CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

216340Orig1s005

Trade Name:	KRAZATI tablet
Generic or Proper Name:	Adagrasib
Sponsor:	Mirati Therapeutics, Inc.
Approval Date:	June 21, 2024
Indication:	KRAZATI is indicated for: • Colorectal cancer (CRC) o In combination with cetuximab, for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic CRC, as determined by an FDA-approved test, who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

NDA 216340/S-005

ACCELERATED APPROVAL

Mirati Therapeutics, Inc.
Attention: Rosa Ferrao
Executive Director, Regulatory Affairs
3545 Cray Court
San Diego, CA 92121

Dear Rosa Ferrao:

Please refer to your December 21, 2023, supplemental new drug application (sNDA), and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Krazati (adagrasib) tablet.

This "Prior Approval" sNDA provides for the new indication of Krazati (adagrasib) in combination with cetuximab for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under accelerated approval pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and 21 CFR 314.510, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the accelerated approval statutory provisions and regulations.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling text for the Prescribing Information and Patient Package Insert, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also, within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

ACCELERATED APPROVAL REQUIREMENTS

Pursuant to section 506(c) of the FDCA and 21 CFR 314.510 you are required to conduct further adequate and well-controlled clinical trials intended to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If required postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated June 11, 2024. This requirement is listed below.

4650-1 Complete clinical trial, Study 849-010, "A Randomized Phase 3 Study of adagrasib 600 mg twice daily in combination with cetuximab versus chemotherapy in patients with advanced colorectal cancer with *KRAS* G12C mutation with disease progression on or after first-line therapy."

The timetable you submitted on June 11, 2024, states that you will conduct this trial according to the following schedule:

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Trial Completion:	03/2027
Final Report Submission:	09/2027

Submit clinical protocols to your IND 138735 for this product. FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.

You must submit reports of the progress of each clinical trial required under section 506(c) (listed above) to this NDA approximately every 180 days (see section 506B(a)(2) of the FDCA) (hereinafter "180-day reports").

You are required to submit two 180-day reports per year for each open study or clinical trial required under section 506(c). One report will be a standalone submission and the other report will be combined with your application's annual status report (ASR) required under section 506B(a)(1) of the FDCA and 21 CFR 314.81(b)(2). The standalone 180-day report will be due 180 days after the date of approval of the original NDA (with a 60-day grace period). Submit the other 180-day report with your application's ASR. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted.[3] Depending on the date of approval of the original application, you may be required to submit a 180-day report shortly after receipt of this letter.

Your 180-day reports must include the information listed in 21 CFR 314.81(b)(2)(vii)(a). FDA recommends that you use FORM FDA 3989, *PMR/PMC Annual Status Report for Drugs and Biologics,* to submit your 180-day reports.[4]

180-day reports must be clearly designated "**NDA 216340/S-005 180-Day AA PMR Progress Report**."

FDA will consider the submission of your application's ASR under section 506B(a)(1) and 21 CFR 314.81(b)(2), in addition to the submission of reports 180 days after the date of approval of the original NDA each year (subject to a 60-day grace period), to satisfy the periodic reporting requirement under section 506B(a)(2).

Submit final reports to this NDA as a supplemental application. For administrative purposes, the cover page of all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

[3] You are required to submit information related to your confirmatory trial as part of your annual reporting requirement under section 506B(a)(1) until the FDA notifies you, in writing, that the Agency concurs that the study requirement has been fulfilled or that the study either is no longer feasible or would no longer provide useful information.
[4] FORM FDA 3989, along with instructions for completing this form, is available on the FDA Forms web page at https://www.fda.gov/about-fda/reports-manuals-forms/forms.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. Colorectal cancer is an adult-related condition that rarely occurs in pediatric patients.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Rebecca Cohen, Regulatory Health Project Manager, at (240) 402-4998.

Sincerely,

{See appended electronic signature page}

Chana Weinstock, M.D.
Deputy Division Director (acting)
Division of Oncology 3
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

REBECCA L COHEN
06/21/2024 12:26:50 PM

CHANA WEINSTOCK
06/21/2024 12:31:03 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216340Orig1s005

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KRAZATI safely and effectively. See full prescribing information for KRAZATI.

KRAZATI® (adagrasib) tablets, for oral use
Initial U.S. Approval: 2022

RECENT MAJOR CHANGES

• Indications and Usage (1.1, 1.2)	06/2024
• Dosage and Administration (2.1, 2.2, 2.3)	06/2024
• Warnings and Precautions (5.1, 5.2, 5.3, 5.4)	06/2024

INDICATIONS AND USAGE

KRAZATI is an inhibitor of the RAS GTPase family indicated for:

Non-small cell lung cancer (NSCLC)*

- As a single agent, for the treatment of adult patients with *KRAS* G12C-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least one prior systemic therapy. (1.1)

Colorectal cancer (CRC)*

- In combination with cetuximab, for the treatment of adult patients with *KRAS* G12C-mutated locally advanced or metastatic CRC, as determined by an FDA-approved test, who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. (1.2)

*These indications are approved under accelerated approval based on objective response rate (ORR) and duration of response (DOR). Continued approval for these indications may be contingent upon verification and description of a clinical benefit in confirmatory trials. (1.1, 1.2)

DOSAGE AND ADMINISTRATION

- Recommended dosage as a single agent for NSCLC and in combination with cetuximab for CRC: 600 mg orally twice daily. (2.2)
- Swallow tablets whole with or without food. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 200 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Gastrointestinal Adverse Reactions: Monitor patients for diarrhea, nausea and vomiting and provide supportive care as needed. Withhold, reduce the dose or permanently discontinue based on severity. (2.3, 5.1)
- QTc Interval Prolongation: Avoid concomitant use of KRAZATI with other products with a known potential to prolong the QTc interval. Monitor ECG and electrolytes particularly potassium and magnesium, in patients at risk, and in patients taking medications known to prolong the QT interval. Correct electrolyte abnormalities. Withhold, reduce the dose, or permanently discontinue based on severity. (2.3, 5.2)
- Hepatotoxicity: Monitor liver laboratory tests prior to the start of KRAZATI and monthly for 3 months after and as clinically indicated. Reduce the dose, withhold, or permanently discontinue based on severity. (2.3, 5.3)
- Interstitial Lung Disease (ILD) / Pneumonitis: Monitor for new or worsening respiratory symptoms. Withhold KRAZATI for suspected ILD/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis are identified. (2.3, 5.4)

ADVERSE REACTIONS

- Single agent use in NCSLC: The most common adverse reactions (≥ 25%) were nausea, diarrhea, vomiting, fatigue, musculoskeletal pain, hepatotoxicity, renal impairment, edema, dyspnea, and decreased appetite. The most common (≥ 2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, decreased hemoglobin, increased alanine aminotransferase, increased aspartate aminotransferase, hypokalemia, hyponatremia, increased lipase, decreased leukocytes, decreased neutrophils and increased alkaline phosphatase. (6.1)
- In combination with cetuximab in CRC: The most common adverse reactions (≥ 25%) were rash, nausea, diarrhea, vomiting, fatigue, musculoskeletal pain, hepatotoxicity, headache, dry skin, abdominal pain, decreased appetite, edema, anemia, and cough. The most common (≥ 2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, decreased potassium, decreased magnesium, decreased hemoglobin, increased aspartate aminotransferase, increased lipase, decreased albumin, and increased alanine aminotransferase. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mirati Therapeutics, Inc. at 1-844-MIRATI-1 (1-844-647-2841) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

See full prescribing information for clinically significant drug interactions with KRAZATI. (7)

- Strong CYP3A4 Inducers: Avoid concomitant use. (7.1)
- Strong CYP3A4 Inhibitors: Avoid concomitant use until adagrasib concentrations have reached steady state. (7.1)
- Sensitive CYP3A4 Substrates: Avoid concomitant use with sensitive CYP3A4 substrates. (7.2)
- Sensitive CYP2C9 or CYP2D6 Substrates or P-gp Substrates: Avoid concomitant use with sensitive CYP2C9 or CYP2D6 substrates or P-gp substrates where minimal concentration changes may lead to serious adverse reactions. (7.2)
- Drugs That Prolong QT Interval: Avoid concomitant use with KRAZATI. (7.3)

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1. *KRAS* G12C-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer

KRAZATI, as a single-agent, 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 *[see Dosage and Administration (2.1)]*, who have received at least one prior systemic therapy.

This indication is approved under accelerated approval based on objective response rate (ORR) and duration of response (DOR) *[see Clinical Studies (14.1)]*. Continued approval for this indication may be contingent upon verification and description of a clinical benefit in a confirmatory trial.

1.2. *KRAS* G12C-Mutated Locally Advanced or Metastatic Colorectal Cancer

KRAZATI in combination with cetuximab is indicated for the treatment of adult patients with *KRAS* G12C-mutated locally advanced or metastatic colorectal cancer (CRC), as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*, who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

This indication is approved under accelerated approval based on ORR and DOR *[see Clinical Studies (14.2)]*. Continued approval for this indication may be contingent upon verification and description of a clinical benefit in a confirmatory trial.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Non-Small Cell Lung Cancer

Select patients for treatment of locally advanced or metastatic NSCLC with KRAZATI based on the presence of *KRAS* G12C mutation in plasma or tumor specimens *[see Clinical Studies (14.1)]*. If no mutation is detected in a plasma specimen, test tumor tissue.

Colorectal Cancer

Select patients for treatment of locally advanced or metastatic CRC with KRAZATI based on the presence of *KRAS* G12C mutation in tumor specimens *[see Clinical Studies (14.2)]*.

Information on FDA-approved tests for the detection of a *KRAS* G12C mutation is available at: https://www.fda.gov/CompanionDiagnostics

2.2 Recommended Dosage

The recommended dosage of KRAZATI as a single agent or in combination with cetuximab is 600 mg orally twice daily until disease progression or unacceptable toxicity.

Refer to the cetuximab prescribing information for cetuximab dosage information *[see Clinical Studies (14.2)]*.

Take KRAZATI at the same time every day with or without food *[see Clinical Pharmacology (12.3)]*. Swallow tablets whole. Do not chew, crush or split tablets.

If vomiting occurs after taking KRAZATI, do not take an additional dose. Resume dosing at the next scheduled time.

If a dose is inadvertently missed, it should be skipped if greater than 4 hours have elapsed from the expected dosing time. Resume dosing at the next scheduled time.

2.3 Dosage Modifications for Adverse Reactions

Recommended dose reductions for adverse reactions for use of KRAZATI as a single agent or in combination with cetuximab are outlined in Table 1. If adverse reactions occur, a maximum of two dose reductions are permitted. Permanently discontinue KRAZATI in patients who are unable to tolerate 600 mg once daily.

Table 1: Recommended KRAZATI Dosage Reductions for Adverse Reactions

Dose Reduction	Dosage
First dose reduction	400 mg twice daily
Second dose reduction	600 mg once daily

Refer to the cetuximab prescribing information for dose modifications for adverse reactions associated with cetuximab.

When KRAZATI is administered in combination with cetuximab, withhold or permanently discontinue cetuximab when KRAZATI is withheld or permanently discontinued.

Treatment with KRAZATI as a single agent may be continued if cetuximab is permanently discontinued. *[see Clinical Pharmacology (12.1), Clinical Studies (14.2)]*.

The recommended dosage modifications for adverse reactions are provided in Table 2.

Table 2: Recommended KRAZATI Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modification†
Nausea or vomiting despite appropriate supportive care (including anti-emetic therapy) *[see Warnings and Precautions (5.1)]*	Grade 3 or 4	• Withhold KRAZATI until recovery to ≤ Grade 1 or return to baseline. • Resume KRAZATI at the next lower dose level.
Diarrhea despite appropriate supportive care (including anti-diarrheal therapy) *[see Warnings and Precautions (5.1)]*	Grade 3 or 4	• Withhold KRAZATI until recovery to ≤ Grade 1 or return to baseline. • Resume KRAZATI at the next lower dose level.
QTc Interval Prolongation *[see Warnings and Precautions (5.2)]*	QTc absolute value greater than 500 ms or Greater than an increase of 60 ms from baseline	• Withhold KRAZATI until QTc interval less than 481 ms or return to baseline. • Resume KRAZATI at the next lower dose level.
	Torsade de pointes, polymorphic ventricular tachycardia or signs or symptoms of serious or life-threatening arrhythmia	• Permanently discontinue KRAZATI
Hepatotoxicity *[see Warnings and Precautions (5.3)]*	Grade 2 AST or ALT	• Decrease KRAZATI to the next lower dose level.
	Grade 3 or 4 AST or ALT	• Withhold KRAZATI until recovery to ≤ Grade 1 or return to baseline. • Resume KRAZATI at the next lower dose level.
	AST or ALT > 3 × ULN with total bilirubin > 2 × ULN in the absence of alternative causes	• Permanently discontinue KRAZATI
Interstitial Lung Disease / Pneumonitis *[see Warnings and Precautions (5.4)]*	Any Grade	• Withhold KRAZATI if ILD/pneumonitis is suspected. • Permanently discontinue KRAZATI if ILD/pneumonitis is confirmed
Other Adverse Reactions *[see Adverse Reactions (6.1)]*	Grade 3 or 4	• Withhold KRAZATI until ≤ Grade 1 or return to baseline.

Adverse Reaction	Severity*	Dosage Modification†
		• Resume KRAZATI at the next lower dose level.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ILD = Interstitial Lung Disease; ULN = upper limit of normal

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

† When KRAZATI is administered in combination with cetuximab, withhold or permanently discontinue treatment with cetuximab when withholding or permanently discontinuing treatment with KRAZATI.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 200 mg, oval shaped, white to off-white, immediate release film coated tablets with "200" on one side and stylized "M" on the opposite side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Adverse Reactions

KRAZATI can cause severe gastrointestinal adverse reactions.

In the pooled safety population *[see Adverse Reactions (6.1)]*, who received single-agent KRAZATI, serious gastrointestinal adverse reactions observed were gastrointestinal bleeding in 3.8% including 0.8% Grade 3 or 4, gastrointestinal obstruction in 1.6% including 1.4% Grade 3 or 4, colitis in 0.5% including 0.3% Grade 3, ileus in 0.5%, and stenosis in 0.3%. In addition, nausea, diarrhea, or vomiting occurred in 89% of 366 patients, including 9% Grade 3. Nausea, diarrhea, or vomiting led to dosage interruption or dose reduction in 29% of patients and permanent discontinuation of adagrasib in 0.3%.

In patients who received KRAZATI in combination with cetuximab *[see Adverse Reactions (6.1)]*, serious gastrointestinal adverse reactions included gastrointestinal bleeding in 8.5% including 1.1% Grade 3 or 4, gastrointestinal obstruction in 5.3% including 5.3% Grade 3 or 4, colitis in 1.1% including 1.1% Grade 3 and ileus in 1.1%. In addition, nausea, diarrhea, or vomiting occurred in 92% of 94 patients, including 6% Grade 3. Nausea, diarrhea, or vomiting led to adagrasib dose interruption or dose reduction in 23% of patients.

Monitor and manage patients using supportive care, including antidiarrheals, antiemetics, or fluid replacement, as indicated. Withhold, reduce the dose, or permanently discontinue KRAZATI based on severity *[see Dosage and Administration (2.3)]*.

5.2 QTc Interval Prolongation

KRAZATI can cause QTc interval prolongation, which can increase the risk for ventricular tachyarrhythmias (e.g., torsades de pointes) or sudden death.

In the pooled safety population *[see Adverse Reactions (6.1)]* who received single-agent KRAZATI, 6% of 366 patients with at least one post-baseline electrocardiogram (ECG) assessment had an average QTc ≥ 501 msec and 11% of patients had an increase from baseline of QTc > 60 msec. KRAZATI causes concentration-dependent increases in the QTc interval *[see Clinical Pharmacology (12.2)]*.

In patients who received KRAZATI in combination with cetuximab *[see Adverse Reactions (6.1)]*, 5% of 93 patients with at least one post-baseline electrocardiogram (ECG) assessment had an average QTc ≥ 501 msec and 16% of patients had an increase from baseline of QTc > 60 msec.

Avoid concomitant use of KRAZATI with other products with a known potential to prolong the QTc interval *[see Drug Interactions (7.3) and Clinical Pharmacology (12.2)]*. Avoid use of KRAZATI in patients with congenital long QT syndrome and in patients with concurrent QTc prolongation.

Monitor ECGs and electrolytes, particularly potassium and magnesium, prior to starting KRAZATI, during concomitant use, and as clinically indicated in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, and in patients who are unable to avoid concomitant medications that are known to prolong the QT interval. Correct electrolyte abnormalities. Withhold, reduce the dose, or permanently discontinue KRAZATI depending on severity *[see Dosage and Administration (2.3)]*.

5.3 Hepatotoxicity

KRAZATI can cause hepatotoxicity, which may lead to drug-induced liver injury and hepatitis.

In the pooled safety population of 366 patients *[see Adverse Reactions (6.1)]* who received single-agent KRAZATI, drug-induced 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. Hepatotoxicity leading to dose interruption or reduction occurred in 12% of patients. Adagrasib was discontinued due to hepatotoxicity in 0.5% of patients.

In patients who received KRAZATI in combination with cetuximab *[see Adverse Reactions (6.1)]*, 29% had increased alanine aminotransferase (ALT)/increased aspartate aminotransferase (AST); 5% were Grade 3 and 1.1% were Grade 4. The median time to first onset of increased

ALT/AST was 4 weeks (range: 0.1 to 27). Overall hepatotoxicity occurred in 38%, and 10% were Grade 3 or 4. Hepatotoxicity leading to adagrasib dose interruption or reduction occurred in 12% of patients.

Monitor liver laboratory tests (AST, ALT, alkaline phosphatase and total bilirubin) prior to the start of KRAZATI and monthly for 3 months or as clinically indicated, with more frequent testing in patients who develop transaminase elevations. Reduce the dose, withhold, or permanently discontinue KRAZATI based on severity *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)]*.

5.4 Interstitial Lung Disease / Pneumonitis

KRAZATI can cause interstitial lung disease (ILD)/pneumonitis, which can be fatal.

In the pooled safety population *[see Adverse Reactions (6.1)]* who received single-agent KRAZATI, ILD/pneumonitis occurred in 4.1% of patients, 1.4% were Grade 3 or 4, and one case was fatal. The median time to first onset for ILD/pneumonitis was 12 weeks (range: 5 to 31 weeks). Adagrasib was discontinued due to ILD/pneumonitis in 0.8% of patients.

In patients who received KRAZATI in combination with cetuximab *[see Adverse Reactions (6.1)]*, Grade 1 ILD/pneumonitis occurred in 1.1% of patients. The time to first onset for ILD/pneumonitis was 38 weeks.

Monitor patients for new or worsening respiratory symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever) during treatment with KRAZATI. Withhold KRAZATI in patients with suspected ILD/pneumonitis and permanently discontinue KRAZATI if no other potential causes of ILD/pneumonitis are identified *[see Dosage and Administration (2.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.1)]*
- QTc Interval Prolongation *[see Warnings and Precautions (5.2)]*
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*
- Interstitial Lung Disease (ILD)/Pneumonitis *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to adagrasib as a single agent at 600 mg orally twice daily in 366 patients with NSCLC and other solid tumors enrolled in KRYSTAL-1 and KRYSTAL-12 (NCT04685135), respectively. Among 366 patients who received adagrasib, 39% of patients were exposed for 6 months or longer and 12% were exposed for greater than one year. In this pooled safety population, the most common (≥ 25%) adverse reactions were nausea (70%), diarrhea (69%), vomiting (57%), fatigue (55%), musculoskeletal pain (38%), hepatotoxicity (37%), renal impairment (33%), edema (30%), dyspnea (26%), and decreased appetite (29%). In this pooled safety population, the most common Grade 3 or 4 (≥ 2%) laboratory abnormalities were decreased lymphocytes (20%), decreased hemoglobin (7%), increased alanine aminotransferase (4.5%), increased aspartate aminotransferase (4.2%), hypokalemia (3.6%), hyponatremia (3.4%), increased lipase (2.5%), decreased leukocytes (2.5%), decreased neutrophils (2.3%), and increased alkaline phosphatase (2.0%).

The data described in WARNINGS AND PRECAUTIONS and below also reflects exposure to adagrasib in combination with cetuximab in 94 patients with *KRAS* G12C-mutated, locally advanced or metastatic CRC in KRYSTAL-1.

Non-Small Cell Lung Cancer

The safety of adagrasib was evaluated in patients with *KRAS* G12C-mutated, locally advanced or metastatic NSCLC in KRYSTAL-1 *[see Clinical Studies (14.1)]*. Patients received adagrasib 600 mg orally twice daily (n = 116). Among patients who received adagrasib, 45% were exposed for 6 months or longer and 4% were exposed for greater than one year.

The median age of patients who received adagrasib was 64 years (range 25 to 89), 56% female, 84% White, 8% Black or African American, and 4.3% Asian.

Serious adverse reactions occurred in 57% of patients who received adagrasib. Serious adverse reactions in ≥ 2% of patients were pneumonia (17%), dyspnea (9%), renal impairment (8%), sepsis (5%), hypoxia (4.3%), pleural effusion (4.3%), respiratory failure (4.3%), anemia (3.4%), cardiac failure (3.4%), hyponatremia (3.4%), hypotension (3.4%), muscular weakness (3.4%), pyrexia (3.4%), dehydration (2.6%), diarrhea (2.6%), mental status changes (2.6%), pulmonary embolism (2.6%), and pulmonary hemorrhage (2.6%). 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 discontinuation of adagrasib due to an adverse reaction occurred in 13% of patients. Adverse reactions which resulted in permanent discontinuation of adagrasib 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.

Dose interruptions of adagrasib due to an adverse reaction occurred in 77% of patients. Adverse reactions requiring dosage interruption in ≥ 2% of patients who received adagrasib included nausea, hepatotoxicity, fatigue, vomiting, pneumonia, renal impairment, diarrhea, QTc interval

prolongation, anemia, dyspnea, increased lipase, decreased appetite, dizziness, hyponatremia, muscular weakness, increased amylase, pneumonitis, sepsis and decreased weight.

Dose reductions of adagrasib due to an adverse reaction occurred in 28% of patients. Adverse reactions which required dose reductions in ≥ 2% of patients who received adagrasib included hepatotoxicity, fatigue, nausea, diarrhea, vomiting, and renal impairment.

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. The most common laboratory abnormalities (≥ 25%) were decreased lymphocytes, increased aspartate aminotransferase, decreased sodium, decreased hemoglobin, increased creatinine, decreased albumin, increased alanine aminotransferase, increased lipase, decreased platelets, decreased magnesium, and decreased potassium.

Table 3 summarizes the adverse reactions in KRYSTAL-1.

Table 3: Adverse Reactions (≥ 20%) in Patients with *KRAS* G12C-mutated NSCLC Who Received Adagrasib in KRYSTAL-1

Adverse Reaction	**Adagrasib 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
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[*]	41	7
Hepatobiliary Disorders		
Hepatotoxicity[*,†]	37	10
Renal and Urinary Disorders		
Renal impairment[*,‡]	36	6
Respiratory		

Adverse Reaction	Adagrasib N = 116	
	All Grades (%)	Grade 3 or 4 (%)
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.
† Hepatotoxicity includes mixed liver injury, blood alkaline phosphatase increased, alanine aminotransferase increased, aspartate aminotransferase increased, liver function test increased, blood bilirubin increased, and bilirubin conjugated increased.
‡ Renal impairment includes acute kidney injury and increased blood creatinine.

Table 4 summarizes the laboratory abnormalities in KRYSTAL-1.

Table 4: Select Laboratory Abnormalities Occurring (≥ 25%) That Worsened from Baseline in Patients with *KRAS* G12C-mutated NSCLC Who Received Adagrasib in KRYSTAL-1

Laboratory Abnormality	Adagrasib*	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Lymphocytes decreased	64	25
Hemoglobin decreased	51	8
Platelets decreased	27	0
Chemistry		
Aspartate aminotransferase increased	52	6
Sodium decreased	52	8
Creatinine increased	50	0

Laboratory Abnormality	Adagrasib*	
	All Grades (%)	Grade 3 or 4 (%)
Albumin decreased	50	0.9
Alanine aminotransferase increased	46	5
Lipase increased	35	1.8
Magnesium decreased	26	0
Potassium decreased	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.

Colorectal Cancer

The safety of adagrasib combined with cetuximab was evaluated in 94 patients with *KRAS* G12C-mutated, locally advanced or metastatic CRC in KRYSTAL-1 *[see Clinical Studies (14.2)]*. Patients started treatment with adagrasib 600 mg twice daily in combination with cetuximab weekly (n = 17) or every two weeks (n = 77). Among patients who received adagrasib in combination with cetuximab, 60% were exposed for greater than 6 months and 12% were exposed for greater than 12 months.

Serious adverse reactions occurred in 30% of patients who received adagrasib in combination with cetuximab. The most common serious adverse reactions (≥2%) were pneumonia (4.3%), pleural effusion, pyrexia, acute kidney injury, dehydration, and small intestinal obstruction (2.1% each).

A fatal adverse reaction of pneumonia occurred in 1 patient who received adagrasib in combination with cetuximab.

Adverse reactions leading to discontinuation of adagrasib occurred in 2 patients. Adverse reactions which resulted in permanent discontinuation of adagrasib (1 patient each) included abdominal pain and prolonged QT interval.

Adverse reactions leading to dose interruptions of adagrasib occurred in 62% of patients. The most common adverse reactions or laboratory abnormalities leading to dose interruption in ≥ 2% of patients who received adagrasib included diarrhea, nausea, vomiting, abdominal pain, dizziness, headache, pneumonia, alanine aminotransferase increased, aspartate aminotransferase increased, dyspnea, fatigue, pleural effusion, rash, anemia, electrocardiogram QT prolongation, blood bilirubin increased, blood creatinine increased, decreased appetite, dehydration, hemorrhage, hypomagnesemia, lipase increased, muscular weakness, musculoskeletal pain, and pyrexia.

Adverse reactions leading to dose reductions of adagrasib occurred in 35% of patients. The most common adverse reactions or laboratory abnormalities leading to dose reductions in ≥ 2% of patients who received adagrasib included fatigue, increased aspartate aminotransferase, increased alanine aminotransferase, nausea, decreased appetite, electrocardiogram QT prolongation, dizziness, acute kidney injury, diarrhea, dysarthria, and vomiting.

The most common adverse reactions (≥ 20%) were rash, nausea, diarrhea, vomiting, fatigue, musculoskeletal pain, hepatotoxicity, headache, dry skin, abdominal pain, decreased appetite, edema, anemia, dizziness, cough, constipation, and peripheral neuropathy.

The most common laboratory abnormalities (≥ 25%) were decreased lymphocytes, decreased hemoglobin, decreased leukocytes, increased alanine aminotransferase, decreased magnesium, decreased albumin, increased lipase, decreased potassium, increased aspartate aminotransferase, increased creatinine, decreased sodium, decreased calcium, increased amylase, and increased alkaline phosphatase.

Table 5 summarizes the adverse reactions in patients with metastatic CRC in KRYSTAL-1.

Table 5: Adverse Reactions (≥ 20 %) in Patients with *KRAS* G12C-mutated CRC Received Adagrasib in Combination with Cetuximab in KRYSTAL-1

Adverse Reaction*	**Adagrasib in Combination with Cetuximab N = 94**	
	All Grades (%)	**Grade 3 or 4 (%)**
Skin and subcutaneous tissue disorders		
Rash†	84	4.3
Dry skin	36	0
Gastrointestinal Disorders		
Nausea	68	2.1
Diarrhea†	65	5
Vomiting†	57	0
Abdominal pain†	30	4.3
Constipation	23	0
General Disorders and Administration Site Conditions		
Fatigue†	57	3.2
Musculoskeletal pain†	47	4.3
Edema†	28	0
Hepatobiliary Disorders		
Hepatotoxicity†	38	10
Nervous System Disorders		
Headache	37	4.3
Dizziness†	24	2.1
Peripheral neuropathy†	20	1.1

Adverse Reaction*	Adagrasib in Combination with Cetuximab N = 94	
	All Grades (%)	Grade 3 or 4 (%)
Metabolism and Nutrition Disorders		
Decreased appetite	30	0
Blood and lymphatic system disorders		
Anemia	27	7
Respiratory		
Cough†	25	0

* Graded per CTCAE version 5.0.
† Grouped term; includes multiple related terms.

Other clinically relevant adverse reactions observed in less than 20% of patients were infusion related reactions (15%).

Table 6 summarizes the laboratory abnormalities in patients with metastatic CRC in KRYSTAL-1.

Table 6: Selected Laboratory Abnormalities (≥ 25%) in Patients Who Received Adagrasib in Combination with Cetuximab in KRYSTAL-1

Laboratory Abnormality	Adagrasib in Combination with Cetuximab*	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Lymphocytes decreased	63	17
Hemoglobin decreased	48	5
Leukocytes decreased	27	1.1
Chemistry		
Alanine aminotransferase increased	51	2.2
Magnesium decreased	49	7
Albumin decreased	46	2.2
Lipase increased	41	3.3
Potassium decreased	40	9
Aspartate aminotransferase increased	39	4.3

Laboratory Abnormality	Adagrasib in Combination with Cetuximab*	
	All Grades (%)	Grade 3 or 4 (%)
Creatinine increased	30	1.1
Sodium decreased	30	0
Calcium decreased	29	1.1
Amylase increased	29	0
Alkaline phosphatase increased	29	1.1

* The denominator used to calculate the rate varied from 82 to 92 based on the number of patients with a baseline value and at least one post-treatment value.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on KRAZATI

Strong CYP3A4 Inducers

Avoid concomitant use of KRAZATI with strong CYP3A inducers.

Adagrasib is a CYP3A4 substrate. Concomitant use of KRAZATI with a strong CYP3A inducer reduces adagrasib exposure *[see Clinical Pharmacology (12.3)]*, which may reduce the effectiveness of KRAZATI.

Strong CYP3A4 Inhibitors

Avoid concomitant use of KRAZATI with strong CYP3A inhibitors until adagrasib concentrations have reached steady state (after approximately 8 days).

Adagrasib is a CYP3A4 substrate. If adagrasib concentrations have not reached steady state, concomitant use of a strong CYP3A inhibitor will increase adagrasib concentrations, *[see Clinical Pharmacology (12.3)],* which may increase the risk of KRAZATI adverse reactions.

7.2 Effects of KRAZATI on Other Drugs

Sensitive CYP3A Substrates

Avoid concomitant use of KRAZATI with sensitive CYP3A substrates unless otherwise recommended in the Prescribing Information for these substrates.

Adagrasib is a CYP3A inhibitor. Concomitant use with KRAZATI increases exposure of CYP3A substrates *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions related to these substrates.

Sensitive CYP2C9 Substrates

Avoid concomitant use of KRAZATI with sensitive CYP2C9 substrates where minimal concentration changes may lead to serious adverse reactions unless otherwise recommended in the Prescribing Information for these substrates.

Adagrasib is a CYP2C9 inhibitor. Concomitant use with KRAZATI increases exposure of CYP2C9 substrates *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions related to these substrates.

Sensitive CYP2D6 Substrates

Avoid concomitant use of KRAZATI with sensitive CYP2D6 substrates where minimal concentration changes may lead to serious adverse reactions unless otherwise recommended in the Prescribing Information for these substrates.

Adagrasib is a CYP2D6 inhibitor. Concomitant use with KRAZATI increases exposure of CYP2D6 substrates *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions related to these substrates.

P-gp Substrates

Avoid concomitant use of KRAZATI with P-gp substrates where minimal concentration changes may lead to serious adverse reactions unless otherwise recommended in the Prescribing Information for these substrates.

Adagrasib is a P-gp inhibitor. Concomitant use with KRAZATI increases exposure of P-gp substrates *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions related to these substrates.

7.3 Drugs That Prolong QTc Interval

Avoid concomitant use of KRAZATI with other product(s) with a known potential to prolong the QTc interval. If concomitant use cannot be avoided, monitor electrocardiogram and electrolytes prior to starting KRAZATI, during concomitant use, and as clinically indicated *[see Warnings and Precautions (5.2)]*. Withhold KRAZATI if the QTc interval is > 500 ms or the change from baseline is > 60 ms *[see Dosage and Administration (2.3)]*.

Adagrasib causes QTc interval prolongation *[see Clinical Pharmacology (12.2)]*. Concomitant use of KRAZATI with other products that prolong the QTc interval may result in a greater increase in the QTc interval and adverse reactions associated with QTc interval prolongation, including Torsade de pointes, other serious arrythmias, and sudden death *[see Warnings and Precautions (5.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on the use of KRAZATI in pregnant women. In animal reproduction studies, oral administration of adagrasib to pregnant rats and rabbits during the period of organogenesis did not cause adverse development effects or embryo-fetal lethality at exposures below the human exposure at the recommended dose of 600 mg twice daily *(see Data)*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In a rat embryo-fetal development study, once daily oral administration of adagrasib to pregnant rats during the period of organogenesis resulted in maternal toxicity (reduced body weight and food intake, and adverse clinical signs leading to moribund condition and early termination) and lower fetal body weight at 270 mg/kg dose level (approximately 2 times the recommended dose of 600 mg twice daily based on body surface area [BSA]). Adagrasib induced skeletal malformations, such as bent limbs, and skeletal variations, such as bent scapula, wavy ribs, and supernumerary short cervical ribs at 270 mg/kg, which were secondary to maternal toxicity and reduced fetal body weight.

In a rabbit embryo-fetal development study, once daily oral administration of adagrasib during the period of organogenesis resulted in lower fetal body weight and increased litter frequency of unossified sternebra at 30 mg/kg (approximately 0.11 times the human exposure based on area under the curve [AUC] at the clinical dose of 600 mg twice daily). This skeletal variation was associated with maternal toxicities, including reduced mean body weight and decreased food consumption. Adagrasib exposure did not cause adverse developmental effects and did not affect embryo-fetal survival in rabbits at doses up to 30 mg/kg once daily.

8.2 Lactation

Risk Summary

There are no data on the presence of adagrasib or its metabolites in human milk, the effects on the breastfed child, or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with KRAZATI and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

Infertility

Based on findings from animal studies, KRAZATI may impair fertility in females and males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of KRAZATI has not been established in pediatric patients.

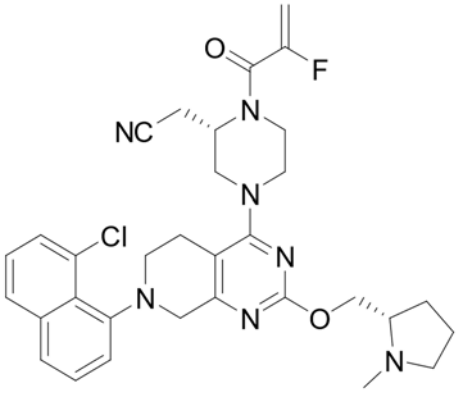
8.5 Geriatric Use

Of 116 patients with metastatic NSCLC who received adagrasib 600 mg orally twice daily in KRYSTAL-1, 49% (57 patients) were ≥ 65 years of age and 13% (15 patients) were ≥ 75 years of age. No overall differences in safety or effectiveness were observed between older and younger patients.

Of 94 patients with metastatic CRC who received adagrasib 600 mg orally twice daily in combination with cetuximab in KRISTAL-1, 33% (31 patients) were ≥ 65 years of age and 2.1% (2 patients) were ≥ 75 years of age. No overall differences in safety or effectiveness were observed between older and younger patients.

11 DESCRIPTION

Adagrasib is an irreversible inhibitor of KRAS G12C and belongs to the RAS GTPase family. The molecular formula is $C_{32}H_{35}ClFN_7O_2$ and the molecular weight is 604.1 g/mol. The chemical name is {(2*S*)-4-[7-(8-chloronaphthalen-1-yl)-2-{[(2*S*)-1-methylpyrrolidin-2-yl]-methoxy}-5,6,7,8-tetrahydropyrido[3,4-*d*]pyrimidin-4-yl]-1-(2-fluoroprop-2-enoyl)piperazin-2-yl}acetonitrile. Adagrasib has the following chemical structure:



Adagrasib is a crystalline solid. The solubility of adagrasib in the aqueous media decreases over the range pH 1.2 to 7.4 from > 262 mg/mL to < 0.010 mg/mL.

KRAZATI (adagrasib) tablets for oral administration contain 200 mg of adagrasib. The following are inactive ingredients: colloidal silicon dioxide, crospovidone, magnesium stearate (vegetable sourced), mannitol, and microcrystalline cellulose. The tablet film coating contains hypromellose, maltodextrin, medium chain triglycerides (vegetable sourced), polydextrose, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Adagrasib is an irreversible inhibitor of KRAS G12C that covalently binds to the mutant cysteine in KRAS G12C and locks the mutant KRAS protein in its inactive state that prevents downstream signaling without affecting wild-type KRAS protein. Adagrasib inhibited tumor cell growth and viability in cells harboring *KRAS* G12C mutations and resulted in tumor regression in *KRAS* G12C-mutated tumor xenograft models with minimal off-target activity. Adagrasib in combination with cetuximab had increased antitumor activity in some cell line-derived and patient-derived *KRAS* G12C-mutant CRC tumor xenograft models compared to adagrasib or cetuximab alone.

12.2 Pharmacodynamics

Adagrasib exposure-response relationships and the time course of pharmacodynamic response are unknown.

Cardiac Electrophysiology

Adagrasib increased QTc in a concentration-dependent manner. Based on the concentration-QTcF relationship, the mean (90% CI) QTcF change from baseline (ΔQTcF) was 18 (15, 21) ms at the mean steady-state maximum concentration ($C_{max,ss}$) in patients after administration of adagrasib 600 mg twice daily *[see Warnings and Precautions (5.2)]*.

12.3 Pharmacokinetics

The pharmacokinetics of adagrasib were studied in healthy subjects and in patients with *KRAS* G12C-mutated NSCLC or CRC. Adagrasib pharmacokinetic data are presented as mean (percent coefficient of variation) unless otherwise specified.

Adagrasib AUC and C_{max} increase dose proportionally over the dose range of 400 mg to 600 mg (0.67 to 1 times the approved recommended dose). Adagrasib steady-state was reached within 8 days following administration of the approved recommended dosage and accumulation was approximately 6-fold.

Absorption

The median (min, max) T_{max} of adagrasib is approximately 6 (6, 12) hours.

Effect of Food

No clinically significant differences in the pharmacokinetics of adagrasib were observed following administration of a high-fat and high-calorie meal (containing approximately 900 to 1000 calories, 50% from fat).

Distribution

The apparent volume of distribution of adagrasib is 942 L (57%). Human plasma protein binding of adagrasib is approximately 98% in vitro.

Elimination

The adagrasib terminal elimination half-life is 23 hours (16%) and the apparent oral clearance (CL/F) is 37 L/h (54%) in patients.

Metabolism

Adagrasib is metabolized primarily by CYP3A4 following single dose administration. Adagrasib inhibits its own CYP3A4 metabolism following multiple dosing to steady-state which permits CYP2C8, CYP1A2, CYP2B6, CYP2C9, and CYP2D6 to contribute to its metabolism at steady-state.

Excretion

Following a single oral dose of radiolabeled adagrasib, approximately 75% of the dose was recovered in feces (14% as unchanged) and 4.5% recovered in urine (2% as unchanged).

Specific Populations

No clinically significant differences in the pharmacokinetics of adagrasib based on age (19 to 89 years), sex, race (White, Black or African American, or Asian), body weight (36 to 146 kg), ECOG PS (0, 1), tumor type (NSCLC or CRC), or tumor burden. No clinically significant differences in the pharmacokinetics of adagrasib are expected in patients with mild to severe renal impairment (CLcr 15 to < 90 mL/min estimated by Cockcroft-Gault equation) or in patients with mild to severe hepatic impairment (Child-Pugh classes A to C).

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

The following table describes the effect of other drugs on the pharmacokinetics of adagrasib.

Table 7: Effect of Other Drugs on Adagrasib

Concomitant Drug	**Adagrasib Dosage**	**Changes in C_{max} or AUC of Adagrasib**	
		C_{max} % Decrease	**AUC % Decrease**
Rifampin (a strong CYP3A inducer)	600 mg single dose	88%	95%
	600 mg multiple doses	> 61%*	> 66%*

C_{max} = maximum plasma concentration; AUC = area under the plasma concentration-time curve

* Predicted changes in C_{max} or AUC of adagrasib.

Strong CYP3A Inhibitors: Adagrasib C_{max} increased by 2.4-fold and AUC increased by 4-fold following concomitant use of a single dose of 200 mg (0.33 times the approved recommended dose) with itraconazole (a strong CYP3A inhibitor). No clinically significant differences in the pharmacokinetics of adagrasib at steady state were predicted when used concomitantly with itraconazole.

No clinically significant differences in the pharmacokinetics of adagrasib were predicted or observed when used concomitantly with efavirenz (a moderate CYP3A inducer), pantoprazole (a proton pump inhibitor), or rosuvastatin (a BCRP/OATP substrate).

The following table describes the effect of adagrasib on the pharmacokinetics of other drugs.

Table 8: Effect of Adagrasib on Other Drugs

Concomitant Drug	Adagrasib Dosage	Fold Increase of Concomitant Drug	
		C_{max}	AUC
Midazolam (a sensitive CYP3A substrate)	400 mg* twice daily	4.8-fold	21-fold
	600 mg twice daily	3.1-fold†	31-fold†
Warfarin (a sensitive CYP2C9 substrate)	600 mg twice daily	1.1-fold†	2.9-fold†
Dextromethorphan (a sensitive CYP2D6 substrate)	400 mg* twice daily	1.9-fold	1.8-fold
	600 mg twice daily	1.7-fold†	2.4-fold†
Digoxin (a P-gp substrate)	600 mg twice daily	1.9-fold†	1.5-fold†

C_{max} = maximum plasma concentration; AUC = area under the plasma concentration-time curve

* 0.66 times the approved recommended dosage.

† Predicted changes in C_{max} or AUC of concomitant drug.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Adagrasib may inhibit CYP2B6.

Transporter Systems: Adagrasib may be a substrate of BCRP and may inhibit MATE-1/MATE-2K.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with adagrasib.

Adagrasib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay and was not genotoxic in an in vitro chromosomal aberration assay or an in vivo micronucleus assay in rats.

Fertility studies were not conducted with adagrasib. In toxicology studies of up to 13-weeks in duration in rats, oral administration of adagrasib induced phospholipidosis which increased vacuolation in female reproductive organs, including vacuolation in ovaries (corpora lutea, macrophage or interstitial cells) and uterus (glandular epithelium), and atrophy with mucification of the vaginal mucosa at doses ≥ 150 mg/kg (approximately equal to or greater than the human exposure at the recommended dose based on area under the curve [AUC]). These findings reversed after cessation of dosing in the 28-day study but in the 13-week study, pigmented macrophage aggregates were observed in the ovaries of female rats after the recovery period. In a 28-day repeat-dose toxicology study, oral administration of adagrasib to male rats induced atrophy and epithelial vacuolation of the prostate gland and seminal vesicles at 300 mg/kg (approximately 1.6 times the human exposure at the recommended dose based on AUC). These findings resolved after cessation of treatment.

13.2 Animal Toxicology and/or Pharmacology

Phospholipidosis (vacuolation and/or presence of foamy macrophages) was observed in multiple organs (e.g., lung, trachea, heart, skeletal, ovaries, uterus, adrenal gland, kidney, liver, lymph nodes, spleen, thymus, and thyroid in rats; and heart and lung in dogs) after repeated oral administration of adagrasib in rats and dogs. In toxicology studies of up to 13-week duration in rats, phospholipidosis was observed at doses ≥ 150 mg/kg (approximately ≥ 2 times the human exposure at the recommended dose based on AUC). In a dog 28-day toxicity study, this effect was observed at 25 mg/kg (approximately equal to the human exposure at the recommended dose based on AUC). The extent of vacuolization and the presence of foamy macrophages were more prominent in the rat compared to dogs, and evidence of reversibility after cessation of treatment was noted for most organs. The significance of this finding in humans in unknown.

14 CLINICAL STUDIES

14.1 Non-Small Cell Lung Cancer

The efficacy of adagrasib was evaluated in KRYSTAL-1 (NCT03785249), a multicenter, single-arm, open-label expansion cohort study. Eligible patients were required to have locally advanced or metastatic *KRAS* G12C-mutated NSCLC who previously received treatment with a platinum-based regimen and an immune checkpoint inhibitor, an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, and at least one measurable lesion as defined by Response Evaluation criteria in Solid Tumors (RECIST v1.1). Identification of a *KRAS* G12C mutation was prospectively determined by local testing using tissue specimens. Patients received adagrasib 600 mg orally twice daily until unacceptable toxicity or disease progression. Tumor assessments were performed every 6 weeks. The major efficacy outcome measures were confirmed objective response rate (ORR) and duration of response (DOR) as evaluated by blinded independent central review (BICR) according to RECIST v1.1.

In the efficacy population, *KRAS* G12C mutation status was determined by prospective local testing using tumor tissue specimens. Of the 112 patients with *KRAS* G12C mutation, tissue samples from 88% (98/112) patients were tested retrospectively using the QIAGEN *therascreen* KRAS RGQ PCR Kit. While 89% (87/98) of patients were positive for *KRAS* G12C mutation, 11% (11/98) did not have a *KRAS* G12C mutation identified. In addition, plasma samples from 63% (71/112) patients were tested retrospectively using Agilent Resolution ctDx FIRST assay. While 66% (47/71) of patients were positive for *KRAS* G12C mutation, 34% (24/71) did not have a *KRAS* G12C mutation identified.

A total of 112 patients had at least one measurable lesion at baseline as assessed by BICR according to RECIST v1.1.

The baseline demographic and disease characteristics in the efficacy population were: median age 64 years (range: 25 to 89), 55% female, 83% White, 8% were Black or African American, 4% Asian, 4% race not reported, 0.9% American Indian or Alaska Native, 16% Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 and 83% ECOG PS 1. Tumor histology was 97% adenocarcinoma and 89% of patients had metastatic disease. Patients received a median of 2 prior systemic therapies (range 1 to 7); 43% received 1 prior line, 35% received 2 prior lines, 10% received 3 prior lines and 12% received 4 or more prior lines, 98% received both prior platinum and prior anti-PD-1/PD-L1 therapy. Sites of extra-thoracic disease included bone 42%, brain 30%, adrenals 21%, and liver 21%.

Efficacy results are summarized in Table 9.

Table 9: Efficacy Results for KRYSTAL-1

Efficacy Parameter	Adagrasib (n = 112)
Objective Response Rate (95% CI)*	43 (34, 53)
Complete response rate, %	0.9
Partial response rate, %	42
Duration of Response*	
Median† in months (95% CI)	8.5 (6.2, 13.8)
Patients with duration ≥ 6 months‡, %	58

CI = Confidence Interval
* Assessed by BICR.
† Estimate using Kaplan-Meier method.
‡ Observed proportion of patients with duration of response beyond landmark time.

14.2 Colorectal Cancer

The efficacy of adagrasib in combination with cetuximab was evaluated in KRYSTAL-1, a multicenter, single-arm, open-label expansion cohort study. Eligible patients were required to have locally advanced or metastatic *KRAS* G12C-mutated CRC and to have previously received

therapy with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, a VEGF inhibitor if eligible, and an ECOG PS of 0 or 1.

Patients initiated treatment with adagrasib 600 mg orally twice daily in combination with cetuximab administered either biweekly (77 patients with 500 mg/m^2 every two weeks) or weekly (17 patients with 400 mg/m^2 initial dose followed by 250 mg/m^2 weekly). Treatment continued until unacceptable toxicity or disease progression. Tumor assessments were performed every 6 weeks. Adagrasib discontinuation required cetuximab discontinuation, however patients could continue to receive adagrasib if cetuximab was discontinued *[see Dosage and Administration (2.3)]*. Six patients continued with adagrasib single agent therapy after discontinuing cetuximab. The length of time these 6 patients received adagrasib alone ranged from 43 days to 3 years. Patient treatment with adagrasib after disease progression continued if a patient was clinically stable and considered to be deriving clinical benefit by the investigator.

The major efficacy outcome measures were confirmed ORR and DOR according to RECIST v1.1 as assessed by BICR.

In the efficacy population, *KRAS* G12C mutation status was determined by prospective local testing using tumor tissue specimens. Of the 94 patients with *KRAS* G12C mutation, tissue samples from 79% (74/94) patients were tested retrospectively using the QIAGEN *therascreen* KRAS RGQ PCR Kit. Of the 74 tissue samples submitted, 81% (60/74) yielded a result with 93% (56/60) positive for *KRAS* G12C and 7% (4/60) without a *KRAS* G12C mutation identified.

The baseline demographic and disease characteristics in the efficacy population were: median age 57 years (range: 24 to 75 years), 53% female, 71% White, 14% were Black or African American, 5% Asian, 1.1% American Indian or Alaska Native, 9% reported as other; 51% ECOG PS 0 and 49% ECOG PS 1. Tumor histology was 100% adenocarcinoma and 99% of patients had metastatic disease. Patients received a median of 3 prior systemic therapies (range 1 to 9); 9% received 1 prior line, 36% received 2 prior lines, 31% received 3 prior lines and 25% received 4 or more prior lines. Sites of metastatic disease included lung (71%), liver (64%) and bone (14%).

Efficacy results are summarized in Table 10.

Table 10: Efficacy Results for KRYSTAL-1

Efficacy Parameter	Adagrasib (n = 94)
Objective Response Rate (95% CI)*	34 (25, 45)
Complete response rate, %	0
Partial response rate, %	34.0
Duration of Response*	
Median† in months (95% CI)	5.8 (4.2, 7.6)
Patients with duration ≥ 6 months‡, %	31

CI = Confidence Interval
* Assessed by BICR.
† Estimate using Kaplan-Meier method.

ǂ Observed proportion of patients with duration of response beyond landmark time.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

KRAZATI (adagrasib) tablets, 200 mg, oval shaped, white to off-white, immediate release, film coated tablets with “200” on one side and stylized “M” on the other side.

KRAZATI (adagrasib) tablets are packaged in high-density polyethylene, white opaque, square bottles with desiccant and polypropylene, white, child resistant closures with a tamper-proof heat induction seal.

NDC 80739-812-12: 200 mg, bottle containing 120 tablets.

NDC 80739-812-18: 200 mg, bottle containing 180 tablets.

Storage and Handling

Store tablets at room temperature, 20°C to 25°C (68°F to 77°F). Temperature excursions between 15°C and 30°C (59°F to 86°F) are permitted *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Gastrointestinal Adverse Reactions

Advise patients that KRAZATI can cause severe gastrointestinal adverse reactions and to contact their healthcare provider for signs or symptoms of severe or persistent gastrointestinal adverse reactions *[see Warnings and Precautions (5.1)]*.

QTc Interval Prolongation

Advise patients that KRAZATI can cause QTc interval prolongation and to contact their healthcare provider for signs or symptoms of arrhythmias *[see Warnings and Precautions (5.2)]*.

Hepatotoxicity

Advise patients that KRAZATI can cause hepatotoxicity and to immediately contact their healthcare provider for signs or symptoms of liver dysfunction *[see Warnings and Precautions (5.3)]*.

Interstitial Lung Disease (ILD)/Pneumonitis

Advise patients that KRAZATI can cause ILD / pneumonitis and to contact their healthcare provider immediately for new or worsening respiratory symptoms *[see Warnings and Precautions (5.4)]*.

Drug Interactions

Advise patients to inform their healthcare providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions (7.1)]*.

Missed Dose

If a dose of KRAZATI is missed by greater than 4 hours, resume dosing at the next scheduled time *[see Dosage and Administration (2.2)]*.

Lactation

Advise women not to breastfeed during treatment with KRAZATI and for 1 week after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

Inform patients that KRAZATI may cause infertility *[see Use in Specific Populations (8.3)]*.

MIRATI
THERAPEUTICS

KRAZATI (adagrasib)

Manufactured for:

Mirati Therapeutics, Inc.

3545 Cray Court

San Diego, CA 92121, U.S.A.

PATIENT INFORMATION
KRAZATI® (krah zah tee)
(adagrasib)
Tablets

What is KRAZATI?

KRAZATI is a prescription medicine used in adults:

- alone to treat non-small cell lung cancer (NSCLC)
  - that has spread to other parts of the body or cannot be removed by surgery, **and**
  - whose tumor has an abnormal *KRAS* G12C gene, **and**
  - who have received at least one prior treatment.
- in combination with a medicine called cetuximab to treat colon or rectal cancer (CRC)
  - that has spread to other parts of the body or cannot be removed by surgery, **and**
  - whose tumor has an abnormal *KRAS* G12C gene, **and**
  - who have previously received certain chemotherapy medicines.

Your healthcare provider will perform a test to make sure that KRAZATI is right for you.

It is not known if KRAZATI is safe and effective in children.

Before taking KRAZATI, tell your healthcare provider about all of your medical conditions, including if you:

- have any heart problems, including heart failure and congenital long QT syndrome.
- have liver problems.
- are pregnant or plan to become pregnant. It is not known if KRAZATI can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if KRAZATI passes into your breastmilk. Do not breastfeed during treatment and for 1 week after your last dose of KRAZATI.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. KRAZATI can affect the way other medicines work, and other medicines can affect how KRAZATI works.

How should I take KRAZATI?

- Take KRAZATI exactly as your healthcare provider tells you to take it. Do not change your dose or stop taking KRAZATI unless your healthcare provider tells you to.
- Your healthcare provider may change your dose, or temporarily or permanently stop treatment with KRAZATI if you develop certain side effects.
- For colon or rectal cancer, you will also receive cetuximab through a vein in your arm (intravenously) given by your healthcare provider. Your healthcare provider will permanently or temporarily stop your treatment with cetuximab if your treatment with KRAZATI is permanently or temporarily stopped.
- Take your prescribed dose of KRAZATI 2 times each day, at about the same time each day.
- Take KRAZATI either with food or without food.
- Swallow KRAZATI tablets whole. Do not chew, crush or split tablets.
- If you vomit after taking a dose of KRAZATI, do not take an extra dose. Take your next dose at your next scheduled time.
- If you miss a dose of KRAZATI, take the dose as soon as you remember. If it has been more than 4 hours, do not take the dose. Take your next dose of KRAZATI at your next scheduled time. Do not take 2 doses at the same time to make up for a missed dose.

What are possible side effects of KRAZATI?

KRAZATI can cause serious side effects, including:

- **Stomach and intestinal (gastrointestinal) problems.** Stomach and intestinal side effects including nausea, diarrhea, or vomiting, are common with KRAZATI but can also sometimes be severe. KRAZATI can also cause serious stomach and intestinal side effects such as bleeding, obstruction, inflammation of the colon (colitis), and narrowing (stenosis).
  - **Call your healthcare provider if you develop any of the signs or symptoms of stomach or intestinal problems listed above during treatment with KRAZATI**.
  - Your healthcare provider may prescribe an antidiarrheal medicine or anti-nausea medicine, or other treatment, as needed.
- **Changes in the electrical activity of your heart called QTc prolongation.** Certain changes can occur in the electrical activity of your heart during treatment with KRAZATI and can be seen on a test called an

electrocardiogram (ECG or EKG). QTc prolongation can increase your risk for irregular heartbeats that can be life-threatening, such as torsades de pointes, and can lead to sudden death.

- You should not take KRAZATI if you have congenital long QT syndrome or if you currently have QTc prolongation. See **"Before taking KRAZATI, tell your healthcare provider about all of your medical conditions, including if you:"**
  - Your healthcare provider should monitor the electrical activity of your heart and the levels of body salts in your blood (electrolytes) especially potassium and magnesium before starting and during treatment with KRAZATI if you have heart failure, a slow heart rate, abnormal levels of electrolytes in your blood, or if you take a medicine that can prolong the QT interval of your heartbeat.
  - **Tell your healthcare provider if you feel dizzy, lightheaded, or faint, or if you get abnormal heartbeats during treatment with KRAZATI.**

- **Liver problems.** Abnormal liver blood test results are common with KRAZATI and can sometimes be severe. Your healthcare provider should do blood tests before starting and during treatment with KRAZATI to check your liver function. Tell your healthcare provider right away if you develop any signs or symptoms of liver problems, including:
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark or "tea-colored" urine
  - light-colored stools (bowel movements)
  - tiredness or weakness
  - nausea or vomiting
  - bleeding or bruising
  - loss of appetite
  - pain, aching or tenderness on the right side of your stomach area (abdomen)
- **Lung or breathing problems.** KRAZATI may cause inflammation of the lungs that can lead to death. Tell your healthcare provider or get emergency medical help right away if you have new or worsening shortness of breath, cough, or fever.

The most common side effects of KRAZATI when used alone for NSCLC include:

- nausea
- diarrhea
- vomiting
- tiredness
- muscle and bone pain
- kidney problems
- swelling
- decreased appetite
- trouble breathing

The most common side effects of KRAZATI when used in combination with cetuximab for CRC include:

- skin rash
- nausea
- diarrhea
- vomiting
- tiredness
- muscle and bone pain
- headache
- dry skin
- stomach pain
- decreased appetite
- swelling
- low red blood cell count
- cough
- dizziness
- constipation
- nerve damage in the arms and legs

Certain abnormal blood test results are common during treatment with KRAZATI, when used alone or in combination with cetuximab. Your healthcare provider will monitor you for abnormal blood tests and treat you if needed.

KRAZATI may cause fertility problems in males and females, which may affect your ability to have children. Talk to your healthcare provider if this is a concern for you.

These are not all of the possible side effects of KRAZATI.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store KRAZATI?

- Store KRAZATI at room temperature between 68°F to 77°F (20°C to 25°C).
- KRAZATI comes in a child-resistant container.
- KRAZATI comes with a desiccant (drying agent) in the container to keep the medicine dry. Do not remove the desiccant from the container after opening. Do not eat or swallow the desiccant.

Keep KRAZATI and all medicines out of the reach of children.

General information about the safe and effective use of KRAZATI.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use KRAZATI for a condition for which it was not prescribed. Do not give KRAZATI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about KRAZATI that is written for health professionals.

What are the ingredients in KRAZATI?

Active ingredient: adagrasib

Inactive ingredients: colloidal silicon dioxide, crospovidone, magnesium stearate (vegetable sourced), mannitol, and microcrystalline cellulose. The tablet film coating contains hypromellose, maltodextrin, medium chain triglycerides (vegetable sourced), polydextrose, talc, and titanium dioxide.

Manufactured for: Mirati Therapeutics, Inc. 3545 Cray Court San Diego, CA 92121, U.S.A.

For more information, go to www.KRAZATI.com or call 1-844-MIRATI-1 (1-844-647-2841)

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 06/2024

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

REBECCA L COHEN
06/21/2024 12:26:50 PM

CHANA WEINSTOCK
06/21/2024 12:31:03 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216340Orig1s005

OFFICER/EMPLOYEE LIST

Officer/Employee List

NDA 216340 /S-005

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Auth, Doris
Bi, Youwei
Cohen, Rebecca
Fedowitz, Michele
Fuller, Barbara
Kolhatkar, Rohit
Leu, Lily
Moore, Jason
Mushti, Sirisha
Redwood, Susan
Srivastava, Geetika
Taylor, Sheryse
Tezak, Zivana
Thompson, Matthew
Weinstock, Chana
Xiong, Ye

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216340Orig1s005

MULTI-DISCIPLINE REVIEW

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

NDA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	216340/ S-005
Priority or Standard	Priority
Submit Date(s)	12/21/24
Received Date(s)	12/21/24
PDUFA Goal Date	6/21/24
Division/Office	DO3/OOD
Review Completion Date	June 21, 2024
Established/Proper Name	adagrasib
(Proposed) Trade Name	Krazati
Pharmacologic Class	KRAS inhibitor
Code name	MRTX849
Applicant	Mirati Therapeutics Inc.
Doseage form	Tablet
Applicant proposed Dosing Regimen	600 mg orally twice daily
Applicant Proposed Indication(s)/Population(s)	Adagrasib in combination with cetuximab, for the treatment of adult patients with *KRAS* G12C-mutated locally advanced or metastatic CRC who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	KRAZATI in combination with cetuximab, for the treatment of adult patients with *KRAS* G12C-mutated locally advanced or metastatic CRC who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy
Recommended Dosing Regimen	Adagrasib 600mg BID with cetuximab 400 mg/m2 initial dose followed by 250 mg/m2 weekly OR cetuximab 500mg/m2 Q2W

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OSI	Courtney McGuire
OSE/DEPI	
OSE/DMEPA	Tingting Gao
OSE/DRISK	
Other	

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

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Adagrasib is an irreversible inhibitor of KRAS G12C and belongs to the RAS GTPase family. Adagrasib was initially approved on December 12, 2022 as a single agent for the treatment of adult patients with *KRAS* G12C-mutated locally advanced or metastatic NSCLC who have received at least one prior systemic therapy.

The Applicant is seeking approval of the following proposed indication:

> "KRAZATI in combination with cetuximab is indicated for the treatment of adult patients with *KRAS* G12C-mutated locally advanced or metastatic colorectal cancer (CRC), as determined by an FDA-approved test, who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy."

The Applicant's proposed dose of adagrasib in combination with cetuximab is 600 mg by mouth twice daily (BID).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The data submitted from Study 849-001 meets the statutory evidentiary requirement for accelerated approval. The recommendation for accelerated approval is based on the results of Study 849-001, a multicenter, single arm, multiple expansion cohort trial evaluating patients with KRAS-G12C mutated advanced or metastatic colorectal cancer who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, and a VEGF inhibitor, if eligible. The efficacy population includes 94 patients enrolled to the Phase 1 Substudy (n=32) and Phase 2 Cohort G (n=62) who received treatment with adagrasib 600 mg BID in combination with cetuximab either biweekly (77 patients with 500 mg/m^2 every two weeks) or weekly (17 patients with 400 mg/m^2 initial dose followed by 250 mg/m^2 weekly). The primary study objective was to evaluate the clinical efficacy of adagrasib in combination with cetuximab via objective response rate (ORR) per RECIST v1.1 as assessed by blinded independent central review (BICR). The key secondary objective was to evaluate the duration of response (DOR).

Study 849-001 demonstrated an ORR of 34% (95% CI: (25, 45)) and a median DOR of 5.8 months (95% CI: 4.2 to 7.6 months) for the combination of adagrasib and cetuximab in the enrolled population. These results are considered clinically meaningful when considering that this is a patient population with previously treated advanced disease and responses observed on this study are substantially better than what has been observed with available therapies. Supportive data demonstrating the activity of single agent adagrasib was provided from Phase 2 Cohort C (n=44) and Cohort F (n=42), which was considered in assessing the necessity of both adagrasib

and cetuximab for the observed treatment effect.

The safety profile of single agent adagrasib has been previously characterized in the original NDA application that supported the approval for patients with previously treated KRAS G12C mutated NSCLC. The safety of adagrasib in combination with cetuximab is consistent with the safety profile observed when each component of the combination regimen is administered as a single agent.

There was limited data provided from a small dose optimization cohort (n=27) evaluating adagrasib at 400 mg BID combined with cetuximab. With a relatively short median follow up of 5.6 months, an improvement in the safety profile appeared to be demonstrated compared to the 600 mg BID dose: grade 3-4 adverse events (48%), dose interruptions (41%), and dose reductions (19%). The observed ORR in this cohort was also comparable to that observed in the 600 mg BID cohort (36% (95% CI: 18, 58)). This suggests that the dose of adagrasib may not be optimized. However due to the small sample size, differences in duration of follow up and exposure adagrasib in the dose optimization cohorts, and the limitations associated with single arm trials, no conclusions can be made regarding the optimized dose based on these single arm comparisons.

This is the first accelerated approval of an oral targeted therapy intended for the treatment of patients with advanced or metastatic KRAS G12C-mutated CRC. The observed ORR and DOR are reasonably likely to predict clinical benefit and demonstrate a clinically meaningful improvement over available therapies for this disease. The safety profile of adagrasib in combination with cetuximab is acceptable and taken with the observed responses demonstrate an overall favorable benefit-risk profile. No new safety signals were identified during the review, no new Warnings and Precautions were added to the adagrasib USPI, and no REMS is required for this indication. No corresponding labeling changes were made to the cetuximab USPI (no corresponding sNDA submitted) as the doses used in Study 849-001 were the labeled/approved doses for cetuximab, and no new safety signals were identified.

A PMR was issued to complete Study 849-010, entitled “A Randomized Phase 3 Study of adagrasib 600 mg twice daily in combination with cetuximab versus chemotherapy in patients with advanced colorectal cancer with KRAS G12C mutation with disease progression on or after first-line therapy.” This study (b) (4) and is expected to have its initial PFS readout submitted to the FDA in (b) (4); results are intended to confirm benefit of adagrasib in CRC. During a teleconference held between Mirati and the FDA on May 23, 2024, Mirati agreed that they would withdraw the accelerated approval of adagrasib in CRC should Study 849-010 fail to meet its primary endpoint.

A dose optimization PMR was issued at the time of the original approval of adagrasib to conduct a randomized clinical trial to further evaluate the safety of adagrasib 600 mg BID compared to an (b) (4) in patients with KRAS G12C-mutated NSCLC who have received at least one prior systemic therapy. Results are expected to inform labeled starting dose of

adagrasib (b) (4).

A supplemental premarket application (sPMA) for a companion diagnostic test using DNA extracted from formalin-fixed, paraffin-embedded (FFPE), colorectal cancer tissue (therascreen® KRAS RGQ PCR Kit) by Qiagen for contemporaneous review and approval with this supplemental NDA (sNDA).

1.3. Benefit-Risk Assessment

[Do not insert text here. Use the table]

Benefit-Risk Summary and Assessment

Colorectal cancer (CRC) is estimated to be the fourth most common cancer diagnosed and the second most common cause of cancer death in the United States (US) in 2024, comprising 7.6% of all new cancer cases with an estimated 152,810 new cases of CRC and 53,010 CRC deaths (SEER 22). The 5-year relative survival rate for patients diagnosed with metastatic CRC is 15.7% and median survival has been observed to be between 2 to 3 years (SEER 22, Biller et al. 2021). However, patients with metastatic CRC who have progressed following standard treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy and targeted therapies such as an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy, the prognosis is poor with a survival of approximately 5 months observed in patients who received placebo in clinical trials of regorafenib or FTD/TPI in the third-line setting. Available treatment options are limited for patients with refractory CRC and include treatment with regorafenib, FTD/TPI alone or in combination with bevacizumab, or fruiquintinib. Regorafenib was approved in 2012 based on data from the CORRECT trial that demonstrated an improvement in OS in patients receiving regorafenib compared to patients receiving placebo (HR 0.77, [95% CI: 0.64, 0.94]); median OS was 6.4 months (95% CI: 5.8, 7.3) compared to 5 months (95% CI: 4.4, 5.8) in patients who received placebo (Stivarga PI). FTD/TPI was initially approved in 2015 based on data from the RECOURSE trial that demonstrated an improvement in overall survival (OS) in patients treated with FTD/TPI compared to placebo (HR 0.68, [95% CI 0.58, 0.81]). The median OS of patients treated with FTD/TPI was 7.1 months (95% CI: 6.5, 7.8) compared to 5.3 months (95% CI: 4.6, 6) in patients who received placebo (Lonsurf PI). FTD/TPI in combination with bevacizumab was approved in 2023 based on data from the SUNLIGHT trial that demonstrated an improvement in OS in patients receiving FTD/TPI in combination with bevacizumab compared to patients receiving FTD/TPI alone (HR 0.61 [95% CI 0.49, 0.77]). The median OS of patients treated with FTD/TPI and bevacizumab was 10.8 months (95% CI: 9.4, 11.8) compared to 7.5 months (95% CI: 6.3, 8.6) in patients who received FTD/TPI (Lonsurf PI). Fruiquintinib was approved in 2023 based on data from the FRESCO-2 trial that demonstrated an improvement in OS in patients receiving fruiquintib compared to patients receiving best supportive care (BSC) (HR 0.66 [95% CI: 0.55, 0.80]); median OS was 7.4 months (95% CI: 6.7, 8.2) compared to 4.8 months (95% CI: 4.0, 5.8) in patient who received BSC (FRUZAQLA PI). Despite the demonstrated improvements in OS with these therapies, Investigator-assessed ORR observed in these studies ranges from 1% to 6.3% (Grothley 2013, Mayer 2015, Prager 2023, Dasari 2023).

KRAS is the most frequently mutated RAS protein occurring in approximately 50% of patients with CRC. KRAS G12C mutated colorectal cancer is a molecularly distinct form of colorectal cancer that does not have an FDA approved targeted therapy. KRAS G12C mutations occur in approximately 3% of all patients with CRC and are associated with a poor prognosis (TCGA 2012, Henry 2021, Nassar 2021).

Adagrasib is an irreversible inhibitor of KRAS G12C and belongs to the RAS GTPase family. The proposed dosage of adagrasib is 600 mg BID in combination with cetuximab.

The Applicant submitted data from Study 849-001 (KRYSTAL-1), a multicenter, single arm, dose escalation and multicohort expansion study, to support an accelerated approval of adagrasib and cetuximab for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic colorectal cancer (CRC) who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. The primary efficacy population included 94 patients enrolled to the Phase 1 Substudy (n=32) and Phase 2 Cohort G (n=62) who received treatment with adagrasib 600 mg BID in combination with cetuximab either biweekly (77 patients with 500 mg/m^2 every two weeks) or weekly (17 patients with 400 mg/m^2 initial dose followed by 250 mg/m^2 weekly). The ORR per RECIST v1.1 as assessed by BICR was 34% (95% CI: (25, 45)). The median DOR was 5.8 months (95% CI: 4.2 to 7.6 months) with 31% of patients experiencing a durable response that lasted at least 6 months. Supportive data demonstrating the activity of single agent adagrasib was provided from Phase 2 Cohort C (n=44) and Cohort F (n=42), which was considered in assessing the necessity of both adagrasib and cetuximab for the observed treatment effect. The ORR in these patients was 22% (95% C.I. [14, .32]), substantially lower than the ORR observed with the contribution, demonstrating the need for both components of the adagrasib + cetuximab regimen.

The data submitted to support the safety review of adagrasib and cetuximab is adequate to characterize the toxicity in patients with locally advanced or metastatic KRAS G12C-mutated CRC. The safety profile observed in patients who received adagrasib 600 mg BID in combination with cetuximab is generally consistent with the safety profile associated with each single agent drug in the combination regimen. Although the safety profile was determined to be acceptable and easily managed with dose modification guidelines included in the USPI, there were a numerically high number of grade 3-4 adverse events (62%), dose interruptions (68%) and dose reductions (35%). There was limited data provided from a small dose optimization cohort (n=27) that had a median follow up of 5.6 months that demonstrated an improvement in the safety profile: grade 3-4 adverse events (48%), dose interruptions (41%), and dose reductions (19%). The observed ORR in the dose optimization cohort was also comparable to that observed in the pivotal cohort (36% (95% CI: 18, 58)). This suggests that the dose of adagrasib may not be optimized. However due to the small sample size, differences in duration of follow up and exposure adagrasib in the dose optimization cohorts, and the limitations associated with single arm trials, no conclusions can be made regarding the optimized dose based on these single arm comparisons. A dose optimization PMR was issued at the time of the original approval of adagrasib to conduct a randomized clinical trial to further evaluate the safety of adagrasib 600 mg BID compared to (b) (4) in patients with KRAS G12C-mutated NSCLC who have received at least one prior systemic therapy. As the updated population PK analysis indicates that there are no significant differences in the PK of adagrasib based on tumor type (NSCLC or CRC), (b) (4) .

Risk minimization strategies have been instituted via management guidelines in the US Prescribing Information (USPI) and the Medication Guide. Significant adverse events associated with adagrasib include gastrointestinal adverse reactions, QTc interval prolongation, hepatotoxicity, and pneumonitis/interstitial lung disease and these safety concerns are adequately addressed in the Warnings and Precautions and dose modification guidelines in the USPI.

No labeling changes were made to the cetuximab USPI as the doses used in Study 849-001 were the labeled/approved doses for cetuximab and no new safety signals were identified.

A supplemental premarket application (sPMA) was submitted for a companion diagnostic test using DNA extracted from formalin-fixed, paraffin-embedded (FFPE), colorectal cancer tissue (therascreen® KRAS RGQ PCR Kit) by Qiagen for contemporaneous review and approval with this supplemental NDA. Two studies were conducted to demonstrate the concordance in mutation status of CRC samples tested with the therascreen KRAS RGQ PCR Kit. The results demonstrate a positive percentage agreement (PPA) of 96.3% (95% CI: 89.4, 98.8), a negative percentage agreement (NPA) of 96.4% (95% CI: 91.3, 98.6), and an overall percentage agreement (OPA) of 96.4% (95% CI: 92.7, 98.2) The accuracy of this assay for detecting KRAS G12C-mutated locally advanced or metastatic CRC has been adequately demonstrated during the 510(k) clearance.

The data submitted meets the statutory evidentiary requirement for accelerated approval and provides preliminary evidence of the effectiveness of adagrasib in combination with cetuximab for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic CRC who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. The review team recommends granting accelerated approval. A PMR for fully-enrolled confirmatory study (Study 849-010) will be issued with the approval of this sNDA. A PMR issued for the adagrasib NSCLC approval is evaluating the (b) (4). An sPMA for a the therascreen® KRAS RGQ PCR Kit by Qiagen will be approved contemporaneously with this sNDA.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Colorectal cancer (CRC) accounts for 7.6% of all new cancer cases - It is estimated that there will be 152,810 new cases of CRC and 53,010 CRC deaths in the US in 2024 (SEER 22) - The 5-year relative survival rate for patients with metastatic CRC is 15.7% - KRAS G12C mutations occur in approximately 3% of all patients with CRC and are associated with a poor prognosis (TCGA 2012, Henry 2021, Nassar 2021).	Refractory CRC is a serious and life-threatening condition with a poor prognosis.
Current Treatment Options	- Standard of care therapy after treatment with a fluoropyrimidine-, oxaliplatin-, and irinotecan-based regimens includes treatment with either regorafenib or FTD/TPI, both of which were approved based on improvements in overall survival (OS) - Response rates observed with available therapies are very low and range from 1% to 6.3% (Grothley 2013, Mayer 2015, Prager 2023, Dasari 2023) - In the CORRECT trial, regorafenib demonstrated an improvement in OS in patients receiving regorafenib compared to patients receiving placebo (HR 0.77, [95% CI: 0.64, 0.94]). The Investigator-assessed ORR is 1.0% (95% CI: 0.3, 2.3). - In the RECOURSE trial, FTD/TPI demonstrated an improvement in OS in patients treated with FTD/TPI compared to placebo (HR=0.68, [95% CI 0.58, 0.81]). The Investigator-assessed ORR is 1.6% (95% CI not available). - In the SUNLIGHT trial, FTD/TPI in combination with bevacizumab demonstrated an improvement in OS in patients treated with FTD/TPI and bevacizumab compared to FTD/TPI (HR 0.61 [95% CI 0.49, 0.77]). The Investigator-assessed ORR is 6.3% (95% CI: 3.5, 9.9). - In the FRESCO-2 trial, fruiquintinib demonstrated an improvement in	Standard of care options for the treatment of patients with metastatic CRC who have progressed on fluoropyrimidine-, oxaliplatin and irinotecan-based chemotherapy and targeted therapies such as an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy is limited and have demonstrated only modest improvement in outcomes, with ORRs ranging from 1.0%-6.7%. There are no targeted therapies that are FDA-approved for use in patients with KRAS G12C-mutated CRC, in any line of therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	OS in patients treated with fruiquintinib compared to BSC (HR 0.66 [95% CI: 0.55, 0.80]). The Investigator-assessed ORR is 1.5% (95% CI: 0.6, 3.1).	
Benefit	- In Study 849-001, in 94 patients treated with adagrasib 600 mg BID in combination with cetuximab, the ORR per BICR was 34% (95% CI: 25,45) with a median DOR of 5.8 months (95% CI: 4.2 to 7.6 months). - The ORR of adagrasib in combination with cetuximab was numerically higher than the ORR observed in patients treated with single agent adagrasib (22% (95% CI: 14, 32)), demonstrating the necessity of adagrasib and cetuximab for the treatment effect observed with the combination regimen. - The observed ORR from Study 849-001 is substantially higher than the ORRs observed with available therapy in the third line setting. - A PMR was issued to complete the fully enrolled Study 849-010, entitled "A Randomized Phase 3 Study of adagrasib 600 mg twice daily in combination with cetuximab versus chemotherapy in patients with advanced colorectal cancer with KRAS G12C mutation with disease progression on or after first-line therapy."	The study demonstrated a clinically meaningful ORR and duration of response in patients with KRAS G12C mutated advanced or metastatic CRC who have previously been treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, and a VEGF inhibitor, if eligible. Results of a randomized study in the second line CRC setting will be submitted as a PMR to confirm the benefit of adagrasib. An sPMA for a companion diagnostic test (therascreen® KRAS RGQ PCR Kit) by Qiagen will be approved contemporaneously with this sNDA.
Risk and Risk Management	- The safety analysis population included 94 patients treated with adagrasib 600 mg BID in combination with cetuximab. - The overall safety profile of adagrasib in combination with cetuximab for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic CRC in Study 849-001 was consistent with the safety profile observed for adagrasib and cetuximab when each is administered as a single agent. - Significant risks associated with adagrasib in combination with cetuximab include gastrointestinal adverse reactions, QTc interval	The safety of adagrasib and cetuximab has been well characterized and no new safety concerns were identified during this review. No new Warnings/Precautions were identified and no REMS will be required. The observed adverse reactions were manageable with dose modifications. The risks associated with this regimen are considered acceptable in the context of the clinical efficacy in an advanced

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	prolongation, hepatotoxicity, and pneumonitis/interstitial lung disease. - The most common adverse reactions (≥ 25%) were rash, nausea, diarrhea, vomiting, fatigue, musculoskeletal pain, hepatotoxicity, headache, dry skin, abdominal pain, decreased appetite, edema, anemia, and cough. - The most common (≥ 2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, decreased potassium, decreased magnesium, decreased hemoglobin, increased alanine aminotransferase, increased lipase, decreased albumin, and increased aspartate aminotransferase. - Serious adverse reactions occurred in 30% of patients. Adverse reactions leading to dose interruptions of adagrasib occurred in 62% of patients. Adverse reactions leading to dose reductions of adagrasib occurred in 35% of patients. - A small dose optimization cohort (n=27) with a short median follow up evaluating a dose of 400 m BID of adagrasib appeared to demonstrate an improvement in the overall safety profile, most notably with lower dose reductions than the 600 mg BID cohort (41% vs. 62%) and comparable ORR (36% (95% CI: 18, 58)). A dose optimization PMR issued at the time of the original approval of adagrasib will evaluate the safety of adagrasib 600 mg BID compared to (b) (4) in patients with KRAS G12C-mutated NSCLC in the second line-plus setting.	or metastatic KRAS G12C-mutated CRC population previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. Results of a randomized study performed as a dose PMR for the adagrasib NSCLC approval are awaited to inform possible future labeling of a (b) (4) dose. No corresponding labeling changes were made to the cetuximab USPI during review of this sNDA.

1.4. Patient Experience Data

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

				Section of review where discussed, if applicable [e.g., Section 6.1 Study endpoints]
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	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)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

X Jamie R. Brewer

Cross Discipline Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

Colorectal cancer (CRC) is the third most commonly-diagnosed cancer in men and second in women worldwide (1). Approximately 153,020 new cases of CRC and 52,550 deaths are expected in the United States (US) in 2023 (2). It is now the second most common cause of cancer deaths in the US (2).

The rate of new cases of CRC was 37.7 per 100,000 males and females per year based on 2015–2019 cases, age-adjusted (3). CRC is more common in males than females, and more common among those of African American descent than among whites and those of Hispanic descent.

Table 1: Rate of New Cases per 100,000 Persons by Race/Ethnicity & Sex: Colorectal Cancer

	Males	Females
ALL RACES	42.1	32.0
Non-Hispanic white	42.3	32.5
Non-Hispanic black	50.4	37.2
Non-Hispanic Asian/pacific islander	35.3	25
Non-Hispanic American/Indian Alaska Native	52.3	45.1
Hispanic	39.6	32.5

Source – SEER 22 (2016-2020) seer.cancer.gov

Data from SEER database suggests that the incidence of CRC has been rising in individuals who are under the age of 50 years while decreasing in individuals in older age groups (4). The proportion of new CRC cases among adults under the age of 55 years increased from 11 to 20 percent between 1995 and 2019 (2). While it is known that genetic and environmental factors contribute toward risk for CRC, the reasons for the rise in incidence in the younger population is not fully understood.

The median age at diagnosis for CRC in the US is 66 years (4). Age distribution for diagnosis of colorectal cancer is presented in Table 2

Table 2: Percent of New Cases by Age Group: Colorectal Cancer

Age group	Percentage of new cases (%)
<20	0.3
20-34	2
35-44	4.9
45-54	15
55-64	23
65-74	26
75-84	19
>84	10

Source - seer.cancer.gov

The death rate from CRC was 13.1 per 100,000 males and females per year based on 2016–2020 deaths, age-adjusted (3). Death rare by race/ethnicity is presented below in Table 3

Table 3 : Death Rate per 100,000 Persons by Race/Ethnicity & Sex: Colorectal Cancer

	Males	Females
ALL RACES	15.7	11
Non-Hispanic white	15.5	11.1
Non-Hispanic black	22.3	14.3
Non-Hispanic Asian/pacific islander	10.9	7.7
Non-Hispanic American/Indian Alaska Native	20.8	14.3
Hispanic	13.5	8.5

Source - seer.cancer.gov

At diagnosis, 22% of patients have metastatic disease and 36% of patients have regional spread. Current median survival of metastatic CRC (mCRC) in the US is approximately 33 months but can vary based on certain factors including tumor specific factors (e.g., KRAS or BRAF mutations). (5) Median survival for patients in the 3rd line setting is approximately 5 months (Lonsurf USPI, Stivarga USPI, Fruzaqla USPI).

RAS proteins, including KRAS, are part of a family of small GTPases that are activated in

response to growth factor binding to regulate intracellular signaling pathways responsible for growth, migration, survival, and differentiation of cells. The *RAS* family of genes comprises 3 members, *KRAS*, *NRAS*, and *HRAS*, which are mutated in nearly 25% of all human cancers. *KRAS* is the most frequently mutated gene of the *RAS* family, with *KRAS* mutations occurring in approximately 50% of CRC The most common *KRAS* mutations are missense mutations affecting residues (codons) 12, 13, and 61 (6). Mutation of KRAS glycine specifically to cysteine (*KRAS* G12C mutation) accounts for 7% of *KRAS* mutations in CRC, representing approximately 3% of all CRC patients (7,8, 9, 10, 11).

2.2. Analysis of Current Treatment Options

The current standard of care for front-line treatment of patients with mCRC includes chemotherapy with a fluoropyrimidine-based regimen in combination with oxaliplatin or irinotecan and a biologic agent based on the biomarker profile and sidedness of the tumor. Patients with left-sided tumors that are KRAS wild type can receive systemic chemotherapy in combination with an anti-EGFR antibody as front-line therapy. Bevacizumab, an inhibitor of VEGF, is approved for use in combination with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy in front-line as well as those whose disease have progressed on a first-line bevacizumab-containing regimen. In patients with microsatellite-instability high (MSI-H) mCRC (4-5% of the metastatic population) pembrolizumab is approved as front-line therapy (12).

Ziv-Aflibercept, a soluble receptor for VEGF is approved for use in combination with fluorouracil, leucovorin, and irinotecan (FOLFIRI) in patients with mCRC that is resistant to or has progressed following an oxaliplatin-containing regimen. Ramucirumab is a VEGF receptor 2 antagonist approved for use in combination with FOLFIRI for the treatment of patients with mCRC whose disease has progressed on a first-line bevacizumab-, oxaliplatin- and fluoropyrimidine-containing regimen.

Approved therapies in the 3rd line setting include regorafenib, trifluridine/tipiracil (FTD/TPI) in combination with bevacizumab and Fruquintinib, which have demonstrated modest effects on OS, as described in Table 4.

Table 4: FDA Approved-Third Line Therapy for mCRC

Treatment	Investigator-Assessed ORR (%)	Investigator-Assessed Median DOR (months)	Investigator-Assessed Median PFS (months)	Median OS (months)
Regorafenib[1]	1.0% (95% CI: 0.3 to 2.3%)	Not Evaluable[2]	1.9 (95% CI: 1.9 to 2.3)	6.4 (95% CI: 5.8 to 7.3)
Trifluridine/tipiracil[3]	1.6% (Not Available)	Not Available[4]	2.0 (95% CI: 1.9 to 2.1)	7.1 (95% CI: 6.5 to 7.8)
Trifluridine/tipiracil and bevacizumab[5]	6.3% (95% CI: 3.5 to 9.9%)	Not Available[6]	5.6 (95% CI: 4.5 to 5.9)	10.8 (95% CI: 9.4 to 11.8)
Fruquintinib[7]	1.5% (95% CI: 0.6–3.1%)	10.7 months[8] (95% CI:3.9 to NE)	3.7 (95% CI: 3.5 to 3.8)	7.4 (95% CI: 6.7 to 8.2)

Source: 1,2= Grothery A etal, Lancet. 2013 Jan 26;381(9863):303-12 ;2, 4= Mayer RJ et al, N Engl J Med 2015; 372:1909-1919;5,6= https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-trifluridine-and-tipiracil-bevacizumab-previously-treated-metastatic-colorectal-cancer;7, 8= https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-burst-edition-fda-approval-fruzaqla-fruquintinib-adult-patients-metastatic-colorectal

Immune checkpoint inhibitors (pembrolizumab, nivolumab in combination with ipilimumab) are also approved for treatment after prior systemic therapy in patients with MSI-H mCRC and patients with tumor burden mutation-high (TMB-H) mCRC; however, most of these patients would have typically received immunotherapy as first-line therapy. The combination of encorafenib (a BRAF inhibitor) and cetuximab is approved for patients with BRAF-mutated mCRC (4-5% of the population of patients with metastatic disease) who have received one or two prior regimens (13).

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

On December 12, 2022, adagrasib was granted accelerated approval 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 approved dosage of adagrasib was 600 mg orally twice daily until disease progression or unacceptable toxicity. At the time of approval of the original NDA, a dose optimization PMR was issued to conduct a randomized clinical trial to further evaluate the safety of adagrasib 600 mg BID compared to an alternative dosage in patients with KRAS G12C-mutated NSCLC who have received at least one prior systemic therapy

3.2. Summary of Presubmission/Submission Regulatory Activity

The following were the milestone correspondence:

Table 5: Key Regulatory Interactions

Date	IND/NDA	
October 29, 2018	IND 138735	Study May Proceed Letter issued for Study 849-001 (KRYSTAL-1).
October 31, 2020	IND 152345	Study May Proceed Letter issued for Study 849-010- An open-label, randomized (1:1), Phase 3 clinical trial comparing the efficacy of adagrasib administered in combination with cetuximab versus chemotherapy (FOLFIRI or mFOLFOX6) in the second-line treatment setting for patients with KRAS G12C-mutant CRC.
December 21, 2022	IND 152345	Breakthrough Therapy Designation was granted to adagrasib in combination with cetuximab for the treatment of patients with advanced or metastatic colorectal cancer (CRC) with KRAS G12C mutation who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based hemotherapy, and an antiVEGF therapy, based on preliminary clinical data which demonstrated an objective response rate of 46.4%
February 15, 2023	IND 152345	Updated (b) (4) for 849-010 submitted: Mirati revised the (b) (4) as follows:

		(b) (4) [redacted]
October 10, 2023	IND 152345	Pre-sNDA meeting - Mirati provided data for planned safety data package, including data cut off dates, that will support the planned sNDA submission. This was agreed upon by the agency.
May 23, 2024	NDA 216340/ S-005	Teleconference with Mirati- Mirati stated that the PFS final analysis for fully-enrolled confirmatory Study 849-010 is projected at (b) (4) [redacted], with a subsequent planned sNDA submission. Mirati stated agreement to withdraw the accelerated approval CRC indication for adagrasib if Study 849-010 failed to meet its primary endpoint.

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

4.1. Office of Scientific Investigations (OSI)

The Division of Oncology 3 consulted OSI to audit the overall trial conduct for the study 849-001 trial. Two clinical sites, Dr. Rona Yaeger (Site 806) and Dr. Marcelo V Negrao (Site 848), and the imaging CRO ((b) (4)) were selected for audit. The FDA review team reviewed study site characteristics and chose these sites based on the number of patients enrolled, performance of patients enrolled at these sites compared to the overall study population, frequencies of protocol deviations, and prior inspection history (either no history of prior inspection or remote history of inspection).

Based on the inspection findings, Study 849-001 data generated at Site #806 appear acceptable in support of the proposed indication in the sNDA.

During the inspection of Site #848, it was noted that there were five instances of unsigned notes, and OSI review identified multiple inconsistencies between the dates and/or frequency of AE reporting for the following laboratory abnormalities (elevated creatinine [Grade 2], hypokalemia [Grade 1], increased amylase [Grade 2], and magnesium [Grade 1]). However, these adverse reactions were all captured in the ADAE dataset. These findings were reviewed in detail with the clinical and safety teams. Despite these isolated deficiencies of AE reporting, the FDA determined that these abnormalities in reporting were unlikely to change the analysis of safety of the drug regimen. FDA has concluded that data generated at Site #848 overall appear acceptable in support of the proposed indication in the sNDA.

Based on the results of the inspection, the imaging review data generated by (b) (4) appear acceptable in support of the proposed indication in the sNDA.

Overall, no significant discrepancies between the source documents and data line listings were observed. Study files and subject case records were well maintained. The inspection confirmed adequate compliance with Good Clinical Practice (GCP) principles and regulations. The major efficacy endpoint and adverse event (AE) data reported in the application were audited in detail and were determined to be verifiable against the source data recorded at the clinical sites. Based on the inspection findings, the study appears to have been conducted adequately and the data generated by the inspected entities appear to be acceptable in support of this New Drug Application (NDA).

4.2. Product Quality

This submission did not contain new product information.

4.3. Clinical Microbiology

This submission did not contain new clinical microbiology information.

4.4. Devices and Companion Diagnostic Issues

The therascreen® KRAS RGQ PCR Kit is a real-time qualitative PCR assay used on the Rotor-

Gene Q MDx instrument for the detection of seven somatic mutations in the human KRAS oncogene, using DNA extracted from formalin-fixed, paraffin-embedded (FFPE), colorectal cancer (CRC) tissue. The test is intended as a companion diagnostic to identify patients KRAS G12C mutated mCRC who may benefit from treatment with adagrasib in combination cetuximab. The accuracy of this assay for detecting KRAS G12C mutated mCRC has been adequately demonstrated during the 510(k) clearance.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant proposed edits to Section *12.1 Mechanism of Action* of the USPI based on nonclinical in vivo data.

In Study report PH-MRTX849-027, PDX-derived mouse xenograft model CR2528 showed adagrasib had moderate antitumor activity and cetuximab had minimal to no antitumor activity. The combination had much greater antitumor activity.

PDX-derived mouse xenograft model CR6256 showed adagrasib had high antitumor activity and cetuximab had moderate antitumor activity. The antitumor activity of the combination did not differ from adagrasib alone during the dosing phase.

CDX-derived mouse xenograft model SW1463 showed adagrasib and cetuximab both had moderate antitumor activity with adagrasib being more active. The combination had much greater antitumor activity.

Overall, the totality of the in vivo data indicate adagrasib in combination with cetuximab had increased antitumor activity in some cell line-derived and patient-derived KRAS G12C-mutant CRC models compared to adagrasib or cetuximab alone.

Pharmacology/toxicology has no approvability issues.

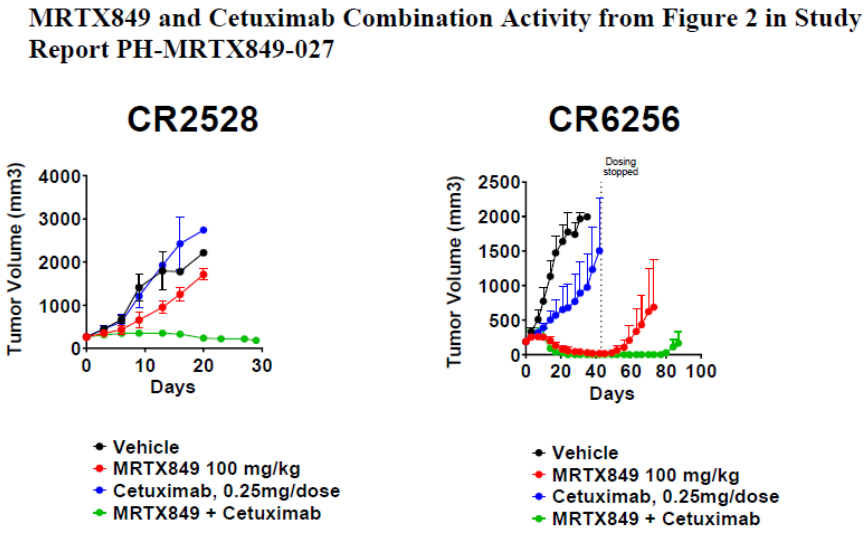
5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Study Report PH-MRTX849-027

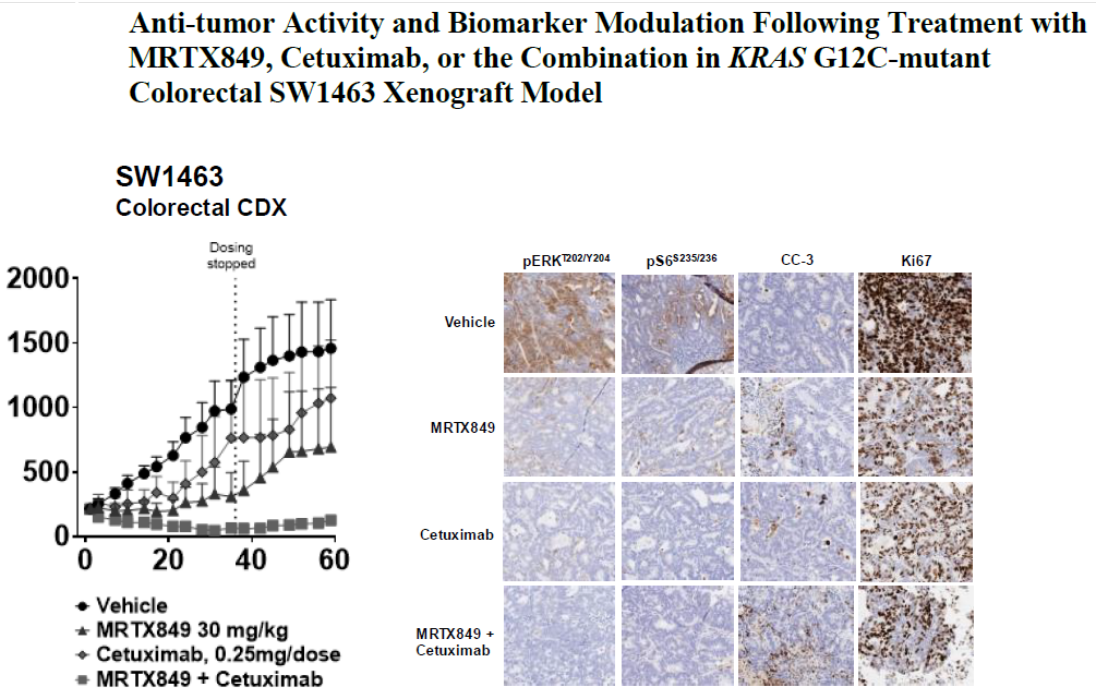
Figure 1: Adagrasib and cetuximab combination activity



(Excerpted from Applicant's submission)

MRTX849 at 100 mg/kg was administered orally daily and cetuximab at 0.25 mg/dose was administered IP Q3D to mice bearing PDX models with an average starting tumor volume ~250 mm3. MRTX849 was formulated (b) (4) *as a solution in 10% Captisol in 50 mM citrate buffer pH 5.0 in all studies. Data are shown as mean tumor volume +/- standard error of the mean (sem).*

Figure 2: Antitumor activity of adagrasib and cetuximab



(Excerpted from Applicant's submission)

MRTX849 at 30 mg/kg QD via oral gavage, cetuximab at 0.25 mg/dose Q3D via intraperitoneal injection, or the combination was administered to mice bearing the cell line-derived xenograft model, SW1463. Dosing was initiated when tumors were on average ~300 mm3. MRTX849 was formulated (b) (4) *as a solution*

in 10% Captisol 50 mM citrate buffer pH 5.0. Data shown represent the average of 5 tumors per treatment group with error bars indicating sem. For immunohistochemistry analysis, mice bearing SW1463 tumors were treated with a single dose of MRTX849 at 30 mg/kg PO, cetuximab at 0.25 mg/dose IP, or the combination and tumors were harvested 24 hours later. Tumors sections were fixed, embedded, and stained for pERK, pS6, Ki67 and cleaved caspase-3 (CC-3). 10X representative images are shown.

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Primary Reviewer Team Leader

6 Clinical Pharmacology

6.1.Executive Summary

This supplemental New Drug Application (sNDA) is for a new indication for adagrasib in combination with cetuximab in patients who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy and is supported by the colorectal cancer (CRC) Phase 1 sub study Cohorts 1, Phase 2 Cohort G, C and F, and Phase 1b Dose Optimization Expansion Cohort in Study 849-001 (KRYSTAL-1). The proposed dosing regimen of adagrasib in combination with cetuximab for the proposed indication of KRAS G12C-mutated locally advanced or metastatic CRC previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy is 600 mg orally BID.

The pivotal study (Study 849-001) provided evidence of the efficacy of adagrasib 600 mg BID in combination with cetuximab in patients with CRC previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

The clinical pharmacology review team assessed whether the proposed dosage is sufficiently optimized. The team reviewed data from 27 patients enrolled in the ongoing Phase 1b Dose Optimization Expansion Cohort of Study 849-001 administered adagrasib 400 mg BID in combination with cetuximab. Although the interim analysis of the adagrasib 400 mg BID combination cohort was limited by a 6-month follow-up duration, the ORR was comparable to the rate observed with adagrasib 600 mg BID in combination with cetuximab in the Phase 1 CRC sub study and Phase 2 Cohort G. However, there was a higher rate of adverse events (i.e., TEAEs leading to dose reduction or dose interruption) in the 600 mg BID combination cohort. Despite the comparable ORR and observed safety profile of the adagrasib administered at the 400 mg BID dose, the limited duration of follow-up, small sample size of the 400 mg BID combination cohort, and non-randomized design of the dosage optimization, limits the interpretation of the dose optimization cohort. The results from the Phase 1b Dose Optimization Expansion Cohort of Study 849-001 should be interpreted with caution.

The results of the updated population PK analysis with additional pooled data were consistent with previously conducted analyses. No clinically significant differences were observed in the PK of adagrasib based on age, sex, race, body weight, tumor type (NSCLC or CRC), tumor burden, mild to severe renal impairment, or mild to severe hepatic impairment. Furthermore, there are flat exposure-safety relationships in patients with NSCLC and CRC. Based on these data, the Applicant (b) (4) .

In summary, the proposed dosage of adagrasib 600 mg BID has demonstrated acceptable efficacy, however it has not been determined whether the 600 mg BID dosage represents an

optimized dosage from PK, safety, and efficacy perspectives as there was limited evaluation of adagrasib 400 mg BID. PMR (b) (4) is intended to optimize adagrasib dosage in NSCLC due to poor tolerability observed at 600 mg BID. Given the results of the PK analysis of adagrasib in patients with CRC receiving adagrasib in combination with cetuximab are consistent with the results of PK analysis of adagrasib in patients with NSCLC receiving single agent adagrasib, (b) (4) . The overall assessment of (b) (4) dosage in CRC patients will be revisited and leveraged by the totality of evidence including pharmacological activity, PK, E-R, and disease specific attributes.

REVIEW ISSUE	RECOMMENDATIONS/COMMENTS
Pivotal or supportive evidence of effectiveness	The pivotal trial provided evidence of effectiveness of adagrasib in combination with cetuximab for the proposed indication of KRAS G12C-mutated locally advanced or metastatic CRC in patients who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy with an ORR of 34% (95% CI: 25, 45) and median response duration of approximately 6 months (95% CI: 4, 8). Overall safety profile is consistent with the known safety profile of adagrasib.
General dosing instructions	The recommended dosing regimen is 600 mg orally BID of adagrasib in combination with cetuximab
Dosing in patient subgroups (intrinsic and extrinsic factors)	Results of updated population PK analysis are consistent with previously conducted analyses with no clinically significant differences in the PK of adagrasib based on based on age, sex, race, body weight, tumor type (NSCLC or CRC), tumor burden, mild to severe renal impairment, and mild to severe hepatic impairment. No dosage modifications are recommended for these factors.

Labeling:
The proposed labeling is acceptable upon the Applicant and FDA reaching agreements to the FDA recommended revisions to the labeling.

Action:
The Office of Clinical Pharmacology has reviewed the information contained in Supplement 5

of NDA 216340 and concluded that this efficacy supplement is approvable from a clinical pharmacology perspective.

6.2.Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Clinical studies conducted to characterize adagrasib PK and clinical pharmacology have been previously summarized in Module 2.7.2 in the original NDA 216340 for the NSCLC indication. For the current sNDA, the PK of adagrasib in combination with cetuximab in patients with KRAS G12C-mutated colorectal cancer (CRC) from Study 849-001 Phase 1 Substudy (cetuximab combination in CRC) is summarized below.

Following a single-dose administration of 600 mg adagrasib capsules under fasting conditions in combination with cetuximab, median (range) t_{max} of adagrasib was 6 (2 – 6) hours. Geometric mean C_{max} and AUC_{τ} were 297 ng/mL and 1390 h*ng/mL, respectively. The between-patient variability for C_{max} and AUC_{τ} was high, with geometric CV% of 273% and 491%, respectively.

Following multiple dosing of adagrasib 600 mg BID in combination with cetuximab, median t_{max} at steady state was approximately 4 hours. Geometric mean steady-state C_{max} ($C_{max,ss}$) was 2230 ng/mL. Geometric mean AUC during a dosage interval at steady state ($AUC_{\tau,ss}$) was 22700 h*ng/mL. Between-patient variability for $C_{max,ss}$ and $AUC_{\tau,ss}$ were moderate (ie, 39.4% and 54.6%, respectively).

The steady-state average concentration for adagrasib was 1990 ng/mL and exceeded the target efficacious average concentration of 1544 ng/mL (derived from the least sensitive preclinical model). Geometric mean accumulation ratios (R_{ac}) based on $C_{max,ss}$ (R_{ac} [C_{max}]) was 6.68 and R_{ac} based on AUC (R_{ac} [AUC]) was 11.8. Geometric mean minimum concentration (C_{min}) at steady state was 1660 ng/mL. The mean peak-to-trough (PTR) value was 1.23, indicating a “flat” PK profile at steady state for patients receiving 600 mg BID. Geometric mean apparent total clearance from plasma after oral administration at steady state (CL_{ss}/F) values was 3.26 L/h for adagrasib 600 mg BID given in combination with cetuximab.

Population PK analysis using data from 252 patients with advanced solid tumors with KRAS G12C mutation and 101 healthy subjects was used to develop the original adagrasib population PK model (original Module 2.7.2).

An additional population PK analysis was performed on patients with CRC, and the variability of PK parameters was evaluated through a formal covariate analysis. The effect of tumor type (CRC) on apparent clearance (CL/F) and apparent volume of distribution of the central compartment (Vc/F) was not significant, confirming no significant PK differences in patients with CRC and patients with solid tumors. The updated population PK model was used to derive post hoc estimates of the steady-state exposure of adagrasib in patients with advanced solid tumors (Section 3.2 of Module 2.7.2, Summary of Clinical Pharmacology).

Overall, these data show that steady-state exposure in patients with CRC receiving adagrasib 600 mg BID in combination with cetuximab was similar to patients with advanced solid tumors receiving single agent adagrasib 600-mg BID.

Reviewer's comment: *The PK of adagrasib has been adequately characterized in the initial NDA 216340. Results of PK data in CRC patients receiving adagrasib in combination with cetuximab are consistent with data submitted in the original NDA 216340. Descriptive statistics of adagrasib (600 mg BID) steady-state exposure parameters in patients with CRC and NSCLC are presented in Table 2.*

Table 6. Descriptive Statistics of Adagrasib Steady-State Exposure Parameters for 400 mg BID and 600 mg BID in Patients with Advanced Solid Tumors

PK Parameter	CRC		NSCLC	Other Cancer
	400 mg BID (n = 25)	600 mg BID (n = 179)	600 mg BID (n = 223)	600 mg BID (n = 22)
$AUC_{tau,ss}$ (ng.h/mL)				
Mean (CV%)	17700 (53.1%)	24000 (43.0%)	28900 (39.2%)	26100 (103.9%)
Median [Q05; Q95]	16400 [7910; 28400]	23300 [10500; 41700]	27200 [14200; 48700]	20800 [6420; 36400]
Geo. Mean	15800	21900	26900	20600
$C_{ave,ss}$ (ng.h/mL)				
Mean (CV%)	1470 (53.1%)	2000 (43.0%)	2410 (39.2%)	2170 (103.9%)
Median [Q05; Q95]	1370 [659; 2360]	1940 [875; 3480]	2270 [1180; 4060]	1730 [535; 3030]
Geo. Mean	1320	1820	2240	1720
$C_{max,ss}$ (ng/mL)				
Mean (CV%)	1560 (51.4%)	2120 (43.2%)	2570 (39.1%)	2290 (101.7%)
Median [Q05; Q95]	1430 [730; 2450]	2010 [933; 3770]	2390 [1240; 4320]	1860 [556; 3260]
Geo. Mean	1410	1940	2390	1820
$C_{min,ss}$ (ng/mL)				
Mean (CV%)	1360 (55.5%)	1840 (43.4%)	2220 (40.2%)	2020 (106.9%)
Median [Q05; Q95]	1290 [577; 2260]	1790 [782; 3160]	2130 [1050; 3780]	1610 [508; 2760]
Geo. Mean	1210	1680	2050	1590
$T_{max,ss}$ (h)				
Mean (CV%)	4.96 (17.9%)	5.14 (19.4%)	5.07 (17.5%)	5.45 (16.7%)
Median [Q05; Q95]	5.00 [4.00; 6.30]	5.00 [3.50; 6.50]	5.00 [4.00; 6.50]	5.50 [4.03; 6.98]
Geo. Mean	4.88	5.02	5.00	5.38
PTR				
Mean (CV%)	1.17 (6.2%)	1.16 (9.9%)	1.17 (9.9%)	1.15 (8.7%)
Median [Q05; Q95]	1.16 [1.08; 1.26]	1.13 [1.05; 1.36]	1.15 [1.04; 1.34]	1.12 [1.06; 1.29]
Geo. Mean	1.17	1.16	1.16	1.15

Source: MIRA-PMX-MRTX849-4848, Table 7.

Abbreviations: $AUC_{tau,ss}$ = area under the curve over the dosing interval under steady state; BID = twice-daily; $C_{ave,ss}$ = average concentration at steady state; $C_{max,ss}$ = maximum concentration at steady state; $C_{min,ss}$ = minimum concentration at steady state; CRC = colorectal cancer; CV = coefficient of variation; NSCLC = Nonsquamous non-small cell lung cancer; PTR = peak to trough ratio ($C_{max,ss}$ /$C_{min,ss}$); Q05 = fifth percentile; Q95 = 95th percentile; $T_{max,ss}$ = time of maximum concentration at steady state.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed starting dosage of adagrasib in combination with cetuximab for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic CRC, who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy is 600 mg BID.

The clinical pharmacology properties of adagrasib have been extensively characterized in the original NDA 216340 for NSCLC Module 2.7.2.

Exposure-response analysis evaluating the relationship between adagrasib exposure and ORR identified no ER relationships between adagrasib plasma exposure (from the tested dose levels of 400 mg and 600 mg BID in combination with cetuximab) and the probability of response. The absence of ER relationship for the efficacy endpoint (ORR) suggested that exposure over the tested dose range may have already represented a plateau of the ER relationship.

Exposure-safety analysis was also conducted to evaluate the relationship between adagrasib (single agent or in combination with cetuximab) exposure measures and treatment-emergent adverse events of interest including any Grade ≥ 3 TEAEs, diarrhea, nausea, vomiting, ALT > 3 x ULN, lipase > 3 x ULN, or hyponatremia in patients NSCLC from Study 849-001 Phase 1/1b Monotherapy Dose Finding Segment and Phase 2 Cohort A (NSCLC) and in patients with CRC from Study 849-001 Phase 1 substudy, Phase 2 Cohorts C, F, and G, and Phase 1b dose optimization expansion cohort. No significant exposure-safety relationships for treatment-emergent adverse events of interest were identified, except for adagrasib $C_{max,Week1-3}$ and the probability of AST > 3 x ULN.

Reviewer's comment: *FDA generally agrees with the Applicant's position that the proposed dosage of adagrasib 600 mg BID has demonstrated acceptable efficacy, however, no dose-response relationship for ORR was observed between the 400 mg and 600 mg BID dosages. Based on these data and limited available data in the 400 mg BID dosage group, the optimized dosage for adagrasib is inconclusive.*

1. *ORR was comparable between response-evaluable patients who received adagrasib 600 mg BID + cetuximab (standard QW or Q2W dosages) (n=94 from Phase 1 substudy cohort 1 and Phase 2 cohort G) and patients who received adagrasib 400 mg BID + cetuximab (Q2W) (n=25). Summary of efficacy endpoints for both adagrasib dosing regimens in patients with CRC are presented in Table 3.*
2. *The incidence of treatment-emergent adverse reactions leading to dosage reduction or dosage interruption were substantially lower at the 400 mg BID dosage compared with the 600 mg BID dosage in combination with cetuximab. Summary of safety endpoints for both adagrasib dosing regimens in patients with CRC are presented in Table 4.*
3. *Given that updated population PK analysis indicate no clinically significant differences in*

the PK of adagrasib based on tumor type (NSCLC or CRC) and safety profile attributed to adagrasib is similar, (b) (4)

Table 7. Summary of Efficacy Results Comparing Adagrasib 400 mg and 600 mg BID in Combination with Cetuximab in CRC in Study 849-001 Phase 1 Substudy Cohort 1, Phase 2 Cohort G, and Phase 1b Dose Optimization Expansion Cohort

Efficacy Endpoint	Adagrasib 400 mg BID + Cetuximab Q2W (N=25) DCO 30 Jun 2023	Adagrasib 600 mg BID + Cetuximab* (N=94) DCO 12 Dec 2023
Median follow-up duration	6 months	Cohort 1 = 30 months Cohort G = 10 months
OS, median (95% CI)	NR (NE, NE)	16 months (12, 19)
PFS, median (95% CI)	NR (5, NE)	7 months (6, 7)
ORR (95% CI)	36% (18, 58)	34% (25, 45)
DOR, median	4 months (3, NE)	6 months (4, 8)

**500 mg/m² Q2W (n=15 in Cohort 1 and n=62 in Cohort G) or 400 mg/m² followed by 250 mg/m² QW (n=17 in Cohort 1)*

Source: Table 14.2.1.1.1 in Study 849-001 Final CSR (full analysis set) and Table 14.2.1.1.1 in Study 849-001 –Phase 1b Dose Optimization Expansion Interim CSR (full analysis set)

Abbreviations: BID = twice daily, Q2W = every 2 weeks, DCO = data cut-off, OS = overall survival, PFS = progression-free survival, ORR = overall response rate, DOR = duration of response, NE = not estimable

Table 8. Summary of Treatment-emergent Adverse Reactions Comparing Adagrasib 400 mg and 600 mg BID in Combination with Cetuximab in CRC in Study 849-001 Phase 1 Substudy Cohort 1, Phase 2 Cohort G, and Phase 1b Dose Optimization Expansion Cohort

Safety endpoints	Adagrasib 400 mg BID + Cetuximab Q2W (N=27) *DCO 30 Jun 2023*	Adagrasib 600 mg BID + Cetuximab* (N=94) *DCO 12 Dec 2023*
Grade ≥3 TEAE	56%	66%
Any TEAE with outcome of death	7%	4%
Treatment-emergent SAE	33%	30%
Dose discontinuation due to TEAE **adagrasib** **cetuximab**	 4% 7%	 2% 9%

Dose reduction due to TEAE		
adagrasib	19%	35%
cetuximab	15%	6%
Dose interruption due to TEAE		
adagrasib	48%	70%
cetuximab	41%	57%

**500 mg/m² Q2W (n=15 in Cohort 1 and n=62 in Cohort G) or 400 mg/m² followed by 250 mg/m² QW (n=17 in Cohort 1)*

Source: Table 14.3.1.2.1 in Study 849-001 Final CSR (full analysis set) and Table 14.3.1.2.1 in Study 849-001 –Phase 1b Dose Optimization Expansion Interim CSR (full analysis set).

Abbreviations: BID = twice daily, Q2W = every 2 weeks, DCO = data cut-off, TEAE = treatment-emergent adverse effects, SAE = serious adverse effects

Therapeutic Individualization

Covariate analysis was performed in the previous population PK analysis conducted in the original NDA. In the present analysis, the effect of CRC was tested to account for potential differences in the apparent clearance (CL/F) and apparent central volume of distribution (Vc/F) in patients with CRC vs. other subjects (i.e., patients with other cancer types or healthy subjects).

Reviewer's comment: *FDA agrees with the Applicant's conclusion based on the updated population PK analysis. The final population PK model included data from 556 patients and healthy volunteers, of which 37% had CRC. The effect of CRC and adagrasib formulation (73% capsule, 18% tablet, or 9% both) on adagrasib exposure in the final population PK model were not considered clinically meaningful in the population PK analysis.*

Outstanding Issues

Although adagrasib 600 mg BID has demonstrated acceptable efficacy, whether the 600 mg BID dosage represents an optimized dosage has not been determined given the limited evaluation of adagrasib 400 mg BID. The optimized dosage of adagrasib in combination with cetuximab in CRC will be re-evaluated following (b) (4) and final analysis of Phase 1b dosage optimization expansion cohort (400 mg BID dosage).

PMR (b) (4) is intended to optimize adagrasib dosage in NSCLC due to a numerically high incidence of Grade 3-4 adverse events, dose interruptions and dose reductions observed at 600 mg BID in CRC and its comparable safety profile between CRC and NSCLC, (b) (4) . The supportive evidence includes similarity in *in vitro* pharmacological activity between NSCLC and CRC at the same adagrasib exposure,

comparable PK across cancer types, and a flat exposure-efficacy relationship inclusive of 25 CRC patients receiving 400 mg BID of adagrasib. The disease specific attributes that would also support the benefit (b) (4) , include the relatively low incidence of brain metastasis in CRC which typically necessitates a higher systemic exposure, and the likely low susceptibility to efficacy loss with the combination use of adagrasib and cetuximab.

6.3.Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Efficacy and safety results from Study 849-001 Phase 1 Substudy and Phase 2 Cohort G support the selection of 600 mg BID as an effective and safe dose.

From a clinical efficacy perspective, the 600-mg BID dose level resulted in durable clinical benefit with an ORR per BICR of 34% (95% CI: 25%, 45%) and median duration of response of 6 months (95% CI: 4, 8) in patients with advanced CRC with KRAS G12C mutation.

From a clinical safety perspective, the 600-mg BID dose level has an acceptable safety profile that included manageable gastrointestinal (GI) events, laboratory abnormalities, and QT prolongation. For patients receiving 600 mg BID in combination with cetuximab in the Phase 2 Cohort G, the median times to the first dose reduction or first dose interruption were 48 and 2 weeks, respectively. The occurrence of an adverse event resulting in first dose reduction or interruption was observed in approximately 34% and 31% of patients, respectively. Adverse events that led to dose modification included nausea, fatigue, ALT/AST increased, decreased appetite, dermatitis acneiform dizziness, electrocardiogram QT prolonged, diarrhea, dysarthria, and vomiting.

Pharmacokinetics

To support the original NDA in NSCLC, population PK analysis was performed with data from a total of 353 patients and 4 clinical studies (Studies 849-001, 849-004, 849-005, and 849-006) to characterize the PK profile of adagrasib and to assess the impact of potential covariates ((b) (4) Report MIRA-PMX-MRTX849-1556, original Module 2.7.2). Overall, a 2-compartment model with sequential zero-order then first-order absorption and linear elimination adequately described the PK of adagrasib in both patients and healthy subjects. 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), ECOG PS (0, 1), baseline tumor burden, mild and moderate renal impairment (CLCR ≥ 30 mL/min or eGFR ≥ 30 mL/min/1.73 m2), or mild hepatic impairment (NCI-ODWG criteria).

The previous population PK model developed in patients mostly with NSCLC and healthy volunteers was updated with additional data from patients with CRC (n=207) from Study 849-001 (Phase 1 Substudy; Phase 2 Cohorts C, F, and G; and Phase 1b Dose Optimization Expansion Cohort). The final population PK model was similar to the original population PK model used in

submission in patients with NSCLC.

Complete absorption is expected to occur within 8 hours (i.e., 5 times the absorption half-lives). The estimated rate of absorption is similar to the estimated K_a of the original PK model, where complete absorption was estimated to occur within 9 hours after dosing.

The CL/F and Vc/F of adagrasib were 34.6 L/h and 811 L, respectively. The BSV of CL/F and V_c/F were 50.9% and 63.6%, respectively.

Post-hoc PK parameters were derived with the final population PK model and simulations were performed to derive exposure parameters of adagrasib for both the 400- and 600-mg BID dose levels. Overall, steady-state exposures for 600 mg BID in patients with CRC were similar to patients with NSCLC or other solid tumors.

Reviewer's comment: *FDA considers the Applicant's population PK analysis appropriate and agrees with the Applicant's assessment. The parameter estimates of the updated population PK model are consistent with the previous analysis in the original NDA for the NSCLC indication.*

6.3.2. Clinical Pharmacology Questions

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

Adagrasib 600 mg BID dose level was selected as the proposed dose for patients with CRC with KRAS G12C mutation taking into consideration exposure-response (ER) analyses, clinical safety and efficacy, and benefit-risk assessment.

Exposure-response (ER) analyses of the probability of response per BICR were performed in patients with CRC treated with adagrasib in combination with cetuximab from Study 849-001 (i.e., Phase 1b 400-mg BID Dose Optimization Expansion Cohort; Phase 2 Cohort G, C and F; and Phase 1 Substudy). Results showed the following:

- In patients with CRC receiving single agent adagrasib or adagrasib in combination with cetuximab, no relationship between adagrasib exposure and the probability of any Grade ≥ 3 TEAEs, diarrhea, nausea, vomiting, ALT > 3 x ULN, lipase > 3 x ULN, or hyponatremia was observed. However, a statistically significant relationship between adagrasib $C_{max,Week1-3}$ and the probability of AST > 3 x ULN was observed.
- No ER relationships were observed between adagrasib plasma exposure (from the tested dose levels of 400 mg and 600 mg BID in combination with cetuximab) and the probability of response. The absence of ER relationship for the efficacy endpoint (ORR) suggested that exposure over the tested dose range may have already represented a plateau of the ER relationship.

From a clinical efficacy perspective, the 600 mg BID dose level in combination with cetuximab resulted in durable clinical benefit with an ORR per BICR of 34.0% (95% CI: 24.6% to 44.5%) and

median DOR 5.78 months (95% CI: 4.17 to 7.62 months) in patients with advanced CRC with *KRAS* G12C mutation who have previously received treatment and have no available standard treatment. The BICR ORR of 34% demonstrates a > 5-fold increase and a clinically meaningful improvement over standard-of-care therapies ranging in response rate between 1% to 6% for patients with advanced CRC with an unmet medical need.

Reviewer's comment: *FDA generally agrees that the clinical pharmacology program provides evidence of effectiveness of adagrasib 600 mg BID in combination with cetuximab; however, no dose-response relationship for ORR was observed between the 400 mg and 600 mg BID dosages. Given the comparable efficacy and better tolerability of the 400 mg BID dosage, the optimized dosage for adagrasib is inconclusive given the significantly shorter duration of follow-up in the 400 mg BID dosage group (6 months) compared to the pooled 600 mg BID dosage group (12 months), small sample size, and lack of dosage randomization between the two dosages. Refer to Section 6.2.2. General Dosing and Therapeutic Individualization for more details.*

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

From a clinical safety perspective, the 600 mg BID dose level in combination with cetuximab had an acceptable safety profile comparable to the 400 mg BID dose that included manageable gastrointestinal events, laboratory abnormalities, and QT prolongation. A detailed analysis of the safety of adagrasib in combination with cetuximab is presented in Section 8.2.

Exposure-Safety

A total of 312 patients in Study 849-001 with solid tumors (mostly NSCLC) (Phase 1/1b Adagrasib Monotherapy Dose-Finding Segments and Phase 2 Cohort A [NSCLC]) and with CRC (Phase 1 Substudy; Phase 2 Cohorts C, F, and G; and Phase 1b Dose Optimization Expansion Cohort) with exposure parameters of adagrasib at steady state were included in the exposure-safety analysis. Of the patients included, 203 (65%) were patients with CRC, and 109 (35%) were patients from the previous ER analysis in NSCLC. Out of the 203 patients with CRC, 178 (88%) and 25 (12%) received the planned doses of 600 mg BID and 400 mg BID, respectively. Safety endpoints included in the exposure-safety analysis included any grade ≥3 TEAEs, diarrhea, nausea, vomiting, ALT > 3 x ULN, AST > 3 x ULN, lipase > 3 x ULN, and hyponatremia.

Any grade ≥3 TEAEs

Overall, the effect of tumor type did not appear to impact the overall safety profile, except for any Grade ≥ 3 adverse events in non-CRC tumor type using $C_{max,ss}$ and $C_{max,ss,mean}$ as exposure metrics (p-value <0.05). For this reason, the exposure-safety analysis reported in this section (and for the analyses below) was performed in patients with CRC. A total of 130 patients (64%) presented with any Grade ≥ 3 adverse events. The observed probability of any Grade ≥ 3 adverse events in patients with $C_{max,ss,mean}$ in the first, second, third, and fourth quartiles were 57%, 69%, 67%, and 63%, respectively. No statistically significant ER relationship between $C_{max,ss,mean}$ and the probability of any Grade ≥ 3 adverse events was observed (p-value of

exposure = 0.25). The effects of age, sex, race, ECOG PS, formulation, weight, and combination with cetuximab were not statistically significant at p-value = 0.05. Similar results were observed for $C_{max,ss}$, whereby no statistically significant ER relationship was observed (p-value for exposure = 0.26); however, the effect of age was significant (p-value = 0.04), with older patients having lower probability of Grade ≥ 3 adverse events.

Diarrhea

A total of 155 patients (76%) presented with diarrhea (any grade). The observed probability of diarrhea in patients with $C_{max,ss,mean}$ in the first, second, third, and fourth quartiles were 78%, 86%, 78%, and 69%, respectively. No statistically significant ER relationship was observed between $C_{max,ss,mean}$ and the probability of diarrhea (p-value for exposure = 0.16). In addition, the effects of age, sex, race, ECOG PS, formulation, weight, and combination with cetuximab were not statistically significant at p-value = 0.05. Similar results were observed for $C_{max,ss}$ whereby no statistically significant ER relationship was observed (p-value for exposure = 0.83).

Nausea

A total of 160 patients (79%) presented with nausea (any grade). The observed probability of nausea in patients with $C_{max,ss,mean}$ in the first, second, third, and fourth quartiles were 78%, 76%, 90%, and 73%, respectively. No statistically significant ER relationship was observed between $C_{max,ss,mean}$ and the probability of nausea (p-value for exposure = 0.74). The effect of sex was significant (p-value = 0.03), with females more likely to experience nausea. The effects of age, race, ECOG PS, formulation, weight, and combination with cetuximab were not statistically significant at p-value = 0.05. Similar results were observed for $C_{max,ss}$ whereby no statistically significant ER relationship was observed (p-value for exposure = 0.14).

Vomiting

A total of 125 patients (62%) presented with vomiting (any grade). The observed probability of vomiting in patients with $C_{max,ss,mean}$ in the first, second, third, and fourth quartiles were 55%, 63%, 71%, and 55%, respectively. No statistically significant ER relationship between $C_{max,ss,mean}$ and the probability of vomiting was observed (p-value of exposure = 0.9). The effect of sex was significant (p-value = 0.01) with females more likely to experience vomiting. The effects of age, race, ECOG PS, formulation, weight, and combination with cetuximab were not statistically significant at p-value = 0.05. Similar results were observed for $C_{max,ss}$ whereby no statistically significant ER relationship was observed (p-value of exposure = 0.17).

ALT or AST > 3 x ULN

A total of 21 patients (10%) or 23 patients (11%) presented with ALT or AST > 3 × ULN, respectively. The observed probability of ALT > 3 × ULN in patients with $C_{max,Week1-3}$ in the first, second, third, and fourth quartiles were 6%, 15%, 10%, and 10%, respectively. The observed probability of AST > 3 × ULN in patients with $C_{max,Week1-3}$ values in the first, second, third, and fourth quartiles were 4%, 8%, 17%, and 12%, respectively. A statistically significant ER relationship was observed between $C_{max,Week1-3}$ and the probability of AST > 3 × ULN (p-value for exposure effect = 0.03), but not for ALT > 3 x ULN (p-value for exposure effect = 0.9). The

effects of age, sex, race, ECOG PS, formulation, weight, and combination with cetuximab were not statistically significant at p-value = 0.05 for ALT > 3 x ULN, but patients receiving adagrasib in combination with cetuximab were significantly less likely to have AST elevation (p-value = 0.03).

Lipase > 3 x ULN

A total of 14 patients (7%) presented with lipase > 3 × ULN. The observed probability of lipase > 3 × ULN in patients with $C_{max,ss,mean}$ in the first, second, third, and fourth quartiles were 10%, 6%, 4%, and 8%, respectively. No statistically significant ER relationship between $C_{max,ss,mean}$ and the probability of lipase > 3 × ULN was observed (p-value for exposure = 0.97). In addition, the effect of sex was statistically significant (p-value = 0.0304), with females less likely to experience lipase elevations. However, 3 females out of 203 patients included in the analysis had lipase > 3 × ULN result, and this should be interpreted with caution because of the low number of subjects. The effects of age, race, ECOG PS, formulation, weight, and combination with cetuximab were not statistically significant at p-value = 0.05. Similar results were observed for the probability of lipase > 3 × ULN as a function of $C_{max,ss}$, whereby no statistically significant ER relationship was observed (p-value for exposure = 0.95).

Hyponatremia

A total of 21 patients (10%) presented with hyponatremia. The observed probability of hyponatremia in patients with $C_{max,ss,mean}$ in the first, second, third, and fourth quartiles were 12%, 12%, 6%, and 8%, respectively. No statistically significant ER relationship between $C_{max,ss,mean}$ and the probability of hyponatremia was observed (p-value for exposure = 0.5). In addition, the effect of ECOG PS was statistically significant (p-value = 0.04), with patients having a worse ECOG PS score more likely to experience hyponatremia. The effects of age, sex, race, formulation, weight, and combination with cetuximab were not statistically significant at p-value = 0.05. Similar results were observed for the probability of hyponatremia as a function of $C_{max,ss}$ whereby statistically no significant ER relationship was observed (p-value for exposure = 0.065). The effects of age, sex, race, ECOG PS, formulation, weight, and combination with cetuximab were not statistically significant at p-value = 0.05 for $C_{max,ss}$.

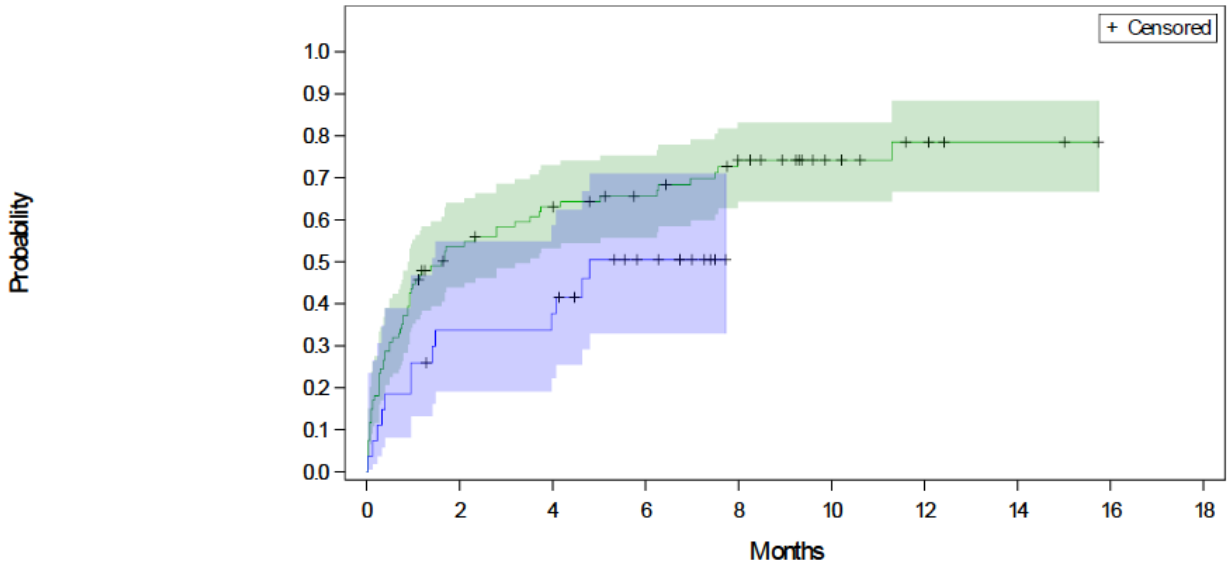
In conclusion, in 203 patients with CRC included in the exposure-safety analysis, 178 patients (88%) and 25 patients (12%) started treatment at 600 mg BID and 400 mg BID, respectively. In patients with CRC receiving single agent adagrasib or adagrasib in combination with cetuximab, no relationship between adagrasib exposure and the probability of any Grade ≥ 3 TEAEs, diarrhea, nausea, vomiting, ALT > 3 × ULN, lipase > 3 × ULN, or hyponatremia was observed. A statistically significant relationship between adagrasib $C_{max,Week1-3}$ and the probability of AST > 3 × ULN was observed (p-value for exposure effect = 0.03). The effect of adagrasib formulation was not statistically significant at p-value = 0.05 for all tested safety endpoints.

Tolerability by dosage

In patients administered the tablet formulation of adagrasib, the percentage of patients with a treatment related gastrointestinal TEAE was higher for adagrasib 600 mg BID plus cetuximab (88.9%) than for adagrasib 400 mg BID plus cetuximab (74.1%). The most common adagrasib and/or cetuximab treatment related gastrointestinal TEAE was nausea in both dose groups, with a higher frequency in patients receiving 600 mg BID plus cetuximab (61.1% versus 51.9%). The percentage of patients with a gastrointestinal TEAE leading to an adagrasib and/or cetuximab dose reduction or interruption was higher in patients who received adagrasib 600 mg BID plus cetuximab (22.2%) than in patients who received adagrasib 400 mg BID plus cetuximab (11.1%).

The inverted Kaplan-Meier Plot for specific TEAEs leading to adagrasib dosage modification in CRC by dose was produced to compare the pattern of the time to onset for different follow-up periods by data cutoff (June 2023) given the difference in event rate observed between the two dosages could be confounded by time. Figure 1 showed that across the shared follow-up time, patients treated with adagrasib 400mg BID and cetuximab had a numerically lower risk of experiencing any of these specific TEAEs leading to adagrasib dose interruption or reduction compared to those treated with adagrasib 600mg BID + cetuximab. The two curves started to separate early on which remained separated for the shared follow-up time, indicating that the numeric difference in AE event rate between the two dosages was not likely confounded by follow-up time.

Figure 3. Inverted Kaplan-Meier Plot: Time to onset of any TEAE leading to adagrasib dose modification



Reviewer's comment: *The FDA generally agrees with the Applicant's assessment but cautions that the interpretation of results from the E-R analysis is limited due to the narrow exposure range explored and confounding effect of dosage modifications. Given the stated limitations, the current E-R analysis for safety and efficacy is not adequate to support 600 mg BID dosage as an optimized dosage. The dosage for CRC will be re-evaluated pending completion of PMR* (b) (4) *and final analysis of Phase 1b dosage optimization expansion cohort. The combination use of adagrasib with cetuximab did not show an elevated risk for safety, suggesting that the extrapolation of safety from single agent adagrasib administration to the combination regimen is feasible. Refer to Section 6.2.2. General Dosing and Therapeutic Individualization for more details.*

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

There are no new data for alternative dosing regimens for subpopulations based on intrinsic patient factors in this submission. Results of the final population PK model are consistent with previous findings the initial NDA 216340.

Reviewer's comment: *No changes are warranted in the currently approved labeling regarding dosing for subpopulations based on intrinsic patient factors for the proposed dosage of 600 mg BID. However, for patients weighing over 100 kg, AUC is expected to decrease by >20%.* (b) (4) *given the observed difference in weight distribution between the CRC and NSCLC population (Figure 2), and the exposure distribution for CRC patients weighing >100 kg with adagrasib 600 mg BID is expected to align with exposures in CRC patients receiving 400 mg BID (Figure 3).*

Figure 4. Body weight distribution by cancer type

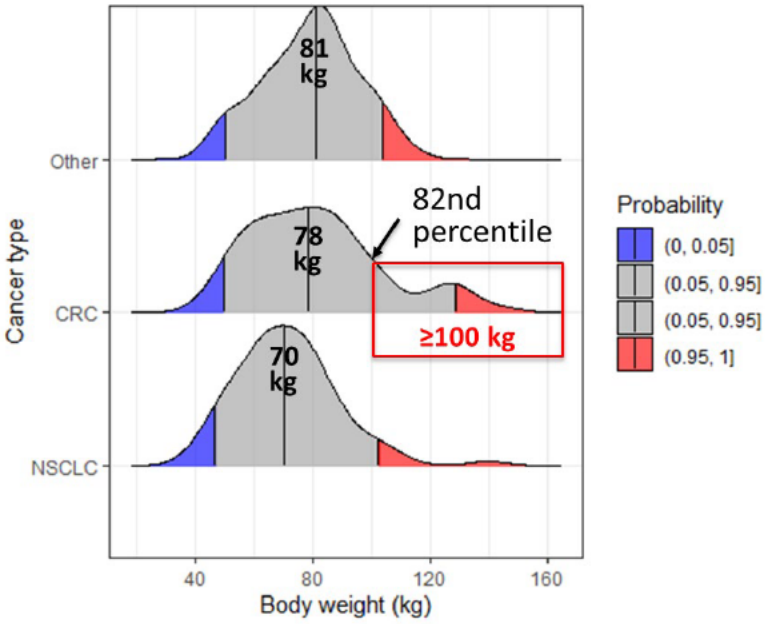
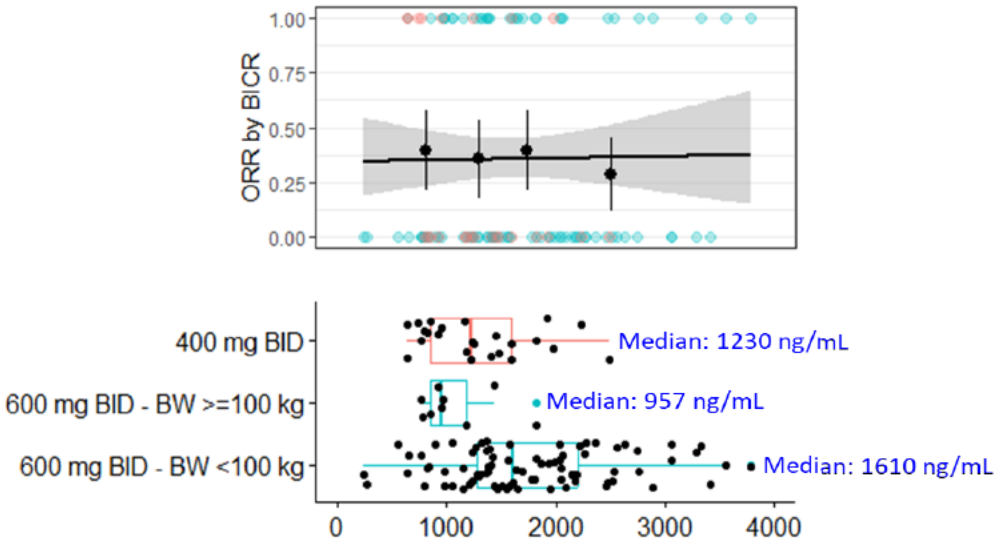


Figure 5. Exposure and ORR by 100 kg body weight cutoff in CRC patients



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

There are no new data for clinically relevant food-drug or drug-drug interactions in this submission.

Reviewer's comment: *No changes are warranted in the currently approved labeling regarding dosing for food-drug or drug-drug interactions.*

6.3.2.5 Question on clinically relevant specifications?

None.

X Lily Leu	X Jason Moore
Clinical Pharmacology Primary Reviewer	Clinical Pharmacology Team Leader
X Ye Xiong	X Youwei Bi
Pharmacometrics Primary Reviewer	Pharmacometrics Team Leader

7 Sources of Clinical Data and Review Strategy

7.1.Table of Clinical Studies

Mirati has submitted data from Study 849-001 to demonstrate the safety and efficacy of adagrasib in combination with cetuximab for the treatment of patients with advanced or metastatic colorectal cancer (CRC) with KRAS G12C mutation who have previously been treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, in addition to an anti-vascular endothelial growth factor (VEGF) therapy (if eligible).

Study 849-001 is an ongoing phase 1/2 multiple expansion cohort trial of adagrasib in patients with advanced solid tumors with KRAS G12C mutation (refer to Figure 4). The Phase 1 Substudy Cohort 1 and Phase 2 Cohort G, which was comprised of 94 patients (32 in the Phase 1 Substudy Cohort 1 and 62 in Phase 2 Cohort G) with advanced or metastatic CRC harboring a KRAS G12C mutation provided pivotal efficacy data of adagrasib 600 mg BID in combination with cetuximab for the proposed indication. All patients were enrolled in the United States.

In addition to pivotal data from the Phase 1 Substudy Cohort 1 and Phase 2 Cohort G combined, data from the Phase-1b Dose Optimization Cohort evaluating a lower dose of adagrasib (400 mg BID) in combination with cetuximab and Phase 2 Cohorts C and F were submitted to support the assessment of the benefit-risk of single agent adagrasib (600 mg BID).

Figure 6 : Schema for Study 849-001

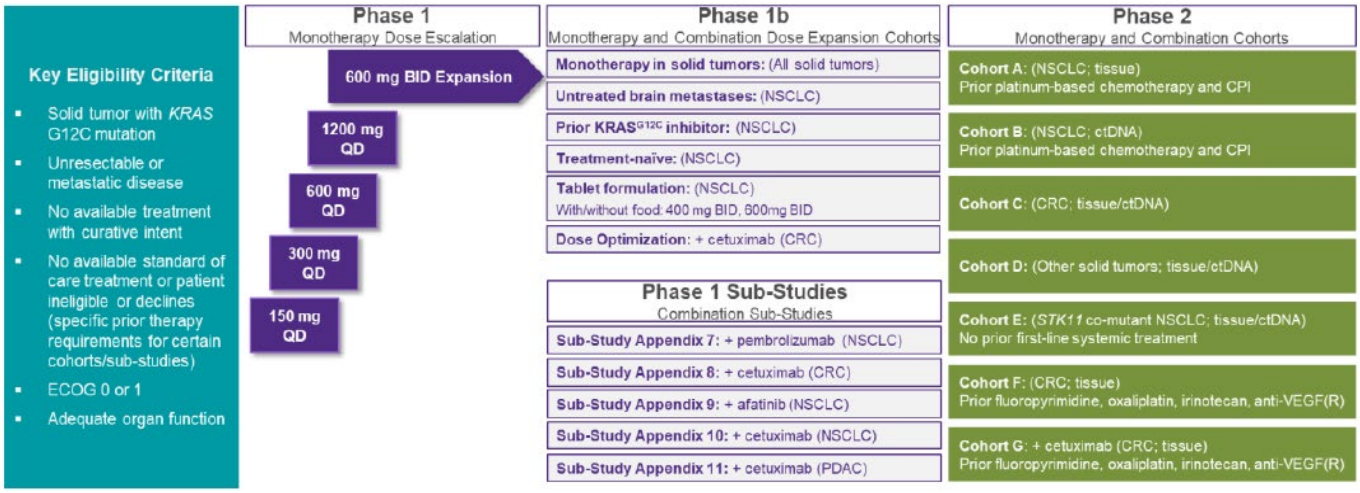


Table 9: Data from Study 849-001 to support the efficacy and safety assessment

Segment CSR Status Start Date[1] SCE Data Cutoff Date	Study Drug Starting Dose, Route & Regimen	Study Objective	No. Pts[2] Enrolled	Diagnosis Inclusion Criteria (Prior Systemic Therapy)
Pivotal Cohorts and Sub-Studies Studies (Combination)				
Phase 1 Substudy Cohort 1 Final 23 Apr 2020 30 Jun 2023	A: Oral/600 mg BID C: IV/400 mg/m^2 initial dose; 250 mg/m^2 QW or C: IV/500 mg/m^2 Q2W	Safety, tolerability, PK, MTD/RP2D, clinical activity	32	CRC with *KRAS* G12C mutation in tumor tissue and/or ctDNA No available treatment with curative intent; no available standard-of-care treatment, or patient was ineligible or declined treatment.
Phase 2 Cohort G Final 08 Feb 2022 30 Jun 2023	A: Oral/600 mg BID C: IV/500 mg/m^2 Q2W	Clinical activity/ efficacy, safety, tolerability, PK	62	CRC with *KRAS* G12C mutation in tumor tissue Prior treatment with at least a fluoropyrimidine, oxaliplatin, irinotecan, a VEGF(R) inhibitor[3].
Supportive Cohorts (Combination and Monotherapy)				
Phase 2 Cohort C Final 22 Jan 2020 01 Mar 2023	A: Oral/600 mg BID	Clinical activity, safety, tolerability, PK	44	CRC with *KRAS* G12C mutation in tumor tissue and/or ctDNA. No available treatment with curative intent; no available standard-of-care treatment, or patient was ineligible or declined treatment.
Phase 2 Cohort F Final 28 May 2021 01 Mar 2023	A: Oral/600 mg BID	Clinical activity, safety, tolerability, PK	42	CRC with *KRAS* G12C mutation in tumor tissue Prior treatment with at least a fluoropyrimidine, oxaliplatin, irinotecan, a VEGF(R) inhibitor[3].
Phase 1b Dose Optimization Expansion Cohort Interim 24 Oct 2022 30 Jun 2023	A: Oral/400 mg BID C: IV/500 mg/m^2 Q2W	Safety, tolerability, PK, clinical activity	27	CRC with *KRAS* G12C mutation in tumor tissue and/or ctDNA Prior treatment with at least a fluoropyrimidine, oxaliplatin, irinotecan, a VEGF(R) inhibitor[3].

A: Adagrasib, C: Cetuximab, BID = twice daily

[1] Date of first informed consent.

[2] As of the data cutoff date for each cohort.

[3] Patients known to have MSI-H or dMMR phenotype must have previously received or not be eligible to receive a PD-1 inhibitor; whereas patients known to have *BRAF* V600E mutation must have previously received a BRAF inhibitor.

Source: Table 1 from Integrated Summary of Efficacy.

7.2.Review Strategy

The clinical and statistical reviewers followed the below strategy to assess the efficacy and safety of adagrasib in combination with cetuximab in this application.

1. Published literature on the epidemiology, biology, and treatment of mCRC.
2. Relevant meeting minutes from IND 152345.
3. The 849-001 trial study report, protocol, protocol amendments, Independent Review Committee Charter, statistical analysis plan and amendments, select case report forms, and patient narratives.
4. Review and analysis of relevant efficacy and safety datasets and SAS programming algorithms to confirm efficacy measures and evaluate the risk:benefit profile.
5. The Applicant's Summary of Clinical Safety and the Integrated Summary of Safety
6. Consultation reports from OSI.
7. The Applicant's responses to FDA requests for additional information.
8. The regulatory history of other drugs approved for mCRC.
9. Review and evaluation of proposed labeling.
10. Information provided by the Applicant in response to FDA Information Requests

The FDA also reviewed the following:

1. Clinical Investigator Financial Disclosure documents
2. Site-specific inspection data provided by the FDA Office of Scientific Investigations

8 Statistical and Clinical and Evaluation

8.1.Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 849-001

Trial Design

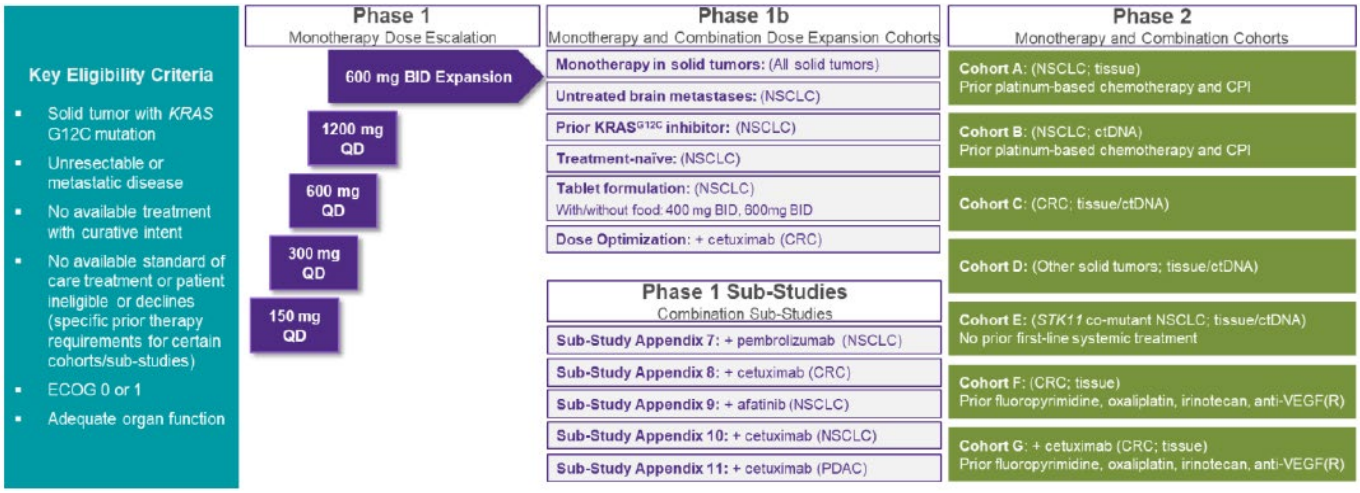
Study 849-001 is a first-in-human, Phase 1/2, dose escalation and multiple expansion cohort trial of adagrasib as a single agent or in combination with other anticancer therapies in patients with advanced solid tumors with KRAS G12C mutation. This study included a Phase-1 dose escalation, Phase-1b dose expansion cohorts, a single-arm Phase-2 portion, and exploratory Phase 1 Substudies.

The Phase 1 dose escalation part was planned to assess safety and to determine maximum tolerated dose of adagrasib.

The Phase 1b expansion cohorts were implemented to allow additional evaluation of safety, tolerability, PK and/or early evidence of clinical activity prior to selection of the RP2D and regimen that would be evaluated in Phase 2.

The Phase 2 segment of the study was designed to evaluate the clinical activity/efficacy of single agent adagrasib and in combination with selected cancer therapeutic agents in cohorts of patients having tumors with KRAS G12C mutation and specified tumor histology, treatment history or baseline characteristics. In Phase 2, separate cohorts of patients stratified by histological diagnosis, prior therapy and/or tumor co-mutations were to be evaluated for the clinical activity/efficacy of adagrasib. Refer to Figure 2 below for list of pre-specified cohorts in Phase-2. Separate stopping rules for futility were planned for each of these cohorts.
In addition to phases 1, 1b and 2, additional Substudies as part of Phase-1 were planned to efficiently prepare for adagrasib efficacy trials. These cohort Substudies included Phase 1 dose finding evaluations of adagrasib in combination with the checkpoint inhibitor pembrolizumab or with the EGFR inhibitors cetuximab or afatinib.

Figure 7: Schema for Study 849-001



The key inclusion criteria are listed below:

1. Histologically confirmed diagnosis of a solid tumor malignancy with KRAS G12C mutation (and for Cohort E, a qualifying STK11 mutation):
    - in Phase 2 Cohorts A, B, and E squamous or non-squamous NSCLC
    - in Phase 2 Cohorts C, F, and G, adenocarcinoma of the colon or rectum

2. Unresectable or metastatic disease.

3. In Phase 2 CRC Cohort F, patients must have previously received standard treatment

    for metastatic disease, and must have previously received at least a fluoropyrimidine, irinotecan, oxaliplatin, and (if eligible) a VEGF/VEGF receptor (VEGFR) inhibitor that is FDA approved for treatment of CRC (bevacizumab, ramucirumab, ziv-aflibercept, or a bevacizumab biosimilar), and have progressed during or within 3 months (106 days) of the last administration of chemotherapy.
    - Patients known to have MSI-H or dMMR metastatic CRC must have previously received or not be eligible to receive a PD-1 inhibitor (e.g., pembrolizumab).
    - Patients known to have metastatic CRC with a BRAF V600E mutation must have previously received a BRAF inhibitor (e.g. encorafenib).
    - Patients who had withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease are eligible.
    - Patients who had received adjuvant chemotherapy and had recurrence during or within 6 months (183 days) of completion of the adjuvant chemotherapy are allowed to count the adjuvant therapy as standard treatment.

4. In Phase 2 Cohort G, patients must have previously received treatment with fluoropyrimidine, irinotecan, oxaliplatin, and (if eligible) a VEGF/VEGF receptor (VEGFR) inhibitor.
    - Patients known to have MSI-H or dMMR metastatic CRC must have previously received or not be eligible to receive a PD-1 inhibitor (e.g., pembrolizumab).
    - Patients known to have metastatic CRC with a BRAF V600E mutation must have previously received a BRAF inhibitor (e.g., encorafenib).

5. Presence of tumor lesions to be evaluated per RECIST 1.1:
    - In cohorts that do not include a statistical evaluation of clinical activity, patients may have measurable or evaluable disease.
    - In cohorts that include a statistical evaluation of clinical activity patients must have measurable disease.

The key exclusion criteria are listed below:

1. Ongoing need for a medication with any of the following characteristics that cannot be switched to alternative treatment prior to study entry; known risk of Torsades de Pointes; substrate of CYP3A with narrow therapeutic index; strong inducer of CYP3A and/or P-gp; strong inhibitor of BCRP; and proton pump inhibitors.

2. Prior treatment with a therapy targeting KRAS G12C mutation:
   Specific to the following Phase 1/1b cohorts: adagrasib tablets administered at 400 and 600 mg BID, dose optimization CRC cohort, the phase 1 substudies evaluating adagrasib administered in combination with cetuximab in patients with NSCLC and PDAC.

The primary data to support the efficacy review of adagrasib in combination with cetuximab for the proposed indication came from the Phase 1 Substudy Cohort 1 and Phase 2 Cohort G, which consisted of a total of 94 patients (32 in the Phase 1 Substudy Cohort 1 and 62 in Phase 2 Cohort G) with advanced or metastatic CRC harboring a KRAS G12C mutation. In addition, supportive data from a lower dose of adagrasib (400mg) in combination with cetuximab from the Phase 1b Dose Optimization Cohort and single agent adagrasib from Phase 2 Cohorts C and F were submitted to assist with the assessment of efficacy of the proposed regimen of adagrasib 600 mg BID in combination with cetuximab.

Study Endpoints

The major efficacy endpoints of Study 849-001 were objective response rate (ORR) and duration of response (DoR) as assessed by BICR per RECIST 1.1.

ORR was defined as the percentage of patients documented to have a best overall response (BOR) of confirmed complete response (CR) or partial response (PR). DoR was defined as the

time from date of the first documentation of confirmed objective tumor response (CR or PR) to the first documentation of progressive disease (PD) or to death due to any cause.

Tumor imaging assessments were performed at baseline and every 6 weeks until Week 49 (~12 months) and then every 12 weeks thereafter. Tumor response was assessed in accordance with RECIST version 1.1 by a blinded independent review committee (BICR).

Statistical Analysis Plan

Analysis Population:
- all patients who have measurable disease at baseline and received at least one dose of adagrasib were included in the primary efficacy analysis.

Analysis Methods:
- Frequency and percentage of confirmed ORR along with the exact 2-sided 95% confidence interval (CI) using Clopper-Pearson method were calculated. In addition to ORR, the frequency and percentage of confirmed CR and PR were also presented.
- DOR was be calculated for each patient with a confirmed response of CR or PR. Number of patients with a documented progression or death following first observation of response were presented. Patients will be censored on the date of the last evaluable disease assessment if;
    - patients with a confirmed response but experienced neither documented disease progression nor death, as of the cut-off date for the analysis
    - If a PD or death occur after ≥2 consecutive missed tumor assessments,
    - lost-to-follow-up, or
    - withdrew consent.

  If a patient received subsequent anti-cancer treatment prior to documented PD or death, then the patient will be censored on the date of the last evaluable disease assessment before the initiation of the new therapy.
- The Kaplan-Meier method was used to analyze DOR. Median DOR along with corresponding 2-sided 95% CIs will be presented. The proportion of patients with observed DORs of at least 6 months was presented.

Sample Size determination:
- The total sample size of the efficacy population includes a combined patient population with CRC harboring a KRAS G12C mutation from the Phase 1 Substudy Cohort 1 and Phase 2 Cohort G . For the Phase 1 Substudy Cohort 1, the planned sample size was up to 30 patients. A total of 60 patients were planned to be included in Phase 2 Cohort G to exclude an ORR of 5% from the 95% confidence interval assuming a true ORR of 30%.

Protocol Amendments

The original protocol for Study 849-001 was finalized on October 29, 2018, and nine

amendments were submitted following the finalization of original protocol. A brief summary of relevant protocol amendments related to the analysis of the primary endpoints for the proposed indication are included below.

Amendment 3 (11/14/2019):
- Added Substudy pilot Phase 1 evaluations of adagrasib administered in combination with selected cancer therapeutic agents pembrolizumab (Appendix 7 of the protocol) or cetuximab (Appendix 8 of the protocol).

Amendment 4 (2/20/2020):
- Added eligible histological subtypes for NSCLC and CRC to the entry criteria.
- Added Substudy pilot Phase 1 evaluation of adagrasib administered in combination with the cancer therapeutic agent afatinib (Appendix 9).

Amendment 5 (5/18/2020):
- Added a Phase 1b cohort to evaluate the safety and clinical activity of adagrasib in patients with limited brain metastases.

Amendment 6 (12/23/2020):
- In the cetuximab combination substudy described in Appendix 8 of the protocol, patients with CRC who experience SD compared to baseline measurements (as opposed to nadir measurements) were allowed to crossover from the main study. Additionally, use of cetuximab in the Q2W regimen was allowed.
- Updated summary of clinical activity.

Amendment 7 (4/12/2021):
- Changed the name of the population for the Phase 2 efficacy analysis from modified Intent-to-Treat population to Full Analysis Set.

Amendment 8 (10/25/2021):
- Added background information and statistical design for Phase 2 Cohort G to evaluate the clinical activity/efficacy of the combination of adagrasib and cetuximab in patients with CRC with KRAS G12C mutation detected in tumor tissue.
- Added an exploratory objective to evaluate patients with brain metastases using RANO-BM criteria.
- Updated warnings and precautions and the duration of cetuximab infusions for the 500 mg/m2 Q2W regimen to 120-minutes in accordance with revised product labeling.
- Updated the definition of the Full Analysis Set to include patients with measurable disease at baseline.

Amendment 9 (8/1/2022):
- Increased sample size for Phase 2 Cohort G from 40 to 60 patients and updated the

statistical design for Cohort G
- Phase 1b cohort to evaluate the safety, PK, and clinical activity of adagrasib in combination with cetuximab (dose optimization CRC cohort), which will enroll patients with CRC with KRAS G12C mutation patients to receive adagrasib administered at 400 mg BID in combination with cetuximab 500 mg/m2 Q2W.
- Updated the minimum number of unstained slides required for prospective or retrospective KRAS G12C mutation testing of tumor tissue samples from 5 to 7 unstained slides (unless Sponsor approves fewer).

8.1.2. Study Results

Results for the analysis of the pivotal cohorts (Phase 2 Cohort G, Phase 1 Substudy Cohort 1) and supportive data from the Phase-1b Dose Optimization Cohort that evaluated a lower dose of adagrasib (400 mg BID) in combination with cetuximab and Phase 2 Cohorts C and F were reviewed to assess the risk-benefit profile of single agent adagrasib (600 mg BID) and are presented in this section.

Compliance with Good Clinical Practices

The Applicant reported that this study was conducted in accordance with International Ethics Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2022), Guidelines for Good Clinical Practice (GCP) (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] 1996), ICH E6 (R2), and concepts that have their origin in the Declaration of Helsinki (World Medical Association 1996, 2008, and 2013). This study was conducted under a protocol reviewed and approved by an IRB and was conducted by scientifically and medically qualified persons.

Financial Disclosure

The Applicant provided financial disclosure information for the 849-001 trial. There were a total of 1447 investigators and sub-investigators. One investigator certified that they had financial interest or arrangements with the Applicant. The applicant provided details of the disclosable financial interests as well as the description of the steps taken to minimize potential bias.

The FDA review team concluded that integrity of Study 849-001 data were not affected by financial interest of the investigator and is unlikely to have impact on the interpretation of the results.

Data Quality and Integrity

Data were submitted in CDISC format. There were no data quality or integrity issues identified.

Patient Disposition

Study 849-001 was initiated on December 26, 2018. The Phase 1 Substudy Cohort 1 started enrolling patients April 23, 2020, and Phase 2 Cohort G started enrolling patients approximately 22 months afterward. The median follow-up duration was 30.0 months for Phase 1 Substudy Cohort 1 and 10.0 months for Phase 2 Cohort G. The study is still ongoing at the time of this supplemental drug application. The data cutoff date for the primary analysis of efficacy was June 30, 2023. The table below summarizes the number of patients enrolled in each of the pivotal and supportive cohorts along with the corresponding data cutoff dates implemented for each cohort's study report.

Table 10: Data from Study 849-001 to support the efficacy and safety assessment.

Segment CSR Status Start Date[1] SCE Data Cutoff Date	**Study Drug Starting Dose, Route & Regimen**	**Study Objective**	**No. Pts[2] Enrolled**	**Diagnosis Inclusion Criteria (Prior Systemic Therapy)**
Pivotal Cohorts and Sub-Studies Studies (Combination)				
Phase 1 Substudy Cohort 1 Final 23 Apr 2020 30 Jun 2023	A: Oral/600 mg BID C: IV/400 mg/m^2 initial dose; 250 mg/m^2 QW or C: IV/500 mg/m^2 Q2W	Safety, tolerability, PK, MTD/RP2D, clinical activity	32	CRC with *KRAS* G12C mutation in tumor tissue and/or ctDNA No available treatment with curative intent; no available standard-of-care treatment, or patient was ineligible or declined treatment.
Phase 2 Cohort G Final 08 Feb 2022 30 Jun 2023	A: Oral/600 mg BID C: IV/500 mg/m^2 Q2W	Clinical activity/ efficacy, safety, tolerability, PK	62	CRC with *KRAS* G12C mutation in tumor tissue Prior treatment with at least a fluoropyrimidine, oxaliplatin, irinotecan, a VEGF(R) inhibitor[3].
Supportive Cohorts (Combination and Monotherapy)				
Phase 2 Cohort C Final 22 Jan 2020 01 Mar 2023	A: Oral/600 mg BID	Clinical activity, safety, tolerability, PK	44	CRC with *KRAS* G12C mutation in tumor tissue and/or ctDNA. No available treatment with curative intent; no available standard-of-care treatment, or patient was ineligible or declined treatment.
Phase 2 Cohort F Final 28 May 2021 01 Mar 2023	A: Oral/600 mg BID	Clinical activity, safety, tolerability, PK	42	CRC with *KRAS* G12C mutation in tumor tissue Prior treatment with at least a fluoropyrimidine, oxaliplatin, irinotecan, a VEGF(R) inhibitor[3].
Phase 1b Dose Optimization Expansion Cohort Interim 24 Oct 2022 30 Jun 2023	A: Oral/400 mg BID C: IV/500 mg/m^2 Q2W	Safety, tolerability, PK, clinical activity	27	CRC with *KRAS* G12C mutation in tumor tissue and/or ctDNA Prior treatment with at least a fluoropyrimidine, oxaliplatin, irinotecan, a VEGF(R) inhibitor[3].

A: Adagrasib, C: Cetuximab, BID = twice daily
[1] Date of first informed consent.
[2] As of the data cutoff date for each cohort.
[3] Patients known to have MSI-H or dMMR phenotype must have previously received or not be eligible to receive a PD-1 inhibitor; whereas patients known to have *BRAF* V600E mutation must have previously received a BRAF inhibitor.
Source: Table 1 from Applicant's Integrated Summary of Efficacy.

Patients who permanently discontinued adagrasib treatment also permanently discontinued cetuximab, as cetuximab as a single agent is not indicated for the use of *KRAS* mutant CRC. However, if cetuximab was permanently discontinued patients could continue with single agent adagrasib.

Thirty-two patients in Phase 1 Substudy Cohort 1, and 62 patients in Phase 2 Cohort G were enrolled and treated with adagrasib and cetuximab. As of the data cutoff date, 76 patients (81%) had discontinued treatment, with the majority of discontinuations (n=62) due to disease progression or deterioration in global health. A total of nine patients withdrew consent and two patients each discontinued due to death or adverse events.

The patient disposition in the dose optimization cohort and the adagrasib single agent cohorts (presented as a pooled cohort) are also included in the table below.

Table 11: Summary of Patient Disposition

	600mg BID adagrasib+cetuximab N = 94 n (%)	**400mg BID adagrasib+cetuximab N = 27 n (%)**	**600mg BID adagrasib N = 86 n (%)**
Total	**94 (100)**	**27 (100)**	**86 (100)**
Ongoing	**18 (19)**	**23 (85)**	**8 (9)**
Treatment discontinued	**76 (81)**	**4 (15)**	**72+6 (91)**
Progressive Disease/deterioration	62 (66)	1 (4)	62 (72)
Withdrawal By Patient	9 (10)	1 (4)	2 (2)
Death	2 (2)	2 (7)	2 (2)
Adverse event	2 (2)	0	3 (4)
Other	1 (1)	0	3 (4)

Source: ADSL dataset

Protocol Violations/Deviations

A total of 29 protocol deviations were reported from the Phase 1 substudy cohort 1 (n=5) and cohort G (n=24). The most common protocol deviation was related to concomitant medications. This included one patient using concomitant rivaroxaban, which lead to a TESAE of Grade 3 rectal hemorrhage which may have been secondary to increased exposure of rivaroxaban as a result of drug-drug interaction with adagrasib. A total of seven patients had a protocol deviation related to informed consent including one patient who was enrolled on trial but had not received irinotecan treatment in the past. Other less common protocol deviations are listed in Table 11.

Table 12: Summary of protocol deviation in the Phase 1 Substudy Cohort 1 and Phase 2 Cohort G

Category Deviation [n (%)]	Phase 1 Substudy Cohort 1[a] (N = 32)	Cohort G (N = 62)	Phase 1 Substudy Cohort 1[a] + Cohort G (N = 94)
Any Important Deviation	5 (15.6)	24 (38.7)	29 (30.9)
Concomitant Medication	2 (6.3)	18 (29.0)	20 (21.3)
Other Protocol Violations	2 (6.3)	18 (29.0)	20 (21.3)
Informed Consent	3 (9.4)	4 (6.5)	7 (7.4)
Informed Consent (ICF)	3 (9.4)	4 (6.5)	7 (7.4)
Eligibility	0	3 (4.8)	3 (3.2)
Inclusion/Exclusion Criteria	0	2 (3.2)	2 (2.1)
Other Protocol Violations	0	1 (1.6)	1 (1.1)
Dosing	1 (3.1)	1 (1.6)	2 (2.1)
Study Drug Administration	1 (3.1)	1 (1.6)	2 (2.1)
Study Procedures	0	2 (3.2)	2 (2.1)
Study Procedure/Assessments	0	1 (1.6)	1 (1.1)
Study Visit Schedule	0	1 (1.6)	1 (1.1)
ECG	0	1 (1.6)	1 (1.1)
Inclusion/Exclusion Criteria	0	1 (1.6)	1 (1.1)

Source: CSR document pivotal cohort

***Reviewer's comment**: There were a nominally higher number of protocol deviation reported for Cohort G. This was due to a greater number of protocol deviations related to concomitant medications, study eligibility and study procedures compared to other cohorts. The protocol deviations are unlikely to have had a meaningful an impact on the study results.*

Table of Demographic Characteristics

Demographics and baseline disease characteristics of patients enrolled in the pivotal cohort (Phase 1 Substudy Cohort 1 and Phase 2 Cohort G), dose optimization cohort and the adagrasib single agent cohort (Phase 2 Cohorts C and F) are shown in Table 12 and Table 13.

Table 13: Demographic and Baseline Characteristics of patients enrolled in the pivotal cohort, dose optimization cohort and the adagrasib single agent cohort.

	600mg BID adagrasib+cetuximab N = 94 N (%)	**400mg BID adagrasib+cetuximab N = 27 N (%)**	**600mg BID adagrasib N = 86 N (%)**
Median Age (min-max) years	56 (24 - 75)	59 (37 - 81)	57 (29 - 82)
Age Group			
< 65 years	63 (67)	17 (63)	60 (70)
≥ 65 years	31 (33)	10 (37)	26 (30)
Sex			
Female	50 (53)	15 (56)	40 (47)
Male	44 (47)	12 (44)	46 (53)
Race			
White	67 (71)	20 (74)	70 (81)
Black or African American	13 (14)	2 (7)	9 (10)
Other	8 (9)	3 (11)	4 (5)
Asian	5 (5)	2 (7)	3 (4)
American Indian or Alaska Native	1 (1)	0 (0)	0 (0)
Ethnicity			
Not Hispanic or Latino	75 (80)	26 (96)	79 (90)
Hispanic or Latino	16 (17)	1 (3.7)	6 (7)
Missing	3 (3.2)	0 (0)	3 (3.4)
ECOG 0	48 (51)	11 (41)	46 (53)
ECOG 1	46 (49)	16 (59)	40 (47)

Source: ADSL data set

Reviewer's comment: *The median age of the patients enrolled in the pivotal efficacy cohort was 56 years, which is lower than the reported median age of diagnosis of colorectal cancer of 66 years (reference SEER). Sixty seven percent of the patients were less than 65 years of age. The majority of patients enrolled in the pivotal safety cohort were white. There were a limited number of patients who identified as Black, Asian, Pacific Islander, or American Indian/Alaskan Native enrolled to the study and only 17% of the patients identified as Hispanic or Latino. Numerically similar baseline characteristics were noted in the dose optimization and adagrasib single agent cohorts.*

Table 14: Baseline Disease Characteristics and Prior Therapy

	600mg BID adagrasib+cetuximab N = 94 N (%)	**400mg BID adagrasib+cetuximab N = 27 N (%)**	**600mg BID adagrasib N = 86 N (%)**
Liver metastasis	60 (64)	19 (70)	59 (69)
Lung metastasis	67 (71)	18 (67)	58 (67)
Right sided	19 (31)*	7 (30)	9 (26)
Left sided	32 (51)*	16 (70)	25 (74)
% with > 2 prior therapies	52 (55)	12 (44)	51 (59)
Median No. Prior Therapies	3	2	3
PRIOR THERAPY			
Fluoropyrimidine	94 (100)	27 (100)	86 (100)
Oxaliplatin	93 (99)	27(100)	85 (99)
Irinotecan	89 (95)	27(100)	77 (90)
Regorafenib and/or Trifluridine/tipiracil	14 (15)	2 (7)	18 (21)
Checkpoint Inhibitor	8 (9)	0	9 (10)
Any Prior Radiotherapy	32 (34)	9 (36)	33 (38)
Any Prior Surgery	76 (81)	19 (76)	77 (90)

*tumor sided information was available for 51 of the 94 total patients
Source: ADSL data set

In the pivotal efficacy cohort, almost two third of the patients had lung or liver metastasis. Information regarding sidedness of the tumor was missing from 33 patients. Among the patients for whom tumor sidedness was known, 51% (n=32) had a left sided tumor and 31% (n=19) had a right sided tumor. The median number of prior therapies was three and 95% or higher of the patients had received fluorouracil, irinotecan or oxaliplatin.

While no statistical comparisons can be made with the single arm dose optimization cohort or the adagrasib single agent cohort, the baseline disease characteristics as well as exposure to prior therapies was numerically similar in the pivotal efficacy cohort when compared to the dose optimization and single agent adagrasib cohorts.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The median compliance was 94.9% (43% to 100%), and most patients (66 of 94 patients, 70.2%) were > 80% compliant. All patients received concomitant medications, the most common of which were antiemetics (87%). Other commonly used concomitant mediations were antibacterial drugs (85%) and analgesics (79%). A total of 54% of patients used antidiarrheals and 53% used medications for constipation. Dermatological preparations of corticosteroids were used by 52% of the patients, including 38% who used other anti-acne preparations and 51% who used systemic steroids. A total of 33% needed magnesium supplement and 21% needed potassium supplement. A total of 41% patients were on antithrombotics.

Reviewer's comment: *There were no specific concerns with treatment compliance or concomitant medication use during the study that would be expected to impact safety or efficacy of adagrasib in combination with cetuximab. The use of the commonly noted concomitant medications is expected given that this is a pretreated, advanced CRC population and considering the known adverse event profile observed with adagrasib (e.g., nausea and diarrhea) and cetuximab (e.g., diarrhea, rash, hypomagnesemia and hypokalemia).*

Efficacy Results – Primary Endpoint

<u>ORR and DOR per BICR:</u>
As of the data cutoff date, 32 out of the 94 patients enrolled in the combined 600mg BID adagrasib+cetuximab pivotal cohort who had received at least one dose of adagrasib experienced a confirmed response (all partial responses) resulting in an ORR of 34% (95% CI: (25, 45)). No complete responses were recorded. The median DOR was 5.8 months (95% CI: 4.2 to 7.6 months) with maximum DOR of 19 months. Among the 32 responders, 10 (31%) patients had a durable response that lasted 6 months or longer.

The ORR in the dose optimization cohort was 36% (95% CI: 18, 58) with a corresponding median DOR of 4 months (95% CI: 2.8, NE) and 22% (95% CI: 14, 32) in the pooled adagrasib single agent cohort with a corresponding median DOR of 9.5 months (95% CI: 5.6 , 15.2).

Reviewer's comment: *These three cohorts are compared descriptively, and interpretation of the results from the dose optimization cohort are further limited by the very small sample size and shorter duration of follow up.*

Table 15: BICR Assessed ORR and DOR Results

	600mg BID adagrasib+cetuximab N = 94	**400mg BID adagrasib+cetuximab N = 27**	**600mg BID adagrasib N = 86**
# Responses/N*	32/94	9/25	19/86
ORR (95% CI)	**34** (25, 45)	**36** (18, 58)	**22** (14, 32)
Complete Response (n)	0	0	0
Partial Response (n)	32	9	19
Duration of Response			
# Events	23/32 (72%)	2/9 (22%)	10/19 (47%)
Median (95% CI)	5.8 (4.2, 7.6)	4 (2.8, NE)	9.5 (5.6 , 15.2)
Min, Max (months)	1.4+, 19	1+, 5.7+	1.2+, 16.7
Observed duration ≥ 6 months (%)	31%	0	47%

* No. of patients with measurable disease at baseline
NE: Not evaluable
Source: FDA Reviewer's analysis

A higher ORR of 43% in the pivotal cohort was observed based on the investigator assessment of tumor responses.

Table 16: Investigator Assessed ORR and DOR Results

	600mg BID adagrasib+cetuximab N = 94	**400mg BID adagrasib+cetuximab N = 27**	**600mg BID adagrasib N = 86**
# Responses/N*	40/94	14/25	16/86
ORR (95% CI)	**43** (32, 53)	56 (35, 76)	19 (11, 28)
Complete Response (n)	0	0	0
Partial Response (n)	40	14	19
Duration of Response			
# Events	28/40	3/14	14/16

Median (95% CI)	5.9 (5.5, 7.6)	NR (2.8, NE)	4.3 (3.2 , 9.2)
Min, Max (months)	1.2+, 19.7	1.4+, 5.7+	2.3, 15.2
Observed duration ≥ 6 months (%)	54%	0	50%

* No. of patients with measurable disease at baseline
Source: FDA Reviewer's analysis

Discordance Analysis:
Overall, a high discordance rate of 35.1% was observed between BICR and Investigator assessment of best overall response (BOR). The majority of these discrepancies were due to a relatively large number (16) of patients who were assessed as having stable disease (SD) by BICR and had PR by Investigator.

Prior to submission of this sNDA, Mirati further investigated the data from the most recent BICR data transfer, and observed an imbalance favoring SD over PR among the adjudicated cases on the primary endpoint of BOR in Phase 2 Cohort G. There was a high level of discordance between BICR Reader 1 and BICR Reader 2 in these cases both on the selection of baseline lesions, and the measurements of target lesions at baseline and on study. Subsequently, Mirati engaged the BICR Vendor noting the discrepancies in the BICR adjudication process and between BICR Readers for an examination of whether any systemic errors could be identified. Mirati did not discuss or disclose the Investigator assessment either at the patient level or in aggregate, such that the BICR Vendor remained blinded to these factors. In accordance with the BICR Charter, a Chief Medical Officer (CMO) Review was requested. The CMO Review did not entail an independent re-adjudication, but rather a review of the existing adjudicated cases. Overall, the adjudication of individual cases was deemed reasonable by the BICR Vendor, and differences were attributed to judgment calls of reviewers, rather than any systemic pattern.

Mirati consequently received the final BICR transfer unchanged by the above-mentioned review. Therefore, the final Table, Listing and Figures (TFLs), and the top-line results shared with the FDA, reflect this final data transfer and include the discrepancy between BICR and PI assessments, but also between BICR Readers and the adjudicated outcome.

Table 17: Cross-Tabulation of Investigator and BICR assessed BOR

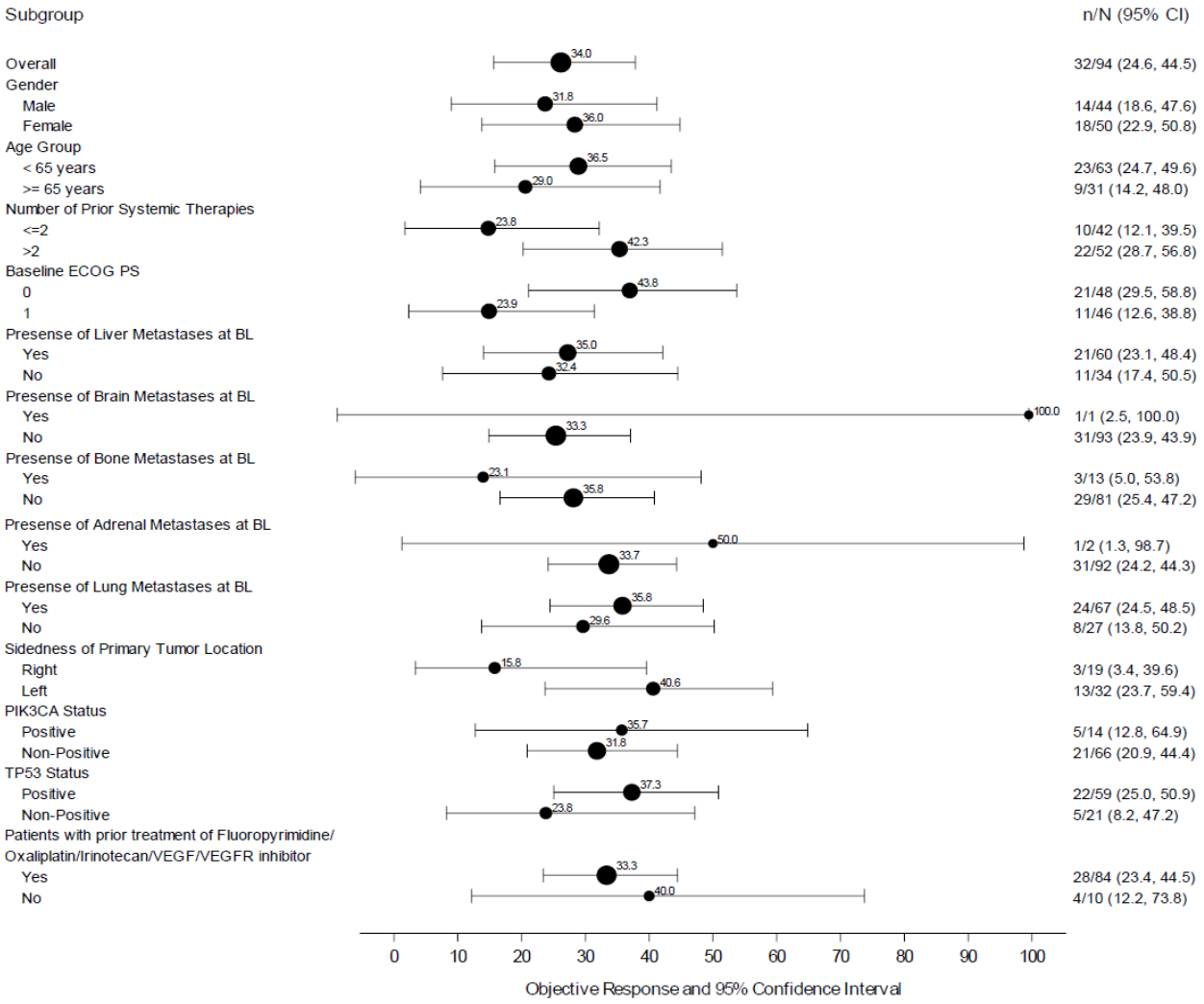
		BOR per Investigator				
		PR	**SD**	**PD**	**NE**	**Total**
BOR per BICR	**PR**	24	8	0	0	32
	SD	16	28	4	0	44
	PD	0	5	1	0	6
	NE	0	0	0	8	8
	Total	40	41	5	8	**94**

Source: FDA Reviewer's analysis

Exploratory Subgroup Analyses:

Exploratory subgroup analyses of ORR as assessed by BICR were performed, based on some of the demographic characteristics and disease characteristics at baseline in the pivotal cohort. Due to the small overall study sample size and consequently small sample size for the subgroups, the results are considered exploratory and should be interpreted with caution.

Figure 8: Subgroup Analysis of ORR per BICR in the pivotal cohort - Forest Plot



Source: CSR for pivotal trial- Figure 3

***Reviewer's comment**: The subgroup analysis is exploratory. A notable difference in response rates in the subgroup analysis was observed in the right sided primary tumor subgroup who had a numerically lower ORR at 15% as compared to the left sided primary tumor subgroup who had an ORR of 40.6%. However, the information regarding the sidedness of the primary tumor was*

missing from 33 patients in the pivotal efficacy cohort. Overall, the exploratory subgroup analysis was not suggestive of differential efficacy signal based on the subgroups analyzed.

Efficacy Results – Secondary and other relevant endpoints

No additional data to report. Refer to the results section above.

Dose/Dose Response

See Section 6.2.2 of this review.

Durability of Response

Refer to the subsection "Efficacy Results – Primary Endpoint" above for durability of response results.

Persistence of Effect

Persistence of effect is characterized by duration of response data, discussed in the "Efficacy Results – Primary Endpoint" subsection.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

No COA (PRO) endpoints were reported in the study.

Additional Analyses Conducted on the Individual Trial

Additional analyses to assess the efficacy results in each individual cohort included in the pooled pivotal and supportive cohorts was conducted. The ORR and DOR results within each individual cohort that contributed to the over results of the pooled pivotal and supportive cohorts are included in the table below.

Table 18: ORR within Phase-1 and Phase-2 subcohorts

	600mg BID Adagrasib+cetuximab N = 94			**600mg BID Adagrasib N = 86**		
	Combined N = 94	Ph 2 Cohort G N=62	Ph 1 substudy N=32	Combined N = 86	Ph 2 Cohort C N=44	Ph 2 Cohort F N=42

# Responses/N1	32/94	18/62	14/32	19/86	10/44	9/42
ORR (95% CI)	**34** (25, 45)	**29** (18, 42)	**44** (26, 62)	**22** (14, 32)	**23** (11, 38)	**21** (10, 37)
Duration of Response						
# Events %	23/32 (72%)	12/18 (33%)	11/14 (79%)	10/19 (47%)	5/10 (50%)	5/9 (56%)
Median (95% CI)	5.8 (4.2,7.6)	5.8 (4.1, NE)	6 (3.8, 13.9)	9.5 (5.6,15.2)	9.5 (7, NE)	15.2 (2.8, NE)
Min, Max (months)	1.4+, 19	2.4, 8.5	1.4+, 19	1.2+, 16.7	1.2+, 10.2	1.4+, 16.7
Obs duration ≥ 6 months (%)	31%	28%	36%	47%	60%	33%

Source: FDA Reviewer's analysis.

***Reviewer's comment**: The investigator assessed ORR in the pivotal efficacy cohort was higher than that in the single agent adagrasib cohort but numerically similar to the ORR noted in the dose optimization cohort. However, given that these are single arm non-randomized cohorts, no statistical comparison can be made. It is also noted that the number of patients in the dose optimization cohort was only 27. Numerically it appears that addition of cetuximab to the adagrasib results in an improvement in ORR and is necessary for the observed treatment effect of the combination regimen. A conclusion about whether the combination regimen containing the lower dose of adagrasib with cetuximab has similar efficacy to the pivotal efficacy cohort cannot be determined based on the data submitted to this sNDA.* (b) (4)

[redacted]

8.1.3 Integrated Review of Effectiveness

The efficacy of adagrasib in combination with cetuximab is supported by data from single arm cohorts in Study 849-001. The primary endpoint of BICR assessed ORR in patients treated with adagrasib at 600mg BID in combination with cetuximab was 34% (95% CI: [25, 45]) with a median duration of response at 5.8 months (95% CI: 4.2 to 7.6 months).

The ORR observed in the pooled single agent adagrasib cohort is numerically lower at 22% (95% C.I. [14, 32]) and the ORR in the dose optimization cohort is numerically similar to the ORR observed in the pivotal cohort at 36% (95% CI: 18, 58). However, the results need to be

interpreted with caution due to the small sample size in the dose optimization cohort.

8.1.4 Integrated Assessment of Effectiveness

The efficacy results from the pivotal efficacy cohorts that received the combination of adagrasib 600mg BID with cetuximab, demonstrated a clinically meaningful overall response rate as well as duration of response in patients with advanced or metastatic colorectal cancer (CRC) with KRAS G12C mutation who have previously been treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, and an anti-vascular endothelial growth factor (VEGF) therapy (if indicated).

While single arms of non-randomized cohorts in clinical trials cannot be statistically compared to each other, it is noted that the response of adagrsib in combination with cetuximab is numerically higher than that noted in the single agent adagrasib cohorts. Additionally, the response rate noted in the dose optimization cohort evaluating a lower combination dose of adagrasib at 400mg BID with cetuximab is numerically similar to the pivotal efficacy cohort (adagrasib 600mg BID in combination with cetuximab). However, the dose optimization cohort has a small sample size and a much shorter duration of exposure to treatment as compared to the median duration of exposure to treatment in the pivotal safety cohorts which further limits a meaningful comparison of efficacy.

Based on the data submitted to this sNDA, the necessity of both adagrasib and cetuximab for the observed treatment effect has been demonstrated. The reported ORR in this previously treated patient population with mCRC is numerically higher than available therapies in the late line advanced or metastatic CRC setting that are approved for a non-selected, all-comer population. Adagrasib administered at 600 mg BID in combination with cetuximabs appears reasonably likely to be substantially better than available therapy. The results support granting accelerated approval to this application.

A PMR was issued to complete Study 849-010, entitled “A Randomized Phase 3 Study of adagrasib 600 mg twice daily in combination with cetuximab versus chemotherapy in patients with advanced colorectal cancer with KRAS G12C mutation with disease progression on or after first-line therapy.” This study (b) (4) and is expected to have its initial PFS readout submitted to the FDA in (b) (4); results are intended to confirm benefit of adagrasib in CRC.

A supplemental premarket application for a companion diagnostic test using DNA extracted from formalin-fixed, paraffin-embedded (FFPE), colorectal cancer tissue (therascreen® KRAS RGQ PCR Kit) by Qiagen for contemporaneous review and approval with this supplemental NDA.

8.2. Review of Safety

8.2.1 Safety Review Approach

The safety analysis of adagrasib in combination with cetuximab was based on safety data submitted from Study 849-001. The pivotal safety cohort population included 94 patients all of whom received at least one dose of the study treatment (adagrasib 600mg BID and cetuximab). A total of 32 patients were enrolled in the Phase 1 Substudy Cohort 1, and 62 patients were enrolled in the Phase 2 Cohort G. Safety monitoring during the study included but was not limited to vital signs assessment, collection of hematology and chemistry laboratory tests, and performing ECGs. AEs were assessed on each visit using the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE) Version 5.0. Adverse Events (AEs) were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 26.0.

The safety analysis is supported by data from the Phase 1b dose optimization cohort of 27 patients who received adagrasib at a dose of 400mg BID in combination with cetuximab (referred to as the dose optimization cohort) and 88 patients with CRC who received adagrasib 600mg BID as single agent (Phase 2 cohort C n=44; Phase 2 cohort F n=42, Phase 1/1b adagrasib monotherapy dose-finding segments n=2) (referred to as the single agent adagrasib cohort).

Table 19: Definition of Safety cohorts analyzed.

	Pivotal safety cohort Adagrasib 600mg BID + cetuximab		**Dose optimization cohort Adagrasib 400mg BID + cetuximab**	**Single agent Adagrasib cohort Adagrasib 600mg BID**		
Cohorts	Phase 1 substudy Cohort 1	Phase 2 Cohort G	Dose optimization cohort	Phase 2 cohort C	Phase 2 cohort F	Phase 1/1b Adagrasib monotherapy
n	32	62	27	44	42	2

Source: ADSL data set

For each patient in the safety population the worst grade of each treatment emergent adverse event (TEAE) and the worst grade of each laboratory abnormality was included in the safety analysis. The safety of single agent adagasib has been well characterized in studies of adult patients with KRAS G12C mutated NSCLC. The safety of cetuximab as a single agent and in combination with other anticancer therapies has been well characterized in studies in adult patients with multiple tumor types. Based on the available data from this trial, there were no new safety signal observed in patients treated with adagrasib 600 mg BID in combination with cetuximab.

8.2.2 Review of the Safety Database

Overall Exposure

The median duration of adagrasib treatment in the pivotal safety cohort was numerically higher at 7.4 months (range: 0–36.4) than in the dose optimization and single agent adagrasib cohorts (5.4 months each). The enrollment for the dose optimization cohort started later and the median duration of adagrasib treatment was therefore shorter at 5.4 months. The single agent adagrasib cohorts had a shorter duration of exposure to adagrasib (5.4 months) as compared to the pivotal safety cohort likely due to more progression of disease and treatment discontinuation. The compliance with the adagrasib dosing schedule in the pivotal safety cohort was 91% (range: 22.3% - 100.0%) and was numerically lower than that observed in the dose optimization cohort at 97% (range: 84.8–100).

Table 20: Summary of exposure to Adagrasib in the safety cohorts

	600mg BID adagrasib+cetuximab N = 94 n (%)	**400mg BID adagrasib+cetuximab N = 27 n (%)**	**600mg BID adagrasib N = 88 n (%)**
Compliance (%)			
Median (Range)	94.9 (42.9–100)	98.8 (84.8–100)	96.4 (49.5–100)
Relative Dose Intensity (%)			
Median (Range)	90.7 (22.3–100)	97.1 (75.3–100)	94 (40–100)
Treatment Duration (months)			
Median (Range)	7.4 (0–36.4)	5.6 (0.4–7.7)	5.6 (0.4–32.3)

Source: ADEX dataset

In the pivotal safety cohort, a total of 77 patients received cetuximab every 2 weeks (Q2W) dosing and 17 patients received every week (QW). All patients in the dose optimization cohort received cetuximab Q2W dosing.

The median duration of exposure to cetuximab was 7.1 months (range: 0.2 to 34.5 months) in the pivotal safety cohort. The dose optimization cohort started enrollment later and the median exposure for cetuximab was numerically lower at 5.5 months (range: 0.5-7.7 months).

Table 21: Summary of exposure to cetuximab

Exposure	**600mg BID adagrasib+cetuximab N = 94 n (%)**	**400mg BID adagrasib+cetuximab N = 27 n (%)**
Treatment Duration (months)		

Exposure	600mg BID adagrasib+cetuximab N = 94 n (%)	400mg BID adagrasib+cetuximab N = 27 n (%)
Median (Range)	7.1 (0.2–34.5)	5.5 (0.5–7.7)
Total Number of Q2W Infusions		
Mean (SD)	14.5 (10.5)	10.8 (4.9)
Median (Range)	14 (1–57)	12 (1–17)
Total Number of QW Infusions		
Mean (SD)	22.7 (18.2)	0
Median (Range)	23 (1–66)	0

Source: ADEX dataset

All patients from pivotal safety cohort, dose optimization cohort and the single agent adagrasib cohort received at least 1 dose of the assigned study treatment. The pivotal safety population was identical to the FAS (n=94).

Table 22: Demographics of the safety cohorts

	600mg BID adagrasib+cetuximab N = 94 N (%)	400mg BID adagrasib+cetuximab N = 27 N (%)	600mg BID adagrasib N = 88 N (%)
Median Age (min-max) years	57 (24 - 75)	59 (37 - 81)	57 (29 - 82)
Age Group			
< 65 years	63 (67)	17 (63)	62 (70)
>= 65 years	31 (33)	10 (37)	26 (30)
Female	50 (53)	15 (56)	41 (47)
Male	44 (47)	12 (44)	47 (53)
Race			
White	67 (71)	20 (74)	72 (82)
Black Or African American	13 (14)	2 (7)	9 (10)
Other	8 (9)	3 (11)	4 (5)

Asian	5 (5)	2 (7)	3 (3)
American Indian Or Alaska Native	1 (1)	0 (0)	0 (0)
Ethnicity			
Not Hispanic or Latino	75 (80)	26 (96)	79 (90)
Hispanic or Latino	16 (17)	1 (3.7)	6 (7)
Missing	3 (3.2)	0 (0)	3 (3.4)

Source: ADSL dataset

Reviewer's comment: *A limitation of the safety database for the proposed regimen of adagrasib 600 mg BID in combination with cetuximab is that the data were derived from single arm cohorts, and therefore it is difficult to make any comparative assessment of the safety or to fully characterize the toxicity associated with the combination regimen. Consistent with FDA practice for labeling, FDA listed all TEAEs without making a post hoc determination of relatedness.*

Single arms of non-randomized trials cannot be statistically compared to each other to determine whether a higher dose of adagrasib at 600mg BID with cetuximab has increased toxicity as compared to the lower dose of adagrasib at 400mg BID with cetuximab. In addition, the shorter median duration of exposure to treatment in the dose optimization cohort compared to median duration of exposure to treatment in the pivotal safety cohort and a small sample size (n=27) limits the ability to make any meaningful conclusions regarding comparative safety assessments between the two combination dosing regimens. Although the incidence of treatment emergent adverse reactions leading to dosage reduction or dosage interruption were numerically lower in the dose optimization cohort compared to the pivotal cohort, the exposure-safety relationship for treatment emergent adverse events in general was similar between the two dosing regimens (see Sections 6.2.2 and 6.3.2 for additional details).

The baseline characteristics of the pivotal safety population are in general consistent with what is expected in the advanced CRC population who have progressed on prior therapies.

Adequacy of the safety database:

The sample size, duration of treatment, and the duration of follow up for adverse events in the pivotal study cohorts were adequate for the safety analysis of this population with a severe and life-threatening disease. There were a limited number of patients who identified as Black, Asian, Pacific Islander, American Indian/Alaskan Native enrolled to the study, and the proportion of patients in these racial and ethnic groups was not consistent with the observed incidences of colorectal cancer in a nonselected advanced CRC population. However, KRAS G12C mutations are thought to occur in only approximately 3% of all CRC patients and the distribution of KRAS mutations among different racial and ethnic minorities has not been fully

characterized. Therefore, despite the limited enrollment of patients from historically minoritized racial and ethnic groups and based on the low incidence of KRAS G12C mutations in patients with CRC, FDA determined that the population demographics were adequate for an assessment of safety.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The submission quality was adequate for this review. The submission was clearly organized and included adequate narratives of AEs as agreed upon by the Applicant and FDA. The OSI Investigations inspected three clinical sites. No major issues were identified at any of the sites. The study was conducted according to GCP and there were no data integrity issues identified during the review of this submission.

Categorization of Adverse Events

The safety and tolerability assessment of adagrasib in combination with cetuximab and single agent adagrasib was based on the frequency of adverse event-related deaths, AEs (Grade 1-4), serious AEs (SAEs), AEs leading to discontinuation, AEs leading to treatment interruptions, AEs leading to dose reductions, select AEs of interest, clinical laboratory assessments (including hematology, serum chemistry, and liver and thyroid function tests), and vital sign measurements. AEs were coded using MedDRA Version 26.0. The MedDRA preferred terms (PT) and the corresponding verbatim terms included in the datasets were reviewed to check for accuracy of MedDRA coding using random audit. Comparison of the applicant's MedDRA PTs to the verbatim terms did not show significant discrepancies. AEs and laboratory values were graded for severity using the NCI CTCAE Version 5.0.

Treatment emergent adverse events (TEAE) are AEs with onset or worsening during the treatment period, defined as occurring between the first study treatment intake and up to 30 days after the last study treatment intake. SAEs were defined as any AE that at, any dose that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, is medically significant, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Reviewer's comment: The definitions of TEAEs and SAEs were acceptable.

Routine Clinical Tests

An assessment of KRAS G12C tumor mutation status to determine eligibility to enroll in this trial was established by an Applicant-provided central test or by a Applicant-approved local test result obtained any time prior to screening. For the pivotal efficacy cohorts, patients enrolled in Phase 1b Cohort 1 could have confirmation of KRAS G12C mutation either from tumor tissue or

a blood sample. Patients enrolled in Phase 2 Cohort G must have had confirmation of KRAS G12C mutation confirmation from the tumor tissue.

Routine hematology tests (hemoglobin, platelet count, WBC with differential) were collected on screening and then days 1 and 15 of every cycle and, and at treatment withdrawal.

The following chemistry parameters – albumin, electrolytes (sodium, potassium, chloride, total calcium, magnesium, phosphate), blood urea nitrogen (BUN), serum creatinine, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin (if total bilirubin is ≥ 2×ULN and no evidence of Gilbert's syndrome, then fractionate into direct and indirect bilirubin), total protein, uric acid, albumin, glucose (non-fasted), lipase (pancreatic), amylase, creatine kinase (if abnormal, fractionation of isoenzymes is recommended but not required), were collected on screening and then days 1 and 15 of every cycle and at the end of treatment withdrawal.

Pregnancy Test and Follicle-Stimulating Hormone (FSH) were collected if the patient was a woman of childbearing potential. Urine or serum pregnancy tests was performed by the local laboratory at Screening and End of Treatment.

All laboratory data were graded using NCI-CTCAE Version 5.0.

Deaths

At the data cut-off date of June 30, 2023, there were a total of 44 deaths in the pivotal safety cohort. The majority of deaths were from disease progression. There was one death that occurred within 28 days of the last dose of study treatment due to an adverse event (pneumonia)and one death that occurred after 28 days from last study treatment that was determined to be due to an adverse event (septic shock). The cause for 4 deaths was unknown, all of which occurred after 28 days from last study treatment.

The majority of deaths in the dose optimization and single agent adagrasib cohorts were from disease progression. There was one death due to a TEAE reported in the dose optimization (vomiting) and single agent adagrasib cohorts (cardiac arrest) each.

Table 23: Summary of deaths in the safety cohorts

	600mg BID adagrasib+cetuximab N = 94 N (%)	**400mg BID adagrasib+cetuximab N = 27 N (%)**	**600mg BID adagrasib N = 88 N (%)**
Total Deaths	**44 (47)**	**2 (7)**	**63 (72)**
Disease progression	38 (40)	1 (4)	58 (66)

TEAE After 28 days	1 (1) Pneumonia 1 (1) Septic shock	1 (4) Vomiting	1 (1) Cardiac arrest
Unknown	4 (4)	0 (0)	4 (5)

Source: ADSL dataset

Death narratives for all the 4 deaths noted from a TEAE in all 3 safety cohorts are provided below:

Death narratives of the two patients in the pivotal safety cohort

61-year-old female with metastatic CRC with prior therapy with Fluorouracil (5FU), oxaliplatin, irinotecan, regorafenib, trifluridine/tipiracil and bevacizumab. On day 42 of treatment with adagrasib and post three infusions of cetuximab, the patient experienced grade 3 pneumonia and was admitted to the hospital. Adagrasib was held. She then had an episode of aspiration pneumonia leading to clinical deterioration, and then needed ventilatory support. On Day 48, the patient died from pneumonia. Pneumonia as a cause of death is unlikely to be directly related to adagrasib or cetuximab but may be related to overall health deterioration as a result of disease state.

60-year-old female with metastatic CRC with prior therapy with 5FU, oxaliplatin, irinotecan and anti-VEGF therapy. On day 230 of treatment patient was confirmed to have taken adagrasib along with last dose of cetuximab and then on day 246 developed grade 3 abdominal pain and was admitted to the hospital. It is unclear if the patient continued adagrasib from days 230 through day 246. During the admission on Day 246, patient was diagnosed with bacteremia (methicillin resistant staphylococcus aureus), and evaluation noted vegetation on the mitral valve. Abdominal pain resolved by Day 252, but the patient developed grade 4 respiratory failure and septic shock on Day 259. On day 266 her WBC count was noted to be normal. The patient subsequently passed away from day 268. Sepsis as a cause of death is unlikely to be directly related to adagrasib or cetuximab but rather to overall health deterioration as a result of disease state.

Death narrative of the one patient in the dose optimization cohort

50-year-old male with metastatic CRC with prior therapy with 5FU, oxaliplatin, irinotecan and anti-VEGF therapy. Patient developed grade 4 anaphylactic reaction on day 1 of the study that started two minutes after initiation of cetuximab infusion. Cetuximab was permanently discontinued and the patient continued to receive single agent adagrasib. On day 84 scans showed stable systemic disease but new brain metastasis, but the patient was continued on single agent adagrasib, with the last dose on day 112, at which time there was no clinical sign of systemic progression. On Day 126 patient developed hematemesis and died. No autopsy was performed, however clinical assessment was suggestive of disease progression in the GI tract.

The death is therefore unlikely to be related to adagrasib or cetuximab.

Death narrative of the one patient in the adagrasib single agent cohort

62-year-old female with metastatic CRC with prior therapy with 5FU, oxaliplatin. Patient was noted to have grade 2 QT prolongation on her ECG noted on Day 8 which resolved by Day 12 and was again noted on Day 84 of treatment. Baseline ECG from screening was indicative of prior inferior cardiac wall ischemia. On day 85 patient was found pulseless at home and died. The cause of death was determined to be cardiac arrest. No autopsy was performed. No cause of death is available. Given insufficient information regarding medical status near the time of death as well as evidence of prior cardiac insult on the baseline ECG, it is unlikely that the death was related to single agent adagrasib.

Reviewer's comment: *Most deaths in all the safety cohorts were related to disease progression. On review of the death narratives related to fatal adverse events, none were thought to be attributed to study treatment with adagrasib or cetuximab.*

Serious Adverse Events

SAEs were noted in 28 patients (30%) in the pivotal safety cohort and the most common reported SAE was pneumonia. A numerically similar percentage of patients reported SAE in the dose optimization (9/27 patients [33%]) and adagrasib single agent cohorts (26/88 patients [30%]). Table 23 includes SAEs reported in 2 or more patients.

Table 24: Summary of serious adverse events (≥2 patients) in the safety cohorts

	600mg BID adagrasib+cetuximab N = 94 N (%)	**400mg BID adagrasib+cetuximab N = 27 N (%)**	**600mg BID adagrasib N = 88 N (%)**
Patients with serious AEs	**28 (30)**	**9 (33)**	**26 (30)**
Pneumonia*	4 (4.3)	0 (0.0)	0 (0.0)
Small Intestinal Obstruction	2 (2.1)	0 (0.0)	2 (2.3)
Abdominal Pain *	1 (1.1)	0 (0.0)	2 (2.3)
Nausea	0 (0.0)	0 (0.0)	2 (2.3)
Vomiting *	0 (0.0)	1 (3.7)	2 (2.3)
Pleural Effusion	2 (2.1)	0 (0.0)	1 (1.1)
Pyrexia *	2 (2.1)	0 (0.0)	2 (2.3)

Dizziness *	1 (1.1)	0 (0.0)	2 (2.3)
Syncope	1 (1.1)	2 (7)	0 (0.0)
Acute Kidney Injury *	2 (2.1)	0 (0.0)	3 (3.4)
Dehydration	2 (2.1)	0 (0.0)	1 (1.1)

*-Grouped terms
Source: ADAE data set

Reviewer's comment: *Based on the data submitted in the sNDA and review of the serious adverse events, no new safety signal is identified for adagrasib. There is not a numerical increase in rate of serious adverse events in the pivotal safety cohort as compared to the dose optimization cohort or adagrasib single agent cohort.*

Dropouts and/or Discontinuations Due to Adverse Effects

A total of two patients in the pivotal safety cohort discontinued treatment due to an adverse event. The reported AEs leading to discontinuation were abdominal pain and prolonged QT interval.

Adagrasib dose was reduced due to an AE in 33 patients (35%) and interrupted in 58 patients (68%) in the pivotal safety cohort. Dose reductions and interruption due to an AE were noted in 5 patients (19%) and 11 patients (41%) respectively in the dose optimization cohorts. Dose reductions and interruption due to an AE were noted in 32 patients (36%) and 43 patients (49%) respectively in the single agent cohorts.

The most common reasons (≥2%) for dose interruption and dose reduction of adagrasib due to an AE is reported below in Table 24 and Table 22.

Table 25: Adverse Events (≥2%) leading to for dose interruption of adagrasib in the safety cohorts.

	600mg BID adagrasib+cetuximab N = 94 N (%)	**400mg BID adagrasib+cetuximab N = 27 N (%)**	**600mg BID adagrasib N = 88 N (%)**
Last action taken for study treatment - drug interrupted - due to AEs	**58 (62)**	**11 (41)**	**43 (49)**
Diarrhea*	9 (10)	0 (0)	7 (8)
Nausea	8 (9)	1 (3.7)	5 (6)

Vomiting*	8 (9)	3 (11)	7 (8)
Abdominal Pain*	6 (6)	0 (0)	2 (2.3)
Dizziness *	4 (4.3)	0 (0)	2 (2.3)
Headache *	4 (4.3)	0 (0)	1 (1.1)
Pneumonia *	4 (4.3)	0 (0)	1 (1.1)
Alanine Aminotransferase Increased	3 (3.2)	1 (3.7)	0 (0)
Aspartate Aminotransferase Increased	3 (3.2)	0 (0)	1 (1.1)
Dyspnoea *	3 (3.2)	0 (0)	2 (2.3)
Fatigue *	3 (3.2)	1 (3.7)	1 (1.1)
Pleural Effusion	3 (3.2)	0 (0)	0 (0)
Rash *	3 (3.2)	2 (7)	2 (2.3)
Anaemia	2 (2.1)	0 (0)	3 (3.4)
QT prolonged *	2 (2.1)	0 (0)	2 (2.3)
Blood Bilirubin Increased	2 (2.1)	0 (0)	0 (0)
Blood Creatinine Increased	2 (2.1)	0 (0)	3 (3.4)
Decreased Appetite	2 (2.1)	0 (0)	0 (0)
Dehydration	2 (2.1)	0 (0)	2 (2.3)
Haemorrhage *	2 (2.1)	0 (0)	1 (1.1)
Hypomagnesaemia	2 (2.1)	0 (0)	0 (0)
Lipase Increased	2 (2.1)	0 (0)	0 (0)
Muscular Weakness	2 (2.1)	0 (0)	2 (2.3)
Musculoskeletal Pain *	2 (2.1)	0 (0)	3 (3.4)
Pyrexia *	2 (2.1)	0 (0)	1 (1.1)

*-Grouped terms
Source: ADAE dataset

Table 26: Adverse events (≥2%) leading to dose reduction of adagrasib in the safety cohorts.

	600mg BID adagrasib+cetuximab N = 94 N (%)	400mg BID adagrasib+cetuximab N = 27 N (%)	600mg BID adagrasib N = 88 N (%)
Study treatment - dose reduced - due to AEs	**33 (35)**	**5 (19)**	**32 (36)**
AST elevation	7 (7)	0 (0)	1 (1.1)
Fatigue*	7 (7)	2 (7)	9 (10)
ALT elevation	6 (6)	0 (0)	1 (1.1)
Nausea	5 (5)	0 (0)	8 (9)
Decreased Appetite	4 (4.3)	0 (0)	0 (0)
QT prolongation	3 (3.2)	0 (0)	3 (3.4)
Dizziness *	3 (3.2)	0 (0)	1 (1.1)
Acute Kidney Injury *	2 (2.1)	0 (0)	0 (0)
Diarrhoea *	2 (2.1)	0 (0)	6 (7)
Dysarthria	2 (2.1)	0 (0)	0 (0)
Vomiting *	2 (2.1)	0 (0)	7 (8)

*-Grouped terms
Source: ADAE dataset

Almost two thirds of the patients required dose interruption and a third required dose reduction of adagrasib when administered at 600 mg BID due to an AE in the pivotal safety cohort. The AEs leading to dose interruption or reduction for adagrasib are consistent with the known safety profile of the drug and there did not appear to be a meaningful increase in dose modifications related to any specific AE.

Dose interruption was numerically higher in the pivotal safety cohort as compared to that the dose optimization cohort and the adagrasib single agent cohort. Diarrhea as a reason for treatment interruption was numerically more common in the pivotal safety cohort than the dose optimization cohort, however numerically similar to the adagrasib single agent cohort. Dose reductions were also numerically higher in the pivotal safety cohort as compared to the dose optimization cohort.

Cetuximab treatment was withdrawn (permanently discontinued) due to an AE in 11 patients (12%) in the pivotal safety cohorts and in 3 patients (11%) in the dose optimization cohort. The majority of cetuximab withdrawal (4/11 patients) was due to infusion reactions in the pivotal

safety cohort. Other reasons for treatment withdrawal in the pivotal safety cohorts and the dose optimization cohorts are listed below in Table 17.

Table 27: Adverse event leading to cetuximab withdrawal in the safety cohorts.

	600mg BID adagrasib+cetuximab N = 94 N (%)	**400mg BID adagrasib+cetuximab N = 27 N (%)**	**600mg BID adagrasib N = 88 N (%)**
Last action taken for combination treatment - drug withdrawn - due to AEs	**11 (12)**	**3 (11)**	**0 (0)**
Infusion Related Reaction	4 (4.3)	1 (3.7)	0 (0)
Abdominal Pain (GT)	1 (1.1)	0 (0)	0 (0)
Alanine Aminotransferase Increased	1 (1.1)	0 (0)	0 (0)
Arrhythmia (GT)	1 (1.1)	0 (0)	0 (0)
Flushing	1 (1.1)	0 (0)	0 (0)
Malaise	1 (1.1)	0 (0)	0 (0)
Pneumothorax	1 (1.1)	0 (0)	0 (0)
Rash (GT)	1 (1.1)	0 (0)	0 (0)
Anaphylactic Reaction	0 (0)	1 (3.7)	0 (0)
Malignant Neoplasm Progression	0 (0)	1 (3.7)	0 (0)

Source: ADAE dataset

Reviewer's comment: *Although there is a numerically higher number of dose reductions and interruptions for adagrasib in the pivotal safety cohorts compared to what was observed in the dose optimization cohort, FDA cautions that there are multiple limitations in this comparison based on the small sample size of the dose optimization cohort and shorter duration of follow up. Given these facts and that there was no evidence of differences in the exposure-safety relationship for adagrasib 600 mg BID and 400 mg BID, a definitive conclusion cannot be made that there is clinically meaningful improvement in safety of the combination regimen at the lower dose compared to the higher dose.*

The incidence of cetuximab withdrawal was comparable in the pivotal safety cohort as compared to the dose optimization cohorts.

Significant Adverse Events

The following AEs already appear as Warnings/Precautions in the adagrasib label, and the label was updated with information related to incidence of these AEs in patients receiving the combination of adagrasib and cetuximab. No new potential Warnings/Precautions were identified during this review.

Gastrointestinal adverse events

In patients who received adagrasib in combination with cetuximab, serious gastrointestinal adverse reactions included gastrointestinal bleeding in 8.5% including 1.1% Grade 3 or 4 (b) (4) , gastrointestinal obstruction in 5.3% including 5.3% Grade 3 or 4, colitis in 1.1% including 1.1% Grade 3 and ileus in 1.1%. In addition, nausea, diarrhea, or vomiting occurred in 92% of 94 patients, including 6% Grade 3. Nausea, diarrhea, or vomiting led to adagrasib dose interruption or dose reduction in 23% of patients.

QTc interval prolongation

In patients who received adagrasib in combination with cetuximab, 5% of 93 patients with at least one post-baseline electrocardiogram (ECG) assessment had an average QTc ≥ 501 msec and 16% of patients had an increase from baseline of QTc > 60 msec.

Hepatotoxicity

In patients who received adagrasib in combination with cetuximab, 29% had increased alanine aminotransferase (ALT)/increased aspartate aminotransferase (AST); 5% were Grade 3 and 1.1% were Grade 4. The median time to first onset of increased ALT/AST was 4 weeks (range: 0.1 to 27). Overall hepatotoxicity occurred in 38%, and 10% were Grade 3 or 4. Hepatotoxicity leading to adagrasib dose interruption or reduction occurred in 12% of patients.

Interstitial lung disease/pneumonitis

In patients who received adagrasib in combination with cetuximab, Grade 1 ILD/pneumonitis occurred in 1.1% of patients. The time to first onset for ILD/pneumonitis was 38 weeks.

Treatment Emergent Adverse Events and Adverse Reactions

In the pivotal safety cohort, all patients reported a treatment emergent adverse event (TEAE). The most common reported TEAEs (≥ 20%) in the pivotal safety cohort were rash, nausea, diarrhea, vomiting, fatigue, musculoskeletal pain, hepatotoxicity, headache, dry skin, abdominal pain, decreased appetite, edema, anemia, dizziness, cough, constipation, and peripheral neuropathy.

Grade 3 or 4 AEs were reported in 58 (62%) patients, the most common grade 3 or 4 TEAEs (≥2%) were anemia, diarrhea, rash, abdominal pain, headache, musculoskeletal pain, nausea, fatigue, and dizziness.

In the dose optimization cohort, all patients reported a TEAE and 13 patients (48%) reported grade 3 or 4 AE. The most common reported TEAE (≥20%) in the dose optimization cohort were rash, nausea, diarrhea, vomiting, fatigue, musculoskeletal pain, headache, dry skin, abdominal pain, decreased appetite and edema.

In the single agent adagrasib cohorts, all patients reported TEAE and 44 patients (50%) reported grade 3 or 4 AE. The most common reported TEAE(≥20%) in the dose optimization cohort were nausea , diarrhea, vomiting, fatigue, musculoskeletal pain, abdominal pain, decreased appetite, edema, and constipation.

Table 28: Treatment emergent adverse events (≥20%) in the safety cohorts

	600mg BID adagrasib+cetuximab N = 94 N (%)		**400mg BID adagrasib+cetuximab N = 27 N (%)**		**600mg BID adagrasib N = 88 N (%)**	
	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)	All grades n (%)	Grades 3-4 n (%)
Patients with TEAEs	94 (100)	58 (62)	27 (100)	13 (48)	88 (100)	44 (50)
Rash *	80 (85)	4 (4.3)	21 (78)	2 (7)	13 (15)	1 (1.1)
Nausea	64 (68)	2 (2.1)	18 (67)	0 (0.0)	63 (72)	5 (6)
Diarrhea *	61 (65)	5 (5)	16 (59)	0 (0.0)	63 (72)	6 (7)
Vomiting *	54 (57)	0 (0.0)	14 (52)	0 (0.0)	55 (63)	4 (4.5)
Fatigue *	54 (57)	3 (3.2)	15 (56)	4 (15)	55 (63)	5 (6)
Musculoskeletal Pain *	44 (47)	4 (4.3)	7 (26)	1 (3.7)	36 (41)	2 (2.3)
Headache *	35 (37)	4 (4.3)	8 (30)	0 (0.0)	12 (14)	0 (0.0)
Dry Skin	34 (36)	0 (0.0)	8 (30)	0 (0.0)	5 (6)	0 (0.0)
Abdominal Pain *	28 (30)	4 (4.3)	6 (22)	0 (0.0)	23 (26)	5 (6)
Decreased Appetite	28 (30)	0 (0.0)	6 (22)	0 (0.0)	25 (28)	0 (0.0)
Oedema (GT)	26 (28)	0 (0.0)	9 (33)	0 (0.0)	25 (28)	1 (1.1)
Dizziness (GT)	23 (24)	2 (2.1)	3 (11)	0 (0.0)	12 (14)	1 (1.1)
Cough (GT)	23 (24)	0 (0.0)	4 (15)	0 (0.0)	8 (9)	0 (0.0)
Constipation	22 (23)	0 (0.0)	4 (15)	0 (0.0)	19 (22)	0 (0.0)

Neuropathy Peripheral (GT)	19 (20)	1 (1.1)	1 (3.7)	0 (0.0)	16 (18)	1 (1.1)

*-Grouped term
Source: ADAE data set

Reviewer's comment: *Treatment emergent adverse events such as rash was increased in the combination cohorts (pivotal safety cohort and dose optimization cohort) consistent with safety profile of cetuximab. Other gastrointestinal side effects (i.e., nausea, diarrhea, vomiting) were numerically similar in the pivotal safety cohort, dose optimization and single agent cohorts. Grade 3 and 4 reported AEs were numerically higher (66% vs 55%) in the pivotal safety cohort as compared to the dose optimization cohort. However, the dose optimization cohort has a smaller sample size as well as a shorter duration of exposure to adagrasib and cetuximab. Given the limitations with comparing single arm cohorts, no clinically meaningful conclusions can be drawn regarding the safety and tolerability of the combination regimen of adagrasib 600 mg BID compared to adagrasib 400 mg.*

Laboratory Findings

Laboratory abnormalities were graded according to the NCI CTCAE v 5.0. The evaluation of laboratory abnormalities included the worst grade of each laboratory event compared to the baseline laboratory value. The denominator of each laboratory abnormality may differ based on the number of patients with a baseline lab value for each laboratory test.

Table 29: Laboratory abnormalities (≥20%) reported in the safety cohorts.

	600mg BID adagrasib+cetuximab N = 94 N (%)		**400mg BID adagrasib+cetuximab N = 27 N (%)**		**600mg BID adagrasib N = 88 N (%)**	
	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)
HEMATOLOGY						
Lymphopenia	52/82 (63)	14/82 (17)	17/25 (68)	6/25 (24)	54/87 (62)	20/87 (23)
Anemia	44/92 (48)	5/92 (5)	12/27 (44)	0/27 (0.0)	43/88 (49)	7/88 (8)
Leukopenia	25/92 (27)	1/92 (1.1)	6/27 (22)	1/27 (3.7)	19/88 (22)	2/88 (2.3)
Thrombocytopenia	21/92 (23)	0/92 (0.0)	8/27 (30)	0/27 (0.0)	18/88 (20)	1/88 (1.1)
CLINICAL CHEMISTRY						
ALT elevation	47/92 (51)	2/92 (2.2)	11/27 (41)	0/27 (0.0)	27/88 (31)	2/88 (2.3)

Hypomagnesemia	45/92 (49)	6/92 (7)	13/27 (48)	0/27 (0.0)	18/88 (20)	0/88 (0.0)
Lipase elevation	38/92 (41)	3/92 (3.3)	9/27 (33)	0/27 (0.0)	18/88 (20)	2/88 (2.3)
Hypokalemia	37/92 (40)	8/92 (9)	5/27 (19)	0/27 (0.0)	22/88 (25)	4/88 (4.5)
AST elevation	36/92 (39)	4/92 (4.3)	8/27 (30)	0/27 (0.0)	36/88 (41)	2/88 (2.3)
Creatinine rise	28/92 (30)	1/92 (1.1)	6/27 (22)	0/27 (0.0)	48/88 (55)	1/88 (1.1)
Hyponatremia	28/92 (30)	0/92 (0.0)	11/27 (41)	0/27 (0.0)	36/88 (41)	0/88 (0.0)
Hypoalbuminemia (Calcium corrected)	27/92 (29)	1/92 (1.1)	8/27 (30)	0/27 (0.0)	15/88 (17)	1/88 (1.1)
Alk Phos elevation	27/92 (29)	1/92 (1.1)	4/27 (15)	0/27 (0.0)	27/88 (31)	1/88 (1.1)
Amylase elevation	27/92 (29)	0/92 (0.0)	5/27 (19)	0/27 (0.0)	13/88 (15)	0/88 (0.0)
Hyperbilirubinemia	20/92 (22)	3/92 (3.3)	4/27 (15)	0/27 (0.0)	7/88 (8)	0/88 (0.0)

Source- ADLB dataset

Reviewer's comment: *Hematological laboratory abnormalities were numerically similar in all three safety cohorts that were analyzed. Hypomagnesemia and hypokalemia were numerically higher in the combination cohorts (pivotal safety cohort and dose optimization cohort) as compared to adagrasib single agent y cohort which is expected given the known association of this adverse event with cetuximab. While there are limitations in making comparisons among the single arm CRC cohorts, FDA notes numerically higher rates of liver enzyme elevation (i.e., AST, ALT, alkaline phosphatase), Grade 3-4 hypomagnesemia (7% vs 0) and hypokalemia (9% vs 0) were reported in the pivotal safety cohort as compared to dose optimization cohort.*

Vital Signs

Patient's vital signs (weight, temperature, blood pressure, pulse rate, and respiratory rate) were assessed at the following time points:

-At screening
-Days 1 and 15 of every cycle and at the end of treatment visit.

There were no clinically meaningful changes in vital sign measurements over the course of the trial.

Electrocardiograms (ECGs)

In Study 849-001, electrocardiograms were collected in triplicate pre-dose at baseline (on Cycle 1 Day 1, or where applicable, on PK Lead-In Period Day 1), 4 hours after the first dose, pre-dose and 4 hours post-dose on Cycle 1 Day 8 and Cycle 2 Day 1, and pre-dose on Day 1 of Cycles 3 and 5.

QT

In the pivotal safety cohorts, 32 (34.4%) patients had a maximum change from baseline (at any time point) in QT corrected using Fridericia's formula (QTcF) ≤ 30 msec, 46 (49.5%) patients had a maximum change from baseline (at any time point) in QTcF > 30 msec to ≤ 60 msec, and 15 (16.1%) patients had a maximum change from baseline (at any time point) in QTcF > 60 msec. Thirty-eight (40.9%) patients had QTcF >450 to ≤ 480 msec, 12 (12.9%) patients had QTcF > 480 to ≤ 500 msec, and 5 (5.4%) patients had QTcF > 500 msec. Two (2.1%) patients experienced a Grade 3 adverse reaction of electrocardiogram QT prolonged, however there were no Grade > 3 events. There were no TEAEs of Torsades de Pointes (TdP), ventricular fibrillation, sudden death, or ventricular tachycardia/supraventricular tachycardia.

In the dose optimization cohort, 14 (51.9%) patients had a maximum change from baseline (at any time point) in QTcF ≤ 30 msec, 9 (33.3%) patients had a maximum change from baseline (at any time point) in QTcF > 30 msec to ≤ 60 msec, and 4 (14.8%) patients had a maximum change from baseline (at any time point) in QTcF > 60 msec. Seven (25.9%) patients had QTcF > 450 to ≤ 480 msec; 6 (22.2%) patients had QTcF > 480 to ≤ 500 msec; and no patients had QTcF > 500 msec. No patients experienced TEAEs of electrocardiogram QT prolonged. There were no TEAEs of Torsades de Pointes (TdP), ventricular fibrillation, sudden death, or ventricular tachycardia/ supraventricular tachycardia.

Immunogenicity

An assessment of immunogenicity is not considered necessary for this targeted small molecule inhibitor.

8.2.4 Analysis of Submission-Specific Safety Issues

The FDA did not identify submission-specific safety issues that required further analysis.

8.2.5 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Clinical outcome assessment analyses were not performed.

8.2.6 Safety Analyses by Demographic Subgroups

Age- <65 years vs ≥65 years
In the pivotal safety cohorts, TEAE and laboratory abnormalities were analyzed between patients in the age <65 years subgroup (n=63) and age ≥65 years subgroup (n=31).

Treatment emergent adverse events were reported in all patients, however Grade 3-4 TEAE were higher in the age < 65 years vs age ≥65 years (67% vs 52%). Clinically relevant Grade 1-4 TEAE and/or Grade 3-4 TEAE, respectively, which were numerically different in the age <65 years vs age ≥65 years groups (absolute difference ≥10% included diarrhea (60% vs 74%, and 6% vs 3%), vomiting (54% vs 65% and no Grade 3-4), abdominal pain (33% vs 23% and 3% vs 6%), constipation (17% vs 35% and no Grade 3-4), dry skin (33% vs 42% and no Grade 3-4),

decreased appetite (25% vs 39% and no Grade 3-4), dizziness (17% vs 32% and 2% vs6%) and blurry vision (6% vs 19% and no Grade 3-4).

Significant clinically relevant laboratory abnormalities Grade 1-4 and/or Grade 3-4 laboratory abnormalities, respectively, (absolute difference ≥10%) included hypomagnesemia (44% vs 60%, and 5% vs 10%), lipase elevation (35% vs 53% and 5% vs 0), amylase elevation (24% vs 40%, no Grade 3-4), lymphopenia (54% vs 84% and 18% vs 16%) and anemia (44% vs 57% and 6% vs,3%).

A similar analysis was done for patients ≥75 years compared to those <75 years, and no major differences in safety were observed.

Sex- Male vs Female
In the pivotal safety cohorts, TEAE and laboratory abnormalities were analyzed between males (n=44) and females (n=50).

Overall, Grade 3-4 TEAE were similar in the two subgroups (59% vs 64%). Clinically relevant Grade 1-4 TEAE and/or Grade 3-4 TEAE, respectively, which were numerically different in the males and females (absolute difference ≥10%) included diarrhea (59% vs 70%, and 2% vs 8%), nausea (52%, vs 82% and 2% vs 2%), vomiting (50% vs 64% and no Grade 3-4), decreased appetite (36% vs 24% and no Grade 3-4), urinary tract infection (5% vs 20% and no Grade 3-4) and infusion related reactions (20% vs 10% and no Grade 3-4).

Significant clinically relevant laboratory abnormalities and/or Grade 3-4 laboratory abnormalities (absolute difference ≥10%) included ALT rise (38% vs 62% and 0 vs 4%), creatinine rise (38% vs 24% and 0 vs 4%) and hypokalemia (29% vs 50% and 5% vs 12%).

Race- Nonwhite vs White
In the pivotal safety cohorts, TEAEs were analyzed between nonwhite (n=27) patients and white patients (n=67).

Overall, Grade 3-4 TEAE were numerically similar between the two subgroups (59% vs 63%).

Significant clinically relevant laboratory abnormalities Grade 1-4 and/or Grade 3-4 laboratory abnormalities (absolute difference ≥10%) included rise in AST (56% vs 32%, and 4% vs 5%), lymphopenia (50% vs 70%, and 8% vs21%)

Reviewer's comment: *There were a limited number of patients who identified as Black, Asian, Pacific Islander, or American Indian/Alaskan Native enrolled to the study and only 17% of the patients identified as Hispanic or Latino, therefore a more granular evaluation of AEs in each racial or ethnic group is likely to be uninformative and was not conducted.*

ECOG- ECOG Performance Status (PS) 1 vs ECOG Performance Status 0
In the pivotal safety cohorts, TEAE and laboratory abnormalities were analyzed between patients with ECOG PS 1 (n=46) vs ECOG PS 0 (n=48).

Grade 3-4 TEAE were not increased in patients with ECOGPS 1 vs 0 (59% vs 65%). Clinically relevant Grade 1-4 TEAE and/or Grade 3-4 TEAE which were numerically different in the patients with ECOG PS 1 vs 0 (absolute difference ≥10%) included nausea (74% vs 63%, 0 vs 4%), diarrhea (70% vs 60% and 4% vs 6%), dyspepsia (22% vs6% and no Grade 3-4 0 vs 6%, 0), hemorrhage (22% vs 8% and 2% vs 0) and headache (41% vs 33% and 4% vs 4%).

Significant clinically relevant laboratory abnormalities Grade 1-4 and/or Grade 3-4 laboratory abnormalities (absolute difference ≥10%) included ALT rise (58% vs45% and 2% vs 2%) anemia (56% vs 40% and 11% vs0), decrease in albumin (51% vs 40% and 2% vs 2%) and lipase elevation (49% vs34% and 2% vs 4%).

Reviewer's comment: *A formal assessment of the differences noted in the above subgroups would be challenging given the limited number of patients enrolled to the study and belonging to each subgroup. Any numerical differences in the incidence of adverse events between subgroups should be interpreted with caution. Overall, the type of TEAEs and incidence of AEs observed were generally similar in the subgroups evaluated and there was no suggestion of a new safety signal associated with any of the subgroup demographics.*

8.2.7 Specific Safety Studies/Clinical Trials

No additional safety concerns were identified that required dedicated studies.

8.2.8 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable

Human Reproduction and Pregnancy

No additional safety explorations related to human reproduction and pregnancy were performed during this review. Refer to the USPI for available information about use in individuals who are pregnant, lactating or capable of human reproduction.

Pediatrics and Assessment of Effects on Growth

The Applicant submitted a Pediatric Study Plan describing their plan to request a full waiver of pediatric studies due to the rarity of advanced or metastatic colorectal cancer in pediatric patients and the fact that conducting these studies would be impossible or highly impracticable. FDA agrees that the indication for the treatment of patients with colorectal cancer qualifies for

a waiver of the PREA requirements. The safety and effectiveness of adagrasib in pediatric patients have not been established.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable

8.2.9 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

There were no new safety concerns identified in the postmarket setting that were updated in this submission.

Expectations on Safety in the Postmarket Setting

Potential safety concerns beyond those observed in clinical trials and conveyed in the proposed product labeling are not expected in the postmarket setting. Routine postmarket pharmacovigilance will be conducted to monitor for unexpected adverse event.

8.2.10 Integrated Assessment of Safety

The assessment of safety of adagrasib in combination with cetuximab for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic CRC who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy was primarily based on data from Study 849-001, which included 94 patients in the pivotal safety cohorts (Phase 1 substudy Cohort 1 and Phase 2 Cohort G) who received at least one dose of adagrasib 600 mg BID in combination with cetuximab. The safety database for Study 849-001 was determined to be adequate for the safety review of this sNDA. The toxicity profile of single agent adagrasib has been well characterized for patients with NSCLC based on data from Study 849-001. The safety analysis is supported by data from Study 849-001 Phase 1b dose optimization cohort of 27 patients who received adagrasib at dose 400mg BID in combination with cetuximab and 88 patients with CRC who received single agent adagrasib 600mg BID (Phase 2 cohort C n=44; Phase 2 cohort F n=42, and Phase 1/1b adagrasib monotherapy dose-finding segments n=2).

The key risks associated with the combination regimen of adagrasib and cetuximab include gastrointestinal adverse reactions, QTc interval prolongation, hepatotoxicity, and pneumonitis/interstitial lung disease. These adverse events were also determined to be key risks during the FDA assessment of single agent adagrasib for the treatment of NSCLC. No new key risks were identified during the review of this sNDA.

While the overall safety profile for adagrasib 600 mg BID in combination with cetuximab appears generally consistent with the safety profile of single agent adagrasib, when considering the safety profile of the combination regimen administered in the dose optimization cohorts

there is a numerically higher number of Grade 3-4 TEAEs (62% vs 48%), dose reductions (35% vs 19%) and dose interruptions (62% vs 41%). While this numerical difference in advese events was noted between the pivotal cohort and the dose optimization cohort, interpretation of the data is limited by the small sample size and shorter duration of follow up. A dose optimization postmarketing requirement (PMR) was issued at the time of approval of single agent adagrsib for the treatment of KRAS G12C-mutated NSCLC to evaluate alternative doses of adagrasib that may provide similar efficacy with improved safety as compared to adagrasib 600 mg BID. Given that the updated population PK analysis indicates no clinically significant differences in the PK of adagrasib based on tumor type (NSCLC or CRC), (b) (4)

The clinical review team has determined that the risks of treatment with adagrasib 600 mg BID in combination with cetuximab in adult patients with KRAS G12C-mutated locally advanced or metastatic CRC who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy are considered acceptable.

No labeling changes were made to the cetuximab USPI (no corresponding sNDA submitted) as the doses used in Study 849-001 were the labeled/approved doses for cetuximab, and no new safety signals were identified.

8.3 Statistical Issues

There were no outstanding statistical issues with the study design, statistical analysis plan, or efficacy analyses.

8.4 Conclusions and Recommendations

The data submitted has provided substantial evidence of the effectiveness of adgrasib 600 mg BID in combination with cetuximab for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic CRC who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy and the Applicant provided data supporting a favorable risk-benefit ratio of the proposed combination regimen. The results of Study 849-001 for ORR demonstrated that patients treated with adagrasib 600 mg BID in combination with cetuximab had a clinically relevant improvement in BICR-ORR of 34% (95% CI: (25, 45), which is substantially better than responses rates observed with available therapy. The median DOR was 5.8 months (95% CI: 4.2 to 7.6 months) with a maximum DOR of 19 months.

The safety profile is manageable and no new safety signals were identified during the review. The adverse events associated with adagrasib 600 mg BID in combination with cetuximab are described in the USPI and the risks of severe and serious adverse reactions are adequately

described in the Warning and Precautions and Dosage Modifications sections of the product labeling. The safety profile of adagrasib 600 mg BID in combination with cetuximab was consistent with the known safety profile of single agent adagrasib for the treatment of KrAs G12C-mutated NSCLC. Although treatment with adagrasib 600 mg BID in combination with cetuximab is associated with a moderate incidence of TEAEs and was observed to have a higher rate of Grade 3-4 AEs, dose reductions and dose interruptions than the adagrasib and cetuximab regimen evaluated in the dose optimization cohort, the small sample size and short duration of follow up in the dose optimization cohort limit the ability to conclude that adagrasib 400 mg BID in combination is the optimized dose. Based on a comparable improvement in response rate over available therapies for the two combination regimens; a safety profile for adagrasib 600 mg BID in combination with cetuximab that is comparable to what has been described for single agent adagrasib; and PK analysis demonstrating that there is no observed difference in the exposure-safety relationship for adagrasib 600 mg BID and 400 mg BID, the review team has concluded that the benefit-risk profile of adagrasib 600 mg BID in combination with cetuximab is favorable. The data submitted meets the statutory evidentiary requirement for accelerated approval and provides preliminary evidence of the effectiveness of adagrasib in combination with cetuximab for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic CRC who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. The review team recommends granting accelerated approval. A PMR for a confirmatory study will be issued with the approval of this sNDA; Study 849-010,“A Randomized Phase 3 Study of adagrasib 600 mg twice daily in combination with cetuximab versus chemotherapy in patients with advanced colorectal cancer with KRAS G12C mutation with disease progression on or after first-line therapy”. This study has been fully enrolled and the progression fee survival final analysis is anticipated at the end of 2025. During the review of the sNDA, FDA met with the Applicant to discuss timing of analyses and submission of results of the confirmatory trial. During this meeting the Applicant stated agreement that in the event Study 849-010 fails to meet its primary endpoint and the benefit of adagrasib and cetuximab in CRC is not confirmed as planned, they would withdraw the indication for KRAS G12C mutated locally advanced or metastatic CRC.

X Sirisha L Mushti

Primary Statistical Reviewer

X Chi Song

Statistical Team Leader

X Geetika Srivastava

Primary Clinical Reviewer

X Jamie R. Brewer

Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The Division did not refer this application to the Oncologic Drugs Advisory Committee (ODAC) or seek input from Special Government Employees (SGEs) for this NDA as no significant review issues were identified during the review of this application.

10 Pediatrics

The Applicant submitted an initial Pediatric Study Plan on May 21, 2021, describing their plan to request a full waiver of the PREA requirements to conduct pediatric investigations in all pediatric age groups due to the rarity of advanced or metastatic colorectal cancer in pediatric patients and the fact that conducting these studies would be impossible or highly impracticable. FDA agrees that the indication for the treatment of patients with colorectal cancer qualifies for a waiver of the PREA requirements.

11 Labeling Recommendations

11.1 Prescription Drug Labeling

The Applicant proposed additions and edits for the proposed indication in colorectal cancer. Revisions to proposed language were required and are summarized below.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
1 Indications and Usage	KRAZATI in combination with cetuximab is indicated for the treatment of adult patients with *KRAS* G12C-mutated locally advanced or metastatic colorectal cancer (CRC) who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.	FDA generally agreed; minor formatting edits for clarity
2 Dosage and Administration	2.1 Patient Selection Added patient selection for KRAS G12C mutated CRC. 2.2 Dosing Inserted statement on dosing for combination with cetuximab 2.3 Dosage modifications for adverse reactions Reference to cetuximab PI for cetuximab dosage modifications Inserted statement that cetuximab should be permanently discontinued whenever adagrasib is permanently discontinued	2.1, 2.2 FDA agreed 2.3 FDA generally agreed but added recommendation that cetuximab should be withheld whenever adagrasib is withheld
5 Warnings and Precautions	5.1 QTc Interval Prolongation; minor edits	Each Warning and Precaution updated with experience from KRYSTAL-1 trial for combination adagrasib/cetuximab in CRC
6 Adverse Reactions	6.1 CRC safety added	FDA agreed; minor edits to reflect grouping of terms
8 Use in Specific Populations	8.5 Geriatric Use Added percentage of ≥ 65 for combination with cetuximab	FDA generally agreed; percentage of ≥ 75 added per recommendation in Geriatric Guidance

12 Clinical Pharmacology	12.1 Mechanism of Action Added statements on (b) (4) and increased anti-tumor activity of combination adagrasib/cetuxumab in some *KRAS* G12C-mutant tumor models compared to adagrasib or cetuximab alone.	12.1 Retained only the statement on increased tumor activity for combination; other statements not supported by submitted data
14 Clinical Studies	14.2 Colorectal Cancer Description of population and efficacy for *KRAS* G12C-mutated CRC	FDA generally agreed; edited to reflect efficacy population, clarify criteria for major efficacy outcome measures, inclusion of Kaplan-Meier as estimate for duration of response; deleted (b) (4)
17 Patient Counseling Information	(b) (4)	FDA deleted; evidence not sufficient

11.2 Patient Labeling

Minor edits to align with USPI

12 Risk Evaluation and Mitigation Strategies (REMS)

The clinical review team determined that safe use of adagrasib plus cetuximab for the treatment of adult patients with *KRAS* G12C-mutated locally advanced or metastatic colorectal cancer (CRC) who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy can be adequately implemented in the postmarketing setting without issuing a REMS for this combination regimen. The product label for adagrasib contains information on common and clinically significant adverse reactions that have been observed with adagrasib plus cetuximab. Product labeling also includes dose modification and management guidelines for these events and a patient medication guide has been provided. Risk management based on labeling and routine pharmacovigilance is expected to ensure the safe use of adagrasib plus cetuximab.

13 Postmarketing Requirements and Commitment

The review team recommends issuing the following postmarketing requirement (PMR):

1. Complete clinical trial, Study 849-010, "A Randomized Phase 3 Study of adagrasib 600 mg twice daily in combination with cetuximab versus chemotherapy in patients with advanced colorectal cancer with KRAS G12C mutation with disease progression on or after first-line therapy."

   Trial Completion: 03/2027

   Final Report Submission: 09/2027

   Submit the datasets with the final report submission.

14 Division Director (DHOT)

X

15 Division Director (OCP)

X

16 Division Director (OB) Comments

X

17 Division Director (Clinical) Comments

X

18 Office Director (or designated signatory authority) Comments

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

19 Appendices

19.1 References

1. U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2022 submission data (1999-2020): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; https://www.cdc.gov/cancer/dataviz, released in June 2023.

2. Global Cancer Observatory. International Agency for Research on Cancer. World Health Organization. Available at: https://gco.iarc.fr/ (Accessed on January 23, 2023).

3. Siegel RL, Miller KD, Wagle NS, Jemal A, CA Cancer J Clin. 2023;73(1):17.

4. https://seer.cancer.gov/statfacts/html/colorect.html

5. https://seer.cancer.gov

6. Ostrem JM, Shokat KM. Direct small-molecule inhibitors of KRAS: from structural insights to mechanism-based design. Nat Rev Drug Discov. 2016;15(11):771-785. doi:10.1038/nrd.2016.139

7. The Cancer Genome Atlas (TCGA) Network. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012;487(7407):330-337.

8. Giannakis M, Mu XJ, Shukla SA, et al. Genomic correlates of immune-cell infiltrates in colorectal carcinoma [published correction appears in Cell Rep. 2016 Oct 18;17(4):1206]. Cell Rep. 2016;15(4):857-865.

9. Yaeger R, Chatila WK, Lipsyc MD, et al. Clinical sequencing defines the genomic landscape of metastatic colorectal cancer. Cancer Cell. 2018;33(1):125-136.e3.

10. Henry JT, Coker O, Chowdhury S, et al. Comprehensive clinical and molecular characterization of KRASG12C-mutant colorectal cancer. JCO Precis Oncol. 2021;5:613-621.

11. Nassar AH, Adib E, Kwiatkowski DJ. Distribution of KRASG12C Somatic Mutations across Race, Sex, and Cancer Type. N Engl J Med. 2021;384(2):185-187.

12. Venook AP, Donna Niedzwiecki, Heinz-Josef Lenz. Effect of First-Line Chemotherapy Combined with Cetuximab or Bevacizumab on Overall Survival in Patients with KRAS Wild-Type Advanced or Metastatic Colorectal Cancer: A Randomized Clinical Trial. JAMA.

2017 Jun 20;317(23):2392-2401. doi: 10.1001/jama.2017.7105.

13. Kopetz S, Grothey A, Yaeger R, N Engl J Med 2019; 381:1632-1643
DOI: 10.1056/NEJMoa1908075.

14. Garcia J, Hurwitz HI, Sandler AB, Miles D, Coleman RL, Deurloo R, Chinot OL. Bevacizumab (Avastin®) in cancer treatment: A review of 15 years of clinical experience and future outlook. Cancer Treat Rev. 2020 Jun;86:102017. doi: 10.1016/j.ctrv.2020.102017. Epub 2020 Mar 26. PMID: 32335505.

19.2 Financial Disclosure

Covered Clinical Study (Name and/or Number): 849-001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1447		
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 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)

19.3 OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Bioanalytical Method Validation

The bioanalytical method (HPLC/MS/MS) used in clinical study 849-001 for this NDA supplement (S-05) is the same as that described in original NDA 216340. Analytical methodology was unchanged across method versions. The bioanalytical method life cycle information is provided in **Table 1**. A summary of method validation for adagrasib is presented in **Table 2.** The in-study analytical result for Studies 849-001 colorectal cancer (CRC) cohorts are shown in **Tables 3 and 4**. The incurred sample reproducibility, the calibration curve and QC samples met the acceptability criteria in the guidance. The Applicant's bioanalytical methods validation to quantify adagrasib plasma concentrations are acceptable.

Table 1. Bioanalytical Method Life Cycle Information

	Method Validation MTX8HPP	Clinical Study 849-001 Report 8398399 Interim No. 4	Clinical Study 849-001 Report 8398399 Interim No. 5
Analyte	Adagrasib	Adagrasib	Adagrasib
Validation type	Full	NA	NA
eCTD reference number	Not available		
Method ID	MTX8HPP	MTX8HPP	MTX8HPP
Duration of time method was in use	27 Jul 2018 to 04 Sep 2018	28 Jan 2021 to 11 April 2023	28 Jan 2021 to 28 Jul 2023
Bioanalytical site	(b) (4)		
Matrix	Plasma	Plasma	Plasma
Platform	HPLC-MS/MS		
Format	NA		
Stock reference, lot number, expiration date	MRTX849, Lot EW5243-753-P1, Retest date: (b) (4)	MRTX849, EW5243-753-P1 Retest date (b) (4) and (b) (4) Lot D-317-54, Retest date: (b) (4) and (b) (4) Lot CPo126416-01-01-01-29-01-RS, Retest date: (b) (4)	MRTX849, EW5243-753-P1 Retest date (b) (4) and (b) (4) Lot D-317-54, Retest date: (b) (4) and (b) (4) Lot CPo126416-01-01-01-29-01-RS, Retest date: (b) (4)
Calibration range from LLOQ to ULOQ	1.00 to 3000 ng/mL	1.00 to 3000 ng/mL	1.00 to 3000 ng/mL
Matrix study population	Healthy subjects	Patients	Patients
Link to reports and applicable amendments	VAL-MRTX849-004, Addendum No. 1, and Addendum No. 2	8398399 Interim Report No. 4	8398399 Interim Report No. 5
Synopsis of amendment history	Amendment 1: To measure the effect of analytes not measured with the assay, to extend solution stability, to extend frozen matrix stability Amendment 2: To extend frozen matrix stability	NA	NA

eCTD = Electronic Common Technical Document; HPLC = high performance liquid chromatography; ID = identification; LLOQ = lower limit of quantification; MS = mass spectrometry; NA = not applicable; No. = number; ULOQ = upper limit of quantitation

Table 2. Summary of Method Performance of MTX8HPP

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 1 VAL-MRTX849-004, issued 27 May 2021** **Addendum 2 VAL-MRTX849-004, issued 17 Oct 2022**
Method description	Determination of adagrasib in K_2EDTA human plasma by protein precipitation followed by HPLC with MS/MS detection. Analytical column was Waters XBridge C18 (50 x 2.1 mm, 5 µm particle size). The LC instrument was a Shimadzu Prominence 20 series with column temperature at 35°C and autosampler temperature at 5°C. Flow rate was 1.00 mL/min. Gradient (%B) was: 45% at 0.01 to 0.10 min., ramp to 90% from 0.10 min. to 0.85 min. Hold at 90% from 0.85 min to 1.75 min. There was an autosampler rinse at 1.00 min. (mode: before and after sampling, 200 µL rinse volume). Ramp to 45% from 1.75 to 2.05 min. Hold at 45% until 2.75 min. Mobile phase A was: [Ammonium Formate 1 M (aq)]: Water: Formic Acid (1:100:0.1) and mobile phase B was: [Ammonium Formate 1 M (aq)]: Acetonitrile: Methanol: Formic Acid (1:50:50:0.1). The mass spectrometer was Sciex API 4500, with ESI+ ionization, ionspray voltage 3000 V, 625°C source temperature, nitrogen gas (collision at 11, curtain at 30, nebulizing at 65, and auxiliary at 65), entrance potential 10 V, acquisition time 2.00 min, cycle time 3.5 min. Transitions monitored were 604.4 > 98.0 (adagrasib) and 584.4 > 98.0 (ISTD1). Compound specific settings were (ISTD1): Dwell time of 50 (40), de-clustering potential of 120 (120), collision energy of 30 (31), and collision cell exit potential of 13 (18).
Materials used for standard calibration curve and concentration	MRTX849, Lot EW5243-753-P1, Mirati Therapeutics, Inc. MRTX849, Lot D-317-54, (b) (4) MRTX849, Lot CPo126416-01-01-01-29-01-RS, (b) (4) (b) (4) Stock solution: 1.00 mg/mL in acetonitrile:DMSO (50:50) MRTX810, Lot EW4069-1529-P1, Mirati Therapeutics, Inc. MRTX810, Lot EW35741-8-P1, (b) (4) Stock solution: 0.100 mg/mL in acetonitrile:DMSO (50:50)
Validated assay range	1.00 to 3000 ng/mL
Material used for QCs and concentration	MRTX849, Lot EW5243-753-P1, Mirati Therapeutics, Inc. MRTX849, Lot D-317-54, (b) (4) MRTX849, Lot CPo126416-01-01-01-29-01-RS, (b) (4) (b) (4) 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 4.3, Table 6.4
	Interbatch Precision (%RSD)	2.3% to 15.4%	
	Total Error	NR	
Selectivity and matrix effect	Selectivity for adagrasib 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: Accuracy (% bias): -16.8% 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 2400 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 6 hours in human plasma at RT condition	VAL-MRTX849-004, Section 4.14, Table 6.12 – 6.18
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 1492 days at -60°C to -80°C	VAL-MRTX849-004 Addendum No 1 Section 1, Table 6.8 Addendum No 2 Section 1, Table 6.5
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

Table 3. Method Performance in Study 849-001 (Interim 4)

Method Performance in Study 849-001 (Interim 4) Bioanalytical Report: 8398399 Interim 4		
Assay passing rate	142 of 156 runs (91%) met acceptance criteria	8398399 Int.4 Section 1
Standard curve performance	Cumulative accuracy (% bias) -1.5% to 1.0% Cumulative precision (%CV) ≤ 6.3%	8398399 Int.4 Section 1 Table 9.3
QC performance	Cumulative accuracy (% bias) 0.0% to 1.6% Cumulative precision (%CV) ≤ 7.4% Total Error: NR	8398399 Int.4 Section 1 Table 9.5
Method reproducibility	Incurred sample reanalysis was performed in 319 samples (5.3% of total study samples) and 312 (97.8%) of samples were within ±20% of the original results	8398399 Int.4 Section 4.8 Table 9.7
Study sample analysis stability	Samples were received intact, frozen on dry ice, and stored at -60°C to -80°C. Samples were collected beginning 15 Jan 2019 and analyzed by 11 Apr 2023. Samples were analyzed in multiple subsets resulting in all samples analyzed within 944 days of collection (within the established stability limit of 1492 days at -60°C to -80°C). A total of 53 samples were received thawed. These samples were not analyzed. Samples that were not received frozen on dry ice were: returned, shipped to the correct entity, or were marked "Do Not Analyze".	8398399 Int.4 Section 4.4, Section 5.6
Standard calibration curve performance during accuracy and precision	There were 142 calibrator sets of 2 replicates each of 8 concentration levels from 1.00 to 3000 ng/mL (a total of 2272 data points). 31 datapoints were rejected due to failed acceptance criteria (≥ ±5% of nominal, ≥ ±20% at LLOQ), 1 datapoint was rejected due to carryover, and 1 datapoint had no reportable value.	

Table 4. Method Performance in Study 849-001 (Interim 5)

Method Performance in Study 849-001 (Interim 5) Bioanalytical Report: 8398399 Interim 5		
Assay passing rate	154 of 168 runs (92%) met acceptance criteria	8398399 Int.5 Section 1
Standard curve performance	Cumulative accuracy (% bias) -1.5% to 1.0% Cumulative precision (%CV) ≤ 6.3%	8398399 Int.5 Section 1 Table 9.3
QC performance	Cumulative accuracy (% bias) -0.4% to 1.4% Cumulative precision (%CV) ≤ 7.2% Total Error: NR	8398399 Int.5 Section 1 Table 9.5
Method reproducibility	Incurred sample reanalysis was performed in 319 samples (4.9% of total study samples) and 312 (97.8%) of samples were within ±20% of the original results	8398399 Int.5 Section 1 Table 9.7
Study sample analysis stability	Samples were received intact, frozen on dry ice, and stored at -60°C to -80°C. Samples were collected beginning 15 Jan 2019 and analyzed by 28 Jul 2023. Samples were analyzed in multiple subsets resulting in all samples analyzed within 944 days of collection (within the established stability limit of 1492 days at -60°C to -80°C).	8398399 Int.5 Section 4.4, Section 5.6
Standard calibration curve performance during accuracy and precision	There were 168 calibrator sets of 2 replicates each of 8 concentration levels from 1.00 to 3000 ng/mL (a total of 2688 data points). 34 datapoints were rejected due to failed acceptance criteria (≥ ±15% of nominal, ≥ ±20% at LLOQ), 1 datapoint was rejected due to carryover, and 1 datapoint had no reportable value.	

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Sheryse Taylor, Ph.D.	OOD/DHOT	Sections: 5	**Select one:** x Authored _Approved
	Signature: Sheryse N. Taylor -S Digitally signed by Sheryse N. Taylor -S Date: 2024.05.24 17:49:54 -04'00'			
Nonclinical Team Leader	Matthew Thompson, Ph.D.	OOD/DHOT	Sections: 5	**Select one:** _Authored x Approved
	Signature: Matthew D. Thompson -S Digitally signed by Matthew D. Thompson -S Date: 2024.05.24 14:49:07 -04'00'			
Clinical Pharmacology Reviewer	Lily Leu, Pharm.D.	CDER/OTS/OCP/ DCPII	Sections: 6, 19.4	**Select one:** x Authored _Approved
	Signature: Lily L. Leu -S Digitally signed by Lily L. Leu -S Date: 2024.05.28 11:43:47 -04'00'			
Clinical Pharmacology Team Lead	Jason Moore, Pharm.D.	CDER/OTS/OCP/ DCPII	Sections: 6, 19.4	**Select one:** _Authored x Approved
	Signature: Jason N. Moore Jr -S Digitally signed by Jason N. Moore Jr -S Date: 2024.05.28 14:59:25 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Pharmacometrics Reviewer	Ye Xiong, Ph.D.	CDER/OTS/OCP/DPM	Sections: 6, 19.4	**Select one:** x Authored _Approved
	Signature: Ye Xiong -S Digitally signed by Ye Xiong -S Date: 2024.06.10 14:23:35 -04'00'			
Pharmacometrics Team Leader	Youwei Bi, Ph.D.	CDER/OTS/OCP/DPM	Sections: 6, 19.4	**Select one:** _Authored x Approved
	Signature: Youwei Bi -S Digitally signed by Youwei Bi -S Date: 2024.05.28 14:27:39 -04'00'			
Clinical Pharmacology Division Director	Nam Atiqur Rahman, Ph.D.	CDER/OTS/OCP/DCP II	Sections: 6, 19.4	**Select one:** _Authored x Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S Date: 2024.05.28 12:00:19 -04'00'			
Clinical Reviewer	Geetika Srivastava, M.D., M.S.P.H.	CDER/OND/OOD/DO3	Sections: 1,2,3,4, 7, 8, 9, 11, 19	**Select one:** x Authored _Approved
	Signature: Geetika Srivastava -S Digitally signed by Geetika Srivastava -S Date: 2024.05.28 19:10:29 -04'00'			
Clinical Team Leader	Jamie Brewer, M.D.	CDER/OND/OOD/DO3		**Select one:** _Authored x Approved
	Signature: *See final signature in AA*			
Associate Director for Labeling (ADL)	Doris Auth, Pharm.D.	OCE	Sections: Label	**Select one:** _Authored x Approved
	Signature: Doris Auth -S Digitally signed by Doris Auth -S Date: 2024.05.28 14:07:58 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Jamie Brewer, M.D.	CDER/OND/OOD/DO3		**Select one:** _Authored x Approved
	Signature: *See final signature in AA*			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Deputy Division Director	Chana Weinstock, M.D.	CDER/OND/OOD/DO3		Select one: Authored X Approved
	Signature:	*See final signature in AA*		

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/s/

JAMIE R BREWER
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CHANA WEINSTOCK
06/21/2024 11:55:44 AM

MEMORANDUM

MEMO DATE: May 31, 2024

TO: To the file for NDA 216340 S-005

FROM: Sheryse Taylor, PhD
Nonclinical Reviewer
Division of Hematology Oncology Toxicology
Office of Oncologic Diseases

THROUGH: Matthew D Thompson, PhD, MPH
Nonclinical Team Lead
Division of Hematology Oncology Toxicology
Office of Oncologic Diseases

Application Type	NDA
Application Number(s)	216340/ S-005
Received Date(s)	12/21/24
Division/Office	DO3/OOD
Established/Proper Name	adagrasib
(Proposed) Trade Name	Krazati
Pharmacologic Class	inhibitor of the RAS GTPase family
Applicant	Mirati Therapeutics Inc.
Dosage form	Tablet
Applicant Proposed Indication(s)/Population(s)	In combination with cetuximab, for the treatment of adult patients with *KRAS* G12C-mutated locally advanced or metastatic CRC who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy

Recommendation

The nonclinical team reviewed Section 12.1 of the Applicant's proposed label. The nonclinical reviewer's revisions are detailed below.

Currently approved label

Adagrasib is an irreversible inhibitor of KRAS G12C that covalently binds to the mutant cysteine in KRAS G12C and locks the mutant KRAS protein in its inactive state that prevents downstream signaling without

affecting wild-type KRAS protein. Adagrasib inhibits tumor cell growth and viability in cells harboring KRAS G12C mutations and results in tumor regression in KRAS G12C-mutated tumor xenograft models with minimal off-target activity.

Applicant's proposed label

Adagrasib is an irreversible inhibitor of KRAS G12C that covalently binds to the mutant cysteine in KRAS G12C and locks the mutant KRAS protein in its inactive state that prevents downstream signaling without affecting wild-type KRAS protein. Adagrasib inhibits tumor cell growth and viability in cells harboring KRAS G12C mutations and results in tumor regression in KRAS G12C-mutated tumor xenograft models with minimal off-target activity.

(b) (4)

FDA edits were made and accepted by the Applicant

Adagrasib is an irreversible inhibitor of KRAS G12C that covalently binds to the mutant cysteine in KRAS G12C and locks the mutant KRAS protein in its inactive state that prevents downstream signaling without affecting wild-type KRAS protein. Adagrasib inhibited tumor cell growth and viability in cells harboring KRAS G12C mutations and resulted in tumor regression in KRAS G12C-mutated tumor xenograft models with minimal off-target activity. Adagrasib in combination with cetuximab had increased antitumor activity in some cell line-derived and patient-derived KRAS G12C-mutant CRC tumor xenograft models compared to adagrasib or cetuximab alone.

Revisions to Section 12.1 were made to more accurately reflect the findings of the provided nonclinical data. Minor additional changes were made for tense consistency with the rest of 12.1.

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/s/

SHERYSE TAYLOR
06/03/2024 09:13:30 AM

MATTHEW D THOMPSON
06/03/2024 11:04:19 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216340Orig1s005

PRODUCT QUALITY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number:** NDA-216340-SUPPL-005
   sNDA Recommendation: Approval
   sNDA Managed by: OND

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement	PA	12/21/2023	12/21/2023	12/27/2023	06/21/2024	01/11/2024

3. **Provides For:**
   - addition of the following proposed indication:
     KRAZATI®(adagrasib) in combination with cetuximab is indicated for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic CRC who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. The presence of KRAS G12C mutation to be determined by an FDA-approved test.

4. **Review #**: 01

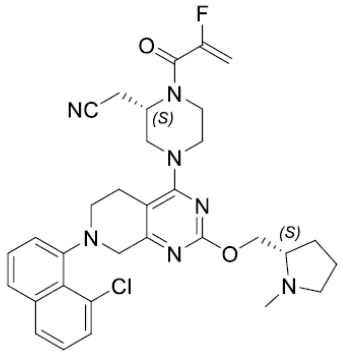
5. **Clinical Review Division**: OOD/DO II

6. **Name and Address of Applicant**:
   Mirati Therapeutics Inc.
   3545 Cray Court
   San Diego, CA 92121
   Contact: Vincent Caralli, Executive Director, Regulatory Affairs
   Phone: 619-816-3670
   Email: caralliv@mirati.com

7. **Drug Product**:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product	Orphan designation #
Krazati (adagrasib)	Tablet	200 mg	oral	Rx	Yes	20-7563

8. Chemical Name and Structure of Drug Substance:

	**USAN**: adagrasib **Chemical name**: {(2S)-4-[7-(8-chloronaphthalen-1-yl)-2-{[(2S)-1-methylpyrrolidin-2-yl]-methoxy}-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-yl]-1-(2-fluoroprop-2-enoyl)piperazin-2-yl}acetonitrile **Molecular formula**: $C32H3_5ClFN_7O_2$ **MW**: 604.1 g/mol

9. Indication: 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, who have received at least one prior systemic therapy.

10. Supporting/Related Documents: None.

11. Disciplines/Consults: None.

12. Executive Summary:

This supplement provides for addition of the following proposed indication:

- KRAZATI®(adagrasib) in combination with cetuximab is indicated for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic CRC who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. The presence of KRAS G12C mutation to be determined by an FDA-approved test.

The supplement provides updated PI. There are no CMC related changes in sections 2, 3, 11 and 16.

The applicant has claimed categorical exclusion from the determination of an environmental assessment under 21 CFR Part 25.31 (b). Under 21 CFR 25.31 (b), a categorical exclusion exists for action on an NDA if estimated concentration of the active pharmaceutical substance at the point of entry into the aquatic environment will be below 1 ppb. The calculated EIC-Aquatic concentration of (b) (4) ppb falls below the limit of 1 ppb.

To the best of the sponsor's knowledge, no extraordinary circumstances, as referenced in 21 CFR 25.21, exist relative to this action. Therefore, the request for categorical exclusion may be granted.

From a CMC perspective the changes proposed in S005 are adequate.

13. Conclusions & Recommendations:

This supplement is recommended for approval.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer:
Qi Charles Liu, Ph.D., CMC reviewer, Branch 1, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

16. Secondary Reviewer:
Rohit Kolhatkar, Ph.D., SPQA, Branch 1, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ

Qi Charles Liu

Digitally signed by Qi Charles Liu
Date: 1/11/2024 11:01:25AM
GUID: 53b4299e000120abe375af2240eda3f5

Rohit Kolhatkar

Digitally signed by Rohit Kolhatkar
Date: 1/11/2024 11:04:19AM
GUID: 57bf531500b52a2eccd5395bec77ebc2
Comments: concur with the recommendation to approve from CMC standpoint

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216340Orig1s005

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 5/21/2024

To: Rebecca Cohen, Regulatory Project Manager
Division of Oncology 3 (DO3)

Doris Auth, Associate Director for Labeling, DO3

From: Rachael Conklin, Team Leader
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for KRAZATI™ (adagrasib) tablets, for oral use

NDA: 216340, S-005

Background:
In response to DO3's consult request dated December 27, 2023, OPDP has reviewed the proposed Prescribing Information (PI) and Patient Package Insert (PPI) for supplement 005 for KRAZATI™ (adagrasib) tablets, for oral use. This supplement supports the new indication in combination with cetuximab, for the treatment of adult patients with *KRAS* G12C-mutated locally advanced or metastatic colorectal cancer (CRC), as determined by an FDA-approved test, who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. This indication is approved under accelerated approval based on objective response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of a clinical benefit in confirmatory trials.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on May 9, 2024, and our comments are provided below.

PPI:
A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI were sent under separate cover.

Thank you for your consult. If you have any questions, please contact Rachael Conklin at rachael.conklin@fda.hhs.gov

PI:

Section	Statement from Draft (if applicable)	OPDP Comments
HIGHLIGHTS OF PRESCRIBING INFORMATION: ADVERSE REACTIONS	"In combination with cetuximab in CRC: The most common adverse reactions (≥ 25%) were diarrhea, nausea, vomiting, fatigue, hepatotoxicity, anemia, edema, decreased appetite, and rash. The most common (≥ 2%) Grade 3 or 4 laboratory abnormalities were decreased lymphocytes, decreased hemoglobin, decreased magnesium, increased alanine aminotransferase, decreased albumin, decreased potassium, increased lipase and increased aspartate aminotransferase."	OPDP acknowledges the comment to the applicant to update based on table 5 and we agree that the adverse reactions in the highlights should be updated to be consistent with table 5 in section 6.1. Specifically, we note the following adverse reactions that occurred at a rate ≥ 25% from table 5 are currently missing from the highlights: • abdominal pain (30%) • musculoskeletal pain (47%) • dry skin (36%) • headache (37%) Additionally, we recommend revising the order of the adverse reactions and laboratory abnormalities in the highlights so that they are presented in decreasing order of frequency (e.g., right now rash (84%) appears last in the list of ARs in the highlights, when it should appear first).

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/s/

RACHAEL E CONKLIN
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 17, 2024
To:	Rebecca Cohen, RN, MPH, OCN Regulatory Project Manager **Division of Oncology III (DO3)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, MSN, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Kelle Caruso, PharmD, BCPS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	KRAZATI (adagrasib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 216340
Supplement Number:	S-005
Applicant:	Mirati Therapeutics, Inc.

1 INTRODUCTION

On December 21, 2023, Mirati Therapeutics, Inc. submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy to their New Drug Application (NDA) 216340/S-005 for KRAZATI (adagrasib) tablets. With this supplement, the Applicant proposes to add an indication for KRAZATI in combination with cetuximab for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic colorectal cancer (CRC) who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology III (DO3) on January 12, 2024, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for KRAZATI (adagrasib) tablets.

2 MATERIAL REVIEWED

- Draft KRAZATI (adagrasib) tablets PPI received on December 21, 2023, and received by DMPP and OPDP on May 9, 2024.
- Draft KRAZATI (adagrasib) tablets Prescribing Information (PI) received on December 21, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 9, 2024.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
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RACHAEL E CONKLIN
05/17/2024 12:00:25 PM

BARBARA A FULLER
05/17/2024 12:04:31 PM

LASHAWN M GRIFFITHS
05/17/2024 12:20:52 PM

Clinical Inspection Summary

Date	May 6, 2024
From	Courtney McGuire, MD Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Geetika Srivastava, MD, Clinical Reviewer Jamie Brewer, MD, Clinical Team Leader Rebecca Cohen, Regulatory Project Manager Division of Oncology 3 (DO3)
NDA #	sNDA 216340, Supplement 5
Applicant	Mirati Therapeutics, Inc.
Drug	adagrasib
NME (Yes/No)	No
Therapeutic Classification	RAS GTPase inhibitor
Proposed Indication	Treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic colorectal cancer (CRC) who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.
Consultation Request Date	January 31, 2024
Summary Goal Date	May 21, 2024
Action Goal Date	June 21, 2024
PDUFA Date	June 21, 2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Applicant, Mirati Therapeutics, Inc., submitted clinical data from Study ID 849-001 (NCT03785249) to the Agency in support of a supplemental New Drug Application (sNDA 216340, S5) for adagrasib. The proposed indication is for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic colorectal cancer (CRC) who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

Two domestic clinical investigators (CIs), Drs. Yaeger and Negrao, were selected for clinical inspections. The CRO ((b) (4)) was chosen for inspection of the conduct of the central imaging review.

Inspection of the imaging CRO, (b) (4), revealed no significant discrepancies or regulatory violations or Good Clinical Practice (GCP) noncompliance. Inspection of Dr. Negrao revealed few unreported, nonserious adverse events (AEs) in 2 subjects and other protocol deviations related to unreported concomitant medication use and missed study assessments for one study

visit. Despite these protocol deviations, the inspections for both Dr Negrao and Dr. Yaeger did not find significant concerns regarding the study conduct and management of the clinical trial, GCP or regulatory compliance. Based on the results of these inspections, data generated by the inspected CIs and the imaging CRO and submitted by the Applicant appear acceptable in support of the proposed indication.

II. BACKGROUND

The Agency granted accelerated approval on December 12, 2022, for adagrasib (MRTX849) for the treatment of KRAS G12C-mutant non-small cell lung cancer (NSCLC). On December 21, 2023, Mirati Therapeutics, Inc. submitted sNDA 216340, S5 seeking approval of adagrasib in combination with cetuximab for the treatment of adult patients with *KRAS G12C*-mutated locally advanced or metastatic CRC who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

The primary evidence of efficacy for adagrasib for the proposed indication and the focus of the BIMO inspections are the CRC, dual-therapy cohorts (adagrasib + cetuximab) from Study 849-001 (i.e., Phase 2 Cohort G and a Phase 1 Sub-study Cohort 1). Additional safety data from CRC cohorts in Study 849-001 provide supportive safety data.

Study Design

Study 849-001 is an ongoing, multicenter, phase 1/2, dose finding, multiple expansion cohort study evaluating the safety, pharmacokinetic (PK), and clinical activity / efficacy of adagrasib.

Phase 1 sub-study, Appendix 8, Cohort 1 was an open-label, single-arm, dose finding study evaluating adagrasib in combination with cetuximab in adagrasib -naïve patients with *KRAS G12C* mutated CRC. The starting study drug dosage was adagrasib 600 mg by mouth twice daily (po BID) and intravenous (IV) cetuximab 400 mg/m^2 on Cycle 1 Day 1 followed by 250 mg/m^2 weekly beginning on Cycle 1 Day 8. The protocol allowed adagrasib dosage reduction during treatment for individual patients or subsequent groups of patients depending on tolerability observed.

Phase 2 Cohort G was an open-label, single-arm study evaluating the safety and clinical activity / efficacy of adagrasib in combination with cetuximab in patients with *KRAS G12C* mutated, previously treated, advanced or metastatic CRC. All enrolled subjects received adagrasib 600 mg po BID and IV cetuximab 500 mg/m^2 administered every 2 weeks (Q2W) on Days 1 and 15 of each 28-day cycle. The protocol allowed adagrasib dose modifications for toxicities.

Subjects in both Cohort G and the Phase 1 sub-study continued to receive study treatment at the discretion of the Investigator for reasons including but not limited to disease progression (i.e., objective disease progression according to RECIST 1.1 per Investigator), unacceptable

adverse events (AEs), patient refusal, or death. Patients experiencing clinical benefit in the judgment of the Investigator could continue study treatment beyond disease progression. Patients discontinuing treatment were followed for receipt of subsequent anti-cancer therapies and survival.

Endpoints

- *Primary endpoint*: Objective response rate (ORR) in accordance with RECIST 1.1 in individual patients with CRC with KRAS G12C mutation.

- *Secondary efficacy endpoints*: Duration of Response (DOR), Progression-free survival (PFS), One-year survival rate, Overall survival

The final analysis of efficacy was based on blinded independent central review of tumor scans, with the Investigator's assessment of disease used for secondary analyses.

Study Status
As of the data cut-off of June 30, 2023, the study enrolled the following subjects across 39 study centers in the United States.

Safety population:

All Cohorts:	N= 213
Cohorts G:	N= 62
Sub-study Cohort 1:	N= 32

Efficacy population:

Cohort G + Sub-study Cohort 1:	N= 94
Cohort G:	N= 62
Phase 1 Sub-study Cohort 1:	N= 32

Dr. Rona Yaeger (Site 806), Dr. Marcelo V Negrao (Site 848), and the imaging CRO ((b) (4)) were inspected.

RESULTS

1. **Dr. Rona Yaeger (Site 806/ 849-001)**
   Memorial Sloan Kettering Cancer Center - New York
   300 East 66th Street
   New York, New York, 10065
   United States

Inspection Dates: March 6, 2024, to March 12, 2024

This investigator was inspected as a routine PDUFA inspection for Study 849-001. Dr. Yaeger was previously inspected in January 2020, and there were no observations.

As of the data cutoff date (July 24, 2023), the site screened 51 subjects, and 39 subjects were enrolled and received treatment (inclusive of all cohorts). Three subjects completed treatment and remain in long-term follow-up. The study was ongoing and open to enrollment at the time of the inspection.

The inspection reviewed subject-related source documents for all 21 subjects in Cohort G and the Phase 1 substudy including the following: medical and research records containing informed consent forms (ICFs), inclusion/exclusion criteria, visit notes, laboratory reports, imaging and radiological scans, investigational product (IP) administrations, and AE/SAE logs. The inspection compared these source documents, eCRFs, and data line listings to verify eligibility, protocol deviations, demographic information, completion of baseline ophthalmology examinations, current medications, AEs/SAEs, and vital signs.

The inspection reviewed the following study-related documents: signed investigator agreements, financial disclosures, CV, ICF and amendments, protocol and amendments, IRB approvals / correspondences, study staff training records / logs, delegation of authority log, screening and enrollment log, detailed enrollment log, research pharmacy shipping records, IP accountability logs, IP storage and temperature logs, sponsor communications, laboratory certificates of accreditation, protocol deviation log, and monitoring reports / activities. The inspection also reviewed additional study-related processes including electronic database access and AE reporting.

The inspection verified that tumor assessments for the primary efficacy endpoint (ORR) were performed at specified time points and submitted to the central imaging CRO. The secondary endpoint, OS, was verified by comparison of the subject source data against the provided data line listings for the following: enrollment dates, subject survival status, and cause of death. There were no deficiencies or under-reporting of AEs. There were no significant protocol deviations that impacted data integrity.

Based on the results of the inspection, Study 849-001 data generated at Dr. Yaeger's site appear acceptable in support of the proposed indication in the sNDA.

2. **Dr. Marcelo V Negrao (Site 848/ 849-001)**
University of Texas MD Anderson Cancer Center
1400 Holcombe Blvd. Unit 432
Houston, Texas 77030, United States

Inspection Dates: February 26, 2024, to March 1, 2024

This investigator was inspected as a routine PDUFA inspection for Study 849-001. This was the first FDA inspection for this investigator.

As of the data cut-off (June 30, 2023), there were 61 subjects screened and 45 subjects enrolled and treated with IP. A total of 32 subjects discontinued or were off study. The site currently has 6 active subjects and 4 subjects in long-term follow-up.

The inspection reviewed subject-related source documents for all 7 subjects in Cohort G, including ICFs, study entrance notes, clinic notes, progress notes, patient portal communications, SAE report forms, and CRFs. The inspection compared these source documents and data line listings to verify eligibility, adverse events, imaging results, concomitant medications (spot check), and completion of baseline ophthalmology examinations. Additional review of source records for safety events occurred for 2 subjects enrolled in other CRC cohorts at the site.

Study-related records reviewed included the protocol and amendments, signed investigator agreements, delegation of authority logs, ICFs and amendments, IRB approvals, Financial Disclosures, CV, clinical site training records, notes to file, laboratory qualifications, enrollment log, deviation logs, IP labeling, IP shipping and storage, and monitoring visit records. Additional study-related processes reviewed included central submission of MRI scans, electronic records system access, and AE reporting.

The inspection verified that tumor assessments for the primary efficacy endpoint (ORR) were performed at specified time points and submitted to the central imaging CRO. The secondary endpoint, OS, was verified by comparison of the subject source data against the provided data line listings for the following: enrollment dates, subject survival status, and cause of death.

The inspection identified the following unreported protocol deviations:

- Unsigned study progress notes

  Subject (b) (6) (Cohort G): 4 unsigned notes including (b) (6) (Cycle 3, Day 15), (b) (6) (Cycle 5, Day 1), (b) (6) (Cycle 5, Day 13), and (b) (6) (Cycle 8, Day 1).

  Subject (b) (6) (Cohort G): 1 unsigned note on (b) (6) (Cycle 1, Day 1).

  Reviewer comment. All 5 instances of unsigned notes are protocol deviations. In his response dated March 19, 2024, Dr. Negrao acknowledged responsibility and

submitted a corrective and preventative action plan, which appears acceptable.

The 4 notes for Subject (b) (6) *included abnormal laboratory findings. Since they were unsigned, it was not clear Dr. Negrao reviewed the findings for clinical significance and/or need for AE reporting.*

Given the unclear clinical investigator review, an additional query of the AE and laboratory data listings for Subject (b) (6) *was conducted by OSI to understand the potential impact of these protocol deviations on AE reporting of abnormal laboratory values. The OSI review identified multiple inconsistencies between the dates and/or frequency of AE reporting for the following CTCAE laboratory abnormalities: creatinine increased (Grade 2), hypokalemia (Grade 1), serum amylase increased (Grade 2), hypomagnesemia (Grade 1), blood bilirubin increased (Grade 1, on* (b) (6)*), and hypokalemia (Grade 3, on* (b) (6)*). However, with the exception of the CTCAE terms blood bilirubin increased and hypokalemia (Grade 3), the AE database already captures each AE and severity at other timepoints for this subject and all laboratory values are present in the laboratory data file. These database discrepancies were shared with the clinical review team by email on April 10, 2024, as several of these AE associated laboratory changes are included in the Sponsor's proposed drug labeling.*

- There were isolated unreported protocol deviations in Subject (b) (6) (Cohort G) and Subject (b) (6) (Cohort G) related to missed assessments for a study visit and unreported concomitant medications, respectively.

  Reviewer comment. These deviations did not appear to have resulted in subject harm.

Deficiencies in AE reporting were observed for the following 2 subjects enrolled at the site:

- Subject (b) (6) (Cohort G): cough, lethargy, fatigue, dry skin/rash, and lower extremity edema.

  Reviewer comment. In his response dated March 19, 2024, Dr. Negrao acknowledged responsibility and submitted a corrective and preventative action plan, which appears acceptable. With the exception of edema, the AE database already captures treatment emergent events for each preferred term (PT) at other timepoints for this subject. In addition, moderate fatigue/lethargy represents a previously reported AE, but at increased severity. Overall, the findings are unlikely to impact the overall interpretation of safety and efficacy for the proposed drug product; the nonserious AEs did not lead to study drug discontinuation and are not unexpected for the patient's underlying disease, comorbidities, and treatment. The findings were shared with the clinical review team by email on April 10, 2024, for the purpose of accurately

capturing AE severity and incidence.

- Subject [redacted] (Cohort G): nausea, vomiting, and diarrhea noted on a [redacted], telehealth visit.

  Reviewer comment. While all the PTs are captured for the subject, vomiting appears to be a new AE event, and it is unclear whether the nausea and diarrhea are increase in severity of ongoing intermittent AEs. Overall, as these events appear nonserious and did not lead to study drug discontinuation, the findings in this single subject are unlikely to impact the overall interpretation of safety and efficacy for the proposed drug product.

Despite these isolated deficiencies of AE reporting, the data generated at Dr. Negrao's site appear acceptable in support of the proposed indication in the sNDA.

3. [redacted] **(Study 849-001)**

Inspection dates: [redacted], to [redacted]

[redacted] was inspected as a routine PDUFA inspection for Study 849-001. The firm was previously inspected in [redacted] and there were no observations.

This inspection reviewed [redacted]'s responsibilities to perform an independent central imaging review for Study 849-001. Records reviewed included organizational charts, readers qualifications and training, financial disclosures statements, correspondences, standard operating procedures, Master Service Agreement between [redacted] and Mirati, Independent Review Charter, Site Imaging Manual, Project Communication Plan between [redacted] and Mirati, Electronic Data Capture systems, Quality Management System, and study plan adherence. [redacted]'s data collection and handling procedures, data transfer, adherence to the protocol and review charter, and adjudication procedures were also reviewed and found to be adequate.

The inspection verified source records for 17 subjects selected at random and compared with the data listing provided by the Sponsor to the FDA for the baseline scan dates and those obtained at the primary endpoint time points for targeted lesions. The inspection verified tumor dimensional measurements, percentage change from Baseline, percentage change in NADIR, dates, and disease progression qualifiers. No discrepancies were observed, including both adjudicated and unadjudicated data where applicable. The following table lists the subjects whose tumor measurements were verified:

Table 1. Unique Subject IDs for Verified Measurements

(b) (6)
Bold. Cases with adjudication.

Based on the results of the inspection, the imaging review data generated by (b) (4) appear acceptable in support of the proposed indication in the sNDA.

{See appended electronic signature page}

Courtney McGuire, M.D.
Primary reviewer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Michele Fedowitz, M.D.
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Good Clinical Practice Assessment Branch
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Jenn Sellers, M.D., Ph.D.
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Good Clinical Practice Assessment Branch
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cc:
Review Division/Deputy Division Director acting/Chana Weinstock
Review Division/Project Manager/ Rebecca Cohen
Review Division/Clinical Team Lead/ Jamie Brewer
Review Division/Clinical Reviewer/ Geetika Srivastava
OSI/Office Director/David Burrow
OSI/GCP Program Analysts/Yolanda Patague

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

COURTNEY S MCGUIRE
05/06/2024 02:32:23 PM

MICHELE B FEDOWITZ
05/06/2024 02:41:46 PM

JENN W SELLERS
05/06/2024 02:54:17 PM

LABEL AND LABELING OR LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 8, 2024
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 216340/S-005
Product Name, Dosage Form, and Strength:	Krazati (adagrasib) tablets, 200 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Mirati Therapeutics Inc.
FDA Received Date:	December 21, 2023
TTT ID #:	2023-7597
DMEPA 2 Safety Evaluator:	Ngoc-Linh Do, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 REASON FOR REVIEW

Mirati Therapeutics Inc. submitted an Efficacy Supplement for Krazati (adagrasib) tablets to add an additional indication, in combination with cetuximab for the treatment of adult patients with *KRAS* G12C-mutated locally advanced or metastatic colorectal cancer (CRC) who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy when given in combination. Subsequently, the Division of Oncology 2 (DO2) requested that we review the proposed Krazati Prescribing Information (PI) and Patient Information (PPI) for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed revisions to Krazati PI and PPI. We find the revised PPI acceptable from a medication error perspective. However, the proposed edits to Section 2 could be improved for clarity.

We note there were no edits made to Section 3 (Dosage Forms and Strengths) or Section 16 (How Supplied/Storage and Handling).

4 CONCLUSION & RECOMMENDATIONS

The revised PPI is acceptable from a medication error perspective. However, we determined that Section 2.2 (Recommended Dosage) could be improved for clarity. We provide our recommendations in Section 4.1 for the Division.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. Dosage and Administration Section

a. For Section 2.2 (Recommended Dosage), we recommend the following revisions:

(b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Krazati received on December 21, 2023 from Mirati Therapeutics Inc.

Table 2. Relevant Product Information for Krazati	
Initial Approval Date	December 12, 2022
Active Ingredient	adagrasib
Indication	• treatment of adult patients with *KRAS* G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), who have received at least one prior systemic therapy • (proposed) the treatment of adult patients with *KRAS* G12C-mutated locally advanced or metastatic colorectal cancer (CRC) who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. The presence of *KRAS* G12C mutation is to be determined by an FDA-approved test.
Route of Administration	Oral
Dosage Form	tablets
Strength	200 mg

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Krazati</th></tr>
<tr><td>Dose and Frequency</td><td>
<u>Non-Small Cell Lung Cancer (NSCLC)</u>
600 mg orally twice daily until disease progression or unacceptable toxicity.
<u>(Proposed) Colorectal Cancer (CRC)</u>
in combination with cetuximab, 600 mg orally twice daily until disease progression or unacceptable toxicity
Refer to the cetuximab prescribing information for cetuximab dosage information.
Table 1: Recommended KRAZATI Dosage Reductions for Adverse Reactions
<table>
<tr><td>Dose Reduction</td><td>Dosage</td></tr>
<tr><td>First dose reduction</td><td>400 mg twice daily</td></tr>
<tr><td>Second dose reduction</td><td>600 mg once daily</td></tr>
</table>
If permanent discontinuation of cetuximab is recommended, treatment with KRAZATI as a single agent can be continued.
Permanently discontinue treatment with cetuximab when permanently discontinuing treatment with KRAZATI.
</td></tr>
<tr><td>How Supplied</td><td>
200 mg oval shaped, white to off-white, immediate release, film coated tablets with “200” on one side and stylized “M” on the other side.
Available in:

200 mg tablets in bottle containing 120 tablets (NDC 80739-812-12)
200 mg tablets in bottle containing 180 tablets (NDC 80739-812-18)

</td></tr>
<tr><td>Storage</td><td>at room temperature, 20°C to 25°C (68°F to 77°F). Temperature excursions between 15°C and 30°C (59°F to 86°F) are permitted</td></tr>
<tr><td>Container Closure</td><td>high density polyethylene (HDPE), white, opaque bottles with induction seal, child-resistant polypropylene (PP) caps, and two 1 g desiccant canisters. Bottle sizes are 215 cc (for 180 count 200 mg tablets) and 150 cc (for 120 count 200 mg tablets).</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 16, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, NDA 216340. Our search did not identify any previous reviews since the date of our last search on May 20, 2022[a], and we considered our previous recommendations to see if they are applicable for this current review.

[a] Goa, T. Label and Labeling Review for Krazati (Adagrasib) (NDA 216340). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 MAY 19. TTT ID No.: 2021-2133.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Krazati labels and labeling submitted by Mirati Therapeutics Inc.

- Prescribing Information and Patient Information (Image not shown) received on December 21, 2024, available from:
  \\CDSESUB1\EVSPROD\nda216340\0078\m1\us\adagrasib-uspi-tracked.docx (PI)

  \\CDSESUB1\EVSPROD\nda216340\0078\m1\us\adagrasib-ppi-tracked.docx (PPI)

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

NGOC - LINH DO
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216340Orig1s005

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 152345

MEETING MINUTES

Mirati Therapeutics, Inc.
Attention: Lyndsy Hassett
Director, Regulatory Affairs
3545 Cray Court
San Diego Ca 92121

Dear Lyndsy Hassett:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for adagrasib (MRTX849.)

We also refer to the video conference between representatives of your firm and the FDA on October 10, 2023. The purpose of the meeting was to discuss the proposed content of and additional regulatory considerations for a planned sNDA submission in Q4 2023 for adagrasib in combination with cetuximab for the treatment of advanced or metastatic CRC with KRAS G12C mutation following treatment fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, (b) (4).

A copy of the official minutes of the video conference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (240) 402-4998.

Sincerely,

{See appended electronic signature page}

Rebecca Cohen, R.N., M.P.H., O.C.N.
Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO3
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

FDA U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-sNDA

Meeting Date and Time: Tuesday, October 10, 2023, 1:00-2:00 PM (EST)
Meeting Location: Teleconference

Application Number: 152345
Product Name: MRTX849

Indication: In combination with cetuximab is indicated for the treatment of patients with advanced or metastatic CRC with *KRAS* G12C mutation who have previously been treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, (b) (4) (b) (4)

Sponsor Name: Mirati Therapeutics Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

FDA ATTENDEES

Lola Fashoyin-Aje, M.D., M.P.H., Deputy Division Directory, OOD/DO3
Steven Lemery, M.D., M.H.S., Director, OOD/DO3
Jamie Brewer, M.D., Clinical Team Leader, OOD/DO3
Geetika Srivastava MD, MSPH, Clinical Reviewer, OOD/DO3
Joyce Cheng, M.D., Ph.D., Statistics Team Lead, OB/DBV
Sirisha Mushti, PhD, Statistical Reviewer, DBV
Ramesh Raghavachari, Ph.D., Product Quality Team Leader, OPQ
Charles Qi, Ph.D., Product Quality Reviewer, OPQ
Rebecca Cohen, M.P.H., Regulatory Health Project Manager, ORO/DROOD

SPONSOR ATTENDEES

Clinical Development
Chuck Baum, M.D., Ph.D., C.E.O., President, Founder & Head R&D
Alan Sandler, M.D., E.V.P., Chief Medical Officer
Hirak Der-Torossian, M.D., Vice President, Clinical Development
Regulatory Affairs
Rosa Ferrao Executive Director, Regulatory Affairs
Lyndsy Hassett Director, Regulatory Affairs
Biometrics
Xiaohong Yan, Ph.D., Executive Director, Biostatistics
Sam Mao, M.S., Executive Director, Statistical Programming

Bifeng Ding, M.S., Associate Director, Biostatistics
Safety/ Pharmacovigilance
Susan Welsh, M.D., M.B.A., S.V.P., Pharmacovigilance, Chief Safety Officer
Jingying Cui, M.D., Senior Director, Global Safety Officer
Clinical Pharmacology
Jonathan Tran, Pharm.D., Vice President, Clinical Pharmacology & Nonclinical Development
Cornelius Cilliers, Ph.D., Director, Clinical Pharmacology
Executive/Supporting
James Christensen, Ph.D., Chief Scientific Officer
Denise Bruns, Ph.D., Senior Vice President, Integrative Sciences
Kenna Anderes, Ph.D., Vice President, Translational Medicine, and Companion Diagnostics
Kevin Watt, M.B.A., Executive Director, Program Management

BACKGROUND
Regulatory

On August 11, 2023, Mirati Therapeutics Inc (Mirati) submitted a Type B, Pre-sNDA, meeting request, to discuss the proposed content and additional regulatory considerations of the sNDA planned for submission in Q4 2023. On August 17, 2023, a Type B, Pre-sNDA, teleconference was granted.

Clinical

Mirati intends to submit a supplemental NDA (sNDA) for adagrasib (MRTX849), based on the results of Study 849-001 is an ongoing, first-in-human, multi-center, dose, and activity finding study with multiple expansion cohorts. The study includes a Phase 1/1b segment, a Phase 2 segment, and exploratory Phase 1 sub-studies and is evaluating adagrasib as a single agent and in combination with other anti-cancer therapies in patients with advanced solid tumor malignancies who harbor a KRAS G12C mutation.

For the proposed sNDA submission planned for Q4 2023, Mirati will primarily rely on results deriving from the colorectal cancer (CRC) cohorts in the study, wherein patients were required to have had disease progression on or after treatment with a fluoropyrimidine, oxaliplatin, irinotecan and anti VEGF(R) inhibitor or have no available standard of care options. Mirati has previously described the proposed data package for this submission; the current submission reflects a revised proposal.

The planned efficacy and safety data packages will represent pooled analysis sets as shown below. For efficacy (See Table 1), Mirati plans to pool patients from the Phase 1 sub-study (n=32) with patient data from the Phase 2 Cohort G (n=62), to support a request for accelerated of adagrasib in combination with cetuximab in patients with metastatic KRAS G12C mutation who have previously been treated with

fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, (b) (4)
(b) (4)

Table 1: Topline Efficacy Results (by BICR) from Study 849-001

Efficacy Outcomes	Pooled Pivotal Data	Phase 1b Sub-study	Phase 2 Cohort G
N	**94**	**32**	**62**
ORR, % (95% CI)	34.0 (24.6, 44.5)	43.8 (26.4, 62.3)	29.0 (18.2, 41.9)
Best Overall Response, n (%)			
Complete Response (CR)	0	0	0
Partial Response (PR)	32 (34.0)	14 (43.8)	18 (29.0)
Stable Disease (SD)	48 (51.1)	12 (37.5)	36 (58.1)
Progressive Disease (PD)	6 (6.4)	2 (6.3)	4 (6.5)
Not Evaluable (NE)	8 (8.5)	4 (12.5)	4 (6.5)
DCR, % (95% CI)	85.1 (76.3, 91.6)	81.3 (63.6, 92.8)	87.1 (76.1, 94.3)
Median DOR, months (95% CI)	5.78 (4.17, 7.62)	5.98 (3.84, 13.90)	5.78 (4.14, NE)
Responding Patients with Response Duration of ≥ 6 months, n (%)	10 (31.3)	5 (35.7)	5 (27.8)
Median PFS, months (95% CI)	6.90 (5.65, 7.43)	6.80 (4.17, 8.94)	6.93 (5.52, 8.28)
Median Follow-Up, months (95% CI)	11.89 (10.15, 14.29)	30.00 (28.81, NE)	9.95 (9.23, 11.01)

Abbreviations: BICR = blinded independent review committee; CI = Confidence Interval; DCR = Disease Control Rate; DOR = Duration of Response; NE = Not Estimable; ORR = Objective Response Rate; PFS = Progression-free Survival

Source: Sponsor meeting package

The ORR by investigator assessment was as follows: Pooled (42.6% [95% CI: 32.4, 53.2]; n=94); Phase 1b Sub-study (40.6% [95% CI:23.7, 59.4]; n=28); Phase 2 Cohort G (43.5% [95% 31.0, 56.7]; n=62). The median DOR was approximately 6 months across the three analysis sets and comparable between BICR and Investigator assessment except for the Phase 2b Sub-study cohort where the median DOR was nearly double at 11.24 months.

To support the contribution of components assessment, the sNDA will include data from Cohort C and Cohort F of the Phase 2 portion of Study 849-001. Both cohorts investigated adagrasib as a single agent in patients with advanced or metastatic CRC harboring a KRAS G12C mutations. Cohort C (n=44; ORR 22.7% [95% CI: 24.6%, 44.5%]) enrolled patients who have no SOC treatment or are ineligible or declined; the median DOR is 9.5 months (95% CI: 7.13, NE) by BICR per RECIST v1.1. Cohort F (n=42; ORR 21.4% [95% CI: 10.3%, 36.8%]) enrolled patients with disease progression on or after treatment with a fluoropyrimidine, oxaliplatin, irinotecan and an anti-VEGF(R) inhibitor; the median DOR is 15.2 months (95% CI: 2.8, NE) by BICR per RECIST v1.1. The pooled ORR (i.e., Cohort C and Cohort F) is 22.1% (95% CI: 13.9%, 32.3%). Mirati has previously discussed the safety data package, including data cut off dates, that will support the planned sNDA submission; the meeting package includes a revised proposal as shown below in Table 2 and Table 3.

Table 2: Proposed Safety Data Package (Study 849-001)

Study 849-001 Cohorts for ISS	Number of Patients (n)	DCO Date
ISS Cohort Breakdown Previously Aligned with the Agency		
CRC-Specific Cohorts		
Combination with cetuximab		
Phase 2 Cohort G[1]	62	30 Jun 2023
Phase 1 Sub-study[1, 2]	32	30 Jun 2023
Cross-over to combination therapy (post-crossover)[2, 3]	6	30 Jun 2023
Phase 1b Dose Optimization Expansion Cohort[4]	27	30 Jun 2023
Monotherapy		
Phase 2 Cohort F[1]	42	01 Mar 2023
Phase 2 Cohort C[1]	44	01 Mar 2023
Supportive Cohorts in Other Solid Tumors		
Monotherapy		
Phase 1/1b Adagrasib Monotherapy Dose Finding Segments[1]	25	01 Jan 2023
Phase 2 Cohort A (NSCLC – tumor tissue) [1]	116	01 Jan 2023
Phase 2 Cohort B (NSCLC – ctDNA)[1]	60	01 Jan 2023
Phase 2 Cohort D (other solid tumors)[1]	67	01 Jan 2023
Sub-Total	**481**	
Additional ISS Cohorts for Agency Alignment		
Combination with cetuximab		
Phase 1 sub-study NSCLC (adagrasib with cetuximab)[1]	10	01 Jan 2023
Phase 1 sub-study PDAC (adagrasib with cetuximab)[1]	3	01 Jan 2023
Monotherapy		
Phase 1b Dose Expansion – Untreated Brain Metastasis NSCLC[1]	30	01 Jan 2023
Phase 1b Dose Expansion – Prior G12C Inhibitor NSCLC[1]	12	01 Jan 2023
Phase 1b Dose Expansion – Tablet Formulation NSCLC[1]	2	01 Jan 2023
Phase 1b Dose Expansion – Treatment-Naïve NSCLC[1]	24	01 Jan 2023
Phase 2 Cohort E (NSCLC with *STK11* co-mutation)[1]	34	01 Jan 2023
Sub-Total	**115**	
Total of Patients for ISS	**596**	

BID=Twice Daily; CRC=Colorectal Cancer; ctDNA=Circulating Tumor DNA; DCO=Data Cutoff; ISS=Integrated Summary of Safety; NSCLC=Non-Small Cell Lung Cancer; PDAC=Pancreatic Ductal Adenocarcinoma

[1] Adagrasib starting dose of 600 mg BID; [2] Study 849-001 (Protocol Version 10, Appendix 8) includes a Phase 1 sub-study for the combination of adagrasib with

cetuximab and contains 2 cohorts: Cohort 1 (n=32) for patients with *KRAS* G12C-mutant CRC (KRAS G12C inhibitor-naïve) and Cohort 2 (n=6) for cross-over patients with *KRAS* G12C-mutant CRC switching from earlier monotherapy cohorts of Study 849-001 (Phase 2 Cohort C) to the combination with cetuximab. Pre-crossover safety data from the 6 crossover patients is presented in Phase 2 Cohort C as part of the adagrasib monotherapy experience, whereas the post-crossover safety is included as part of the combinatorial safety experience; [3] Five of the six crossover patients-initiated combination therapy at an adagrasib dose of 600 mg BID and the remaining patient started combination therapy at a 400mg BID dose of adagrasib;[4] Adagrasib starting dose of 400 mg BID

Source: Sponsor meeting package

Table 3: Revised Proposal for Safety Data in Planned sNDA

Adagrasib + Cetuximab				Adagrasib Monotherapy		(Adagrasib + Cetuximab) + (Adagrasib Monotherapy)
CRC			Any Solid Tumor	CRC	Any Solid Tumor	Any Solid Tumor
Adagrasib 600 mg BID (N=99)[1,2,3]	Adagrasib 400 mg BID (N=28)[2,4]	Adagrasib Any Dose (N=127)[1,4]	Adagrasib 600 mg BID (N=112)[1,5]	Adagrasib 600 mg BID (N=86)[6]	Adagrasib 600 mg BID (N=456)[7]	Adagrasib 600mg BID (N=568)[8]

Source: Sponsor meeting package.

To verify clinical benefit of adagrasib in combination with cetuximab, Mirati plans to submit the results of Study 849-010, an ongoing, open-label, randomized (1:1), Phase 3 clinical trial comparing the efficacy of adagrasib in combination with cetuximab to chemotherapy (FOLFIRI or mFOLFOX6) in the second-line treatment setting for patients with KRAS G12C-mutant CRC. Patients will have previously experienced radiographic disease progression on or after treatment with a standard first-line fluoropyrimidine-based chemotherapy regimen containing either oxaliplatin or irinotecan. Co-primary endpoints for this study are overall survival (OS) and progression free survival (PFS). As of September 8, 2023, the study has completed the planned enrollment of 420 patients and 421 patients have been enrolled.

SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSES

REGULATORY

1. Does the Agency agree that the proposed content of the supplemental new drug application for adagrasib in combination with cetuximab for the indication of advanced CRC harboring a KRAS G12C mutation constitutes a fileable marketing application?

FDA Response: The proposed content of the application appears reasonable; however, a determination regarding whether the application is fileable is made during the filing review.

In the planned sNDA submission,

a. Clarify whether the 400 mg BID dosage in the Phase 1b and 600 mg BID dosage in Phase 2 Cohort G and the Phase 1 sub-study in CRC patients in Study 849-001 were administered with food or without regard to food and provide justification for the dosing strategy with regard to food in the dose optimization part of the study.
b. Provide justifications based on PK/PD, efficacy, and safety data for the selection of 600 mg BID dosage for the Phase 2 Cohort G study and planned marketing application.
c. Clarify the formulation(s) used in each cohort and/or sub-study supporting the planned sNDA submission, and to-be-marketed formulation. Further clarify whether a food-effect study and/or a bioequivalence study are necessary for the to-be-marketed formulation if it is different from the formulation(s) used in the clinical studies supporting marketing application.

Refer to Additional Comments below for data to support the sNDA submission.

2. Does the Agency agree that the 21 May 2021 agreed iPSP supports a request of a full waiver from PREA requirements for all pediatric age groups as part of the planned sNDA submission?

FDA Response: FDA acknowledges the agreed iPSP dated May 21, 2021, however FDA does not make a formal decision pertaining to granting a waiver of required pediatric assessments until the time of the approval of the marketing application.

3. In accordance with 2023 guidance, Assessing User Fees Under the Prescription Drug User Fee Amendments of 2022 under PDUFA VII, it is Mirati's understanding that an application fee does not apply to an efficacy supplement for a new indication (advanced CRC with a KRAS G12C mutation) under approved NDA 216340. Can the Agency confirm an Application Fee does not apply for the assessment of this supplement?

FDA Response: Supplements (including efficacy supplements) are not assessed PDUFA user fees under PDUFA VII.

CLINICAL

4. To adequately update the currently approved USPI, Mirati intends to pool additional safety data to that proposed and agreed with the Agency per the May 2023 FDA Preliminary Meeting Comments (ID: 5175024). Mirati seeks alignment on the following:
   a. Does the Agency agree with the revised ISS safety dataset planned for submission with the sNDA?

      FDA Response: FDA does not object to the Mirati's plan for revised ISS.

   b. Does the Agency agree with the proposed safety population for describing the Warnings and Precautions and Adverse Reactions section of the draft USPI?

      FDA Response: FDA acknowledges Mirati's proposed labeling changes to the USPI. A final decision on the label content will be made during the review of the sNDA and labeling negotiations.

   c. Does the Agency agree with the revised plan for the 120-day safety update?

      FDA Response: FDA does not object to Mirati's plan for 120-day update.

5. Does the Agency agree that topline efficacy data (ORR and DOR of sufficient magnitude) pooled from 94 patients (32 from dedicated Phase 1 sub-study and 62 Phase 2 Cohort G) outlined in Table 4 and Table 5 enables an sNDA submission under an Accelerated Approval pathway for the combination therapy of adagrasib with cetuximab in patients with metastatic KRAS G12C mutant CRC in the late-line setting?

   FDA Response: FDA has concerns regarding the proposed data submission from the pivotal trial intended to support the planned sNDA. The adequacy of the proposed single-arm trial to support an approval will be dependent on an observed ORR of sufficient magnitude with a durable response. FDA notes the discrepancy between the Investigator-assessed ORR and the BICR-ORR for the Phase 2 Cohort G, which can limit the interpretability of the single-arm study results. In the sNDA, provide a detailed assessment of this discrepancy, including but not limited to, a patient-level review of the ORR discordance.

   FDA notes that the full analysis set (primary efficacy population) includes patients who received at least one dose of adagrasib and cetuximab and had RECIST-defined measurable disease at baseline per BICR. In general, the primary efficacy population should include all patients who received at least one dose of

adagrasib and cetuximab. Clarify how many patients in each of the cohorts submitted for efficacy analysis had measurable disease at baseline.

As a condition of accelerated approval, a drug must demonstrate a clinically meaningful advantage over available therapy at the time of approval. Therefore, FDA recommends that Mirati considers the changing landscape of treatments for the proposed indication when deciding whether to submit an sNDA under the accelerated approval pathway or defer submission of a marketing submission to such time that the results of the final analysis of the primary endpoints from Study 849-010 are available.

Mirati's 10/10/2023 Response to FDA Comment: Mirati acknowledges the Agency's comments, and requests further discussion of Question 5 at the pre-sNDA meeting. Mirati provides additional clarification for the 3 topics raised by the Agency in support of the upcoming discussion.

Discordance
When draft tables, figures and listing (TFLs) became available from the pivotal Phase 1 sub-study and Phase 2 Cohort G, Mirati observed a discrepancy between the overall response rate by BICR and by Investigator assessment. Overall, a high discordance rate of 35.1% was observed between BICR and Investigator assessment across the pooled data. This discordance rate was similar between the Phase 1 Sub-study (34.4%) and Phase 2 Cohort G (35.5%). However, the impact on ORR was more pronounced for Phase 2 Cohort G due to a significantly higher imbalance in cases switching from a best overall response (BOR) of PR (by Investigator) to SD (by BICR), versus cases switching from SD (by Investigator) to PR (by BICR).

As a result, Mirati further investigated the draft data from the most recent BICR data transfer, and observed an imbalance favoring SD over PR among the adjudicated cases on the primary endpoint of BOR in Phase 2 Cohort G. There was a high level of discordance between BICR Reader 1 and BICR Reader 2 in these cases both on the selection of baseline lesions, and the measurements of target lesions at baseline and on study.

Subsequently, Mirati engaged the BICR Vendor noting the discrepancies in the BICR adjudication process and between BICR Readers for an examination of whether any systemic errors could be identified. Mirati did not discuss or disclose the Investigator assessment either at the patient level or in aggregate, such that the BICR Vendor remained blinded. In accordance with the BICR Charter, a Chief Medical Officer (CMO) Review was requested. The CMO Review did not entail an independent re-adjudication, but rather a review of the existing adjudicated cases. Overall, the adjudication of individual cases was deemed reasonable by the BICR Vendor, and differences were attributed to judgment calls of reviewers, rather than any systemic pattern.

Mirati consequently received the final BICR transfer unchanged by the above-mentioned review. Therefore, the final TFLs, and the top-line results shared with the FDA, reflect this final data transfer and include the discrepancy between BICR and PI assessments, but also between BICR Readers and the adjudicated outcome.

Mirati has requested individual patient-level BICR narratives from the BICR Vendor for all cases from the pivotal Phase 1 sub-study and Phase 2 Cohort G adjudicated based on the primary adjudication endpoint of BOR, so as to perform a detailed independent review of the BICR process including adjudication. As requested by the Agency in the Preliminary Comments, Mirati will provide a detailed assessment of the discrepancies, including a patient-level review of the ORR discordance, in the upcoming sNDA submission.

FAS The pivotal data proposed to support the sNDA submission under an Accelerated Approval pathway includes 94 patients (62 from Phase 2 Cohort G and 32 from the Phase 1 substudy of Study 849-001). Of these 94 patients, all had received at least one dose of both adagrasib and cetuximab, and had measurable disease at baseline; therefore, Mirati clarifies that the Full Analysis Set (FAS) reflects all enrolled patients in these two cohorts.

Late-Line CRC Treatment Landscape
Mirati acknowledges the Agency's comment regarding the potential for a changing landscape of treatments for the proposed indication as a condition of accelerated approval.

Pooled, topline efficacy data for pivotal Phase 2 Cohort G and Phase 1 sub-study indicates an ORR of 34.0% (95% CI: 24.6%, 44.5%) and a median DOR of 5.8 months (95% CI: 4.2, 7.6) by BICR.

An ORR of 34.0% demonstrates an >5-fold increase and a clinically meaningful improvement over the current standard of care therapies in CRC, including the combination regimen of trifluridine/tipiracil and bevacizumab recently approved in August 2023, which range in response rates between 1.0 to 6.4%.

Mirati believes that topline efficacy data for the combination of adagrasib 600 mg BID with cetuximab demonstrates an effect on ORR that is large in magnitude and durable over currently approved standard of care therapies, supporting the pursuit of an Accelerated Approval in patients with advanced KRAS G12C-mutant CRC, who currently face poor prognosis and an unmet medical need.

Discussion During the 10/10/23 Meeting: FDA acknowledged Mirati's response regarding the BICR assessment and discordance between Investigator- and BICR ORR. FDA acknowledged the clarification regarding the

FAS with respect to the presence of measurable disease and requested clarification regarding whether any enrolled patients were excluded from the FAS for not having measurable disease at baseline. Mirati confirmed that no patients with non-measurable disease were enrolled- i.e., the FAS represents all patients enrolled.

Additional Clinical Pharmacology Comments:

The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products –Content and Format" (available at: https://www.fda.gov/media/74346/download). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers using text attributes, tables, and figures as outlined in the above guidance.

6. Address the following questions in the Summary of Clinical Pharmacology:
   a. Identify individuals who required dose modifications and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.

   b. What is the exposure-response relationships for efficacy, safety, and biomarkers?

7. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.

8. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with minimum and maximum values as appropriate.

9. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
   a. Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

   b. Identify individual subjects with dose modifications; the time to the first dose reduction, interruption, or discontinuation; the reasons for dose modifications in the datasets.

10. Submit the following for the population pharmacokinetic analysis reports:
    a. Standard model diagnostic plots.

    b. Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line, and the population prediction line.

    c. Model parameter names and units in tables.

    d. Summary of the report describing the clinical application of modeling results.

    Refer to the following pharmacometrics data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

11. Submit the following information and data to support the population pharmacokinetic analysis:
    a. SAS transport files (*.xpt) for all datasets used for model development and validation

    b. A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets

    c. Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)

12. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers, and safety) relationships in the targeted patient population. Refer to Guidance for Industry for population PK, exposure-response relationships, and pharmacometrics data and models submission guidelines.

13. Use the laboratory analysis dataset (adlb.xpt) for the laboratory-based adverse reactions and the adverse event analysis dataset (adae.xpt) for the non-laboratory-based adverse reactions (individual and pooled terms as appropriate) to evaluate the exposure-response relationship for safety and the effect of intrinsic and extrinsic factors on safety based on the maximum toxicity grade compared to baseline.

14. Include a variable that identifies the maximum toxicity grade compared to baseline for laboratory-based adverse reactions in laboratory analysis dataset (adlb.xpt) and for non-laboratory-based adverse reactions (individual or pooled where applicable) in adverse event analysis dataset (adae.xpt) to support these

analyses. A description of the pooled non-laboratory-based adverse reactions should be provided in the reviewer guide and consistent with common pooled terms used to inform labeling if applicable.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could

result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[2]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating, "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package to be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[6]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- Assessment Aid[7]

SUBMISSIONS WITH REAL-WORLD EVIDENCE

CDER strongly encourages sponsors to identify uses or proposed uses of real-world evidence (RWE) to support a regulatory decision regarding product safety and/or effectiveness. For recommendations on specific information to include in submission cover letters, see the guidance for industry *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products.*[8] For questions or clarification, contact cdermedicalpolicy-realworldevidence@fda.hhs.gov.

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[6] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[7] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project
[8] https://www.fda.gov/media/124795/download

RACE AND ETHNICITY DIVERSITY PLANS

Refer to FDA Draft Guidance “Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials- Guidance for Industry” at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diversity-plans-improve-enrollment-participants-underrepresented-racial-and-ethnic-populations, for recommendations on the approach to develop and submit a Race and Ethnicity Diversity Plan to enroll representative numbers of participants from underrepresented racial and ethnic populations in the United States, in clinical trials during the development of your product. The Diversity Plan should be developed and discussed with FDA early in clinical development, preferably before initiation of any trials intended to support registration.

Although this draft Guidance specifically focusses on race and ethnicity Diversity Plans for the enrollment of members of racial and ethnic populations that have historically been underrepresented in clinical trials, FDA encourages sponsors to consider expanding the Diversity Plan to also account for other underrepresented populations (e.g., based on other demographic characteristics such as sex, age, gender, etc.).

Submit the Diversity Plan under eCTD Module 1.6 if included in meeting background package, otherwise submit under Module 2.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

REBECCA L COHEN
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