed focal gyral edema. Brain MRI on Day 122 demonstrated a subacute to chronic intraparenchymal hematoma at the right precentral gyrus and mild chronic small vessel ischemic changes within the periventricular and subcortical white matter. EEG on Day 124 showed intermittent bursts of diffuse, frontally predominant, semirhythmic delta consistent with generalized rhythmic delta activity and mild to moderate, diffuse slowing of the background consistent with mild to moderate, diffuse encephalopathy, and no epileptiform activity, with a subsequent report on Day 126 indicating diffuse onset nonconvulsive ictal activity constituting greater than 50% of the recorded period. She was subsequently treated with anticonvulsants. On Day 144, the patient required intubation and was admitted to the ICU for ventilatory and supportive care; she was transitioned to hospice care and died on Day 144 due to **mental status change**.	Mental Status Changes It is unclear what the underlying etiology of the mental status change was and if and how much cerebrovascular accident and/or seizures have contributed. Additionally, it is unclear if disease progression contributed as well. As such, FDA agrees with classification of the fatal event being due to mental status change.	Yes
849-001(b) (6)	76-year-old male with a medical history that included dyspnea, cough, essential hypertension, and coronary artery disease.	Sudden Death	Yes

Patient ID	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality	Included in U.S. Prescribing Information
	During study participation, the patient developed Grade 2 pulmonary hypertension on Day 131 thought to be secondary to underlying lung cancer and was seen by a right heart specialist and treated with tadalafil from Day 147 to Day 189, riociguat from Day 177 to Day 196, and inhaled treprostinil starting on Day 264. On Day 266, the patient was found unresponsive at home and died due to Grade 5 **malignant neoplasm progression**. The investigator assessed the overall cause of death as the underlying malignancy, with the differential for an acute event including pulmonary embolism and pulmonary hypertension-related cardiac event, potentially related to the initiation of treatment with an inhaled vasodilator two days earlier. A widened QTcF interval was observed approximately six months prior to death however no subsequent electrocardiograms were provided for review.	Given the confounding factors in the patient's course, including the start of a new drug days prior to death, and the patient being found unresponsive without a work-up being done, FDA has classified the fatal event as due to sudden death.	
849-001-(b) (6)	72-year-old female who was taken off study treatment due to radiologically confirmed disease progression on Day 169. Patient underwent palliative radiation for skeletal metastases on Day 177. On Day 194, the patient enrolled into hospice with worsening pleural effusions and dyspnea, with death the same day due to respiratory failure secondary to **malignant neoplasm progression**; autopsy not performed. Last treatment was on Day 166.	Malignant Neoplasm Progression The patient experienced progressive disease and treatment was discontinued prior to death; as such, FDA agrees that death was likely due to disease progression.	No
849-001-(b) (6)	63-year-old male who reported worsening nausea, vomiting, diarrhea and inability to tolerate the medication. Study treatment was discontinued on Day 19 due to patient request and global deterioration of health, and the patient transitioned to hospice care. The patient died at home due to malignant neoplasm progression on Day 44, with metastatic disease to the liver and brain.	Malignant Neoplasm Progression Given the patient's known widespread metastatic disease, global deterioration of health, and discontinuation of treatment prior to demise, FDA agrees with the determination that the patient's death was most likely due to disease progression.	No
849-001-(b) (6)	55-year-old female who during study participation, developed transient Grade 3	Respiratory Failure	Yes

Patient ID	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality	Included in U.S. Prescribing Information
	heart failure on Day 96, found to have no significant coronary artery disease; study treatment was interrupted between Days 85 and 137. Additionally, patient underwent stereotactic radiosurgery to 23 brain metastases on Day 123 and radiation to an abdominal metastasis on Study Day 130. Restaging CT scans on Day 134 showed disease progression in the chest. Patient resumed treatment from Day 138 to 175. CT scans on Day 176 revealed a right hilar mass obliterating the right middle and upper lobe bronchi with interval development of total post-obstructive collapse/consolidation of the right middle and upper lobes, bulky mediastinal adenopathy, increased right pleural effusion, and increased pericardial effusion. A pleural catheter was placed on Day 184 to manage a recurrent pleural effusion. On Day 188, the patient presented with increased dyspnea and respiratory distress and was hospitalized for respiratory failure and transferred to the ICU. The patient elected transition to comfort care and died of **respiratory failure** on Day 190.	FDA agrees with the investigators assessment of the cause of death of respiratory failure.	
849-001- (b) (6)	58-year-old female patient who developed a post-obstructive pneumonia during a screening bronchoscopy and biopsy of a left lung mass on Day -9, prior to initiating study therapy with adagrasib. On Day -7, the patient was hospitalized for Grade 3 post-obstructive pneumonia and treated with antibiotics, inhaled bronchodilators, and corticosteroids and discharged on Day -5. On Day 8, the patient presented to clinic for a study visit, was mildly hypotensive and had Grade 1 diarrhea, which was improving. He was otherwise tolerating treatment well. Of note, mean QTcF intervals were 456 ms pre-dose and 447 ms post-dose, and random blood glucose was in the normal range. The patient was treated on-study for a total of 9 days and on Day 10, the patient was reported to have died **without a cause of death provided**. The patient's daughter notified the clinic staff that	Sudden Death Given potential confounding factors with comorbid conditions, and the patient's death being reported without patient evaluation, FDA has classified the fatal event as due to sudden death.	Yes

Patient ID	Brief Narrative (Bolded AE is the condition to which the investigator attributed the patient's death)	FDA's Assessment of Causality	Included in U.S. Prescribing Information
	the patient died due to "glucose was too low." An autopsy was not done.		
849-001 (b) (6)	76-year-old male who experienced vomiting and was found to have small bowel obstruction and disease progression by CT imaging on Day 173 (which also corresponded to the day of the last study treatment dose). The patient was hospitalized on Day 176, with a subsequent decision to pursue hospice (Day 182). The patient died on Day 197 due to Grade 5 **malignant neoplasm progression**. No autopsy was done.	Malignant Neoplasm Progression Given the imaging findings and the patient's corresponding symptoms, FDA agrees with the determination of death due to disease progression.	No
849-001 (b) (6)	50-year-old female with a history that included asthma, COPD, and baseline tumor involvement of the distal right pulmonary artery. Upon initiation of treatment, the patient developed rapid symptomatic improvement and resolution of a palpable, left cervical lymph node prior to the event. On Day 28, the patient started coughing up blood and died due to Grade 5 **pulmonary hemorrhage**. The investigator noted that the patient had a hilar lesion adjacent to branch of pulmonary artery which likely ruptured while on treatment, possibly due to rapid treatment response, and led to catastrophic bleeding.	Pulmonary hemorrhage FDA agrees with the investigators assessment of the cause of death of pulmonary hemorrhage.	Yes
849-001 (b) (6)	66-year-old male with a history of COPD, pulmonary embolism, current tobacco use, coronary artery disease, myocardial infarction, and hypertension. On Day 8, the patient developed leg weakness, and on Day 10, he presented with dyspnea and difficulty walking. The patient was hospitalized for Grade 3 pulmonary emboli and Grade 3 leg weakness. On Day 11, computed tomography angiography (CTA) chest revealed 2 new pulmonary emboli in the right lower lobe and right middle lobe pulmonary arteries. Treatment included enoxaparin, inhaled bronchodilators, corticosteroids, supplemental oxygen. He was subsequently transitioned to hospice care. On Day 16, the patient died due to **pulmonary emboli**.	Pulmonary Embolism FDA agrees with the investigators assessment of the cause of death of pulmonary embolism.	Yes

Serious Adverse Events

Data:

Among 116 patients enrolled in Study 849-001 Cohort A, treatment emergent SAEs were reported in 60.3% of patients in Cohort A (Applicant Table 27). The most common (≥ 2% patients) events were pneumonia (11.2%); dyspnea (9.5%); malignant neoplasm progression (6.9%); blood creatinine increased, lung infection, and sepsis (each 5.2%); hypoxia and pleural effusion (each 4.3%); anemia, hyponatremia, hypotension, muscular weakness, pyrexia, and respiratory failure (each 3.4%); and acute kidney injury, cardiac failure, dehydration, diarrhea, mental status changes, pulmonary embolism, and pulmonary hemorrhage (each 2.6%). Treatment emergent SAEs were most often (≥ 5% patients) reported in the SOCs were infections and infestations and respiratory, thoracic and mediastinal disorders (each 20.7%); cardiac disorders and investigations (each 8.6%); neoplasms benign, malignant, and unspecified (incl cysts and polyps) (each 6.9%); gastrointestinal disorders, metabolism and nutrition disorders, and nervous system disorders (each 6.0%); general disorders and administration site conditions and vascular disorders (each 5.2%).

Applicant Table 26: Treatment-emergent SAEs reported in ≥ 2% Patients in Cohort A

	Adagrasib 600 mg Twice Daily		
System Organ Class Preferred Term [n (%)]	**Cohort A (N=116)**	**Other (N=144)**	**Total (N=260)**
Patients with at least 1 Serious TEAE	70 (60.3)	56 (38.9)	126 (48.5)
Blood and lymphatic system disorders	5 (4.3)	0	5 (1.9)
Anaemia	4 (3.4)	0	4 (1.5)
Cardiac disorders	10 (8.6)	12 (8.3)	22 (8.5)
Pericardial effusion	2 (1.7)	5 (3.5)	7 (2.7)
Cardiac failure	3 (2.6)	2 (1.4)	5 (1.9)
Gastrointestinal disorders	7 (6.0)	9 (6.3)	16 (6.2)
Nausea	2 (1.7)	4 (2.8)	6 (2.3)
Diarrhoea	3 (2.6)	1 (<1)	4 (1.5)
General disorders and administration site conditions	6 (5.2)	6 (4.2)	12 (4.6)
Pyrexia	4 (3.4)	2 (1.4)	6 (2.3)
Infections and infestations	24 (20.7)	14 (9.7)	38 (14.6)
Pneumonia	13 (11.2)	2 (1.4)	15 (5.8)
Lung infection	6 (5.2)	2 (1.4)	8 (3.1)
Sepsis	6 (5.2)	1 (<1)	7 (2.7)
Investigations	10 (8.6)	3 (2.1)	13 (5.0)
Blood creatinine increased	6 (5.2)	1 (<1)	7 (2.7)

System Organ Class Preferred Term [n (%)]	Adagrasib 600 mg Twice Daily Cohort A (N=116)	 Other (N=144)	 Total (N=260)
Metabolism and nutrition disorders	7 (6.0)	8 (5.6)	15 (5.8)
Dehydration	3 (2.6)	3 (2.1)	6 (2.3)
Hyponatraemia	4 (3.4)	2 (1.4)	6 (2.3)
Musculoskeletal and connective tissue disorders	5 (4.3)	2 (1.4)	7 (2.7)
Muscular weakness	4 (3.4)	0	4 (1.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (6.9)	5 (3.5)	13 (5.0)
Malignant neoplasm progression	8 (6.9)	5 (3.5)	13 (5.0)
Psychiatric disorders	5 (4.3)	1 (<1)	6 (2.3)
Mental status changes	3 (2.6)	1 (<1)	4 (1.5)
Renal and urinary disorders	3 (2.6)	4 (2.8)	7 (2.7)
Acute kidney injury	3 (2.6)	2 (1.4)	5 (1.9)
Respiratory, thoracic and mediastinal disorders	24 (20.7)	12 (8.3)	36 (13.8)
Dyspnoea	11 (9.5)	2 (1.4)	13 (5.0)
Hypoxia	5 (4.3)	1 (<1)	6 (2.3)
Pleural effusion	5 (4.3)	1 (<1)	6 (2.3)
Respiratory failure	4 (3.4)	2 (1.4)	6 (2.3)
Pulmonary embolism	3 (2.6)	1 (<1)	4 (1.5)
Pulmonary haemorrhage	3 (2.6)	0	3 (1.2)
Vascular disorders	6 (5.2)	4 (2.8)	10 (3.8)
Hypotension	4 (3.4)	2 (1.4)	6 (2.3)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Note: For each system organ class and preferred term, patients are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Module 2.7.4

The Applicant's Position:

SAEs commonly observed in this study include manifestations of comorbidities expected for this population. Notably, 47.4% of patients in Cohort A have dyspnea at baseline, and 33.5% have COPD; on-study, the most commonly reported SAEs include pneumonia/lung infection and dyspnea, and these SAEs are observed more frequently in Cohort A than the overall population. SAEs not clearly due to underlying disease and occurring in ≥5% include blood creatinine increased/acute kidney injury.

The FDA's Assessment:

With events of malignant neoplasm progression excluded from the FDA analysis of SAEs, FDA identified that SAEs occurred in 57% of patients in the primary safety population, with the most common (≥ 2% of patients) events listed below in FDA - Table 28. The incidence of SAEs occurred in 46% of patients in the FDA pooled safety population. The most common (≥ 2% of

patients) SAEs in the pooled safety population are also listed below in FDA - Table 28. Serious adverse events were most frequent in the system organ classes of infections and infestations and respiratory, thoracic, and mediastinal disorders. As described above, incidences of adverse events were analyzed without consideration of relatedness to the study therapy.

FDA - Table 27: Treatment-emergent SAEs reported in ≥ 2% Patients

	Adagrasib 600 mg Twice Daily	
System Organ Class Preferred Term [n (%)]	**Cohort A (N=116)**	**Total (N=366)**
Patients with at least 1 Serious TEAE	66 (57)	168 (46)
Blood and lymphatic system disorders	6 (5)	10 (2.7)
Anemia	4 (3.4)	7 (1.9)
Cardiac disorders	11 (9)	38 (10)
Cardiac failure*	4 (3.4)	9 (2.5)
Arrhythmia*	2 (1.7)	12 (3.3)
Pericardial effusion	2 (1.7)	8 (2.2)
Gastrointestinal disorders	10 (9)	35 (10)
Diarrhea*	3 (2.6)	6 (1.6)
Nausea	2 (1.7)	8 (2.2)
Vomiting	2 (1.7)	7 (1.9)
General disorders and administration site conditions	7 (6)	18 (4.9)
Pyrexia	4 (3.4)	7 (1.9)
Infections and infestations	28 (24)	68 (19)
Pneumonia*	20 (17)	33 (9)
Sepsis	6 (5)	11 (3.0)
Metabolism and nutrition disorders	8 (7)	29 (8)
Hyponatremia	4 (3.4)	11 (3.0)
Dehydration	3 (2.6)	8 (2.2)
Musculoskeletal and connective tissue disorders	5 (4.3)	10 (2.7)
Muscular weakness	4 (3.4)	6 (1.6)
Psychiatric disorders	5 (4.3)	13 (3.6)
Mental status changes	3 (2.6)	8 (2.2)
Renal and urinary disorders	9 (8)	19 (5)
Renal impairment*	9 (8)	16 (4.4)
Respiratory, thoracic and mediastinal disorders	36 (30)	64 (17)
Dyspnea	11 (9)	17 (4.6)
Hypoxia	5 (4.3)	7 (1.9)
Pleural effusion	5 (4.3)	8 (2.2)
Respiratory failure*	5 (4.3)	11 (3.0)

System Organ Class Preferred Term [n (%)]	Adagrasib 600 mg Twice Daily Cohort A (N=116)	 Total (N=366)
Pulmonary embolism	3 (2.6)	6 (1.6)
Pulmonary hemorrhage	3 (2.6)	3 (0.8)
Vascular disorders	6 (5)	18 (4.9)
Hypotension	4 (3.4)	8 (2.2)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
* Grouped term.
Note: For each system organ class and preferred term, patients are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: ADSL and ADAE datasets

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Among 116 patients enrolled in Study 849-001 Cohort A, discontinuation of study treatment resulted from TEAEs for 14.7% of patients (Applicant Table 29). Other than progression of disease (n = 2), no single AE led to the discontinuation of more than 1 patient. AEs leading to discontinuation were small intestinal obstruction, pyrexia, pneumonia, encephalitis, lung infection, sepsis, alanine aminotransferase increased, aspartate aminotransferase increased, ejection fraction decreased, muscular weakness, malignant neoplasm progression, cerebrovascular accident, pneumonitis, respiratory failure, dyspnea, pulmonary embolism, pulmonary hemorrhage, and hypotension.

Applicant Table 28: Treatment-emergent Adverse Events Leading to Discontinuation of Study Treatment by System Organ Class and Preferred Term

System Organ Class Preferred Term [n (%)]	Adagrasib 600 mg Twice Daily Cohort A (N=116)	 Other (N=144)	 Total (N=260)
Patients with at least 1 TEAE Leading to Discontinuation of Study Treatment	17 (14.7)	10 (6.9)	27 (10.4)
Cardiac disorders	0	1 (<1)	1 (<1)
Cardiac arrest	0	1 (<1)	1 (<1)
Ear and labyrinth disorders	0	0	0
Vertigo	0	0	0
Gastrointestinal disorders	1 (<1)	1 (<1)	2 (<1)
Nausea	0	1 (<1)	1 (<1)
Small intestinal obstruction	1 (<1)	0	1 (<1)

System Organ Class Preferred Term [n (%)]	Adagrasib 600 mg Twice Daily Cohort A (N=116)	 Other (N=144)	 Total (N=260)
General disorders and administration site conditions	1 (<1)	1 (<1)	2 (<1)
Fatigue	0	1 (<1)	1 (<1)
Pyrexia	1 (<1)	0	1 (<1)
Hepatobiliary disorders	0	1 (<1)	1 (<1)
Hepatic failure	0	1 (<1)	1 (<1)
Infections and infestations	4 (3.4)	3 (2.1)	7 (2.7)
Pneumonia	1 (<1)	1 (<1)	2 (<1)
Encephalitis	1 (<1)	0	1 (<1)
Lung infection	1 (<1)	0	1 (<1)
Pneumonia streptococcal	0	1 (<1)	1 (<1)
Sepsis	1 (<1)	0	1 (<1)
Wound infection	0	1 (<1)	1 (<1)
Investigations	2 (1.7)	0	2 (<1)
Alanine aminotransferase increased	1 (<1)	0	1 (<1)
Aspartate aminotransferase increased	1 (<1)	0	1 (<1)
Ejection fraction decreased	1 (<1)	0	1 (<1)
Metabolism and nutrition disorders	0	1 (<1)	1 (<1)
Failure to thrive	0	1 (<1)	1 (<1)
Musculoskeletal and connective tissue disorders	1 (<1)	0	1 (<1)
Muscular weakness	1 (<1)	0	1 (<1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.7)	0	2 (<1)
Malignant neoplasm progression	2 (1.7)	0	2 (<1)
Nervous system disorders	1 (<1)	0	1 (<1)
Cerebrovascular accident	1 (<1)	0	1 (<1)
Respiratory, thoracic and mediastinal disorders	5 (4.3)	2 (1.4)	7 (2.7)
Pneumonitis	1 (<1)	1 (<1)	2 (<1)
Respiratory failure	1 (<1)	1 (<1)	2 (<1)
Dyspnoea	1 (<1)	0	1 (<1)
Pulmonary embolism	1 (<1)	0	1 (<1)
Pulmonary haemorrhage	1 (<1)	0	1 (<1)
Vascular disorders	1 (<1)	0	1 (<1)
Hypotension	1 (<1)	0	1 (<1)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Note: For each system organ class and preferred term, patients are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: Module 2.7.4

The Applicant's Position:

TEAEs leading to treatment discontinuation were reported for 14.7% of patients in Cohort A and 10.4% among patients treated at 600 mg twice daily. TEAEs that were assessed as ADRs and led to treatment discontinuation included ALT increased and AST increased, which were reported in 1 patient in Cohort A, with nausea and fatigue reported in 1 patient each in other cohorts.

The FDA's Assessment:

Based on FDA analysis excluding malignant neoplasm progression, TEAEs leading to treatment discontinuation were reported for 13% of patients in the primary safety population; TEAEs leading to treatment discontinuation were reported for 9% of the pooled patient population (FDA - Table 30). Adverse events which resulted in treatment discontinuation occurring in two patients each (1.7%) were pneumonia and pneumonitis, and occurring in one patient each (0.9%) were cerebrovascular accident, dyspnea, decreased ejection fraction, encephalitis, hepatotoxicity, hypotension, muscular weakness, pulmonary embolism, pulmonary hemorrhage, pyrexia, respiratory failure, sepsis, and small intestinal obstruction. Incidences of adverse events were analyzed without consideration of relatedness to the study therapy.

FDA - Table 29: Treatment-emergent Adverse Events Leading to Discontinuation of Study Treatment by System Organ Class and Preferred Term

	Adagrasib 600 mg Twice Daily	
System Organ Class Preferred Term [n (%)]	**Cohort A (N=116)**	**Total (N=366)**
Patients with at least 1 TEAE Leading to Discontinuation of Study Treatment	15 (13)	33 (9)
Cardiac disorders	0	2 (0.5)
Cardiac arrest	0	2 (0.5)
Gastrointestinal disorders	1 (0.9)	2 (0.5)
Nausea	0	1 (0.3)
Small intestinal obstruction	1 (0.9)	1 (0.3)
General disorders and administration site conditions	1 (0.9)	5 (1.4)
Fatigue*	0	4 (1.1)
Pyrexia	1 (0.9)	1 (0.3)
Hepatobiliary disorders	1 (0.9)	2 (0.5)
Hepatotoxicity*	1 (0.9)	2 (0.5)
Infections and infestations	4 (3.4)	6 (1.6)
Pneumonia*	2 (1.7)	3 (0.8)
Encephalitis	1 (0.9)	1 (0.3)
Sepsis	1 (0.9)	1 (0.3)
Wound infection	0	1 (0.3)
Investigations	1 (0.9)	2 (0.5)

System Organ Class Preferred Term [n (%)]	Adagrasib 600 mg Twice Daily Cohort A (N=116)	 Total (N=366)
Ejection fraction decreased	1 (0.9)	2 (0.5)
Metabolism and nutrition disorders	0	2 (0.5)
Failure to thrive	0	1 (0.3)
Dehydration	0	1 (0.3)
Musculoskeletal and connective tissue disorders	1 (0.9)	1 (0.3)
Muscular weakness	1 (0.9)	1 (0.3)
Nervous system disorders	1 (0.9)	2 (0.5)
Cerebrovascular accident	1 (0.9)	1 (0.3)
Seizure	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders	6 (5)	9 (2.5)
Pneumonitis	2 (1.7)	3 (0.8)
Respiratory failure	1 (0.9)	2 (0.5)
Dyspnea	1 (0.9)	1 (0.3)
Pulmonary embolism	1 (0.9)	2 (0.5)
Pulmonary hemorrhage	1 (0.9)	1 (0.3)
Vascular disorders	1 (0.9)	1 (0.3)
Hypotension	1 (0.9)	1 (0.3)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
* Grouped term.
Note: For each system organ class and preferred term, patients are included only once, even if they experienced multiple events in that system organ class or preferred term.
Source: ADSL and ADAE datasets

Dose Interruption/Reduction Due to Adverse Effects

Data:

Among 116 patients enrolled in Study 849-001 Cohort A, TEAEs leading to study treatment interruption or dose reduction were reported for 81.9% of patients. The most common (≥5% in all patients) AEs leading to interruption or dose reduction were nausea (22.4%); fatigue (15.5%); alanine aminotransferase increased (13.8%); vomiting (12.9%); aspartate aminotransferase increased (11.2%); diarrhea (9.5%); blood alkaline phosphatase increased (6.9%); electrocardiogram QT prolonged (6.9%); anemia, pneumonia, and blood creatinine increased (each 6.0%); lipase increased (5.2%); and dyspnea (5.2%).

Among 260 patients in the total group treated at a starting dose of adagrasib, 600 mg twice daily, TEAEs leading to study treatment interruption or dose reduction were reported for 76.5% of patients. The most common (≥5% in all patients) AEs leading to interruption or dose reduction were nausea (19.6%); fatigue (13.8%); vomiting (12.7%); diarrhea (11.5%); alanine

aminotransferase increased (11.2%); aspartate aminotransferase increased (9.2%); electrocardiogram QT prolonged, blood creatinine increased, and dyspnea (5.4%).

The Applicant's Position:
TEAEs leading to dose interruption or reduction and occurring with adagrasib treatment were generally manageable with treatment interruptions and/or dose reductions. Patients undergoing dose modification typically showed improvement and were generally able to restart and continue adagrasib treatment.

The FDA's Assessment:
FDA agrees with the Applicant's position that TEAEs leading to dose interruption or reduction and occurring with adagrasib treatment appeared to be generally manageable given the context of this serious, life-threatening disease.

In the primary safety population, TEAEs leading to study treatment interruption occurred in 77% of patients and dose reductions occurred in 57% of patients. In total, treatment interruption or dose reduction were reported for 82% of patients. The most common (≥ 5% in all patients) AEs leading to interruption or dose reduction were nausea (22%); hepatotoxicity (17%); fatigue (16%); vomiting (13%); renal impairment, diarrhea, and pneumonia (each 9%); electrocardiogram QT prolonged (7%); anemia (6%); dyspnea and increased lipase (each 5%).

Among the 366 patients in the pooled safety population, TEAEs leading to study treatment interruption or dose reduction were reported for 72% of patients. The most common (≥ 5% in all patients) AEs leading to interruption or dose reduction were nausea (18%); vomiting (13%); diarrhea and hepatotoxicity (each 12%); fatigue (11%); renal impairment (8%), pneumonia (6%); electrocardiogram QT prolonged (5%).

Significant Adverse Events

Data:

Among 116 patients enrolled in Study 849-001 Cohort A, the most common (≥ 5% patients) Grade ≥3 treatment emergent AEs were anemia (13.8%); pneumonia (12.1%); dyspnea (10.3%); hyponatremia (8.6%); hypoxia (7.8%); fatigue, lipase increased, and malignant neoplasm progression (each 6.9%); acute kidney injury, electrocardiogram QT prolonged, lung infection, and lymphocyte count decreased (each 6.0%); and alanine aminotransferase increased, aspartate aminotransferase increased, and sepsis (each 5.2%).

Among 260 patients in the total group treated at a starting dose of adagrasib, 600 mg twice daily, the most common (≥ 5% patients) Grade ≥3 treatment emergent AEs were anemia (9.6%), dyspnea (7.7%), pneumonia and hypoxia (each 6.2%), hyponatremia (5.8%), lipase increased, alanine aminotransferase increased, aspartate aminotransferase increased, lymphocyte count decreased, and malignant neoplasm progression (each 5.0%)

The Applicant's Position:

QTc interval prolongation (b) (4) considered significant AEs and are included in the Warnings and Precautions section of the draft adagrasib US Prescribing Information.

The FDA's Assessment:

Among the 116 patients in the primary safety population, 79%% of patients experienced a Grade ≥3 adverse event. The most common (≥ 5% of patients) Grade ≥3 events, excluding laboratory abnormalities and malignant neoplasm progression, were pneumonia (19%); dyspnea and hepatotoxicity (each 10%); hypoxia (8%); fatigue and musculoskeletal pain (each 7%); renal impairment and electrocardiogram QT prolonged (each 6%); sepsis (5%).

Among the 366 patients in the pooled safety population, 69% of patients experienced a Grade ≥3 adverse event. The most common (≥ 5% of patients) Grade ≥3 events, excluding laboratory abnormalities and malignant neoplasm progression, were pneumonia (10%); fatigue (8%); dyspnea and hepatotoxicity (each 7%).

In addition to increased transaminases (addressed in Section 8.2.5.1) and QTc interval prolongation (addressed in Section 8.2.5.2), other adverse events of special interest include gastrointestinal toxicity (addressed in Section 8.2.5.3) and pneumonitis/interstitial lung disease (addressed in Section 8.2.5.4).

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Adverse Events

Among 116 patients enrolled in Study 849-001 Cohort A, the most common (≥20% patients) TEAEs (Module 2.7.4) were diarrhea (69.0%), nausea (69.0%), fatigue (58.6%), vomiting (56.0%), dyspnea (35.3%), anemia (34.5%), blood creatinine increased (32.8%), decreased appetite (30.2%), alanine aminotransferase increased and edema peripheral (each28.4%), aspartate aminotransferase increased (26.7%), constipation (22.4%), hyponatremia (22.4%), and dizziness (20.7%).

Among 260 patients in the total group treated at a starting dose of adagrasib, 600 mg twice daily, TEAEs occurring in ≥ 20% patients were diarrhea (69.6%), nausea (67.3%), vomiting (56.2%), fatigue (55.4%), anemia (31.5%), edema peripheral (30.0%), blood creatinine increased (29.6%), decreased appetite (28.5%), aspartate aminotransferase increased (27.7%), alanine aminotransferase increased (27.3%), dyspnea (27.3%), and constipation (20.8%).

Among 260 patients in the total group treated at a starting dose of adagrasib, 600 mg twice daily, the most common SOCs in which TEAEs were reported (≥ 20% patients) were gastrointestinal disorders (95.8%); general disorders and administration site conditions (76.5%); investigations (70.0%); metabolism and nutrition disorders (63.1%); respiratory, thoracic and mediastinal disorders (52.7%); nervous system disorders (49.2%); musculoskeletal and connective tissue disorders (48.1%); infections and infestations (41.2%); skin and subcutaneous tissue disorders (36.5%); blood and lymphatic system disorders (35.4%); psychiatric disorders (28.1%); vascular disorders (24.6%); and renal and urinary disorders (20.0%).

Adverse Drug Reactions

The Sponsor reviewed all safety data through the data cutoff date to determine which AEs warranted inclusion in labeling as ADRs. The ISS pooled database (265 patients) 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 849-001 Cohort A.

To provide a robust dataset at the intended dose, and to maximize the potential for identifying AEs that were related to adagrasib use, ADRs were evaluated in patients with any tumor type who were treated with adagrasib monotherapy at a starting dose of 600 mg twice daily. Medical review was based on a broad evaluation of all AEs (frequency, severity, temporal association, duration, outcome, plausible mechanism, de/rechallenge, confounders), changes in laboratory values, and vital signs. In addition, medical review of all AEs reported was undertaken, with special attention to common events, Grade ≥ 3 events, and SAEs. A review of all frequently occurring AEs was performed, with consideration of events expected to occur at a particular incidence in patients with known underlying diseases to identify an appropriate initial threshold for identifying ADRs.

Treatment emergent AEs of any grade of severity (i.e., Grade 1 to 4) identified as ADRs and occurring in ≥ 10% of patients Study 849-001 Cohort A were diarrhea (69.0%), nausea (69.0%), fatigue (including asthenia, 58.6%), vomiting (56.0%), decreased appetite (30.2%), dizziness (including vertigo and vestibular disorder, 21.6%, and ECG QT prolonged (19.8%).

Treatment emergent laboratory abnormalities of any grade of severity (i.e., Grade 1 to 4) identified as ADRs and occurring in ≥ 15% of patients Study 849-001 Cohort A were lymphocyte count decreased (64.2%), aspartate aminotransferase increased (52.2%), hyponatremia (52.2%), blood creatinine increased (50.4%), alanine aminotransferase increased (45.1%), blood alkaline phosphatase increased (40.7%), lipase increased (34.5%), and amylase increased (19.5%).

The Applicant's Position:

The AEs that were assessed as ADRs were fatigue (including asthenia), nausea, vomiting, diarrhea, decreased appetite, electrocardiogram QT prolonged, and dizziness (including vertigo). Laboratory abnormalities assessed as ADRs were transaminases increased (including aspartate aminotransferase increased and alanine aminotransferase increased), blood alkaline phosphatase increased, amylase increased, lipase increased, lymphocyte count decreased

(including lymphopenia), blood creatinine increased and hyponatremia.

The FDA's Assessment:

The most common TEAEs were generally consistent between the primary safety and pooled safety populations.

Among the 116 patients in the primary safety population, the most common (≥ 20% patients) TEAEs (FDA - Table 31), excluding laboratory abnormalities, were diarrhea (70%), nausea (69%), fatigue (59%), vomiting (56%), musculoskeletal pain (41%), hepatotoxicity (37%), renal impairment (36%), dyspnea (35%), edema (32%), decreased appetite (30%), cough and pneumonia (each 24%), dizziness (23%), constipation (22%), abdominal pain (21%), and prolonged electrocardiogram QT (20%).

Among the 366 patients in the pooled safety population, the most common (≥ 20% patients) TEAEs, excluding laboratory abnormalities, were nausea (70%), diarrhea (69%), vomiting (57%), fatigue (55%), musculoskeletal pain (38%), hepatotoxicity (37%), renal impairment (33%), edema (30%), dyspnea (26%), decreased appetite (29%), abdominal pain (23%), constipation (22%), and dizziness (21%).

FDA did not perform an independent analysis of the incidence of drug-related adverse reactions.

FDA - Table 30: Most Common Treatment-Emergent Adverse Events (≥ 20%) in the Primary Safety Population

Adverse Effects	**Adagrasib 600 mg Twice Daily N = 116**	
	All Grades (%)	**Grade 3 or 4 (%)**
Gastrointestinal Disorders		
Diarrhea*	70	0.9
Nausea	69	4.3
Vomiting*	56	0.9
Constipation	22	0
Abdominal pain*	21	0
General Disorders and Administration Site Conditions		
Fatigue*	59	7
Edema*	32	0

Adverse Effects	Adagrasib 600 mg Twice Daily N = 116	
	All Grades (%)	Grade 3 or 4 (%)
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain*	41	7
Hepatobiliary Disorders		
Hepatotoxicity*	37	10
Renal and Urinary Disorders		
Renal impairment*	36	6
Respiratory		
Dyspnea*	35	10
Cough*	24	0.9
Metabolism and Nutrition Disorders		
Decreased appetite	30	4.3
Infections and Infestations		
Pneumonia*	24	17
Nervous System Disorders		
Dizziness*	23	0.9
Cardiac Disorders		
Electrocardiogram QT prolonged	20	6

* Grouped term.
Source: ADSL and ADAE datasets

Laboratory Findings

Data:

Among 116 patients enrolled in Study 849-001 Cohort A, the most common treatment emergent laboratory abnormalities of any grade of severity in ≥ 15% of patients were lymphocyte count decreased (64.2%), aspartate aminotransferase increased (52.2%), hyponatremia (52.2%), blood creatinine increased (50.4%), alanine aminotransferase increased (45.1%), blood alkaline phosphatase increased (40.7%), lipase increased (34.5%), and amylase increased (19.5%). These laboratory abnormalities were assessed as ADRs with adagrasib treatment.

The most common (≥2%) Grade ≥3 treatment emergent hematology abnormalities were lymphocytes decreased (23.6%), hemoglobin decreased (8.0%), and neutrophils decreased (2.8%).

The most common (≥2%) treatment-emergent Grade ≥3 serum chemistry abnormalities were hyponatremia (8.0%), aspartate aminotransferase increased (6.2%), alanine aminotransferase increased (5.3%), alkaline phosphatase increased (4.4%), and hypokalemia (3.5%). No patients met the Hy's Law criteria for potential drug-induced liver injury.

No patients experienced Grade ≥3 amylase increases based on the laboratory data, and 2 patients experienced Grade 3 lipase increases on treatment based on the laboratory data. Increased lipase and amylase were not associated with pancreatitis and were generally transient.

The Applicant's Position:

Laboratory abnormalities that were assessed as ADRs are transaminases increased (including aspartate aminotransferase increased and alanine aminotransferase increased), blood alkaline phosphatase increased, amylase increased, lipase increased, lymphocyte count decreased, blood creatinine increased and hyponatremia.

The FDA's Assessment:

The most common treatment-emergent laboratory abnormalities were generally consistent between the primary safety and FDA pooled safety populations.

Among the 116 patients in the primary safety population, the most common (≥ 15% patients) treatment emergent laboratory abnormalities of any grade of severity (FDA - Table 31) were decreased lymphocytes (64%), increased aspartate aminotransferase and hyponatremia (each 52%), decreased hemoglobin (51%), increased creatinine and decreased albumin (each 50%), increased alanine aminotransferase (46%), increased alkaline phosphatase (41%), increased lipase (35%), decreased platelets (27%), hypomagnesemia and hypokalemia (each 26%), decreased leukocytes (20%), increased amylase (19%), hyperkalemia (17%), and hypocalcemia (albumin-adjusted, 16%).

In the primary safety population, the most common (≥ 2% of patients) treatment-emergent Grade ≥3 hematologic laboratory abnormalities (FDA - Table 31) were decreased lymphocytes (25%), decreased hemoglobin (8%), decreased neutrophils (2.8%), and decreased leukocytes (2.7%).

In the primary safety population, the most common (≥ 2% of patients) treatment-emergent Grade ≥3 serum chemistry laboratory abnormalities (FDA - Table 31) were hyponatremia (8%), increased aspartate aminotransferase (6%), increased alanine aminotransferase (5%), increased

alkaline phosphatase (4.4%), hypokalemia (3.5%).

Among the 366 patients in the pooled safety population, the most common (≥ 15% patients) treatment emergent laboratory abnormalities of any grade of severity were decreased lymphocytes (62%), decreased hemoglobin (52%), increased aspartate aminotransferase (50%), increased creatinine (48%), hyponatremia (47%), increased alanine aminotransferase (43%), decreased albumin (39%), increased alkaline phosphatase (36%), increased lipase (27%), hypokalemia (26%), hypomagnesemia (23%), decreased platelets (22%), decreased leukocytes and increased amylase (each 19%), and hypocalcemia (albumin-adjusted, 16%).

In the pooled safety population, the most common (≥ 2% of patients) treatment-emergent Grade ≥3 hematologic laboratory abnormalities were decreased lymphocytes (20%), decreased hemoglobin (7%), decreased leukocytes (2.5%), and decreased neutrophils (2.3%).

In the pooled safety population, the most common (≥ 2% of patients) treatment-emergent Grade ≥3 serum chemistry laboratory abnormalities were increased alanine aminotransferase (4.5%), increased aspartate aminotransferase (4.2%), hypokalemia (3.6%), hyponatremia (3.4%), increased lipase (2.5%) and increased alkaline phosphatase (2.0%).

FDA did not perform an independent analysis of the incidence of drug-related laboratory abnormalities.

FDA - Table 31: : Most Common Laboratory Abnormalities (≥ 25%) in the Primary Safety Population

Laboratory Abnormality	Adagrasib 600 mg Twice Daily*	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Decreased lymphocytes	64	25
Decreased hemoglobin	51	8
Decreased platelets	27	0
Chemistry		
Increased aspartate aminotransferase	52	6
Decreased sodium	52	8
Increased creatinine	50	0
Decreased albumin	50	0.9
Increased alanine aminotransferase	46	5

Laboratory Abnormality	Adagrasib 600 mg Twice Daily*	
	All Grades (%)	Grade 3 or 4 (%)
Increased lipase	35	1.8
Decreased magnesium	26	0
Decreased potassium	26	3.5

* Denominator used to calculate the rate varied from 106 to 113 based on the number of patients with a baseline value and at least one post-treatment value.
Source: ADSL and ADLB datasets

Vital Signs

Data:

Among 116 patients enrolled in Study 849-001 Cohort A, there did not appear to be any clinically significant mean or median change from baseline for pulse, systolic blood pressure, diastolic blood pressure, respiratory rate, temperature, or weight. Likewise, no meaningful change was identified in the total group (n = 260) treated with adagrasib 600 mg twice daily.

The Applicant's Position:

No clinically relevant changes in vital signs were observed.

The FDA's Assessment:
FDA agrees with the Applicant's analysis of vital sign assessments.

Electrocardiograms (ECGs)

Data:

ECGs were scheduled for collection in triplicate at 8 nominal time points and as unscheduled assessments when warranted (see Section 8.2 for the schedule of assessments). All patients enrolled in Cohort A underwent ECG testing at baseline, typically with a single ECG at screening and 1 or 2 triplicate sets before the first dose (either with the PK lead-in dose or on Cycle 1 Day 1). Additional scheduled time points were pre-dose on Cycle 1 Day 8, Cycle 2 Day 1, Cycle 3 Day 1, and Cycle 5 Day 1, and at peak on Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 2 Day 1. For the 116 patients enrolled into Cohort A, approximately 2300 ECGs were performed, and automated intervals were reported into the database and summarized.

Among 116 patients enrolled in Study 849-001 Cohort A, there did not appear to be any clinically significant mean or median change from baseline for heart rate. QTcF interval was increased on Day 8 compared to baseline (median values 414.6 msec [range: 358 to 478 msec] and 440.1 msec [range: 377 to 543 msec] at baseline and postdose on Day 8, respectively), but there was not continued increase after Day 8 (median predose values 436.7 msec [range: 378 to 496 msec], 430.5 msec [range: 377 to 478 msec], and 431.3 msec [range: 356 to 521 msec] on Day 1 of Cycles 2, 3, and 5, respectively). Forty-four patients (38.6%) had QTcF ≥ 450 to ≤ 480 msec, 12 patients (10.5%) had QTcF > 480 to ≤ 500 msec, and 10 patients (8.8%) had QTcF > 500 msec. The maximum change from baseline in QTcF was > 30 to ≤ 60 msec for 55 patients (48.2%) and > 60 msec for 17 patients (14.9%).

The Applicant's Position:

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

The FDA's Assessment:

FDA agrees with the Applicant's assessment that QTc interval prolongation can occur in patients treated with adagrasib. While no definitive arrhythmias related to QTc prolongation have been observed, cases of sudden death have been observed (see Section 8.2.4 - Deaths).

Similar rates and severity of QTc prolongation were observed in the pooled safety population as those observed in the primary safety population (as described by the Applicant above). With regards to the 366 patients in the pooled safety population, there did not appear to be any clinically significant mean or median change from baseline for heart rate. QTcF interval was increased on Day 8 compared to baseline (median values 415.9 msec [range: 355 to 490 msec] and 441.3 msec [range: 338 to 625 msec] at baseline and postdose on Day 8, respectively), but there was not continued increase after Day 8 (median predose values 436.3 msec [range: 334 to 533 msec], 434.0 msec [range: 226 to 490 msec], and 435.7 msec [range: 332 to 521 msec] on Day 1 of Cycles 2, 3, and 5, respectively). One hundred forty-three patients (39%) had QTcF ≥ 450 to ≤ 480 msec, 36 patients (10%) had QTcF > 480 to ≤ 500 msec, and 23 patients (6%) had QTcF > 500 msec. The maximum change from baseline in QTcF was > 30 to ≤ 60 msec for 178 patients (49%) and > 60 msec for 41 patients (11%).

QT

Data:

See above under ECGs. A thorough QT study has not been conducted.

The Applicant's Position:

No dedicated QT studies were conducted. QTc interval prolongation can occur in patients treated with adagrasib.

The FDA's Assessment:
FDA acknowledges that no dedicated QT studies were conducted and agrees with the Applicant's assessment of QTc interval prolongation.

Immunogenicity

Data:

Not applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment:
FDA agrees with the Applicant's position.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1 Increased Transaminases

Data:

Two patients in Phase 2, Cohort A, of Study 849-001 had notable elevations of both bilirubin and aspartate aminotransferase/alanine aminotransferase, and both also had notable elevations in alkaline phosphatase and, therefore, did not meet the criteria for Hy's Law for hepatic function abnormality.

The Applicant's Position:

Patients treated with adagrasib did not exhibit evidence of drug-induced liver injury meeting the Hy's Law criteria.

The FDA's Assessment:
FDA agrees with the characterization that increased transaminases is an adverse event of special interest. However, given the relatedness between increased transaminases and other hepatobiliary adverse events and in order to comprehensively evaluate this safety signal, FDA

evaluated hepatotoxicity as a grouped term including the following preferred terms: increased aspartate aminotransferase, mixed liver injury, increased blood alkaline phosphatase, increased gamma-glutamyltransferase, increased alanine aminotransferase, increased blood bilirubin, increased hepatic enzyme, increased conjugated bilirubin conjugated, increased liver function test).

In the pooled safety population of 366 patients, drug-induced liver injury (reported as "mixed liver injury") was reported in 0.3% of patients, including 0.3% Grade 3. A total of 32% of patients who received adagrasib had increased alanine aminotransferase (ALT)/increased aspartate aminotransferase (AST); 5% were Grade 3 and 0.5% were Grade 4. The median time to first onset of increased ALT/AST was 3 weeks (range: 0.1 to 48). Overall hepatotoxicity occurred in 37%, and 7% were Grade 3 or 4.

FDA - Table 33 below provides the incidence of patients who had an event of each preferred term included in the FDA's grouped term for hepatotoxicity.

FDA – Table 32: Hepatotoxicity in the Pooled Safety Population

Preferred term, n (%)	Adagrasib 600 mg BID (N=366)	
	All Grades (%)	Grades 3-4 (%)
Increased AST	28	4.1
Increased ALT	25	4.9
Increased blood alkaline phosphatase	20	2.7
Increased blood bilirubin	3.3	0.8
Mixed liver injury	0.3	0.3
Increased GGT	0.3	0.3
Increased liver function test	0.3	0
Increased bilirubin conjugated	0.3	0
Increased hepatic enzyme	0.3	0

Of the 137 patients who experienced an event of hepatotoxicity, 45 patients (12% of the pooled safety population) required a dose reduction and/or interruption. Hepatotoxicity events resolved in 42 of 45 (93%) of the cases following dose reduction or interruption. Adagrasib was discontinued due to hepatotoxicity in 0.5% of patients. The dose modification guidelines for hepatoxicity are provided in the product label and state that adagrasib should be reduced to

the next lower dose level for Grade 2 AST or ALT elevation and, for Grade 3 or 4 AST or ALT elevation, adagrasib should be withheld until recovery to Grade ≤1 or return to baseline and then resumed at the next lower dose level. Adagrasib should be permanently discontinued for AST or ALT > 3 x ULN with total bilirubin > 2 x ULN in the absence of alternative causes of LFT abnormalities (e.g., viral hepatitis, disease progression in the liver).

Laboratory abnormalities in liver function testing that worsened from baseline were also observed in patients who received adagrasib 600 mg BID. Shifts in AST and ALT occurred in 50% and 43% of patients, respectively, in the pooled safety population. A total of 4.2% and 4.5% of patients had shifts to Grade 3 or 4 AST and ALT values, respectively. These results are reflective of the adverse event data in which events of increased AST and ALT consist of the majority of events that comprise the grouped terms for hepatotoxicity.

Based upon FDA analysis, six potential Hy's Law cases were identified and reviewed. Of those, only one case met laboratory criteria for Hy's Law, however, it was in the setting of biliary obstruction from disease progression. In the remaining five cases, laboratory criteria for Hy's Law were not met due to concurrently increased alkaline phosphatase. As such, FDA agrees with the Applicant's assessment that no events of drug-induced liver injury met Hy's Law criteria. However, there was an adverse event reported of "mixed liver injury" that did not meet criteria for Hy's Law but appeared consistent with drug-induced liver injury (patient ID# 849-001-(b) (6)). The patient, a 70-year-old female with NSCLC, experienced a Grade 3 elevation in AST, Grade 2 elevation in ALT, and Grade 2 elevation in alkaline phosphatase elevation on Day 57 of study therapy. Total bilirubin remained within the normal range. Study treatment was discontinued and abdominal ultrasound revealed splenomegaly, hepatomegaly, and new portal hypertension compared with a CT scan from Study Day 41. On Study Day 64, she was hospitalized with Grade 3 mixed liver injury and Grade 2 drug hypersensitivity with rash. Liver function tests continued to increase and work-up for other causes of liver injury (e.g., antinuclear antibody, antimitochondrial antibody, actin smooth muscle antibody, Epstein-Barr Virus, cytomegalovirus antibody, and viral hepatitis panel) were negative. Skin biopsy was consistent with a drug-induced hypersensitivity reaction and liver biopsy revealed moderately active hepatitis with hepatocyte injury. The patient improved clinically after initiation of steroids with improvement in the rash and liver function tests. The adverse effect was deemed to have resolved on Study Day 72. The investigator deemed that the mixed liver injury was most consistent with drug-induced liver injury related to treatment with adagrasib.

Based on FDA analysis, hepatotoxicity has been included in the Warnings and Precautions section of the U.S. Prescribing Information (Section 5.3).

8.2.5.2 QT Prolongation

Data:

Data are presented above in the ECG section.

The Applicant's Position:

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

The FDA's Assessment:
FDA agrees with the Applicant's position that QTc interval prolongation can occur in patients treated with adagrasib. While no definitive arrhythmias related to QTc prolongation have been observed, cases of sudden death have been observed (see Section 8.2.4 – Deaths for additional information regarding these events).

Given the potential severity of electrocardiogram QT prolongation events, QTc Interval Prolongation has been included in the Warnings and Precautions section of the U.S. Prescribing Information (Section 5.2).

8.2.5.3 Gastrointestinal Adverse Reactions

The FDA's Assessment
In order to comprehensively evaluate the safety signal from gastrointestinal toxicities and to assess the frequency of serious gastrointestinal toxicities, FDA used the following grouped terms (shown in FDA - Table 34 below) in its analysis:

FDA - Table 33: MedDRA PTs Combined into Gastrointestinal GTs

Grouped Term (GT)	MedDRA Preferred Terms (PTs) Used in Applicant Safety Datasets
Gastrointestinal bleeding	gastrointestinal hemorrhage, rectal hemorrhage, hematochezia, upper gastrointestinal hemorrhage, hematemesis, anal hemorrhage, esophageal varices hemorrhage,
Diarrhea	diarrhea, colitis, enteritis
Nausea*	nausea
Vomiting	retching, vomiting
Gastrointestinal obstruction	small intestinal obstruction, large intestinal obstruction, duodenal obstruction

* Not a grouped term

In total, gastrointestinal adverse events were frequently observed among patients treated with adagrasib 600 mg BID. Among the 366 patients in the pooled safety population, diarrhea occurred in 70% of patients, nausea occurred in 69% of patients, and vomiting occurred in 56% of patients. In total, 89% of patients experienced diarrhea, nausea, and/or vomiting. Grade 3 nausea, diarrhea, and/or vomiting occurred in 9% of patients. There were no Grade 4 or fatal events of nausea, diarrhea, or vomiting. Nausea, diarrhea, and/or vomiting led to dose interruption and/or reduction in 29% of patients and permanent discontinuation in one patient (0.3%; due to vomiting). Nausea, diarrhea, and/or vomiting events resolved in 85 of 106 (80%) of the cases following dose reduction or interruption. In general, nausea, vomiting, and diarrhea were manageable with dose interruptions or reductions.

In addition, in the pooled safety population, serious gastrointestinal adverse reactions observed were gastrointestinal bleeding in 3.8% of patients, including 0.8% Grade 3 or 4, gastrointestinal obstruction in 1.6% of patients, including 1.4% Grade 3 or 4, colitis in 0.5% of patients, including 0.3% Grade 3, ileus in 0.5% of patients, and stenosis in 0.3% of patients.

Given the frequency and potential severity of gastrointestinal adverse events, Gastrointestinal Adverse Reactions has been included in the Warnings and Precautions section of the U.S. Prescribing Information (Section 5.1).

8.2.5.4 Interstitial Lung Disease/Pneumonitis

The FDA's Assessment

Among the 366 patients in the pooled safety population, interstitial lung disease (ILD)/pneumonitis was observed in 4.1% of patients, with 1.4% Grade 3 or 4. There was one case of fatal ILD/pneumonitis. ILD/pneumonitis led to dose interruption or reduction in seven patients (1.9%) and permanent discontinuation in three patients (0.8%). For the fatal case of ILD/pneumonitis (patient ID# 849-001 (b) (6)), the patient was a 61-year-old female with NSCLC who was previously treated with chemotherapy and immunotherapy, and was known to have a history of pneumonitis. Prior to enrollment on study the patient was reported as having Grade 2 pneumonitis secondary to either gemcitabine directly or radiation recall pneumonitis caused by gemcitabine. The patient subsequently experienced Grade 3 pneumonitis following pembrolizumab, which resolved after pembrolizumab was discontinued. The patient experienced recurrent pneumonitis while on treatment with vinorelbine; the pneumonitis stabilized and improved, except for intermittent flaires, managed on prednisone and mycophenolate mofetil. Ten days prior to starting on study treatment, a CT scan revealed interval diminished inflammation. The patient remained on treatment with mycophenolate mofetil and prednisone when she enrolled into the study. On Study Day 43, the patient presented with complaints of increased shortness of breath with any activity and increased reliance on home oxygen. Imaging revealed multifocal diffuse coarse bilateral ground glass opacification, which was concerning for drug induced pneumonitis versus a flare of her

underlying chronic organizing pneumonitis, potentially precipitated by study treatment; these findings were considered as worsening of the patient's baseline pneumonitis. Treatment included methylprednisolone IV for 3 days and an increase in the dosage of prednisone from 20 mg QD to 80 mg QD. The patient's hypoxia worsened and on Study Day 44, the patient was hospitalized and admitted to the intensive care unit. The patient was treated with methylprednisolone, as well as cefepime, vancomycin, furosemide, and etanercept and her oxygenation requirement improved during the course of hospitalization. On Study Day 59, the patient was discharged to a rehabilitation hospital. The adverse event was considered related to adagrasib, which was interrupted due to the event and not restarted (last treatment was on Study Day 43). Then, on Study Day 66, the patient complained of sudden shortness of breath; oxygen saturation was 66% and the patient was transported to the emergency department where she was placed on comfort measures only. On Study Day 68, the patient died with the cause of death reported as pneumonitis. No autopsy was performed. The patient's physician considered decompensation and ultimate respiratory failure due to progressive pneumonitis.

Given the seriousness and severity of ILD/pneumonitis adverse events, Interstitial Lung Disease/Pneumonitis has been included in the Warnings and Precautions section of the U.S. Prescribing Information (Section 5.4).

8.2.5.5 Ocular Toxicities

The FDA's Assessment:

Ophthalmology examinations were required at Screening; thereafter, they were only required as clinically indicated. Ophthalmology examination results, including visual acuity, slit lamp (lens, other), fundoscopy posterior segment (vitreous body, retina, optic nerve head, fundus, optic disc) were summarized by eye and listed for the safety population. Treatment-emergent adverse events of eye disorders occurred in 15% of patients in the primary safety population (see FDA table below).

Although 15% of patients reported an ocular adverse event, less than 3% had a post-baseline ophthalmic examination. The lack of on-treatment ophthalmology examinations in 97% of patients precludes any useful evaluation of adagrasib's effect on the ocular system. FDA will continue to monitor for treatment-emergent adverse events of eye disorders associated with adagrasib.

FDA - Table 34: Eye Disorders Treatment Emergent Adverse Events in the Primary Safety Population

System Organ Class Preferred Term [n (%)]	Cohort A N=116 N (%)
Eye disorders	17 (15%)
Eye pain	3 (3%)
Vision blurred	3 (3%)
Visual impairment	3 (3%)
Dry eye	2 (2%)
Eye disorder	1 (1%)
Eye hemorrhage	1 (1%)
Eye inflammation	1 (1%)
Lacrimation increased	1 (1%)
Ocular hyperemia	1 (1%)
Periorbital edema	1 (1%)
Photophobia	1 (1%)
Scleral pigmentation	1 (1%)
Vitreous floaters	1 (1%)

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data:

Not applicable

The Applicant's Position:
Not applicable

The FDA's Assessment:
Not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

Data:

Age

Among 260 patients treated at 600 mg twice daily, decreased appetite, edema peripheral, and fatigue were more common in ≥ 65 year-old patients compared to those < 65 years (35.0%, 34.2%, and 62.4% versus 23.1%, 26.6%, and 49.7%, respectively). When the age range categories were expanded further, decreased appetite was more common in the ≥ 75 year-old patients (23.1% in patients < 65 years, 31.4% in patients ≥ 65 to < 75 years, and 45.2% in patients ≥ 75 years). There did not appear to be a relationship between age and the common gastrointestinal TEAEs, including diarrhea, nausea, and vomiting.

Sex

Among 260 patients treated at 600 mg twice daily, 56.9% patients were female. Gastrointestinal TEAEs including diarrhea, nausea, and vomiting, were more common in women compared to men (74.3%, 73.0%, and 64.2% versus 63.4%, 59.8%, and 45.5%, respectively). Fatigue was more common in men compared to women (61.6% versus 50.7%).

Race

Among 260 patients treated at 600 mg twice daily, 83.1% were White, and 16.9% were Non-White. There did not appear to be a relationship between TEAEs and race.

The Applicant's Position:

Analysis of the frequency of AEs by demographic features is limited by sample size of some subgroups but suggest that decreased appetite and fatigue may be more common in older patients; diarrhea, nausea, and vomiting more common in female patients; and fatigue more common in male patients. These differences are minor and the overall safety profile is similar regardless of age, sex, and race.

The FDA's Assessment:

FDA agrees that there were generally no major differences in the type, frequency, and severity of adverse events observed in patient subgroups including age, race, and sex when compared with the overall study population. However, the sample size of some demographic subgroups, was small, making it difficult to draw substantial conclusions about whether the intrinsic factor had an effect on safety.

8.2.8. Specific Safety Studies/Clinical Trials

Data:

Not applicable as no studies with adagrasib were conducted to evaluate a specific safety concern.

The Applicant's Position:

Not applicable.

The FDA's Assessment:
FDA agrees with the Applicant's position.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data:

Not applicable.

The Applicant's Position:

Refer to Section 5, Nonclinical Pharmacology/Toxicology, for information on the potential carcinogenicity of adagrasib.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Human Reproduction and Pregnancy

Data:

No clinical studies of adagrasib have been conducted in pregnant or breastfeeding women. No pregnancies were reported by any female subject receiving adagrasib or the partner of any male subject receiving adagrasib.

The Applicant's Position:

There are no data available for adagrasib in pregnant women. Patients should be informed of the potential hazards to the fetus if adagrasib is used during pregnancy, or if the patient becomes pregnant while taking adagrasib.

It is not known if adagrasib or its metabolites are present in human milk. Because of the potential risk for adagrasib to cause adverse effects in breastfed children, a decision must be made to discontinue breast feeding or discontinue adagrasib while breastfeeding.

The extent to which adagrasib is present in seminal fluid is unknown. There are no clinical studies to evaluate the effect of adagrasib on fertility.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Pediatrics and Assessment of Effects on Growth

Data:

Not applicable.

The Applicant's Position:

Adagrasib was not studied in pediatric patients. In the Agreed Initial Pediatric Study Plan (iPSP), the Applicant has been granted a full waiver for studies in the pediatric population as *KRAS* G12C mutation is not a relevant target in pediatric cancers.

The FDA's Assessment:
FDA agrees with the Applicant's position with the caveat that FDA issued an "Agreed Initial Pediatric Study Plan-Agreement" letter on May 10, 2021, in response to the Applicant's initial pediatric study plan requesting a full waiver for studies in the pediatric population. With this NDA, the Applicant submitted the request for a full waiver.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

Not applicable.

The Applicant's Position:

There is no clinical experience with overdose with adagrasib.

The FDA's Assessment:
FDA agrees with the Applicant's position.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

Not applicable.

The Applicant's Position:

There is no postmarketing experience with adagrasib.

The FDA's Assessment:
FDA agrees with the Applicant's position.

Expectations on Safety in the Postmarket Setting

Data:

Not applicable.

The Applicant's Position:

Toxicities are adequately represented in the adagrasib safety database for this submission. Routine pharmacovigilance will continue to be conducted to monitor and update the safety profile of adagrasib. The ongoing and planned clinical studies will contribute additional safety information to further elucidate the safety profile of adagrasib.

The FDA's Assessment:
FDA's review determined that a REMS is not required to ensure safe and effective use of adagrasib. Adagrasib will be prescribed by oncologists who are trained on how to monitor, diagnose, and manage serious adverse reactions caused by anti-neoplastic drugs in accordance with FDA-approved labeling. Additionally, standard practice in oncology dictates informed consent prior to prescribing or administering anti-neoplastic drugs.

8.2.11. Integrated Assessment of Safety

Data:

The key risks with adagrasib are increased transaminases and QT prolongation. Typically, mild to moderate increase in transaminases are observed approximately 2 weeks following initiation of treatment. Among 260 patients treated at 600 mg twice daily, there were no cases meeting

Hy's Law or Grade 5 events. Increase in transaminases is typically adequately managed by dose modification and generally reversible without recurrence after dose reduction. Monitoring of AST, ALT, alkaline phosphatase and total bilirubin should be done prior to the start of adagrasib and monthly for 3 months after starting treatment, and evaluation of abnormalities should include testing for alternative etiologic factors.

QTcF values on-study met criteria thresholds for Grade 3 severity in 14.5% (38/262) patients who received any MRTX849. QTc prolongation was observed after drug exposure reached steady-state and generally reversible without recurrence after dose reduction. Mitigation of the risks of QT prolongation and Torsade de pointes include avoiding use in patients with congenital long QT syndrome and in patients with concurrent QTc prolongation, and monitoring ECGs and electrolytes in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, and in patients who are taking medications that are known to prolong the QT interval.

The Applicant's Position:

Adagrasib is associated with risks that include increased transaminases and QT prolongation. These risks appear to be effectively mitigated through monitoring and early management to limit AE severity.

The FDA's Assessment:

FDA agrees that a key risk associated with adagrasib is QT prolongation. Hepatotoxicity (including increased transaminases) is also considered to be a key risk associated with adagrasib.

Given the frequency of gastrointestinal adverse events and seriousness and severity of ILD/pneumonitis, both of these have also been included in product labeling, along with QTc interval prolongation and hepatotoxicity, as serious adverse reactions included in the Warnings and Precautions section of the label. Dose modification guidelines have been provided for these toxicities. The risks of these appear to be effectively mitigated through monitoring and early management as suggested by the product labeleing to limit AE severity.

Adagrasib shows a high toxicity profile with with 79% of patients experiencing Grade 3 or greater TEAEs and 82% of patients experiencing TEAEs leading to dose reduction and/or interruption. There were high incidences of gastrointestinal adverse reactions with 70% of patients experiencing diarrhea, 69% of patients experiencing nausea, and 56% of patients experiencing vomiting. A dose optimization postmarketing requirement (PMR) will be issued for the Applicant to evaluate an alternative dosage that may provide similar efficacy with improved safety as compared to the 600 mg BID dosage, as very limited clinical evaluations were performed for adagrasib at other dosages.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

There are no major statistical issues in this application.

The primary analysis population was defined as the patients who were treated with at least one dose of adagrasib and had measurable disease at baseline. FDA generally does not agree with excluding patients treated with at least one dose of the investigational treatment from the primary analysis. However, in this trial, only four patients were excluded from the primary analysis population due to the absence of measurable disease at the baseline. FDA conducted a sensitivity analysis by including patients with no measurable disease at baseline as nonresponders. The result of this sensitivity analysis, an ORR of 41% (95% CI: 32% to 51%), was close to the primary analysis result (ORR of 43% with 95% CI from 34% to 53%). Therefore, exclusion of the four patients did not raise concerns regarding the validity of the primary analysis results.

8.4. Conclusions and Recommendations

The FDA's Assessment:

Based on the data from clinical trial Study 849-001, for patients with KRAS G12C mutated NSCLC with disease progression following platinum-based chemotherapy and immune checkpoint inhibitor, adagrasib demonstrated a clinically meaningful overall response rate and duration of response. The demonstrated ORR by BICR per RECIST v1.1 was 43% (95% CI: 34, 53), with a median duration of response of 8.5 months (95% CI: 6.2, 13.8).

Available therapy for this patient population is the same as that for patients without a specific driver mutation and progression of disease following platinum-based chemotherapy with or without an immune checkpoint inhibitor, includes chemotherapy (single agent docetaxel or in combination with ramucirumab), associated with an ORR of 6-23% with median durations of responses in the range of 4 to 9 months, or single agent anti-PD-(L)1 antibody if not received in the first-line setting, associated with an ORR of 14-20% with median durations of response in the range of 16 to 17 months. Sotorasib is another oral targeted therapy which was granted accelerated approval for the treatment of adult patients with KRAS G12C mutated locally advanced or metastatic NSCLC; however, the clinical benefit of sotorasib has not yet been verified in a confirmatory trial. When considered in this context, the ORR along with the durability of responses observed suggest that adagrasib is reasonably likely to provide clinical benefit to patients with KRAS G12C mutated advanced NSCLC who have received at least one prior systemic therapy.

Given the limitations of a single arm clinical trial, the limited duration of follow-up and the number of patients in the primary efficacy analysis population for this application, the current

data are considered adequate to support accelerated approval but not a traditional approval. Results from the ongoing clinical trial entitled, "A Randomized Phase 3 Study of MRTX849 versus Docetaxel in Patients with Previously Treated Non-Small Cell Lung Cancer with KRAS G12C Mutation" may be used to verify the clinical benefit of adagrasib in patients with KRAS G12C mutated NSCLC.

The safety populations used to inform product labeling included 366 patients with KRAS G12C mutated solid tumors treated with adagrasib 600 mg orally twice daily; this includes the subgroup of 116 patients with KRAS G12C mutated NSCLC and disease progression after one prior systemic therapy. In the primary safety population, the most common adverse reactions (≥20%) were diarrhea, nausea, fatigue, vomiting, musculoskeletal pain, hepatotoxicity, renal impairment, dyspnea, edema, decreased appetite, cough, pneumonia, dizziness, constipation, abdominal pain, and QTc interval prolongation. Serious adverse reactions occurred in 57% of patients. Permanent discontinuations due to an adverse reaction occurred in 13% of patients.

While 77% of patients had adagrasib dosing interrupted for an adverse reaction, the majority of dose interruptions were related to gastrointestinal adverse reactions which should be effectively mitigated through monitoring and early management as suggested by the product labeleing.

The submitted evidence meets the statutory evidentiary standard for accelerated approval and provides preliminary evidence of the effectiveness of adagrasib as a single agent in patients with KRAS G12C mutated NSCLC who have received at least one prior systemic therapy. The reviewers recommend granting accelerated approval of adagrasib for the following indication: "KRAZATI is indicated for the treatment of adult patients with KRAS G12C mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy".

X	X
Chuck Song Primary Statistical Reviewer	Anup Amatya Statistical Team Leader

X	X
Katie Chon Jeevan Puthiamadathil Primary Clinical Reviewers	Paz Vellanki Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

FDA did not refer this application to an advisory committee as no significant efficacy or safety issues were identified during the review that required external input for the proposed indication.

10 Pediatrics

The Applicant's Position:

Adagrasib was not studied in pediatric subjects. In the Agreed iPSP, the Applicant has been granted a full waiver for studies in the pediatric population as the *KRAS* G12C mutation is not a relevant target in pediatric cancers.

The FDA's Assessment:

FDA agrees with the Applicant's position with the caveat that FDA issued an "Agreed Initial Pediatric Study Plan-Agreement" letter on May 10, 2021, in response to the Applicant's initial pediatric study plan requesting a full waiver for studies in the pediatric population. With this NDA, the Applicant submitted the request for a full waiver.

11 Labeling Recommendations

Applicant Data: A fully-annotated copy of the Draft USPI is provided with the NDA filing.

The FDA's Assessment: The proposed labeling submitted by the Applicant required extensive revision by FDA. The format, language, and content of the proposed labeling was evaluated and revised for consistency with 21 Code of Federal Regulations (CFR), labeling guidances and current labeling practices of the Office of Oncologic Diseases. The table below summarizes key changes.

(b) (4)

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

The Applicant's Position:

Draft labeling submitted as part of the original NDA describes the indication, usage, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

The FDA's Assessment:

The Applicant is seeking approval of the adagrasib tablets which is different than the adagrasib capsule formulation that was studied in the KRYSTAL-1 clinical trial. The labeling reflects "KRAZATI" where appropriate to reflect the tablet formulation and "adagrasib" to refer to the

capsules.

Note:
The labeling uses both the proprietary name, KRAZATI , and the non-proprietary name adagrasib. The clinical trials, KRYSTAL-1 and KRYSTAL-12 were performed using adagrasib in capsule formulation. The Applicant intended to market the tablet formulation and performed a bridging study *(see Section 19.4.2 for details)* to establish equivalency between the capsule and tablet formulations. Therefore, labeling descriptions of experience from KRYSTAL-1 and KRYSTAL-12 use the non-proprietary name adagrasib (capsule), and dosage instructions and clinical considerations (warnings, etc.) for the 'to be marketed' product use the proprietary name KRAZATI (tablet).

Overall FDA Assessment of Labeling: After careful review and negotiation, the revised labeling has been agreed upon to convey adequate information for the safe and effective use of KRAZATI.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The risks of adagrasib are acceptable in the indicated patient population with a serious and life-threatening condition; the safe use of adagrasib can be adequately implemented in the postmarketing setting through product labeling. No additional risk management strategies are recommended.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The Applicant has agreed to the following postmarketing requirements (PMR).

PMR 1:

Conduct a randomized comparative clinical trial of adagrasib in adult patients with KRAS G12C mutated, locally advanced or metastatic NSCLC who have received at least one prior systemic therapy, to obtain overall survival, progression free survival, overall response rate, and duration of response. This data may be obtained from the ongoing clinical trial entitled, "A Randomized Phase 3 Study of MRTX849 versus Docetaxel in Patients with Previously Treated Non-Small Cell Lung Cancer with KRAS G12C Mutation."

Final Protocol Submission:	12/2022
Trial Completion:	06/2025
Final Report Submission:	12/2025

Rationale: Adagrasib is being considered under accelerated approval for the treatment of adult patients with KRAS G12C mutated advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy. Overall response rate supported by duration of response from a cohort of patients in KRYSTAL-1, a multicenter, multicohort, open-label, non-randomized trial is the basis for potential accelerated approval. Conversion to traditional or regular approval is contingent upon verification of clinical benefit, which may be provided by data from the ongoing randomized controlled trial of adagrasib compared with docetaxel for patients with KRAS G12C mutated locally advanced or metastatic NSCLC, who have received at least one prior platinum-based chemotherapy and an anti-PD-(L)1 antibody.

PMR 2:

Conduct a multicenter, randomized clinical trial to further characterize serious adverse events, including gastrointestinal toxicity, and compare the safety of adagrasib 600 mg twice daily versus an alternative daily dosage in patients with locally advanced or metastatic, KRAS G12C mutated, non-small cell lung cancer who have received at least one prior systemic therapy. Include a comparative analysis of dose- and exposure-response relationships for safety including further characterization of the rates of Grade ≥3 adverse reactions, serious adverse reactions, and dose reductions, interruptions, and discontinuations due to adverse reactions. Additionally, conduct efficacy analyses including a comparative analysis of dose- and exposure-response relationships for efficacy for the two dosing regimens. Incorporate systematically assessed patient-reported outcome assessments to evaluate tolerability and conduct exploratory exposure response analyses.

Final Protocol Submission:	10/2022 (completed)
Study Completion:	06/2025
Final Report Submission:	10/2025

Submit the datasets with the final report submission.

Rationale: The proposed dosage of 600 mg BID for adagrasib administered without regard to food has not been determined as an optimal dosage, particularly given the high percentages of patients who experienced Grade ≥3 TEAEs, serious TEAEs, and those who required dose reductions or interruptions in Study KRYSTAL-1, phase 2 cohort A. Additionally, high incidences of gastrointestinal (GI) adverse reactions were observed with the 600 mg BID dose, which may be improved by giving an alternative oral dosage. A dose optimization study should be conducted as a PMR to investigate an alternative dosage that may provide comparable efficacy with improved safety as compared to 600 mg BID dose.

PMR 3:

Conduct a clinical pharmacokinetic trial to evaluate the effect of repeated doses of a strong CYP2C8 inhibitor on the steady-state pharmacokinetics of adagrasib. Refer to the following FDA Guidance for Industry for additional details: "Clinical Drug Interaction Studies-Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

Draft Protocol Submission:	02/2023
Final Protocol Submission:	04/2023
Study Completion:	08/2023
Final Report Submission:	03/2024

Rationale: Adagrasib is metabolized by CYP2C8 at steady-state. A clinical trial to evaluate the effect of repeated doses of a strong CYP2C8 inhibitor on the steady-state pharmacokinetics of adagrasib will inform if excessive drug toxicity occurs due to elevated drug levels, and determine if dose adjustment is needed for adagrasib.

PMR 4:

Conduct a clinical pharmacokinetic trial to evaluate the effect of a BCRP inhibitor on the single-dose pharmacokinetics of adagrasib. Refer to the following FDA Guidance for Industry for additional details: "Clinical Drug Interaction Studies-Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

Draft Protocol Submission:	03/2023
Final Protocol Submission:	05/2023

Study Completion:	09/2023
Final Report Submission:	04/2024

Rationale: Adagrasib is a BCRP substrate. A clinical trial to evaluate the effect of repeated doses of a BCRP inhibitor on the steady-state pharmacokinetics of adagrasib will inform if excessive drug toxicity occurs due to elevated drug levels, and determine if dose adjustment is needed for adagrasib.

PMR 5:

Conduct a clinical pharmacokinetic trial to evaluate the effect of repeated doses of adagrasib (at steady-state) on the single dose pharmacokinetics of a sensitive CYP2B6 substrate. Refer to the following FDA Guidance for Industry for additional details: "Clinical Drug Interaction Studies-Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

Draft Protocol Submission:	04/2023
Final Protocol Submission:	06/2023
Study Completion:	10/2023
Final Report Submission:	05/2024

Rationale: Adagrasib is a CYP2B6 inhibitor. A clinical trial to evaluate the effect of repeated doses of adagrasib (at steady-state) on the single dose pharmacokinetics of a sensitive CYP2B6 substrate will inform if excessive drug toxicity occurs due to elevated drug levels, and determine if dose restrictions are needed for adagrasib.

PMR 6:

Conduct a clinical pharmacokinetic trial to evaluate the effect of repeated doses of adagrasib (at steady-state) on the single dose pharmacokinetics of a probe MATE-1/-2K substrate. Refer to the following FDA Guidance for Industry for additional details: "Clinical Drug Interaction Studies-Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

Draft Protocol Submission:	05/2023
Final Protocol Submission:	07/2023
Study Completion:	11/2023
Final Report Submission:	06/2024

Rationale: Adagrasib is a MATE-1/-2K inhibitor. A clinical trial to evaluate the effect of repeated doses of adagrasib (at steady-state) on the single dose pharmacokinetics of a probe MATE-1/-2K substrate will inform if excessive drug toxicity occurs due to elevated drug levels, and determine if dose restrictions are needed for adagrasib.

14 Division Director (DHOT) (NME ONLY)

X

John Leighton

15 Division Director (OCP)

X

Nam Atiqur Rahman

16 Division Director (OB)

X

17 Division Director (Clinical)

X

Harpreet Singh

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

Richard Pazdur

19 Appendices

19.1. References

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19.2. Financial Disclosure

The Applicant's Position:

The Applicant provided financial disclosure in Form FDA 3455 for all clinical investigators involved in Studies 849-001, 849-011 and 849-015. No concerns were identified regarding the overall integrity of the data.

The FDA's Assessment:

FDA agrees with the Applicant's position with the caveat that on March 17, 2022, Mirati submitted their 120-Day Safety Update Report along with an updated list of investigators and FORM FDA 3454. FDA agrees that the total number of investigators (principal investigators and sub-investigators) was updated to 1000 from 985. The number of investigators with disclosable financial interests/arrangements was updated to 1 instead of 2, and the category of significant payments of other sorts was updated to 1 instead of 2 due to an initial error by the Applicant.

Covered Clinical Study (Name and/or Number):* 849-001, 849-011, 849-015

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1000		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):		

1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3. **Nonclinical Pharmacology/Toxicology**

Data:

All relevant data are presented in Section 5, Nonclinical Pharmacology/Toxicology.

The Applicant's Position:

Not applicable.

The FDA's Assessment:
FDA agrees with the Applicant's position.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Summary of Bioanalytical Method Validation and Performance

Human Plasma
A bioanalytical method using protein precipitation and high-performance liquid chromoatography (HPLC) analysis with tandem mass spectrometric (MS/MS) detection was developed and validated to measure adagrasib concentrations in human plasma samples.

The calibration curve ranged from 1.00 to 3000 ng/mL and the quality control (QC) samples across this range were used for determination of the accuracy and precision of the method. The cumulative accuracy (% bias) values of QC samples, based on the accepted calibration standards across the range, were -3.7 to 2.0% (all QC levels). The inter-batch precision values, based on the percent of relative standard deviation (%RSD), were 2.3 to 15.4% (all QC levels). A summary of bioanalytical method validation and performance to measure adagrasib in human plasma is shown in **Table 35**.

Table 35. Summary of bioanalytical method validation and performance to measure adagrasib in human plasma

Bioanalytical method validation report name, amendments, and hyperlinks	Validation of a Method for the Determination of MRTX849 in Human Plasma by HPLC with MS/MS Detection **Method Validation Report VAL-MRTX849-004, issued 11 Oct 2018** **Addendum VAL-MRTX849-004, issued 21 May 2021**		
Method description	Determination of MRTX849 in human plasma containing K_2EDTA by HPLC with MS/MS detection; protein precipitation/HPLC-MS/MS; Waters XBridge C18, 50 x 2.1 mm, 5 µm particle size; column temperature 35°C and autosampler temperature 5°C; flow rate 1.00 mL/min; gradient settings 0.01 (45%), 0.10 (45%), 0.85 (90%), 1.00 (rinse), 1.75 (90%), 2.05 (45%), and 2.75 (stop) minutes; mobile phase A: [Ammonium Formate 1 M (aq)]: Water: Formic Acid (1:100:0.1), mobile phase B [Ammonium Formate 1 M (aq)]: Acetonitrile: Methanol: Formic Acid (1:50:50:0.1); Mass spectrometer Sciex API 4500, ESI+ ionization, ionspray 3000 V, 625°C, nitrogen gas, entrance potential 10 V, acquisition time 2.00 min, cycle time 3.5 min.		
Materials used for standard calibration curve and concentration	MRTX849, Lot EW5243-753-P1, Mirati Therapeutics, Inc. MRTX810, Lot EW4069-1529-P1, Mirati Therapeutics, Inc.		
Validated assay range	1.00 to 3000 ng/mL		
Material used for QCs and concentration	MRTX849, Lot EW5243-753-P1, Mirati Therapeutics, Inc. Stock solution: 1.00 mg/mL in acetonitrile:DMSO (50:50)		
Minimum required dilutions	NA		
Source and lot of reagents	NA		
Regression model and weighting	Linear, weighted ($1/x^2$)		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	VAL-MRTX849-004, Section 4.3, Table 6.2
	Cumulative accuracy (% bias) from LLOQ to ULOQ	-2.2% to 3.0%	
	Cumulative precision (%RSD) from LLOQ to ULOQ	2.1% to 6.4%	
Performance of QCs during accuracy and precision runs	**Cumulative accuracy (% bias) in 5 QC levels**	-3.7% to 2.0%	VAL-MRTX849-004, Section 4.4, Table 6.4
	Interbatch Precision (%RSD)	2.3% to 15.4%	

	Total error	NR	NR
Selectivity and matrix effect	Selectivity for MRTX849 with respect to endogenous compounds and matrix effect were considered acceptable in 6 of 6 lots of human plasma tested. Interlot accuracy and precision at LLOQ and ULOQ: Accuracy (% bias): -10.7% to -2.3% Precision (%RSD): 5.8% Matrix factor (mean [%RSD]) of 6 lots of human plasma: 0.961 (4.0%) to 1.08 (4.9%)		VAL-MRTX849-004, Section 4.9, Table 6.7, Table 6.8
Interference and specificity	No significant chromatographic interferences were detected at either the retention time of the analyte or ISTD.		VAL-MRTX849-004, Section 4.7
Hemolysis effect	No significant effect of 2% hemolysis at 3.00 ng/mL and 2400 ng/mL Accuracy (% bias): -2.1% to 2.0% Precision (%RSD): 3.2% to 5.0%		VAL-MRTX849-004, Section 4.12, Table 6.10
Lipemic effect	No significant effect of lipemia at 3.00 ng/mL and 2400 ng/mL: Accuracy (% bias): -2.1% to 0.0% Precision (%RSD): 3.7% to 4.5%		VAL-MRTX849-004, Section 4.13, Table 6.11
Dilution linearity and hook effect	10-fold dilution of 24,000 ng/mL Accuracy (% bias): 5.8% Precision (%RSD): 2.3% Hook effect: NA		VAL-MRTX849-004, Section 4.6 Table 6.5
Bench-top/ post extraction storage stability	193 hours at 2°C to 8°C for processed samples		VAL-MRTX849-004, Section 4.15 and 4.18, Table 6.15 and 6.18
	30 hours in human plasma at RT condition		
Freeze-thaw stability	4 cycles at -10°C to -30°C 4 cycles at -60°C to -80°C		VAL-MRTX849-004, Section 4.16, Table 6.16
Long-term storage stability	211 days at -10°C to -30°C 399 days at -60°C to -80°C		VAL-MRTX849-004 Addendum No 1 Section 1, Table 6.8
Parallelism	NA		NA

Carryover	Carryover was evaluated during each validation run by injecting 2 carryover blanks (zero sample) after the ULOQ standard. There was no significant carryover evident in the carryover blanks injected directly after the ULOQ standard samples.	VAL-MRTX849-004 Section 4.8
Method Performance in Study 849-001 (Interim 1 Phase 1/1b) Bioanalytical Report: 8398399		
Assay passing rate	47 of 56 runs (84%) met acceptance criteria	8398399 Section 1
Standard curve performance	Cumulative accuracy (% bias): -2.0% to 1.5% Cumulative precision (%CV): ≤ 6.5%	8398399 Section 4.5 Table 9.3
QC performance	Cumulative accuracy (% bias): -2.1% to 2.1% Cumulative precision (%CV): ≤ 6.2% Total error: NR	8398399 Section 4.5 Table 9.5
Method reproducibility	Incurred sample reanalysis was performed in 145 samples (8.9% of total study samples), and 141 (97.2%) of samples were within ±20% of the original results.	8398399 Section 1 Section 4.7 Table 9.7
Study sample analysis stability	Samples were received intact, frozen in dry ice, and stored at -60°C to -80°C. Samples were collected beginning 15 Jan 2019 and analyzed by 10 Oct 2020. Study samples were analyzed in multiple subsets, so all samples were analyzed within established stability limit of 247 days at -60°C to -80°C.	8398399 Section 4.4
Standard calibration curve performance during accuracy and precision	47 calibrator sets of 2 replicates each of 8 concentration levels from 1.00 to 3000 ng/mL (total 752 datapoints) – 10 datapoints rejected due to failed acceptance criteria of > ±15.0% (±20% for LLOQ) from nominal	
Method Performance in Study 849-001 (Interim 2 Phase 2 Cohort B/C/D) Bioanalytical Report: 8398399		
Assay passing rate	82 of 90 runs (91%) met acceptance criteria	8398399 Section 1
Standard curve performance	Cumulative accuracy (% bias): -2.0% to 1.4% Cumulative precision (%CV): ≤ 6.3%%	8398399 Section 1 Table 9.3
QC performance	Cumulative accuracy (% bias): -2.1% to 1.6% Cumulative precision (%CV): ≤ 8.9% Total error: NR	8398399 Section 1 Table 9.5
Method reproducibility	Incurred sample reanalysis was performed in 206 samples (6.5% of total study samples), and 199 (96.6%) of samples were within ±20% of the original results.	8398399 Section 4.7 Table 9.7

Study sample analysis stability	Samples were received intact, frozen in dry ice, and stored at -60°C to -80°C. Samples were collected beginning 15 Jan 2019 and analyzed by 07 Apr 2021, samples were analyzed in multiple subsets resulting in all samples within 344 days, within the established stability limit of 399 days at -60°C to -80°C.	8398399 Section 4.4
Standard calibration curve performance during accuracy and precision	82 calibrator sets of 2 replicates each of 8 concentration levels from 1.00 to 3000 ng/mL (total 1312 datapoints) – 21 datapoints rejected due to failed acceptance criteria of > ±15.0% (±20% for LLOQ) from nominal	
Method Performance in Study 849-001 (Interim 3) Bioanalytical Report: 8398399		
Assay passing rate	97 of 106 runs (92%) met acceptance criteria	8398399 Section 1
Standard curve performance	Cumulative accuracy (% bias): -1.7% to 1.2% Cumulative precision (%CV): ≤ 6.3%	8398399 Section 1 Table 9.3
QC performance	Cumulative accuracy (% bias): -2.1% to 1.6% Cumulative precision (%CV): ≤ 8.3% Total error: NR	8398399 Section 1 Table 9.5
Method reproducibility	Incurred sample reanalysis was performed in 251 samples (6.5% of total study samples), and 244 (97.2%) of samples were within ±20% of the original results.	8398399 Section 4.7 Table 9.7
Study sample analysis stability	Samples were received intact, frozen in dry ice, and stored at -60°C to -80°C. Samples were collected beginning 15 Jan 2019 and analyzed by 16 Jun 2021, samples were analyzed in multiple subsets resulting in all samples within 344 days, within the established stability limit of 399 days at -60°C to -80°C.	8398399 Section 4.4
Standard calibration curve performance during accuracy and precision	97 calibrator sets of 2 replicates each of 8 concentration levels from 1.00 to 3000 ng/mL (total 1552 datapoints) – 26 datapoints rejected due to failed acceptance criteria of >±15.0% (±20% for LLOQ) from nominal and 1 with no reportable value	
Method Performance in Study 849-004 Bioanalytical Report: 8443902		
Assay passing rate	8 of 8 runs (100%) met acceptance criteria	8443902 Section 1
Standard curve performance	Cumulative accuracy (% bias): -2.7% to 3.0% Cumulative precision (%CV): ≤ 6.4%	8443902 Section 1 Table 10.3
QC performance	Cumulative accuracy (% bias): -2.1% to 1.0% Cumulative precision (%RSD): ≤ 6.7% Total error: NR	8443902 Section 1 Table 10.5

Method reproducibility	Incurred sample reanalysis was performed in 42 samples (10.3% of total study samples), and 42 (100%) of samples were within ± 20% of the original results.	8443902 Section1 Section 5.9 Table 10.6
Study sample analysis stability	Samples were received intact, frozen in dry ice, and stored at -60°C to -80°C. Samples were collected beginning 23 March 2020 and analyzed by 05 January 2021 within established stability limit of 399 days at -60°C to -80°C.	8443902 Section 5.5
Standard calibration curve performance during accuracy and precision	8 analytical runs, each of 8 concentration levels from 1.00 to 3000 ng/mL (total 64 datapoints) – 2 datapoints rejected due to failed acceptance criteria of > ±15.0% (±20% for LLOQ) from nominal	
Method Performance in Study 849-005 Bioanalytical Report: 8443644		
Assay passing rate	4 of 4 runs (100%) met acceptance criteria	8443644 Section 1
Standard curve performance	Cumulative accuracy (% bias): -3.2% to 3.0% Cumulative precision (%CV): ≤ 10.2%	8443644 Section 1 Table 10.3
QC performance	Cumulative accuracy (% bias): -5.4% to 1.4% Cumulative precision (%CV): ≤ 5.3% Total error: NR	8443644 Section 1 Table 10.5
Method reproducibility	Incurred sample reanalysis was performed in 21 samples (14.0% of total study samples), and 21 (100%) of samples were within ±20% of the original results.	8443644 Section 1 and 4.4 Table 10.6
Study sample analysis stability	Samples were received intact, frozen in dry ice, and stored at -60°C to -80°C. Samples were collected beginning 19 Jun 2020 and analyzed by 12 Aug 2020 within established stability limit of 399 days at -60°C to -80°C.	8443644 Section 5.5
Standard calibration curve performance during accuracy and precision	4 calibrator sets of 2 replicates each of 8 concentration levels from 1.00 to 3000 ng/ml (total 64 datapoints) – 0 datapoints rejected	
Method Performance in Study 849-006 Bioanalytical Report: 8445230		
Assay passing rate	36 of 37 runs (97.3%) met acceptance criteria	8445230 Section 1
Standard curve performance	Cumulative accuracy (% bias): -0.7% to 1.0% Cumulative precision (%CV): ≤ 6.4%	8445230 Section 1 Table 16.3

QC performance	Cumulative accuracy (% bias): -1.3% to -0.4% Cumulative precision (%CV): ≤ 5.1% Total error: NR	8445230 Section 1 Table 16.5
Method reproducibility	Incurred sample reanalysis was performed in 141 samples (8.2% of total study samples), and 140 (99.3%) of samples were within ±20% of the original results.	8445230 Section 1 and 11.14 Table 16.7
Study sample analysis stability	Samples were received intact, frozen in dry ice, and stored at -60°C to -80°C. Samples were collected beginning 02 Jul 2020 and analyzed by 30 Dec 2020 within established stability limit of 399 days at -60°C to -80°C.	8445230 Section 11.4
Standard calibration curve performance during accuracy and precision	36 calibrator sets of 2 replicates each of 4 concentration levels from 3.00 to 2400 ng/mL (total 288 datapoints) – 9 datapoints rejected due to failed acceptance criteria of > ±15.0% (±20% for LLOQ) from nominal	
Method Performance in Study 849-011 **Bioanalytical Report: 8452495**		
Assay passing rate	62 of 65 runs (95.4%) met acceptance criteria	8452495 Section 1
Standard curve performance	Cumulative accuracy (% bias): -2.0% to 2.0% Cumulative precision (%CV): ≤ 5.5%	8452495 Section 1 Table 9.3
QC performance	Cumulative accuracy (% bias): -1.3% to 2.1% Cumulative precision (%CV): ≤ 5.7% Total error: NR	8452495 Section 1 Table 9.5
Method reproducibility	Incurred sample reanalysis was performed in 186 samples (7.0% of total study samples), and 184 (98.9%) of samples were within ±20% of the original results.	8452495 Section 4.8 Table 9.10
Study sample analysis stability	Samples were received intact, frozen in dry ice, and stored at -60°C to -80°C. Samples were collected beginning 19 Jun 2020 and analyzed by 16 Apr 2021 within established stability limit of 399 days at -60°C to -80°C.	8452495 Section 4.4
Standard calibration curve performance during accuracy and precision	58 calibrator sets of 2 replicates each of 4 concentration levels from 3.00 to 2400 ng/mL (total 464 datapoints) – 2 datapoints rejected due to significant carryover observed	
Method Performance in Study 849-015 **Bioanalytical Report: 8466904**		
Assay passing rate	56 of 57 runs (98.2%) met acceptance criteria	8466904 Section 1

Standard curve performance	Cumulative accuracy (% bias): -3.2% to 2.0% Cumulative precision (%CV): ≤ 6.2%	8466904 Section 1 Table 9.3
QC performance	Cumulative accuracy (% bias): -1.3% to 2.9% Cumulative precision (%CV): ≤ 5.7% Total error: NR or	8466904 Section 1 Table 9.5
Method reproducibility	Incurred sample reanalysis was performed in 195 samples (7.7% of total study samples), and 187 (95.9%) of samples were within ±20% of the original results.	8466904 Section 4.8 Table 9.12
Study sample analysis stability	Samples were received intact, frozen in dry ice, and stored at -60°C to -80°C. Samples were collected beginning 24 Apr 2021 and analyzed by 28 Jul 2021, samples were analyzed in multiple subsets resulting in all samples within 56 days, within the established stability limit of 399 days at -60°C to -80°C.	8466904 Section 4.4
Standard calibration curve performance during accuracy and precision	51 calibrator sets of 2 replicates each of 4 concentration levels from 3.00 to 2400 ng/mL (total 408 datapoints) – 1 datapoint rejected due to no internal standard response	

CV=coefficient of variation; LLOQ=lower limit of quantification; NA=not applicable; NR=not reported; QC=quality control; RSD=relative standard deviation; RT=room temperature; ULOQ=upper limit of quantification.

Source: Table 36 from Applicant's 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Human Urine

A bioanalytical method using solid-phase extraction and HPLC with MS/MS was developed and validated to measure adagrasib concentraitons in human urine samples.

The calibration curve ranged from 0.0500 to 50.0 ng/mL in untreated urine, with a corresponding range of 0.0455 to 45.5 ng/mL in CHAPS treated urine. QC samples across this range were used for the determination of the precision and accuracy of the method. The cumulative accuracy (% bias) of the QC samples, based on the accepted calibration standards across the range, were -6.5 to 1.0% (all QC levels). The inter-batch precision values (%RSD), were 2.9 to 10.6% (all QC levels). A summary of the bioanalytical method validation and performance to measure adagrasib in human urine is shown in **Table 36**.

Table 36. Summary of bioanalytical method validation and performance to measure adagrasib in human urine

Bioanalytical method validation report name, amendments, and hyperlinks	Validation of a Method for the Determination of MRTX849 in Human Urine by HPLC with MS/MS Detection **Method Validation Report VAL-MRTX849-013, issued 12 Aug 2021**		
Method description	Determination of MRTX849 in human urine treated with CHAPS 163mM(aq) (10:1/v:v); solid-phase extraction/ HPLC-MS/MS; analytical column: Synergi PolarRP, 50 × 3 mm, 4 µm particle size; SPE plate: SOLA HRP 10 mg/2mL/96-well plate; column temperature 40°C and autosampler temperature 5°C; flow rate 0.800 mL/min, gradient 0.5 (50%), 2.00 (80%), 2.40 (95%), 2.80 (rinse), 3.40 (95%), 3.50 (50%), 4.20 (stop) minutes; mobile phase A is ammonium formate 20 mM (aq):formic acid (100:0.1) and mobile phase B is acetonitrile:methanol:formic acid (50:50:0.1); Mass spectrometer Sciex API 5500, ESI+ ionization, ionspray 2000 V, 600°C, nitrogen gas, entrance potential 10 V, acquisition time 3.80 min, cycle time 5.00 min.		
Materials used for standard calibration curve and concentration	MRTX849, Lot D-317-54, (b) (4) Stock solution: 1.00 mg/mL in acetonitrile:DMSO (50:50) MRTX849-d5, Lot AU-07-FEB-2019-001288, Mirati Therapeutics, Inc Stock solution: 2.50 ng/mL in acetonitrile:water (40:60)		
Validated assay range	0.0500 to 50.0 ng/mL in untreated urine; 0.0455 to 45.5 ng/mL in treated urine		
Material used for QCs and concentration	MRTX849, Lot D-317-54, (b) (4) Stock solution: 1.00 mg/mL in acetonitrile:DMSO (50:50)		
Minimum required dilutions	NR		
Source and lot of reagents	NR		
Regression model and weighting	Linear, weighted $1/x^2$		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	7	VAL-MRTX849-013 Section4.3 Table 7.2
	Cumulative accuracy (% bias) from LLOQ to ULOQ	-1.6% to 3.3%	
	Cumulative precision (%RSD) from LLOQ to ULOQ	2.8% to 13.2%	
	Cumulative accuracy (% bias) in 5 QC levels	-6.5% to -1.0%	VAL-MRTX849-013

Performance of QCs during accuracy and precision runs	**Interbatch Precision %RSD**	2.9% to 10.6%	Section 4.4 Table 7.6
	Total error	NR	NR
Selectivity and matrix effect	Selectivity for MRTX849 with respect to endogenous compounds and matrix effect were considered acceptable in 9 of 9 lots of human urine tested. Interlot accuracy and precision at LLOQ: Accuracy (% bias): -7.6% to -14.2% Precision (%RSD): 15.1% Matrix factor (mean [%RSD]) of 6 lots of human urine: 0.978 (3.5%) to 1.01 (1.0%)		VAL-MRTX849-013 Section 4.9 Table 7.10 Table 7.11
Interference and specificity	No significant chromatographic interferences were detected at either the retention time of the analyte or IS.		VAL-MRTX849-013 Section 4.7
Hemolysis effect	NA		NA
Lipemic effect	NA		NA
Dilution linearity and hook effect	10-fold dilution = 400 ng/mL Accuracy (% bias): -1.3% Precision (%RSD): 2.9% Hook effect: NA	1000-fold dilution = 24,000 ng/mL Accuracy (% bias): -1.3% Precision (%RSD): 3.3% Hook effect: NA	VAL-MRTX849-013 Section 4.6 Table 7.6 Table 7.9
Bench-top/process stability	24 hours at RT for treated human urine samples 6 hours at RT for untreated urine 109 hours processed storage stability at 2°C to 8°C 48 hours refrigerated for untreated urine		VAL-MRTX849-013 Section 1 Table 7.15 Table 7.21 Table 7.18 Table 7.22
Freeze-thaw stability	5 cycles at -10°C to -30°C 6 cycles at -60°C to -80°C 1 cycle at -60°C to -80°C for untreated urine		VAL-MRTX849-013 Section 1 Table 7.16 Table 7.23
Long-term storage	55 days in treated human urine at -10°C to -30°C 194 days in treated human urine at -60°C to -80°C 54 days in untreated urine at -10°C to -30°C 274 days in untreated urine at -60°C to -80°C		VAL-MRTX849-013 Section 1 Table 7.17 Table 7.24
Parallelism	NR		NR
Carryover	Carryover was evaluated during each validation run by analyzing 2 blank matrix samples after the ULOQ standard. There was no significant carryover evident in the carryover blanks injected directly after the ULOQ standard samples.		VAL-MRTX849-013 Section 4.8

Method Performance in Study 849-004 Bioanalytical Report: 8443902		
Assay passing rate	4 of 7 runs (57%) met acceptance criteria	8443902 Section 1
Standard curve performance	Cumulative accuracy (% bias): -7.8% to 5.5% Cumulative precision (%CV): ≤ 9.6%	8443902 Section 1 Table 10.8
QC performance	Cumulative accuracy (% bias): -8.0% to -2.0% Cumulative precision (%CV): ≤ 9.6% Total error: NR	8443902 Section 1 Table 10.10
Method reproducibility	Incurred sample reanalysis was performed in 28 samples (10.4% of total study samples), and 28 (100%) of samples were within ±20% of the original results.	8443902 Section 1 and 4.4 Table 10.6
Study sample analysis stability	Samples were received intact, frozen in dry ice, and stored at -60°C to -80°C. Samples were collected beginning 30 Jun 2020 and analyzed by 03 Mar 2021 within established stability limit of 274 days in untreated urine at -60°C to -80°C.	8443902 Section 5.1 and 5.5
Standard calibration curve performance during accuracy and precision	4 calibrator sets of 2 replicates each of 8 concentration levels from 0.0500 to 50.0 ng/mL (total 64 datapoints) – 3 datapoints rejected due to failed acceptance criteria of > ±15.0% (±20% for LLOQ) from nominal	
Method Performance in Study 849-005 Bioanalytical Report: 8443644		
Assay passing rate	3 of 4 runs (75%) met acceptance criteria	8443644 Section 2
Standard curve performance	Cumulative accuracy (% bias): -3.2% to 3.2% Cumulative precision (%CV): ≤ 3.9%	8443644 Section 2 Table 10.8
QC performance	Cumulative accuracy (% bias): -6.8% to 4.8% Cumulative precision (%CV): ≤ 5.7% Total error: NR	8443644 Section 2 Table 10.10
Method reproducibility	Incurred sample reanalysis was performed in 21 samples (19.4% of total study samples), and 20 (95.2%) of samples were within ±20% of the original results.	8443644 Section 2 and 5.9 Table 10.12
Study sample analysis stability	Samples were received intact, frozen in dry ice, and stored at -60°C to -80°C. Samples were collected beginning 19 Jun 2020 and analyzed by 22 Aug 2020 within established stability limit of 274 days in untreated urine at -60°C to -80°C.	8443644 Section 5.5

Standard calibration curve performance during accuracy and precision	3 calibrator sets of 2 replicates each of 8 concentration levels from 0.0500 to 50.0 ng/mL (total 48 datapoints) – 1 datapoint rejected due to failed acceptance criteria of >±15.0% (±20% for LLOQ) from nominal

CHAPS=3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonic; CV=coefficient of variation; DMSO=dimethyl sulfoxide; LLOQ=lower limit of quantification; NA=not applicable; NR=not reported; QC=quality control; RSD=relative standard deviation; RT=room temperature; ULOQ=upper limit of quantification.
Source: Table 37 from Applicant's 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

19.4.2. Clinical PK Bridging of Adagrasib Formulations

Applicant's clinical development, including their pivotal Study **849-001**, used a capsule formulation. The to-be-marketed formulation has since been evaluated in Applicant's currently ongoing confirmatory Study **849-012**, which showed comparable PK in patients who received 600 mg BID tablets (n=40) vs. those who received 600 mg BID capsules (n=139) (**Table 37**).

Table 37. Descriptive statistics of secondary PK parameters by formulation following 600 mg BID

Parameters	Capsule (N=139)	Tablet (N=40)	Overall (N=179)
$AUC_{tau,ss}$ (ng.h/mL)			
Mean (CV%)	30000 (56.9%)	32100 (82.9%)	30400 (64.1%)
Median [Q5; Q95]	26400 [14100;51000]	25800 [14400;54300]	26100 [14100;51000]
Geometric Mean	26900	27200	27000
$C_{ave,ss}$ (ng.h/mL)			
Mean (CV%)	2500 (56.9%)	2670 (82.9%)	2540 (64.1%)
Median [Q5; Q95]	2200 [1170;4250]	2150 [1200;4530]	2180 [1170;4250]
Geometric Mean	2240	2270	2250
$C_{max,ss}$ (ng/mL)			
Mean (CV%)	2650 (55.5%)	2820 (79.9%)	2690 (62.2%)
Median [Q05;Q95]	2350 [1270;4630]	2280 [1300;4770]	2310 [1270;4630]
Geo. Mean	2390	2410	2390
$C_{min,ss}$ (ng/mL)			
Mean (CV%)	2310 (58.9%)	2490 (86.5%)	2350 (66.7%)
Median [Q05;Q95]	2000 [1080;3910]	1960 [1050;4230]	2000 [1050;3940]
Geo. Mean	2060	2090	2070
T_{max} (h)			
Mean (CV%)	4.49 (20.5%)	4.38 (13.9%)	4.46 (19.2%)
Median [Q05;Q95]	4.00 [3.50;6.05]	4.50 [3.50;5.50]	4.00 [3.50;6.00]
Geo. Mean	4.40	4.34	4.39
$T_{1/2}$ (h)			
Mean (CV%)	39.9 (97.7%)	40.6 (84.8%)	40.0 (94.7%)
Median [Q05;Q95]	31.1 [17.9;81.0]	31.4 [19.1;81.4]	31.1 [17.9;82.1]
Geo. Mean	33.7	34.3	33.8
PTR			
Mean (CV%)	1.16 (8.5%)	1.16 (7.2%)	1.16 (8.2%)
Median [Q05;Q95]	1.15 [1.04;1.29]	1.15 [1.05;1.30]	1.15 [1.05;1.30]
Geo. Mean	1.16	1.16	1.16

$AUC_{tau,ss}$ = 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; PTR = peak to trough ratio; Q5 = 5th percentile; Q95 = 95th percentile; $T_{1/2}$= half-life; T_{max}= time of maximum concentration.
Source: Table 7 from Applicant's MIRA-PMX-MRTX849-4124_PPK Report

19.4.3. Population PK Analysis

19.4.3.1. Executive Summary

The FDA's Assessment:

The population PK (PopPK) analysis described the PK of adagrasib by a two-compartment model with sequential zero-order then first-order absorption and linear elimination. The Applicant's PopPK model is acceptable to investigate covariate effects and sources of variability in PK exposure parameters. Adagrasib exhibited moderate between-subject PK variability (BSV), particularly for CL/F and Vc/F with BSV of 58% and 65%. No clinically significant differences in the PK of adagrasib were observed based on age (19 to 89 years), sex, race (White, Black and Asian), body weight (36 to 139 kg), ECOG PS (0, 1), baseline tumor burden, mild and moderate renal impairment (CLcr ≥ 30 mL/min or eGFR ≥30 mL/min/1.73 m2), and mild hepatic impairment (NCI-ODWG criteria). No dose adjustments for adagrasib are warranted based on these covariates. The PopPK model is acceptable to derive individual predicted exposure metrics at steady state for Study 846-001 for exposure-response (E-R) analysis.

19.4.3.2. PPK Assessment Summary

The Applicant's Position:

General Information		
Objectives of PPK Analysis		• *Perform a population PK analysis of adagrasib in patients with advanced solid tumors with KRAS* G12C *mutation and healthy subjects.* • *Investigate sources of variability in PK and exposure parameters of adagrasib.*
Study Included		*849-001, 849-004, 849-005, 849-006*
Dose(s) Included		*Single Dose – 200 mg, 600 mg.* *Multiple Dose – 150 mg QD, 300 mg QD, 600 mg QD, 400 mg BID, 600 mg BID*
Population Included		*Patients with advanced solid tumors with KRAS* G12C *mutation and healthy subjects*
Population Characteristics (Applicant Table 21 and Applicant Table 22)	General	*Age median (range, XX% subj >=65 yr, XX% subj >=75 yr)* - *61.0 yrs (19.0 - 89.0, 33.9% subj >=65 yr, 9.1% subj >=75)* *Weight median (range) – 76.3 (36.0 – 139) kg* *Male – 186 (52.7%)* *Race:* - *White (264, 74.8%)* - *Black or African American (60, 17%)* - *Asian (17, 4.8%)* - *American Indian or Alaskan Native (1, 0.3%) Multiple (1, 0.3%)* - *Other (10, 2.8%)*
	Organ Impairment	*Hepatic (NCI-ODWG):* - *Normal Hepatic Function (318, 90.1%)*

		- *Mild Hepatic Impairment (32, 9.1%)* - *Moderate Hepatic Impairment (3, 0.8%)* - *Severe Hepatic Impairment (0, 0%)* *Renal (CLcr):* - *Normal Renal Function (181, 51.3%)* - *Mild Renal Impairment (126, 35.7%)* - *Moderate Renal Impairment (40, 11.3%)* - *Severe Renal Impairment (6, 1.7%)*
	Pediatrics (if any)	*None*
No. of Patients, PK Samples, and BLQ		*A total of 353 subjects with at least one measurable concentration of Adagrasib were included in the population PK analysis. Of a total of 3602 samples, 84 (2.3%) presented concentrations of adagrasib below the limit of quantitation (BLQ) on treatment.*
Sampling Schedule	Rich Sampling	- 849-001 Intensive Sampling - predose, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96 h - 849-004 – Predose, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120 and 144 h postdose - 849-005 - predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240 and 264 h postdose - 849-006 - single dose - 0, 0.5, 1 , 2, 4, 6, 8, 12, 24, 48, 72, 96,120 and 144 h postdose - 849-006 – multiple dose - predose, 2, 4, 6, 8, 12 and 24 h postdose
	In ITT Population	849-001 Sparse Sampling -C1D1, C1D8, C2D1 – predose and 4 h -C3D1, C5D1 – predose
Covariates Evaluated	Static	*Body Weight, Age, Sex, Race, ECOG PS, Cancer Type, Sum of largest diameter of target lesion, hepatic function, renal function*
	Time-varying	*CLcr, eGFR, albumin, ALP, ALT, AST, bilirubin*

Final Model	**Summary**	**Acceptability [FDA's comments]**
Software and Version	NONMEM v7.4 – population PK analysis. R v4.1.1 – further analysis and presentation of results.	Acceptable
Model Structure	*Two-compartment model with sequential zero-order then first-order absorption and linear elimination*	Acceptable
Model Parameter Estimates	Applicant Table 23	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	*Population estimates as well as BSV were robustly estimated with RSE values less than 20%. In addition, ETA shrinkage for CL/F and Vc/F were deemed acceptable (i.e., less than 20%). Adagrasib exhibited moderate between-subject PK variability, particularly for CL/F and Vc/F with BSV of approximately 58% and 65%, respectively. Body weight was a covariate for CL/F and Vc/F with exponents of 0.661 and 1.30, respectively*	Acceptable

BLQ for Parameter Accuracy	*Concentrations below the limit of quantification (BLQ) of were set to missing. Due to the low number of concentrations that were BLQ, a truncated likelihood method that takes into account the censoring of BLQ data (M3 method) was not considered. Concentrations that were BLQ were deemed not to have a significant impact on the population PK analysis.*	Acceptable
GOF, VPC	Applicant Figure 10, Applicant Figure 11 and Applicant Figure 12	Acceptable
Significant Covariates and Clinical Relevance	Applicant Figure 13	Acceptable
Analysis Based on Simulation (optional)	*Not applicable*	NA
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.3 PK	*No clinically meaningful differences in the pharmacokinetics of adagrasib were observed based on age (19 to 89 years), sex, race (White, Black, and Asian), body weight (36 to 139 kg), ECOG PS (0, 1), baseline tumor burden,* (b) (4)	Acceptable

Applicant Table 38: Summary of Baseline Demographics and Characteristics in the Dataset, Stratified by Study

Characteristics	849-001 (N=252)	849-004 (N=28)	849-005 (N=6)	849-006 (N=67)	Overall (N=353)
Populations					
Patients with Advanced Malignancies	252 (100%)	0 (0%)	0 (0%)	0 (0%)	252 (71.4%)
Healthy Subjects	0 (0%)	28 (100%)	6 (100%)	67 (100%)	101 (28.6%)
Sex					
Female	143 (56.7%)	5 (17.9%)	0 (0%)	19 (28.4%)	167 (47.3%)
Male	109 (43.3%)	23 (82.1%)	6 (100%)	48 (71.6%)	186 (52.7%)
Race					
White	210 (83.3%)	19 (67.9%)	4 (66.7%)	31 (46.3%)	264 (74.8%)
Black or African American	20 (7.9%)	6 (21.4%)	1 (16.7%)	33 (49.3%)	60 (17.0%)
Asian	11 (4.4%)	3 (10.7%)	0 (0%)	3 (4.5%)	17 (4.8%)
American Indian or Alaska Native	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)
Native Hawaiian or Other Pacific Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Multiple	0 (0%)	0 (0%)	1 (16.7%)	0 (0%)	1 (0.3%)
Other	10 (4.0%)	0 (0%)	0 (0%)	0 (0%)	10 (2.8%)
Cancer Types					
NSCLC	181 (71.8%)	0 (0%)	0 (0%)	0 (0%)	181 (51.3%)
CRC	48 (19.0%)	0 (0%)	0 (0%)	0 (0%)	48 (13.6%)
Ovarian/Fallopian Tube Cancer	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)
Cholangiocarcinoma	4 (1.6%)	0 (0%)	0 (0%)	0 (0%)	4 (1.1%)
Endometrial Cancer	2 (0.8%)	0 (0%)	0 (0%)	0 (0%)	2 (0.6%)
Pancreatic Cancer	6 (2.4%)	0 (0%)	0 (0%)	0 (0%)	6 (1.7%)
Mucinous Appendiceal Adenocarcinoma	4 (1.6%)	0 (0%)	0 (0%)	0 (0%)	4 (1.1%)
Unknown Primary	2 (0.8%)	0 (0%)	0 (0%)	0 (0%)	2 (0.6%)

Characteristics	849-001 (N=252)	849-004 (N=28)	849-005 (N=6)	849-006 (N=67)	Overall (N=353)
Gastroesophageal Junction Tumor	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)
Other	3 (1.2%)	0 (0%)	0 (0%)	0 (0%)	3 (0.8%)
Not Applicable	0 (0%)	28 (100%)	6 (100%)	67 (100%)	101 (28.6%)
ECOG PS					
0	66 (26.2%)	0 (0%)	0 (0%)	0 (0%)	66 (18.7%)
1	185 (73.4%)	0 (0%)	0 (0%)	0 (0%)	185 (52.4%)
Missing	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)
Healthy Subject	0 (0%)	28 (100%)	6 (100%)	67 (100%)	101 (28.6%)
Hepatic Function (NCI-ODWG)					
Normal Hepatic Function	217 (86.1%)	28 (100%)	6 (100%)	67 (100%)	318 (90.1%)
Mild Hepatic Impairment	32 (12.7%)	0 (0%)	0 (0%)	0 (0%)	32 (9.1%)
Moderate Hepatic Impairment	3 (1.2%)	0 (0%)	0 (0%)	0 (0%)	3 (0.8%)
Severe Hepatic Impairment	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Renal Function (eGFR)					
Normal Renal Function	101 (40.1%)	6 (21.4%)	3 (50.0%)	38 (56.7%)	148 (41.9%)
Mild Renal Impairment	118 (46.8%)	9 (32.1%)	3 (50.0%)	29 (43.3%)	159 (45.0%)
Moderate Renal Impairment	33 (13.1%)	5 (17.9%)	0 (0%)	0 (0%)	38 (10.8%)
Severe Renal Impairment	0 (0%)	8 (28.6%)	0 (0%)	0 (0%)	8 (2.3%)
Renal Function (CLcr)					
Normal Renal Function	109 (43.3%)	10 (35.7%)	6 (100%)	56 (83.6%)	181 (51.3%)
Mild Renal Impairment	109 (43.3%)	6 (21.4%)	0 (0%)	11 (16.4%)	126 (35.7%)
Moderate Renal Impairment	34 (13.5%)	6 (21.4%)	0 (0%)	0 (0%)	40 (11.3%)
Severe Renal Impairment	0 (0%)	6 (21.4%)	0 (0%)	0 (0%)	6 (1.7%)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; CLcr = creatinine clearance; eGFR = estimated glomerular filtration rate; NCI-ODWG = National Cancer Institute- Organ Dysfunction Working Group; NSCLC = non-small cell lung cancer; CRC = colorectal cancer.

Applicant Table 39: Summary of Baseline Characteristics and Laboratory Values in the Dataset, Stratified by Study

Characteristics	849-001 (N=252)	849-004 (N=28)	849-005 (N=6)	849-006 (N=67)	Overall (N=353)
Age (years)					
Mean (CV%)	62.8 (17.3%)	63.3 (11.5%)	45.2 (27.6%)	41.2 (28.8%)	58.5 (23.7%)
Median [Min, Max]	63.0 [25.0, 89.0]	63.0 [50.0, 75.0]	43.5 [30.0, 65.0]	40.0 [19.0, 60.0]	61.0 [19.0, 89.0]
Body Weight (kg)					
Mean (CV%)	74.0 (26.6%)	80.4 (15.7%)	86.1 (4.0%)	80.0 (14.9%)	75.9 (23.8%)
Median [Min, Max]	72.7 [36.0, 139]	81.1 [55.0, 104]	85.3 [81.4, 90.8]	80.1 [56.9, 109]	76.3 [36.0, 139]
BSA (m^2)					
Mean (CV%)	1.82 (14.1%)	1.92 (9.3%)	2.03 (4.0%)	1.94 (9.4%)	1.86 (13.0%)
Median [Min, Max]	1.81 [1.28, 2.56]	1.94 [1.51, 2.28]	2.03 [1.93, 2.13]	1.93 [1.56, 2.34]	1.86 [1.28, 2.56]
Missing	8 (3.2%)	0 (0%)	0 (0%)	0 (0%)	8 (2.3%)
BMI (kg/m^2)					
Mean (CV%)	26.2 (22.7%)	27.4 (13.5%)	27.6 (6.4%)	26.8 (10.8%)	26.4 (20.0%)
Median [Min, Max]	25.6 [14.7, 45.3]	27.1 [21.1, 37.7]	28.2 [24.8, 29.7]	27.1 [20.1, 32.2]	26.2 [14.7, 45.3]
Missing	8 (3.2%)	0 (0%)	0 (0%)	0 (0%)	8 (2.3%)
CLcr (mL/min)					
Mean (CV%)	91.0 (38.1%)	68.3 (55.2%)	127 (12.7%)	113 (19.7%)	93.9 (36.9%)
Median [Min, Max]	83.3 [35.8, 234]	74.1 [16.0, 152]	125 [108, 155]	111 [67.1, 164]	91.3 [16.0, 234]
eGFR ($mL/min/1.73m^2$)					
Mean (CV%)	87.6 (36.5%)	60.0 (56.5%)	97.4 (22.0%)	91.8 (14.4%)	86.4 (35.1%)
Median [Min, Max]	83.9 [31.3, 241]	64.9 [10.5, 115]	94.0 [74.9, 135]	92.5 [64.4, 118]	85.1 [10.5, 241]
Albumin (g/dL)					
Mean (CV%)	3.67 (14.4%)	4.18 (9.5%)	4.45 (9.3%)	4.36 (6.3%)	3.85 (14.6%)
Median [Min, Max]	3.70 [2.00, 4.90]	4.20 [3.20, 4.80]	4.55 [3.70, 4.80]	4.30 [3.50, 5.20]	3.90 [2.00, 5.20]
ALP (U/L)					
Mean (CV%)	114 (65.5%)	69.8 (24.8%)	62.7 (22.1%)	69.0 (27.5%)	101 (66.4%)
Median [Min, Max]	92.5 [35.0, 559]	67.5 [46.0, 135]	58.5 [48.0, 83.0]	67.0 [33.0, 126]	80.0 [33.0, 559]
ALT (U/L)					
Mean (CV%)	21.5 (71.7%)	18.8 (59.5%)	25.7 (37.9%)	20.1 (46.2%)	21.1 (66.6%)
Median [Min, Max]	18.0 [5.00, 123]	15.0 [5.00, 50.0]	23.5 [15.0, 44.0]	17.0 [10.0, 54.0]	17.0 [5.00, 123]
AST (U/L)					
Mean (CV%)	25.2 (58.4%)	18.2 (33.0%)	21.3 (9.7%)	21.0 (23.9%)	23.8 (54.4%)
Median [Min, Max]	21.0 [7.00, 143]	18.0 [8.00, 35.0]	21.0 [18.0, 24.0]	20.0 [13.0, 34.0]	20.0 [7.00, 143]
Bilirubin (mg/dL)					
Mean (CV%)	0.483 (63.4%)	0.436 (35.5%)	0.450 (33.7%)	0.407 (50.6%)	0.465 (60.2%)
Median [Min, Max]	0.400 [0.150, 2.30]	0.400 [0.200, 0.800]	0.450 [0.300, 0.700]	0.400 [0.100, 1.10]	0.400 [0.100, 2.30]
Sum of Longest Diameter of target lesion (mm)					
Mean (CV%)	70.8 (73.8%)	NA	NA	NA	50.5 (108.2%)
Median [Min, Max]	63.0 [0, 307]	0 [0, 0]	0 [0, 0]	0 [0, 0]	39.0 [0, 307]
Missing	2 (0.8%)	0 (0%)	0 (0%)	0 (0%)	2 (0.6%)

Abbreviations: ALP = Alkaline Phosphatase; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase; BMI = body mass index; BSA = body surface area; NA = not available.

Applicant Table 40: Parameter Estimates and SE from Final Population PK Model

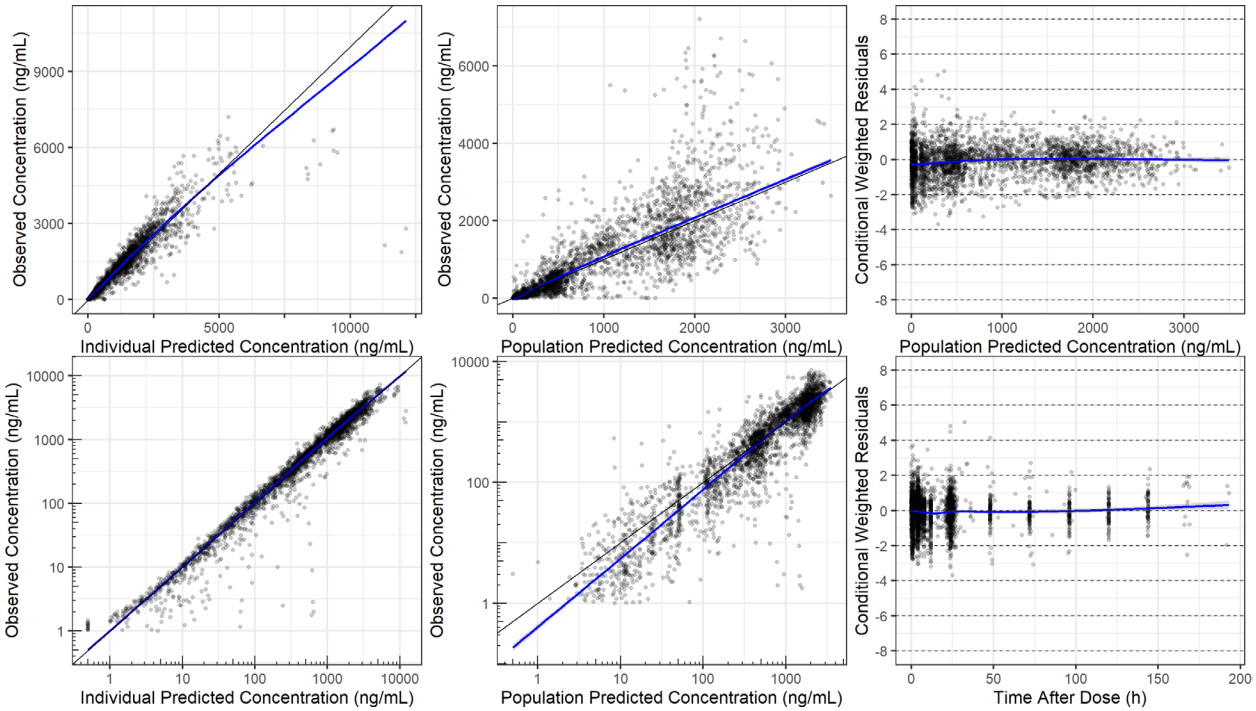
Parameter	Estimate (RSE)	BSV (RSE)	Shrinkage
Ka (h^{-1})	**0.399 (14.3%)**	103 (13.4%)	33.9%
D1 (h)	**2.96 (8.44)**	4.2 (11.7%)	49.1%
CL/F (L/h)	**35.9 (4.18%)** × $(BW/76.6)^{0.661}$ (18.7%) × 0.720 for ≥7 doses of adagrasib (1.37%)	57.5% (4.03%)	5.2%
Vc/F (L)	**776 (7.41%)** × $(BW/76.6)^{1.30}$ (9.42%)	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

Abbreviations: 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)

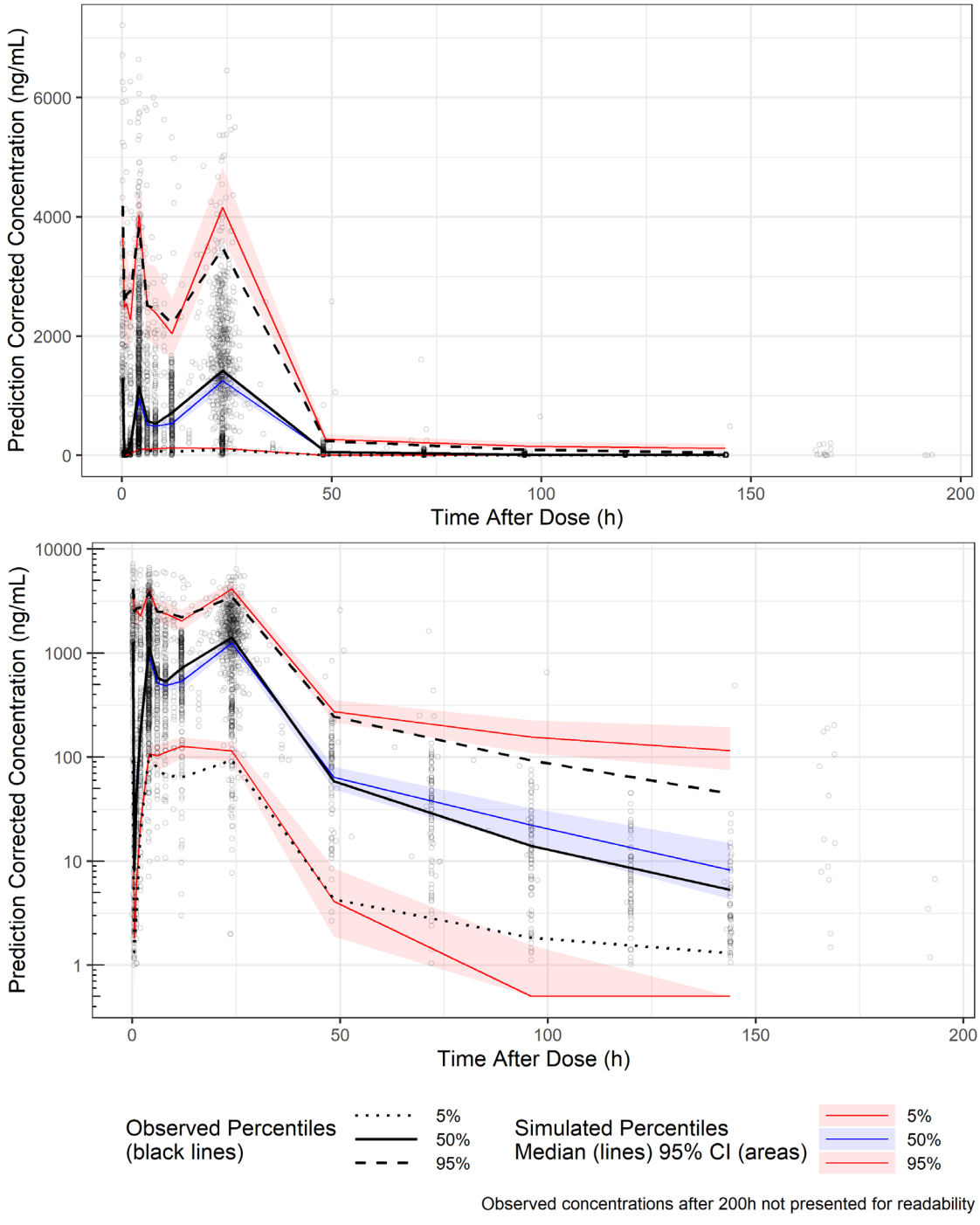
[a] BSV (RSE) and shrinkage could not be estimated for peripheral parameters (Q/F and Vp/F)

Applicant Figure 12: Goodness-of-fit Plots for the Final Population PK Model (OBS-PRED/IPRED, CWRES-TIME/PRED)

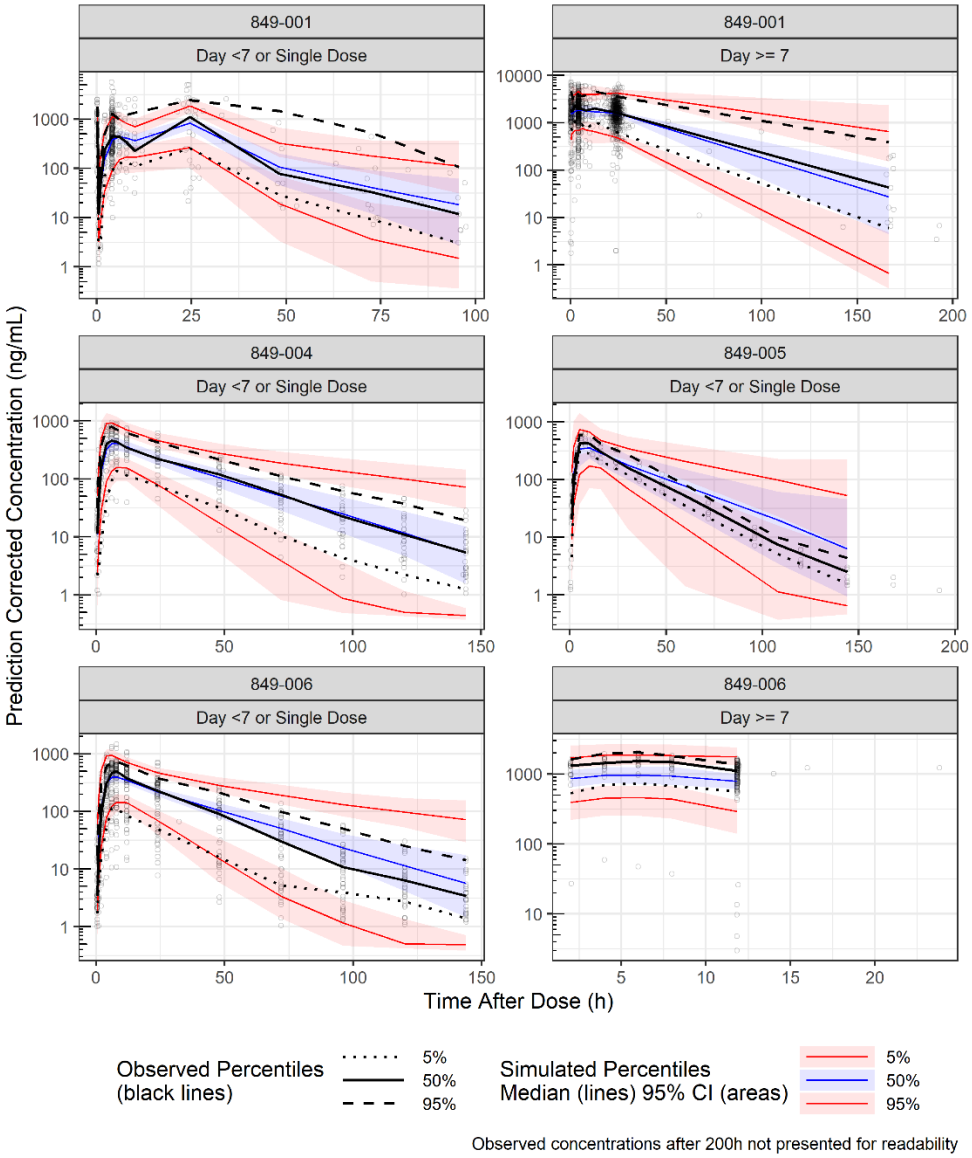


Black circles = observed data; black line = identity line; blue line = smoothing function. Note: the goodness-of-fit of the final model is the same as the based model since no covariates were included during the covariate analysis.

Applicant Figure 13: Visual Predictive Check of Final Population PK Model - All Studies and Occasions

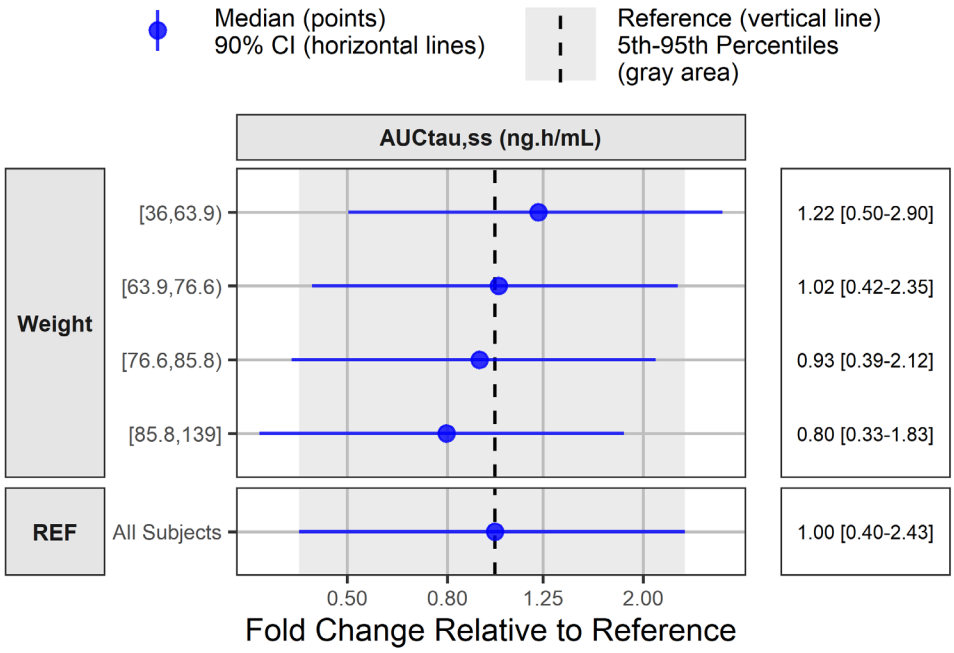


Applicant Figure 14: Prediction-Corrected Visual Predictive Check of adagrasib by Study and Occasions: Semi-Log Scale



Note: the Day <7 or Single Dose panel for study 849-001 includes the PK lead-in phase

Applicant Figure 15: Impact of Body Weight on $AUC_{tau,ss}$ for adagrasib for 600 mg Twice Daily 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 adagrasib. The shaded area represents the 5th and 95th percentiles of exposure in all subjects

The FDA's Assessment:

Applicant's PopPK analysis is acceptable to describe the observed PK and derive individual predicted exposure metrics at steady state for Study 846-001 for exposure-response (E-R) analysis. The PK parameter estimates for CL/F and Vc/F and the associated BSV were estimated with RSE<20% and the ETA shrinkages for CL/F and Vc/F were <20%. The GOF plots and pcVPC plots stratified by study, dose level and before Day 7 and after Day 7 did not show an apparent model misspecification in describing the observed PK in Study 846-001. While slight overpredictions were noted in describing PK data from Study 849-005 (single dose study), and 849-006 (DDI study), the model generally captures the steady-state PK at the proposed dose level (600 mg).

Auto-inhibition of adagrasib is described by including the number of doses (≥7 doses) on the CL/F term. GOF plots based on dose levels did not indicate a notable bias among the time after the first dose. It should be also noted that the estimates of time-dependent clearance due to the auto-inhibition are largely based on dose levels of 400 mg and 600 mg. Data is limited to characterize dose-dependent auto-inhibition at dose level below 400 mg or above 600 mg.

Applicant's rationale to support the labeling language Section 12.3 Special population are following:

- Body weight is a significant covariate, however, the magnitude of impact is not

considered clinically meaningful: the predicted PK exposures for body weight range (36 to 139 kg) are 0.8 to 1.2 folds of those with the reference body weight (76.6 kg).

- Age, race, sex, ECOG (0, 1), baseline tumor burden (i.e., sum of longest diameters of tumor lesion) and hepatic impariemnt (NCI-ODWG) were identified as statistically significant covariates in stepwise covariate search. Adding sex or tumor burden in the model increased BSV. For the rest of covariates, the reduction in BSV was less than 5%. No significant difference in steady-state PK exposures was observed based on age groups (25 - 60, 61 - 68, and 69 - 89 years old), ECOG (0, 1) and hepatic function (normal and mild HI). Limited data was available in patients with moderate (n=2) and severe (n=0) hepatic function. AUCtau,ss and Cmax,ss in patients with Asian origin were approximately 25% and 27% higher than those observed in patients of White origin, respectively. These differences were likely associated with the lower body weight in Asian patients.
- Renal impariement by eGFR and CrCL as continuous variable was a statistically significant covariate but resulting in <5% reduction in BSV. Hence, it was not retained in the final PopPK model. The individual predicted PK exposures at steady state by renal function did not indicate clinically meaningful difference in PK exposures between normal, mild and moderate renal impairment.

The reviewer generally agrees with the Applicant rationale and the labeling language.

The Applicant evaluated the impact of concomitant medications (CYP2C8 inhibitors, H2 antagonists, and antacid). The reviewer notes that the current PopPK analysis has limitations to support any meaningful conclusion for CYP2C8 inhibitors due to the small sample size (e.g., strong CYP2C8 inhibitors [n= 2] and moderate CYP2C8 inhibitor [n=23]) and lack of details of dosing information for these conmedications (e.g., tested as static covariates rather than time-varying covariates, and durations of treatment). Similarly, no meaningful conclusions can be drawn for the impact of H2 antagonists and antacids due to limitations in administration time versus PK sampling, which occurred over a wide time window (e.g., administration within 3 days of PK sampling) and lack of dosing information (duration of treatment, dosing time relative to adagrasib, etc) which are critical to capture the impact of H2 antagonist/antacid on absoroption phase.

19.4.3.3. PPK Review Issues

Applicant's PopPK analysis is acceptable for the purpose of the PopPK model to support the Applicant's proposed labeling language in special populations and to derive individual predicted exposure metrics at steady state for Study 846-001 for exposure-response (E-R) analysis. However, the Applicant's PopPK analysis cannot be used to support the potential dose adjustment for DDIs given the limitations on sample size, PK samples and dosing information for concomitant medications.

19.4.3.4. Reviewer's Independent Analysis

N/A

19.4.4. Exposure-Response Analysis

19.4.4.1. ER (efficacy) Executive Summary

The FDA's Assessment:

The E-R relationships for efficacy measures were assessed in patients with advanced, unresectable or metastatic solid tumor malignancy with KRAS G12C mutation in Study 849-001 (Phase 1/1b and Phase 2 Cohort A). Efficacy endpoints were the objective response rate (ORR), progression free survival (PFS), and overall survival (OS). The reviewer generally agrees with the Applicant's conclusions that no relationship between adagrasib exposure (i.e., Cmin or Cavg) and ORR was observed based on the PK and efficacy data from 118 patients. It should be noted that all patients included in the E-R analysis all received a starting dose of 600 mg BID adagrasib. Any meaningful inference or extrapolation of the findings cannot be made for dosages other than 600 mg BID.

19.4.4.2. ER (efficacy) Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis		To characterize adagrasib exposure-response relationships for measures of efficacy in patients with advanced, unresectable or metastatic solid tumor malignancy with KRAS G12C mutation in Study 849-001 (Phase 1/1b and Phase 2 Cohort A). Efficacy endpoints were the objective response rate (ORR), progression free survival (PFS), and overall survival (OS) data.
Study Included		Study 849-001 (Phase 1/1b and Phase 2 Cohort A). All patients included in exposure-efficacy analysis were NSCLC patients and started treatment at the planned 600 mg BID of adagrasib
Endpoint		*Primary:* • Response rate (ORR) • Progression free survival (PFS) • Overall survival (OS) *Secondary: None*
No. of Patients (total, and with individual PK)		*Total of 127 patients with data on ORR, PFS and OS.* *118 patients with PK and response*
Population Characteristics (Applicant Table 24)	General	*Age: 64.0 (25.0, 89.0) years* *Weight: 69.5 (36.8, 138.6) kg* *Males: 52 (44.1%) male* *White: 99 (83.9%)* *Black: 9 (7.6%)* *Asian: 5 (4.2%)*

		Other: 5 (4.2%)	
	Pediatrics (if any)	*None*	
Dose(s) Included		*600 mg twice daily*	
Exposure Metrics Explored (range)		$C_{min,Week2\text{-}6}$*: 771 (0, 4510) ng/mL* $C_{ave,Week2\text{-}6}$*: 1670 (321, 4840) ng/mL* $C_{min,Week2\text{-}6}$*: The minimum of all simulated concentrations from Weeks 2 to 6.* $C_{ave,Week2\text{-}6}$*: The average of all simulated concentrations from Weeks 2 to 6.*	
Covariates Evaluated		*ECOG PS at baseline, age at baseline, sex, and race*	
Final Model Parameters		**Summary**	**Acceptability [FDA's comments]**
Model Structure		*ORR: logistic regression without covariates* *OS and PFS: no model, Kaplan Meier curves were produced*	**See Section 19.4.4.5**
Model Parameter Estimates		Applicant *Table 42: for ORR*	
Model Evaluation		*Based on AIC, -2LL and visual inspection (simulated probability of response as function of exposure vs observed probability of response by quartile of exposure)*	
Covariates and Clinical Relevance		*No covariate was found to be significant*	
Simulation for Specific Population		*No simulation performed for specific population*	
Visualization of E-R relationships		Applicant Figure 16: *ORR vs* $C_{min,week2\text{-}6}$ Applicant Figure 17: *PFS by median of* $C_{min,week2\text{-}6}$ Applicant Figure 18: *OS by median of* $C_{min,week2\text{-}6}$ Applicant Table 26 F *baseline demographics stratified by median of* $C_{min,week2\text{-}6}$ Applicant Table 44: *baseline demographics stratified by quantiles of* $C_{min,week2\text{-}6}$	
Overall Clinical Relevance for ER		No relationship between adagrasib exposure and efficacy endpoints (i.e., ORR, OS and PFS) was observed.	
Labeling Language		**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics		None	

Applicant Table 41: Summary of Baseline Characteristics and Risk Factors in the Dataset

Exposure Parameters and Baseline Characteristics	Overall (N=118)
Age (yrs)	
Mean (CV%)	63.8 (15.1%)
Median [Min, Max]	64.0 [25.0, 89.0]
Dose Interruption	
No Dose Interruption	20 (16.9%)
Dose Interruption	98 (83.1%)
Baseline ECOG PS	
0	24 (20.3%)
1	93 (78.8%)
Missing	1 (0.8%)
Sex	
Female	66 (55.9%)
Male	52 (44.1%)
Race	
White	99 (83.9%)
Black	9 (7.6%)
Asian	5 (4.2%)
Other	5 (4.2%)
Baseline Weight (kg)	
Mean (CV%)	72.0 (25.9%)
Median [Min, Max]	69.5 [36.8, 139]
$C_{min,Week2-6}$ (ng/mL)	
Mean (CV%)	970 (105.0%)
Median [Min, Max]	771 [0, 4510]
$C_{ave,Week2-6}$ (ng/mL)	
Mean (CV%)	1870 (46.9%)
Median [Min, Max]	1670 [321, 4840]

$C_{ave,Week2-6}$ = Average concentration from Weeks 2 to 6; $C_{min,Week2-6}$ = Minimum concentration from Weeks 2 to 6; N=Number of subjects

Applicant Table 42: Table of Model parameters – ORR vs $C_{min,Week2-6}$

Parameters	Estimate	Standard Error	p-value	Lower 95% Confidence Interval	Upper 95% Confidence Interval
Intercept	-0.155	0.256	0.544	-0.661	0.346
Exposure ($C_{min\ Week2-6}$)	-1.54E-05	0.000182	0.933	-0.000378	0.000343

Applicant Table 43: Covariate Distribution over $C_{min,Week2-6}$ Median for All Subjects Included in the ER Analysis of ORR, PFS and OS

Baseline Characteristics	[0, 771) (ng/mL) (N=59)	[771,4506] (ng/mL) (N=59)
Dose Interruption		
No Dose Interruption	3 (5.1%)	17 (28.8%)
Dose Interruption	56 (94.9%)	42 (71.2%)
Age (years)		
Mean (CV%)	64.8 (16.5%)	62.9 (13.4%)
Median [Min, Max]	65.0 [25.0, 89.0]	64.0 [40.0, 85.0]
ECOG PS		
0	15 (25.4%)	9 (15.3%)
1	43 (72.9%)	50 (84.7%)
Missing	1 (1.7%)	0 (0%)
Sex		
Female	31 (52.5%)	35 (59.3%)
Male	28 (47.5%)	24 (40.7%)
Race		
White	47 (79.7%)	52 (88.1%)
Black	7 (11.9%)	2 (3.4%)
Asian	3 (5.1%)	2 (3.4%)
Other	2 (3.4%)	3 (5.1%)
Baseline Weight (kg)		
Mean (CV%)	71.2 (24.3%)	72.9 (27.5%)
Median [Min, Max]	66.9 [36.8, 115]	71.9 [39.0, 139]

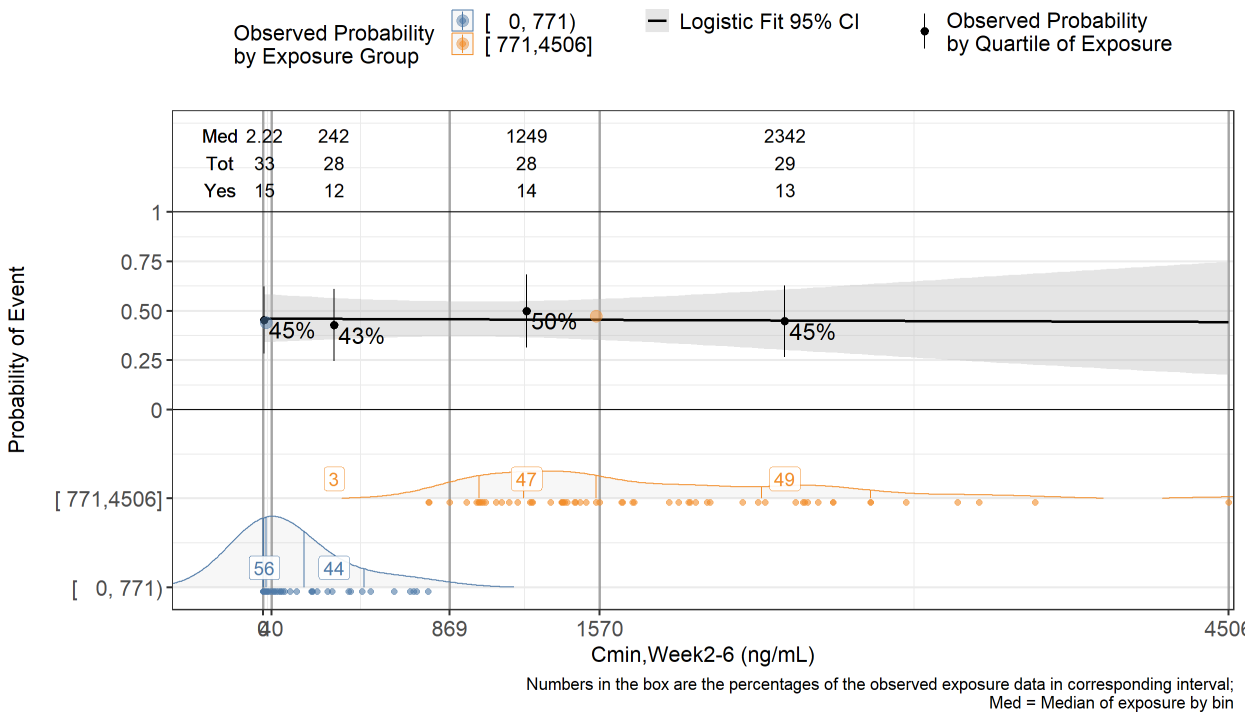
$C_{min,Week2-6}$ = Minimum concentration from Weeks 2 to 6; N=Number of subjects

Applicant Table 44: Covariate Distribution over $C_{min,Week2-6}$ Quartiles for All Subjects Included in the ER Analysis of ORR, PFS and OS

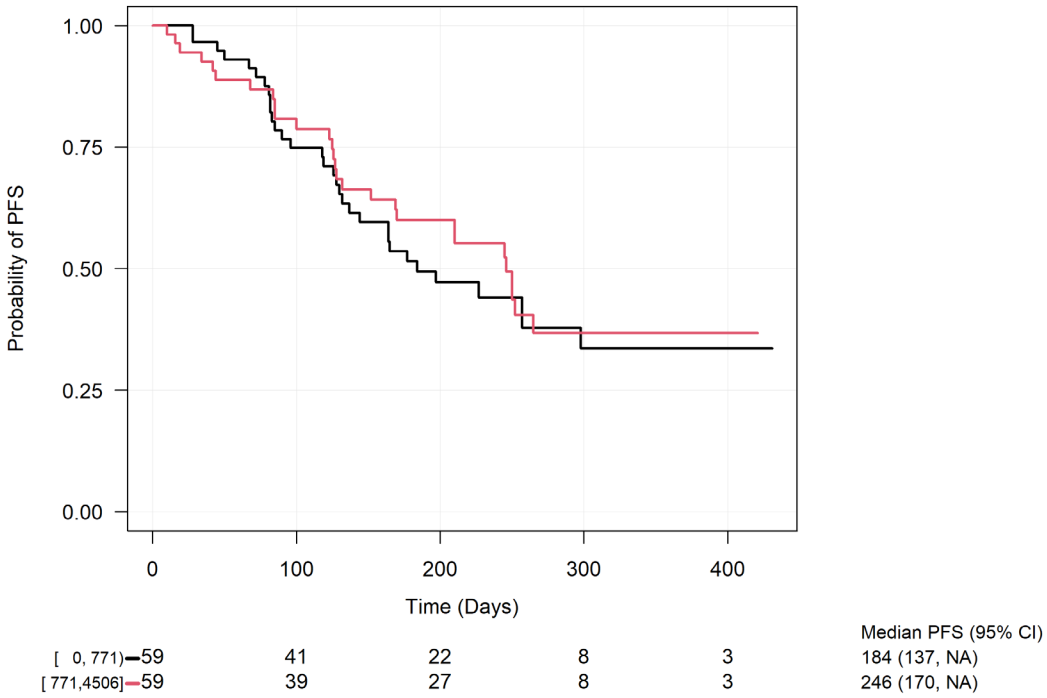
Baseline Characteristics	$C_{min,Week2-6}$ (ng/mL)			
	[0.0, 15.8) (N=30)	[15.8, 771.2) (N=29)	[771.2,1542.7) (N=29)	[1542.7,4505.9] (N=30)
Dose Interruption				
No Dose Interruption	2 (6.7%)	1 (3.4%)	8 (27.6%)	9 (30.0%)
Dose Interruption	28 (93.3%)	28 (96.6%)	21 (72.4%)	21 (70.0%)
Age (years)				
Mean (CV%)	63.8 (19.1%)	65.8 (13.7%)	64.8 (12.9%)	61.0 (13.4%)
Median [Min, Max]	65.0 [25.0, 78.0]	64.0 [50.0, 89.0]	64.0 [40.0, 84.0]	61.0 [43.0, 85.0]
ECOG PS				
0	6 (20.0%)	9 (31.0%)	2 (6.9%)	7 (23.3%)
1	23 (76.7%)	20 (69.0%)	27 (93.1%)	23 (76.7%)
Missing	1 (3.3%)	0 (0%)	0 (0%)	0 (0%)
Sex				
Female	17 (56.7%)	14 (48.3%)	15 (51.7%)	20 (66.7%)
Male	13 (43.3%)	15 (51.7%)	14 (48.3%)	10 (33.3%)
Race				
White	24 (80.0%)	23 (79.3%)	26 (89.7%)	26 (86.7%)
Black	4 (13.3%)	3 (10.3%)	0 (0%)	2 (6.7%)
Asian	1 (3.3%)	2 (6.9%)	1 (3.4%)	1 (3.3%)
Other	1 (3.3%)	1 (3.4%)	2 (6.9%)	1 (3.3%)
Baseline Weight (kg)				
Mean (CV%)	70.7 (20.7%)	71.7 (27.9%)	75.9 (18.2%)	69.9 (35.0%)
Median [Min, Max]	65.6 [46.5, 109]	67.6 [36.8, 115]	77.1 [48.4, 104]	66.2 [39.0, 139]

$C_{ave,Week2-6}$ = Average concentration from Weeks 2 to 6; N=Number of subjects

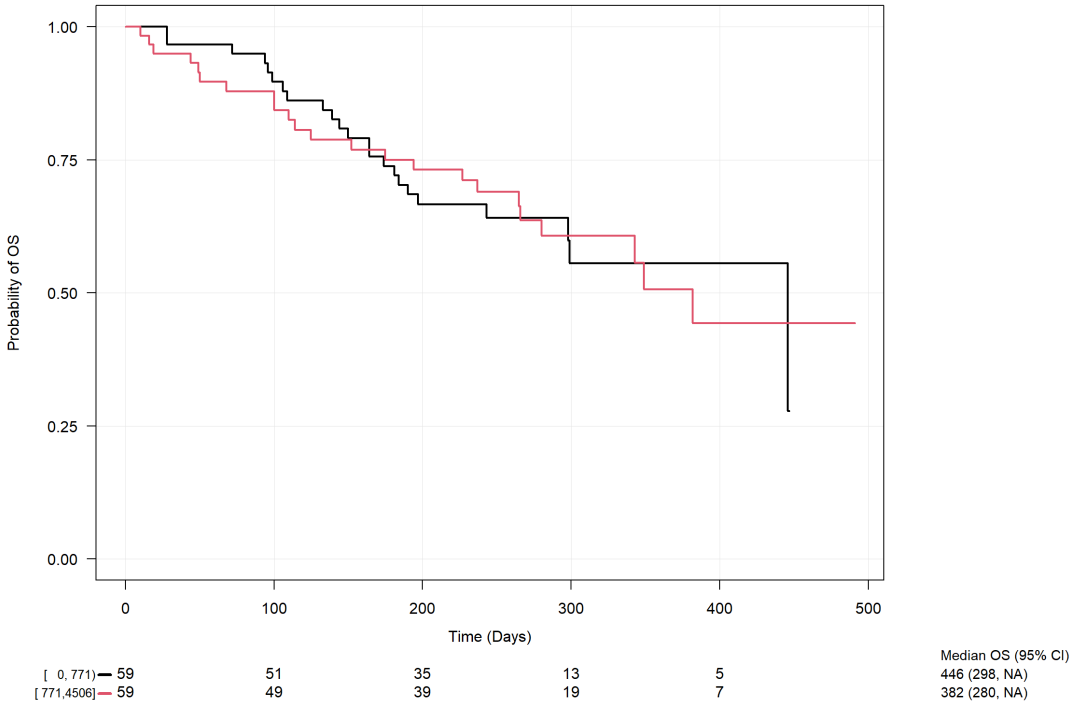
Applicant Figure 16: ER Curves of ORR vs $C_{min,Week2-6}$ in 118 Patients



Applicant Figure 17: ER Curves of PFS vs $C_{min,Week2-6}$ in 118 Patients



Applicant Figure 18: ER Curves of OS vs $C_{min,Week2-6}$ in 118 Patients



19.4.4.3. ER (safety) Executive Summary

The FDA's Assessment:

The E-R relationships for safety measures were assessmed in patients with advanced, unresectable or metastatic solid tumor malignancy with KRAS G12C mutation in Study 849-001 (Phase 1/1b and Phase 2 Cohort A). The evaluated safety variables were any grade ≥3 treatment emergent AEs, diarrhea, nausea, vomiting, increase in ALT, AST, lipase, and hyponatremia. The reviewer generally agrees with the Applicant's conclusions that no relationship between adagrasib exposure (i.e., Cmin or Cavg) and the safety variables was observed based on the PK and safety data from 132 patients). It should be noted that most patients (96.2%) included in the E-R analysis were started treatment at one dose level (the planned 600 mg BID of adagrasib). Any meaningful inference or extrapolation of the findings can not be made for the dose levels other than 600 mg BID.

19.4.4.4. ER (safety) Assessment Summary

The Applicant's Position:

General Information			
Goal of ER analysis		To characterize adagrasib exposure-response relationships for measures of safety in patients with advanced, unresectable or metastatic solid tumor malignancy with KRAS G12C mutation in Study 849-001 (Phase 1/1b and Phase 2 Cohort A).	
Study Included		Study 849-001 (Phase 1/1b and Phase 2 Cohort A).	
Population Included		*125 (94.7%) patients were NSCLC patients, 4 (3.0%) were CRC patients, 1 (0.8%) was patient with mucinous appendiceal adenocarcinoma and 2 (1.5%) were patient of other cancer types*	
Endpoint		Any Grade ≥3 treatment emergent AEs, diarrhea, nausea, vomiting, increase in ALT, AST and lipase, and hyponatremia	
No. of Patients (total, and with individual PK)		*Total number of patients: 141* *132 with exposure data*	
Population Characteristics (Applicant Table 28)	General	*-Age median (range): 64.0 (25.0, 89.0) years* *-Weight median (range): 71.1 (36.0, 139) kg* *-Male: 57 (43.2%)* *-White 112 (84.8%)* *- Black: 9 (6.8%)* *- Asian: 6 (4.5%)* *- Other: 5 (3.8%)*	
	Organ impairment	*--Hepatic NCI:* *Normal Liver Function : 16 (87.9%)* *Mild Liver Impairment : 15 (11.4%)* *Moderate Liver Impairment: 1 (0.8%)* *-Renal (based on CrCL):* *Normal Renal Function: 54 (40.9%)* *Mild Renal Impairment: 59 (44.7%)* *Moderate Renal Impairment: 19 (14.4%)*	
	Pediatrics (if any)	*None*	
	Geriatrics (if any)	*-Age median in subjects >= 65 years old: 70.0 (65.0, 89.0)* *>= 65 to <75 years: 45 (73.8%)* *>= 75 to <89 years: 16 (26.2%)* *-n (XX%) male*	
Dose(s) Included		*Planned dose n (%):* *600 mg BID: 127 (96.2%)* *150 mg QD: 1 (0.8%)* *300 mg QD: 1 (0.8%)* *600 mg QD: 2 (1.5%)* *1200 mg QD: 1 (0.8%)*	
Exposure Metrics Explored (range)		$C_{max,ss}$ (ng/mL): 282 to 12600 $C_{ave,ss}$ (ng/mL): 191 to 12200 $C_{max,Week1-3}$ (ng/mL): 211 to 12336	
Covariates Evaluated		None	
Final Model Parameters		**Summary**	**Acceptability [FDA's comments]**
Model Structure		*Logistic regression: response = f(Exposure)*	**See Section 19.4.4.5**
Model Parameter Estimates		Applicant Table 29, Applicant Table 30 *and Applicant Table 48: for all studied AEs*	

Model Evaluation	Statistical significance of the estimate of regression coefficient for exposure. *Visual inspection (simulated probability of response as function of exposure vs observed probability of response by quartile of exposure)*	
Covariates and Clinical Relevance	*No covariate was assessed*	
Simulation for Specific Population	*No simulation performed for specific population*	
Visualization of E-R relationships	Applicant Figure 17 *to* Applicant Figure 24	
Overall Clinical Relevance for ER	No relationship between adagrasib exposure and safety endpoints of interest (i.e., any Grade ≥3 TEAEs, diarrhea, nausea, vomiting, increase in ALT, AST and lipase, and hyponatremia) was observed.	
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	None	

Applicant Table 45: Summary of Baseline Characteristics in the Dataset

Characteristics	**Overall (N=132)**
Planned Treatment	
600 mg BID	127 (96.2%)
150 mg QD	1 (0.8%)
300 mg QD	1 (0.8%)
600 mg QD	2 (1.5%)
1200 mg QD	1 (0.8%)
Disease	
CRC	4 (3.0%)
Mucinous Appendiceal Adenocarcinoma	1 (0.8%)
NSCLC	125 (94.7%)
Other	2 (1.5%)
Age (years)	
Mean (CV%)	63.7 (15.2%)
Median [Min, Max]	64.0 [25.0, 89.0]
Baseline Weight (kg)	
Mean (CV%)	72.4 (25.6%)
Median [Min, Max]	71.1 [36.0, 139]
Sex	
Female	75 (56.8%)
Male	57 (43.2%)
Race	
White	112 (84.8%)
Black	9 (6.8%)
Asian	6 (4.5%)
Other	5 (3.8%)

Characteristics	Overall (N=132)
Renal Function	
Normal Renal Function	54 (40.9%)
Mild Renal Impairment	59 (44.7%)
Moderate Renal Impairment	19 (14.4%)
Hepatic Function	
Normal Liver Function	116 (87.9%)
Mild Liver Impairment	15 (11.4%)
Moderate Liver Impairment	1 (0.8%)
Age Group	
[25,65)	71 (53.8%)
[65,75)	45 (34.1%)
[75,89]	16 (12.1%)

Applicant Table 46: Covariate Distribution over Cmax,ss Quartiles for All Subjects Included in the ER Analysis of AEs

Covariate	Cmax,ss (ng/mL)			
	[282, 1414) (N=33)	[1414, 1861) (N=33)	[1861, 2555) (N=33)	[2555,12588] (N=33)
Planned Treatment				
600 mg BID	28 (84.8%)	33 (100%)	33 (100%)	33 (100%)
150 mg QD	1 (3.0%)	0 (0%)	0 (0%)	0 (0%)
300 mg QD	1 (3.0%)	0 (0%)	0 (0%)	0 (0%)
600 mg QD	2 (6.1%)	0 (0%)	0 (0%)	0 (0%)
1200 mg QD	1 (3.0%)	0 (0%)	0 (0%)	0 (0%)
Disease				
CRC	3 (9.1%)	0 (0%)	0 (0%)	1 (3.0%)
NSCLC	29 (87.9%)	33 (100%)	32 (97.0%)	31 (93.9%)
Other	1 (3.0%)	0 (0%)	0 (0%)	1 (3.0%)
Mucinous Appendiceal Adenocarcinoma	0 (0%)	0 (0%)	1 (3.0%)	0 (0%)
Age (years)				
Mean (CV%)	62.6 (17.7%)	66.6 (13.9%)	63.2 (14.8%)	62.4 (14.0%)
Median [Min, Max]	63.0 [25.0, 79.0]	65.0 [48.0, 89.0]	63.0 [40.0, 79.0]	64.0 [43.0, 85.0]
Baseline Weight (kg)				
Mean (CV%)	83.4 (19.1%)	75.1 (20.0%)	71.9 (27.6%)	59.3 (24.9%)
Median [Min, Max]	82.5 [52.2, 115]	73.0 [55.6, 137]	70.9 [42.3, 139]	58.4 [36.0, 105]
Sex				
Female	16 (48.5%)	17 (51.5%)	16 (48.5%)	26 (78.8%)
Male	17 (51.5%)	16 (48.5%)	17 (51.5%)	7 (21.2%)
Race				
White	29 (87.9%)	29 (87.9%)	27 (81.8%)	27 (81.8%)
Black	2 (6.1%)	1 (3.0%)	3 (9.1%)	3 (9.1%)
Asian	0 (0%)	2 (6.1%)	1 (3.0%)	3 (9.1%)
Other	2 (6.1%)	1 (3.0%)	2 (6.1%)	0 (0%)
Renal Function				
Normal Renal Function	17 (51.5%)	15 (45.5%)	13 (39.4%)	9 (27.3%)
Mild Renal Impairment	13 (39.4%)	15 (45.5%)	12 (36.4%)	19 (57.6%)
Moderate Renal Impairment	3 (9.1%)	3 (9.1%)	8 (24.2%)	5 (15.2%)
Hepatic Function				
Normal Liver Function	28 (84.8%)	27 (81.8%)	31 (93.9%)	30 (90.9%)
Mild Liver Impairment	5 (15.2%)	5 (15.2%)	2 (6.1%)	3 (9.1%)
Moderate Liver Impairment	0 (0%)	1 (3.0%)	0 (0%)	0 (0%)
Age Group				
[25,65)	19 (57.6%)	16 (48.5%)	17 (51.5%)	19 (57.6%)
[65,75)	10 (30.3%)	9 (27.3%)	13 (39.4%)	13 (39.4%)
[75,89]	4 (12.1%)	8 (24.2%)	3 (9.1%)	1 (3.0%)

Note: AEs included: Any Grade ≥3 Adverse Events; Diarrhea ; Nausea; Vomiting ; Laboratory tests; Alanine transferase (ALT) > 3 x upper limit of normal (ULN); Aspartate transferase (AST) > 3 x ULN; Lipase > 3 x ULN; Amylase > 3 x ULN; Hyponatremia

Applicant Table 47: Covariate Distribution over $C_{max,Week1-3}$ Quartiles for All Subjects Included in the ER Analysis of AEs

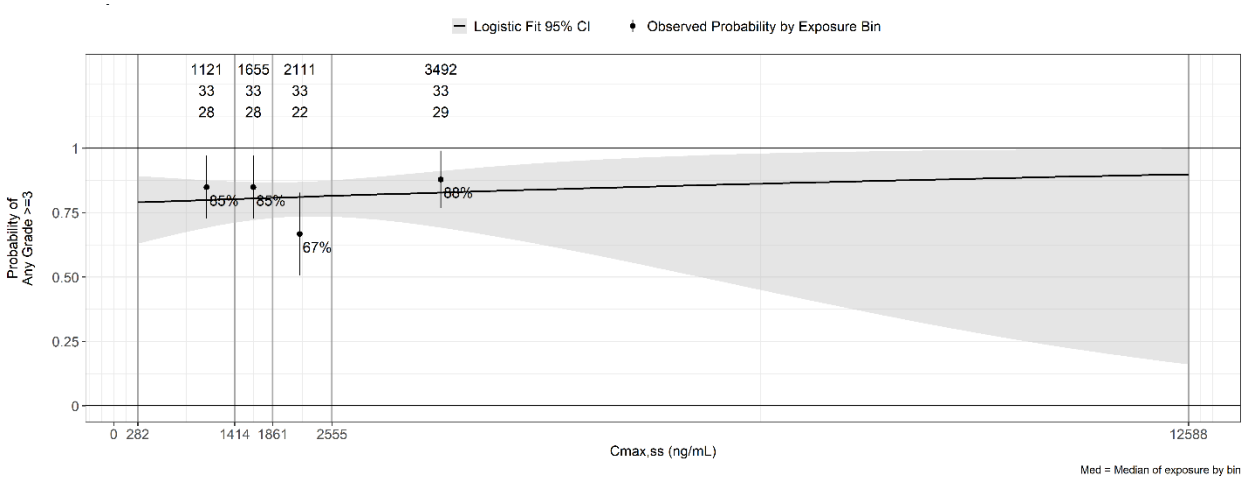
Covariate	$C_{max,Week1-3}$ (ng/mL)			
	[212, 1816) (N=33)	[1816, 2386) (N=33)	[2386, 3180) (N=33)	[3180,12337] (N=33)
Planned Treatment				
600 mg BID	28 (84.8%)	33 (100%)	33 (100%)	33 (100%)
150 mg QD	1 (3.0%)	0 (0%)	0 (0%)	0 (0%)
300 mg QD	1 (3.0%)	0 (0%)	0 (0%)	0 (0%)
600 mg QD	2 (6.1%)	0 (0%)	0 (0%)	0 (0%)
1200 mg QD	1 (3.0%)	0 (0%)	0 (0%)	0 (0%)
Disease				
CRC	3 (9.1%)	0 (0%)	0 (0%)	1 (3.0%)
NSCLC	29 (87.9%)	32 (97.0%)	33 (100%)	31 (93.9%)
Other	1 (3.0%)	0 (0%)	0 (0%)	1 (3.0%)
Mucinous Appendiceal Adenocarcinoma	0 (0%)	1 (3.0%)	0 (0%)	0 (0%)
Age (years)				
Mean (CV%)	62.5 (17.4%)	62.7 (14.7%)	65.3 (15.5%)	64.3 (13.4%)
Median [Min, Max]	63.0 [25.0, 84.0]	61.0 [40.0, 79.0]	66.0 [42.0, 89.0]	64.0 [43.0, 85.0]
Baseline Weight (kg)				
Mean (CV%)	83.4 (19.3%)	77.5 (25.3%)	70.7 (21.8%)	58.0 (21.4%)
Median [Min, Max]	82.5 [55.6, 137]	73.0 [44.0, 139]	71.3 [39.0, 105]	58.1 [36.0, 86.6]
Sex				
Female	15 (45.5%)	16 (48.5%)	18 (54.5%)	26 (78.8%)
Male	18 (54.5%)	17 (51.5%)	15 (45.5%)	7 (21.2%)
Race				
White	30 (90.9%)	28 (84.8%)	26 (78.8%)	28 (84.8%)
Black	1 (3.0%)	2 (6.1%)	5 (15.2%)	1 (3.0%)
Asian	0 (0%)	2 (6.1%)	0 (0%)	4 (12.1%)
Other	2 (6.1%)	1 (3.0%)	2 (6.1%)	0 (0%)
Renal Function				
Normal Renal Function	18 (54.5%)	20 (60.6%)	9 (27.3%)	7 (21.2%)
Mild Renal Impairment	12 (36.4%)	11 (33.3%)	18 (54.5%)	18 (54.5%)
Moderate Renal Impairment	3 (9.1%)	2 (6.1%)	6 (18.2%)	8 (24.2%)
Hepatic Function				
Normal Liver Function	26 (78.8%)	28 (84.8%)	32 (97.0%)	30 (90.9%)
Mild Liver Impairment	6 (18.2%)	5 (15.2%)	1 (3.0%)	3 (9.1%)
Moderate Liver Impairment	1 (3.0%)	0 (0%)	0 (0%)	0 (0%)
Age Group				
[25,65)	19 (57.6%)	21 (63.6%)	14 (42.4%)	17 (51.5%)
[65,75)	11 (33.3%)	8 (24.2%)	13 (39.4%)	13 (39.4%)
[75,89]	3 (9.1%)	4 (12.1%)	6 (18.2%)	3 (9.1%)

Applicant Table 48: Parameter Estimates from Final ER Model of (endpoint)

Model	Term	Estimate	SE	Statistic	p.Value	Conf.Low	Conf.High
Any Grade ≥3 Adverse Events vs $C_{max,ss}$	(Intercept)	1.303928	0.449358	2.901757	0.003711	0.366531	2.14493
	Exposure slope	7.00E-05	0.000185	0.377565	0.705754	-0.00024	0.000499
Diarrhea vs $C_{max,ss}$	(Intercept)	0.772724	0.381765	2.024082	0.042962	-0.02109	1.499836
	Exposure slope	6.17E-05	0.000155	0.398604	0.690185	-0.00022	0.00041
Nausea vs $C_{max,ss}$	(Intercept)	0.94694	0.375711	2.520397	0.011722	0.16989	1.67633
	Exposure slope	1.56E-05	0.000148	0.105297	0.91614	-0.00026	0.00035
Vomiting vs $C_{max,ss}$	(Intercept)	0.333683	0.336242	0.992389	0.321008	-0.34816	1.002931
	Exposure slope	1.28E-06	0.000131	0.009746	0.992224	-0.00026	0.000281
ALT > 3 x ULN vs $C_{max,Week1-3}$	(Intercept)	-1.52432	0.59972	-2.54172	0.011031	-2.63916	-0.31087
	Exposure slope	-0.00013	0.000219	-0.575	0.56529	-0.00061	0.000236
AST > 3 x ULN vs $C_{max,Week1-3}$	(Intercept)	-0.98328	0.633819	-1.55136	0.120815	-2.18592	0.269813
	Exposure slope	-0.00033	0.000252	-1.29293	0.196036	-0.00086	0.000106
Lipase > 3 x ULN vs $C_{max,ss}$	(Intercept)	-1.54872	0.631734	-2.45155	0.014224	-2.69879	-0.27704
	Exposure slope	-0.00025	0.000294	-0.84124	0.400215	-0.00091	0.000206
Hyponatremia vs $C_{max,ss}$	(Intercept)	-0.77078	0.491228	-1.56909	0.116628	-1.6777	0.222785
	Exposure slope	-0.00026	0.000225	-1.16675	0.24331	-0.00075	0.000111

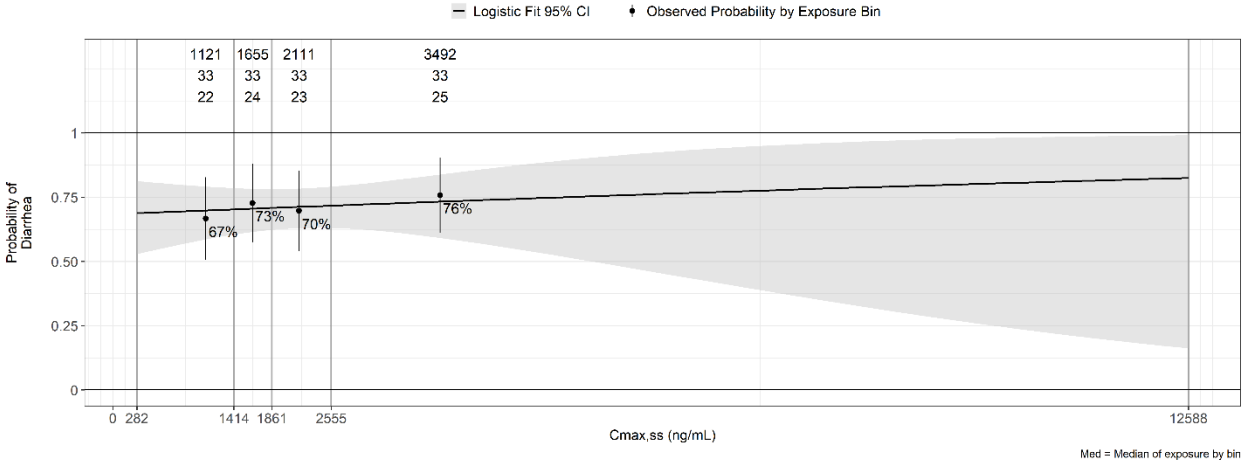
Conf.High = upper limit of 95% confidence interval; Conf.Low = lower limit of 95% confidence interval; SE = standard error.

Applicant Figure 19: ER Curves of Any Grade ≥3 Adverse Events vs Cmax,ss in 132 Patients



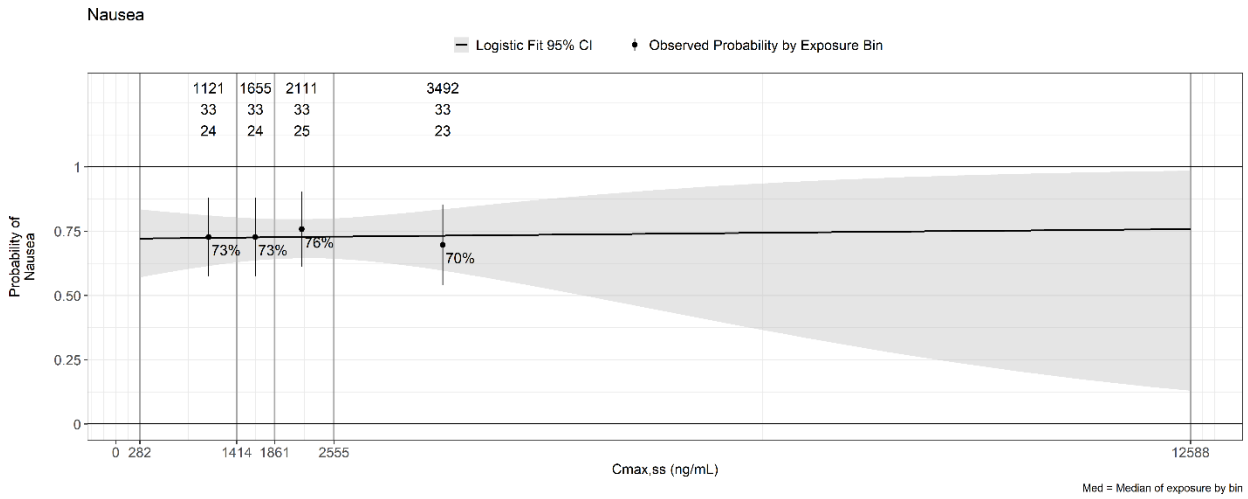
$C_{max,ss}$ = maximum concentration at steady state; CI = confidence interval

Applicant Figure 20: ER Curves of Diarrhea vs Cmax,ss in 132 Patients



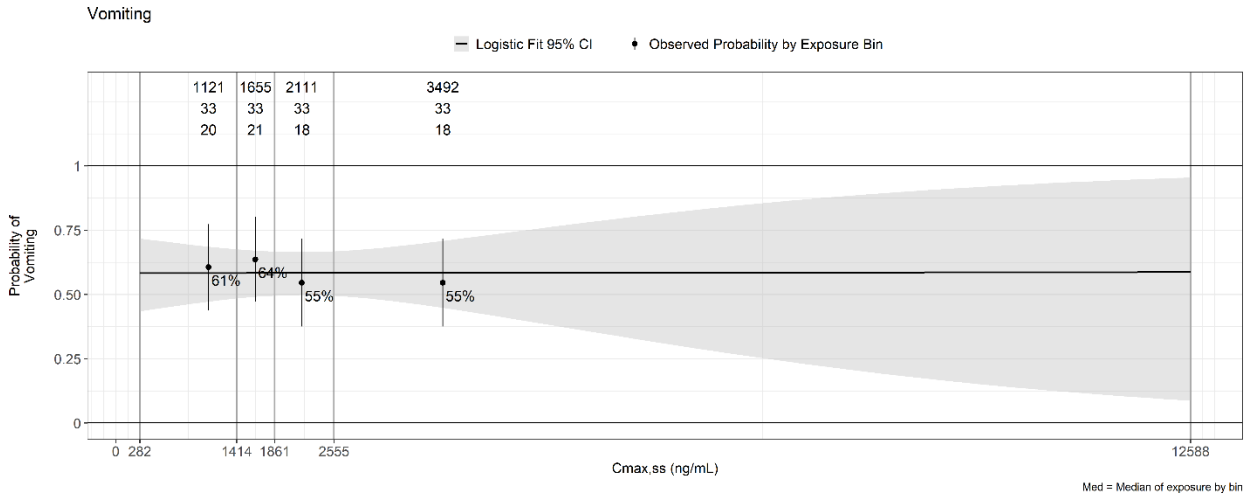
$C_{max,ss}$ = maximum concentration at steady state; CI = confidence interval

Applicant Figure 21: ER Curves of Nausea vs Cmax,ss in 132 Patients



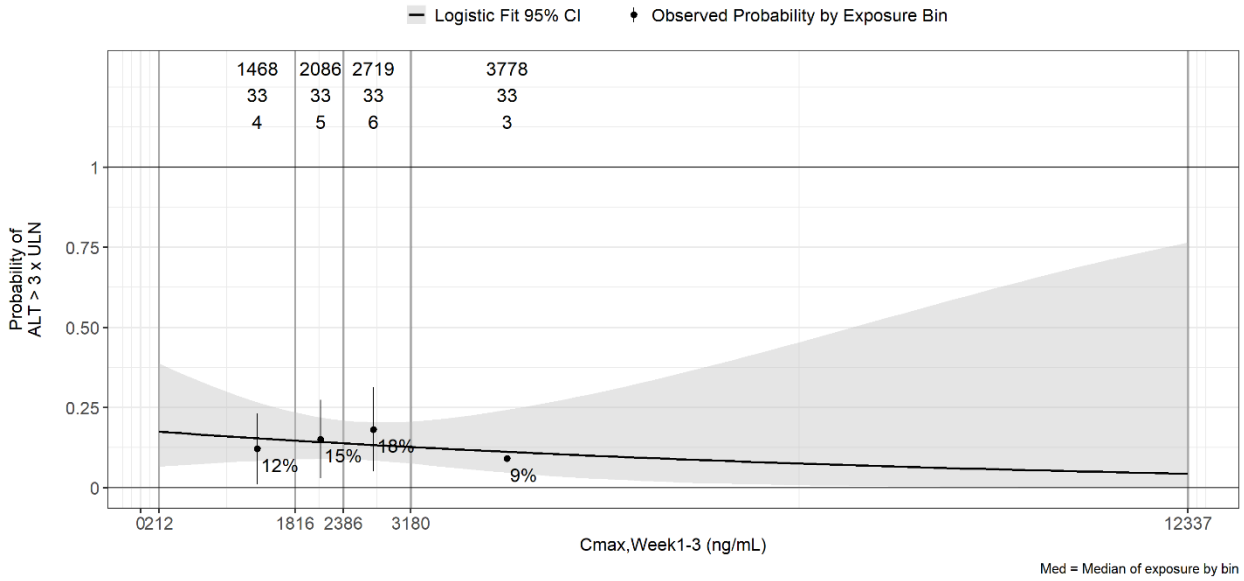
$C_{max,ss}$ = maximum concentration at steady state; CI = confidence interval

Applicant Figure 22: ER Curves of Vomiting vs Cmax,ss in 132 Patients



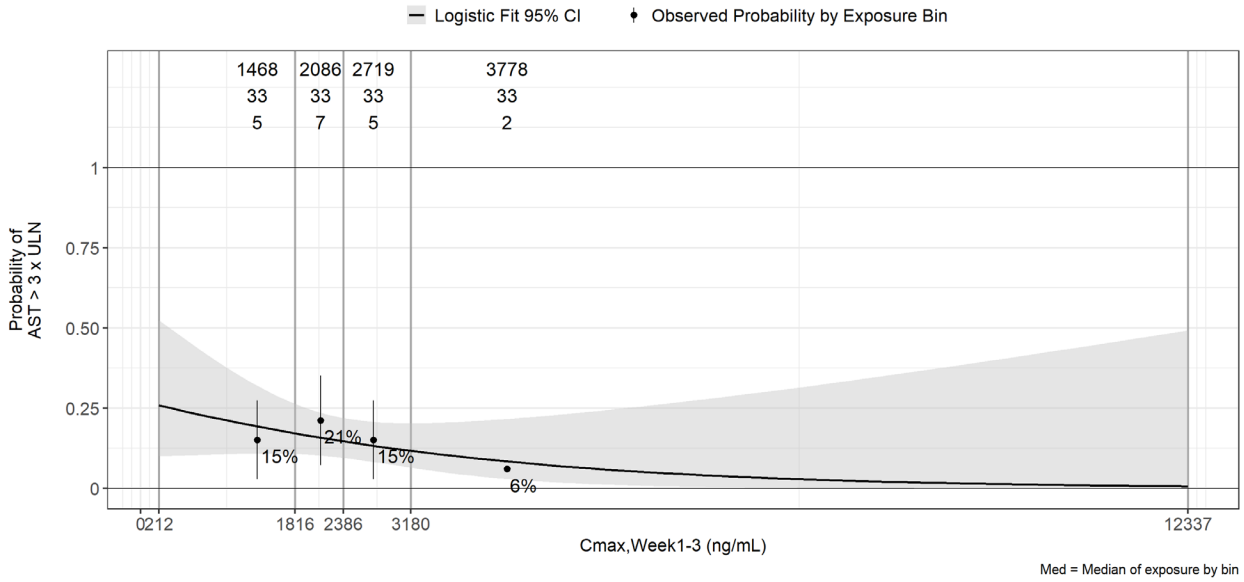
$C_{max,ss}$ = maximum concentration at steady state; CI = confidence interval

Applicant Figure 23: ER Curves of ALT > 3 x ULN vs $C_{max,Week1-3}$ in 132 Patients



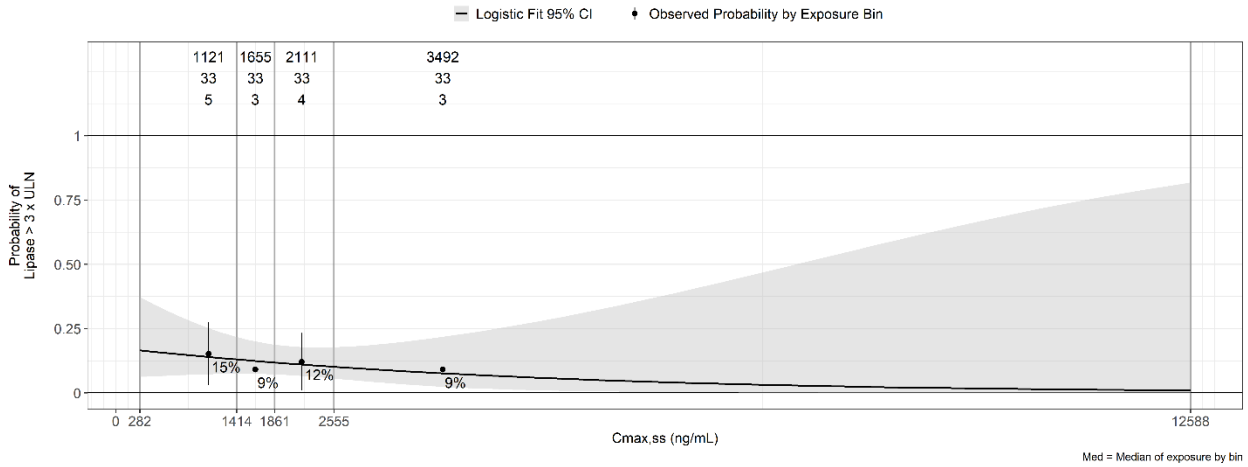
ALT = alanine transferase; $C_{max,Week1-3}$ = maximum concentration from Week 1 to 3; CI = confidence interval

Applicant Figure 24: ER Curves of AST > 3 x ULN vs $C_{max,Week1-3}$ in 132 Patients



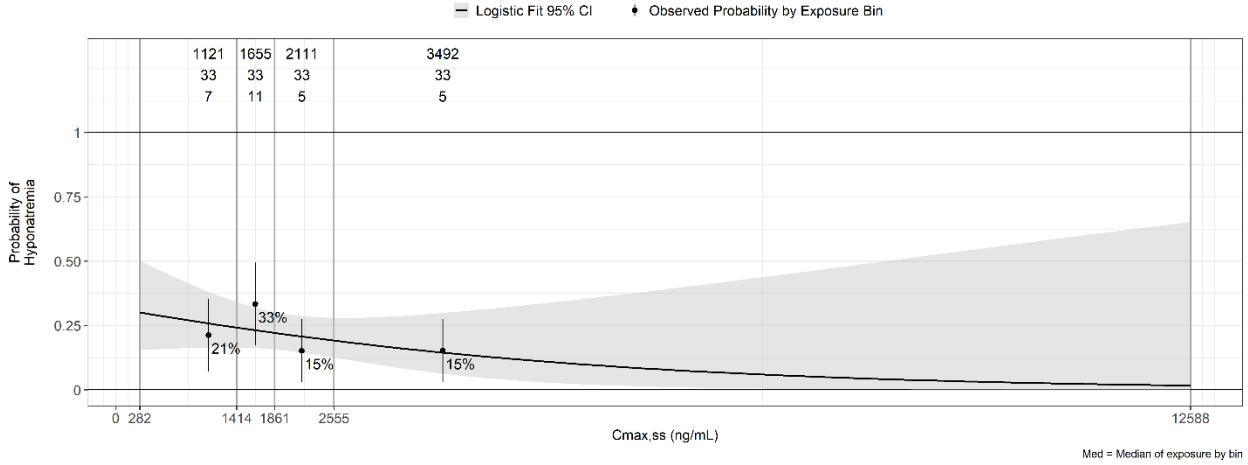
AST = aspartate transferase; $C_{max,Week1-3}$ = maximum concentration from Week 1 to 3; CI = confidence interval

Applicant Figure 25: ER Curves of Lipase > 3 x ULN vs $C_{max,ss}$ in 132 Patients



$C_{max,ss}$ = maximum concentration at steady state; CI = confidence interval

Applicant Figure 26: ER Curves of Hyponatremia vs $C_{max,ss}$ in 132 Patients



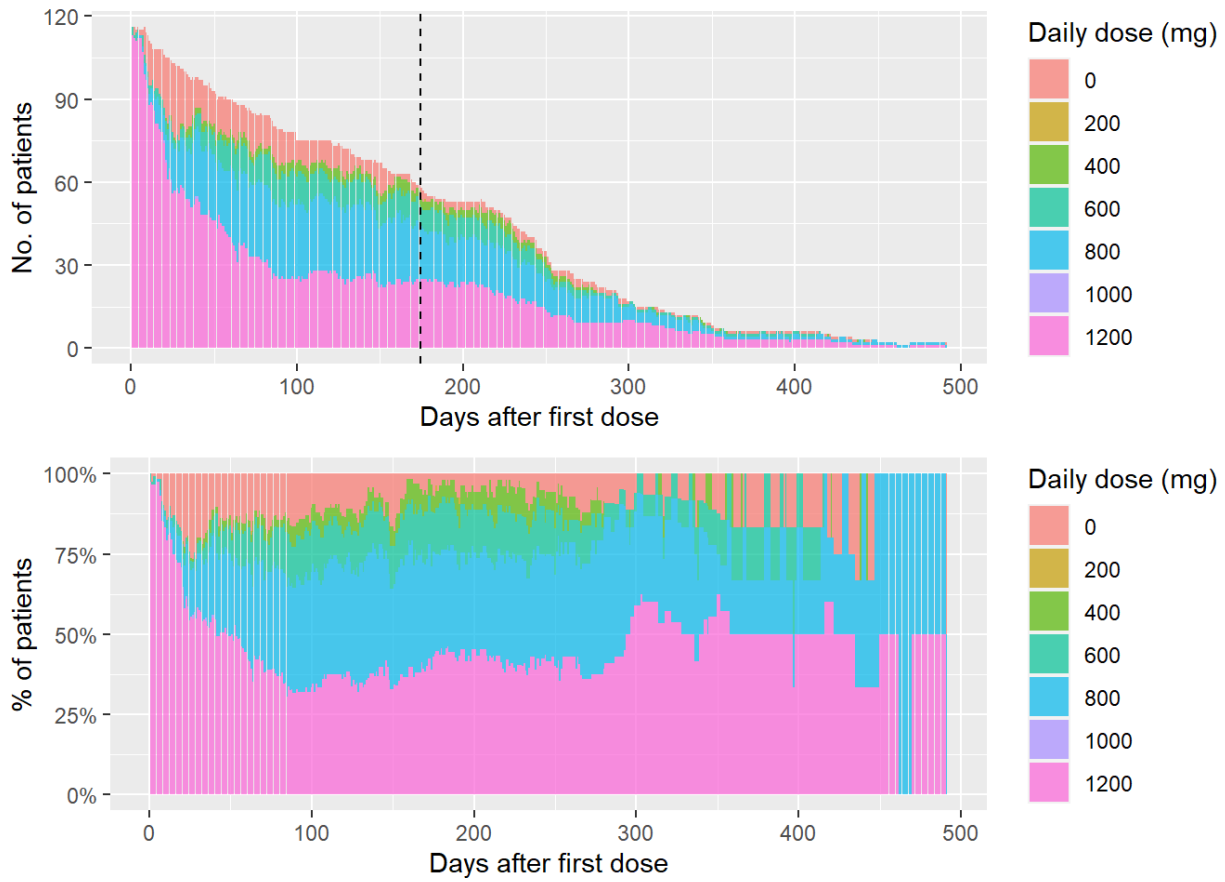
$C_{max,ss}$ = maximum concentration at steady state; CI = confidence interval

19.4.4.5. ER Review Issues

E-R analysis for efficacy

While all patients started with 600 mg BID, there were high rates of dose interruption and dose reduction during the treatment period (Figure 25). Therefore, the exposure metrics used for evaluation of ER relationship for efficacy (e.g., $C_{min,Week2\text{-}6}$ [the minimum concentration from Weeks 2 to 6], and $C_{ave,Week2\text{-}6}$ [average concentration of adagrasib from Weeks 2 to 6]) are likely confounded by dose modifications during the treatment.

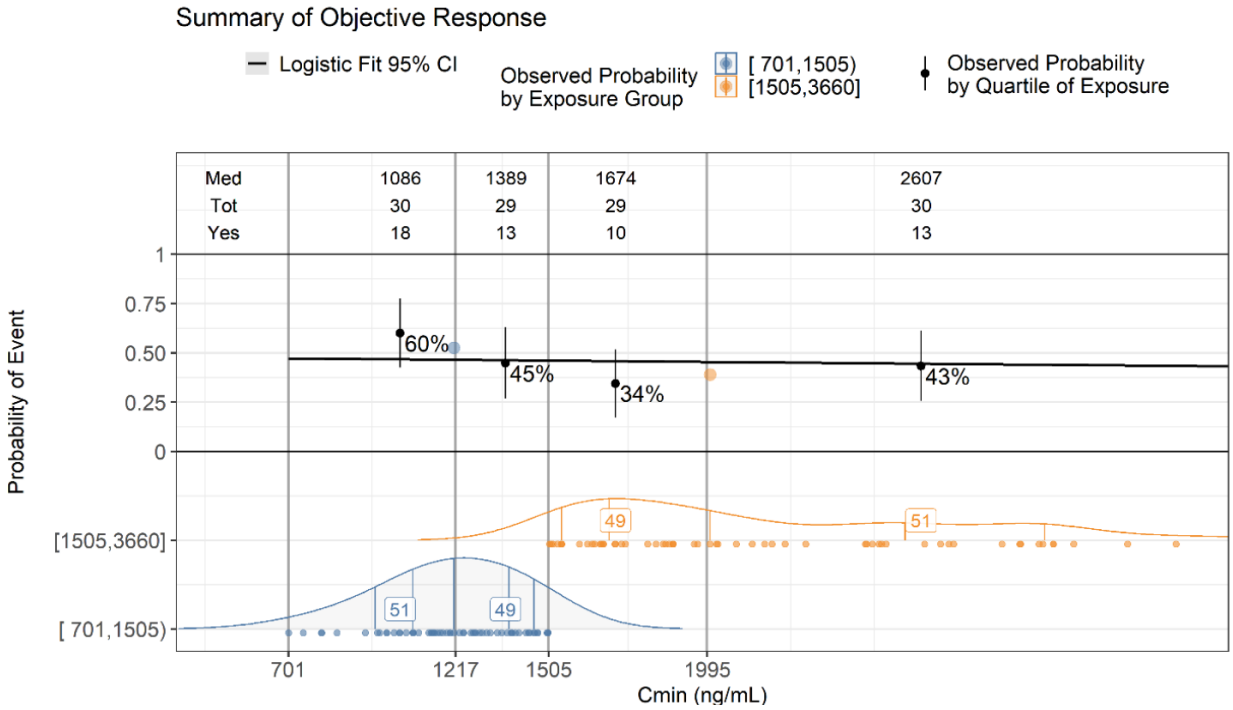
Figure 27. Dose distribution by days after first dose



Source: Reviewer's figure. The top panel shows the number of patients for each daily dose by time (days after first dose) and the bottom panel shows the proportion of patients receiving each dose daily dose level along days after first dose.

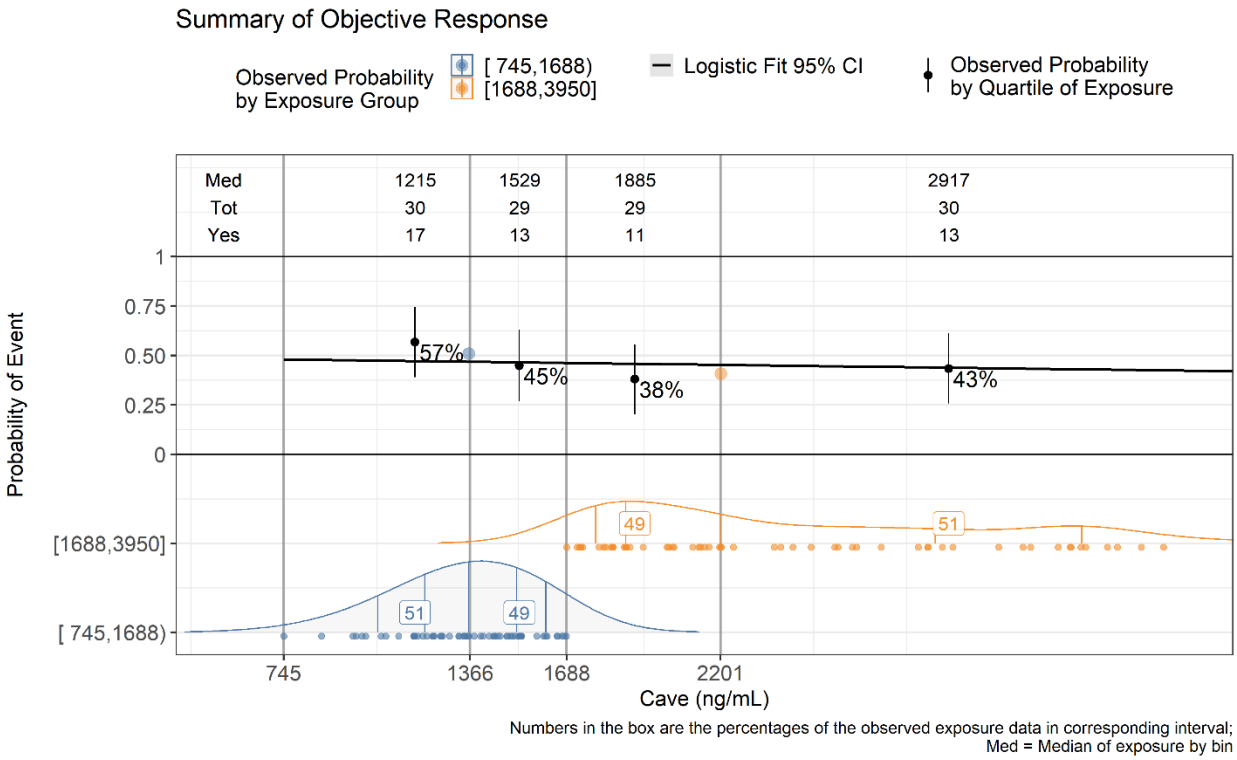
Per FDA's request, the Applicant provided a sensitivity ER analysis for ORR using the mean adagrasib trough (Cmin) and average (Cave) concentrations from the first dose up to the occurrence of best response for responders or up to the last dose for non-responders and evaluated the following covariate effects on the ER relationship for ORR: age, sex, race, baseline ECOG, prior systemic regimen, smoking history, and metastases at baseline. The results of the univariate E-R analysis of ORR based on the Cmin and Cave are presented in Figures below.

Figure 28. Sensitivity E-R analysis for probability of ORR as a function of Cmin



Source: Applicant's IR response dated on 5/27/2022 (SN029). Cmin: mean of adagrasib Ctrough from the first dose up to the occurrence of best response for responders or up to the last dose for non-responders.

Figure 29. Sensitivity E-R analysis for probability of ORR as a function of Cave



Source: Applicant's IR response dated on 5/27/2022 (SN029). **Cave**: mean of adagrasib average concentrations from the first dose up to the occurrence of best response for responders or up to the last dose for non-responders.

In this sensitivity analysis, the effect of Cmin was not statistically significant (p-value = 0.843) in the univariate logistic regression model. Among the covariates evaluated, only smoking history was significant with "Current Smoker" having a pvalue lower than 0.05. When adjusted for smoking history, the effect of Cmin remained insignificant in the logistic regression model. Similarly, the effect of Cave was not statistically significant (p-value = 0.767) in the univariate logistic regression model. When adjusted for smoking history, the effect of Cave remained insignificant in the logistic regression model.

The reviewer generally agrees with the Applicant's conclusion that lower and higher Cmin or Cave values observed at the planned dose level (600 mg BID) in Study 849-001 (Phase 1/1b and Phase 2 Cohort A) were associated with similar probabilities of ORR.

E-R analysis for safety

The Applicant used the following exposure metrics to conduct E-R analysis for safety

- Cmax,ss: The maximum concentration of adagrasib was derived after each dose from Week 2 until the final dose and averaged in each subject.

- Cave,ss: The average concentration of adagrasib was derived after each dose from Week 2 until the final dose and averaged in each subject
- For ALT > 3 x ULN and AST > 3 x ULN, the maximum and average concentrations from Weeks 1 to 3 were used to assess exposure-response relationships ($C_{max,Week1-3}$ and $C_{ave,Week1-3}$) as the median onset time to AST and ALT elevations was approximately 3 weeks after dosing.

Given the high rate of dose interruption and modification during the treatment period, these exposure metrics are likely confounded by dose changes (mainly due to AEs) for each individual during the treatment. Therefore, the reviewer conducted E-R analyses for the safety variables using the exposure metrics (Cmax,ss, and Cavg,ss) derived based on the initial dose (600 mg BID) before any dose modification and interruptions. Similar to those performed by Applicant, a univariate logistic regression was performed with the AEs as binary response variables and the exposure metrics as the continuous explanatory variable. No statistically significant E-R relationships were observed for the safety variables at the dose level of 600 mg BID (Table 35).

Table 49. Univariate logistic regression for safety variables with Cmax,ss and Cavg,ss derived based on initial dose (600 mg BID)

	Exposures	Estimate	Pr(>|z|)	Exposures	Estimate	Pr(>|z|)
Any Grade ≥3 AEs	(Intercept)	4.80E-01	0.44	(Intercept)	3.96E-01	0.53
	Cmax,ss	3.92E-04	0.11	Cavg,ss	4.57E-04	0.09
Diarrhea	(Intercept)	7.39E-01	0.09	(Intercept)	7.91E-01	0.07
	Cmax,ss	6.31E-05	0.68	Cavg,ss	4.60E-05	0.77
Nausea	(Intercept)	9.50E-01	0.03	(Intercept)	9.45E-01	0.03
	Cmax,ss	1.14E-05	0.94	Cavg,ss	1.44E-05	0.92
Vomiting	(Intercept)	4.33E-01	0.26	(Intercept)	4.07E-01	0.29
	Cmax,ss	-3.63E-05	0.78	Cavg,ss	-2.81E-05	0.84
ALT > 3x ULN	(Intercept)	-7.10E-01	0.31	(Intercept)	-6.17E-01	0.38
	Cmax,ss	-4.38E-04	0.12	Cavg,ss	-5.10E-04	0.10
AST > 3x ULN	(Intercept)	-1.40E+00	0.03	(Intercept)	-1.33E+00	0.04
	Cmax,ss	-1.73E-04	0.47	Cavg,ss	-2.16E-04	0.41
Lipase > 3 x	(Intercept)	-1.81E+00	0.01	(Intercept)	-1.80E+00	0.01
	Cmax,ss	-9.36E-05	0.69	Cavg,ss	-1.03E-04	0.68
Hyponatrimia	(Intercept)	-7.74E-01	0.16	(Intercept)	-7.64E-01	0.16
	Cmax,ss	-2.10E-04	0.30	Cavg,ss	-2.28E-04	0.30

Source: Reviewer's Analysis. SE = standard error.

19.4.4.6. Reviewer's Independent Analysis

The FDA generally agrees with the Applicant's conclusions on E-R relationship for efficacy and safety, however, hightlights the limitation of the E-R evaluation to inform any PK range beyond the dose level (600 mg BID). The reviewer's analysis is presented in the previous section.

19.4.4.7. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

The FDA's Assessment:

The Applicant's proposed dosing regimen of 600 mg BID has demonstrated acceptable efficacy and a high toxicity profile. The current E-R analyses for safety and efficacy cannot be used to support the recommended 600 mg BID dosage as an optimal dosage due to the narrow PK exposures resulting mainly from evaluation of one dose level of 600 mg BID. Therefore, a PMR regarding dose optimization is warranted to evaluate an alternative dosing regimen for adagrasib that may provide similar efficacy with improved safety as compared to 600 mg BID. The Applicant also needs to update E-R analyses to support the alternative dosing regimen.

19.4.4.8. Additional PopPK and E-R analysis to support clinical bridging ofadagrasib formulation

To support clinical bridging of adagrasib formulations (capsules and tablets), the Applicant proposed additional PopPK analysis and ER analysis for efficacy using preliminary emerging PK and clinical response data in the adagrasib 600 mg BID arm of Study 849-012. On 8/12/2022, the Applicant provided the updated PopPK and E-R analysis using clinical efficacy and safety data from approximately 30 patients receiving the adagrasib 200 mg tablet formulation in Study 849-012 and 116 patients receiving the capsule formulation from Cohort A in Study 849-001 Cohort A, each for the first 84 days of treatment.

Applicant's position: Information Amendment received on 8/12/2022 (SN 041):
A PopPK analysis of was performed by combining concentration-time profiles of adagrasib in patients who received the capsule and tablet formulations in studies 849-001 (Phase 1/1b and Phase 2 Cohort A) and 849-012. Additionally, the relative bioavailability between the capsule and tablet formulations was evaluated. Results showed the followings:

- A two-compartment model with sequential zero-order then first-order absorption and linear elimination adequately described adagrasib PK from Study 849-001 Phase 1/1b and Phase 1 Cohort A and study 849-012. Addition of a relative bioavailability parameter to account for differences between the capsule and tablet formulations significantly improved the model.

- A total of 1000 bootstrap runs provided an estimated relative bioavailability of the tablet of 94.04% compared to the capsule formulation, with the 90% confidence interval of 81.34% to 111.33%, which is within the regulatory bioequivalence boundary of 80.00% to 125.00%. Based on the above analysis of clinical experience in Studies 849 001 and 849-012, the proposed commercial tablet formulation is bioequivalent to the capsule formulation.

E-R analyses of ORR were performed after pooling data from studies 849-001 (Phase 1/1b and Phase 2 Cohort A) and 849-012 using the following PK endpoints: minimum concentration from Week 2 to 6 (Cmin,Week2-6), and Cmin and Cave from the first dose up to the occurrence of best response for responders or up to the last dose for non-responders. Three E-R analyses were performed:

- Analysis #1: This analysis was performed with a cutoff based on data collected up to 94 days using investigator assessed response data. In consideration of the different follow-up times for patients treated with capsules in Cohort A versus those initiating treatment with tablets in Study 849-012, efficacy assessment for the first 84 days of treatment for both groups (corresponding to the time of the second tomography scan for assessment of ORR) along with any response confirmations documented within 94 days were utilized in order to include the entirety of the protocol-specified window (± 10 days) for the second tomography scan.
- Analysis #2: This analysis was performed without any cutoff time for ORR (investigator assessed response data).
- Analysis #3: This analysis was performed based on data from BICR for study 849-001 Phase 2 Cohort A pooled with investigator assessed response data for studies 849-001 Phase 1/1b and 849-012 without a cutoff time.

Results from the 3 E-R analyses showed that the effects of Cmin,Week2-6, Cmin and Cave were not statistically significant in the logistic regression model, suggesting that higher and lower adagrasib exposure were associated with similar probabilities of ORR. The effect of formulation was not statistically significant for the Cmin,Week2-6, Cmin and Cave models.

FDA assessment:

The reviewer generally agrees with the updated PopPK estimating slightly lower BA (relative BA of 94%) for tablet formulation, and no apparent exposure-efficacy relationship based on the pooled data with capsule and tablet formulations. These results support that a similar ORR is expected between tablet and capsule formulations at the dose of 600 mg BID.

19.4.5. Physiologically-based Pharmacokinetic Modeling

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's PBPK analyses to support the intended uses. The PBPK analyses were presented in the following reports:

- MRT/3/B: Development of a PBPK model for MRTX849 (adagrasib) within the Simcyp population-based simulator and subsequent evaluation of the DDI liability (victim and perpetrator) for MRTX849 600 mg bid in cancer patients.
- MRT/3/C: PBPK model assessment of the impact of hepatic impairment on the steady-state pharmacokinetics of MRTX849 (adagrasib).

The Division of Pharmacometrics has reviewed the PBPK reports, supporting modeling files, and the Applicant's responses to FDA's information requests (IRs) submitted on April 29 and July 29, 2022, and conclude the following:

- The adagrasib PBPK model is adequate to predict the PK of adagrasib following a single oral dose administration (200 mg and 600 mg), or multiple oral dose administration (400 mg BID and 600 mg BID) in healthy subjects and cancer patients.
- The adagrasib PBPK model is adequate to predict the effect of itraconazole (a strong CYP3A inhibitor) on adagrasib PK following multiple dose administration of adagrasib (600 mg BID) in healthy subjects. About 9% increase in adagrasib exposure was predicted when coadministered with itraconazole at steady state. The results indicated that no significant DDI would be expected for 600 mg BID adagrasib with itraconazole due to the strong adagrasib mediated auto-inhibition effect on CYP3A4.
- The adagrasib PBPK model is inadequate to accurately predict the magnitude of effect of gemfibrozil (a strong CYP2C8 inhibitor) on adagrasib PK following multiple dose administration of adagrasib (600 mg BID) in healthy subjects. However, the modeling analysis, along with in vitro study results, indicated that a potential clinically significant interaction between adagrasib and a strong CYP2C8 inhibitor cannot be ruled out.
- The adagrasib PBPK model is adequate to estimate the effect of rifampin (a strong CYP3A inducer) on adagrasib PK following multiple dose administration of adagrasib (600 mg BID) in healthy subjects. The model predicted at least a 66% decrease in adagrasib exposure at steady state when coadministered with rifampin.
- The adagrasib PBPK model is adequate to predict the effect of efavirenz (a moderate CYP3A inducer) on adagrasib PK following multiple dose administration of adagrasib (600 mg BID) in healthy subjects. The model predicted about 25% decrease in adagrasib exposure at steady state when coadministered with efavirenz.
- The adagrasib PBPK model is adequate to predict the effect of adagrasib on midazolam (a sensitive CYP3A substrate) PK following multiple dose administration of adagrasib (600 mg

BID) in healthy subjects. The model predicted a 31-fold increase in midazolam exposure when coadministered with adagrasib at steady state.

- The adagrasib PBPK model is adequate to predict the effect of adagrasib on the PK of dextromethorphan (a sensitive CYP2D6 substrate) and warfarin (a sensitive CYP2C9 substrate) following multiple dose administration of adagrasib (600 mg BID) in healthy subjects. The model predicted AUC ratios were 2.37 and 2.93 for dextromethorphan and warfarin, respectively, when coadministered with adagrasib at steady state.
- The adagrasib PBPK model is adequate to predict the effect of adagrasib on digoxin (a P-gp substrate) PK following multiple dose administration of adagrasib (600 mg BID) in healthy subjects. The model predicted a 1.86-fold and 1.48-fold increase in digoxin Cmax and AUC, respectively, when coadministered with adagrasib at steady state.
- The adagrasib PBPK model is inadequate to predict the effect of adagrasib on rosuvastatin (a BCRP/OATP substrate) PK following multiple dose administration of adagrasib (600 mg BID) in healthy subjects. However, the modeling analysis indicated that the observed exposure change of rosuvastatin with adagrasib is unlikely driven by the inhibitory effect of adagrasib towards BCRP/OATP. This analysis also provided supporting information that adagrasib interaction with BCRP/OATP substrates is unlikely to be clinically significant.
- The adagrasib PBPK model is inadequate to predict the effect of adagrasib on bupropion (a CYP2B6 substrate) or metformin (a MATE-1/2K substrate) PK following multiple dose administration of adagrasib (600 mg BID) in healthy subjects. The bupropion and metformin models have not been adequately validated as substrates of CYP2B6 and MATE-1/2K, respectively.
- The PBPK modeling and simulation along with sensitivity analyses indicated that there is minor difference in predicted unbound exposure changes of adagrasib in HI patients versus matched healthy subjects following multiple dose administration of adagrasib (600 mg BID). The predicted unbound AUC ratios ranged from 0.71 to 1.22 in mild, moderate and severe HI patients.

19.4.5.1 Part A: DDI Assessment

Applicant's PBPK Modeling Effort

PBPK software

Simcyp V18 (Simcyp Ltd, UK) was used to develop the PBPK models and predict the effects of adagrasib on the PK of midazolam, dextromethorphan, warfarin, bupropion, digoxin, rosuvastatin, and metformin, and the effects of itraconazole, gemfibrozil, rifampin and efavirenz on the PK of adagrasib in healthy subjects.

Model development

Adagrasib

Absorption was described using a first order absorption model with a lag time (tlag) of 0.5 h. The fraction absorbed (fa) of 0.85 and absorption rate constant (ka) of 0.64 h^{-1} were predicted from permeability data in Caco-2 cells (Table 48).

A minimal PBPK model, without a single-adjusting compartment, was used to simulate the distribution phase of adagrasib PK profiles. The volume of distribution at steady state (Vss) (7.91 L/kg) was predicted in Simcyp using method 3 (Membrane potential model). The fraction unbound in plasma (f_u) and blood and plasma ratio were 0.023 and 0.7, respectively (Table 48).

Adagrasib was primarily metabolized by CYP3A4 with minor contributions from CYP2C8, 1A2, 2B6, 2C9 and 2D6 following a single dose administration. Total CLint and fraction metabolized by CYP3A4 and CYP2C8 were refined based on the total clearance (CL/F=47.9 L/h) reported in the clinical PK study 849-005 and clinic DDI study results with itraconazole (Study 849-006), respectively. An additional hepatic intrinsic clearance (additional HLM CLint) was assigned in the model to represent the contribution of other CYP enzymes to the metabolism of adagrasib.

Following oral administration, the unchanged parent drug accounted for 1.8% and 14% of the dose administered in urine (4.16% of total administered radioactivity) and feces (73.1% of total administered radioactivity), respectively. Renal clearance of 0.8622 L/h was obtained from the clinical PK study 849-005.

The in vitro inhibition constant (Ki) values of CYP2B6 ((b) (4) µM) and MATE ((b) (4) µM) were incorporated in the adagrasib model to simulate the DDI between adagrasib and bupropion (a CYP2B6 substrate) or adagrasib and metformin (a MATE-1/2K substrate). Sensitivity analyses were conducted to evaluate the effect of a range of Ki values on the predicted DDI (Table 48).

The in vitro Ki values of CYP3A4 (8.2 µM) and KI (1.85 µM) and kinact (2.1 h-1) values for adagrasib mediated time dependent inhibition of CYP3A4 were incorporated in the adagrasib model to simulate the DDI between adagrasib and midazolam (a sensitive CYP3A4 substrate) (Table 48).

For CYP2C9, CYP2D6 and P-gp, the in vitro obtained Ki values were refined based on clinical DDI study results with warfarin, dextromethorphan and digoxin, respectively (Study 849-006). The Ki values of 0.32 µM, 0.66 µM and 0.018 µM for CYP2C9, CYP2D6 and P-gp were incorporated in the final model for DDI evaluation, respectively (Table 48).

As the population PK analysis indicated that the adagrasib PK is similar between healthy subjects and cancer patients (Population PK analysis report MIRAPMX-MRTX849-1556), the virtual "healthy volunteer" population (Sim-NEurCaucasian) model was used as the basis to simulate the adagrasib PK profiles in cancer patient.

Table 50 Adagrasib PBPK model input parameter values

Parameter	Value	Method/Comment	References
Physchem and Blood Binding			
MW (g/mol)	604.1		
log P	5.02	Calculated from log D7.4 (3.6)	R3256_01SGA17AUG18
pKa values	3.33, 8.82	Diprotic base	
B:P	0.70		PK-MRTX849-018
fu_p	0.023	Average of 3 concentrations Most highly bound to AGP	PK-MRTX849-016, PK-MRTX849-036
Absorption:	***1st order model***		
fu_{gut}	0.023	Assumed equal to fu_p	
Caco-2 pH 7.4:7.4 P_{app} ($x10^{-6}$cm/s)	6.84	Propranolol P_{app} (22.6 $x10^{-6}$cm/s) used for calibration of Caco-2 cells	20MIRAP1
Q_{gut} (L/h)	8.35	Predicted from Caco-2 data	
f_a	0.85		
k_a (h^{-1})	0.64		
t_{lag} (h)	0.5	Added to capture absorption phase	
Distribution:	***Minimal PBPK model***		
V_{ss} (L/kg)	7.91	Predicted – Method 3	
Kp Scalar	1.695		
Elimination:	***Enzyme kinetics model***		
CYP3A4 Cl_{int} (µL/min/pmol)	11.76	Final model values (fm_{CYP3A4} = 83%) refined to fit clinical PK and DDI data (Section 3.2.3.2.1)	
CYP2C8 Cl_{int} (µL/min/pmol)	(b) (4)		
Additional HLM CL_{int} (µL/min/mg)	141.6		
CL_R (L/h)	0.8622	Calculated from fe*CL/F, where reported fe = 0.018 and CL/F = 47.9 L/h	849-005
Interaction			
CYP3A4 k_{inact} (h^{-1})	2.1	Derived from reported value (0.035 min^{-1})	PK-MRTX849-013
CYP3A4 K_I (µM)	1.85		
fu_{inc}	0.04	1 mg/ml, CYP3A4 K_I	PK-MRTX849-032
CYP3A4 K_i (µM)	8.2		PK-MRTX849-013
CYP2B6 K_i (µM)	(b) (4)		
CYP2C9 K_i (µM)	0.32	10-fold reduction of *in vitro* value	
CYP2D6 K_i (µM)	0.66	40-fold reduction of *in vitro* value	
fu_{inc}	0.14	0.25 mg/ml, all CYP K_i	PK-MRTX849-032
P-gp K_i (µM)	0.018	Calculated from IC_{50} then 15-fold reduction applied	PK-MRTX849-012
MATEs K_i (µM)	(b) (4)		(b) (4)

Source: PBPK study report MRT-3-B and Applicant's response to FDA's Information Request dated April 29, 2022.

Victim drug models

The default PBPK models of midazolam, dextromethorphan, warfarin, bupropion, digoxin, rosuvastatin, metformin, itraconazole, gemfibrozil, rifampin and efavirenz in Simcyp (V18) were used for DDI predictions.

FDA's assessment

1. In the clinical DDI study 849-006, a solution formulation of itraconazole was used to evaluate its effect on the PK of adagrasib. Hydroxypropyl-β-cyclodextrin (HP-β-CD) is used as an excipient in the itraconazole solution (Sporanox®) for oral dosing. It has been shown that HP-β-CD may have impact on the rate and extent of the drug absorption when co-administered with itraconazole solution, leading to a potential underestimation of the DDI effect with itraconazole[1,2]. An information request was issued requesting the Applicant to evaluate the potential impact of HP-β-CD in the itraconazole solution on the observed DDI between itraconazole and adagrasib.
2. Adagrasib demonstrated strong time-dependent inhibition of CYP3A4 at steady state as evidenced by a greater than 20-fold increase in midazolam exposure when coadministered with multiple dose adagrasib (400 mg BID). CYP3A4 is the major enzyme involved in the metabolism of adagrasib following a single dose administration, however, due to the strong time dependent inhibition of CYP3A4, it is expected that the metabolism of adagrasib at steady-state would be mainly driven by other enzymes instead of CYP3A4. In vitro CYP phenotyping studies showed that adagrasib was metabolized via CYP3A4, CYP2C8 and CYP2D6, and CYP2C8 and CYP2D6 were reported to account for 28% and less than 5% of the CYP mediated metabolism of adagrasib, respectively. An information request was issued requesting the Applicant to evaluate the DDI liability of adagrasib as a victim of CYP2C8 at steady-state following multiple dose administration of 600 mg adagrasib.

Applicant's response to FDA's IR and FDA's assessment

1. In the response to the FDA's IR, the Applicant provided binding constant data ($k_{complex}$=1620 M^{-1}) and in vitro permeability of adagrasib in the presence of HP-β-CD. No changes in permeability of adagrasib was observed with HP-β-CD at the molar ratio between adagrasib and HP-β-CD similar to the clinical setting. Based on the findings in the literature[3,4], these data and information suggested that the likelihood that HP-β-CD in the itraconazole solution would impact adagrasib absorption was low.
2. The Applicant conducted an in vitro chemical inhibition study with human hepatocytes to evaluate the contribution of CYP2C8 and other CYP enzymes to adagrasib metabolism in the presence of CYP3cide to inhibit all CYP3A4 mediated metabolism. The study results indicated that CYP2C8 accounted for about 46% of non-CYP3A4 mediated hepatic metabolism of adagrasib in the presence of the strong CYP2C8 inhibitor, gemfibrozil glucuronide. In addition,

[1] Durk MR, Jones NS, Liu J, Nagapudi K, et al. Understanding the Effect of Hydroxypropyl-β-Cyclodextrin on Fenebrutinib Absorption in an Itraconazole-Fenebrutinib Drug-Drug Interaction Study. Clin Pharmacol Ther. 2020; 108: 1224-1232.

[2] Tachibana T, Kitamura S, Kato M, Mitsui T, et al. Model Analysis of the Concentration Dependent Permeability of P-gp Substrates. Pharm Res. 2010; 27: 442-446.

[3] Durk MR, Jones NS, Liu J, Nagapudi K, et al. Understanding the Effect of Hydroxypropyl-β-Cyclodextrin on Fenebrutinib Absorption in an Itraconazole-Fenebrutinib Drug-Drug Interaction Study. Clin Pharmacol Ther. 2020; 108: 1224-1232.

[4] Tachibana T, Kitamura S, Kato M, Mitsui T, et al. Model Analysis of the Concentration Dependent Permeability of P-gp Substrates. Pharm Res. 2010; 27: 442-446.

the contributions of each of other four enzymes (CYP1A2, CYP2B6, CYP2C9 and CYP2D6) were suggested to be less than 25%.

Model application

The developed PBPK model was used to simulate the DDI for adagrasib in the following scenarios:

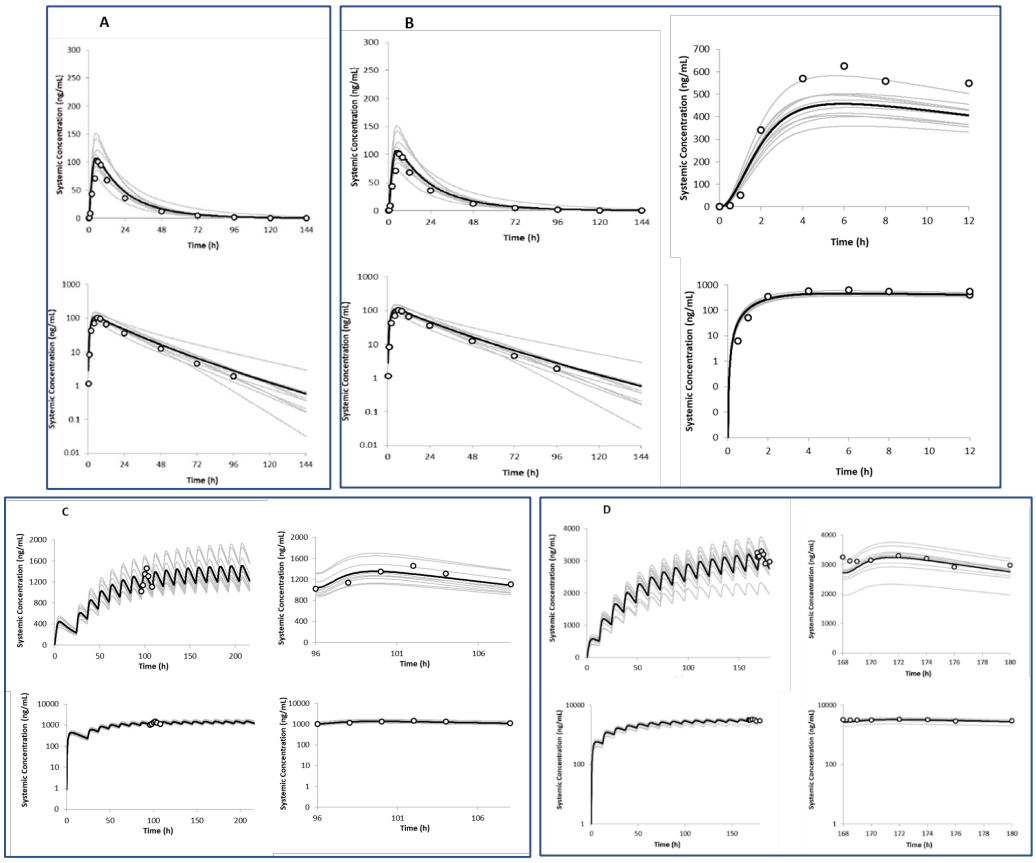
- To predict the effect of itraconazole (a strong CYP3A inhibitor) on the PK of adagrasib following multiple dose administration of adagrasib (600 mg BID) in healthy subjects.
- To predict the effect of gemfibrozil (a strong CYP2C8 inhibitor) on the PK of adagrasib following multiple dose administration of adagrasib (600 mg BID) in healthy subjects.
- To predict the effect of rifampin (a strong CYP3A inducer) and efavirenz (a moderate CYP3A4 inducer) on the PK of adagrasib following multiple dose administration of adagrasib (600 mg BID) in healthy subjects.
- To predict the effect of adagrasib on the PK of midazolam (a sensitive CYP3A4 substrate) following multiple dose administration of adagrasib (600 mg BID) in healthy subjects.
- To predict the effect of adagrasib on the PK of dextromethorphan (a sensitive CYP2D6 substrate) and warfarin (a sensitive CYP2C9 substrate) following multiple dose administration of adagrasib (600 mg BID) in healthy subjects.
- To predict the effect of adagrasib on the PK of digoxin (a P-gp substrate) following multiple dose administration of adagrasib (600 mg BID) in healthy subjects.
- To predict the effect of adagrasib on the PK of rosuvastatin (a BCRP/OATP substrate) following multiple dose administration of adagrasib (600 mg BID) in healthy subjects.
- To predict the effect of adagrasib on the PK of bupropion (a CYP2B6 substrate) and metformin (a MATE-1/2K substrate) following multiple dose administration of adagrasib (600 mg BID) in healthy subjects.

Results

1. Can adagrasib PBPK model describe adagrasib PK in healthy subjects and cancer patients?

Yes. The adagrasib model was able to capture the observed adagrasib PK profiles following a single oral dose administration (200 mg and 600 mg), or multiple oral dose administration (400 mg BID and 600 mg BID) in healthy subjects and cancer patients (Figure 30 and Table 49). It was noted that the population PK analysis indicated that the adagrasib PK is similar between healthy subjects and cancer patients (MIRAPMX-MRTX849-1556).

Figure 30 Observed (dots) and simulated (lines) adagrasib plasma concentration-time profiles (geometric mean) following a single dose (A: 200 mg; B: 600 mg) or multiple dose (C: 400 mg bid; D: 600 mg BID) administration of adagrasib in healthy subjects or cancer patients. A and C: healthy subjects and C and D: cancer patients.



Sources: Observed data were from: A: Study 849-006; B: Study 849-001; C: Study 849-006; and D: Study 849-001. Predicted PK profiles were from Applicant's response to FDA's Information Request dated April 29, Figure 2 (A) and FDA's reviewer's simulations using the Applicant's model (B, C and D).

Table 51 Simulated and observed adagrasib Cmax and AUC values across 200-600 mg doses

	200 mg single dose (Day 1, study 849-006, cohort 1)		400 mg BID (Day 9, study 849-006, cohort 4)		600 mg single dose (Day 1, study 849-001)		600 mg BID (Day 8, study 849-001)	
	C_{max} (ng/ml)	AUC_{last} (ng/ml.h)	C_{max} (ng/ml)	AUC_{tau} (ng/ml.h)	C_{max} (ng/ml)	AUC_{tau} (ng/ml.h)	C_{max} (ng/ml)	AUC_{tau} (ng/ml.h)
Predicted	84.1	2248	1214	13256	386	3763	2845	31820
Observed	85.6	1948	1270	12700	558	4308	3253	31600
Pred/Obs	**0.98**	**1.15**	**0.96**	**1.04**	**0.69**	**0.87**	**0.87**	**1.01**

Sources: Predicted PK profiles were from Applicant's response to FDA's Information Request dated April 29, Table 5. Observed data were from Study 849-001 and Study 849-006.

2. Can adagrasib PBPK model predict the effect of itraconazole (a strong CYP3A inhibitor) on the PK of adagrasib following multiple dose administration of adagrasib (600 mg BID) in healthy subjects?

Yes. The adagrasib model validated using clinical DDI data between midazolam and adagrasib (600 mg SD and 400 mg BID) and itraconazole and adagrasib (200 mg SD) was adequate to predict the effect of itraconazole on the PK of adagrasib following multiple dose administration of adagrasib (600 mg BID) in healthy subjects. About 9% increase in adagrasib exposure was predicted when coadministered with itraconazole at steady state (Table 50). The results indicated that no significant DDI for 600 mg BID adagrasib with itraconazole would be expected due to the strong adagrasib mediated auto-inhibition effect on CYP3A4.

Table 52 Model predicted effects of CYP modulators on the PK of adagrasib and effects of adagrasib on the PK of CYP3A4, CYP2D6, CYP2C9, or P-gp substrates following multiple dose administration of 600 mg BID adagrasib

As a victim	Changes in PK parameters of adagrasib	
	CmaxR[a]	AUCR[a]
Itraconazole (strong CYP3A4 inhibitor), 200 mg QD	1.08	1.09
Rifampin (strong CYP3A4 inducer), 600 mg QD	<0.39	<0.34
Efavirenz (moderate CYP3A4 inducer), 600 mg QD	0.77	0.75
As a perpetrator	Changes in PK parameter of concomitant drugs	
	CmaxR[b]	AUCR[b]
Midazolam (sensitive CYP3A4 substrate), 2 mg	3.10	31.4
Dextromethorphan (sensitive CYP2D6 substrate), 30 mg	1.73	2.37
Warfarin (sensitive CYP2C9 substrate), 10 mg	1.05	2.93
Digoxin (P-gp substrate), 0.25 mg	1.86	1.48

Source: a: Applicant's response to FDA's Information Request dated April 29, 2022; b: PBPK study report MRT-3-B

3. Can adagrasib PBPK model predict the effect of gemfibrozil (a strong CYP2C8 inhibitor) on the PK of adagrasib following multiple dose administration of adagrasib (600 mg BID) in healthy subjects?

No. The adagrasib PBPK model is inadequate to accurately predict the magnitude of effect of gemfibrozil on adagrasib PK following multiple dose administration of adagrasib (600 mg BID). (b) (4)

(b) (4), the model predicted adagrasib exposure (b) (4) when coadministered with gemfibrozil following multiple dose administration of adagrasib (600 mg BID) in healthy subjects. The modeling analysis indicated that a potential clinically significant interaction between adagrasib and a strong CYP2C8 inhibitor cannot be ruled out. (b) (4) adagrasib exposure at steady state with a strong CYP2C8 inhibitor needs to be confirmed using a dedicated clinical DDI study.

4. **Can adagrasib PBPK model predict the effect of rifampin (a strong CYP3A inducer) on the PK of adagrasib following multiple dose administration of adagrasib (600 mg BID) in healthy subjects?**

   Yes. The adagrasib model validated using clinical DDI data between midazolam and adagrasib (600 mg SD and 400 mg BID), itraconazole and adagrasib (200 mg SD) and rifampin and adagrasib (600 mg SD) was able to estimate the effect of rifampin on the PK of adagrasib following multiple dose administration of adagrasib (600 mg BID) in healthy subjects (Table 50). The model predicted at least a 66% decrease in adagrasib exposure at steady state when coadministered with rifampin. The Reviewer acknowledges the following modeling limitation: due to the uncertainties associated with the estimated fmCYP2C8 and fractional contribution of other CYP enzymes (CYP1A2, 2B6, 2C9 and 2D6) involved in the metabolism of adagrasib at steady state, only rifampin mediated induction effect on CYP3A4 was considered when evaluated the DDI between adagrasib and rifampin at steady state. Therefore, the magnitude of reduction in adagrasib exposure with rifampin following multiple dose administration of 600 mg BID adagrasib would be expected to be greater than the predicted values given rifampin is known to induce the other CYP enzymes involved in adagrasib metabolism.

5. **Can adagrasib PBPK model predict the effect of efavirenz (a moderate CYP3A4 inducer) on the PK of adagrasib following multiple dose administration of adagrasib (600 mg BID) in healthy subjects?**

   Yes. The adagrasib model validated using clinical DDI data between midazolam and adagrasib (600 mg SD and 400 mg BID), itraconazole and adagrasib (200 mg SD) and rifampin and adagrasib (600 mg SD) was adequate to predict the effect of efavirenz on the PK of adagrasib following multiple dose administration of adagrasib (600 mg BID) in healthy subjects. The model predicted about 25% decrease in the adagrasib exposure at steady state when coadministered with efavirenz (Table 50).

6. **Can adagrasib PBPK model predict the effect of adagrasib on the PK of midazolam (a sensitive CYP3A4 substrate) following multiple dose administration of adagrasib (600 mg BID) in healthy subjects?**

   Yes. The adagrasib model validated using clinical DDI data between midazolam and adagrasib (600 mg SD and 400 mg BID), itraconazole and adagrasib (200 mg SD) and rifampin and adagrasib (600 mg SD) was adequate to predict the effect of adagrasib on the PK of midazolam (2 mg SD)

following multiple dose administration of adagrasib (600 mg BID) in healthy subjects. The model predicted a 31-fold increase in midazolam exposure when coadministered with adagrasib at steady state (Table 50).

7. **Can adagrasib PBPK model predict the effect of adagrasib on the PK of dextromethorphan (a sensitive CYP2D6 substrate) and warfarin (a sensitive CYP2C9 substrate) following multiple dose administration of adagrasib (600 mg BID) in healthy subjects?**

   Yes. The adagrasib model validated using clinical DDI data between dextromethorphan and adagrasib (600 mg SD and 400 mg BID) and warfarin and adagrasib (600 mg SD and 400 mg BID) was adequate to predict the effect of adagrasib on the PK of dextromethorphan (30 mg SD) and warfarin (10 mg SD), respectively, following multiple dose administration of adagrasib (600 mg BID) in healthy subjects. The model predicted AUC ratios were 2.37 and 2.93 for dextromethorphan and warfarin, respectively, when coadministered with adagrasib at steady state (Table 50).

8. **Can adagrasib PBPK model predict the effect of adagrasib on the PK of digoxin (a P-gp substrate) following multiple dose administration of adagrasib (600 mg BID) in healthy subjects?**

   Yes. The adagrasib model validated using clinical DDI data between digoxin and adagrasib (600 mg SD and 400 mg BID) was adequate to predict the effect of adagrasib on the PK of digoxin (0.25 mg SD) following multiple dose administration of adagrasib (600 mg BID) in healthy subjects. The model predicted a 1.86-fold and 1.48-fold increase in digoxin Cmax and AUC, respectively, when coadministered with adagrasib at steady state (Table 50).

9. **Can adagrasib PBPK model predict the effect of adagrasib on the PK of rosuvastatin (a BCRP/OATP substrate) following multiple dose administration of adagrasib (600 mg BID) in healthy subjects?**

   No. The adagrasib along with the rosuvastatin (substrate) models cannot capture the observed clinical DDI study results between rosuvastatin and adagrasib (600 mg SD and 400 mg BID) and cannot be used to predict the DDI between rosuvastatin and adagrasib (600 mg BID) (Table 51). The modeling analysis showed that when inhibiting BCRP mediated efflux, the rosuvastatin Cmax was (b) (4) AUC; and the magnitude of increase in Cmax is (b) (4) AUC when inhibiting the OATP mediated uptake. Based on the observed rosuvastatin Cmax (1.06-fold) and AUC (1.25-fold) changes with adagrasib (400 mg BID), the observed exposure change of rosuvastatin with adagrasib is unlikely driven by the inhibitory effect of adagrasib towards BCRP/OATP. This analysis also provided supporting information that adagrasib interaction with BCRP/OATP substrates is unlikely to be clinically relevant.

Table 53 PBPK assessment of the effect of adagrasib on the PK of rosuvastatin through inhibition of BCRP or OATP

	Adagrasib (400 mg BID)			Rosuvastatin (5 mg SD)	
	Intestine BCRP Ki (µM)	Liver BCRP Ki (µM)	OATP Ki (µM)	CmaxR	AUCR
Simulated	(b) (4)				
Observed	-	-	-	1.06	1.25

a: (b) (4)

Source: simulated data were from reviewer's simulation and observed data were from clinical study 849-006

10. Can adagrasib PBPK model predict the effect of adagrasib on the PK of bupropion (a CYP2D6 substrate) and metformin (a MATE-1/2K substrate) following multiple dose administration of adagrasib (600 mg BID) in healthy subjects?

No. The bupropion and metformin substrate models have not been adequately validated[5,6]; therefore, they cannot be used to evaluate the potential effect of adagrasib on the PK of CYP2B6 and MATE-1/2K substrates, respectively.

19.4.5.2. Part B: Assessment of the effect of hepatic impairment on adagrasib steady-state exposure

Applicant's PBPK Modeling Effort

The Applicant has conducted a clinical PK study 849-003 to evaluate the effect of HI on the PK of adagrasib following a single dose administration (600 mg). The observed unbound adagrasib AUC ratios in subjects with mild, moderate, and severe HI were 1.01, 1.03 and 1.66, respectively, relative to the subjects with normal liver function.

[5] Apalutamide. Multidisciplinary Review- PBPK Modeling Review. 2018. **Accessed at** https://www.accessdata fda.gov/drugsatfda_docs/nda/2018/210951Orig1s000MultidisciplineR.pdf
[6] Sotorasib. FDA Multidisciplinary Review- PBPK Modeling Review. 2021. Accessed at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214665Orig1s000MultidisciplineR.pdf

The PBPK model developed for adagrasib DDI evaluation was further refined based on the results of the Study 849-003 and utilized to evaluate the effect of HI on the steady state PK of adagrasib (600 mg BID).

PBPK software

Simcyp V21 (Simcyp Ltd, UK) was used to develop the adagrasib PBPK models in hepatic impaired populations and predict the effect of HI on the steady state PK of adagrasib (600 mg BID).

Model development

The developed PBPK platform for DDI assessment was further refined to better capture the observed effects of HI on the single dose PK of adagrasib. (b) (4) The details of model refinement for HI evaluation were as follows:

1. Simcyp Version comparison

Simcyp V18 was used for DDI assessment, while Simcyp V21 was used for the simulations in patients with HI. Thus, the predictive performance of the adagrasib model was firstly compared between V18 and V21 in matched healthy volunteers from the clinical HI Study 849-003 after a single dose administration of 600 mg adagrasib. Note that the original model in V18 assumed the main binding protein was alpha1-acid glycoprotein (AGP) and in the model in V21, binding to both human serum albumin (HAS) and AGP was accounted. The results showed a less than 10% difference in predicted Cmax and AUCinf values as compared to the observed data (Table 52). In addition, the predicted relative changes in fraction unbound in plasma in patients with HI were comparable to the observed data (Table 53). Therefore, the model performance was considered comparable between two versions.

Table 54 Comparison of observed and simulated adagrasib Cmax and AUCinf values in matched healthy volunteers in Simcyp V18 and V21 following a single dose administration of 600 mg adagrasib

	Healthy Volunteers (cohort Mild HI)		Healthy Volunteers (cohort Moderate HI)		Healthy Volunteers (cohort Severe HI)	
	Cmax (ng/mL)	AUCinf (ng*h/mL)	Cmax (ng/mL)	AUCinf (ng*h/mL)	Cmax (ng/mL)	AUCinf (ng*h/mL)
Observed*	389	10690	453	11820	443	12210
Simulated (V18)	369	8757	372	9847	424	10493
S/O (V18)	0.95	0.82	0.82	0.83	0.96	0.86
Simulated (V21)	345	7951	385	10064	400	9453
S/O (V21)	0.89	0.74	0.85	0.85	0.90	0.77
V21/V18	0.93	0.91	1.03	1.02	0.94	0.90

Sources: Simulated data were from applicant's response to FDA's information request dated July 29, 2022, Table 2. Observed data were from Study 849-003.

Table 55 Observed and predicted relative changes in unbound fraction in plasma for adagrasib in patients with HI to those in healthy subjects

Population	Fraction of fu in healthy volunteers		
	Observed	Simulated	Sim/Obs
HV	1.00	1.00	--
Mild HI	1.24	1.27	0.98
Moderate HI	1.40	1.30	1.09
Severe HI	1.73	1.75	0.98

Sources: Simulated data were from applicant's response to FDA's information request dated July 29, 2022, Table 2. Observed data were from Study 849-003.

2. CYP3A4 abundance in HI patients

A recent meta-analysis has shown a general tendency of PBPK analysis to over-predict drug exposures in HI patients especially in moderate and severe HI using Simcyp V15[7]. Simcyp updated the hepatic impairment population files in Simcyp V21 based on recently published

[7] Heimbach T, Chen Y, Chen J, Dixit V, Parrott N, Peters SA, Poggesi I, Sharma P, Snoeys J, Shebley M, Tai G, Tse S, Upreti VV, Wang Y-H, Tsai A, Xia B, Zheng M, Zhu AZX, Hall S (2021). Physiologically-Based Pharmacokinetic Modeling in Renal and Hepatic Impairment Populations: A Pharmaceutical Industry Perspective. Clin Pharmacol Ther 110(2):297-310.

literature data[8,9] (Table 54) in an attempt to improve the predictive performance. For adagrasib analysis, the default HI population model in conjunction with optimized fa, and observed fu was able to describe the observed adagrasib PK data in mild, moderate and sever HI subjects following a single dose of adagrasib.

Table 56 Simcyp V21 system parameters for subjects with normal liver function (healthy), mild (CP-A), moderate (CP-B), and severe (CP-C) hepatic impairment

	Healthy	CP-A	CP-B	CP-C
Abundance (pmol/mg protein)				
CYP3A4 – V18	137	108	56	31
CYP3A4 – V21	137	107	70	43
Albumin (g/L)				
Male	45.2	46.3	38.2	29.7
Female	43.1	45.4	37.5	29.1
AAG (g/L)				
Male	0.793	0.562	0.515	0.461
Female	0.715	0.507	0.464	0.416
Haematocrit (%)				
Male	43.0	38.5	34.5	33.5
Female	38.0	34.0	30.5	29.6
eGFR (ml/min)	94.7	83.7	69.9	66.5

eGFR, estimated glomerular filtration rate

Source: PBPK report MRT-3-C, Table 1

3. CYP2C8 abundance in HI patients

In Simcyp V21, there is no change in the average CYP2C8 abundance in patient populations with mild, moderate and severe HI as compared to the subjects with normal hepatic function. This is based on the observation from a literature report[10], where no difference in the in vitro activity of paclitaxel (a CYP2C8 substrate) in healthy and cirrhotic livers was observed.

In response to FDA's information request, the Applicant provided the population model validation regarding CYP2C8 enzyme abundance assigned in HI populations in Simcyp V21 using the PK data of a substrate for CYP2C8 (pioglitazone, fmCYP2C8=0.63) in HI patients. The clinical PK data for pioglitazone provide in vivo evidence of no change in the average CYP2C8 abundance in HI patient populations (Table 55). Reviewer noted that this assumption of CYP2C8 abundance is subjected to other assumptions such as changes in plasma protein binding and fraction absorbed. These uncertainties and their impact on the derived CYP abundance cannot be quantified without further validation. For adagrasib analysis, uncertainty such as contribution of CYP2C8 pathway to the clearance of adagrasib at steady state was evaluated in the modeling analysis as described in later section.

[8] Murray M, Gillani TB, Ghassabian S, Edwards RJ, Rawling T (2018). Differential effects of hepatic cirrhosis on the intrinsic clearances of sorafenib and imatinib by CYPs in human liver. Eur J Pharm Sci 114:55-63.
[9] Prasad B, Bhatt DK, Johnson K, Chapa R, Chu X, Salphati L, Xiao G, Lee C, Hop CECA, Mathias A, Lai Y, Liao M, Humphreys WG, Kumer SC, Unadkat JD (2018). Abundance of Phase 1 and 2 Drug-Metabolizing Enzymes in Alcoholic and Hepatitis C Cirrhotic Livers: A Quantitative Targeted Proteomics Study. Drug Metab Dispos 46(7):943-952.
[10] Murray M, Gillani TB, Ghassabian S, Edwards RJ, Rawling T (2018). Differential effects of hepatic cirrhosis on the intrinsic clearances of sorafenib and imatinib by CYPs in human liver. Eur J Pharm Sci 114:55-63.

Table 57 Simulated and observed geometric mean Cmax and AUC values and ratios for pioglitazone in subjects with normal hepatic function and patients with moderate-to-severe hepatic impairment (HI)

Population	Simulated data		Observed data		Simulated/Observed	
	Cmax ng/mL	AUCinf ng*h/mL	Cmax ng/mL	AUCinf ng*h/mL	Cmax ng/mL	AUCinf ng*h/mL
HV	980	10933	888	7659	1.10	1.43
Moderate and Severe HI	813	10495	508	7333	1.60	1.43
Moderate and Severe HI / HV	0.830	0.960	0.572	0.957	1.45	1.00

Sources: simulated data were from Applicant's response to FDA's information request dated July 29, 2022, Table 1. Observed data: NDA 21-073 Clinical Pharmacology Review[11]

4. Additional clearance estimation through other enzymes in HI patients

The percentage decrease in additional HLM CLint values in HI patients was calculated based on the average reduction of abundance for the other CYPs (CYP 1A2, 2B6, 2C9, 2D6 and 3A5) involved in the metabolism of adagrasib. The fractional abundance of other enzymes in HI patients relative to the healthy subjects was shown in Table 56. The average fraction of other enzymes in patients with mild, moderate and severe HI relative to the healthy subjects was 0.88, 0.67 and 0.40, respectively.

Table 58 Hepatic CYP abundance in healthy subjects and hepatic impairment (HI) populations (CP-A, CP-B, CP-C) and fraction of CYP abundance in HI populations relative to healthy subjects in Simcyp V21

	V21 hepatic CYP abundance (pmol/mg)				Fraction of normal		
CYP	**NEC**	**CP-A**	**CP-B**	**CP-C**	**CP-A**	**CP-B**	**CP-C**
1A2	52	37.6	17.2	8.81	**0.72**	**0.33**	**0.17**
2B6	21.6	21.6	18.9	16.4	**1.00**	**0.88**	**0.76**
2C9	77.7	77.7	77.7	44.2	**1.00**	**1.00**	**0.57**
2D6	9.4	8.43	5.88	1.59	**0.90**	**0.63**	**0.17**
3A5	103	80	53	32	**0.78**	**0.51**	**0.31**
				All minor enzymes average:	**0.88**	**0.67**	**0.40**

Source: Applicant's response to FDA's information request dated July 29, 2022, Table 13.

[11] https://www.accessdata fda.gov/drugsatfda_docs/nda/99/021073A_Actos_clinphrmr_P2.pdf

5. Adagrasib fraction absorbed optimization in HI patients

A first-order absorption model was applied to describe the oral absorption of adagrasib. It is known that HI leads to not only deficiency in metabolism enzymes, but also alteration in drug absorption by congestion and decrease in the blood flow in the intestinal mucosa[12,13]. Thus, the fraction absorbed (fa) value of adagrasib in healthy subjects was optimized for patients with HI based on the observed adagrasib plasma concentration data in patients with mild, moderate and severe HI in Study 849-003. The Applicant's optimized adagrasib fa values were 0.66, 0.45, and 0.34 in patients with mild, moderate and severe HI, respectively. Reviewer further optimized the adagrasib fa values to better capture the observed AUC values and finally fa values of 0.72, 0.50 and 0.37 were applied in simulations in patients with mild, moderate and severe HI, respectively (Table 57). The fa value in healthy subjects was also optimized to 1.00 to provide better prediction.

Table 59 Observed and simulated adagrasib total Cmax and AUC ratios in hepatic impairment (HI) patients relative to the subjects with normal hepatic function using Applicant's model and FDA reviewer's refined model, following a single dose administration of 600 mg adagrasib.

Population	Observed		Applicant's simulations				Reviewer's simulations			
			Simulated		Sim / Obs		Simulated		Sim / Obs	
	C_{maxR}	AUCR	C_{maxR}	AUCR	C_{maxR}	AUCR	C_{maxR}	AUCR	C_{maxR}	AUCR
Mild HI	1.01	0.87	0.94	1.00	0.93	1.15	0.81	0.89	0.80	1.02
Moderate HI	0.70	0.88	0.74	0.83	1.05	0.94	0.76	0.89	1.09	1.01
Severe HI	0.50	0.98	0.56	0.86	1.12	0.87	0.60	0.97	1.22	0.98

Source: Observed data were from Study 849-003

Model application

The refined model of adagrasib in HI populations was applied to predict the impact of HI on the steady-state PK of adagrasib following multiple-dose administration of adagrasib (600 mg BID). The fa, CYP3A4 abundance and additional HLM clearance values in healthy matched subjects and HI patients in the final model are showed in Table 58. Simulations were performed with 20 trials to ensure an overall simulated population greater than 100 subjects. Subjects in each virtual trial were age, sex, height and weight matched to each group of clinical trials subjects in Study 849-

[12] Amira M Ghoneim[1] and Suzan M Mansour. The Effect of Liver and Kidney Disease on the Pharmacokinetics of Clozapine and Sildenafil: A Physiologically Based Pharmacokinetic Modeling. Drug Des Devel Ther. 2020; 14: 1469–1479.

[13] Lei Sun, Zoe Barter, Lisa von Moltke, and Karen Rowland Yeo. Using physiologically-based pharmacokinetic modeling for predicting the effects of hepatic impairment on the pharmacokinetics of olanzapine and samidorphan given as a combination tablet. CPT Pharmacometrics Syst Pharmacol. 2021 Sep; 10(9): 1071–1080.

003. Unbound PK parameters were calculated using the observed average fu for each group and predicted total PK parameters.

Table 60 Fraction absorbed, CYP3A4 abundance and additional HLM Clint values in HV and HI patients in the final model

Population	fa[a]	CYP3A4 Abundance[b] (pmol/mg protein)	Additional HLM Clint[c] (μL/min/mg)
HV	1	137	141.6
Mild HI	0.72	107	125
Moderate HI	0.50	70	95
Severe HI	0.37	43	56

Sources: a: reviewer's analysis; b: PBPK report MRT-3-C, Table 1; c: Applicant's response to FDA's information request dated July 29, 2022.

Results

Model validation

The refined adagrasib model was able to capture the observed adagrasib PK profiles in patients with mild, moderate and several HI and the matched healthy subjects following a single dose administration of 600 mg adagrasib (Figure 31). A comparison of predicted and observed total and unbound Cmax and AUCinf values and ratios for adagrasib in patients with mild, moderate and severe HI and healthy matched subjects following a single oral dose of 600 mg are shown in **Table 61** and Table 62. All absolute values and the change relative to healthy matched subjects were predicted with a high degree of accuracy (all within 1.25-fold of the observed data, the majority within 1.1-fold).

Figure 31 Observed (dots) and simulated (lines) adagrasib plasma concentration-time profiles (geometric mean) in HI patients and healthy matched subjects following a single dose administration of 600 mg adagrasib

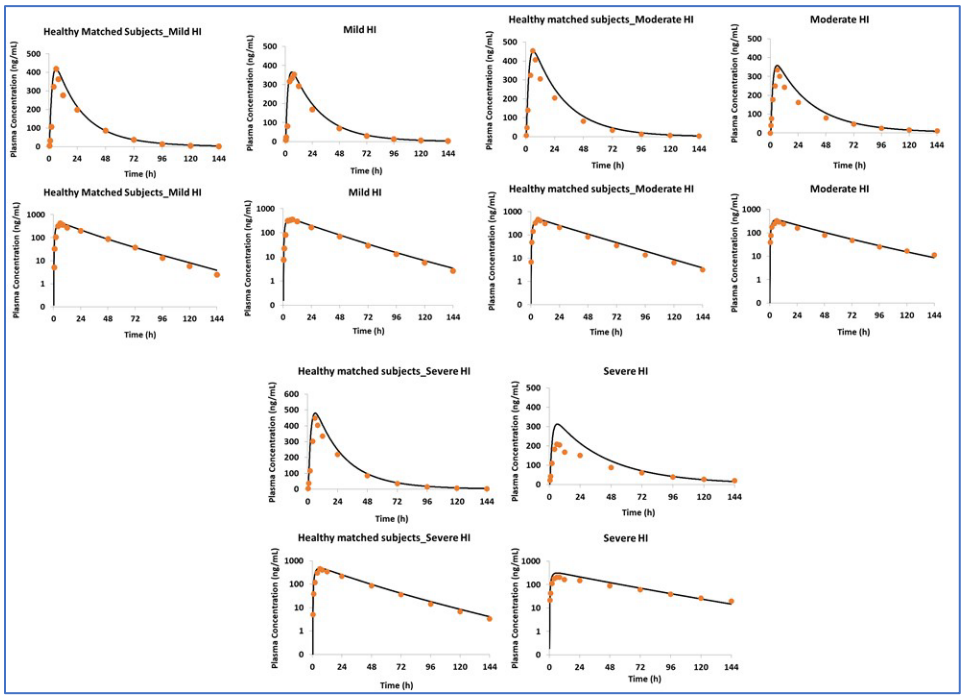


Table 61 Observed and simulated adagrasib geometric mean Cmax and AUC values in hepatic impaired (HI) patients and healthy matched subjects following a single dose administration of 600 mg adagrasib

Population	Total concentrations					
	Simulated		Observed		Sim / Obs	
	Cmax (ng/mL)	AUCinf (ng*h/mL)	Cmax (ng/mL)	AUCinf (ng*h/mL)	Cmax	AUCinf
Mild HI	303	9154	394	9332	0.77	0.98
HV Cohort Mild HI	374	10292	389	10690	0.96	0.96
Moderate HI	323	11759	315	10370	1.02	1.13
HV Cohort Moderate-HI	423	13266	453	11820	0.93	1.12
Severe HI	262	11823	220	11980	1.19	0.99
HV Cohort Severe-HI	430	12242	443	12210	0.97	1.00

Sources: Simulated data were from FDA reviewer's simulations. Observed data were from Study 849-003

Table 62 Observed and simulated adagrasib total and unbound Cmax and AUC ratios in HI patients relative to the healthy matched subjects following a single dose administration of 600 mg adagrasib

Population	Total						Unbound					
	Simulated		Observed		Sim / Obs		Simulated		Observed		Sim / Obs	
	C_{maxR}	AUCR	C_{maxR}	AUCR	C_{maxR}	AUCR	C_{maxR}	AUCR	C_{maxR}	AUCR	C_{maxR}	AUCR
Mild HI	0.81	0.89	1.01	0.87	0.80	1.02	0.94	1.03	1.17	1.01	0.80	1.02
Moderate HI	0.76	0.89	0.70	0.88	1.09	1.01	0.90	1.04	0.82	1.03	1.10	1.01
Severe HI	0.60	0.97	0.50	0.98	1.22	0.98	1.03	1.63	0.84	1.66	1.22	0.98

Sources: Simulated data were from FDA reviewer's simulations. Observed data were from Study 849-003

Model application

The model was used to predict the PK of adagrasib in HI patients and the matched healthy subjects following multiple dose administration of adagrasib (600 mg BID). As shown in Table 61, the total and unbound AUC ratios of adagrasib following 600 mg BID dosing of adagraisb in mild, moderate and severe HI patients versus matched healthy subjects were 0.75, 0.67 and 0.65 and 0.86, 0.78 and 1.10, respectively.

Table 63 Simulated total and unbound steady-state adagrasib Cmax and AUC ratios in HI patients relative to the healthy matched subjects following multiple dose administration of adagrasib (600 mg BID) for 15 days.

Population	Total Concentrations		Unbound Concentration	
	C_{maxR}	AUCR	C_{maxR}	AUCR
Mild HI	0.74	0.75	0.86	0.86
Moderate HI	0.66	0.67	0.78	0.78
Severe HI	0.63	0.65	1.06	1.10

Source: FDA reviewer's simulations

Sensitivity analyses

Uncertainties associated with the metabolic enzyme expression levels and adagrasib mediated enzyme inhibition effects in patients with hepatic impairment were evaluated using sensitivity

analyses. The worst-case scenario-based simulations aided on better understanding of the effects of key input parameters on the adagrasib steady-state PK in patients with HI.

1. fmCYP2C8 values

(b) (4)

Due to the uncertainty regarding the in vitro to in vivo extrapolation of fmCYP2C8 value for adagrasib at steady-state, the reviewer conducted a sensitivity analysis of a potential range of fmCYP2C8 values to assess the potential effects on the exposure change of adagrasib in HI patients versus healthy matched subjects. Note that the additional HLM CLint values were also adjusted correspondingly when fmCYP2C8 values were changed to match the observed PK profiles following a single dose administration of 600 mg adagrasib in HI patients (Table 62). The model validation results were presented in Table 63. Then the model was used to simulate the adagrasib PK in HI patients following multiple dose administration of adagrasib (600 mg BID). The predicted unbound AUC ratios ranged from 0.74 to 1.19 in mild, moderate and severe HI patients, respectively (Table 64).

Table 64 Additional HLM Clint values in HV and HI patients assuming CYP2C8 accounts for 20%, 46% or 80% of non-CYP3A4 mediated metabolism

Population	HI/HV	HLM CLint (µL/min/mg)		
		fmCYP2C8 = 20%	fmCYP2C8 =46%	fmCYP2C8 =80%
HV	1.00	209.8	141.6	52.5
Mild HI	0.88	184	125	46
Moderate HI	0.67	140	95	35
Severe HI	0.40	83	56	21

Source: Applicant's response to FDA's information request dated July 29, 2022,

Table 65 Observed and simulated Cmax and AUC ratios in HI patients relative to healthy matched subjects following a single dose administration of 600 mg adagrasib assuming CYP2C8 accounts for 20% or 80% of non-CYP3A4 mediated metabolism

Model Validation Adagrasib 600 mg SD	Observed			Simulated fmCYP2C8=20%			Simulated fmCYP2C8=80%		
	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
C_{maxR}	1.01	0.70	0.50	0.82	0.72	0.55	0.81	0.79	0.69
AUCR	0.87	0.88	0.98	0.88	0.88	0.97	0.88	0.87	0.97
Sim / Obs C_{maxR}				0.81	1.04	1.11	0.80	1.13	1.39
Sim / Obs AUCR				1.01	1.00	0.99	1.01	0.99	0.99

Source: FDA reviewer's simulations

Table 66 Simulated total and unbound steady-state adagrasib Cmax and AUC ratios in HI patients relative to the healthy matched subjects following multiple dose administration of adagrasib (600 mg BID) for 15 days, assuming CYP2C8 accounts for 20% or 80% of non-CYP3A4 mediated metabolism

Model Application Adagrasib 600 mg BID	Total		Unbound	
	C_{maxR}	AUCR	C_{maxR}	AUCR
fmCYP2C8=20%				
Mild HI	0.76	0.76	0.88	0.88
Moderate HI	0.68	0.69	0.80	0.81
Severe HI	0.67	0.70	1.14	1.19
fmCYP2C8=80%				
Mild HI	0.73	0.74	0.85	0.85
Moderate HI	0.63	0.63	0.74	0.74
Severe H	0.53	0.61	0.90	1.03

Source: FDA reviewer's simulations

2. Hepatic CYP3A4 abundance in patients with HI

The reviewer conducted a sensitivity analysis of hepatic CYP3A4 abundance to explore the potential effects on the exposure change of adagrasib in HI patients versus matched healthy volunteers (HV). As shown in Table 65, the hepatic CYP3A4 abundance in HV (137 pmol/mg protein) and patients with moderate HI (70 pmol/mg protein) were selected to evaluate the effects of CYP3A4 abundance on the exposure change of adagrasib in patients with mild HI. Accordingly, the hepatic CYP3A4 abundance in patients with mild HI (107 pmol/mg protein) and patients with severe HI (43 pmol/mg protein) were selected to evaluate the effects of CYP3A4 abundance on the exposure change of adagrasib in patients with moderate HI. The hepatic CYP3A4 abundance in patients with moderate HI (70 pmol/mg protein) was selected to evaluate the effects of CYP3A4 abundance on the exposure change of adagrasib in patients with severe HI. The hepatic CYP3A4 abundance was also reduced to 0 in patients with severe HI to explore the potential effects. Note that the fa values were also further adjusted correspondingly to match the observed PK profiles following a single dose administration of 600 mg adagrasib. The additional HLM CLint values remained unchanged in each class of HI patient. The model validation results were presented in Table 65. Then, the model was used to simulate the adagrasib PK in HI patients following multiple dose administration of adagrasib (600 mg BID). The predicted

unbound AUC ratios ranged from 0.71 to 1.22 in mild, moderate and severe HI patients (Table 66).

Table 67 Sensitivity analysis of hepatic CYP3A4 abundance. Observed and simulated Cmax and AUC ratios in HI patients relative to healthy matched subjects following a single dose administration of 600 mg adagrasib

Model Validation Adagrasib 600 mg SD	CYP3A4 Abundance (pmol/mg protein)	fa	HLM CLint (µL/min/mg)	Observed		Simulated		Sim / Obs	
				C_{maxR}	AUCR	C_{maxR}	AUCR	C_{maxR}	AUCR
Mild HI	137	0.8	125	1.01	0.87	0.84	0.89	0.83	1.01
	70	0.615				0.76	0.89	0.75	1.02
Moderate HI	107	0.57	95	0.70	0.88	0.81	0.88	1.16	1.00
	43	0.44				0.72	0.88	1.03	1.01
Severe HI	70	0.42	56	0.50	0.98	0.66	0.98	1.32	1.00
	0	0.29				0.55	0.98	1.10	1.00

Source: FDA reviewer's simulations

Table 68 Sensitivity analysis of hepatic CYP3A4 abundance. Simulated total and unbound steady-state adagrasib Cmax and AUC ratios in HI patients relative to the healthy matched subjects following multiple dose administration of adagrasib (600 mg BID) for 15 days.

Model Application 600 mg BID	CYP3A4 Abundance (pmol/mg protein)	Total		Unbound	
		C_{maxR}	AUCR	C_{maxR}	AUCR
Mild HI	137	0.81	0.82	0.94	0.95
	70	0.65	0.66	0.75	0.76
Moderate HI	107	0.73	0.74	0.86	0.87
	43	0.59	0.60	0.70	0.71
Severe HI	70	0.70	0.72	1.18	1.22
	0	0.52	0.54	0.88	0.91

Source: FDA reviewer's simulations

3. Additional HLM CLint values

The reviewer conducted a sensitivity analysis of additional HLM CLint values to explore the potential effects on the exposure change of adagrasib in HI patients versus matched healthy subjects. Note that the fa values were also adjusted correspondingly when HLM CLint values were changed to match the observed PK profiles following a single dose administration of 600

mg adagrasib. The model validation results were presented in Table 67. Then, the model was used to simulate the adagrasib PK in HI patients following multiple dose administration of adagrasib (600 mg BID). The predicted unbound AUC ratios ranged from 0.74 to 1.18 in mild, moderate and severe HI patients (Table 68).

Table 69 Sensitivity analysis of additional HLM CLint values. Observed and simulated Cmax and AUC ratios in HI patients relative to healthy matched subjects following a single dose administration of 600 mg adagrasib.

Model Validation Adagrasib 600 mg SD	CYP3A4 Abundance (pmol/mg protein)	fa	HLM CL_{int} (µL/min/mg)	Observed		Simulated		Sim / Obs	
				C_{maxR}	AUCR	C_{maxR}	AUCR	C_{maxR}	AUCR
Mild HI	107	0.74	141.6	1.01	0.87	0.83	0.89	0.82	1.01
		0.67	95			0.76	0.87	0.75	1.00
Moderate HI	70	0.53	125	0.70	0.88	0.80	0.88	1.15	1.00
		0.45	56			0.70	0.88	1.00	1.00
Severe HI	43	0.42	95	0.50	0.98	0.68	0.98	1.37	1.00
		0.345	30			0.57	0.98	1.05	1.00

Source: FDA reviewer's simulations

Table 70 Sensitivity analysis of additional HLM CLint values. Simulated total and unbound steady-state adagrasib Cmax and AUC ratios in HI patients relative to the healthy matched subjects following multiple dose administration of adagrasib (600 mg BID) for 15 days.

Model Application Adagrasib 600 mg BID	HLM CL_{int} (µL/min/mg)	Total		Unbound	
		C_{maxR}	AUCR	C_{maxR}	AUCR
Mild HI	141.6	0.72	0.73	0.84	0.84
	95	0.77	0.79	0.90	0.91
Moderate HI	125	0.63	0.63	0.74	0.74
	56	0.70	0.71	0.82	0.84
Severe HI	95	0.60	0.62	1.03	1.05
	30	0.67	0.70	1.13	1.18

Source: FDA reviewer's simulations

4. Adagrasib mediated CYP 3A4 TDI effect

The magnitude of adagrasib mediated CYP3A4 TDI effect might be changed in patients with HI. The reviewer conducted a sensitivity analysis of Kinact values (TDI parameter: maximal rate of

CYP3A4 inactivation) to explore the potential effects on the exposure change of adagrasib in HI patients versus matched healthy subjects. It was assumed that the fraction absorbed in patients with mild and moderate HI remained unchanged. The Kinact value was reduced to match the observed single dose PK of adagrasib in patients with mild and moderate HI. In patients with severe HI, the adagrasib mediated CYP3A4 TDI effect was deactivated in the model, and the fraction absorbed was reduced to 0.77 to match the observed single dose PK of adagrasib in patients with severe HI. The model validation results were presented in Table 69. Then, the model was used to simulate the adagrasib PK in HI patients following multiple dose administration of adagrasib (600 mg BID). The predicted unbound AUC ratios ranged from 0.82 to 1.07 in mild, moderate and severe HI patients (Table 70).

Table 71 Sensitivity analysis of adagrasib mediated CYP3A4 TDI effect. Observed and simulated Cmax and AUC ratios in HI patients relative to healthy matched subjects following a single dose administration of 600 mg adagrasib.

Model Validation Adagrasib 600 mg SD	CYP3A4 Abundance (pmol/mg protein)	fa	HLM CLint (µL/min/mg)	Kinac (1/h)	Observed		Simulated		Sim / Obs	
					CmaxR	AUCR	CmaxR	AUCR	CmaxR	AUCR
Mild HI	107	1.00	125	1.00	1.01	0.87	0.93	0.89	0.92	1.02
Moderate HI	70	1.00	95	0.18	0.70	0.88	1.20	0.87	1.72	0.99
Severe HI	43	0.77	56	0.00	0.50	0.98	1.11	0.99	2.23	1.00

Source: FDA reviewer's simulations

Table 72 Sensitivity analysis of adagrasib mediated CYP3A4 TDI effect. Simulated total and unbound steady-state adagrasib Cmax and AUC ratios in HI patients relative to the healthy matched subjects following multiple dose administration of adagrasib (600 mg BID) for 15 days.

Model Application Adagrasib 600 mg BID	Kinac (1/h)	Total		Unbound	
		CmaxR	AUCR	CmaxR	AUCR
Mild HI	1.00	0.92	0.92	1.06	1.07
Moderate HI	0.18	0.89	0.87	1.04	1.02
Severe HI	0.00	0.51	0.49	0.86	0.82

Source: FDA reviewer's simulations

In conclusion, the PBPK modeling and simulation along with the sensitivity analyses indicated that there is minor difference in predicted unbound exposure changes of adagrasib in HI patients versus matched healthy subjects following multiple dose administration of adagrasib (600 mg BID). The predicted unbound AUC ratios ranged from 0.71 to 1.22 in mild, moderate and severe HI patients.

19.5. **Additional Safety Analyses Conducted by FDA**

None.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Clinical Reviewer	Katie Chon, Pharm. D.	CDER/OOD/DO2	Sections: 1,2,3,4,6,7,8,9,10, 19	**Select one:** X Authored ___ Approved
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	Signature: See Cross-Disciplinary Team Lead			
Statistical Reviewer	Chi Song, Ph.D.	CDER/OTS/DBV	Sections: 8.1, 8.3	**Select one:** X Authored ___ Approved
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Division Director	Shenghui Tang, Ph.D.	CDER/OTS/DBV	Sections: 8.1, 8.3	**Select one:** ___ Authored _X__ Approved

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Clinical Division Director (Signatory)	Harpreet Singh, M.D.		Sections: All	**Select one:** ___ Authored _x__Approved
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