CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

214665Orig1s009

Trade Name: LUMAKRAS

Generic or Proper Name: sotorasib

Sponsor: Amgen Inc.

Approval Date: January 16, 2025

Indication: Lumakras is an inhibitor of the RAS GTPase family indicated for:

KRAS G12C-mutated Locally Advanced or Metastatic 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.

This indication is approved under accelerated approval based on overall response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

KRAS G12C-mutated Metastatic Colorectal Cancer (mCRC)
In combination with panitumumab, for the treatment of adult patients with KRAS G12C-mutated mCRC as determined by an FDA approved-test, who have received prior 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 214665/S-009

SUPPLEMENT APPROVAL

Amgen Inc.
Attention: Stephanie Hansen, Pharm.D.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop: 27-2-D
Thousand Oaks, CA 91320-1799

Dear Dr. Hansen:

Please refer to your supplemental new drug application (sNDA) dated April 17, 2024, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lumakras (sotorasib) tablets.

We acknowledge receipt of your major amendment dated September 16, 2024, which extended the goal date by three months.

This Prior Approval supplemental new drug application adds a new indication of Lumakras, in combination with panitumumab, for the treatment of adult patients with KRAS G12C-mutated metastatic colorectal cancer as determined by an FDA approved test, who have received prior fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. This supplement also provides for updates to the U.S. Prescribing Information (USPI) Dosage and Administration sections (2.1, Patient Selection; 2.2, Recommended Dosage and Administration; 2.3, Dosage Modifications for Adverse Reactions) and to the Warning and Precautions sections (Section 5.1, Hepatotoxicity; Section 5.2, Interstitial Lung Disease [ILD]/Pneumonitis).

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

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).

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-*

[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.

Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

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 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

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, call Nataliya Fesenko, Pharm.D., Senior Regulatory Health Project Manager, at (240) 402-6376.

Sincerely,

{See appended electronic signature page}

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

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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/

CHANA WEINSTOCK
01/16/2025 01:55:21 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214665Orig1s009

LABELING

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

LUMAKRAS® (sotorasib) tablets, for oral use
Initial U.S. Approval: 2021

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	01/2025
Dosage and Administration (2.1,2.2, 2.3)	01/2025
Warnings and Precaution (5.1, 5.2)	01/2025

----------INDICATIONS AND USAGE----------
LUMAKRAS is an inhibitor of the RAS GTPase family indicated for:

KRAS G12C-mutated Locally Advanced or Metastatic 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)

This indication is approved under accelerated approval based on overall response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). (1.1)

KRAS G12C-mutated Metastatic Colorectal Cancer (mCRC)
In combination with panitumumab, for the treatment of adult patients with *KRAS* G12C-mutated mCRC as determined by an FDA approved-test, who have received prior fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy. (1.2)

----------DOSAGE AND ADMINISTRATION----------
Recommended dosage as a single agent for NSCLC and in combination with panitumumab for mCRC:

- 960 mg orally once daily. (2.2)
- Swallow tablets whole with or without food. (2.2)

----------DOSAGE FORMS AND STRENGTHS ----------
Tablets: 320 mg, 240 mg, 120 mg. (3)

----------CONTRAINDICATIONS ----------
None. (4)

----------WARNINGS AND PRECAUTIONS ----------

- Hepatotoxicity: Monitor liver function tests every 3 weeks for the first 3 months of treatment then once monthly as clinically indicated. Consider administering systemic corticosteroids and withhold, reduce the dose, or permanently discontinue LUMAKRAS based on the severity. (2.3, 5.1)
- Interstitial Lung Disease (ILD)/Pneumonitis: Monitor for new or worsening pulmonary symptoms. Immediately withhold LUMAKRAS for suspected ILD/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis are identified. (2.3, 5.2)

----------ADVERSE REACTIONS ----------

- Single agent in NSCLC: The most common adverse reactions (≥ 20%) were diarrhea, musculoskeletal pain, nausea, fatigue, hepatotoxicity, and cough. The most common laboratory abnormalities (≥ 25%) were decreased lymphocytes, decreased hemoglobin, increased aspartate aminotransferase, increased alanine aminotransferase, decreased calcium, increased alkaline phosphatase, increased urine protein, and decreased sodium. (6.1)
- In combination with panitumumab in CRC: The most common adverse reactions (≥ 20%) in clinical trials of LUMAKRAS in combination with panitumumab are rash, dry skin, diarrhea, stomatitis, fatigue and musculoskeletal pain. The most common Grade 3 or 4 laboratory abnormalities in ≥ 2 patients (4.3%) were decreased magnesium, decreased potassium, decreased corrected calcium, and increased potassium. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS ----------

- Acid-Reducing Agents: Avoid coadministration with proton pump inhibitors (PPIs) and H_2 receptor antagonists. If an acid-reducing agent cannot be avoided, administer LUMAKRAS 4 hours before or 10 hours after a local antacid. (2.4, 7.1)
- Strong CYP3A4 Inducers: Avoid coadministration with strong CYP3A4 inducers. (7.1)
- CYP3A4 Substrates: Avoid coadministration with CYP3A4 substrates for which minimal concentration changes may lead to therapeutic failures of the substrate. If coadministration cannot be avoided, adjust the substrate dosage in accordance to its Prescribing Information. (7.2)
- P-gp substrates: Avoid coadministration with P-gp substrates for which minimal concentration changes may lead to serious toxicities. If coadministration cannot be avoided, decrease the substrate dosage in accordance to its Prescribing Information. (7.2)

----------USE IN SPECIFIC POPULATIONS ----------
Lactation: Advise not to breastfeed. (8.2)

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

Revised: 01/2025

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 (NSCLC)

LUMAKRAS 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 overall 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 clinical benefit in a confirmatory trial(s).

1.2 *KRAS G12C*-mutated Metastatic Colorectal Cancer (mCRC)

LUMAKRAS, in combination with panitumumab, is indicated for the treatment of adult patients with *KRAS G12C*-mutated metastatic colorectal cancer (mCRC), as determined by an FDA-approved test, who have received prior fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy *[see Dosage and Administration (2.1) and Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

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

KRAS G12C-mutated mCRC
Select patients for treatment of mCRC 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 *KRAS* G12C mutations is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage and Administration

LUMAKRAS as a Single Agent for *KRAS* G12C-mutated Locally Advanced or Metastatic NSCLC

The recommended dosage of LUMAKRAS is 960 mg (three 320 mg tablets or four 240 mg tablets or eight 120 mg tablets) orally once daily until disease progression or unacceptable toxicity.

LUMAKRAS in Combination with Panitumumab for *KRAS* G12C-mutated mCRC

The recommended dosage of LUMAKRAS is 960 mg (three 320 mg tablets or four 240 mg tablets or eight 120 mg tablets) orally once daily in combination with panitumumab until disease progression or unacceptable toxicity. Administer the first dose of LUMAKRAS prior to first panitumumab infusion.

Refer to the panitumumab full prescribing information for recommended panitumumab dosage information.

Take the daily dose of LUMAKRAS at the same time each day with or without food *[see Clinical Pharmacology (12.3)]*. Swallow tablets whole. Do not chew, crush or split tablets. If a dose of LUMAKRAS is missed by more than 6 hours, take the next dose as prescribed the next day. Do not take 2 doses at the same time to make up for the missed dose.

If vomiting occurs after taking LUMAKRAS, do not take an additional dose. Take the next dose as prescribed the next day.

Administration to Patients Who Have Difficulty Swallowing Solids

Disperse tablets in 120 mL (4 ounces) of non-carbonated, room-temperature water without crushing. No other liquids should be used. Stir or swirl the cup for approximately 3 minutes until tablets are dispersed into small pieces (the tablets will not completely dissolve) and drink immediately or within 2 hours. The appearance of the mixture may range from pale yellow to bright yellow. Swallow the tablet dispersion. Do not chew pieces of the tablet. Rinse the container with an additional 120 mL (4 ounces) of water and drink. If the mixture is not consumed immediately, stir the mixture again to ensure that tablets are dispersed.

2.3 Dosage Modifications for Adverse Reactions

LUMAKRAS dose reduction levels are summarized in Table 1.

If adverse reactions occur, a maximum of two dose reductions are permitted. Discontinue LUMAKRAS if patients are unable to tolerate the minimum dose of 240 mg once daily.

When LUMAKRAS is administered in combination with panitumumab, and LUMAKRAS is temporarily withheld or permanently discontinued, temporarily withhold or permanently discontinue panitumumab, respectively *[see Clinical Studies (14.2)]*. Refer to the full prescribing information of panitumumab for dose modifications for adverse reactions associated with the use of panitumumab.

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

Refer to Table 2 for dose modification guidelines and management of adverse reactions associated with the use of LUMAKRAS as a single agent or as combination therapy with panitumumab.

Table 1. Recommended LUMAKRAS Dose Reduction Levels for Adverse Reactions

Dose Reduction Level	Dose
First dose reduction	480 mg (two 240 mg or four 120 mg tablets) once daily
Second dose reduction	240 mg (one 240 mg or two 120 mg tablets) once daily

Table 2. Recommended LUMAKRAS Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity[a]	Dosage Modification[b]
Hepatotoxicity *[see Warnings and Precautions (5.1)]*	AST or ALT > 3 × and up to 5 × ULN (or > 3 × and up to 5 × baseline if baseline abnormal) with symptoms or AST or ALT > 5 × ULN (or > 5 × baseline if baseline abnormal)	• Withhold LUMAKRAS until recovery to ≤ 3 × ULN or to ≤ 3 × baseline if baseline abnormal. • Resume LUMAKRAS at the next lower dose level.
	AST or ALT > 3 × ULN with total bilirubin > 2 × ULN	• Permanently discontinue LUMAKRAS if no alternative cause is identified. • If alternative cause is identified, do not resume LUMAKRAS until AST/ALT/bilirubin return to baseline.
Interstitial Lung Disease (ILD)/ pneumonitis *[see Warnings and Precautions (5.2)]*	Any Grade	• Withhold LUMAKRAS if ILD/pneumonitis is suspected. • Permanently discontinue LUMAKRAS if ILD/pneumonitis is confirmed.
Nausea or vomiting despite appropriate supportive care (including anti-emetic therapy) *[see Adverse Reactions (6.1)]*	Grade 3 to 4	• Withhold LUMAKRAS until recovery to ≤ Grade 1 or baseline. • Resume LUMAKRAS at the next lower dose level.
Diarrhea despite appropriate supportive care (including anti-diarrheal therapy) *[see Adverse Reactions (6.1)]*	Grade 3 to 4	• Withhold LUMAKRAS until recovery to ≤ Grade 1 or baseline. • Resume LUMAKRAS at the next lower dose level.
Other adverse reactions *[see Adverse Reactions (6.1)]*	Grade 3 to 4	• Withhold LUMAKRAS until recovery to ≤ Grade 1 or baseline. • Resume LUMAKRAS at the next lower dose level.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

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

[b] When LUMAKRAS is administered in combination with panitumumab, withhold or permanently discontinue treatment with panitumumab when withholding or permanently discontinuing treatment with LUMAKRAS.

2.4 Coadministration of LUMAKRAS with Acid-Reducing Agents

Avoid coadministration of proton pump inhibitors (PPIs) and H_2 receptor antagonists with LUMAKRAS. If treatment with an acid-reducing agent cannot be avoided, take LUMAKRAS 4 hours before or 10 hours after administration of a local antacid *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 320 mg, beige, oval-shaped, immediate release, film-coated, debossed with "AMG" on one side and "320" on the opposite side.

Tablets: 240 mg, yellow, oval-shaped, immediate release, film-coated, debossed with "AMG" on one side and "240" on the opposite side.

Tablets: 120 mg, yellow, oblong-shaped, immediate release, film-coated, debossed with "AMG" on one side and "120" on the opposite side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

LUMAKRAS can cause hepatotoxicity and increased alanine aminotransferase (ALT) or increased aspartate aminotransferase (AST) which may lead to drug-induced liver injury and hepatitis.

In the pooled safety population of patients with NSCLC who received single agent LUMAKRAS 960 mg *[see Adverse Reactions (6.1)]*, hepatotoxicity occurred in 27% of patients, of which 16% were Grade ≥ 3. Among patients with hepatotoxicity who required dosage modifications, 64% required treatment with corticosteroids.

In this pooled safety population of patients with NSCLC who received single agent LUMAKRAS 960 mg, 17% of patients who received LUMAKRAS had increased ALT/increased AST; of which 9% were Grade ≥ 3. The median time to first onset of increased ALT/AST was 6.3 weeks (range: 0.4 to 42). Increased ALT/AST leading to dose interruption or reduction occurred in 9% of patients treated with LUMAKRAS. LUMAKRAS was permanently discontinued due to increased ALT/AST in 2.7% of patients. Drug-induced liver injury occurred in 1.6% (all grades) including 1.3% (Grade ≥ 3).

In this pooled safety population of patients with NSCLC who received single agent LUMAKRAS 960 mg, a total of 40% patients with recent (≤ 3 months) immunotherapy prior to starting LUMAKRAS had an event of hepatotoxicity. An event of hepatotoxicity was observed in 18% of patients who started LUMAKRAS more than 3 months after last dose of immunotherapy and in 17% of those who never received immunotherapy. Regardless of time from prior immunotherapy, 94% of hepatotoxicity events improved or resolved with dosage modification of LUMAKRAS, with or without corticosteroid treatment.

In the pooled safety population of patients with CRC who received LUMAKRAS 960 mg in combination with panitumumab *[see Adverse Reactions (6.1)]*, hepatotoxicity occurred in 15% of patients, of which 4.8% were Grade 3. A total of 7% of patients who received LUMAKRAS had increased ALT or increased AST, of which 0.8% were Grade 3. The median time to first onset of increased ALT or increased AST was 10 weeks (range: 2 to 22). Increased ALT or increased AST leading to dose interruption occurred in 2.4% of patients. A total of 3.2% of patients who received LUMAKRAS had hyperbilirubinemia, of which 2.4% were Grade 3. The median time to first onset of hyperbilirubinemia was 12 weeks (range: 0, 29). Hyperbilirubinemia leading to dose interruption occurred in 1.6% of patients. Among patients with hepatotoxicity, 21% received corticosteroids.

Monitor liver function tests (ALT, AST, alkaline phosphatase and total bilirubin) prior to the start of LUMAKRAS, every 3 weeks for the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients who develop transaminase and/or bilirubin elevations. Withhold, reduce the dose or permanently discontinue LUMAKRAS based on severity of the adverse reaction *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)].* Consider administering systemic corticosteroids for the management of hepatotoxicity.

5.2 Interstitial Lung Disease (ILD)/Pneumonitis

LUMAKRAS can cause ILD/pneumonitis that can be fatal.

In the pooled safety population of patients with NSCLC who received single agent LUMAKRAS 960 mg *[see Adverse Reactions (6.1)]*, ILD/pneumonitis occurred in 2.2% of patients, of which 1.1% were Grade ≥ 3, and 1 case was fatal. The median time to first onset for ILD/pneumonitis was 8.6 weeks (range: 2.1 to 36.7 weeks). LUMAKRAS was permanently discontinued due to ILD/pneumonitis in 1.3% of LUMAKRAS-treated patients. Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold LUMAKRAS in patients with suspected ILD/pneumonitis and permanently discontinue LUMAKRAS if no other potential causes of ILD/pneumonitis are identified *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)]*.

In the pooled safety population of patients with CRC who received LUMAKRAS 960 mg in combination with panitumumab, 1 patient experienced a Grade 1 event of ILD/pneumonitis *[see Adverse Reactions (6.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Hepatotoxicity *[see Warnings and Precautions (5.1)]*
- Interstitial Lung Disease (ILD)/Pneumonitis *[see Warnings and Precautions (5.2)]*

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 LUMAKRAS as a single agent at 960 mg orally once daily until disease progression or unacceptable toxicity in 549 patients with NSCLC with *KRAS G12C* mutation in the following trials: CodeBreaK 200

(NCT04303780), CodeBreaK 100 (NCT03600883), CodeBreaK 101 (NCT04185883) and CodeBreaK 105 (NCT04380753). Among these 549 patients who received LUMAKRAS, 44% were exposed for 6 months or longer and 21% were exposed for greater than one year.

The pooled safety population described in WARNINGS AND PRECAUTIONS also reflects exposure to LUMAKRAS 960 mg once daily in combination with panitumumab in 126 patients who received LUMAKRAS in combination with panitumumab for mCRC in CodeBreaK 300 (NCT05198934) and CodeBreaK 101 (NCT04185883). Among the 126 patients who received LUMAKRAS 960 mg in combination with panitumumab, 40% were exposed for 6 months or longer and 10% were exposed for greater than one year.

Metastatic Non-Small Cell Lung Cancer

The safety of LUMAKRAS was evaluated in a subset of patients with *KRAS G12C*-mutated locally advanced or metastatic NSCLC in CodeBreaK 100 *[see Clinical Studies (14.1)]*. Patients received LUMAKRAS 960 mg orally once daily until disease progression or unacceptable toxicity (n = 204). Among patients who received LUMAKRAS, 39% were exposed for 6 months or longer and 3% were exposed for greater than one year.

The median age of patients who received LUMAKRAS was 66 years (range: 37 to 86); 55% female; 80% White, 15% Asian, and 3% Black.

Serious adverse reactions occurred in 50% of patients treated with LUMAKRAS. Serious adverse reactions in ≥ 2% of patients were pneumonia (8%), hepatotoxicity (3.4%), and diarrhea (2%). Fatal adverse reactions occurred in 3.4% of patients who received LUMAKRAS due to respiratory failure (0.8%), pneumonitis (0.4%), cardiac arrest (0.4%), cardiac failure (0.4%), gastric ulcer (0.4%), and pneumonia (0.4%).

Permanent discontinuation of LUMAKRAS due to an adverse reaction occurred in 9% of patients. Adverse reactions resulting in permanent discontinuation of LUMAKRAS in ≥ 2% of patients included hepatotoxicity (4.9%).

Dosage interruptions of LUMAKRAS due to an adverse reaction occurred in 34% of patients. Adverse reactions which required dosage interruption in ≥ 2% of patients were hepatotoxicity (11%), diarrhea (8%), musculoskeletal pain (3.9%), nausea (2.9%), and pneumonia (2.5%).

Dose reductions of LUMAKRAS due to an adverse reaction occurred in 5% of patients. Adverse reactions which required dose reductions in ≥ 2% of patients included increased ALT (2.9%) and increased AST (2.5%).

The most common adverse reactions (≥ 20%) were diarrhea, musculoskeletal pain, nausea, fatigue, hepatotoxicity, and cough. The most common laboratory abnormalities (≥ 25%) were decreased lymphocytes, decreased hemoglobin, increased aspartate aminotransferase, increased alanine aminotransferase, decreased calcium, increased alkaline phosphatase, increased urine protein, and decreased sodium.

Table 3 summarizes the common adverse reactions observed in CodeBreaK 100.

Table 3. Adverse Reactions (≥ 10%) of Patients with *KRAS G12C*-Mutated NSCLC who Received LUMAKRAS in CodeBreaK 100*

Adverse Reaction	LUMAKRAS N = 204	
	All Grades (%)	Grades 3 to 4 (%)
Gastrointestinal disorders		
Diarrhea	42	5
Nausea	26	1
Vomiting	17	1.5
Constipation	16	0.5
Abdominal pain[a]	15	1.0
Hepatobiliary disorders		
Hepatotoxicity[b]	25	12
Respiratory, thoracic, and mediastinal disorders		
Cough[c]	20	1.5
Dyspnea[d]	16	2.9
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[e]	35	8
Arthralgia	12	1.0
General disorders and administration site conditions		
Fatigue[f]	26	2.0
Edema[g]	15	0
Metabolism and nutrition disorders		
Decreased appetite	13	1.0
Infections and infestations		
Pneumonia[h]	12	7
Skin and subcutaneous tissue disorders		
Rash[i]	12	0

* Grading defined by NCI CTCAE version 5.0.

[a] Abdominal pain includes abdominal pain, abdominal pain upper, and abdominal pain lower.

[b] Hepatotoxicity includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, drug-induced liver injury, hepatitis, hepatotoxicity, liver function test increased, and transaminases increased.

[c] Cough includes cough, productive cough, and upper-airway cough syndrome.

[d] Dyspnea includes dyspnea and dyspnea exertional.

[e] Musculoskeletal pain includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, and pain in extremity.

[f] Fatigue includes fatigue and asthenia.

[g] Edema includes generalized edema, localized edema, edema, edema peripheral, periorbital edema, and testicular edema.

[h] Pneumonia includes pneumonia, pneumonia aspiration, pneumonia bacterial, and pneumonia staphylococcal.

[i] Rash includes dermatitis, dermatitis acneiform, rash, rash-maculopapular, and rash pustular.

Table 4 summarizes the selected laboratory adverse reactions observed in CodeBreaK 100.

Table 4. Select Laboratory Abnormalities (≥ 20%) that Worsened from Baseline in Patients with *KRAS G12C*-Mutated NSCLC who Received LUMAKRAS in CodeBreaK 100

Laboratory Abnormalities	LUMAKRAS N = 204*	
	Grades 1 to 4 (%)	Grades 3 to 4 (%)
Chemistry		
Increased aspartate aminotransferase	39	9
Increased alanine aminotransferase	38	11
Decreased calcium	35	0
Increased alkaline phosphatase	33	2.5
Increased urine protein	29	3.9
Decreased sodium	28	1.0
Decreased albumin	22	0.5
Hematology		
Decreased lymphocytes	48	2
Decreased hemoglobin	43	0.5
Increased activated partial thromboplastin time	23	1.5

* N = number of patients who had at least one on-study assessment for the parameter of interest.

Metastatic Colorectal Cancer

The safety of LUMAKRAS in combination with panitumumab was evaluated in the CodeBreaK 300 study *[see Clinical Studies (14.2)]*. Patients with *KRAS* G12C-mutated mCRC received LUMAKRAS 960 mg orally once daily in combination with panitumumab 6 mg/kg intravenously (IV) once every 2 weeks (N = 47), LUMAKRAS 240 mg orally once daily in combination with panitumumab 6 mg/kg IV once every 2 weeks (N = 50), or the investigator's choice of standard of care (SOC) trifluridine/ tipiracil or regorafenib (N = 50). Among patients who received LUMAKRAS 960 mg orally once daily in combination with panitumumab, 36% were exposed to LUMAKRAS for greater than 6 months and 6% were exposed for greater than 12 months.

The median age of patients who received LUMAKRAS 960 mg in combination with panitumumab arm was 63 years (range: 37-79 years); 38% were age 65 years or older; 49% were female; 79% were White and 13% were Asian.

Serious adverse reactions occurred in 26% of patients receiving LUMAKRAS 960 mg in combination with panitumumab. Serious adverse reactions in ≥ 2 patients receiving LUMAKRAS 960 mg in combination with panitumumab were sepsis (6%) and intestinal obstruction (4.3%). Fatal adverse reactions occurred in 2 patients (4.3%) receiving LUMAKRAS 960 mg in combination with panitumumab, consisting of cardiac arrest and sepsis (1 patient each).

Permanent discontinuation of LUMAKRAS due to an adverse reaction occurred in 1 patient for decreased corrected calcium.

Dosage interruptions of LUMAKRAS due to an adverse reaction occurred in 26% of patients. Adverse reactions which required dosage interruption in ≥ 2 patients were rash, hepatotoxicity and intestinal obstruction.

A dose reduction of LUMAKRAS due to an adverse reaction occurred in 1 patient for nausea.

The most common adverse reactions (≥ 20%) in patients receiving LUMAKRAS 960 mg in combination with panitumumab were rash, dry skin, diarrhea, stomatitis, fatigue and musculoskeletal pain.

The most common Grade 3-4 laboratory abnormalities in ≥ 2 patients (4.3%) were decreased magnesium, decreased potassium, decreased corrected calcium, and increased potassium.

Table 5 and Table 6 summarize the adverse reactions and laboratory abnormalities, respectively, identified in CodeBreaK 300.

Table 5. Adverse Reactions (≥ 10%) in Patients with *KRAS G12C*-Mutated mCRC who Received LUMAKRAS 960 mg in Combination with Panitumumab in CodeBreaK 300

Adverse Reaction	LUMAKRAS 960 mg in combination with panitumumab N = 47		Trifluridine/tipiracil or regorafenib N = 50	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Skin and subcutaneous tissue disorders				
Rash[a]	87	26	8	2
Dry skin[b]	28	0	2	0
Pruritis	17	0	4	0
Nail Disorder[c]	17	0	0	0
Skin fissure	13	0	0	0
Palmar-plantar erythrodysesthesia syndrome	13	0	10	4
Gastrointestinal disorders				
Diarrhea[d]	28	6	26	0
Stomatitis[e]	26	0	14	0
Nausea	17	2.1	36	4
Constipation	15	2.1	10	0
Abdominal pain[f]	15	0	18	2
Vomiting	13	2.1	10	2
General disorders				
Fatigue[g]	21	0	34	2
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[h]	21	2.1	14	2
Hematological disorders				
Hemorrhage[i]	13	2.1	2	0
Eye disorders				
Conjunctivitis[j]	11	0	2	0

[a] Rash includes dermatitis acneiform, dermatosis, drug eruption, eczema, erythema, hand dermatitis, rash, rash erythematous, rash maculo-papular, rash papular, rash pruritic, rash pustular, and skin toxicity.
[b] Dry skin includes dry skin, xerosis, and xeroderma.
[c] Nail disorders includes nail avulsion, nail cuticle fissure, nail disorder, nail toxicity, and paronychia.
[d] Diarrhea includes diarrhea, gastroenteritis, and diarrhea hemorrhagic.
[e] Stomatitis includes mucosal inflammation, stomatitis, mouth ulceration, angular cheilitis, and cheilitis.
[f] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, and hepatic pain.
[g] Fatigue includes asthenia and fatigue.

[h] Musculoskeletal pain includes arthralgia, back pain, myalgia, musculoskeletal chest pain, bone pain, and pain in extremity.
[i] Hemorrhage includes epistaxis, gastrointestinal hemorrhage, vaginal hemorrhage, rectal hemorrhage, hematochezia, hemorrhage, hemorrhage urinary tract, hematospermia, and hematuria.
[j] Conjunctivitis includes conjunctival hyperemia, conjunctivitis, and conjunctivitis allergic.

Table 6. Select Laboratory Abnormalities (≥ 20%) that Worsened from Baseline in Patients with *KRAS G12C*-Mutated mCRC who Received LUMAKRAS 960 mg in combination with panitumumab in CodeBreaK 300*

Laboratory Abnormalities	LUMAKRAS 960 mg in combination with panitumumab		Trifluridine/tipiracil or Regorafenib	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Chemistry				
Magnesium decreased	76	24	8	0
Calcium (corrected) decreased	74	4.3	46	0
Aspartate aminotransferase increased	39	0	22	2
Alkaline Phosphatase increased	33	2.2	33	0
Creatine kinase increased	30	2.3	7	0
Alanine Aminotransferase increased	28	0	16	2
Potassium decreased	26	7	12	0
Albumin decreased	26	2.2	22	0
Urine protein increased	23	0	22	6
Potassium increased	22	4.3	6	0
Glucose decreased	22	0	2	0
Hematology				
Hemoglobin decreased	30	0	58	6
Lymphocytes decreased	26	2.2	56	8
White blood cells decreased	24	0	48	14

* The denominator used to calculate the rate varied from 44 to 46 in the LUMAKRAS + panitumumab arm and 18 to 50 in the trifluridine/tipiracil or regorafenib arm 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 LUMAKRAS

Acid-Reducing Agents

The solubility of sotorasib is pH-dependent. Coadministration of LUMAKRAS with gastric acid-reducing agents decreased sotorasib concentrations *[see Clinical Pharmacology (12.3)]*, which may reduce the efficacy of sotorasib. Avoid coadministration of LUMAKRAS with proton pump inhibitors (PPIs), H_2 receptor antagonists, and locally acting antacids. If coadministration with an acid-reducing agent cannot be avoided, administer LUMAKRAS 4 hours before or 10 hours after administration of a locally acting antacid *[see Dosage and Administration (2.4)]*.

Strong CYP3A4 Inducers

Sotorasib is a CYP3A4 substrate. Coadministration of LUMAKRAS with a strong CYP3A4 inducer decreased sotorasib concentrations *[see Clinical Pharmacology (12.3)]*, which may reduce the efficacy of sotorasib. Avoid coadministration of LUMAKRAS with strong CYP3A4 inducers.

7.2 Effects of LUMAKRAS on Other Drugs

CYP3A4 Substrates

Sotorasib is a CYP3A4 inducer. Coadministration of LUMAKRAS with a CYP3A4 substrate decreased its plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may reduce the efficacy of the substrate. Avoid coadministration of LUMAKRAS with CYP3A4 sensitive substrates, for which minimal concentration changes may lead to therapeutic failures of the substrate. If coadministration cannot be avoided, increase the sensitive CYP3A4 substrate dosage in accordance with its Prescribing Information.

P-glycoprotein (P-gp) Substrates

Sotorasib is a P-gp inhibitor. Coadministration of LUMAKRAS with a P-gp substrate increased its plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may increase the adverse reactions of the substrate. Avoid coadministration of LUMAKRAS with P-gp substrates, for which minimal concentration changes may lead to serious toxicities. If coadministration cannot be avoided, decrease the P-gp substrate dosage in accordance with its Prescribing Information.

Breast Cancer Resistance Protein (BCRP) Substrates

Sotorasib is a BCRP-inhibitor. Coadministration of LUMAKRAS with a BCRP substrate increased its plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions of the substrate. When coadministered with LUMAKRAS, monitor for adverse reactions of the BCRP substrate and decrease the BCRP substrate dosage in accordance with its Prescribing Information.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on LUMAKRAS use in pregnant women. In rat and rabbit embryo-fetal development studies, oral sotorasib did not cause adverse developmental effects or embryo-lethality at exposures up to 4.6 times the human exposure at the 960 mg clinical dose *(see Data)*.

Refer to the Full Prescribing Information of panitumumab for pregnancy risk information and contraception recommendations when LUMAKRAS is administered in combination with panitumumab.

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 sotorasib to pregnant rats during the period of organogenesis resulted in maternal toxicity at the 540 mg/kg dose level (approximately 4.6 times the human exposure based on area under the curve (AUC) at the clinical dose of 960 mg). Sotorasib did not cause adverse developmental effects and did not affect embryo-fetal survival at doses up to 540 mg/kg.

In a rabbit embryo-fetal development study, once daily oral administration of sotorasib during the period of organogenesis resulted in lower fetal body weights and a reduction in the number of ossified metacarpals in fetuses at the 100 mg/kg dose level (approximately 2.6 times the human exposure based on AUC at the clinical dose of 960 mg), which was associated with maternal toxicity including decreased body weight gain and food consumption during the dosing phase. Sotorasib did not cause adverse developmental effects and did not affect embryo-fetal survival at doses up to 100 mg/kg.

8.2 Lactation

Risk Summary

There are no data on the presence of sotorasib 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 LUMAKRAS and for 1 week after the last dose.

Refer to the Full Prescribing Information of panitumumab for lactation recommendations when LUMAKRAS is administered in combination with panitumumab.

8.4 Pediatric Use

The safety and effectiveness of LUMAKRAS have not been established in pediatric patients.

8.5 Geriatric Use

Of the 357 patients with any tumor type who received LUMAKRAS 960 mg orally once daily in CodeBreaK 100, 46% were 65 and over, and 10% were 75 and over. No overall differences in safety or effectiveness were observed between older patients and younger patients treated with LUMAKRAS as a single agent.

In a pooled analysis of 132 patients who received LUMAKRAS 960 mg in combination with panitumumab for *KRAS* G12C-mutated mCRC, 30% were 65 and over while 9% were 75 and over. No overall differences in safety or efficacy were observed between older patients (≥ 65 years of age) compared to younger patients, treated with LUMAKRAS 960 mg in combination with panitumumab.

8.6 Hepatic Impairment

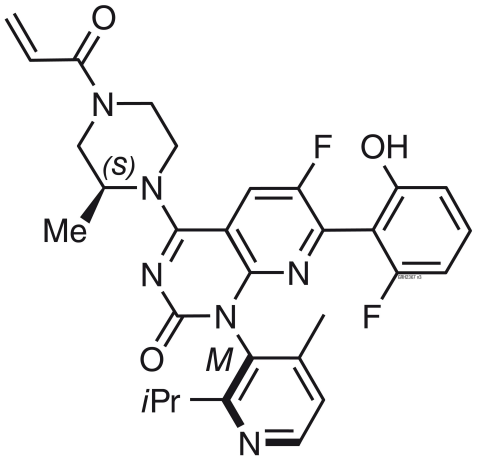
No dosage modification is recommended in patients with mild to moderate hepatic impairment (Child-Pugh A or B).

The effect of severe hepatic impairment (Child-Pugh C) on the safety of LUMAKRAS is unknown. Monitor for sotorasib adverse reactions in patients with hepatic impairment more frequently since these patients may be at increased risk for adverse reactions including hepatotoxicity *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

Sotorasib is an inhibitor of the RAS GTPase family. The molecular formula is $C_{30}H_{30}F_2N_6O_3$, and the molecular weight is 560.6 g/mol. The chemical name of sotorasib is 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1M)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2S)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]pyrido[2,3-d]pyrimidin-2(1H)-one.

The chemical structure of sotorasib is shown below:



Sotorasib has pKa values of 8.06 and 4.56. The solubility of sotorasib in the aqueous media decreases over the range pH 1.2 to 6.8 from 1.3 mg/mL to 0.03 mg/mL.

LUMAKRAS is supplied as film-coated tablets for oral use containing 320 mg, 240 mg or 120 mg of sotorasib. Inactive ingredients in the tablet core are microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. The film coating material consists of polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow and iron oxide red (320 mg tablet only).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sotorasib is an inhibitor of KRAS G12C, a tumor-restricted, mutant-oncogenic form of the RAS GTPase, KRAS. Sotorasib forms an irreversible, covalent bond with the unique cysteine of KRAS G12C, locking the protein in an inactive state that prevents downstream signaling without affecting wild-type KRAS. Sotorasib blocked KRAS signaling, inhibited cell growth, and promoted apoptosis only in *KRAS* G12C tumor cell lines. Sotorasib inhibited *KRAS* G12C *in vitro* and *in vivo* with minimal detectable off-target activity. In mouse tumor xenograft models, sotorasib-treatment led to tumor regressions and prolonged survival, and was associated with anti-tumor immunity in *KRAS* G12C models.

In the setting of *KRAS* G12C-mutant CRC, epidermal growth factor receptor (EGFR) activation has been identified as a mechanism of resistance to KRAS G12C inhibition. In a murine patient-derived colorectal tumor xenograft model, the combination of sotorasib and panitumumab, an EGFR antagonist, had increased antitumor activity compared to either sotorasib or panitumumab alone.

12.2 Pharmacodynamics

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

Cardiac Electrophysiology

At the approved recommended dosage, LUMAKRAS does not cause large mean increases in the QTc interval (> 20 msec).

12.3 Pharmacokinetics

The pharmacokinetics of sotorasib have been characterized in healthy subjects and in patients with *KRAS G12C*-mutated solid tumors, including NSCLC. Sotorasib exhibited non-linear, time-dependent, pharmacokinetics over the dose range of 180 mg to 960 mg (0.19 to 1 time the approved recommended dosage) once daily with similar systemic exposure (i.e., $AUC_{0\text{-}24h}$ and C_{max}) across doses at steady state. Sotorasib systemic exposure was comparable between film-coated tablets and film-coated tablets predispersed in water administered under fasted conditions. Sotorasib plasma concentrations reached steady state within 22 days. No accumulation was observed after repeat LUMAKRAS dosages with a mean accumulation ratio of 0.56 (coefficient of variation (CV):59%).

Absorption

The median time to sotorasib peak plasma concentration is 1 hour.

Effect of Food

When 960 mg LUMAKRAS was administered with a high-fat, high-calorie meal (containing approximately 800 to 1000 calories with 150, 250, and 500 to 600 calories from protein, carbohydrate and fat, respectively) in patients, sotorasib $AUC_{0\text{-}24h}$ increased by 25% compared to administration under fasted conditions.

Distribution

The sotorasib mean volume of distribution (V_d) at steady state is 211 L (CV: 135%). *In vitro*, sotorasib plasma protein binding is 89%.

Elimination

The sotorasib mean terminal elimination half-life is 5 hours (standard deviation (SD): 2). At 960 mg LUMAKRAS once daily, the sotorasib steady state apparent clearance is 26.2 L/hr (CV: 76%).

Metabolism
The main metabolic pathways of sotorasib are non-enzymatic conjugation and oxidative metabolism with CYP3As.

Excretion
After a single dose of radiolabeled sotorasib, 74% of the dose was recovered in feces (53% unchanged) and 6% (1% unchanged) in urine.

Specific Populations

No clinically meaningful differences in the pharmacokinetics of sotorasib were observed based on age (28 to 86 years), sex, race (White, Black and Asian), body weight (36.8 to 157.9 kg), line of therapy, ECOG PS (0, 1), mild and moderate renal impairment (eGFR: ≥ 30 mL/min/1.73 m^2), or mild hepatic impairment (AST or ALT < 2.5 × ULN or total bilirubin < 1.5 × ULN). The effect of severe renal impairment on sotorasib pharmacokinetics has not been studied.

Hepatic Impairment

The mean AUC of sotorasib decreased by 25% in subjects with moderate hepatic impairment (Child-Pugh B) and increased by 4% in subjects with severe hepatic impairment (Child-Pugh C) compared to subjects with normal hepatic function following a single dose of 960 mg LUMAKRAS.

Clinical Studies

Acid-Reducing Agents: Coadministration of repeat doses of omeprazole (PPI) with a single dose of LUMAKRAS decreased sotorasib C_{max} by 65% and AUC by 57% under fed conditions, and decreased sotorasib C_{max} by 57% and AUC by 42% under fasted conditions. Coadministration of a single dose of famotidine (H_2 receptor antagonist) given 10 hours prior to and 2 hours after a single dose of LUMAKRAS under fed conditions decreased sotorasib C_{max} by 35% and AUC by 38%.

Strong CYP3A4 Inducers: Coadministration of repeat doses of rifampin (a strong CYP3A4 inducer) with a single dose of LUMAKRAS decreased sotorasib C_{max} by 35% and AUC by 51%.

Other Drugs: No clinically meaningful effect on the exposure of sotorasib was observed following coadministration of LUMAKRAS with itraconazole (a combined strong CYP3A4 and P-gp inhibitor) and a single dose of rifampin (an OATP1B1/1B3 inhibitor), or metformin (a MATE1/MATE2-K substrate).

CYP3A4 substrates: Coadministration of LUMAKRAS with midazolam (a sensitive CYP3A4 substrate) decreased midazolam C_{max} by 48% and AUC by 53%.

P-gp substrates: Coadministration of LUMAKRAS with digoxin (a P-gp substrate) increased digoxin C_{max} by 91% and AUC by 21%.

MATE1/MATE2-K substrates: No clinically meaningful effect on the exposure of metformin (a MATE1/MATE2-K substrate) was observed following coadministration of LUMAKRAS.

BCRP substrates: Coadministration of LUMAKRAS with rosuvastatin (a BCRP substrate) increased rosuvastatin C_{max} by 70% and AUC by 34%.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Sotorasib may induce CYP2C8, CYP2C9 and CYP2B6. Sotorasib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with sotorasib.

Sotorasib was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay and was not genotoxic in the *in vivo* rat micronucleus and comet assays.

Fertility/early embryonic development studies were not conducted with sotorasib. There were no adverse effects on female or male reproductive organs in general toxicology studies conducted in dogs and rats.

13.2 Animal Toxicology and/or Pharmacology

In rats, renal toxicity including minimal to marked histologic tubular degeneration/necrosis and increased kidney weight, urea nitrogen, creatinine, and urinary biomarkers of renal tubular injury were present at doses resulting in exposures approximately ≥ 0.5 times the human AUC at the clinical dose of 960 mg. Increases in cysteine S-conjugate β-lyase pathway metabolism in the rat kidney compared to human may make rats more susceptible to renal toxicity due to local formation of a putative sulfur-containing metabolite than humans.

In the 3-month toxicology study in dogs, sotorasib induced findings in the liver (centrilobular hepatocellular hypertrophy), pituitary gland (hypertrophy of basophils), and thyroid gland (marked follicular cell atrophy, moderate to marked colloid depletion, and follicular cell hypertrophy) at exposures approximately 0.4 times the human exposure based on AUC at the clinical dose of 960 mg. These findings may be due to an adaptive response to hepatocellular enzyme induction and subsequent reduced thyroid hormone levels (i.e., secondary hypothyroidism). Although thyroid levels were not measured in dogs, induction of uridine diphosphate glucuronosyltransferase known to be involved in thyroid hormone metabolism was confirmed in the *in vitro* dog hepatocyte assay.

14 CLINICAL STUDIES

14.1 *KRAS* G12C-mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer

The efficacy of LUMAKRAS was demonstrated in a subset of patients enrolled in a single-arm, open-label, multicenter trial (CodeBreaK 100 [NCT03600883]). Eligible patients were required to have locally advanced or metastatic *KRAS* G12C-mutated NSCLC with disease progression after receiving an immune checkpoint inhibitor and/or platinum-based chemotherapy, 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).

All patients were required to have prospectively identified *KRAS* G12C-mutated NSCLC in tumor tissue samples by using the QIAGEN *therascreen*® KRAS RGQ PCR Kit performed in a central laboratory. Of 126 total enrolled subjects, 2 (2%) were unevaluable for efficacy analysis due to the absence of radiographically measurable lesions at baseline. Of the 124 patients with *KRAS* G12C mutations confirmed in tumor tissue, plasma samples from 112 patients were tested retrospectively using the Guardant360® CDx. 78/112 patients (70%) had *KRAS G12C* mutation identified in plasma specimen, 31/112 patients (28%) did not have *KRAS G12C* mutation identified in plasma specimen and 3/112 (2%) were unevaluable due to Guardant360® CDx test failure.

A total of 124 patients had at least one measurable lesion at baseline assessed by Blinded Independent Central Review (BICR) according to RECIST v1.1 and were treated with LUMAKRAS 960 mg once daily until disease progression or unacceptable toxicity. The major efficacy outcome measures were objective response rate (ORR), and duration of response (DOR) as evaluated by BICR according to RECIST v1.1.

The baseline demographic and disease characteristics of the study population were: median age 64 years (range: 37 to 80) with 48% ≥ 65 years and 8% ≥ 75 years; 50% Female; 82% White, 15% Asian, 2% Black; 70% ECOG PS 1; 96% had stage IV disease; 99% with non-squamous histology; 81% former smokers, 12% current smokers, 5% never smokers. All patients received at least 1 prior line of systemic therapy for metastatic NSCLC; 43% received only 1 prior line of therapy, 35% received 2 prior lines of therapy, 23% received 3 prior lines of therapy; 91% received prior anti-PD-1/PD-L1 immunotherapy, 90% received prior platinum-based chemotherapy, 81% received both platinum-based chemotherapy and anti-PD-1/PD-L1. The sites of known extra-thoracic metastasis included 48% bone, 21% brain, and 21% liver.

Efficacy results are summarized in Table 7.

Table 7. Efficacy Results for Patients with *KRAS* G12C-mutated NSCLC who Received LUMAKRAS in CodeBreaK 100

Efficacy Parameter	LUMAKRAS N = 124
Objective Response Rate (95% CI)[a]	36 (28, 45)
Complete response rate, %	2
Partial response rate, %	35
Duration of Response[a]	
Median[b], months (range)	10 (1.3+, 11.1)
Patients with duration ≥ 6 months[c], %	58%

CI = confidence interval

[a] Assessed by Blinded Independent Central Review (BICR).

[b] Estimate using Kaplan-Meier method.

[c] Observed proportion of patients with duration of response beyond landmark time.

14.2 *KRAS* G12C-mutated Metastatic Colorectal Cancer

The efficacy of LUMAKRAS in combination with panitumumab was evaluated in CodeBreaK 300 [NCT05198934], a multicenter, randomized, open-label, active-controlled study conducted in previously treated patients with *KRAS G12C*-mutated mCRC. Key eligibility criteria included patients 18 years of age or older, who had received at least one prior line of therapy for mCRC, and who had received

fluoropyrimidine, oxaliplatin, and irinotecan for metastatic disease unless there was a medical contraindication.

All patients were also required to have prospectively identified *KRAS G12C*-mutated mCRC in tumor tissue samples by using the QIAGEN therascreen® KRAS RGQ PCR Kit performed in a central laboratory. Other eligibility criteria included an ECOG PS of ≤ 2 and at least one measurable lesion as defined by RECIST v1.1.

A total of 160 patients with previously treated mCRC with the *KRAS G12C* mutation were randomized 1:1:1 to receive either LUMAKRAS 960 mg orally once daily and panitumumab 6 mg/kg IV every 2 weeks (N = 53), or LUMAKRAS 240 mg orally once daily and panitumumab 6 mg/kg IV every 2 weeks (N = 53), or investigator's choice of SOC trifluridine/tipiracil or regorafenib (N = 54). Randomization was stratified by prior anti-angiogenic therapy (yes or no), time from initial diagnosis of metastatic disease to randomization (≥ 18 months; < 18 months), and ECOG status (0 or 1 versus 2). Patients received treatment until disease progression, lack of clinical benefit or intolerance to treatment. LUMAKRAS discontinuation required panitumumab discontinuation, however, patients could continue to receive LUMAKRAS if panitumumab was discontinued *[see Dosage and Administration (2.3)]*. Four patients randomized to LUMAKRAS 960 mg in combination with panitumumab continued LUMAKRAS single agent therapy after discontinuing panitumumab.

The major efficacy outcome measure was progression-free survival (PFS) as evaluated by BICR according to RECIST 1.1. Additional efficacy outcome measures included overall survival (OS), overall response rate (ORR), and duration of response (DOR). Only the results of the approved dosing regimen LUMAKRAS 960 mg in combination with panitumumab are described below.

Of the 107 patients randomized to either LUMAKRAS 960 mg once daily in combination with panitumumab or the control arms, the median age was 64 years (range: 34-81 years); 46% were age 65 years or older; 50% were female; 74% were White; 17% were Asian and 97% of the patients had ECOG PS 0 or 1. The primary site of disease was colon (69%) or rectum (31%). The median number of prior lines of therapy for metastatic disease was 2. Among the 107 patients, 100% received prior fluoropyrimidine, 99% received prior oxaliplatin, 93% received prior irinotecan and 18% of patients had received prior trifluridine and tipiracil, or regorafenib.

The trial demonstrated a statistically significant improvement in PFS for patients randomized to LUMAKRAS 960 mg in combination with panitumumab compared to the investigator's choice SOC. The final analysis of OS was not statistically significant.

The final analysis of PFS for patients randomized to LUMAKRAS 240 mg in combination with panitumumab compared to investigator's choice of SOC was not statistically significant.

The efficacy results from CodeBreaK 300 are summarized in Table 8 and Figure 1.

Table 8. Efficacy Results for Patients with *KRAS G12C*-mutated mCRC in CodeBreaK 300

Efficacy Parameters	**Sotorasib 960 mg QD + Panitumumab (N = 53)**	**SOC (trifluridine/tipiracil or regorafenib) (N = 54)**
Progression-Free Survival (PFS) per BICR		
Number of Events (%)	32 (60)	35 (65)
Median in months (95% CI)	5.6 (4.2, 6.3)	2 (1.9, 3.9)

Efficacy Parameters	Sotorasib 960 mg QD + Panitumumab (N = 53)	SOC (trifluridine/tipiracil or regorafenib) (N = 54)
Hazard ratio (95% CI)[a]	0.48 (0.3,0.78)	
p-value (2-sided)[b]	0.005	
Overall Survival (OS)[c]		
Deaths (%)	24 (45)	30 (56)
Median in months (95% CI)	NR (8.6, NR)	10.3 (7, NR)
Hazard ratio (95% CI)[a]	0.7 (0.41, 1.18)	
Overall Response Rate (ORR) per BICR		
ORR, % (95% CI)[d]	26 (15, 40)	0 (0, 7)
CR, n (%)	1 (1.9)	0
PR, n (%)	13 (25)	0
Duration of Response (DOR)		
Median in months, (range)[e]	4.4 (1.9+, 6+)	-

N = Number of randomized subjects, NR = Not Reached, QD = once daily, SOC = standard of care, CR = complete response, PR = partial response, BICR = Blinded Independent Central Review Committee, CI = Confidence Interval

[a] Hazard ratios and 95% CIs were estimated using a stratified Cox proportional hazards model.

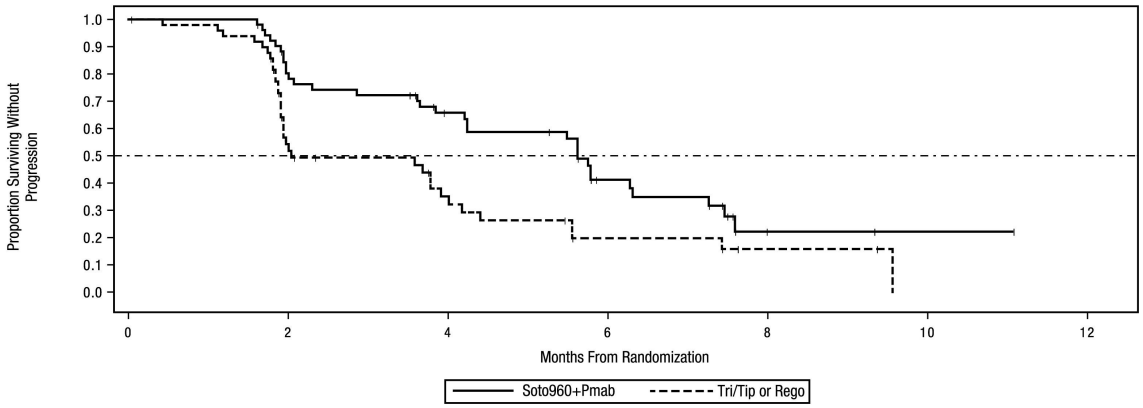
[b] p-value was calculated using a stratified log-rank test.

[c] OS analysis was based on 6-month additional follow-up data from the time of PFS primary analysis.

[d] 95% CIs were estimated using the Clopper-Pearson method.

[e] For DOR + indicates censored subjects.

Figure 1. Kaplan-Meier Curve for Progression-Free Survival in CodeBreaK 300



Soto960+Pmab = Sotorasib 960 mg + Panitumumab. Tri/Tip or Rego = Trifluridine and Tipiracil or Regorafenib.
Censor indicated by vertical bar |. Stratified Cox HR and stratified log-rank p-value for Soto+Pmab vs Tri/Tip Regorafenib are provided.

GRH2602 v6

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

LUMAKRAS (sotorasib) 320 mg tablets are beige, oval-shaped, film-coated, debossed with "AMG" on one side and "320" on the opposite side, and are supplied as follows:

- Carton containing one bottle of 90 tablets with child-resistant closure, NDC 55513-504-50

LUMAKRAS (sotorasib) 240 mg tablets are yellow, oval-shaped, film-coated, debossed with "AMG" on one side and "240" on the opposite side, and are supplied as follows:

- Carton containing one bottle of 120 tablets with child-resistant closure, NDC 55513-512-60

LUMAKRAS (sotorasib) 120 mg tablets are yellow, oblong-shaped, film-coated, debossed with "AMG" on one side and "120" on the opposite side, and are supplied as follows:

- Carton containing two bottles of 120 tablets with child-resistant closure, NDC 55513-488-02
- Carton containing one bottle of 240 tablets with child-resistant closure, NDC 55513-488-24

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F). Excursions permitted from 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

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

Hepatotoxicity

Advise patients to immediately contact their healthcare provider for signs and symptoms of liver dysfunction *[see Warnings and Precautions (5.1)]*.

Interstitial Lung Disease (ILD)/Pneumonitis

Advise patients to contact their healthcare provider immediately to report new or worsening respiratory symptoms *[see Warnings and Precautions (5.2)]*.

Lactation

Advise women not to breastfeed during treatment with LUMAKRAS and for 1 week after the last dose *[see Use in Specific Populations (8.2)]*. Refer to the Full Prescribing Information of panitumumab for lactation information, when LUMAKRAS is used in combination with panitumumab.

Drug Interactions

Advise patients to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, dietary and herbal products. Inform patients to avoid proton pump inhibitors, and H_2 receptor antagonists while taking LUMAKRAS *[see Drug Interactions (7.1) and (7.2)]*.

If coadministration with an acid-reducing agent cannot be avoided, inform patients to take LUMAKRAS 4 hours before or 10 hours after a locally acting antacid *[see Dosage and Administration (2.4)]*.

Missed Dose

If a dose of LUMAKRAS is missed by greater than 6 hours, resume treatment as prescribed the next day *[see Dosage and Administration (2.2)]*.

LUMAKRAS in combination with panitumumab

Advise patients taking LUMAKRAS in combination with panitumumab to:

- take the first dose of LUMAKRAS prior to the first panitumumab infusion *[see Dosage and Administration (2.2)]*.
- stop taking panitumumab whenever LUMAKRAS is withheld or discontinued *[see Dosage and Administration (2.3)]*.

AMGEN

LUMAKRAS® (sotorasib)

Manufactured by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799 U.S.A.

Patent: http://pat.amgen.com/lumakras/

1XXXXXX – V7

PATIENT INFORMATION
LUMAKRAS® (loo-ma-krass)
(sotorasib)
tablets

What is LUMAKRAS?

LUMAKRAS 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 for their cancer.
- in combination with a prescription medicine called panitumumab to treat colon or rectal cancer (CRC):
  - that has spread to other parts of the body **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 LUMAKRAS is right for you.

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

What should I tell my healthcare provider before taking LUMAKRAS?

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

- have liver problems.
- have lung or breathing problems other than lung cancer.
- are pregnant or plan to become pregnant. It is not known if LUMAKRAS will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if LUMAKRAS passes into your breast milk. Do not breastfeed during treatment with LUMAKRAS and for 1 week after the last dose.

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

Especially tell your healthcare provider if you take antacid medicines, including Proton Pump Inhibitor (PPI) medicines or H_2 blockers during treatment with LUMAKRAS. Ask your healthcare provider if you are not sure.

How should I take LUMAKRAS?

- Take LUMAKRAS exactly as your healthcare provider tells you to take it. Do not change your dose or stop taking LUMAKRAS unless your healthcare provider tells you to.
- Take your prescribed dose of LUMAKRAS 1 time each day, at the same time each day.
- For colon or rectal cancer, you will also receive panitumumab through a vein in your arm (intravenously) given by your healthcare provider. You will first take LUMAKRAS before you receive your first dose of panitumumab. Your healthcare provider will temporarily or permanently stop your treatment with panitumumab if your treatment with LUMAKRAS is temporarily or permanently stopped.
- Take LUMAKRAS with or without food.
- Swallow LUMAKRAS tablets whole. Do not chew, crush, or split tablets.
- If you cannot swallow LUMAKRAS tablets whole:
  - Place your prescribed dose of LUMAKRAS in a glass of 4 ounces (120 mL) of non-carbonated, room temperature water without crushing the tablets. Do not use any other liquids.
  - Stir or swirl the cup for about 3 minutes until the tablets are in small pieces (the tablets will not completely dissolve). The color of the mixture may be pale yellow to bright yellow.
  - Drink the LUMAKRAS and water mixture right away or within 2 hours of preparing. Do not chew pieces of the tablet.
  - Rinse the glass with an additional 4 ounces (120 mL) of water and drink to make sure that you have taken the full dose of LUMAKRAS.
  - If you do not drink the mixture right away, stir or swirl the mixture again before drinking.
- If you take an antacid medicine, take LUMAKRAS either 4 hours before or 10 hours after the antacid.
- If you miss a dose of LUMAKRAS, take the dose as soon as you remember. If it has been more than 6 hours, do not take the dose. Take your next dose at your regularly scheduled time the next day. Do not take 2 doses at the same time to make up for a missed dose.

- If you vomit after taking a dose of LUMAKRAS, do not take an extra dose. Take your next dose at your regularly scheduled time the next day.

What are possible side effects of LUMAKRAS?

LUMAKRAS may cause serious side effects, including:

- **Liver problems.** Abnormal liver blood tests are common with LUMAKRAS and can sometimes be severe. Your healthcare provider should do blood tests before starting and during treatment with LUMAKRAS 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.** LUMAKRAS 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.

Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with LUMAKRAS if you develop side effects.

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

- diarrhea
- muscle or bone pain
- nausea
- tiredness
- cough
- changes in certain blood tests

The most common side effects of LUMAKRAS when used in combination with panitumumab for CRC include:

- skin rash
- dry skin
- diarrhea
- mouth sores
- tiredness
- muscle and bone pain
- changes in certain blood tests

These are not all the possible side effects of LUMAKRAS.

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

You may also report side effects to Amgen at 1-800-772-6436 (1-800-77-AMGEN).

How should I store LUMAKRAS?

- Store LUMAKRAS at room temperature between 68°F to 77°F (20°C to 25°C).
- The bottle has a child-resistant closure.

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

General information about the safe and effective use of LUMAKRAS.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use LUMAKRAS for a condition for which it was not prescribed. Do not give LUMAKRAS 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 LUMAKRAS that is written for healthcare professionals.

What are the ingredients in LUMAKRAS?

Active Ingredient: sotorasib

Inactive Ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. Tablet film coating material contains polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow and iron oxide red (320 mg tablet only).

AMGEN

Manufactured by: Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799 U.S.A.

For more information, go to www.LUMAKRAS.com or call 1-800-772-6436 (1-800-77-AMGEN).
This Patient Information has been approved by the U.S. Food and Drug Administration.
Revised: 01/2025
[part number] v3

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/

CHANA WEINSTOCK
01/16/2025 01:55:21 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214665Orig1s009

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

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

[FDA will complete this section.]

Application Type	Supplemental NDA, SE1
Application Number(s)	NDA 214665/S-009
Priority or Standard	Priority
Submit Date(s)	04/17/2024
Received Date(s)	04/17/2024
PDUFA Goal Date	01/17/2025 (3-month extension due to Major Amendment)
Division/Office	OOD-DO3
Review Completion Date	January 15, 2025
Established Name	sotorasib
(Proposed) Trade Name	LUMAKRAS
Pharmacologic Class	inhibitor of the RAS GTPase family
Code name	AMG 510
Applicant	Amgen Inc.
Formulation(s)	Tablets: 320 mg, 240 mg, 120 mg
Dosing Regimen	960 mg orally once daily
Applicant Proposed Indication(s)/Population(s)	In combination with panitumumab, for the treatment of adult patients with KRAS G12C mutated mCRC as determined by an FDA approved test, who have received prior fluoropyrimidine , oxaliplatin and irinotecan based chemotherapy
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	

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

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Reviewers of Multi-Disciplinary Review and Evaluation

[FDA will complete this section.]

Regulatory Project Manager	Nataliya Fesenko
Pharmocology/Toxicology Reviewer(s)	
Pharmocology/Toxicology Team Leader(s)	
Office of Clinical Pharmacology Reviewer(s)	Yue Xiang Ye Xiong
Office of Clinical Pharmacology Team Leader(s)	Jason Moore Youwei Bi
Clinical Reviewer	May Tun Saung
Clinical Team Leader	Jamie Brewer
Safety Analyst (if applicable)	
Statistical Reviewer	Sirisha L Mushti
Statistical Team Leader	Chi Song
Associate Director for Labeling (ADL)	Doris Auth
Cross-Disciplinary Team Leader	Jamie Brewer
Division Director (DHOT)	
Division Director (OCP)	Nam A. Rahman
Deputy Division Director (OB)	Pallavi Mishra-Kalyani
Division Director (OOD)	
Office Director (or designated signatory authority)	Chana Weinstock

Additional Reviewers of Application

OPQ	
Microbiology	
OPDP	
OSI	Courtney McGuire Michele Fedowitz
OSE/DEPI	
OSE/DMEPA	
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

APPEARS THIS WAY ON ORIGINAL

Glossary

AACR	American Association for Cancer Research
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BICR	blinded independent central review
CFR	Code of Federal Regulations
COA	clinical outcome assessment
COVID-19	coronavirus disease-2019
CR	complete response
CRC	colorectal cancer
CSR	clinical study report
DCR	disease control rate
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EOI	event of interest
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire
ER	exposure-response
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HR	hazard ratio
ILD	interstitial lung disease
IND	investigational new drug
IPD	important protocol deviation
IV	intravenously
KRAS	Kirsten rat sarcoma viral oncogene homolog (protein)
KRAS	Kirsten rat sarcoma viral oncogene homolog (DNA)
$KRAS^{G12C}$	KRAS protein with a G12C amino acid substitution
KRAS p.G12C	KRAS gene with a mutation resulting in a G12C amino acid substitution at the protein level
mCRC	metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effect model for repeated measures
MSI-H	microsatellite instability high

NCI-CTCAE	National Cancer Institute- Common Terminology Criteria for Adverse Events
NE	not estimable
NSCLC	non-small-cell-lung cancer
OCE	Oncology Center of Excellence
ORR	objective response rate
OS	overall survival
PA	primary analysis
PBRER	Periodic Benefit Risk Evaluation Report
PD	pharmacodynamic(s)
PFS	progression-free survival
PK	pharmacokinetic(s)
PPK	population pharmacokinetic
PR	partial response
PRO	patient-reported outcome
QD	once daily
RAS	rat sarcoma viral oncogene homolog
RECIST	response evaluation criteria in solid tumors
TA	treatment administered
TC	treatment compliant
t_{max}	time to reach maximum observed plasma concentration
TTR	time to response
ULN	upper limit of normal
US	United States
USPI	US Prescribing Information
VEGF	vascular endothelial growth factor

1 Executive Summary

1.1. Product Introduction

Sotorasib is an inhibitor of the RAS GTPase family. Sotorasib was initially approved under accelerated approval for the treatment of KRAS G12C-mutated locally advanced or metastatic Non-Small Cell Lung Cancer (NSCLC) as determined by an FDA-approved test on May 28, 2021.

The Applicant is seeking traditional approval of sotorasib in combination with panitumuab for the following proposed indication:

(b) (4)

The Applicant's proposed dose of LUMAKRAS is 960 mg orally once daily in combination with panitumumab 6 mg/kg IV every 2 weeks.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness was established via the results of one adequate and well controlled clinical investigation [Study 20190172 (NCT05198934)] plus confirmatory evidence (Study 20190135 Subprotocol H [NCT04185883] and Study 20170543 [NCT03600883) from earlier phase trials.

Study 20170192 (CodeBreak 300) is an open-label, multicenter, randomized, active-control trial designed to evaluate the safety and efficacy of sotorasib in combination with panitumumab compared to investigator's choice of standard of care (SOC) regimens, trifluridine/tipiracil or regorafenib, in 160 adult patients with *KRAS G12C*-mutated mCRC who have received prior fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy. Patients were randomized 1:1:1 to receive either sotorasib 240 mg orally daily (PO QD) with panitumumab 6 mg/kg intravenously (IV) every 2 weeks (Q2W), sotorasib 960 mg PO QD with panitumumab 6 mg/kg IV Q2W, or investigators choice of trifluridine/tipiracil 35 mg/m2 PO twice daily (BID) with food on Days 1 through 5 and Days 8 through 12 or regorafenib 160 mg PO QD for the first 21 days of each 28-day cycle. Patients received treatment until disease progression, lack of clinical benefit, or intolerance of treatment. The primary study objective was to demonstrate superiority of either of the two sotorasib dosage regimens compared to investigator's choice of therapy via progression free survival (PFS) per RECIST v1.1 as assessed by blinded independent central review (BICR). The key secondary objective was to evaluate overall survival (OS) and objective

response rate (ORR); however this study was not powered for OS.

Study 20170192 demonstrated a statistically significant and clinically meaningful improvement in PFS in patients randomized to the sotorasib 960 mg arm with panitumumab compared to those randomized to investigator's choice of standard or care therapy. The stratified hazard ratio was 0.48 (95% confidence interval [CI] 0.3, 0.78; p-value = 0.005), with a median PFS of 5.6 months (95% CI 4.2, 6.3) in the sotorasib 960 mg with panitumumab arm and 2 months (95% CI 1.9, 3.9) in the investigator's choice arm. The efficacy of sotorasib 960 mg with panitumumab is supported by a clinically meaningful improvement in ORR with an ORR of 26% (95% CI 15, 40) in the sotorasib 960 mg with panitumumab arm and 0% (95% CI 0, 7) in the investigator's choice arm.

Due to the submission of additional PFS event data (corrected for error due to unreported scans identified at the time of the updated OS analysis) at the time of the final submission of this sNDA, the final analysis of PFS for patients randomized to sotorasib 240 m in combination with panitumumab compared to investigator's choice of SOC was not statistically significant based on the specified stopping value for the p-value. The ORR in the sotorasib 240 mg with panitumumab arm was also notably low at 6% (95% CI 1.2, 15.7).

The safety profile of single agent sotorasib has been previously characterized in the original NDA that supported the approval for adult patients with *KRAS G12c*-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC). The safety profile of sotorasib in combination with panitumumab is consistent with the safety profile observed when each component of the combination regimen is administered as a single agent.

The submitted evidence meets the statutory evidentiary standard for traditional approval of sotorasib 960 mg in combination panitumumab for the treatment of adult patients with *KRAS G12C*-mutated metastatic colorectal cancer (mCRC), as determined by an FDA-approved test, who have received prior fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy.

1.3. Benefit-Risk Assessment (BRA)

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, for 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 trifluridine/tipiracil in the third-line setting.

Available treatment options are limited for patients with refractory CRC and include treatment with regorafenib, trifluridine/tipiracil 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). Trifluridine/tipiracil was initially approved in 2015 based on data from the RECOURSE trial that demonstrated an improvement in overall survival (OS) in patients treated with trifluridine/tipiracil 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). Trifluridine/tipiracil in combination with bevacizumab was approved in 2023 based on data from the SUNLIGHT trial that demonstrated an improvement in OS in patients receiving trifluridine/tipiracil in combination with bevacizumab compared to patients receiving trifluridine/tipiracil alone (HR 0.61 [95% CI 0.49, 0.77]). The median OS of patients treated with trifluridine/tipiracil 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). Fruquintinib was approved in 2023 based on data from the FRESCO-2 trial that demonstrated an improvement in OS in patients receiving fruquintinib 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). Adagrasib in combination with cetuximab received accelerated approval for the treatment of patients with *KRAS G12C*-mutated locally advanced or metastatic CRC based on a clinically meaningful BICR-ORR of 34% (95%

CI: (25, 45)). Although this therapy is available as a treatment option for patients with *KRAS G12C*-mutated CRC it is not considered in the regulatory assessment of available therapy as it is approved under the accelerated approval pathway.

KRAS is the most frequently mutated RAS protein, representing approximately 50% of RAS mutations occurring in 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 other than adagrasib as described above. 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).

The safety and effectiveness of sotorasib 960 mg in combination with panitumumab for the treatment of adult patients with *KRAS* G12C-mutated mCRC who have previously received fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy is demonstrated by the results of a single open-label, multicenter, randomized, active-control trial, Study 20170192 (CodeBreak 300). In Study 20170192, 160 patients were randomized 1:1:1 to receive either sotorasib 240 mg orally daily (PO QD) with panitumumab 6 mg/kg intravenously (IV) every 2 weeks (Q2W), sotorasib 960 mg PO QD with panitumumab 6 mg/kg IV Q2W, or investigators choice of trifluridine/tipiracil 35 mg/m2 PO twice daily (BID) with food on Days 1 through 5 and Days 8 through 12 or regorafenib 160 mg PO QD for the first 21 days of each 28-day cycle. Patients received treatment until disease progression, lack of clinical benefit, or intolerance of treatment. Randomization was stratified by prior anti-angiogenic therapy, time from initial diagnosis of metastatic disease to randomization, and ECOG performance status. The major efficacy endpoint was PFS. Secondary endpoints included OS and ORR, however the study was not powered for OS. In addition, the study was not designed to include a formal analysis between the sotorasib 960 mg with panitumumab arm and the sotorasib 240 mg with panitumumab arm.

A favorable risk:benefit assessment was made for sotorasib 960 mg in combination with panitumumab based on demonstration of a statistically significant and clinically meaningful improvment in PFS compared to investigator's choice therapy, with a stratified HR of 0.48 (95% CI: 0.3, 0.78; p-value = 0.005). The median PFS was 5.6 months (95% CI 4.2, 6.3) in the sotorasib 960 mg with panitumumab arm and 2 months (95% CI 1.9, 3.9) in the investigator's choice arm. The PFS benefit was supported by a clinically meaningful improvement in ORR of 26% (95% CI 15, 40) in the sotorasib 960 mg with panitumumab arm and 0% (95% CI 0, 7) in the investigator's choice arm. At the time of the final submission of this NDA, the Applicant notified FDA of 5 patients who had scans performed but the results had not been included in the original primary analysis of BICR-assessed PFS. Based on this updated data, the final PFS analysis of sotorasib 240 mg in combination with panitumumab did not meet the specified threshold for statistical significance for the primary PFS analysis.

The data submitted to support the safety review of sotorasib 960 mg in combination with panitumumab is adequate to characterize the toxicity

in patients with *KRAS G12C*-mutated mCRC. The safety profile observed in patients who received sotorasib 960 mg in combination with panitumumab is generally consistent with what has been observed with patients treated with the single agent drugs in the regimen. The most common adverse reactions (≥ 20%) in patients receiving sotorasib 960 mg in combination with panitumumab were rash, dry skin, diarrhea, stomatitis, fatigue, and musculoskeletal pain. The most common Grade 3-4 laboratory abnormalities in ≥ 2 patients (4.3%) were decreased magnesium, decreased potassium, decreased corrected calcium, and increased potassium.

There is sufficient evidence to conclude that both sotorasib 960 mg and panitumumab given in combination are required for the observed treatment effect. It has been previously demonstrated that single-agent panitumumab is not effective for the treatment of patients with RAS-mutant mCRC (Vectibix USPI). Sotorasib has demonstrated some single-agent anti-tumor activity demonstrated in Study 20170543 with a pooled ORR for the sotorasib 960 mg daily dose of 13% (95% CI: 7, 21.9).

Considering the overlapping PK profile and E-R analyses and the comparable safety profiles for the two sotorasib combination regimens, the decision that 960 mg sotorasib in combination with panitumumab is the appropriate dose for approval is based on the favorable clinical benefit demonstrated by the statistically significant improvement in PFS compared to SOC and is supported by the substantial difference in ORR observed with sotorasib 960 mg with panitumumab arm and sotorasib 240 mg with panitumumab arm (26% (95% CI: 15, 40) and 6% (95% CI: 1, 16), respecively). The FDA review team determined that there was not sufficient evidence to support further dose evaluation for patients with *KRAS G12C*-mutated mCRC.

A supplemental premarket application (PMA) for the *therascreen* KRAS RGQ PCR kit was submitted to expand the indication for use as an iad to identify patients with *KRAS* G12C-mytated CRC for treatment with sotorasib in combination with panitumumab. The Center for Devices and Radiological Health (CDRH) recommended approval to expand the indication.

The submitted evidence meets the statutory evidentiary standard for traditional approval of sotorasib 960 mg in combination with panitumumab for the treatment of adult patients with *KRAS G12C*-mutated metastatic colorectal cancer.

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). • There is limited available data regarding the incidence and prevalence of *KRAS G12C*-mutated CRC among different racial and ethnic groups.	Refractory RC is a serious and life-threatening condition with 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 trifluridine/tipiracil, 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	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%. On June 21, 2024, FDA granted accelerated approval to adagrasib in combination with cetuximab for the treatment adult patients with *KRAS G12C*-mutated advanced or metastatic CRC who have received prior treatment with fluoropyrimidine-, oxaliplatin-,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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, fruquintinib demonstrated an improvement in OS in patients treated with fruquintinib 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).	and irinotecan-based chemotherapy based on an BICR-ORR of 34% (95% CI 25, 45). While this therapy is available for the treatment of patients, it is not considered in the regulatory assessment of available therapies.
Benefit	• In Study 20170192, sotorasib 960 mg in combination with panitumumab demonstrated a statistically significant and clinically meaningful improvement in BICR-PFS compared to investigator's choice of SOC therapy (median PFS 5.6 months (95% CI 4.2, 6.3) and 2 months (95% CI 1.9, 3.9), respectively) with a stratified hazard ratio was 0.48 (95% confidence interval [CI] 0.3, 0.78; p-value = 0.005). • The ORR of sotorasib 960 mg in combination with panitumumab was numerically higher than the ORR observed in patients treated with investigator's choice therapy (26% (95% CI 15, 40) compared to 0% (95% CI 0, 7)). • The PFS analysis of sotorasib 240 mg in combination with panitumumab compared to investigator's choice of SOC did not reach statistical significance based on the specified p-value boundary. • The study was not designed to statistically compare the sotorasib 240 mg with panitumumab regimen with the sotorasib 960 mg with panitumumab regimen.	The study demonstrated a clinically meaningful and statistically significant PFS for sotorasib 960 mg in combination with panitumumab accompanied by a numerically higher ORR compared to investigator's choice of SOC.
Risk and Risk Management	• The safety analysis population included 47 patients treated with sotorasib 960 mg in combination with panitumumab in Study 20170192 with supportive data submitted from Study 20190135 Subprotocol H and Study 20170543.	The safety of sotorasib and panitumumab has been well characterized and no new safety concerns were identified during this review. No new Warnings/Precautions were identified,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The overall safety profile of sotorasib 960 mg in combination with panitumumab for the treatment of adult patients with *KRAS G12C*-mutated mCRC in Study 20170192 was consistent with the safety profile observed for sotorasib and panitumumab when each agent is administered as a single agent. • Significant risks associated with sotorasib in combination panitumumab include hepatotoxicity and interstitial lung disease/pneumonitis. • The most common adverse reactions (≥ 20%) in patients receiving sotorasib 960 mg in combination with panitumumab were rash, dry skin, diarrhea, stomatitis, fatigue, and musculoskeletal pain. • Serious adverse reactions occurred in 26% of patients. Adverse reactions leading to dose interruption occurred in 26% of patients. One patient each had a dose reduction or permanent discontinuation of sotorasib due to an adverse reaction.	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 a metastatic *KRAS G12C*-mutated CRC previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. Although the study is not designed for a direct comparison between the two sotorasib arms, the safety of sotorasib 960 mg in combination with panitumumab does not appear to be worse than that observed with sotorasib 240 mg in combination with panitumumab.

1.4. Patient Experience Data

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

x	The patient experience data that was submitted as part of the application, include:		Section where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as	Section 8.2.6 (this analysis is considered exploratory)

			x	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 was not submitted in the application, but was considered in this review.				

X

Jamie R. Brewer
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Disease Background:

Worldwide, colorectal cancer (CRC) is the third most common type of cancer occurring in both men and women and the second leading cause of cancer-related deaths (WHO Statistics, 2022). It was estimated that in 2022 there were approximately 151 030 new cases of CRC in the US (American Cancer Society, 2022). The 5-year survival rate is 90% for patients diagnosed with stage 1 localized disease but declines to 14% for those diagnosed with distant metastatic disease (American Cancer Society, 2022). Consistent with this, GLOBOCAN estimates that the 5-year survival rate for metastatic colorectal cancer (mCRC) if diagnosed late is approximately 6% (GLOBOCAN, 2020).

Oncogenic *RAS* and *KRAS p.G12C* Mutation

Most cases of CRC are sporadic and develop slowly over several years through the adenoma-carcinoma sequence. The adenoma-carcinoma sequence includes the activation of the Kirsten rat sarcoma viral oncogene homolog (*KRAS)* proto-oncogene, and inactivation of the tumor suppressor genes via loss of adenomatous polyposis coli, loss of p53, and loss of heterozygosity for the long arm of chromosome 18 (Vogelstein et al, 1988). The rat sarcoma viral oncogene homolog (*RAS)* family of proto-oncogenes consists of 3 closely related genes that encode guanosine triphosphatases responsible for regulating cellular proliferation and survival (Simanshu et al, 2017; Barbacid, 1987). Different tumor types are associated with mutations in certain isoforms of *RAS*, with *KRAS* being the most frequently mutated isoform in most cancers (Prior et al, 2012). The *KRAS p.G12C* mutation in codon 12 is a single guanine to thymine substitution that results in a glycine to cysteine substitution at amino acid position 12. This structural change in the protein results in a defect in the association of guanosine triphosphatase-activating proteins, thereby reducing the hydrolysis of guanosine triphosphate by the KRAS protein. The resulting accumulation of active, guanosine triphosphate-bound KRAS leads to proliferative and survival signaling in tumor cells (Jones et al, 2017).

Overall, it is estimated that approximately 3% of patients with CRC have the *KRAS p.G12C* mutation (Nassar et al, 2021; American Association for Cancer Research [AACR] Project GENIE Consortium, 2017; Biernacka et al, 2016; Neumann et al, 2009). Mutation of *KRAS* is an adverse prognostic factor in CRC (Bonanno et al, 2010; Jones et al, 2017; Johnson et al, 2013), and the specific *KRAS p.G12C* mutation may be associated with poorer prognosis compared with other *KRAS* mutations (Jones et al, 2017; Modest et al, 2016).

Consistent with this, results from a real-world evidence study conducted by Amgen, (Study 20200246, see Section 1.1 of Module 2.7.3, Summary of Clinical Efficacy), estimated that approximately 3.7% of adult mCRC patient tumors had the *KRAS p.G12C* mutation and showed that patients with mCRC with the *KRAS p.G12C* mutation had shorter median overall survival (OS) and real-world progression-free survival (PFS) compared with patients with mCRC with other *KRAS* mutations or general patients with mCRC (Fakih et al, 2022).

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment and has the following comments. CRC is the 4th most common cancer and cause of cancer death in the U.S. and makes up 7.6% of all new cancer cases in the U.S.[1] While about 30-50% of patients with CRC have a KRAS mutation, approximately 3-7% of patients with CRC, depending on the study, have KRAS G12C mutation.[2-4]

APPEARS THIS WAY
ON ORIGINAL

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Patients with metastatic or unresectable CRC are generally treated with combinations of chemotherapy, immunotherapy, and anti-angiogenic agents or anti-epidermal growth factor receptor (EGFR) inhibitors, with targeted therapies available for select oncogenic mutations such as BRAF V600E (NCCN, 2022). First-line chemotherapy may comprise combining a fluoropyrimidine and oxaliplatin (eg, FOLFOX) or irinotecan (eg, FOLFIRI), with or without a vascular endothelial growth factor (VEGF) inhibitor (eg, bevacizumab), and typically the combination partner with a fluoropyrimidine is alternated for second-line treatment. Some patients may receive all 3 agents simultaneously in first-line therapy (FOLFOXIRI) with or without bevacizumab and with subsequent disease progression have limited options in second-line therapy. Epidermal growth factor receptor inhibitors (eg, cetuximab and panitumumab) are an option for some patients, but these have been shown to be ineffective in clinical studies of subjects with CRC with *KRAS* mutations (Amado et al, 2008).

In the United States (US), there are no approved therapies for CRC specifically targeting the *KRAS p.G12C* mutation or indeed any *KRAS* mutation (Román et al, 2018), thus therapy for patients with CRC with the *KRAS p.G12C* mutation follows the standard of care for the general patient population without targetable mutations. Furthermore, oncogenic *KRAS* mutations rarely occur concomitantly with targetable mutations such as *BRAF*; therefore, patients with *KRAS p.G12C* mutations are not often candidates for these therapies (Scheffler et al, 2019; Gainor et al, 2013), and because anti-EGFR antibodies are ineffective in *KRAS*-mutated CRC, these patients have more limited treatment options than patients whose tumors do not have the *KRAS p.G12C* mutation.

For patients with *KRAS p.G12C*-mutated mCRC who have already received fluoropyrimidine, oxaliplatin, and irinotecan-based therapies, the remaining approved regimens are: the multi-targeted kinase inhibitor, regorafenib; a dual agent therapy consisting of trifluridine (a nucleoside metabolic inhibitor) and tipiracil (a thymidine phosphorylase inhibitor) with or without bevacizumab; or fruquintinib (Applicant – Table 1). These regimens have modest response rates of less than 10%, highlighting the need for additional therapeutic options. The data from studies exploring these regimens are summarized below.

The CORRECT study was a randomized, placebo-controlled, phase 3 study of regorafenib conducted in subjects with colorectal adenocarcinoma who had received currently approved standard therapies, including fluoropyrimidine, oxaliplatin, irinotecan, and bevacizumab, as well as cetuximab or panitumumab for subjects with *KRAS* wild-type tumors (Grothey et al, 2013). Median OS improved from 5.0 months for placebo treatment to 6.4 months for regorafenib treatment ($p = 0.0052$), and median PFS improved from 1.7 months for placebo to 1.9 months for regorafenib ($p < 0.0001$). Response rates were similar in the 2 groups (1.0% for regorafenib versus 0.4% for placebo; $p = 0.19$).

The RECOURSE study was a randomized, double-blind, placebo-controlled phase 3 study of trifluridine and tipiracil in subjects with mCRC who had received prior treatment with a fluoropyrimidine, oxaliplatin, irinotecan, and bevacizumab, and for subjects with *KRAS* wild-type tumors, cetuximab or panitumumab (Mayer et al, 2015). Median OS improved from 5.3 months for placebo to 7.1 months for trifluridine and tipiracil ($p < 0.001$), and median PFS improved from 1.7 months for placebo to 2.0 months for trifluridine and tipiracil ($p < 0.001$). Response rates were similar in the 2 groups (1.6% for trifluridine and tipiracil versus 0.4% for placebo; $p = 0.29$) (Applicant – Table 1).

In the CORRECT study, the subject incidence of grade 3 or higher treatment-emergent adverse events for subjects in the regorafenib group was 78% and the prescribing information includes a boxed warning for hepatotoxicity. In the RECOURSE study, the subject incidence of grade 3 or higher treatment-emergent adverse events for subjects in the trifluridine/tipiracil group was 69% (Applicant – Table 1).

More recently, the combination of trifluridine/tipiracil with bevacizumab was granted traditional approval by the Food and Drug Administration (FDA) for mCRC previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy. This approval was based on results of the phase 3 SUNLIGHT clinical study in patients with mCRC who received a maximum of 2 prior chemotherapy regimens and demonstrated progressive disease or intolerance to the last regimen (Prager et al, 2023; Lonsurf US Prescribing Information [USPI], 2023). Results from the SUNLIGHT study showed that the combination of trifluridine/tipiracil with bevacizumab led to a statistically significant improvement in median OS from 7.5 to 10.8 months ($p < 0.001$) versus trifluridine/tipiracil alone, and a statistically significant improvement in median PFS from 2.4 to 5.6 months ($p < 0.001$). The ORR was 6.1% for the combination and 1.2% for trifluridine/tipiracil alone (Applicant – Table 1).

Another recent approval for previously treated mCRC was fruquintinib, which received FDA approval based on the FRESCO and FRESCO-2 studies on 08 November 2023. The FRESCO study was a multicenter, placebo-controlled trial conducted in China, that evaluated 416 patients with mCRC who had disease progression during or after prior fluoropyrimidine-, oxaliplatin, and irinotecan-based chemotherapy. The FRESCO-2 study was an international randomized double-blind placebo-controlled phase 3 study that evaluated 691 subjects with mCRC who had disease progression during or after prior fluoropyrimidine-, oxaliplatin-, irinotecan-based chemotherapy, an anti-VEGF biological therapy an anti-EGFR biological therapy if RAS wild-type, and at least 1 of trifluridine/tipiracil or regorafenib. In both studies, patients received either fruquintinib 5 mg orally once daily (QD) or placebo for the first 21 days of each 28-day cycle plus best supportive care. In the FRESCO study, ORR was 4.7% in the fruquintinib group and 0% in the control group, and median OS was 9.3 months in the fruquintinib group and 6.6 months in the placebo group ($p < 0.001$) (Li et al, 2018). In the FRESCO-2 study, objective response rate (ORR) was 2% in the fruquintinib group and 0% in the placebo group, median OS was 7.4 months in the fruquintinib group and 4.8 months in the placebo group ($p < 0.001$) (Dasari et

al, 2023). In both studies, the median PFS was 3.7 months in the fruquintinib group and 1.8 months in the placebo group (Dasari et al, 2023; Li et al, 2018) (Applicant – Table 1).

Unmet Need

While the role of *KRAS* mutations in human cancers has been known for decades (Hobbs et al, 2016), no anticancer therapies targeting *KRAS* mutations in CRC are available. Thus, an unmet need exists for therapies that can specifically target CRC driven by *KRAS* mutations, including the approximately 3% of patients with CRC with the *KRAS p.G12C* mutation (AACR Project GENIE Consortium, 2017; Biernacka et al, 2016; Neumann et al, 2009). Outcomes for patients with mCRC who were previously treated with fluoropyrimidine, oxaliplatin and irinotecan chemotherapy are poor. While regorafenib, trifluridine/tipiracil with or without bevacizumab, and fruquintinib have yielded survival gains as shown by the results from CORRECT, RECOURSE, SUNLIGHT, and FRESCO/FRESCO-2 studies, the modest response rates indicate that an unmet medical need remains for patients with mCRC.

The 2 real-world evidence studies conducted by Amgen (Section 1.1.1 of Module 2.7.3, Summary of Clinical Efficacy) also demonstrate that patients with *KRAS p.G12C*-mutated mCRC have poor treatment outcomes, confirming that there is unmet need for additional novel, biomarker driven, anticancer therapies with better efficacy and tolerable safety profiles in this patient population.

Applicant – Table 1. Summary of Treatment Armamentarium Relevant to mCRC Indication –Treatment Options for Chemorefractory Metastatic Colorectal Cancer

Treatment Options for Chemorefractory Metastatic Colorectal Cancer				
Product Name (INN)	Year and Type of Approval	Dosing/Administration	Efficacy Information	Important Safety and Tolerability Issues
Regorafenib	2012 Full	160 mg orally QD on days 1 to 21 of each 28-day cycle	Study 14387 (CORRECT) • median OS: 6.4 months • median PFS: 2.0 months • ORR: 1.0%	hepatotoxicity, infections, hemorrhage, gastrointestinal perforation or fistula, dermatologic toxicity, hypertension, cardiac ischemia and infarction, reversible posterior leukoencephalopathy syndrome, risk of impaired wound healing, and embryo-fetal toxicity,
Trifluridine and Tipiracil	2015 Full	35 mg/m^2 orally BID after meals on days 1 to 5 and 8 to 12 of each 28-day cycle	Study TPU-TAS-102-301 (RECOURSE) • median OS: 7.1 months • median PFS: 2.0 months • ORR: 1.6%	severe myelosuppression and embryo-fetal toxicity

Footnotes are defined on the last page of the table.

Applicant – Table 1. Summary of Treatment Armamentarium Relevant to mCRC Indication –Treatment Options for Chemorefractory Metastatic Colorectal Cancer

Product Name (INN)	Year and Type of Approval	Dosing/Administration	Efficacy Information	Important Safety and Tolerability Issues
Trifluridine and Tipiracil, with Bevacizumab	2023 Full	Trifluridine and tipiracil: 35 mg/m^2 orally BID after meals on days 1 to 5 and 8 to 12 of each 28-day cycle Bevacizumab: 5 mg/kg IV Q2W (days 1 and 15) of each 28-day cycle	Study CL3-05005-007 (SUNLIGHT) • median OS: 10.8 months • median PFS: 5.6 months • ORR: 6.1%	Trifluridine and tipiracil: severe myelosuppression and embryo-fetal toxicity Bevacizumab: gastrointestinal perforations and fistulae, surgery and wound healing complications, hemorrhage, arterial thromboembolic events, venous thromboembolic events, hypertension, posterior reversible encephalopathy syndrome, renal injury and proteinuria, infusion related reactions, embryo-fetal toxicity, ovarian failure, and congestive heart failure
Fruquintinib	2023 Full	5 mg orally QD	Study 2013-013-00CH1 (FRESCO) • median OS: 9.3 months • median PFS: 3.7 months • ORR: 4.7% Study 2019-013-GLOB1 (FRESCO-2) • median OS: 7.4 months • median PFS: 3.7 months • ORR: 2.0%	hypertension, hemorrhagic events, infections, gastrointestinal perforation, hepatotoxicity, proteinuria, palmar-plantar erythrodysesthesia, posterior reversible encephalopathy syndrome, impaired wound healing, arterial thromboembolic events, allergic reactions to FD&C Yellow No. 5 (Tartazine) and No. 6 (Sunset Yellow FCF), and embryo-fetal toxicity

BID = twice daily; INN = International Nonproprietary Name; IV = intravenously; mCRC = metastatic colorectal cancer; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; Q2W = every 2 weeks; QD = once daily
Source: Product prescribing information

The FDA's Assessment:
FDA agrees with the Applicant's position. In addition, on June 21, 2024, FDA granted accelerated approval to adagrasib in combination with cetuximab for the same indication that is requested in this supplemental application, i.e., the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic CRC, as determined by an FDA-approved test, who received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. While adagrasib with cetuximab is not considered available therapy from a regulatory decision-making perspective, it is available as treatment for patients in the U.S. with previously treated KRAS G12C-mutated locally advanced or metastatic CRC.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
Sotorasib (International Nonproprietary Name; AMG 510) was approved in the US under Accelerated Approval on 28 May 2021 for the treatment of adult patients with *KRAS p.G12C*-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least 1 prior systemic therapy.

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

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
A summary of key regulatory interactions with FDA and correspondence pertaining to the marketing application is provided in Applicant - Table 2.

Applicant - Table 2. Summary of Key Regulatory Activity for Sotorasib in mCRC in the US

Date	Regulatory Interaction/Milestone
01 June 2018	IND submitted for Study 20170543, the first-in-human study with sotorasib entitled "A phase 1, First-in-Human, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of AMG 510 in Subjects With Advanced Solid Tumors With a Specific KRAS Mutation."
23 May 2019	OOPD granted Orphan Drug Designation to sotorasib for the treatment of *KRAS p.G12C*-positive Colorectal Cancer.
21 April 2020	FDA agreed with Amgen's iPSP (Reference ID: 4571203), which included plans to request a full waiver for the development of sotorasib for the treatment of previously treated, locally advanced mCRC with *KRAS p.G12C* mutation in all pediatric age groups.
29 July 2021	Type B (EOP2/PP3) Meeting was held with FDA to discuss the key design elements for the proposed phase 3 Study 20190172 (sotorasib + panitumumab combination) and reach agreement with the FDA on the adequacy of the design of Study 20190172 to support approval of the proposed indication.
17 September 2021	Amgen submitted protocol for Study 20190172 entitled, "A phase 3, multicenter, randomized, open-label, active-controlled study to evaluate efficacy and safety of 2 different doses of sotorasib (960 mg & 240 mg) and panitumumab versus investigator's choice (trifluridine and tipiracil, or regorafenib) in previously treated mCRC subjects with *KRAS p.G12C*-mutated mCRC."
11 April 2023	Amgen submitted a Request for BTD for sotorasib in combination with panitumumab for (b) (4)
01 May 2023	Amgen received Written Responses to a Type C meeting (Reference ID: 5166886) on the structure and format of the planned sNDA for the pivotal phase 3 Study 20190172.
May and June 2023	Amgen and FDA reached agreement on the data presentation in the proposed sNDA. Amgen and FDA discussed and agreed on the pooling strategy that will be used for the Summary of Clinical Efficacy and Integrated Summary of Efficacy.
07 June 2023	FDA granted BTD (Reference ID: 5185990) for sotorasib in combination with panitumumab for (b) (4)

Footnotes are defined on the last page of the table.

Applicant - Table 2. Summary of Key Regulatory Activity for Sotorasib in mCRC in the US

Date	Regulatory Interaction/Milestone
25 September 2023	A Type B pre-sNDA meeting was held with FDA to reach agreement on the totality of data from pivotal phase 3 study (Study 20190172) and supportive studies in CRC (Study 20170543 phase 1 and phase 2 and Study 20190135 Subprotocol H) as sufficient evidence to support submission of an sNDA for full approval in the proposed indication. Amgen and FDA discussed and agreed that OS data from OS primary analysis would be included in the sNDA submission and additional safety data with a data cut matching the OS primary analysis would be provided at the time of the 90-day safety update.

CRC = Colorectal Cancer; FDA = Food and Drug Administration; IND = Investigational New Drug; iPSP = initial Pediatric Study Plan; *KRAS p.G12C* = *KRAS* gene with a mutation resulting in a G12C amino acid substitution; mCRC = metastatic CRC; OOPD = Office Of Orphan Products Development; sNDA = supplemental new drug application; US = United States

The FDA's Assessment:

FDA generally agrees with the Applicant's description of the regulatory activity with the addition of the following:

July 29, 2021: FDA did not object to the absence of a single-agent sotorasib arm in Study 20190172 since preliminary evidence suggested that the combination of sotorasib and panitumumab was more efficacious than single-agent sotorasib.

J**uly 15, 2024**: FDA was notified by the Applicant notified FDA of an ongoing Good Clinical Practice Investigation at an Italian site (33013) for Study 20190172. This investigation was initiated after the Applicant became aware of study data being entered in the paper trial records and electronic systems by unauthorized entity(ies) using the pseudonym of trial investigators.

August 26, 2024: Teleconference held between FDA and the Applicant to discuss forgery identified at site 33013.

September 16, 2024: The Applicant submitted a major amendment to address FDA inquiries regarding the issue of forgery at site 33013. See Section 4.1 for additional information related to the investigation of this site.

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

4.1. Office of Scientific Investigations (OSI)

The imaging contract research organization (CRO), (b) (4), and two foreign clinical investigators (CIs), Drs. Meriggi and Salvatore, were inspected.

The inspection of the imaging CRO, (b) (4), revealed no significant discrepancies, regulatory violations, or Good Clinical Practice (GCP) noncompliance. The inspection of Dr. Meriggi identified enrollment of two ineligible subjects, including one that received exclusionary prior chemotherapy (i.e., trifluridine and tipiracil and intermittent regorafenib). Apart from this finding, based on the results of these inspections, data generated by Dr. Meriggi and by the imaging CRO and submitted by the Applicant appeared acceptable in support of the proposed indication.

At the site of Dr. Salvatore (site 33013), the efficacy data appeared acceptable. The safety data, however, were deemed unreliable due to multiple fraudulent activities committed by a clinical research associate (CRA). As a result of the extent of fraudulent activity that was discovered, OSI recommended removal of all safety data obtained at this site from the trial analysis. The totality of the inspection findings and Applicant's responses to FDA's Information Requests identified three types of fraud committed by a CRA employed by a CRO, who was responsible for trial monitoring at Dr. Salvatore's site: (1) signature and document forgery on paper source documents; (2) unauthorized access to three trial electronic systems using fraudulent user accounts created with fake email addresses – these trial electronic systems accessed by the CRA included the Medidata RAVE Electronic Data Capture system (Medidata) and (b) (4) Imaging Portal ((b) (4)) system, which housed the imaging data for the primary efficacy endpoint assessment; and (3) unauthorized access to the (b) (4) system through stolen/borrowed login credentials of a site radiology technician.

OSI reviewed the imaging data flow and audit trail summaries for the (b) (4) system submitted by the Applicant and determined that the imaging data in the (b) (4) system, which were assessed by the Blinded Independent Central Review (BICR), appeared unimpacted by the fraudulent email accounts. However, because this CRA also used existing legitimate credentials and accessed the (b) (4) system at the site level, audit trails could not distinguish his actions from those conducted by the legitimate user. To assess the potential impact, OSI reviewed additional findings from the Applicant-conducted site data audit and identified no apparent discrepancies in the imaging data transferred from the site to the central imaging CRO or the quality control (QC) responses that would impact the overall interpretation of efficacy. Therefore, the efficacy data generated by Dr. Salvatore's site appeared acceptable in support of the proposed indication.

The signature and document forgery impacted the safety data for six enrolled patients over approximately 2 years, with the majority of impacted records consisting of complete electronic medical record (EMR) visit notes documenting safety data such as adverse events (AE), vital signs, physical examinations as well as concomitant medications. Since the EMR used by the site was unvalidated, there was no way to verify the forged records, and therefore, these safety data were unverifiable. In addition, the two fraudulent accounts conducted 6,228 audit actions in the Medidata system impacting 11 patients at this site across a range of Case Report Form (CRF) domains (i.e., screening assessments, concomitant medications, safety assessments, etc.). All source records impacted by forgeries cannot be used to verify these altered EDC data entries. Finally, while OSI did not have evidence that the site's EMR was also breached, because the site's unvalidated EMR lacks both an audit trail and timestamped signatures, we cannot exclude the possibility of additional unauthorized access to the EMR, potentially making all paper source documents unverifiable. Therefore, based on the extent of these fraudulent activities, OSI recommends removal of safety data obtained at Dr. Salvatore's site from the trial analysis.

4.2. Product Quality

No new information is provided in the current submission.

4.3. Clinical Microbiology

No new information is provided in the current submission.

4.4. Devices and Companion Diagnostic Issues

Qiagen submitted a 180 Day PMA Supplement (P110027/S018) for the *therascreen* KRAS RGQ PCR Kit to expand the indication for use as an aid in the identification of patients with KRAS G12C-mutated CRC for treatment with sotorasib with panitumumab. The Qiagen Clinical Performance Study (NCT0534775) occurred during the patient screening portion of the pivotal trial supporting this application, Study 20190172. The positive percent agreement between *therascreen* KRAS RGQ PCR Kit and different local tests was 95% (n=187/199). No KRAS G12C-negative samples based on local tests were submitted for comparison with the *therascreen* KRAS RGQ PCR Kit. CDRH recommended the approval to expand the indication for use of the *therascreen* KRAS RGQ PCR Kit as an aid in the identification of patients with KRAS G12C-mutated CRC for treatment with sotorasib with panitumumab.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Sotorasib is an inhibitor of KRAS G12C, a tumor restricted, mutant oncogenic form of the RAS GTPase, KRAS. In a murine patient derived colorectal tumor xenograft model, the combination of sotorasib and panitumumab, an EGFR antagonist, had increased antitumor activity compared to either sotorasib or panitumumab alone.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:
Not applicable.

5.3. Pharmacology

The Applicant's Position:
Amgen conducted 3 nonclinical pharmacology studies that are described below and are provided in Module 4.2.1.1, Primary Pharmacodynamics.

- Study R20190131: Once Daily Dosing of AMG 510 Inhibited Tumor Growth in a Human *KRAS p.G12C* CRC Patient-Derived Xenograft Model in Female NSG Mice
- Study 154222: The Effect of AMG 510 on Tumor Growth in a Human *KRAS p.G12C* CRC Patient-Derived Xenograft in Female NOD/SCID Mice
- Study 154220: The Effect of AMG 510 in Combination with the Human anti-EGFR Antibody, Panitumumab, on Tumor Growth in the Human *KRAS p.G12C* CRC PDX (#383955) Model in Female NOD/SCID IL2rg NSG Mice

The FDA's Assessment:
See FDA's Executive Summary.

5.4. ADME/PK

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

5.5. Toxicology

The Applicant's Position:

Not applicable.

The FDA's Assessment:
Not applicable.

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Primary Reviewer Supervisor

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6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

The Applicant is seeking approval of sotorasib in combination with panitunumab for the treatment of patients with KRAS G12C -mutated metastatic colorectal cancer (mCRC) based on data from Study 20190172 (CodeBreaK 300).

No clinically relevant difference in the pharmacokinetic (PK) between the two sotorasib dosages was detected. Mean pre-dose and end-of-infusion (EOI) panitumumab concentrations on Cycle 2 day 1 were comparable across the two sotorasib dosage groups and were consistent with what has been observed previously with panitumumab monotherapy.

The results of population PK (popPK) and exposure-response (E-R) analyses were consistent with previously conducted analyses. There were no clinically significant differences observed in the PK of sotorasib based on age, sex, race, body weight, tumor size, mild and moderate renal impairment, and mild hepatic impairment. The results of the E-R analysis for efficacy are confounded by patients' baseline disease on PK and efficacy and are limited by the overlapping exposures between the 240 mg and 960 mg sotorasib groups. Although there was an apparent positive E-R relationships for Grade ≥3 adverse events (AEs) and gastrointestinal (GI) AE, this analysis was also limited by overlapping exposures. The PK and E-R relationship could not differentiate sotorasib doses of 960 mg from 240 mg and the acceptability of 960 mg dosage is primary based on a favorable clinical benefit-risk analysis.

Recommendation:

The Office of Clinical Pharmacology has reviewed the information contained in NDA 214665. This supplement is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations and comments are summarized below:

Supportive evidence of effectiveness	Sotorasib 960 mg in combination panitumumab appears more effective than the control arm based on PFS and ORR in Study CodeBreak 300. Similar to the E-R relationship observed in other indications, the impact of baseline disease on PK and efficacy and overlapping sotorasib exposure precluded the ability to discern exposure-response for efficacy. No E-R safety concern was identified for

	the narrow exposure range observed in the study. The acceptability of 960 mg is primarily based on a favorable clinical benefit-risk analysis.
General dosing instructions	The proposed dosage is 960 mg sotorasib once daily (QD) in combination with 6 mg/kg panitumumab every 2 weeks (Q2W) (b) (4) The proposed combination therapy dosages are the same as the previous approved monotherapy dosages for sotorasib and panitumumab.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose adjustments are recommended based on intrinsic or extrinsic factors. No clinically significant intrinsic or extrinsic factors including age, sex, race, body weight, tumor size, mild and moderate renal impairment, and mild hepatic impairment were identified that affect the PK of sotorasib.
Labeling	The proposed labeling is acceptable upon the Applicant and FDA reaching agreements to the FDA recommended revisions to the labeling.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

The clinical pharmacology of sotorasib was evaluated in patients with previously treated mCRC with KRAS p.G12C mutations across three studies: Studies 20190172, 20190135 Subprotocol H, and 20170543.

Study 20190172 evaluated sotorasib 240 mg and 960 mg in combination with 6 mg/kg panitumumab. After administration of sotorasib, median time to reach maximum observed plasma concentration (t_{max}) was approximately 1 hour for cycle 1 day 1 and cycle 1 day 15 for both dose groups. No sotorasib accumulation was observed on cycle 1 day 15, with a mean accumulation ratio of 0.845 for the 240 mg dose group and 0.663 for the 960 mg dose group. Steady-state plasma concentrations were achieved by cycle 2 day 1 for both 960 and 240 mg dose groups. Less than dose proportional, and similar, pharmacokinetics (PK) were observed between the 240 and 960 mg dose groups. No impact on panitumumab PK was observed when

administered with sotorasib. Exposure of sotorasib was similar to that observed in the monotherapy.

Study 20190135 Subprotocol H, cohorts A and D included subjects with KRAS p.G12C-mutated mCRC receiving 960 mg daily sotorasib in combination with 6 mg/kg panitumumab intravenous (IV) every 2 weeks. Sotorasib was absorbed with a median t_{max} of 1.1 hour on cycle 1 day 1 and cycle 1 day 8. No accumulation was observed with a mean accumulation ratio of 0.733. No impact on sotorasib exposures were observed when co-administered with panitumumab.

Study 20170543 included previously treated subjects with KRAS p.G12C-mutated mCRC receiving sotorasib monotherapy. After administration of sotorasib monotherapy, median t_{max} was approximately 2.0 and 1.5 hours for cycle 1 day 1 and cycle 1 day 15, respectively. No accumulation was observed on cycle 1 day 8, with a mean accumulation ratio of 0.542. Exposure levels for sotorasib 960 mg in subjects with mCRC were similar to/consistent with exposure levels for sotorasib 960 mg in subjects with NSCLC across phase 1 and phase 2 results in Study 20170543.

The clinical pharmacology key conclusions from the exposure-response (ER) analyses are summarized below. Exposure-response analyses for sotorasib in the mCRC indication showed that the independent effect of baseline disease burden on PK and efficacy outcomes limited the ability to interpret the ER relationships for sotorasib. This was also the case for ER analyses of sotorasib in the NSCLC indication.

Significantly positive ER relationships were only identified for grade ≥ 3 adverse events and grade ≥ 3 gastrointestinal (GI) adverse events. No significant ER relationship was found for overall grade ≥ 3 treatment-related adverse events, including specific grade ≥ 3 treatment-emergent adverse events of interest such as diarrhea and hepatotoxicity. Due to the small number of observations (event number ≤ 1) for grade ≥ 3 AST or ALT increase, no positive ER relationships for these events were observed.

Ability to assess ER relationships was limited by the independent effects of baseline disease severity (quantified by baseline tumor size, Eastern Cooperative Oncology Group [ECOG] performance status) on sotorasib exposure, efficacy, and safety.

The Applicant's Position:

Overall, sotorasib exposure was similar for subjects in Studies 20190172, 20190135 Subprotocol H (part 2 cohorts A and D), and 20170543. In subjects with mCRC, the PK at 960 mg were consistent with the exposure levels seen in subjects with NSCLC. Exposures at the 240 mg dose were similar to those observed at the 960 mg dose. No PK drug-drug interactions were observed between sotorasib and panitumumab. Similar to the relationship observed in NSCLC, the impact of baseline disease on sotorasib exposure precluded the ability to discern ER for efficacy. Significantly positive ER relationships were identified for overall grade $\geq$ 3 adverse events and grade $\geq$ 3 GI adverse events. No significant ER relationships for overall grade $\geq$ 3 treatment-related adverse events, specific to grade $\geq$ 3 adverse events of interest, including

diarrhea, ALT increase, AST increase, or hepatotoxicity were identified. The PK/pharmacodynamics (PD) relationships support sotorasib 960 mg as the recommended dose in combination with panitumumab for patients with mCRC.

The FDA's Assessment:
FDA agrees with the Applicant that the PK characteristics of sotorasib are generally similar across tumor types as a monotherapy or in combination. No impact on sotorasib PK was observed when administered with panitumumab. Sotorasib single dose exposure at 240 mg and 960 mg overlapped, which indicates that sotorasib has a saturable absorption. See Section 6.3 for detailed discussion.

In general, FDA agrees with the Applicant's key conclusion regarding the E-R analyses. The results in Study 20190172 are generally consistent with previously reported data in patients with NSCLC. The impact of baseline disease on PK and efficacy confounded the interpretability of the E-R relationship for efficacy. Apparent positive E-R relationships were observed for overall Grade ≥ 3 adverse event (AE) and GI related AE. However, this analysis is limited by a narrow exposure range caused by overlapping exposures in patients administered 240 mg and 960 mg sotorasib. The E-R relationships could not differentiate 960 mg from 240 mg and therefore are not informative to support dosage selection.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:
In subjects with *KRAS p.G12C*-mutated mCRC, steady-state plasma concentrations were achieved by cycle 2 day 1 for both 960 and 240 mg doses of sotorasib. Exposures at the 240 mg dose were similar to those observed at the 960 mg dose. The PK at 960 mg were consistent with the exposure levels seen in subjects with NSCLC. Additionally, sotorasib exposure at 960 mg was similar for subjects in Studies 20170543, 20190172, and 20190135 Subprotocol H (part 2 cohorts A and D). Furthermore, no PK drug-drug interactions were observed between sotorasib and panitumumab.

The ER analysis (Section 3.2 of Module 2.7.2, Summary of Clinical Pharmacology) evaluating the relationship between sotorasib exposure in subjects with mCRC showed that the independent effect of baseline disease burden on PK and efficacy outcomes limited the ability to interpret the ER relationships for sotorasib. This was also the case for ER analyses of sotorasib in the NSCLC indication.

Exposure-response analysis of safety events in subjects with mCRC receiving sotorasib in Studies 20190172 and 20190135 Subprotocol H, identified significantly positive ER relationships for overall grade ≥ 3 adverse events and ≥ 3 GI adverse events. No significant ER relationships

for overall grade ≥ 3 treatment-related adverse events, specific grade ≥ 3 adverse events of interest, including diarrhea, ALT increase, AST increase, or hepatotoxicity, were identified.

The Applicant's Position:
The dose of sotorasib 960 mg QD + panitumumab is effective and generally well tolerated in subjects with *KRAS p.G12C*-mutated mCRC.
The efficacy and safety results from Studies 20190172, and 20190135 Subprotocol H and the results from the integrated analyses confirm that sotorasib 960 mg QD + panitumumab is an effective and safe dose for reducing tumor burden in subjects with mCRC. The median (95% CI) PFS was 3.9 months (3.6, 5.8) in the sotorasib 240 mg + panitumumab group, compared with 2.0 months (1.9, 3.9) in the control group. The median (95% CI) PFS was 5.6 months (4.2, 6.3) in the sotorasib 960 mg + panitumumab group, compared with 2.0 months (1.9, 3.9) in the control group.

The FDA's Assessment:
FDA generally agrees with the Applicant's position. Exposure of both sotorasib and panitumumab were similar between the two dosage groups in Study 20170543 and consistent with the previous monotherapy exposures. Given the confounding effect of the baseline disease on PK and ORR and overlapping exposures, the results of the E-R analyses for efficacy and safety were inconclusive. FDA agrees with Applicant's assessment that the PK characteristics of sotorasib were similar in patients with NSCLC at the equivalent dosage of sotorasib. See section 6.3.1 for additional detail.

6.2.2.2. Therapeutic Individualization

Data:
The influence of demographic and clinical subject characteristic factors on the PK of sotorasib were investigated using population PK (Section 3.1 of Module 2.7.2, Summary of Clinical Pharmacology).

The reference population PK model (Report 157092) developed with data from subjects with NSCLC, CRC and other tumor types was consistent with the PK of sotorasib administered as monotherapy or in combination with panitumumab in subjects with mCRC enrolled in Studies 20170543, 20190135 Subprotocol H, and 20190172. Bodyweight, age, sex, race, country, albumin, chronic kidney disease stage based on estimated glomerular filtration rate evaluated by Modification of Diet in Renal Disease formula, and overall hepatic impairment scores evaluated by National Cancer Institute Organ Dysfunction Working Group criteria did not show significant effects on sotorasib PK. Female sex, Asian race, low albumin and baseline disease were found to significantly affect sotorasib PK, however none of these covariates resulted in clinically meaningful changes in the exposure of sotorasib. Overall, dose adjustment of sotorasib is not needed for any of the covariates tested.

The Applicant's Position:
None of the covariates evaluated in the reference model resulted in clinically meaningful changes in exposure and therefore do not warrant a dose adjustment.

The FDA's Assessment:
FDA generally agrees with the Applicant's position. The effect of evaluated covariates including age (32 to 88 years), sex, race (710 White, 45 Black, 143 Asian), body weight (37 to 158 kg), line of therapy, ECOG PS (0,1), mild or moderate CKD (eGFR) or mild hepatic impairment on the sotorasib exposure are not considered clinically meaningful. This is consistent with previous population PK analysis.

6.2.2.3. Outstanding Issues

Data:
Not applicable.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:
Pharmacokinetics

- Steady-state plasma concentrations were achieved by cycle 2 day 1 for both 960 and 240 mg doses of sotorasib in subjects with CRC.
- In subjects with CRC, the PK at 960 mg were consistent with the exposure levels seen in subjects with NSCLC.
- Exposures at the 240 mg dose were similar to those observed at the 960 mg dose.
- No PK drug-drug interactions were observed between sotorasib and panitumumab.
- Sotorasib exposure at 960 mg was similar for subjects receiving sotorasib monotherapy (Study 20170543), and subjects receiving sotorasib in combination with panitumumab (20190172 and 20190135 Subprotocol H part 2 cohorts A and D).

Exposure-Response

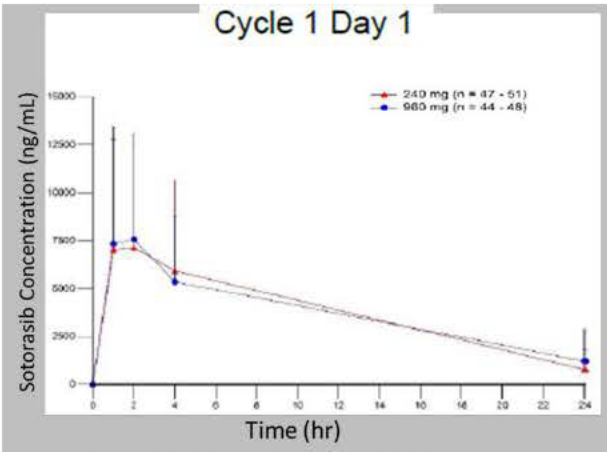
- Significantly positive ER relationships were identified for overall grade ≥ 3 adverse events and grade ≥ 3 GI adverse events.
- No significant ER relationships for overall grade ≥ 3 treatment-related adverse events, specific grade ≥ 3 adverse events of interest, including, diarrhea, ALT increase, AST increase or hepatotoxicity, were identified.
- Similar to the relationship observed in NSCLC, the impact of baseline disease on sotorasib exposure precluded the ability to discern ER for efficacy.

The Applicant's Position:
Sotorasib pharmacokinetics were consistent across studies, disease indication and with or without panitumumab. No drug interactions were observed between sotorasib and panitumumab. No dosing adjustments are necessary based on sex, body weight, race, age, and renal or hepatic function.

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

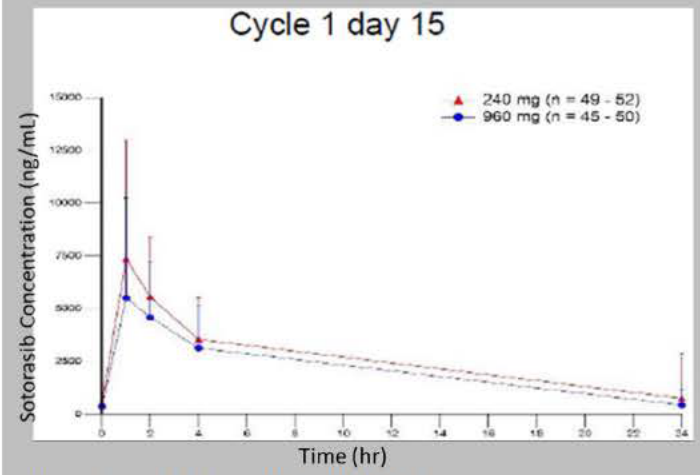
Sotorasib exposures, as assessed by geometric mean of the maximum concentration (C_{max}) and area under the curve from time 0 to 24 hours post-dose (AUC_{0-24}), were similar in the 240 mg and 960 mg dose group following administration of a single dose and multiple doses (**Table 3**). Despite a 4-fold increase in doses (**Figure 1**, **Figure 2**), AUC_{0-24} and C_{max} differed by 10% between 240 mg and 960 mg on Cycle 1 Day 1. There is no accumulation of sotorasib observed on Cycle 1 Day 8 following the multiple doses and the mean accumulation ratio (AR) was 0.9 and 0.7 following administration of 240 and 960 mg sotorasib, respectively. AUC_{0-24} is similar, but C_{max} is 40% higher for the 960 mg compared to 240 mg on Cycle 1 Day 15. FDA agreed that exposures at the 240 mg dose were similar to those observed at the 960 mg dose following single dose and multiple doses. FDA also agreed that there is no apparent impact of panitumumab on sotorasib PK in Study Codebreak 300 as exposure levels for sotorasib 960 mg in combination with panitumumab were similar to the exposure levels for sotorasib 960 mg monotherapy (**Table 4**).

Figure 1. Mean Concentration-Time Profiles Following Single-dose of Sotorasib 240 or 960 mg in Combination with Panitumumab.



Source: Figure 11-1 of Study 20190172

Figure 2. Mean Concentration-Time Profiles Following Multiple-dose of Sotorasib 240 or 960 mg in Combination with Panitumumab.



Source: Figure 11-1 of Study 20190172

Table 3. Descriptive Statistics of Geometric Mean Sotorasib Pharmacokinetic Parameter Estimates Following Single-Dose and Multiple-Dose Oral Administration of 240 or 960 mg Sotorasib in Study 20190172

Time Point	Dosage/ Comparison	AUC_{0-24h} (hr. ng/mL)	C_{max} (ng/mL)	T_{max} (hr)
Cycle 1 Day 1	240 mg (n=52)	73,600 (64%)	7,990 (67%)	1.1 (0.8, 4.5)
	960 mg (n= 52)	77,900 (59%)	7,370 (67%)	1.3 (1, 4)

	Geometric Mean Ratio	0.9	1.1	
Cycle 1 Day 15	240 mg (n=46)	46,300 (57%)	6,970 (62%)	1 (0, 2.4)
	960 mg (n=49)	45,400 (53%)	4,930 (70%)	1.1 (0.9, 4.5)
	Geometric Mean Ratio	1.0	1.4	

AUC_{0-24} = area under the concentration-time curve (AUC) from time 0 to 24 hours post-dose; C_{max} = maximum observed plasma concentration; t_{max} = time to reach C_{max}
Source: Table 11-1 of Study 20190172 CSR

Table 4. Comparison of Geometric Mean (%CV) of Sotorasib Exposures Across Studies

	Sotorasib + Panitumumab		Monotherapy Sotorasib
AUC_{0-24} (hr.ng/mL)	Codebreak 300 960 mg (CRC) N=60	Study 20190135 960 mg (CRC) N = 60	20170543 Ph 2 Part B 960 mg (NSCLC) N =98
Day 1	77900 (59%)	66600 (56%)	76200 (66%)
Day 8	N/A	49800 (53%)	47600 (80%)
Day 15	45400 (53%)	N/A	N/A

AUC_{0-24} = area under the concentration-time curve (AUC) from time 0 to 24 hours post-dose
Source: Table 2.7.4.12.9.1, Applicant's Pooled Safety Outputs in Module 5.3.5.3.

The Applicant collected sparse PK sampling of panitumumab on Cycle 1 and Cycle 2 D1 pre-dose and EOI. The sparse PK sampling was reasonable to support PK analyses of panitumumab. Mean pre-dose and end-of-infusion panitumumab concentrations on Cycle 2 Day 1 were comparable across the two dosage groups (**Table 5**). FDA agreed that PK of panitumumab in Study CodeBreak 300 were consistent with previously reported PK data from analyses of y single agent panitumumab and no update is required for the popPK and E-R analyses.

Table 5. Mean Panitumumab Concentrations Following Multiple IV Infusion Administrations of 6 mg/kg Panitumumab in Patients Cross Studies

Studies	Sample Time	Trough, µg/mL	Peak, µg/mL
Panitumumab 6 mg/kg Q2W + 240 mg sotorasib			
20190172 (N= 46)	Cycle 2 Day 1	42.6 (56%)	150 (41%)
Panitumumab 6 mg/kg Q2W + 960 mg sotorasib			
20190172 (N= 46)	Cycle 2 Day 1	42.1 (51 %)	166 (28%)
Monotherapy Panitumumab 6 mg/kg Q2W			
20030167 (N=46)	Cycle 2 Day 15	33 (51%)	152 (29%)
20030250 (N=42)	Cycle 2 Day 15	33 (54%)	175 (23%)

Source: Table 2.7.4.12.9.1, Applicant's Pooled Safety Outputs in Module 5.3.5.3.

Immunogenicity data were not collected for any studies of panitumumab in combination with sotorasib. The current incidences of antidrug antibodies (ADA) for panitumumab were derived from Integrated Immunogenicity Reports for administration as a monotherapy (dated 09 September 2013) and in combination with oxaliplatin-based chemotherapy (dated 26 August 2013). This data was previously reviewed and verified in the respective NDAs. However, ADA incidence rates from the phase I panitumumab studies and as determined by two screening assay methods (Biacore and ELISA assays) were also reported in the label. FDA updated the ADA incidence rate as determined by Biacore assay only in Section 12.6, as this assay detected a higher ADA incidence rate. FDA only reported available ADA data from the pivotal and registrational studies, to be consistent with the immunogenicity labeling guidance and the current labeling practice.

6.3.2. **Clinical Pharmacology Questions**

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

Data:
Sotorasib PK were consistent across studies, disease indication and with or without panitumumab. No dosing adjustments are necessary based on sex, body weight, race, age, and renal or hepatic function.

Ability to assess ER relationships was limited by the independent effects of baseline disease severity (quantified by baseline tumor size, ECOG performance status) on sotorasib exposure, efficacy, and safety. However, treatment with sotorasib 960 mg in combination with panitumumab resulted in a 30% reduction in the hazard of death when compared with control treatment (hazard ratio [HR] 0.70 [95% CI: 0.41, 1.18], 2-sided p-value = 0.20). Treatment with sotorasib 240 mg + panitumumab resulted in 17% reduction in the hazard of death when compared with control treatment (HR 0.83 [95% CI: 0.49, 1.39], 2-sided p-value = 0.50). A sotorasib dose of 960 mg QD demonstrated higher median PFS, ORR, and disease control rate (DCR) than a sotorasib dose of 240 mg QD, when combined with panitumumab, although the study was not statistically powered for this comparison.

No significant ER relationships for overall grade ≥ 3 treatment-related adverse events, specific to grade ≥ 3 adverse events of interest, including diarrhea, ALT increase, AST increase, or hepatotoxicity were identified. Significantly positive ER relationships were identified for overall grade ≥ 3 adverse events and grade ≥ 3 GI adverse events. When safety across both sotorasib doses (240 and 960 mg QD) was compared, the safety profile of the combination treatment was generally comparable.

The Applicant's Position:
The proposed dose is effective and generally well tolerated in subjects with KRAS p.G12C mCRC. The proposed dosing regimen is supported by the observed efficacy and safety data and demonstrates a favorable benefit-risk profile.

The FDA's Assessment:
FDA generally agrees with the Applicant's position. However, the E-R analysis for efficacy is confounded by the effect of baseline disease on PK and efficacy and is limited by the overlapping exposures of the two dosages that are four-fold different. Although the ORR for 960 mg dosage (26%) was numerically higher compared to 240 mg (6%), univariate and multivariate analyses did not identify a positive E-R relationship. The PK and ER relationships in general are not informative to support the dosage selection and could not differentiate 960 mg from 240 mg. The acceptability of 960 mg is primarily based on clinical benefit-risk analysis.

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

Data:
See Section 6.2.2.1, General Dosing.

The Applicant's Position:
The proposed dose is effective and generally well tolerated in subjects with *KRAS p.G12C*-mutated mCRC. The proposed dosing regimen is supported by the observed efficacy and safety data and demonstrates a favorable benefit-risk profile. No significant exposure-safety relationships for treatment-emergent adverse events of interest were identified.

The FDA's Assessment:
FDA generally agree with Applicant's position. There is no concern related to the analysis for E-R safety. Positive trends were observed between the overall Grade ≥3 TEAE and overall Grade GI related TEAE with sotorasib exposures, while no significant positive relationships for specific Grade ≥3 TEAEs of interest were identified. Similar to the E-R analysis for efficacy, the E-R analysis for safety measures is limited by the narrow exposure range due to the overlapping exposures of the two dosages. Confidence intervals for the probability of AE in each exposure quartiles also overlap.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

Data:
See Section 6.2.2.2, Therapeutic Individualization.

The Applicant's Position:
Intrinsic covariates of age, body weight, sex, race, country, ALT, AST, bilirubin, number of prior anticancer therapies, renal function, and hepatic impairment did not show clinically meaningful effects on sotorasib PK, suggesting no dose adjustments are required for these intrinsic factors.

The FDA's Assessment:
FDA agrees with the Applicant's position. None of the covariates including age, sex, race, body weight, tumor size, mild and moderate renal impairment, and mild hepatic impairment evaluated in the PPK analysis resulted in clinically meaningful changes in exposure and therefore do not warrant a dose adjustment for these intrinsic factors.

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

Data:
There are no new data for clinically relevant food-drug in this submission. No pharmacokinetic drug interactions were observed between sotorasib and panitumumab when administered in combination.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
FDA agrees with the Applicant position. There is no new data regarding food-drug interactions. No drug-drug interaction was predicted between sotorasib and panitumumab given panitumumab is a monoclonal antibody with a low propensity to interact with small molecule drugs.

X	X
Primary Reviewer	Team Leader
Yue Xiang Ye Xiong	Jason Moore Youwei Bi

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:
The clinical studies supporting this supplemental marketing application for the indication in mCRC are provided in Applicant - Table 6. The primary study to support efficacy and safety is the pivotal phase 3 Study 20190172.

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Applicant - Table 6. Listing of All Clinical Studies Including in the Supplemental Marketing Application

Study Number	Study Objectives	Study Design and Type of Control	Investigational Products; Dosage Regimens; Route of Administration	Number of Subjects Enrolled (Actual/Planned)	Key Entry Criteria	Duration of Treatment	Study Status[a]/ Type of Report
Population Pharmacokinetics Study Reports (Module 5.3.3.5)							
157509	characterize the PK of sotorasib	Population PK modelling study	per studies included in analyses	304[b]	subjects with metastatic CRC enrolled in studies included in analyses	-	complete/ Population PK Report
Patient Pharmacokinetics/Pharmacodynamics and Initial Tolerability Study Reports (Module 5.3.4.2)							
157508	characterize exposure-response relationships	exposure-response analysis	per studies included in analyses	164[b]	subjects with metastatic CRC enrolled in studies included in analyses	-	complete/ Exposure-Response Report
Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication (Module 5.3.5.1)							
20190172 (pivotal)	efficacy, safety, tolerability, PROs, PK	phase 3 multicenter, randomized 1:1:1, open-label, active-controlled	sotorasib (960 or 240 mg) PO QD + panitumumab (6 mg/kg) IV Q2W Control group: investigator's choice (trifluridine and tipiracil or regorafenib)	160/ approximately 153	men or women ≥ 18 years of age with metastatic CRC with *KRAS p.G12C* mutation and refractory to fluoropyrimidine and oxaliplatin and irinotecan (unless contraindicated) and received anti-PD-1 therapy if MSI-H (unless contraindicated) with approved indication in country/region	until disease progression[c]	ongoing/ Full CSR

Footnotes are defined on the last page of the table.

Applicant - Table 6. Listing of All Clinical Studies Including in the Supplemental Marketing Application

Study Number	Study Objectives	Study Design and Type of Control	Investigational Products; Dosage Regimens; Route of Administration	Number of Subjects Enrolled (Actual/Planned)	Key Entry Criteria	Duration of Treatment	Study Status[a]/ Type of Report
Uncontrolled Studies (Module 5.3.5.2)							
20170543	safety, tolerability, efficacy, PK, PD	phase 1/2, monotherapy and in combination, nonrandomized/ randomized, open-label, dose exploration	oral doses of sotorasib (CRC monotherapy cohorts only)	Phase 1 60 (CRC) / 283 (all tumor types)	men or women (≥ 18 years) with previously treated advanced solid tumors with *KRAS p.G12C* mutation including CRC with ≥ 2 prior lines of therapy for metastatic disease including nivolumab or pembrolizumab if MSI-H and clinically able to receive checkpoint inhibitors and is approved for that indication in the country/region	until disease progression[c]	ongoing/
			monotherapy treatment groups				Full CSR Phase 1 CRC
Phase 1 Part 1a			180, 360, 720, or 960 mg sotorasib QD				
Part 1b			480 mg sotorasib BID with food				
Part 1d			960 mg sotorasib QD with food				
Part 2a			960 mg sotorasib QD				
Part 2b			480 mg sotorasib BID with food				
Part 2d			960 mg sotorasib QD with food				

Footnotes are defined on the last page of the table.

Applicant - Table 6. Listing of All Clinical Studies Including in the Supplemental Marketing Application

Study Number	Study Objectives	Study Design and Type of Control	Investigational Products; Dosage Regimens; Route of Administration	Number of Subjects Enrolled (Actual/Planned)	Key Entry Criteria	Duration of Treatment	Study Status[a]/ Type of Report
Uncontrolled Studies (Module 5.3.5.2) (continued)							
20170543 (continued)							
Phase 2 Part A	safety, tolerability, efficacy, PK, PD, PRO	monotherapy, multicenter nonrandomized, open-label	960 mg sotorasib PO (recommended phase 2 dose)	62/60 (subjects with CRC)	men or women (≥ 18 years) with previously treated advanced solid tumors with *KRAS p.G12C* mutation that was confirmed by central testing prior to enrollment including metastatic CRC. Subjects had progressed after receiving fluoropyrimidine and oxaliplatin and irinotecan. For subjects with CRC whose tumors were MSI-H, at least 1 of the prior systemic regimens must have included an anti-PD1 therapy if they were clinically able to receive these inhibitors and 1 of these agents was approved for that indication in the country/region.	until disease progression[c]	Full CSR Phase 2 CRC

Footnotes are defined on the last page of the table.

Applicant - Table 6. Listing of All Clinical Studies Including in the Supplemental Marketing Application

Study Number	Study Objectives	Study Design and Type of Control	Investigational Products; Dosage Regimens; Route of Administration	Number of Subjects Enrolled (Actual/Planned)	Key Entry Criteria	Duration of Treatment	Study Status[a]/ Type of Report
Other Studies (Module 5.3.5.4)							
20190135	Master Protocol: Phase 1b study to evaluate the safety, tolerability, PK, and efficacy of multiple investigational regimens of sotorasib in subjects with advanced solid tumors with *KRAS pG12C* mutation as assessed by molecular testing of tumor biopsy specimens						
Subprotocol H	safety, tolerability, PK, efficacy	phase 1b, nonrandomized, open-label	sotorasib PO QD in combination with panitumumab IV Q2W	121/up to 175	adult subjects (≥ 18 years) with previously treated advanced solid tumors with *KRAS p.G12C*	until disease progression[c]	ongoing/ Full CSR
Part 1(Dose Exploration) Cohort A			sotorasib (960, 720, or 480 mg) PO QD + panitumumab (6 mg/kg) IV Q2W (used to identify the recommended phase 2 dose)	8/up to 15	metastatic CRC with at least one prior therapy		
Part 2 (Dose Expansion) Cohort A			sotorasib 960 mg PO QD + panitumumab (6 mg/kg) IV Q2W (recommended phase 2 dose)	40/up to 40	KRASG12C inhibitor naïve metastatic CRC, previously treated with fluoropyrimidine, oxaliplatin, irinotecan, anti-angiogenic agents, and if MSI-H, a checkpoint inhibitor (if approved in the country/region)		

Footnotes are defined on the last page of the table.

Applicant - Table 6. Listing of All Clinical Studies Including in the Supplemental Marketing Application

Study Number	Study Objectives	Study Design and Type of Control	Investigational Products; Dosage Regimens; Route of Administration	Number of Subjects Enrolled (Actual/Planned)	Key Entry Criteria	Duration of Treatment	Study Status[a]/ Type of Report
20190135 Subprotocol H *Part 2 (Dose Expansion) (continued)*							
Cohort B			sotorasib 960 mg PO QD + panitumumab (6 mg/kg) IV Q2W	20/up to 20	any *KRAS p.G12C*-mutated solid tumor refractory to KRASG12C inhibitor therapy		
Cohort C			sotorasib 960 mg PO QD + panitumumab (6 mg/kg) IV Q2W	26/ up to 40	*KRAS p.G12C*-mutated NSCLC, KRASG12C inhibitor naïve, and previously treated with at least 1 prior systemic therapy		
Cohort D			sotorasib 960 mg PO QD + panitumumab (6 mg/kg) IV Q2W	20/up to 20	*KRAS p.G12C*-mutated metastatic CRC, KRASG12C inhibitor naïve, received only 1 prior regimen for metastatic disease		
Cohort H			sotorasib 960 mg PO QD + panitumumab (6 mg/kg) IV Q2W	7/up to 40	metastatic pancreatic cancer, KRASG12C inhibitor naïve, received ≥ 1 prior treatment for metastatic disease or standard of care chemotherapy refused or contraindicated		

BID = twice daily; CRC = colorectal cancer; CSR = clinical study report; IV = intravenous; KRAS = Kirsten rat sarcoma viral oncogene homolog; *KRAS p.G12C* = KRAS gene with a mutation resulting in a G12C amino acid substitution at the protein level; MSI-H = microsatellite instability - high; NSCLC = non-small cell lung cancer; PD = pharmacodynamics; PK = pharmacokinetics; PO = administered orally; PRO = patient-reported outcome; QD = once daily; Q2W = every 2 weeks

[a] Status as of 01 October 2023. The table provides a listing of all clinical studies conducted with sotorasib that are included in this submission. Integrated cross-study efficacy analysis: Studies 20190172, 20170543 (CRC cohorts in phase 1 and phase 2), and 20190135 Subprotocol H (CRC cohorts Part 2 Cohorts A, B, and D). Integrated safety analysis: Studies 20190172, 20170543 (CRC sotorasib monotherapy cohorts in phase 1 and phase 2), and 20190135 Subprotocol H (Part 1 cohort A, Part 2 cohorts A, B, C, D, and H).

[b] Number of subjects contributing data included in the analysis.

[c] Treatment with investigational product continues until disease progression, intolerance of treatment, initiation of another anticancer therapy, withdrawal of consent or death.

The Applicant's Position:
All studies pertinent to the evaluation of efficacy and safety for the indication in mCRC per current supplemental marketing application are summarized above in Applicant - Table 6. The primary support for the efficacy of the proposed indication is based on the results from the phase 3 pivotal Study 20190172 in previously treated subjects with *KRAS p.G12C*-mutated mCRC.

The FDA's Assessment:
FDA agrees with the Applicant's position. In this review, FDA primarily relied on Study 20190172 for the assessment of safety and efficacy of sotorasib in combination with panitumumab for the treatment of adult patients with KRAS G12C mutated mCRC. FDA also reviewed the adverse event and laboratory datasets for Study 20170543 and Study 20190135 Subprotocol H that Amgen submitted to support the safety assessment.

As part of the review strategy, FDA validated all the results for the pivotal trial, Study 20190172. For the supportive trials, Study 20170543 and Study 20190135 Subprotocol H, FDA did not validate the datasets and results, however, the efficacy results as submitted by the Applicant for these trials were considered as part of the contribution of components and safety assessments.

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8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 20190172 (Phase 3), Study 20190135 Subprotocol H (Phase 1b), and Study 20170543 (Phase 1 and Phase 2 Part A)

The Applicant's Description

The efficacy of sotorasib for the treatment of patients with *KRAS p.G12C*-mutated mCRC is demonstrated by the following results:

- Efficacy results from the pivotal phase 3 Study 20190172
- Supporting efficacy results from Study 20190135 Subprotocol H
- Supporting efficacy results from Study 20170543

Efficacy results from the pivotal phase 3 study (Study 20190172, described in Section 2.1 of Module 2.7.3, Summary of Clinical Efficacy) are presented as the primary support for the indication, with supportive data from Studies 20170543 and 20190135 Subprotocol H. Efficacy results are presented in a side-by-side format, including sotorasib monotherapy in subjects with mCRC in Study 20170543, sotorasib + panitumumab doublet therapy in subjects with mCRC in Study 20190172, Study 20190135 subprotocol H Part 2 cohorts A, B, and D. Additionally, results are provided by the pooled sotorasib monotherapy data from the phase 1 and phase 2 portions of Study 20170543 and the pooled sotorasib 960 mg plus panitumumab therapy from Study 20190172 and Study 20190135 Subprotocol H cohorts 2A and 2D in subjects with mCRC.

These supportive studies are briefly described below.

- Study 20190135 Subprotocol H is an ongoing phase 1b, nonrandomized, open-label study evaluating the safety, tolerability, PK, PD, and efficacy of sotorasib in combination with panitumumab and chemotherapy in adults subjects with *KRAS p.G12C*-mutated advanced CRC, NSCLC, or advanced solid tumors (Section 2.3 of Module 2.7.3, Summary of Clinical Efficacy).
- Study 20170543 (phase 1 and phase 2 part B) is an ongoing phase 1/2, open-label, single-group study evaluating the safety, tolerability, PK, PD, and efficacy of sotorasib monotherapy in subjects with *KRAS p.G12C*-mutated advanced solid tumors (NSCLC, CRC, and other tumors) (Section 2.2 of Module 2.7.3, Summary of Clinical Efficacy).

The data cut-off dates used in the efficacy analyses are 19 June 2023 for Study 20190172, 23 May 2023 for Study 20190135 Subprotocol H, and 01 April 2023 for Study 20170543. The data cut-off used for the OS update in Study 20190172 was 18 December 2023.

Trial Design

The Applicant's Description:
Key aspects of study design, endpoints, and statistical methodology for Study 20190172 are summarized in Section 1.3.1 of Module 2.7.3, Summary of Clinical Efficacy. Study narratives for Studies 20170543 and 20190135 Subprotocol H are provided in Sections 2.2 and 2.3 of Module 2.7.2, Summary of Clinical Efficacy.

In Study 20190172, Amgen selected trifluridine/tipiracil and regorafenib as the comparators during study design and conduct because they are approved, available, and standard of care globally.

Amgen sought feedback from health authorities on the adequacy of the design of Study 20190172. Key changes since the original protocol submission are noted in Section 1.4 of Module 2.5, Clinical Overview.

Study design details for the supportive studies are provided in the respective clinical study reports (CSRs).

The FDA's Assessment:
The pivotal trial supporting this application is Study 20190172, which is a global, open-label, randomized, active-controlled clinical trial in patients with KRAS G12C mutated mCRC comparing third-line treatment with sotorasib in combination with panitumumab to investigator's choice of regorafenib or trifluridine and tipiracil. Patients were randomized 1:1:1 to the following treatment groups:

- sotorasib 960 mg orally daily (PO QD) with panitumumab 6 mg/kg IV every 2 weeks (Q2W)
- sotorasib 240 mg PO QD with panitumumab 6 mg/kg IV Q2W
- investigator's choice of trifluridine and tipiracil or regorafenib (chosen prior to randomization)

If sotorasib was discontinued the protocol required that panitumumab was also discontinued, however patients could continue to receive sotorasib if panitumumab was discontinued.

Randomization stratification factors included prior anti-angiogenic therapy (yes vs. no), time from initial diagnosis of metastatic disease to randomization (≥18 months vs. <18 months), and ECOG performance status (0 or 1 vs. 2). Note that trifluridine and tipiracil with bevacizumab and fruquintinib are now available third-line therapies for patients with mCRC, but FDA accepts their exclusion from the control arm because their approvals in the U.S. (August 2, 2023 and November 8, 2023, respectively) were after the June 19, 2023 data cutoff date for the primary analysis of Study 201910712.

Crossover was permitted after the primary analysis for PFS if it demonstrated that sotorasib with panitumumab was statistically and clinically superior to the investigator's choice therapy, and the overall benefit-risk was favorable. Crossover was not permitted for patients who

permanently discontinued investigator's choice therapy for reasons that were not related to disease progression (e.g., adverse event). Patients who discontinued investigator's choice therapy for reasons that were not disease progression, but then later progressed (confirmed by BICR) prior to initiating subsequent therapy were eligible for crossover.

Treatment beyond BICR-assessed progression per RECIST 1.1 was permitted.

Eligibility Criteria

The Applicant's Description:
Study 20190172
Eligible subjects were men or women (≥ 18 years of age) with metastatic colorectal adenocarcinoma with *KRAS p.G12C* mutation as assessed by prospective central molecular testing of tumor biopsy specimens using the analytically validated Qiagen Therascreen KRAS RGQ polymerase chain reaction kit in CRC as an investigational device. Additionally, eligible subjects had received at least 1 prior line of therapy, and must have received fluoropyrimidine, oxaliplatin, and irinotecan for metastatic disease unless there was a medical contraindication agreed upon between the investigator and the Amgen medical monitor. Once consented to the study, subjects provided a medical history and underwent screening assessments to confirm that all eligibility requirements for the study were met. Subjects must have had adequate hematological, renal, and hepatic function and coagulation.

Subjects must have been willing to provide archived tumor tissue samples (formalin-fixed paraffin-embedded sample collected within 5 years) or have agreed to undergo a pretreatment tumor biopsy (excisional or core biopsy) prior to enrollment.

Study 20190135 Subprotocol H
Eligible subjects were men or women (≥ 18 years of age) with a metastatic advanced solid tumor with *KRAS p.G12C* mutation as assessed by molecular testing of tumor biopsy specimens and who have received at least 1 prior systemic therapy for advanced disease were eligible to participate in the study for Part 2 Cohorts A, B, and D. Additional eligibility criteria per study cohort for the cohorts included in this report were as follows:

- For Part 2, Cohort A, subjects must have *KRAS p.G12C*-mutated CRC, be $KRAS^{G12C}$ inhibitor naïve, have been previously treated with fluoropyrimidine, oxaliplatin, irinotecan, anti-angiogenic agents, and if microsatellite instability high (MSI-H), a checkpoint inhibitor (if approved in the region).
- For Part 2 Cohort B, subjects may have any *KRAS p.G12C*-mutated solid tumor but must have had progression on or within 2 months of treatment with a $KRAS^{G12C}$ inhibitor.
- For Part 2 Cohort D, subjects must have *KRAS p.G12C*-mutated mCRC and be $KRAS^{G12C}$ inhibitor naïve and must have received only 1 prior regimen for metastatic disease.

Once consented to the study, subjects provided a medical history and had screening tests to confirm all eligibility requirements of the study had been met. Subjects must have had adequate hematologic, renal, and hepatic function and coagulation.

Subjects had pretreatment tumor biopsy and tumor biopsy on treatment, if clinically feasible.

Study 20170543

Phase 1

Adult subjects (≥ 18 years of age) with advanced solid tumors were eligible for this study. Enrollment was restricted to subjects with *KRAS p.G12C*-mutated advanced solid tumors as assessed by molecular testing of tumor biopsy specimens. Once consented to the study, subjects provided a medical history and had screening safety tests to confirm that all eligibility requirements of the study were met. Subjects provided archived tumor tissue samples (formalin-fixed paraffin-embedded sample collected within 5 years) or had a predose tumor biopsy for the purpose of *KRAS p.G12C* testing.

Subjects must have measurable disease per response evaluation criteria in solid tumors RECIST 1.1 criteria; ECOG performance status of ≤ 2; QTc ≤ 470 msec; ability to take oral medications; adequate hematological, renal, hepatic, and coagulation laboratory assessments.

For phase 1, subjects with CRC must have received ≥ 2 prior systemic regimens in the metastatic setting. For CRC subjects with tumors that are MSI-H, at least 1 of the prior systemic regimens must be treatment with either nivolumab or pembrolizumab if they were clinically able to receive checkpoint inhibitors and 1 of these agents is approved for that indication in the region or country.

Phase 2

Adult subjects (≥ 18 years of age) with advanced solid tumors were eligible for this study. Enrollment was restricted to subjects with *KRAS p.G12C*-mutated solid tumors as assessed by molecular testing. For CRC, the mutation was confirmed by central testing prior to enrollment. Once consented to the study, subjects provided a medical history and had screening tests to confirm that all eligibility requirements of the study were met. Subjects with CRC must have progressed after receiving fluoropyrimidine and oxaliplatin and irinotecan. For subjects with tumors that are MSI-H, at least 1 of the prior systemic regimens must have included an anti-PD1 therapy if they were clinically able to receive inhibitors and 1 of these agents is approved for that indication in the region or country. Subjects must have had measurable disease per RECIST 1.1 criteria; ECOG performance status of ≤ 1; QTc ≤ 470 msec; ability to take oral medications; adequate hematological, renal, hepatic, and coagulation laboratory assessments.

The FDA's Assessment:

FDA agrees with the Applicant's position. Additional details related to key eligibility criteria for each trial are provided below:

Study 20190172
- prior checkpoint inhibitor therapy was required if patient is known to have MSI-H tumor, therapies were available for this indication in the region, and there were no contraindications to treatment
- patients must have received encorafenib with cetuximab if known to have BRAF V600E-mutated tumor, therapies were available in the region, and had no contraindications to treatment
- KRAS G12C inhibitor-naive
- ECOG performance status 0-2

Study 20190135 – Subprotocol H
- KRAS G12C mutation eligibility determination was based on local test
- ECOG performance status 0-2 for Part 2 cohorts A, B, and D

Study 20170543 – Phase 1
- KRAS G12C mutation eligibility determination was based on local test

Study Endpoints

The Applicant's Description:
The primary endpoint in Study 20190172 is PFS; progression was evaluated based on blinded independent central review (BICR) of disease response using response evaluation criteria in solid tumors (RECIST) version 1.1 criteria. Progression-free survival was defined as time from randomization until BICR-assessed disease progression or death from any cause, whichever occurs first. Subjects who did not progress or die were censored at their last evaluable disease assessment date. Primary, secondary, and key secondary endpoints assessed in Study 20190172 and the supporting studies are shown in Applicant - Table 7.

Applicant - Table 7. Efficacy Endpoints in Study 20190172, Study 20190135 Subprotocol H and Study 20170543 Phase 1 and Phase 2 and the Pooled Analysis

Endpoint	Study 20190172	Study 20170543 phase 1	Study 20170543 phase 2	Study 20190135 subprotocol H Phase 1b	Pooled Analysis
PFS	Primary	Secondary	Secondary	Secondary	Included
ORR	Key Secondary	Secondary	Primary	Secondary	Included
DOR	Secondary	Secondary	Secondary	Secondary	Included
TTR	Secondary	Secondary	Secondary	Secondary	Included
DCR	Secondary	Secondary	Secondary	Secondary	Included
OS	Key Secondary	Secondary	Secondary	Secondary	Included
PRO	Secondary	Not Assessed	Exploratory	Not Assessed	Not included

DCR = disease control rate; DOR = duration of response; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcomes; TTS = time to response

The FDA's Assessment:
FDA agrees with the Applicant's description of the trial endpoints. Note that the tumor-based response endpoints in the pivotal trial, such as ORR and DoR, were assessed by BICR per RECIST 1.1.

FDA's efficacy assessment was based on the PFS, OS, ORR, and DoR results from the pivotal trial, Study 20190172. The other endpoints of TTR, DCR, and PRO were not considered as part of the efficacy assessments.

Statistical Analysis Plan and Amendments

The Applicant's Description:
The statistical methods of efficacy endpoints are summarized in Table 2 for Study 20190172 of Module 2.7.3, Summary of Clinical Efficacy and Applicant - Table 8 with full details of the statistical methods for the efficacy analyses across studies provided in the Integrated Summary of Efficacy Supplemental Statistical Analysis Plan (Module 5.3.5.3).
For Study 20190172, blinded endpoint assessment was used to reduce potential bias resulting from the open-label nature of the study; therefore, the primary analysis (PA) was based on the objective endpoint of BICR-assessed PFS.

Applicant - Table 8. Summary of Methods of Statistical Analysis Used in Study 20190172, Study 20170543 (Phase 1 and Phase 2 Part A), and Study 20190135 Subprotocol H

Efficacy Endpoint	Definition	Primary Summary and Analysis Method
PFS	Time from randomization or first dose until disease progression or death from any cause, whichever occurs first for all subjects	Studies with comparator groups: Inferential comparison between treatment groups used the log-rank test stratified by the randomization stratification factors. The HR and its 95% CI was estimated using a Cox proportional hazards model stratified by the randomization stratification factors. All Studies: Distribution characterized based on Kaplan-Meier curves.
OS	Time from randomization or first dose until death from any cause	Same methods as described for PFS.
ORR	Proportion of subjects with objective response (CR + PR), assessed per RECIST v1.1	The ORR was calculated by treatment group and the associated 95% CI estimated using the Clopper-Pearson method. Studies with comparator groups: The inferential comparison between treatment groups will be made using the stratified Mantel Haenszel method.
DOR	Time from first evidence of PR or CR to disease progression or death because of any cause, whichever occurs first. Progression will be based on an BICR assessment of disease response per RECIST v1.1	Characterized using the Kaplan-Meier method based among the subjects who achieve a best response of confirmed PR or better.
TTR	Time from randomization or first dose to first evidence of PR or CR based on BICR	Summarized descriptively for continuous variable. TTR is calculated among subjects who achieved a best response of confirmed PR or better.
DCR	CR + PR + stable disease	Same method as described for ORR.

BICR = Blinded Independent Central Review; CR = complete response; DCR = disease control rate; DOR = duration of response; HR = hazard ratio; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; TTR = time to response;

The FDA's Assessment:

FDA agrees with the Applicant's description of analysis methods for the efficacy endpoints considered as part of the efficacy assessments.

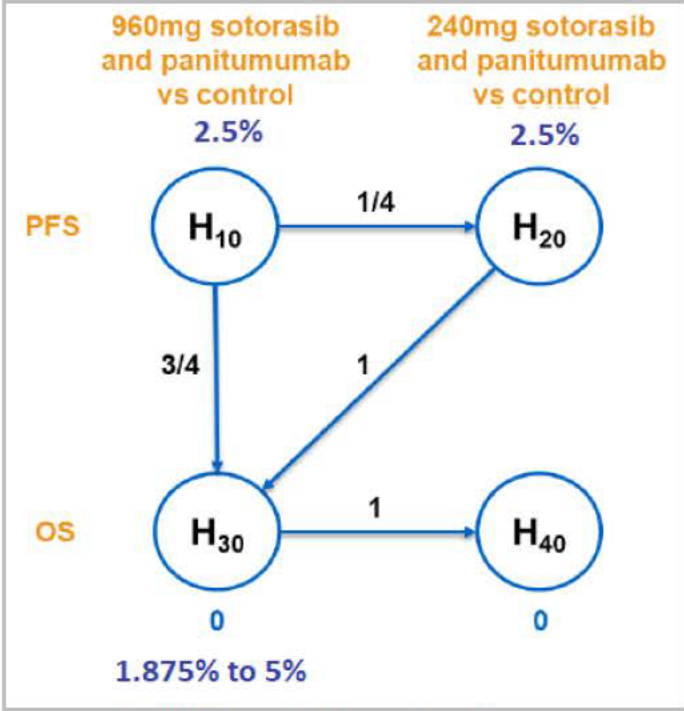
As the efficacy analysis for sotorasib in combination with panitumumab was determined primarily based on the results of Study 20190172, a discussion of the statistical analysis plan in Study 20190172 is presented below.

Sample Size Assumptions:
Assuming a median PFS of 2 months for the investigator's choice control arm (trifluridine and tipiracil or regorafenib) arm and 5 months for either of the sotorasib and panitumumab arms, a total of 90 PFS events across all three arms were required to detect an HR of 0.4 with 90% power at a 1-sided significance level of 1.25% for each comparison. Assuming an enrollment rate of 20 subjects per month after a 3-month ramp-up period and a 10% dropout rate, a total of 153 patients were planned to be randomized (1:1:1) in this study. The primary analysis of PFS was planned to occur when approximately 60 PFS events were observed from the sotorasib 960 mg and panitumumab arm and the investigator's choice arm.

The key secondary endpoints of OS and ORR for each dose level were planned to be evaluated hierarchically following the significance of PFS at primary analysis. The study was not powered to detect a statistical difference in OS between the two sotorasib containing arms. There were 2 planned analyses of OS (1 interim and 1 final). A nominal alpha of 0.01% was allocated for the OS interim analysis. The OS final analysis was planned to be conducted when approximately 77 OS events total (~50% maturity) have been observed from all three arms, expected to be at approximately 6 months after the PFS primary analysis. A median OS of 7.1 months for the investigator's choice (trifluridine and tipiracil or regorafenib) arm and 10.9 months for either of the sotorasib and panitumumab arms, and a 10% dropout rate was assumed as part of the OS analysis plan.

Multiplicity Adjustment in Study 20190172:
The overall type-I error rate (α) was controlled at 5% (2-sided) in this study. The α was split equally between the two primary sotorasib and panitumumab vs control arm comparisons of PFS (2.5%) and the multiple endpoints in this study were planned to be tested using the graphical approach. The figure below provides the α-recycling strategy implemented in this study to test PFS and OS for each of the sotorasib arm. ORR was planned to be tested hierarchically (with 960 mg dose level tested first) after OS using the remaining α (2-sided 1.875% to 5%) when both the OS hypotheses related to each dose level of sotorasib arm are rejected.

Figure 3: Multiplicity Adjustment Strategy in Study 20190172



Source: Study 20190172 Protocol - Statistical methods section.

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Protocol Amendments

The Applicant's Description:

Study 20190172

The protocol for Study 20190172 (originally dated 30 August 2021) was amended 3 times as of the data cut-off date (19 June 2023) for this marketing application. Key changes to the protocol are summarized in Applicant - Table 9 and all major changes are provided in the CSR.

Applicant - Table 9. Study 20190172 Protocol Amendment Summary

Amendment	Major Changes
Original Protocol 30 August 2021	
Amendment 1 08 December 2021	• Add pneumonitis in the key risks for Section 2.3. Benefit/Risk Assessment. • Add additional toxicity of suspected interstitial lung disease/pneumonitis of any grade and recommended actions in Table 6-3. • Add information in Section 6.1.7 that subjects cannot take known CYP3A4 and/or P-gp sensitive substrates with narrow therapeutic index when taking Sotorasib unless approved by Medical Monitor.
Amendment 2 30 August 2022	• The main reasons to conduct this amendment were to make subjects that are unable to complete patient-reported outcomes (PROs) due to language barriers eligible to participate in the study, to clarify prophylactic measures and management of treatment-related skin rashes, and to include minor clarifications of issues in the schedule of activities.
Superseding Amendment 3 13 March 2023	• For clarity, include the requirement for local Kirsten rat sarcoma (*KRAS*) *p.G12C* along with central confirmation to be eligible to participate in the study. • Per agency request, revise inclusion criterion #104 to clarify that subjects with tumors known to have BRAF V600E mutation and presenting a medical contraindication to receiving encorafenib and cetuximab (if available for this indication in the country or region) may be eligible for the trial after investigator discussion with the Amgen medical monitor (Section 5.1). • Per agency request, add to the protocol as exclusion criteria that subjects with a history of clinically significant haemorrhage, and gastrointestinal fistulas or perforations; if urine protein is $\geq$ 2+ and follow-up 24-hour urine collection is $\geq$ 1 g of protein will be ineligible if randomized to the control group and investigator's choice is regorafenib (Section 5.2).

Study 20190135 Subprotocol H

The protocol for Study 20190135 Subprotocol H (originally dated 06 March 2020) was amended 5 times as of the data cut-off date for the Study 20190135 Subprotocol H CSR provided in this marketing application (23 May 2023). Key changes to the protocol are summarized in Applicant - Table 10 and all major changes are provided in the CSR.

Applicant - Table 10. Study 20190135 Subprotocol H Protocol Amendment Summary

Amendment	Major Changes
Original Protocol 06 March 2020	
Amendment 1 22 October 2020	• increased the number of dose expansion cohorts in part 2 of the study from 3 to 6 cohorts and defined the study populations in each expansion cohort • increased the size of part 2 from 60 to 180 subjects (and corresponding total subjects from 90 to 210 subjects • allowed investigative sites to use levoleucovorin if racemic leucovorin was not available
Amendment 2 01 July 2021	• added Cohort G: subjects with prior therapy *KRAS p.G12C* mutated metastatic colorectal cancer who are $KRAS^{G12C}$ inhibitor naïve with at least 1 prior therapy for metastatic disease. Subjects in this cohort to be treated with sotorasib, panitumumab, and FOLFIRI • increased the total number of subjects from 210 to 250 subjects • updated sotorasib status to approved for NSCLC
Amendment 3 05 January 2022	• added Part 2 Cohort H to confirm safety and evaluate preliminary anti-tumor activities of sotorasib in combination with panitumumab in subjects with *KRAS p.G12C*-mutated metastatic pancreatic cancer • increased the number of subjects in Cohort C • added that Cohort C and H are required to have at least 2 responses in the first 20 subjects to continue enrolling subjects. • modified screening assessment, long-term follow-up, thyroid function test, serious adverse event, and tumor biopsy language in schedule of assessments and other sections of protocol • included interstitial lung disease/pneumonitis as a potential risk and adverse drug reaction to sotorasib treatment
Amendment 4 27 April 2022	• clarified that sotorasib did not need to be taken in clinic (ie, not necessarily before panitumumab) except for situations on days when cycle 1 pharmacokinetic (PK) samples were collected and where there was a dose hold and then re-start of both drugs on the same day wherein the panitumumab administration followed the sotorasib administration • removed the incorrectly marked sotorasib PK collection at end of treatment in the schedule of activities table • allowed subjects who refused standard of care (SOC) chemotherapy or for whom SOC chemotherapy was contraindicated to enter Cohort H part of the study • required adequate hepatic laboratory assessment of total bilirubin < 1.5 x upper limit of normal for Cohort H as a requirement to enter the study

Applicant - Table 7. Study 20190135 Subprotocol H Protocol Amendment Summary

Amendment	Major Changes
Amendment 5 09 December 2022	• added cohort Part 2 Cohort I to explore the safety and efficacy of a lower dose of sotorasib (240 mg) in combination with the recommended phase 2 dose of panitumumab and FOLFIRI in subjects who are $KRAS^{G12C}$ inhibitor naïve with at least 1 prior therapy for metastatic disease and updated all associated protocol sections and planned number of subjects to be enrolled. • increased the total number of subjects from 310 to 340 subjects

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Study 20170543

The protocol for Study 20170543 (originally dated 14 May 2018) was amended 10 times as of the data cut-off date for this marketing application. Key changes to the protocol from Amendment 7 to 10 are summarized in Applicant - Table 11 and all major changes are provided in the CSR.

Applicant - Table 11. Study 20170543 Protocol Amendment Summary

Amendment	Major Changes
Amendment 7 08 March 2021	• added the dose comparison portion of the study (phase 2 part B) for subjects with non-small cell lung cancer
Amendment 8 13 May 2021	• modified eligibility criteria: – added exclusion criteria to prohibit coadministration of sotorasib with proton-pump inhibitors, histamine-2 receptor antagonists, and with P-glycoprotein substrates – allowed enrollment of patients with moderate renal impairment ($\geq$ 30 mL/min/1.73 m^2) – allowed subjects enrolled in the long-term follow-up portion of another investigational device or drug study, but not taking/using the respective investigational drug or device, to be considered eligible for enrollment into this study • clarified that the data review team analysis serves as an interim analysis and no intent to use this interim assessment to stop the study early • changed guidance to allow *KRAS p.G12C* mutation confirmation from either central or local laboratory testing • updated collection schedule for patient-reported outcome assessments
Amendment 9 02 September 2021	• changes to allow for flexibility of safety data collection and reporting during the long-term follow-up and end-of-study periods

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Applicant - Table 11. Study 20170543 Protocol Amendment Summary

Amendment	Major Changes
Amendment 10 23 December 2021	• added safety information regarding new risk/adverse drug reaction of pneumonitis • allowed enrollment of subjects who have pancreatic cancer with locally advanced or metastatic disease, with or without prior line of treatment in phase 2 part A • expanded sample size for other solid tumor types in phase 2 part A and modified corresponding futility analyses to account for inclusion of subjects with pancreatic cancer • allowed administration of sotorasib tablets predispersed in water for subjects who have difficulty swallowing solids • added remote assessments to allow continuation of study procedures if a subject was unable or unwilling to attend in-person visits where permitted by national and local authorities. • clarified serious adverse event reporting requirements • updated schedule of assessments to clarify requirements for microscopic exam of urinalysis and cholesterol testing; added assessments for vital signs during safety follow-up in phase 2 part A and sotorasib and its metabolites in phase 2 part B; removed thyroid and cholesterol tests for end-of-treatment visit in phase 1 and phase 2 part A • added COVID-19 information and guidance as per the protocol template • updated list of analytes to specify that the following were optional: fibrinogen, D-Dimer, urine sodium, urine potassium, and urine microscopic exams; added red blood cells, white blood cells, epithelial cells and bacteria under the urine microscopic exams

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The FDA's Assessment:

FDA's efficacy assessment is based on the pivotal trial, Study 20190172, therefore the following discussion is focused on the protocol amendments for this trial. FDA agrees with the Applicant's description of protocol amendments to Study 20190172. Additional key amendments included in this study are as follows:

Amendment 2:

- This amendment allowed continuation on study treatment after BICR-assessed disease progression. The criteria required to received continued treatment with sotorasib and panitumumab post-BICR assessed disease progression, scanning procedures, and determination of stopping therapy were provided.
- Additional details regarding the OS interim analysis and the alpha allocation of 0.01% for

this OS interim look were added in this amendment. As per this amendment, the OS primary analysis was planned to be conducted at approximately 3 months after the OS interim analysis.

Amendment 3:

- The follow-up period was increased to up to 2 years, thereby increasing the total study duration to 3 years.
- The amendment clarified statistical analyses and ORR testing scenarios.
- Revisions were included regarding the overall survival (OS) final analysis timing to be OS-event driven (77 deaths across all three arms; 50% maturity; expected to occur at approximately 6 months after the PFS primary analysis), instead of at a fixed calendar time of 3 months following PFS primary analysis.

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8.1.2. Study Results

Compliance with Good Clinical Practices

Data:
Audits of Studies 20190172, 20190135 Subprotocol H, and 20170543 were included as part of the independent Amgen Quality, Compliance, and audit program performed by Amgen. The audit certificates for these studies are provided in Section 16.1.8 of the CSRs of these respective studies.

Amgen has been closely monitoring the evolving coronavirus disease-2019 (COVID-19) situation across the globe and has, therefore, taken proactive steps to maintain the safety of study participants and support staff, including Amgen representatives, at all clinical study centers, and to maintain study data integrity while maintaining compliance with Good Clinical Practices (GCP). Guidelines on study conduct during the COVID-19 period were documented in the respective study protocols.

The Applicant's Position:
Studies 20190172, 20190135 Subprotocol H, and 20170543 were conducted in accordance with the Code of Federal Regulations (CFR) governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligations of clinical investigators (21 CFR 312.50 to 312.70) in accordance with GCP. Studies 20190172, 20190135 Subprotocol H, and 20170543 were conducted under Investigational New Drug (IND) 139023 and 145154.

The FDA's Assessment:
The protocols for Study 20190172 and Study 20190135 Subprotocol H state that the Investigator will be responsible for the "overall conduct of the study at the site and adherence to requirements of Title 21 of the US Code of Federal Regulations (CFR), ICH guidelines, the external review body, and all other applicable local regulations." The Study 20170543 Clinical Study Report states, "This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines." See Section 4.1 for FDA's assessment on the issue of forgery reported by one of the clinical site investigators.

Financial Disclosure

Data:
See Appendix 19.2.

The Applicant's Position:
Studies 20190172, 20190135 Subprotocol H, and 20170543 were Amgen-sponsored clinical studies. Financial interest or arrangements with clinical investigators have been disclosed (see

Appendix 19.2).

The FDA's Assessment:
Three investigators in Study 20190172 disclosed financial interests. These disclosures did not impact FDA's assessment of efficacy of sotorasib 960 mg in combination with panitumumab's efficacy. See Section 19.2 for details.

Patient Disposition

Data:
Study 20190172
A total of 219 subjects were screened for enrollment into this study and 160 were randomized to either the sotorasib 240 mg + panitumumab group (53 subjects), sotorasib 960 mg + panitumumab group (53 subjects), or control (trifluridine and tipiracil or regorafenib) group (54 subjects). Three subjects (5.6%) never received investigational product in the control group (ineligibility determined for 1 subject, subject request for 1 subject, and other reason for 1 subject [all 1.9%]), while all subjects in both sotorasib + panitumumab groups received investigational product. Further details on subject disposition in Study 20190172 are provided in Section 2.1 of Module 2.7.3, Summary of Clinical Efficacy.

Study 20190135 Subprotocol H
A total of 121 subjects with solid tumors in the Study 20190135 Subprotocol H cohorts which had subjects receiving sotorasib and panitumumab were enrolled at 30 centers in the United States, Canada, Spain, Belgium, Germany, Austria, Italy, and Japan. The first subject was enrolled on 24 June 2020 and the last on 18 May 2023. This study is ongoing; this report includes data through a data cut-off date of 23 May 2023. Further details on subject disposition in Study 20190135 Subprotocol H are provided in Section 2.3 of Module 2.7.3, Summary of Clinical Efficacy.

Study 20170543
Phase 1
A total of 60 subjects with CRC were enrolled into the phase 1 portion of the study. Of the 60 subjects with CRC in the phase 1 portion of the study, 3 subjects were in the sotorasib 180 mg QD cohort, 10 subjects were in the sotorasib 360 mg QD cohort, 14 subjects were in the 480 mg twice daily cohort, 4 subjects were in the sotorasib 720 mg QD cohort, and 29 subjects were in the sotorasib 960 mg QD cohort; results from the 2 largest QD cohorts (360 and 960 mg) are described in the SCE. As of the data cut-off date of 01 April 2023, of the 10 subjects in the 360 mg QD cohort, 1 subject (10%) completed the study and 9 (90%) subjects discontinued the study; the most frequent reason for treatment discontinuation was death

(70%). As of the data cut-off date, 2 subjects (6.9%) in the 960 mg cohort remained on study; the most frequent reason for treatment discontinuation was disease progression (89.7%).

Phase 2

A total of 62 subjects with CRC were enrolled into the phase 2 part of the study. Of the 62 enrolled subjects, 3 subjects (4.8%) were continuing the study as of the data cut-off date (01 April 2023) and 59 subjects (95.2%) had discontinued from the study. Reasons for discontinuation from the study were death (52 subjects, 83.9%), withdrawal of consent (5 subjects, 8.1%), and lost to follow-up (2 subjects, 32%). A total of 61 subjects (98.4%) discontinued sotorasib treatment. The primary reason for treatment discontinuation was disease progression (55 subjects, 88.7%).

The Applicant's Position:

The full analysis sets for the above studies included all randomized subjects in Study 20190172 and all enrolled subjects who received at least 1 dose of investigational product in Studies 20190135 Subprotocol H and 20170543. Study 20190172 randomized 160 subjects to either the sotorasib 240 mg + panitumumab group (53 subjects), sotorasib 960 mg + panitumumab group (53 subjects), or control (trifluridine and tipiracil or regorafenib) group (54 subjects); 3 subjects (5.6%) never received investigational product in the control group, while all subjects in both sotorasib + panitumumab groups received investigational product. Study 20190135 Subprotocol H enrolled 121 subjects, all of whom received sotorasib and panitumumab. Study 20170543 enrolled 60 subjects with CRC into the phase 1 portion of the study and a total of 62 subjects with CRC were enrolled into the phase 2 part of the study, all of whom received sotorasib. Safety analyses included subjects who received at least 1 dose of investigational product.

The FDA's Assessment:

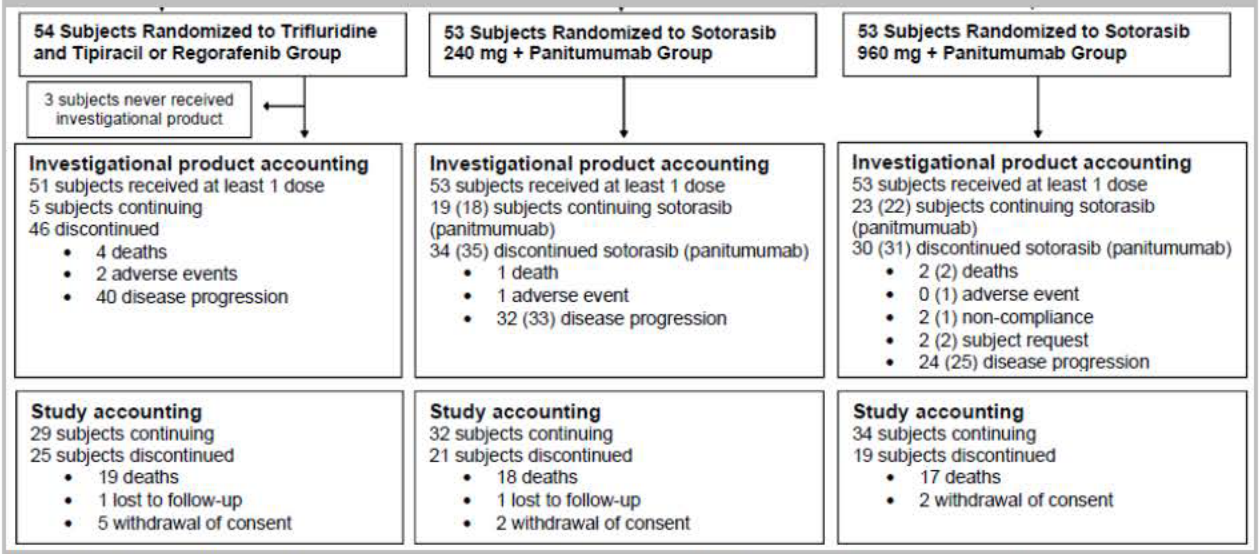
Site 33013 from Study 20190172 was not excluded from FDA's review of efficacy data because FDA determined that the forgery issues only affected the reliability of the safety data from site 33013.

The figure below provides the patient disposition for the pivotal trial, Study 20190172, as of the cutoff date of June 19, 2023 for the PFS primary analysis. The follow-up duration ranged from 0 to 11 months as of the cutoff date.

Overall, 64% and 57% of the patients discontinued both sotorasib and panitumumab in the sotorasib 240 mg and panitumumab arm and sotorasib 960 mg and panitumumab arm. In the control arm, 85% of the patients discontinued the assigned treatment. The major reason for trial drug discontinuation is disease progression across all three arms (60%, 45%, and 74%, respectively).

Approximately 60%, 64%, and 54% were continuing in the trial as of the cutoff date of June 19, 2023. The major reason for trial discontinuation was death across all three arms (~35%). However, as of the updated cutoff date of December 18, 2023, the trial discontinuation rates due to death increased to 51%, 45%, and 54% in the sotorasib 240 mg, sotorasib 960 mg, and control arms respectively.

Figure 4: Patient Disposition in Study 20190172



Note: For the study drug discontinuation, the numbers provided in the parenthesis are related to panitumumab.
Cutoff date: June 19, 2023.
Source: Study 20190172 CSR Figure 9.1.

Ten patients in the sotorasib-containing arms (3 patients in sotorasib 240 mg arm and 7 patients in sotorasib 240 mg arm) continued their treatment beyond BICR-confirmed disease progression. Although crossover was permitted in specific circumstances as previously outlined, patients did not crossover between treatment arms in this trial.

Protocol Violations/Deviations

Data:
Study 20190172

A total of 110 subjects (68.8%) had 226 important protocol deviations (IPDs) (Section 9.2 of Study 20190172 PFS PA). In the sotorasib 240 mg + panitumumab group, 33 subjects (62.3%) had 61 IPDs, of which the most common (>10% of subjects) were missing data (other than treatment administered [TA] [received the wrong treatment or incorrect dose] or treatment compliant [TC] [other treatment compliance]), off-schedule procedures (other than TA or TC), or other deviations.

In the sotorasib 960 mg + panitumumab group, 43 subjects (81.1%) had 100 IPDs, of which the most common (> 10% of subjects) were missing data (other than TA or TC), off-schedule procedures (other than TA or TC), entered study even though entry criteria was not satisfied, received the wrong treatment or incorrect dose, or other deviations. In the control group, 34 subjects (63.0%) had 65 IPDs, of which the most common (> 10% of subjects) was missing data (other than TA or TC), off-schedule procedures (other than TA or TC), and entered study even though entry criteria was not satisfied.

Important protocol deviations due to COVID-19 control measures were reported for 4 subjects (7.5%) in the sotorasib 240 mg + panitumumab group, for 2 subjects (3.8%) in the sotorasib 960 mg + panitumumab group, and for 0 subjects in the control group.

Study 20190135 Subprotocol H

A total of 84 subjects (69.4%) had 269 IPDs (Section 9.2 of Study 20190135 Subprotocol H Interim Analysis 1). The most common (≥ 10% of subjects) IPDs were missing data (other than received the wrong treatment or incorrect dose [TA] or other treatment compliance [TC]), off-schedule procedures (other than TA or TC), or other deviations. Important protocol deviations due to COVID-19 control measures were reported for 6 subjects (5.0%).

Study 20170543

Phase 1

As of the data cut-off date, for the phase 1 CRC portion of the study, 27 of 60 subjects (45.0%) had ≥ 1 important protocol deviation, with a total of 52 IPDs (Section 9.2 of Study 20170543 Interim Analysis 2 [Phase 1 CRC Cohort]). The most common important protocol deviation in the 960 mg QD cohort was missing data (excluding missing data for incorrect treatment, dose, or other treatment compliance) which occurred in 13 subjects (44.8%).

Phase 2:

A total of 40 subjects (64.5%) in the CRC cohort had ≥ 1 important protocol deviation, with a total of 91 IPDs (Section 9.2 of Study 20170543 Interim Analysis 2 [Phase 2 CRC Cohort]). The most common IPDs (≥ 30%) were deviations from GCP (43.5%) and missing data (excluding incorrect treatment or dose or other treatment compliance) (37.1%). The missing data included key safety or laboratory samples (16.1%), screening assessments (16.1%), predose assessments (14.5%), imaging (4.8%), and end of treatment or safety follow-up procedures (1.6%).

A total of 6 subjects (9.7%) in the CRC cohort had ≥ 1 important protocol deviation related to COVID-19 including missing key safety or laboratory samples (4.8%), missing predose assessments (4.8%), and missing imaging (1.6%). One subject (1.6%) also had other deviations of alternative procedures and partial missed visits related to COVID-19.

The Applicant's Position:

The above mentioned IPDs did not affect the overall results of the study.

The FDA's Assessment:

In Study 20190172, the sotorasib 960 mg with panitumumab arm had more protocol deviations than the other two arms, which was driven by the number of procedures that were done off-schedule, the number of patients receiving the wrong dose or drug, and data collection without consent or other GCP violations. Among these common deviations in the sotorasib 960 mg with panitumumab arm, the one that could impact the efficacy data was patients receiving the wrong drug or dose (Table 12). However, the most common deviation was taking sotorasib too early, which is unlikely to affect the efficacy results.

Another protocol deviation category that could impact the efficacy assessment is missing protocol-required imaging. The two patients in the control arm had clinical progression the day after missing the required imaging (n=1) or radiographic progression about two months prior to missing the required imaging (n=1). Thus, these few missing images for the control arm are unlikely to impact the efficacy assessment for the control arm. One patient in the sotorasib 960 mg with panitumumab arm missed required imaging, which was a few days before the patient permanently discontinued treatment; however, the patient has not progressed on his most recent scan, which was 9 months after the missing scan, and remains on trial, so this missing image is unlikely to impact the efficacy assessment for the sotorasib 960 mg arm.

Overall, the protocol deviations reported in Study 21090172 were unlikely to impact the efficacy assessment of this supplemental application. As data from Study 20190135 and Study 20170543 were supportive and did not serve as the basis of the efficacy analysis of sotorasib in combination with panitumumab, FDA did not conduct additional analyses of protocol deviations from these studies.

Table 12. FDA's Analysis of Protocol Deviations in Study 20190172

	Trifluridine/Tipiracil or Regorafenib (N = 54) n (%)	Sotorasib 240 mg + Panitumumab (N = 53) n (%)	Sotorasib 960 mg + Panitumumab (N = 53) n (%)	Total Sotorasib + Panitumumab (N = 106) n (%)
Patients with protocol deviations	**34 (63)**	**33 (62)**	**45 (85)**	**78 (74)**
Missing data (other than TA or TC)	23 (43)	14 (26)	23 (43)	37 (35)
Missing protocol-required imaging	2 (3.7)	0	1 (1.9)	1 (0.9)
Off-schedule procedures (other than treatment administration or t)	7 (13)	9 (17)	15 (28)	24 (23)
Cycle 1 Day 1 Pre-dose procedure(s) performed after trial therapy	0	4 (8)	11 (21)	15 (14)

administration				
Screening procedure(s) performed outside protocol-specified window	5 (9)	4 (8)	3 (6)	7 (7)
Key safety or laboratory sample panels collected outside protocol specified windows	3 (6)	3 (6)	2 (3.8)	5 (4.7)
Entered trial despite not meeting eligibility criteria	9 (17)	5 (9)	9 (17)	14 (13)
Measurable disease per RECIST 1.1	1 (1.9)	0	0	0
Did not receive required prior therapy	5 (9)	1 (1.9)	3 (6)	4 (3.8)
Received wrong treatment or wrong dose	0	5 (9)	9 (17)	14 (13)
Dosed too early with sotorasib	0	3 (6)	7 (13)	10 (9.4)
Incorrect, incomplete, or partial dose of trial drug	0	2 (3.8)	3 (6)	5 (4.7)
Met withdrawal criteria but was not withdrawn	0	0	1 (1.9)	1 (0.9)
Trial drug not held in setting of palliative radiotherapy for pain control	0	0	1 (1.9)	1 (0.9)
Received an excluded concomitant treatment	0	1 (1.9)	0	1 (0.9)
Other deviations	6 (11)	15 (28)	24 (45)	39 (37)
Missed protocol-required visits or missed trial treatment due to Covid-19 measures	0	4 (8)	2 (3.8)	6 (6)
Data collection without consent or other GCP violation	6 (11)	13 (25)	22 (42)	35 (33)
Did not fulfil criteria for treatment beyond progression	0	1 (1.9)	1 (1.9)	2 (1.9)

Abbreviations: TA = treatment administered (received the wrong treatment or incorrect dose), TC = treatment compliant (other treatment compliance), GCP = good clinical practice
Source: ADDV.xpt (SDN 380, submitted April 17, 2024)

Table of Demographic Characteristics

Data:

Study 20190172

Half of the subjects in the study were women (81 subjects [50.6%]). Most subjects were White (109 subjects [68.1%]), and not Hispanic/Latino (145 subjects [90.6%]) (Applicant - Table 13). The median (range) age was 62.0 (34 to 82) years and most subjects were < 65 years (97 subjects [60.6%]). Compared with the control and sotorasib 960 mg + panitumumab

groups, the sotorasib 240 mg + panitumumab group was slightly younger with a higher percentage of Asian subjects (41.5%).

Study 20190135 Subprotocol H

In Study 20190135 Subprotocol H, 59.5% of subjects were women and 40.5% were men (Applicant - Table 14). Most subjects were White (82 subjects, 67.8%) and not Hispanic/Latino (102 subjects, 84.3%). The median (range) age was 60 (30 to 84) years and most subjects were < 65 years (79 subjects, 65.3%). Most subjects were from North America (82 subjects, 67.8%).

Study 20170543

Overall, for phase 1 subjects with CRC (N = 60), more than half of subjects (51.7%) were women, most were White (75.0%), and 2 subjects (3.3%) were Hispanic or Latino (Applicant - Table 15). The median (range) age was 57.5 (31 to 82) years, with more than half of all subjects younger than 65 years (68.3%) Of the 29 subjects in the 960 mg QD cohort, 55.2% were men; most were White (72.4%) or Asian (20.7%). The median (range) age was 58.0 (37 to 82) years in the 960 mg cohort.

For phase 2 subjects with CRC (N = 62), most subjects in the CRC cohort were white (67.7%) and 54.8% were women (Applicant - Table 16). The median (range) age of subjects was 56.0 (31 to 85) years, with 48 subjects (77.4%) who were younger than 65 years of age.

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Applicant - Table 13. Baseline Demographics (Full Analysis Set – Study 20190172)

	Trifluridine and Tipiracil or Regorafenib (N = 54)	Sotorasib 240 mg + Panitumumab (N = 53)	Sotorasib 960 mg + Panitumumab (N = 53)	Total (N = 160)
Sex - n (%)				
Male	24 (44.4)	26 (49.1)	29 (54.7)	79 (49.4)
Female	30 (55.6)	27 (50.9)	24 (45.3)	81 (50.6)
Ethnicity - n (%)				
Hispanic/Latino	8 (14.8)	0 (0.0)	4 (7.5)	12 (7.5)
Not Hispanic/Latino	45 (83.3)	53 (100.0)	47 (88.7)	145 (90.6)
Unknown	1 (1.9)	0 (0.0)	2 (3.8)	3 (1.9)
Race - n (%)				
Asian	12 (22.2)	22 (41.5)	6 (11.3)	40 (25.0)
Black or African American	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.6)
White	37 (68.5)	30 (56.6)	42 (79.2)	109 (68.1)
Other/Unknown	5 (9.3)	0 (0.0)	5 (9.4)	10 (6.3)
Age (years)				
n	54	53	53	160
Mean	61.5	58.2	60.9	60.2
SD	11.7	11.9	11.6	11.7
Median	65.0	58.0	63.0	62.0
Min, Max	34, 81	34, 82	37, 79	34, 82
Age group 1 - n (%)				
< 65 years	26 (48.1)	39 (73.6)	32 (60.4)	97 (60.6)
≥ 65 years	28 (51.9)	14 (26.4)	21 (39.6)	63 (39.4)
Age group 2 - n (%)				
18 - 64 years	26 (48.1)	39 (73.6)	32 (60.4)	97 (60.6)
65 - 74 years	23 (42.6)	8 (15.1)	16 (30.2)	47 (29.4)
75 - 84 years	5 (9.3)	6 (11.3)	5 (9.4)	16 (10.0)
Region - n (%)				
North America	7 (13.0)	5 (9.4)	5 (9.4)	17 (10.6)
Europe	36 (66.7)	28 (52.8)	41 (77.4)	105 (65.6)
Asia	11 (20.4)	19 (35.8)	6 (11.3)	36 (22.5)
Rest of world	0 (0.0)	1 (1.9)	1 (1.9)	2 (1.3)

Data cut-off date: 19 June 2023

N = Number of subjects in the analysis set; n = Number of subjects with observed data.

Source: Table 14-2.1.1 of Study 20190172 PFS PA CSR, dated 28 March 2024

Applicant - Table 14. Baseline Demographics
(Sotorasib and Panitumumab Enrolled Subjects – Study 20190135 Subprotocol H)

	Part 1A CRC 1+ Prior Line Sotorasib + Panitumumab (N = 8)	Part 2A CRC Refractory Sotorasib + Panitumumab (N = 40)	Part 2B Solid Tumor KRAS G12C Refractory Sotorasib + Panitumumab (N = 20)	Part 2C NSCLC 1+ Prior Line Sotorasib + Panitumumab (N = 26)	Part 2D CRC 1 Prior Line Sotorasib + Panitumumab (N = 20)	Part 2H Pancreatic 1+ Prior Line Sotorasib + Panitumumab (N = 7)	Total All Solid Tumor Sotorasib + Panitumumab (N = 121)
Sex - n (%)							
Male	3 (37.5)	10 (25.0)	10 (50.0)	13 (50.0)	10 (50.0)	3 (42.9)	49 (40.5)
Female	5 (62.5)	30 (75.0)	10 (50.0)	13 (50.0)	10 (50.0)	4 (57.1)	72 (59.5)
Ethnicity - n (%)							
Hispanic or Latino	2 (25.0)	4 (10.0)	4 (20.0)	0 (0.0)	3 (15.0)	0 (0.0)	13 (10.7)
Not Hispanic or Latino	5 (62.5)	34 (85.0)	15 (75.0)	25 (96.2)	16 (80.0)	7 (100.0)	102 (84.3)
Missing	1 (12.5)	2 (5.0)	1 (5.0)	1 (3.8)	1 (5.0)	0 (0.0)	6 (5.0)
Race - n (%)							
American Indian or Alaska Native	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Asian	0 (0.0)	13 (32.5)	3 (15.0)	2 (7.7)	5 (25.0)	1 (14.3)	24 (19.8)
Black or African American	1 (12.5)	2 (5.0)	4 (20.0)	0 (0.0)	1 (5.0)	1 (14.3)	9 (7.4)
White	7 (87.5)	22 (55.0)	13 (65.0)	22 (84.6)	13 (65.0)	5 (71.4)	82 (67.8)
Other	0 (0.0)	2 (5.0)	0 (0.0)	2 (7.7)	1 (5.0)	0 (0.0)	5 (4.1)
Age (years)							
n	8	40	20	26	20	7	121
Mean	57.4	56.3	58.0	68.3	61.5	55.3	60.0
SD	16.4	10.6	12.5	8.6	11.1	12.9	11.9
Median	60.5	57.5	58.0	69.0	60.0	57.0	60.0
Q1, Q3	46.0, 68.0	49.5, 63.0	46.5, 66.5	62.0, 74.0	54.0, 70.0	46.0, 64.0	52.0, 69.0
Min, Max	31, 79	30, 78	39, 84	45, 81	40, 82	37, 76	30, 84

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Applicant - Table 14. Baseline Demographics
(Sotorasib and Panitumumab Enrolled Subjects – Study 20190135 Subprotocol H)

	Part 1A CRC 1+ Prior Line Sotorasib + Panitumumab (N = 8)	Part 2A CRC Refractory Sotorasib + Panitumumab (N = 40)	Part 2B Solid Tumor KRAS G12C Refractory Sotorasib + Panitumumab (N = 20)	Part 2C NSCLC 1+ Prior Line Sotorasib + Panitumumab (N = 26)	Part 2D CRC 1 Prior Line Sotorasib + Panitumumab (N = 20)	Part 2H Pancreatic 1+ Prior Line Sotorasib + Panitumumab (N = 7)	Total All Solid Tumor Sotorasib + Panitumumab (N = 121)
Age group - n (%)							
18 - 64 years	5 (62.5)	33 (82.5)	14 (70.0)	8 (30.8)	13 (65.0)	6 (85.7)	79 (65.3)
65 - 74 years	2 (25.0)	4 (10.0)	4 (20.0)	12 (46.2)	5 (25.0)	0 (0.0)	27 (22.3)
75 - 84 years	1 (12.5)	3 (7.5)	2 (10.0)	6 (23.1)	2 (10.0)	1 (14.3)	15 (12.4)
≥ 85 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Region - n (%)							
North America	8 (100.0)	31 (77.5)	13 (65.0)	18 (69.2)	10 (50.0)	2 (28.6)	82 (67.8)
Europe	0 (0.0)	0 (0.0)	4 (20.0)	8 (30.8)	6 (30.0)	4 (57.1)	22 (18.2)
Asia	0 (0.0)	9 (22.5)	3 (15.0)	0 (0.0)	4 (20.0)	1 (14.3)	17 (14.0)
Rest of world	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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Data cut-off date: 23MAY2023
CRC = colorectal cancer; max = maximum; min = minimum; NSCLC = non-small cell lung cancer; N = number of subjects in the analysis set; n = number of subjects with observed data; Q1 = first quartile; Q3 = third quartile.
Source: Table 14a-2.1 of Study 20190135 Subprotocol H Interim Analysis 1

Applicant - Table 15. Baseline Demographics (Phase 1 CRC in Safety Analysis Set – Study 20170543)

	180 mg QD Fasted (N = 3)	360 mg QD Fasted (N = 10)	720 mg QD Fasted (N = 4)	480 mg BID Fed (N = 14)	960 mg QD Fasted or Fed (N = 29)	Total (N = 60)
Sex - n (%)						
Male	2 (66.7)	2 (20.0)	2 (50.0)	7 (50.0)	16 (55.2)	29 (48.3)
Female	1 (33.3)	8 (80.0)	2 (50.0)	7 (50.0)	13 (44.8)	31 (51.7)
Ethnicity - n (%)						
Hispanic or Latino	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (3.4)	2 (3.3)
Not Hispanic or Latino	2 (66.7)	9 (90.0)	3 (75.0)	14 (100.0)	27 (93.1)	55 (91.7)
Missing	1 (33.3)	1 (10.0)	0 (0.0)	0 (0.0)	1 (3.4)	3 (5.0)
Race - n (%)						
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	5 (35.7)	6 (20.7)	11 (18.3)
Black or African American	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	1 (1.7)
White	3 (100.0)	8 (80.0)	4 (100.0)	9 (64.3)	21 (72.4)	45 (75.0)
Multiple	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	1 (1.7)

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Footnotes are defined on the last page of the table.

Applicant - Table 11. Baseline Demographics (Phase 1 CRC in Safety Analysis Set – Study 20170543)

	180 mg QD Fasted (N = 3)	360 mg QD Fasted (N = 10)	720 mg QD Fasted (N = 4)	480 mg BID Fed (N = 14)	960 mg QD Fasted or Fed (N = 29)	Total (N = 60)
Age (years)						
n	3	10	4	14	29	60
Mean	57.0	49.2	62.5	59.5	60.0	58.1
SD	4.4	10.6	9.0	14.6	11.0	12.0
Median	55.0	50.0	61.0	59.5	58.0	57.5
Q1, Q3	54.0, 62.0	44.0, 56.0	55.0, 70.0	48.0, 72.0	52.0, 66.0	50.0, 67.0
Min, Max	54, 62	33, 67	55, 73	31, 79	37, 82	31, 82
Age group - n (%)						
18 - 64 years	3 (100.0)	9 (90.0)	2 (50.0)	8 (57.1)	19 (65.5)	41 (68.3)
65 - 74 years	0 (0.0)	1 (10.0)	2 (50.0)	4 (28.6)	7 (24.1)	14 (23.3)
75 - 84 years	0 (0.0)	0 (0.0)	0 (0.0)	2 (14.3)	3 (10.3)	5 (8.3)

BID = twice daily; CRC = colorectal cancer; QD = once daily
Data cut-off date 01 April 2023.
Source: Table 14k-2.1 of Study 20170543 Interim Analysis 2 (Phase 1 CRC Cohort)

Applicant - Table 16. Baseline Demographics (Phase 2 CRC in Safety Analysis Set – Study 20170543)

	Phase 2 CRC 960 mg QD Fasted (N = 62)
Sex - n (%)	
Male	28 (45.2)
Female	34 (54.8)
Ethnicity - n (%)	
Hispanic or Latino	5 (8.1)
Not Hispanic or Latino	56 (90.3)
Missing	1 (1.6)
Race - n (%)	
American Indian or Alaska Native	0 (0.0)
Asian	17 (27.4)
Black or African American	0 (0.0)
Native Hawaiian or Other Pacific Islander	1 (1.6)
White	42 (67.7)
Multiple	0 (0.0)
Other	2 (3.2)
Age (years)	
n	62
Mean	55.7
SD	11.3
Median	56.0
Min, Max	31, 85
Age group - n (%)	
18 - 64 years	48 (77.4)
65 - 74 years	11 (17.7)
75 - 84 years	2 (3.2)
≥ 85 years	1 (1.6)

CRC = colorectal cancer; Q1 = first quartile; Q3 = third quartile; QD = once daily
Phase 2 data cut-off date 01 March 2021.
Source: Table 14c-2.1 of Study 20170543 Interim Analysis 1 (Phase 1 CRC Cohort)

The Applicant's Position:

Overall, the subjects with mCRC enrolled across the studies had baseline characteristics indicative of subjects with mCRC. Thus, patient population evaluated in the efficacy studies is considered representative of the overall population of patients with mCRC and supportive of the proposed indication.

The FDA's Assessment:

FDA focused the review of baseline demographic on the randomized and pivotal trial, Study

20190172. The baseline demographics were generally well-balanced between the arms except for some subgroups of race, ethnicity, and age. The sotorasib 240 mg arm had more Asian patients, patients enrolled in Asia, and patients 18-64 years old, and less patients 65-74 years old than the other two arms, and the sotorasib 960 mg arm had more White patients than the other two arms. There were no patients in the sotorasib 240 mg arm who reported Hispanic or Latino ethnicity, while 7.5% of patients in the sotorasib 960 mg arm and 14.8% of patients in the control arm reported Hispanic or Latino ethnicity. KRAS mutation is not known to have a differential effect on the prognosis of patients with different races or ethnicities, and to date, FDA is unaware of an association between race/ethnicity and responses to KRAS inhibitor therapy.[5] Standard and supportive care are similar for patients with previously treated mCRC across the enrolling countries. Although young patients may tend to have more aggressive disease; their survival rates may not differ from older patients.[6] Overall, the imbalances between the arms are unlikely to affect the interpretation of the primary endpoint of PFS in Study 20190172.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Study 20190172

Most subjects had prior anti-angiogenic therapy (140 subjects [87.5%]) and baseline ECOG performance status of 0 (97 subjects [60.6%]). The time from initial diagnosis of metastatic disease to randomization was ≥ 18 months for 89 subjects (55.6%). The body site at initial diagnosis was the colon for 106 subjects (66.3%) and the rectum for 54 subjects (33.8%). Most subjects (112 subjects [70.0%]) had liver metastasis. A total of 24 subjects (15.0%) had only 1 prior line of therapy, 68 subjects (42.5%) had a second line of therapy, 42 subjects (26.3%) had a third line of therapy, 18 subjects (11.3%) had a fourth line of therapy, and 8 subjects (5.0%) had 5 or more prior lines of therapy. Best response on prior therapy for most subjects was progression (65 subjects [40.6%]) or non-CR/non-progressive disease (62 subjects [38.8%]).

Study 20190135 Subprotocol H

All subjects had stage IV disease at screening, at least 1 prior line of therapy, and *KRAS p.G12C*-mutated solid tumors. Most subjects had baseline ECOG performance status of 1 (73 subjects, 60.3%). The mean (SD) time from initial cancer diagnosis to enrollment was 32.8 (26.8) months; the time from initial diagnosis of metastatic disease to enrollment was ≥ 18 months for 60 subjects (49.6%) and < 18 months for 57 subjects (47.1%). The primary tumor type in most subjects was CRC (79 subjects, 65.3%), followed by NSCLC (30 subjects, 24.8%), pancreatic cancer (7 subjects, 5.8%), and other (5 subjects, 4.1%); all other primary tumor types occurred in 1 subject each. Most subjects (69 subjects, 57.0%) had liver metastasis; most subjects (106 subjects, 87.6%) did not have brain metastasis.

Most subjects (91 subjects, 75.2%) had prior surgery and 44 subjects (36.4%) had prior radiotherapy for their current malignancy.

Study 20170543

Of the 29 subjects in the phase 1 960 mg cohort, 6.9%, 41.4%, 31.0%, and 20.7% had 1, 2, 3, and ≥ 4 prior lines of anticancer therapies, respectively; 48.3% and 51.7%, had baseline ECOG performance status of 0 and 1, respectively; 58.6% and 3.4% had liver and brain metastasis, respectively. All subjects in the 960 mg cohort received chemotherapy (oxaliplatin 96.6%, irinotecan 93.1%, fluoropyrimidine 100%); 17.2% received TAS-102; 86.2% received antiangiogenic therapy (regorafenib, 6.9%); and 10.3% received anti-programmed cell death-1/programmed death-ligand 1 therapy. Less than half of the subjects (41.4%) in the 960 mg cohort had stage IV disease at initial diagnosis.

In the phase 2 CRC cohort, subjects had an ECOG performance status of 0 (35 subjects, 56.5%) or 1 (27 subjects, 43.5%), and all subjects (100.0%) had stage IV disease at screening. All subjects had received at least 1 prior line of anticancer therapy (median: 3 lines): 3 subjects (4.8%) received 1 prior line, 14 subjects (22.6%) received 2 prior lines, 19 subjects (30.6%) received 3 prior lines, and 26 subjects (41.9%) received ≥ 4 prior lines. All subjects (100.0%) had received prior chemotherapy and all had received platinum-based chemotherapy.
Three subjects (4.8%) had received immunotherapy, with 2 subjects (3.2%) receiving anti-PD-1 or anti-PD-L1 therapies. Per local lab, all subjects (100.0%) were *KRAS p.G12C* mutation positive; per central lab, 60 subjects (96.8%) were *KRAS p.G12C* mutation positive and 2 subjects (3.2%) were unknown (a protocol deviation). Most subjects (60 subjects, 96.8%) had adenocarcinoma and most subjects had liver metastasis (48 subjects, 77.4%). No subject had brain metastasis.

The Applicant's Position:

Overall, the subjects with mCRC enrolled across the studies had baseline characteristics indicative of subjects with mCRC. Thus, the patient population evaluated in the efficacy studies is considered representative of the overall population of patients with mCRC and supportive of the proposed indication.

The FDA's Assessment:

The baseline characteristics were generally well-balanced when comparing each of the sotorasib arms to the control arm in Study 20190172. There were some imbalances in prognostic factors across the two sotorasib arms. The sotorasib 240 mg with panitumumab arm had more poor prognostic factors than the sotorasib 960 mg with panitumumab arm. Compared to the sotorasib 960 mg arm, the sotorasib 240 mg arm had more patients who had 3 prior lines of therapy (18 versus 10 patients), fewer patients who had a response to prior therapy (2 versus 8 patients), more patients who were metastatic at initial diagnosis (29 versus 24 patients), and more left-sided CRC (36 versus 28 patients). Compared to the sotorasib 240 mg arm, the sotorasib 960 mg arm had more patients with poorly differentiated CRC (8 versus 3

patients).

See Section 8.1.3 for FDA's assessment of the impact of these disease characteristics imbalances on FDA's benefit-risk assessment.

Table 17. FDA's Analysis of Baseline Disease Characteristics in Study 20190172

n (%)	Trifluridine and Tipiracil or Regorafenib (N = 54)	Sotorasib 240 mg + Panitumumab (N = 53)	Sotorasib 960 mg + Panitumumab (N = 53)
Baseline ECOG performance status			
0	36 (67)	29 (55)	32 (60)
1	17 (31)	22 (42)	19 (36)
2	1 (2)	2 (4)	2 (4)
Stage at initial diagnosis			
1-2	6 (11)	6 (11)	7 (13)
3	11 (20)	12 (23)	17 (32)
4	26 (48)	29 (55)	24 (45)
Unknown or missing	11 (20)	6 (11)	5 (9)
Body site at initial diagnosis			
Colon	37 (69)	32 (60)	37 (70)
Rectum	17 (32)	21 (40)	16 (30)
Sidedness			
Left	37 (69)	36 (68)	28 (53)
Right	16 (30)	17 (32)	24 (45)
Unknown	1 (1.9)	0	1 (1.9)
Liver metastasis			
Yes	38 (70)	36 (68)	38 (72)
No	16 (30)	17 (32)	15 (28)
Tumor differentiation			
Well	4 (7)	9 (17)	6 (11)

Moderate	26 (48)	26 (49)	24 (45)
Poor	6 (11)	3 (6)	8 (15)
Unknown or Other	18 (33)	15 (28)	15 (28)
Microsatellite stability			
High	0	0	1 (1.9)
Stable	43 (80)	42 (79)	42 (79)
Low	3 (6)	2 (3.8)	3 (6)
Not tested or Unknown	8 (15)	9 (17)	7 (13)
BRAF mutation			
Yes	0	0	0
No	54 (100)	53 (100)	53 (100)
Best response to last prior line of therapy			
Complete response	0 (0.0)	1 (1.9)	0 (0.0)
Partial response	5 (9.3)	1 (1.9)	8 (15.1)
Non-CR/Non-PD	18 (33.3)	25 (47.2)	19 (35.8)
Progression	23 (42.6)	22 (41.5)	21 (39.6)
Unknown	8 (14.8)	4 (7.5)	5 (9.4)
Prior anti-angiogenic therapy			
Yes	48 (89)	47 (89)	45 (85)
No	6 (11)	6 (11)	8 (15)
Number of prior lines of therapy			
1	9 (17)	8 (15)	7 (13)
2	18 (33)	21 (40)	29 (55)
3	14 (26)	18 (34)	10 (19)
4	9 (17)	4 (8)	5 (9)
≥ 5	4 (7)	2 (4)	2 (4)
Prior Therapies			

Oxaliplatin	53 (98)	52 (98)	53 (100)
Irinotecan	51 (94)	51 (96)	49 (92)
Fluoropyrimidine	54 (100)	52 (98)	53 (100)

Abbreviations: CR = complete response, PD = progressive disease
Source: ADSL.xpt (SDN 380, submitted April 17, 2024)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment Compliance

Study 20190172

Compliance with treatment and the corresponding assessments were followed according to the Schedule of Activities (Protocol Section 1.3) and the Treatment Procedures (Protocol Section 8.1.2). Treatment compliance on sotorasib was documented in the medical records and collected in the case report form (CRF) and through subject input into an electronic diary. Additional details on the method(s) used to assess treatment compliance are provided in Protocol Section 6.5.

Study 20190135 Subprotocol H

Compliance with treatment and the corresponding assessments were followed according to the Schedule of Activities (Protocol Section 1.3) and the Treatment Procedures (Protocol Section 6.1). Additional details on the method(s) used to assess treatment compliance are provided in Protocol Section 6.1.

Study 20170543

Sotorasib was dispensed to subjects at the research facility by a qualified staff member. During study visit days, sotorasib administration was done at the study center after all predose assessments were conducted. On non-study visit days, a diary provided to the subject was used to capture compliance with sotorasib administration.

Concomitant Medications

Throughout the studies, investigators could prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Protocol Section 6.1.6 of Study 20190172, Protocol Section 6.1.7 of Study 20190135 Subprotocol H, and Section 6.6 of Study 20170543.

Study 20190172

Concomitant medication use was reported for 53 subjects (100%) in the sotorasib 240 mg + panitumumab group, 50 (94.3%) in the sotorasib 960 mg + panitumumab group and 49 subjects (96.1%) in the control group.

The most common concomitant medications used (> 20% of subjects) in the sotorasib 240 mg + panitumumab group were doxycycline and paracetamol (21 subjects [39.6%] each), minocycline hydrochloride (16 subjects [30.2%]), and dexamethasone, hydrocortisone, and metoclopramide (12 subjects [22.6%] each), and in the sotorasib 960 mg + panitumumab group were doxycycline (28 subjects [52.8%]), paracetamol (17 subjects [32.1%]), magnesium (13 subjects [24.5%]), and dexamethasone (12 subjects [22.6%]). The most common (> 20% of subjects) in the control group was paracetamol (15 subjects [29.4%]) (Table 14-8.3.1 of Study 20190172).

The number of subjects who received subsequent anticancer therapies while on study was 19 subjects (35.8%), 16 subjects (30.2%), and 29 subjects (53.7%) in the sotorasib 240 mg + panitumumab, sotorasib 960 mg + panitumumab, and control groups, respectively, with median (range) time from randomization to start of subsequent anticancer therapy being 4.50 (2.0, 10.4), 6.08 (2.3, 8.9) and 3.29 (0.2, 11.1) months (Table 14-8.3.2 of Study 20190172).

Study 20190135 Subprotocol H

Concomitant medication use was reported for all 121 subjects (100%). The most common (≥ 25% of subjects) were paracetamol (50.4%), ondansetron (41.3%), magnesium oxide (29.8%), doxycycline (28.1%), magnesium sulfate (27.3%), and hydrocortisone (25.6%).

Study 20170543

Phase 1

All subjects with CRC in the phase 1 portion of the study (N = 60) used concomitant medications. The most common medications (frequency ≥ 30%) used were paracetamol (38.3%) and ondansetron (33.3%) and were consistent in the 960 mg QD cohort (paracetamol, 34.5%; ondansetron, 27.6%).

Phase 2

All subjects in the CRC safety analysis set reported use of concomitant medications. The most common medications (frequency ≥ 20%) used by subjects with CRC were ondansetron (21 subjects, 33.9%) and paracetamol (18 subjects, 29.0%).

Rescue Medication

Not applicable

The Applicant's Position:

No formal treatment compliance measurements were planned. Analyses for exposure demonstrated the median relative dose intensity of sotorasib was 100% for both the sotorasib 960 mg and 240 mg groups in Study 20190172, 99% in Study 20190135 Subprotocol H, and 100% for all doses in Study 20170543. Concomitant medication use was consistent with protocol-specified criteria.

The FDA's Assessment:

FDA focused on the pivotal trial, Study 20190172. See Section 8.2.2 (Overall Exposure) for FDA's analysis of treatment compliance.

Subsequent Anticancer Therapy

FDA's analysis of subsequent anticancer therapy (Table 18) was slightly different from the Applicant's. More patients in the control arm had subsequent anticancer therapy than in the sotorasib arms, and the proportion of patients who used subsequent anticancer therapy in the sotorasib arms were similar. About half the patients who received subsequent anticancer therapy in the control arm received a KRAS G12C inhibitor. Only one patient in the sotorasib arms received a subsequent KRAS G12C inhibitor. The proportion of patients who received subsequent trifluridine/tipiracil or regorafenib was numerically lowest in the sotorasib 960 mg arm. The proportion of patients who received subsequent chemotherapy was also numerically lowest in the sotorasib 960 mg arm. Most patients in the trial did not receive subsequent immunotherapy or local therapy. The patients who did receive local therapy were in the sotorasib 960 mg arm.

The use of subsequent anticancer therapy is as expected based on the improved efficacy of the sotorasib regimens compared to control therapy, i.e., less patients in the sotorasib arms used subsequent therapy prior to data cutoff date. Also as expected, most patients who received subsequent therapy in the control arm received a KRAS G12C inhibitor (52%, n=15/29).

Table 18. FDA's Analysis of Subsequent Anti-Cancer Therapy in Study 20190172

	Trifluridine/Tipiracil or Regorafenib (N = 54) n (%)	Sotorasib 240 mg + Panitumumab (N = 53) n (%)	Sotorasib 960 mg + Panitumumab (N = 53) n (%)
Patients who had subsequent anticancer therapy	**29 (54)**	**17 (32)**	**16 (30)**
KRAS G12C inhibitor regimens	15 (28)	0	1 (1.9)
Single-agent sotorasib	4 (7)	0	1 (1.9)
Sotorasib + another drug	2 (3.7)	0	0
Single-agent adagrasib	3 (6)	0	0
adagrasib + another drug	1 (1.9)	0	0
Investigational KRAS G12C inhibitor as a single agent or in combination with another drug	5 (9)	0	0
Patients who got subsequent trifluridine/tipiracil or regorafenib [b]	11 (20)	14 (26)	9 (17)
Chemotherapy-based regimens [a]	6 (11)	6 (11)	3 (6)
Patients who got subsequent immunotherapy	1 (1.9)	0	1 (1.9)

Nivolumab	0	0	1 (1.9)
Investigational agent	1 (1.9)	0	0
Radiation	0	0	3 (6)

[a] chemotherapies were 5-fluorouracil, leucovorin, capecitabine, irinotecan, oxaliplatin with or without bevacizumab
[b] including Trifluridine/Tipiracil with bevacizumab
Source: ADCM.xpt (SDN 380, submitted April 17, 2024)

Concomitant Medications used during Treatment with Trial Drug(s)

FDA analyzed the medications the patients used while on trial treatment for indications that are common among patients with CRC and for indications that would be expected based on the known safety profile of the experimental drugs (e.g., transaminitis for sotorasib and skin toxicity for panitumumab). Dermatological conditions were the most common reasons for use of concomitant medications in the sotorasib arms, and use of concomitant medications for these conditions were much more common in the sotorasib arms compared to the control arm (Table 19). Use of concomitant medication for pain was common across all three arms, with similar rates in all three arms. Hypomagnesemia was more common in the sotorasib arms compared to the control arm. Only patients in the sotorasib arms received concomitant medications for intestinal obstruction and transaminitis. Patients in this trial did not receive other anticancer treatment while on trial treatment.

In summary, the differences in concomitant medication use in Study 20190172 appear to be driven by toxicities related to panitumumab, i.e., dermatologic conditions and hypomagnesemia, rather than sotorasib.

Table 19. FDA's Analysis of the Common Indications for Use of Concomitant Therapy in Study 20190172

	Trifluridine/Tipiracil or Regorafenib (N = 54) n (%)	Sotorasib 240 mg + Panitumumab (N = 53) n (%)	Sotorasib 960 mg + Panitumumab (N = 53) n (%)
Dermatologic conditions [a, b]	7 (13)	47 (89)	46 (87)
Pain [b]	26 (48)	27 (51)	24 (45)
Infection including fever [b]	15 (28)	20 (38)	19 (36)
Hypomagnesemia [b]	1 (1.9)	14 (26)	17 (32)
Nausea and/or vomiting [b]	14 (26)	20 (38)	15 (28)
Constipation [b]	8 (15)	13 (25)	15 (28)
Diarrhea [b]	8 (15)	10 (19)	13 (25)
Mucositis [b]	7 (13)	4 (8)	9 (17)
Thromboembolism [b]	13 (24)	12 (23)	8 (15)
Transaminitis [b,c]	0	3 (6)	4 (8)

Intestinal obstruction	0	1 (1.9)	1 (1.9)

[a] include skin and nails
[b] or prevention of
[c] indications were ALT increased, AST increased, hepatic cytolysis and biological inflammatory syndrome of undetermined origin, hepatic disease, hepatic function disorder, hypertransaminasemia, liver function preservation, and prophylactic liver impairment; drugs were supplements (e.g., amino acids, fatty acids, minerals, vitamins, glutathione), corticosteroids, acetaminophen, silybum marianum (milk thistle), and ursodeoxycholic acid

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:
Study 20190172
Progression-free Survival (Primary Endpoint)
As of 19 June 2023, the median PFS as assessed by central review was 5.6 months (95% CI: 4.2, 6.3) in the sotorasib 960 mg + panitumumab group, 3.9 months (95% CI: 3.6, 5.8) in the sotorasib 240 mg + panitumumab group, and 2.0 months (95% CI: 1.9, 3.9) in the control group. The HR (95% CI) for disease progression or death was 0.5 (0.3, 0.8; 2-sided p-value = 0.005) for the sotorasib 960 mg + panitumumab versus the control and 0.6 (0.4, 0.9; 2-sided p-value = 0.04) for the sotorasib 240 mg + panitumumab versus the control (Applicant - Table 20). The Kaplan-Meier estimated PFS rates were 72.2%, 70.5%, and 49.3% at 3 months for the sotorasib 960 mg + panitumumab, sotorasib 240 mg + panitumumab, and control groups, respectively (Applicant – Figure 5). The PFS benefit observed in the sotorasib 960 mg + panitumumab group versus the control group was consistent across all relevant subgroups. The numerical PFS benefit observed in the sotorasib 240 mg + panitumumab group versus the control group was consistent across all relevant subgroups as well (Section 2.1 of Module 2.7.3, Summary of Clinical Efficacy).

Applicant - Table 20. Summary of Efficacy Results for Study 20190172 (Full Analysis Set)

	Trifluridine and Tipiracil or Regorafenib (N = 54)	Sotorasib 240 mg + Panitumumab (N = 53)	Sotorasib 960 mg + Panitumumab (N = 53)
Progression-free survival per BICR			
Number of PFS events – n (%)	35 (64.8)	35 (66.0)	32 (60.4)
Median (months) (95% CI)[a]	2.04 (1.91, 3.91)	3.91 (3.61, 5.75)	5.62 (4.21, 6.31)
Hazard ratio (95% CI)[b]	-	0.593 (0.372, 0.946)	0.481 (0.297, 0.778)
p-value (2-sided)[c]	-	0.036	0.005
Overall survival			
Number of OS events – n (%)	30 (55.6)	28 (52.8)	24 (45.3)
Median (months) (95% CI)[a]	10.25 (7.00, NE)	11.93 (7.52, NE)	NE (8.61, NE)
Hazard ratio (95% CI)[b]		0.827 (0.491, 1.392)	0.697 (0.411, 1.183)
p-value (2-sided)[c]		0.50	0.20
Objective response rate per BICR			
Number of CR, PR	0	3 PR	1 CR, 13 PR
ORR (95% CI) (%)[d]	0.0 (0.0, 6.6)	5.7 (1.2, 15.7)	26.4 (15.3, 40.3)
Difference of ORR (95% CI)[e]	-	5.5 (-0.7, 11.8)	27.0 (14.9, 39.0)
Duration of response[f]			
Median (months) (95% CI)	-	-	4.4 (3.55, NE)
Range, months	-	1.8+, 3.8+	1.9+, 6.0+
Time to response[f]			
Median months (range)	-	1.77 (1.7, 1.9)	2.05 (1.9, 3.9)
Disease control rate per BICR[g]			
DCR (95% CI) (%)[d]	46.3 (32.6, 60.4)	69.8 (55.7, 81.7)	71.7 (57.7, 83.2)
Difference of DCR (95% CI)[e]		24.0 (5.5, 42.5)	24.2 (6.7, 41.6)

BICR = Blinded Independent Central Review Committee; CR = complete response; DCR = disease control rate; ECOG = Eastern Cooperative Oncology Group; IRT = interactive response technology; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria In Solid Tumors

Data cut-off date: 18 December 2023 for OS and 19 June 2023 for all other endpoints

Randomization stratification factors per IRT are prior anti-angiogenic therapy (yes vs no), time from initial diagnosis of metastatic disease to randomization (≥ 18 months vs < 18 months), and ECOG status (0 or 1 vs 2).

[a] Medians were estimated using the Kaplan-Meier method. 95% CIs were estimated using the method by Klein and Moeschberger with log-log transformation.

[b] Hazard ratios and 95% CIs were estimated using a stratified Cox proportional hazards model. A hazard ratio < 1.0 indicates a lower average event rate and a longer PFS/OS for sotorasib + panitumumab combination relative to (trifluridine and tipiracil or regorafenib).

[c] p-value was calculated using a stratified log-rank test. It was calculated for treatment sotorasib combination with reference to trifluridine and tipiracil or regorafenib.

[d] 95% CIs were estimated using the Clopper-Pearson method.

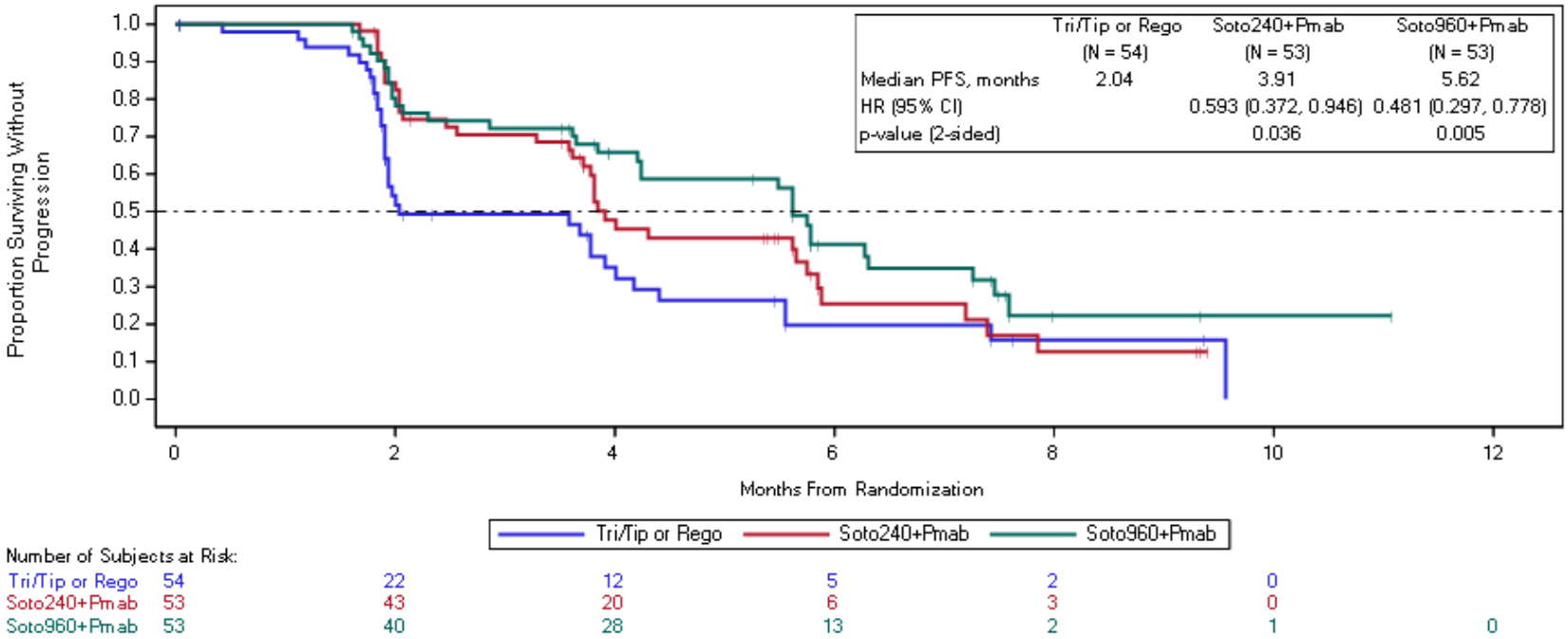
[e] Difference of proportions, 95% CI and p-value were estimated using the stratified Cochran-Mantel-Haenszel method.

[f] Duration of response and time to response were calculated for only for subjects who achieve a confirmed best overall response of PR or CR.

[g] Disease Control Rate is defined as the proportion of subjects with the best overall response of CR or PR or of stable disease per RECIST v1.1 ≥ 7 weeks.

Source: Tables 14-4.1.1, 14-4.2.1, and 14-4.3.1 of Study 20190172 PFS PA CSR, dated 28 March 2024 and Table 14-4.4.1 of Study 20190172 OS Analysis

Applicant – Figure 5. Kaplan-Meier Plot of Progression-free Survival as Assessed by the Blinded Independent Central Review Committee for Study 20190172 (Full Analysis Set)



HR = hazard ratio; PFS = progression-free survival; Soto240+Pmab = sotorasib 240 mg + panitumumab; Soto960+Pmab = sotorasib 960 mg + panitumumab; Tri/Tip or Rego = trifluridine and tipiracil or regorafenib
Data cut-off date: 19 June 2023.
Censor indicated by vertical bar. Stratified Cox HR and stratified log-rank p-value for sotorasib + panitumumab vs trifluridine and tipiracil or regorafenib are provided.
Source: Figure 10-1 of Study 20190172 PFS PA CSR, dated 28 March 2024

Study 20190135 Subprotocol H

No primary efficacy endpoints were included in this study; all primary endpoints are safety endpoints.

Study 20170543

Phase 1

No primary efficacy endpoints were planned for the subjects with CRC in the phase 1 portion of the study.

Phase 2

Overall Response Rate (Primary Endpoint)

As of 01 April 2023, the primary endpoint of ORR (complete response [CR] + partial response [PR]) measured by computed tomography or magnetic resonance imaging and assessed per RECIST 1.1 by an independent radiological central laboratory for subjects with *KRAS p.G12C*-mutated CRC was 11.3% (7 of 62 subjects; 95% CI: 4.66, 21.89); all 7 subjects (11.3%) achieved PR (Applicant - Table 21). No notable treatment-by-subgroup effects were observed. Sensitivity analyses were conducted for response-related endpoints per investigator assessment. The concordance rates between central review and investigator for best overall response, objective response, and disease progression were 71.0%, 85.5%, and 77.4%, respectively.

Applicant - Table 21. Summary of Response by Central Review for Study 20170543 (Phase 2 CRC in Full Analysis Set)

	960 mg QD Fasted (N = 62)
Objective response rate (ORR)	
Confirmed - N1 (%)	7 (11.3)
95% CI[a]	(4.66, 21.89)
Disease control rate (DCR) - n (%)	51 (82.3)
95% CI[a]	(70.47, 90.80)
Duration of response (DOR)[b]	
Observed duration ≥ 6 months - n (%)	3 (42.9)
Observed duration ≥ 12 months - n (%)	1 (14.3)
DOR (KM)(months)	
Median (95% CI)	-
Min, Max (+ for censored)	1.4+, 13.1
Time to objective response (months)[b]	
Median	2.60
Min, Max	1.3, 30.5
Progression-free survival (KM) (months)	
Events - n (%)	49 (79.0)
Median (95 CI)	4.04 (2.79, 4.17)
KM estimate at 6 months	19.46 (9.71, 31.69)
KM estimate at 12 months	11.67 (4.24, 23.23)
Overall survival (KM) (months)	
Events - n (%)	52 (83.9)
Median (95% CI)	10.05 (7.66, 14.29)
KM estimate at 6 months	81.19 (68.61, 89.12)
KM estimate at 12 months	44.20 (31.11, 56.50)

CRC = colorectal cancer; KM = Kaplan-Meier; Max = maximum; Min = minimum; N = Number of subjects in the analysis set; n = Number of subjects with observed data; QD = once daily
Data cut-off date 01 April 2023.
Months are derived as days x (12/365.25).
KM estimates were not provided if the analysis had fewer than 10 subjects. Only min, max were provided.
[a] Exact 95% confidence interval was calculated using the Clopper Pearson method.
[b]Time to response and DOR were calculated among confirmed responders N1.
Source: Table 10-1, Table 10-2, and Table 10-3 of Study 20170543 Interim Analysis 2 (Phase 2 CRC Cohort)

The Applicant's Position:

Results from Study 20190172 characterized the efficacy and safety of sotorasib in combination with panitumumab compared with that of trifluridine and tipiracil or regorafenib in subjects with mCRC. The results show that the sotorasib 960 mg QD in combination with panitumumab demonstrated statistically significant improvement in PFS over standard of care in a highly pre-treated population with *KRAS p.G12C*-mutated mCRC.

The FDA's Assessment:
FDA agrees with the Applicant's description of the results of the comparison of sotorasib 960mg and panitimumab compared to control for the primary endpoint, PFS assessed by central review in study 20190172. Median PFS in sotorasib 960mg arm was 5.6 months (95% CI: 4.2, 6.3) and 2 months (95% CI: 1.9 – 3.9) in the control arm. PFS HR was 0.48 (95% CI: of 0.30, 0.78). FDA also agrees with Applicant's position that the PFS benefit observed in the sotorasib 960 mg + panitumumab group versus the control group was consistent across all relevant subgroups. Summary of the PFS analysis in subgroup for the

FDA notes that although the difference in median PFS between the sotorasib 240 mg andpanitumumab arm and control arm was 1.87 months with a PFS HR of 0.59 (0.37, 0.95), the difference in PFS between the arms was not statistically significant (observed p-value: 0.036 compared to the stopping boundary [p-value scale] of 0.0313).

The efficacy results from the Study 20170543 were not validated by the FDA review team; however, they were considered as part of the assessment of sotorasib anti-tumor activity.

Data Quality and Integrity

Data:

Study Monitoring

The study centers were monitored by Amgen staff and contract research organizations. Centers were visited at regular intervals and a visit log was maintained. Monitors were responsible for reviewing adherence to the protocol; compliance with GCP; and the completeness, accuracy, and consistency of the data. Direct access to subject medical and laboratory records was permitted to verify entries on the study-specific electronic CRFs (eCRFs). Source data verification was conducted for 100% of the subjects enrolled into Study 20190172.

Investigator Meetings and Staff Training

Investigator staff training was provided by Amgen Development and Amgen Clinical Program Operations during a study kickoff investigator meeting, at individual site initiations, and during routine monitoring visits. The sponsor organized additional clinical research associate meetings before study start and during the study to provide information on the investigational product, the study rationale and design, responsibilities under ICH/FDA GCP, and training on the detailed study requirements.

Laboratory Procedures

Central laboratories and other central facilities were used in the studies. Where local laboratories were used, their participation in internal and external quality control, quality assurance, and accreditation schemes was evaluated by the study monitors.

Investigator Responsibilities

The investigators were responsible for all data entered in the CRFs and documented their review and approval of the data by signing a form verifying the validity and completeness of the data. The investigator was responsible for appropriate retention of essential study documents.

Clinical Data Management
Case report form data were captured (through data entry by study center personnel in eCRFs) in an Amgen database system and iMedidata RAVE. Data quality checks were applied using manual and electronic verification methods. An audit trail to support data query resolution and any modification to the data was maintained.

Quality Assurance Audits
Audits of Studies 20190172, 20190135 Subprotocol H, and 20170543 included as part of the independent Amgen Quality, Compliance and Audit program performed by Amgen.

The Applicant's Position:
Amgen conducted a 100% source data verification for Study 20190172 and no data integrity concerns were reported following completion of study center inspections.
No issues that could affect the efficacy results were identified regarding data quality or integrity from Studies 20190172, 20190135 Subprotocol H, and 20170543. Prespecified and additional sensitivity analyses on the primary endpoint showed that any changes in study design and conduct did not reduce the observed treatment benefit of sotorasib monotherapy and sotorasib in combination with panitumumab.

The FDA's Assessment:
FDA acknowledges the Applicant's description of Data Quality and Integrity, but does not agree that that there was no data integrity concern. FDA notes that the Applicant notified FDA of an issue with data quality at a study site in Italy due to a forgery issue (see Section 4.1). FDA determined that the efficacy data at this site appeared adequate for FDA review. In addition, FDA notes that the primary PFS analysis was updated at the time of NDA submission due to unreported scans from five patients that were identified during data cleaning activities conducted by the Applicant. As a result, the final PFS analysis of sotorasib 240 mg in combination with panitumumab compared to investigator's choice of SOC did not meet the specified threshold for statistical significance.

Efficacy Results – Secondary and other relevant endpoints

Data:
Study 20190172
Overall Survival (Key Secondary Endpoint)
As of the data cut-off date for the protocol-specified final OS analysis (18 December 2023), a total of 82 deaths (28, 24, and 30 deaths from sotorasib 240 mg + panitumumab group,

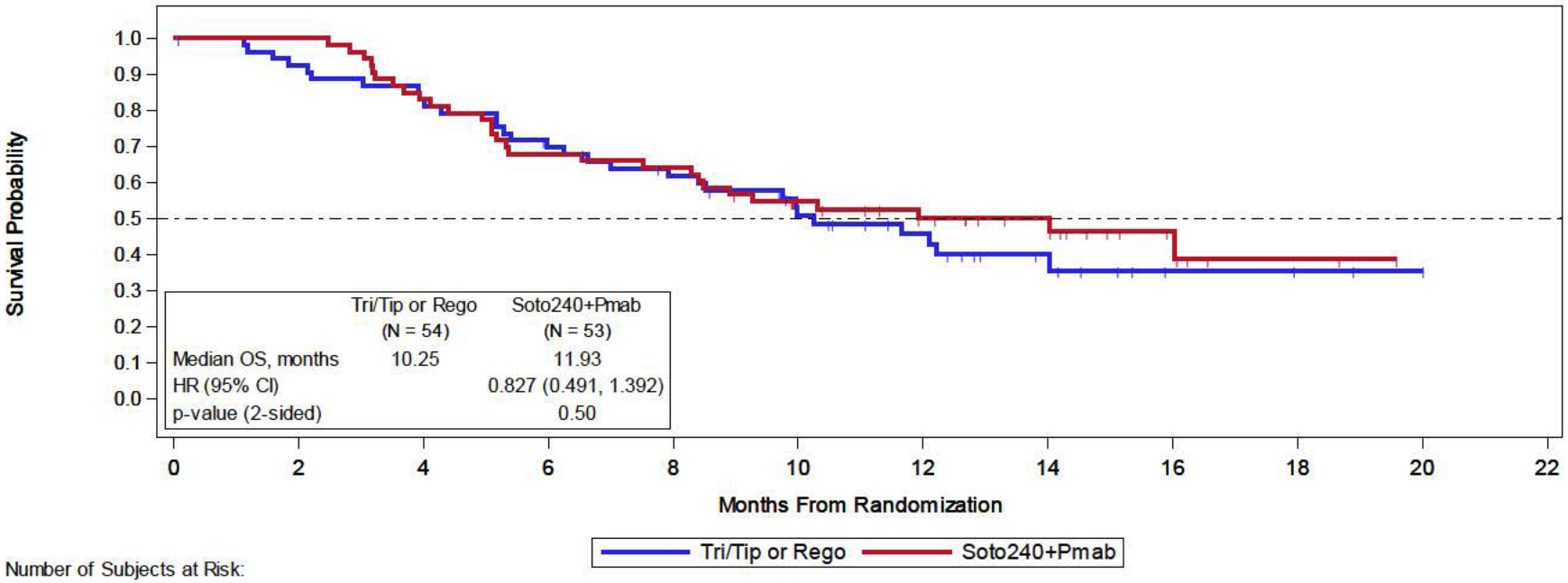
sotorasib 960 mg + panitumumab group, and control group, respectively) were reported (Applicant - Table 20).

Kaplan-Meier plots of OS are presented in Applicant – Figure 6 and Applicant – Figure 7 for sotorasib 240 mg + panitumumab versus control and sotorasib 960 mg + panitumumab versus control, respectively. Treatment with sotorasib 240 mg + panitumumab resulted in 17% reduction in the hazard of death when compared with control treatment (HR 0.83 [95% CI: 0.49, 1.39], 2-sided p-value = 0.50).Treatment with sotorasib 960 mg + panitumumab resulted in a 30% reduction in the hazard of death when compared with control treatment (HR 0.70 [95% CI: 0.41, 1.18], 2-sided p-value = 0.20).

With a median follow-up time of 14.0 months, the median OS was 11.9 months (95% CI: 7.52, not estimable [NE]) in the sotorasib 240 mg + panitumumab group. With a median follow-up time of 13.6 months, the median OS was NE (95% CI: 8.6, NE) in the sotorasib 960 mg + panitumumab group. With a median follow-up time of 12.9 months, the median OS was 10.3 months (95% CI: 7.0, NE) in the control group.

Study 20190172 showed a trend toward improved OS for subjects randomized to sotorasib 960 mg in combination with panitumumab as compared with standard of care. This study was not powered to detect a statistically significant difference in OS.

Applicant – Figure 6. Kaplan-Meier Plot of Overall Survival
(Full Analysis Set in Trifluridine and Tipiracil or Regorafenib and Sotorasib 240 mg + Panitumumab)

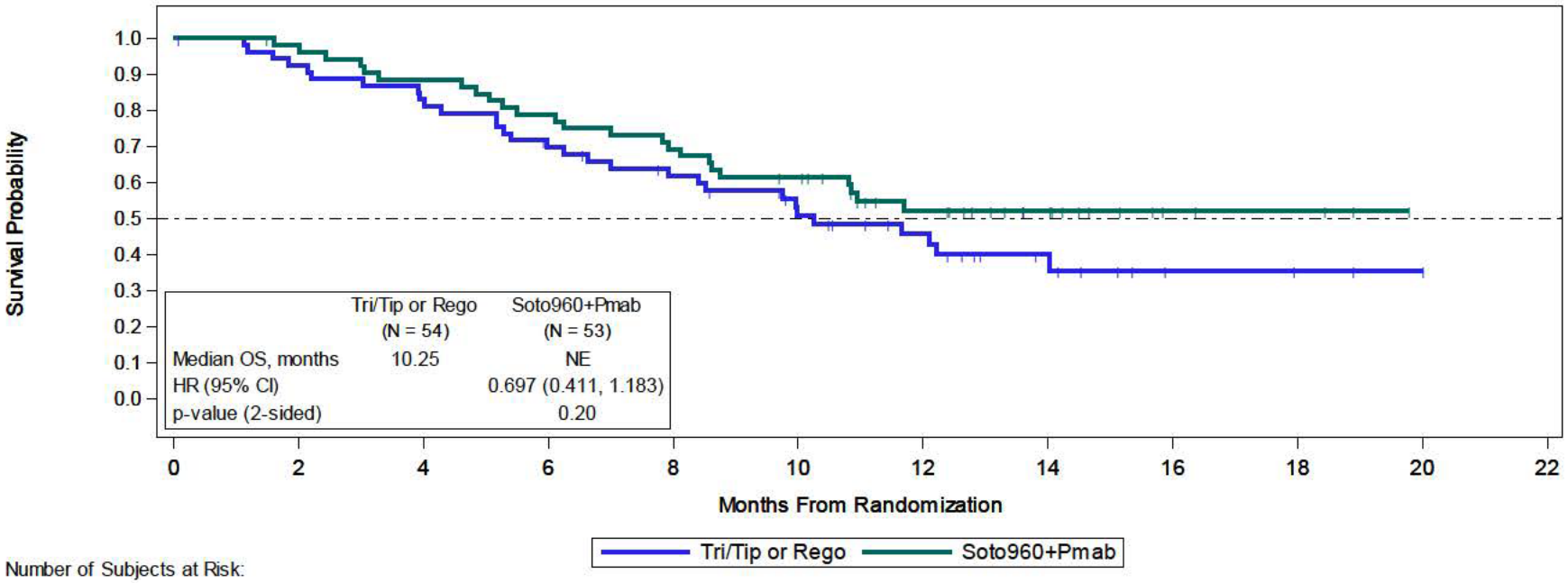


Number of Subjects at Risk:

Tri/Tip or Rego	54	49	44	36	30	22	16	9	3	2	1	0
Soto240+Pmab	53	53	44	36	34	25	19	14	6	2	0	

HR = hazard ratio; NE = not estimable; OS = overall survival; Soto240+Pmab = sotorasib 240 mg + panitumumab; Tri/Tip or Rego = trifluridine and tipiracil or regorafenib
Data cut-off date: 18 December 2023.
Censor indicated by vertical bar. Stratified Cox HR and stratified log-rank p-value for sotorasib + panitumumab vs trifluridine and tipiracil or regorafenib are provided.
Source: Figure 14-4.4.1.2 of Study 20190172 OS Analysis

Applicant – Figure 7. Kaplan-Meier Plot of Overall Survival
(Full Analysis Set in Trifluridine and Tipiracil or Regorafenib and Sotorasib 960 mg + Panitumumab)



Number of Subjects at Risk:

Tri/Tip or Rego	54	49	44	36	30	22	16	9	3	2	1	0
Soto960+Pmab	53	51	46	41	36	31	20	12	4	3	0	

HR = hazard ratio; NE = not estimable; OS = overall survival; Soto960+Pmab = sotorasib 960 mg + panitumumab; Tri/Tip or Rego = trifluridine and tipiracil or regorafenib
Data cut-off date: 18 December 2023.
Censor indicated by vertical bar. Stratified Cox HR and stratified log-rank p-value for sotorasib + panitumumab vs trifluridine and tipiracil or regorafenib are provided.
Source: Figure 14-4.4.1.1 of Study 20190172 OS Analysis

Objective Response Rate (BICR) (Key Secondary Endpoint)
The ORR (95% CI) was 5.7% (1.2, 15.7) in the sotorasib 240 mg + panitumumab group, 26.4% (15.3, 40.3) in the sotorasib 960 mg + panitumumab group, and 0.0% (0.0, 6.6) in the control group (Applicant - Table 20). Objective response rate was not formally statistically tested due to hierarchical testing order.

Duration of Response, Time to Response, and Disease Control Rate
Results from the secondary endpoints of duration of response (DOR), time to response (TTR), and DCR were numerically improved for sotorasib 960 mg in combination with panitumumab vs the control group (Applicant - Table 20).

Study 20190135 Subprotocol H
Results of secondary endpoints for Study 20190135 Subprotocol H are provided in Applicant - Table 22 and summarized in Section 8.1.4.

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Applicant - Table 22. Summary of Response by Central Review for Study 20190135 Subprotocol H (Full Analysis Set)

	Part 2A CRC Refractory (N = 40) n (%)	Part 2D CRC 1 Prior Line (N = 19) n (%)
Objective response rate (ORR)		
Confirmed - N1 (%)	12 (30.0)	4 (21.1)
95% CI[b]	(16.56, 46.53)	(6.05, 45.57)
Disease control rate (DCR) - n (%)	37 (92.5)	18 (94.7)
95% CI[b]	(79.61, 98.43)	(73.97, 99.87)
Duration of objective response (DOR)[c]		
Observed duration ≥ 6 months - n (%)	7 (58.3)	3 (75.0)
Observed duration ≥ 12 months - n (%)	0 (0.0)	1 (25.0)
DOR (KM)(months)		
Median (95% CI)	6.93 (2.96, 8.57)	-
Min, Max (% for censored)	1.2+, 9.7	5.5, 15.3
Time to objective response (months)[c]		
Median	1.45	2.12
Min, Max	1.3, 8.3	1.2, 3.0
Progression-free survival (KM) (months)		
Events - n (%)	32 (80.0)	11 (57.9)
Median (95% CI)	5.72 (3.94, 8.02)	8.51 (2.79, 11.50)
KM estimate at 6 months	46.12 (29.36, 61.33)	64.17 (36.90, 82.09)
KM estimate at 12 months	6.71 (0.69, 23.06)	16.50 (1.17, 48.21)
Overall survival (KM) (months)		
Events - n (%)	27 (67.5)	5 (25.0)
Median (95% CI)	12.78 (10.71, 15.15)	21.09 (9.49, NE)
KM estimate at 6 months	89.72 (74.87, 96.02)	95.00 (69.47, 99.28)
KM estimate at 12 months	56.85 (39.45, 70.97)	78.92 (46.45, 92.95)

CRC = colorectal cancer; DCR = disease control rate; DOR = duration of response; KM = Kaplan-Meier; Max = maximum; Min = minimum; NE = not estimable; ORR = objective response rate; PFS = progression-free survival; OS = overall survival; TTR = time to response
Data cut-off date 23 May 2023.
Months are derived as days x (12/365.25).
KM estimates was not provided if the analysis had fewer than 10 subjects. Only min, max were provided.
[a] N = 19 for response-related endpoints (ORR, DCR, DOR, TTR, PFS), excluding 1 subject with no measurable lesion at baseline per central review. N = 20 for OS.
[b] Exact 95% confidence interval was calculated using the Clopper Pearson method.
[c] Time to response and DOR were calculated among confirmed responders N1.
Source: Table 10-4, Table 10-5, and Table 10-6 of Study 20190135 Subprotocol H Interim Analysis 1

Study 20170543

Results of secondary endpoints for Study 20170543 are provided in Applicant - Table 21 and summarized in Section 8.1.4.

The Applicant's Position:
Sotorasib 960 mg monotherapy demonstrates modest efficacy in mCRC. Sotorasib 960 mg + panitumumab demonstrates more robust activity in mCRC.

The FDA's Assessment:
FDA agrees with the Applicant's description of the results for OS and ORR from Study 20190172. In the sotorasib 240 mg arm, no improvement in OS (neither numerically nor statistically) was demonstrated and the observed response rate of 6% was very low. For the sotorasib 960 mg arm, although the patients treated with sotorasib containing regimen had a numerically improved survival than the patients in control arm (as demonstrated in the survival plot), the difference between the arms was not statistically significant. The response rate was comparatively higher in sotorasib 960 mg arm compared to 240 mg arm (26% and 6% respectively). The median (95% CI) DOR in the sotorasib 960 mg + panitumumab group was 4.4 months (3.55, NE), ranging between 1.9+ months and 6.0+ months. However, note that duration of response in Study 20190172 is modest for the sotorasib 960 mg arm, and this assessment is limited by the small number of responders in this trial.

Dose/Dose Response

Data:
See Section 6.3.2, Clinical Pharmacology Questions.

The Applicant's Position:
Dose response was evaluated using population PK and ER analyses (Section 6.3).

The FDA's Assessment:
The dose response analysis is inconclusive due to confounding effect (e.g., baseline disease) and could not inform dose selection for the narrow and comparable exposure range achieved with sotorasib 240 mg and sotorasib 960 mg arms (See Section 6.1 and Section 19.4.1.).

Durability of Response

Data:
Study 20190172
As of 19 June 2023, an objective response was achieved for 3 subjects (CR for no subjects, PR for 3 subjects) in the sotorasib 240 mg + panitumumab group, for 14 subjects (CR for 1 subject, PR for 13 subjects) in the sotorasib 960 mg + panitumumab group, and for no subjects in the control group (Applicant - Table 20). The duration of the 3 responses in the sotorasib 240 mg + panitumumab group range from 1.8+ months to 3.8+ months (+ indicates censored). The

median (95% CI) DOR in the sotorasib 960 mg + panitumumab group was 4.4 months (3.55, NE), ranging between 1.9+ months and 6.0+ months.

Study 20190135 Subprotocol H

As of 23 May 2023, there were 12 responders (CR for 1 subject, PR for 11 subjects) in cohort 2A and 16 responders (CR for 2 subjects, PR for 14 subjects) in the pooled cohorts 2A and 2D (Applicant - Table 22). The median (95% CI) DOR as assessed by BICR was 6.9 months (3.0, 8.6) for cohort 2A and 7.0 months (5.5, 9.7) in the pooled cohorts 2A and 2D (Section 3.2.2 of Module 2.7.3, Summary of Clinical Efficacy).

Study 20170543

As of 01 April 2023, there were 7 responders (all 7 PR) (Applicant - Table 21). Median DOR was not calculated for CRC responders as the number of responders were small. As of the data cut-off date, the DOR for the 7 responders were 13.14, 11.37, 10.61, 4.17, 4.17, 2.92, and 1.45 months.

The Applicant's Position:

Sotorasib 960 mg in combination with panitumumab demonstrated a clinically meaningful and durable objective response among subjects with mCRC in Studies 20190172 and 20190135 Subprotocol H.

The FDA's Assessment:

The duration of response in Study 20190172 is modest for the sotorasib 960 mg arm, and this assessment is limited by the small number of responders in this trial.

Persistence of Effect

Data:

No long-term efficacy data with the exception of those presented in the preceding sections are included in this supplemental marketing application.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

See FDA's discussion on the primary endpoint and durability of response.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

Study 20190172

Patient-reported outcome results for sotorasib 960 mg + panitumumab are shown below; the results for sotorasib 240 mg + panitumumab are provided in Section 10.3.5 of Study 20190172 PFS PA.

Change from Baseline to Week 8 in Fatigue Severity

Change from baseline over time to week 8 of fatigue at its worst as measured by item 3 of the Brief Fatigue Inventory was compared between treatment groups using the mixed effect model for repeated measures (MMRM) method. The difference in LS means of change from baseline to week 8 between the sotorasib 960 mg + panitumumab group and the control group was -0.89 (95% CI: -1.80, 0.01), suggesting a numerical improvement in fatigue at its worst for the sotorasib 960 mg + panitumumab group.

Change from Baseline to Week 8 in Pain Severity

Change from baseline over time to week 8 of pain at its worst as measured by item 3 from Brief Pain Inventory was compared between treatment groups using the MMRM method. The difference in LS means of change from baseline to week 8 between the sotorasib 960 mg + panitumumab group and the control group was -1.45 (95% CI: -2.32, -0.58), suggesting improvement in pain at its worst for the sotorasib 960 mg + panitumumab group.

Change From Baseline to Week 8 in Physical Functioning

Change from baseline over time to week 8 in physical functioning as measured by the physical function domain of European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire - Core 30 item (EORTC QLQ-C30) was compared between treatment groups using the MMRM method. The difference in LS means of change from baseline to week 8 between the sotorasib 960 mg + panitumumab group and the control group was 5.38 (95% CI: -0.01, 10.78), suggesting a numerical improvement in physical functioning for the sotorasib 960 mg + panitumumab group.

Change From Baseline to Week 8 in Global Health Status/Quality of Life

Change from baseline over time to week 8 in global health status as measured by the global health status/quality of life domain of EORTC QLQ-C30 was compared between treatment groups using the MMRM method. The difference in LS means of change from baseline to week 8 was 9.43 (95% CI: 2.31, 16.56), suggesting improvement in global health status/quality of life for the sotorasib 960 mg + panitumumab group when compared with the control group.

Functional Assessment of Cancer Therapy – General

At week 9, most patients reported not at all or a little bit of symptom bother in the sotorasib 960 mg + panitumumab group (19.4% and 54.8%, respectively). Similarly, at week 9, the most commonly reported responses were not at all and a little bit of symptom bother (41.2% and 23.5%, respectively) in the control group, suggesting that side effect bother was limited and similar across treatment groups.

Patient Global Impression of Change

At week 9, most patients reported improvement in the sotorasib 960 mg + panitumumab group (very much improved 8.6%, much improved 28.6%, minimally improved 25.7%). No change was reported in 31.4% of patients in this group. Most patients in the control group reported no change (52.6%) and considerably less patients reported improvement (very much improved 0.0%, much improved 21.1%, minimally improved 15.8%). These results suggest that patients' global impression of change favored the sotorasib 960 mg + panitumumab treatment group.

EuroQol-5D Level 5 Visual Analog Score

Mean (SD) score at baseline was 71.5 (19.7) in the sotorasib 960 mg + panitumumab group and 72.0 (19.5) in the control group. Overall, visual analog scale changes were favorable for the sotorasib 960 mg + panitumumab group when compared with the control group. At week 9, mean (SD) change from baseline in EuroQol-5 D level 5 visual analog scale scores were 5.0 (23.1) in the sotorasib 960 mg + panitumumab group, compared with -6.1 (18.4) in the control group, indicating a trend of improvement in health status for the sotorasib 960 mg + panitumumab group.

The Applicant's Position:

In Study 20190172, sotorasib 960 mg in combination with panitumumab resulted in improvements in disease- and treatment-related symptoms and overall quality of life when compared with the standard of care group.

The FDA's Assessment:

During the review of this supplemental application, PRO results were not considered when evaluating the benefit profile of sotorasib 960 mg arm. Given that there was no formal statistical analysis plan to evaluate these PRO endpoints, these results are considered descriptive only.

Additional Analyses Conducted on the Individual Trial

Data:

Not applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

No additional analyses were conducted.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

Study 20190172 was designed to compare the efficacy based on PFS of each of the sotorasib with panitumumab arms to investigator's choice of trifluridine/tipiracil or regorafenib. The trial population and trial conduct were adequate to allow for assessment of efficacy of the treatment arms. The baseline disease characteristics between each of the sotorasib arms and the control arm were generally well-balanced. There were imbalances of the baseline disease characteristics between the two sotorasib arms that could impact the prognosis of the patients, but the trial was not designed to compare the efficacy between the two sotorasib arms. The protocol deviations were unlikely to impact the efficacy data. FDA determined that the issue of forgery at clinical site 33013 did not impact the integrity of the efficacy data.

The results of the trial demonstrated that sotorasib 960 mg with panitumumab improved median PFS by 3.58 months compared to investigator's choice, which is both statistically and clinically significant. Including the additional PFS events at the time of the final submission of this sNDA, the median PFS of 1.87 months with the sotorasib 240 mg with panitumumab arm compared to investigator's choice did not meet the specified p-value and was determined to not be statistically significant. The ORR in the sotorasib 240 mg with panitumumab arm was also notably low at 6% (95% CI: 1, 16) compared to sotorasib 960 mg with panitumumab arm, whose ORR was 26% (95% CI: 15, 40).

The trial was not designed to compare OS and interpretation of OS is also confounded by the proportion of patients whose subsequent anticancer therapy was the opposing treatment arm: i.e., 28% of patients in the control arm received anti-KRAS G12C inhibitor after progression, and 17% of the patients in the sotorasib 960 mg arm received trifluridine/tipiracil or regorafenib after progression.

8.1.4. Assessment of Efficacy Across Trials

Primary Endpoints

Data:
The primary endpoints varied across studies as listed in Applicant - Table 7.
Progression-free survival was the primary endpoint for the pivotal phase 3 Study 20190172 and a secondary endpoint in Studies 20190135 Subprotocol H and 20170543.

Kaplan-Meier assessment of PFS as assessed by central review is shown in Applicant – Figure 8 for sotorasib monotherapy. A summary of the side-by-side and pooled analysis of PFS as assessed by central review for sotorasib monotherapy is provided in Table 15 of Module 2.7.3, Summary of Clinical Efficacy. A summary of the side-by-side and pooled analysis of PFS as assessed by central review for sotorasib in combination with panitumumab is provided in Table 18 of Module 2.7.3, Summary of Clinical Efficacy.

An overall summary of key efficacy data from sotorasib monotherapy and the side-by-side and

pooled analyses is shown in Applicant - Table 23. An overall summary of key efficacy data from sotorasib in combination with panitumumab and the side-by-side and pooled analyses is shown in Applicant - Table 24.

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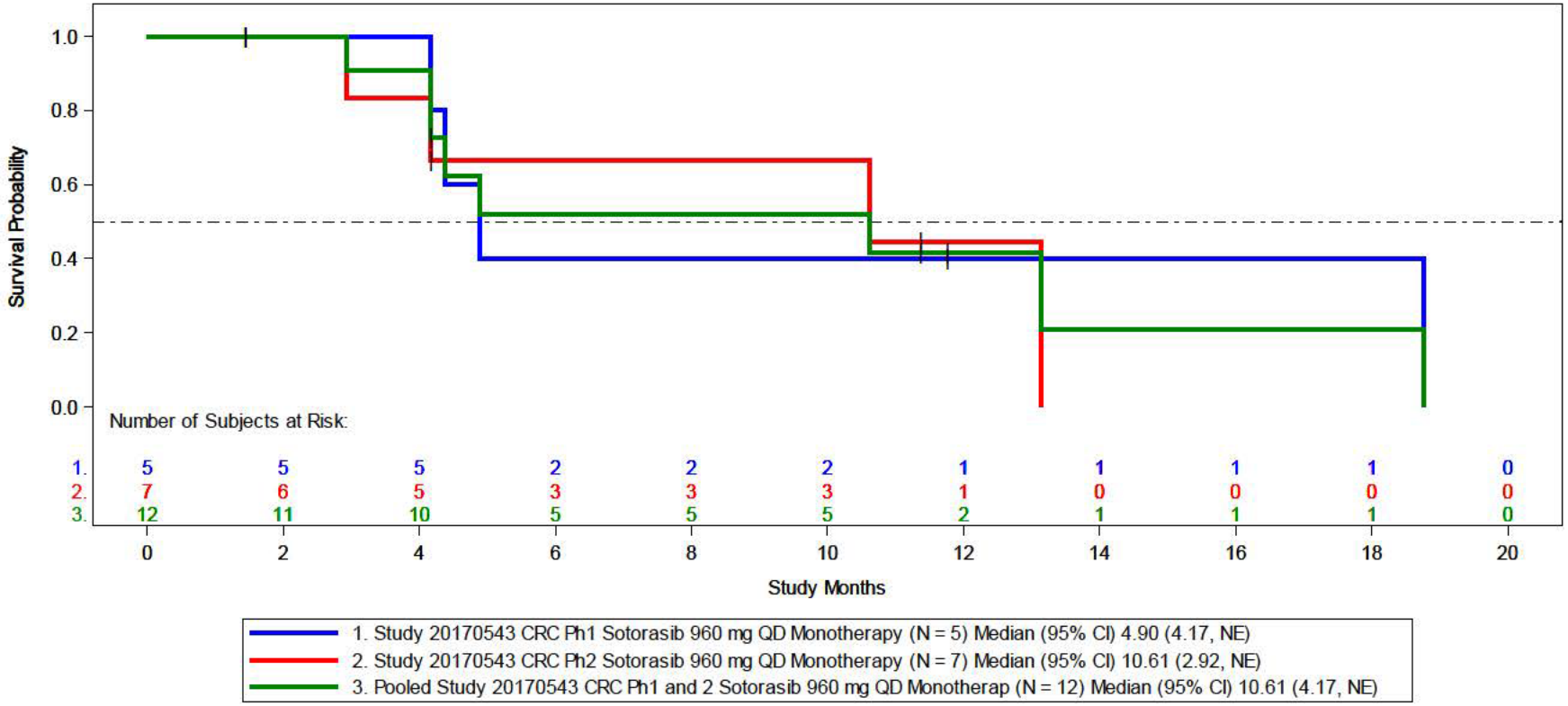
Applicant - Table 23. Overall Summary of Results for Efficacy Endpoints (Sotorasib Monotherapy)

	Study 20170543 CRC Ph1 Sotorasib 360 mg QD Monotherapy (N = 10)	Study 20170543 CRC Ph1 Sotorasib 960 mg QD Monotherapy (N = 29)	Study 20170543 CRC Ph2 Sotorasib 960 mg QD Monotherapy (N = 62)	Pooled Study 20170543 CRC Ph1 and 2 Sotorasib 960 mg QD Monotherapy (N = 91)
Progression-free Survival				
Events - n (%)	6 (60.0)	21 (72.4)	49 (79.0)	70 (76.9)
Median (95% CI)	1.64 (1.38, NE)	5.45 (2.79, 7.49)	4.04 (2.79, 4.17)	4.17 (2.83, 4.80)
Overall Survival				
Number of subjects who died – n (%)	7 (70.0)	21 (72.4)	52 (83.9)	73 (80.2)
Median (months) (95% CI)	8.90 (2.04, 17.64)	17.94 (12.39, 23.03)	10.05 (7.66, 14.29)	12.78 (8.90, 15.64)
Median (months) follow-up time (95% CI)	47.15 (1.35, NE)	41.46 (28.35, NE)	36.80 (35.84, NE)	36.80 (35.84, 43.53)
Objective Response				
Number (%) of subjects who achieved objective response	0 (0.0)	5 (17.2)	7 (11.3)	12 (13.2)
ORR (95% CI) (%)[a]	(0.00, 30.85)	(5.85, 35.77)	(4.66, 21.89)	(7.00, 21.90)
Disease control rate				
Number (%) of subjects who achieved disease control	5 (50.0)	24 (82.8)	51 (82.3)	75 (82.4)
DCR (95% CI)	18.71, 81.29	64.23, 94.15	70.47, 90.80	73.02, 89.60
Time to response (months)[b]				
Number of subjects with objective response	0	5	7	12
Median (range) TTR	-	1.31 (1.2, 2.8)	2.60 (1.3, 30.5)	2.00 (1.2, 30.5)
Duration of response (months)[b]				
Number (%) of subjects DOR events	0 (0.0)	4 (80.0)	4 (57.1)	8 (66.7)
Median (95% CI)	-	-	-	10.61 (4.17, NE)

CRC = colorectal cancer; DCR = disease control rate; QD = once daily; TTR = time to response
Months are derived as days x (12/365.25).
Kaplan-Meier estimates were not provided if the analysis had fewer than 10 subjects. Only min, max were provided.
[a] Exact 95% confidence interval was calculated using the Clopper Pearson method.
[b] Time to response and DOR are calculated among confirmed responders N1.
Source: Table 14, Table 15, and Table 16 of Module 2.7.3, Summary of Clinical Efficacy

Applicant – Figure 8. Kaplan-Meier Plot of Progression-free Survival by Central Review (Sotorasib Monotherapy)



CR = complete response; CRC = colorectal cancer; NE = not estimable; Ph1 = phase 1; Ph2 = phase 2; PR = partial response; QD = once daily
Study (data cut-off date): 20170543 (01 April 2023).
Censor indicated by vertical bar. Radiological progression or death (whichever occurs earlier after confirmed CR/PR) is an event.
Source: Figure 1 of Module 2.7.3, Summary of Clinical Efficacy

Applicant - Table 24. Overall Summary of Results for Efficacy Endpoints (Sotorasib + Panitumumab)

	Study 20190135-H CRC Sotorasib 960 mg QD + Panitumumab Cohort 2A (N = 40)	Study 20190135-H CRC Sotorasib 960 mg QD + Panitumumab Cohort 2A & 2D (N = 59)	Study 20190135-H CRC Sotorasib 960 mg QD + Panitumumab Cohort 2B (N = 11)[a]	Study 20190172 CRC Sotorasib 240 mg QD + Panitumumab (N = 53)	Study 20190172 CRC Sotorasib 960 mg QD + Panitumumab (N = 53)	Pooled Study 20190135-H Cohort 2A, 2D and 20190172 CRC Sotorasib 960 mg QD + Panitumumab (N = 112)
Progression-free Survival						
Events - n (%)	32 (80.0)	43 (72.9)		35 (66.0)	32 (60.4)	75 (67.0)
Median (95% CI)	5.72 (3.94, 8.02)	7.16 (4.37, 8.25)		3.91 (3.61, 5.75)	5.62 (4.21, 6.31)	5.75 (4.40, 7.39)
Overall Survival						
Number of subjects who died – n (%)	27 (67.5)	32 (53.3)	9 (81.8)	28 (52.8)	24 (45.3)	56 (49.6)
Median (months) (95% CI)	12.78 (10.71, 15.15)	13.96 (11.60, 18.76)	5.45 (2.92, NE)	11.93 (7.52, NE)	NE (8.61, NE)	13.96 (11.60, 18.76)
Median (months) follow-up time (95% CI)	20.21 (17.97, 21.75)	19.06 (17.05, 21.75)	NE (7.46, NE)	14.03 (12.19, 15.15)	13.60 (12.39, 14.23)	14.65 (13.31, 17.97)
Objective Response						
Number (%) of subjects who achieved objective response	12 (30.0)	16 (27.1)		3 (5.7)	14 (26.4)	30 (26.8)
95% CI[b]	16.56, 46.53	16.36, 40.27		1.18, 15.66	15.26, 40.33	18.86, 35.98
Disease control rate						
Number (%) of subjects who achieved disease control	37 (92.5)	55 (93.2)		37 (69.8)	38 (71.7)	93 (83.0)
95% CI	79.61, 98.43	83.54, 98.12		55.66, 81.66	57.65, 83.21	74.78, 89.47
Time to response (months)[c]						
Number of subjects with objective response	12	16		3	14	30
Median TTR	1.45	1.45		1.77	2.05	1.94
Duration of response (months)[c]						
Number (%) of subjects DOR events	8 (66.7)	11 (68.8)		0 (0.0)	5 (35.7)	16 (53.3)
Median (95% CI)	6.93 (2.96, 8.57)	6.97 (5.52, 9.69)		-	4.40 (3.55, NE)	6.83 (4.40, 9.69)

CRC = colorectal cancer; DCR = disease control rate; NE = not estimable; QD = once daily; TTR = time to response
Months are derived as days x (12/365.25).
Kaplan-Meier estimates were not provided if the analysis had fewer than 10 subjects. Only min, max were provided.

[a] No BICR assessments were performed for cohort 2B as the cohort was a mixture of different tumor types and subjects had prior treatment with $KRAS^{G12C}$ inhibitors, therefore the subject population was not reflective of the naïve subject population.
[b] Exact 95% confidence interval was calculated using the Clopper Pearson method.
[c] Time to response and DOR are calculated among confirmed responders N1.
Source: Table 17, Table 18, and Table 19 of Module 2.7.3, Summary of Clinical Efficacy

The Applicant's Position:

Results across clinical studies of sotorasib monotherapy and sotorasib in combination with panitumumab, consistently demonstrated the clinical activity of sotorasib in subjects with *KRAS p.G12C*-mutated mCRC, a disease state with high unmet medical need.

The FDA's Assessment:
FDA reviewed the efficacy data for the pivotal trial, Study 20190172, and did not independently verified the efficacy data for Study 20190135 and Study 20170543. Based on the data across trials presented above by the Applicant, sotorasib 960 mg in combination with panitumumab has a numerically higher ORR than sotorasib 960 mg as a single-agent and sotorasib 240 mg in combination with panitumumab. In this circumstance, FDA considered ORR an adequate measure of efficacy for cross trial comparisons as a direct measure of a drug's effect on the tumor. Time to event endpoints cannot be compared across trials due to differences in factors that can impact the prognosis of patients across the trials, such as patient demographics, disease characteristics, standard of care, supportive care, use of subsequent therapy, etc.

While KRAS inhibitors have some single agent anti-tumor activity against mCRC, the addition of anti-EGFR therapy appears to improve the anti-tumor efficacy. Single-agent anti-EGFR therapy does not work in patients with KRAS-mutated CRC because the mutated KRAS molecule is constitutively active downstream to where the anti-EGFR drug works. The necessity of panitumumab to the observed treatment effect of the 960 mg sotorasib arm in Study 20190172 is supported by single agent sotorasib data from Study 20170453.

Secondary and Other Endpoints

Data:
The primary endpoints varied across studies as listed in Applicant - Table 7.

Overall response rate was a key secondary endpoint in the pivotal phase 3 Study 20190172, a secondary endpoint in Study 20190135 Subprotocol H, and the primary endpoint in Study 20170543.

In the phase 1 portion of Study 20170543, there were no responders out of the 10 subjects with CRC in the sotorasib 360 mg cohort and 5 responders (CR for 1 subject, PR for 4 subjects) out of the 29 subjects with CRC in the sotorasib 960 mg cohort. The ORR as assessed by BICR was 17.2% (95% CI: 5.9, 35.8) in the sotorasib 960 mg cohort (Applicant - Table 23). In the phase 2 portion of Study 20170543, there were 7 responders (PR for all 7 subjects) out of the 62 subjects with CRC in the sotorasib 960 mg cohort. The ORR as assessed by BICR was 11.3% (95% CI: 4.7, 21.9) for subjects with CRC in the sotorasib 960 mg cohort. In the pooled analysis, there were 12 responders (CR for 1 subject, PR for 11 subjects) out of the 91 subjects with CRC treated with sotorasib 960 mg. The ORR as assessed by BICR was 13.2% (95% CI: 7.0,

21.9) for subjects with CRC treated with sotorasib 960 mg.

In Study 20190172, there were 3 responders (PR for all 3 subjects) in the sotorasib 240 mg + panitumumab group and 14 responders (CR for 1 subject, PR for 13 subjects) in the sotorasib 960 mg + panitumumab group. The ORR as assessed by BICR was 5.7% (95% CI: 1.2, 15.7) in the sotorasib 240 mg + panitumumab group and 26.4% (95% CI: 15.3, 40.3) in the sotorasib 960 mg + panitumumab group (Applicant - Table 24). In Study 20190135 Subprotocol H, there were 12 responders (CR for 1 subject, PR for 11 subjects) in cohort 2A and 16 responders (CR for 2 subjects, PR for 14 subjects) in the pooled cohorts 2A and 2D. The ORR as assessed by BICR was 30.0% (95% CI: 16.6, 46.5) in cohort 2A and 27.1% (95% CI: 16.4, 40.3) in the pooled cohorts 2A and 2D. In the pooled analysis, including cohorts 2A and 2D from Study 20190135 Subprotocol H and the sotorasib 960 mg + panitumumab group from Study 20190172, there were 30 responders (CR for 3 subjects, PR for 27 subjects). The ORR as assessed by BICR was 26.8% (95% CI: 18.9, 36.0).

The results for other efficacy endpoints are provided in Section 3.2 of Module 2.7.3, Summary of Clinical Efficacy.

The Applicant's Position:
Overall, these efficacy data showed that objective response was achieved in a proportion of subjects with *KRAS p.G12C*-mutated mCRC treated with sotorasib monotherapy and sotorasib in combination with panitumumab.

The FDA's Assessment:

FDA agrees with the Applicant's interpretation of response rates in individual and pooled analysis.

Subpopulations

Data:
Subgroup analyses for ORR, PFS, and OS included the following subgroups: age at baseline; prior lines of anticancer therapy; ECOG performance status at baseline; race; sex; presence of metastases; region; type of cancer; number of body sites of metastatic disease; differentiation; prior regorafenib; prior trifluridine and tipiracil; prior regorafenib and/or trifluridine/tipiracil; prior oxaliplatin; prior irinotecan; prior fluoropyrimidine; and prior oxaliplatin and irinotecan and fluoropyrimidine.

Sotorasib monotherapy treatment effect was generally consistent between the subgroups (Section 3.3.1 of Module 2.7.3, Summary of Clinical Efficacy).

Sotorasib + panitumumab treatment effect was generally consistent between the subgroups (Section 3.3.2 of Module 2.7.3, Summary of Clinical Efficacy). When efficacy endpoints were

analyzed by prior line of therapy for subjects with mCRC in the pooled analysis of Study 20190135 Subprotocol H and Study 20190172, subjects who received 1 prior line of therapy had a median PFS of 8.51 months (95% CI: 4.24, 11.50), compared with a median PFS of 5.32 months (95% CI: 3.84, 7.69) and 5.72 months (95% CI: 4.21, 6.28) for subjects with 2 and > 2 prior lines of therapy, respectively.

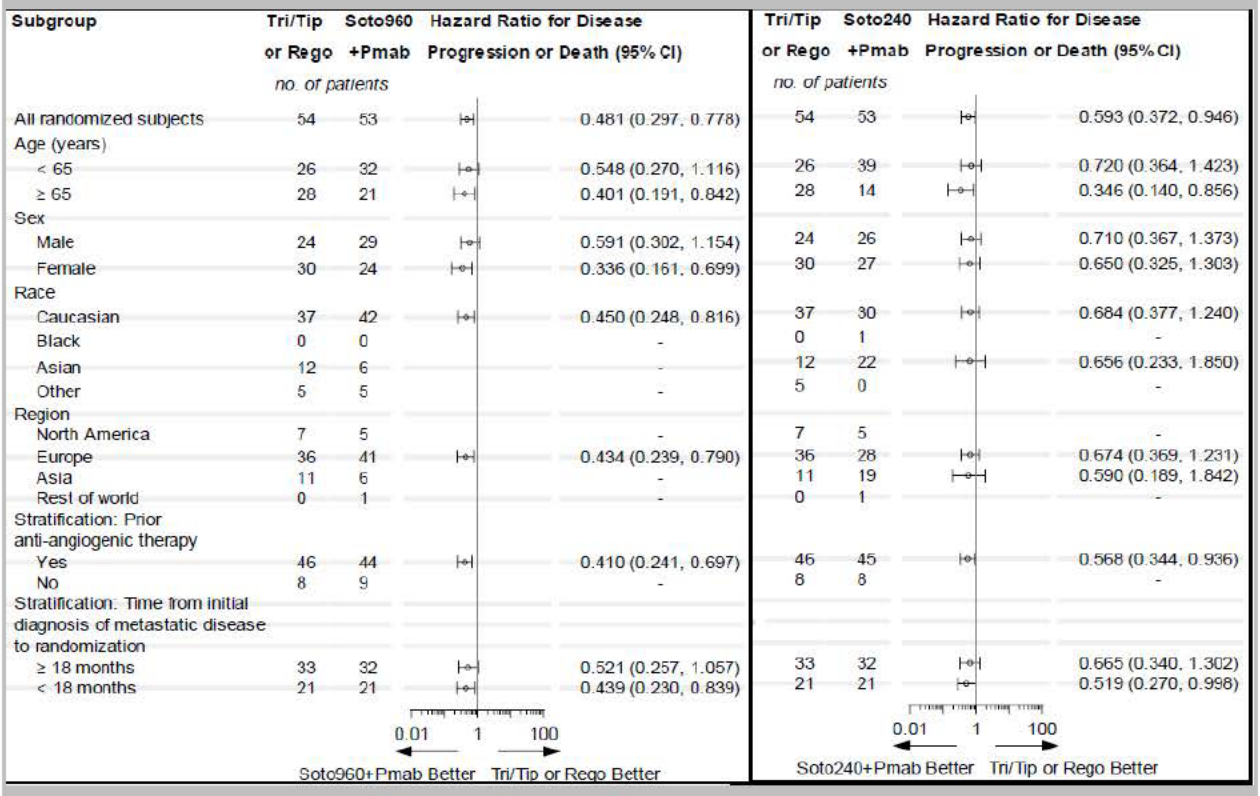
The Applicant's Position:

No notable treatment by-subgroup effects were observed for any subgroups, showing that sotorasib monotherapy and sotorasib in combination with panitumumab treatment effects were generally consistent between subgroups. However, subgroup analysis interpretation may be limited because of the sample size of each subgroup.

The FDA's Assessment:

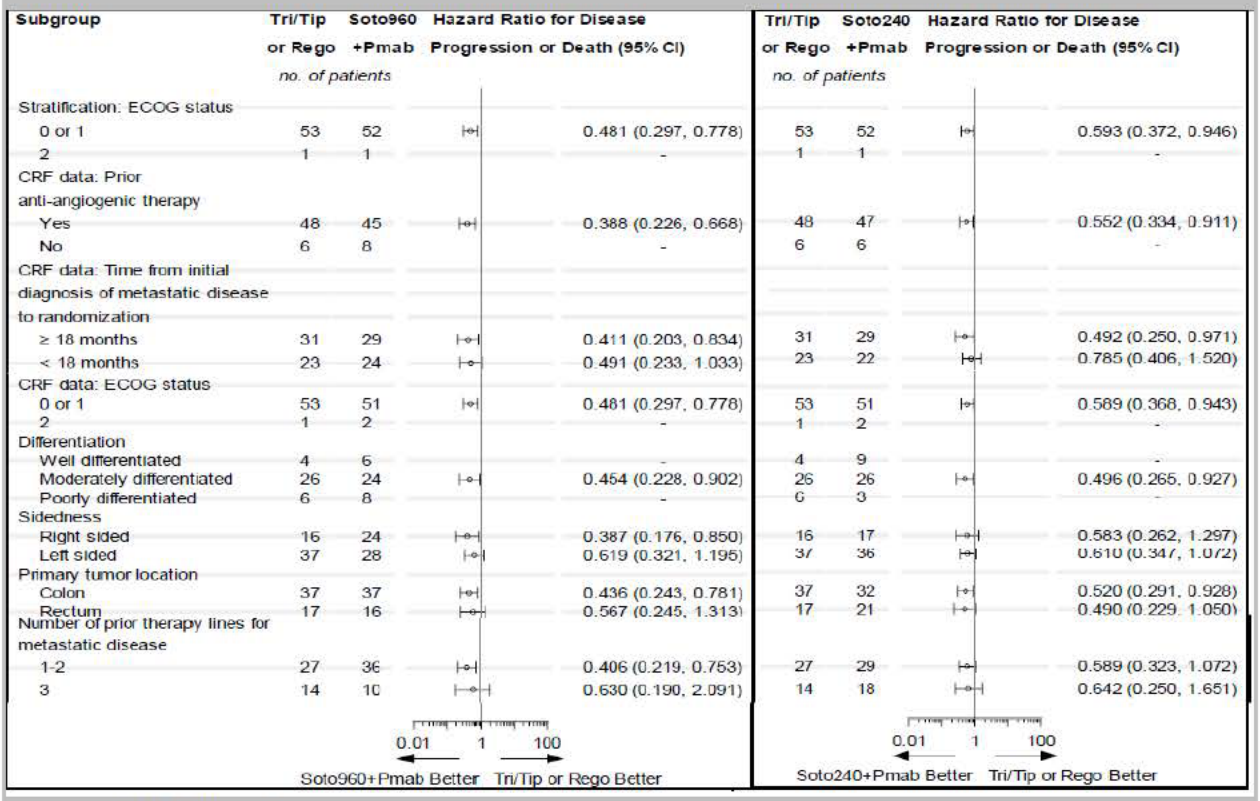
The figures below provide the subgroup analysis of PFS for Study 20190172. Note that this is an exploratory analysis and the observed treatment effects in subgroups with smaller sample size should be interpreted with caution.

Figure 9: Subgroup analysis of PFS - Study 20190172



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

Figure 10: Subgroup analysis of PFS - Study 20190172



Source: Study 20190172 CSR.

Additional Efficacy Considerations

The FDA's Assessment:

Based on the available data, FDA has concluded that the Applicant has demonstrated the necessity of both sotorasib 960 mg and panitumumab for the observed treatment effect. Data regarding the single agent anti-tumor activity of sotorasib was collected in Study 20170543, which demonstrated a lower response rate of 13% compared to 26% observed with sotorasib 960 mg in combination with panitumumab. In addition, it has been established that single agent anti-EGFR therapy, such as panitumumab, is not effective in patients with KRAS-G12C mutated CRC (Vectibix USPI).

FDA notes that Study 20170192 did not contain a single agent sotorasib arm, however based on preliminary data that suggested that treatment with single-agent KRAS inhibitor is less effective than combination treatment with a KRAS inhibitor and anti-EGFR therapy.

8.1.5. Integrated Assessment of Effectiveness

Data:
Data are presented above in Section 8.1.3.

The Applicant's Position:
The pivotal efficacy data in this supplemental marketing application to support approval are obtained from Study 20190172, an ongoing study in which all subjects received prior therapies. In this study, treatment with sotorasib 960 mg + panitumumab demonstrated rapid, durable responses, and improved PFS over standard of care.

Data supporting this supplemental marketing application are obtained from Studies 20190135 Subprotocol H and 20170543.

Results from both Study 20190135 Subprotocol H and Study 20170543 demonstrated the clinical activity of sotorasib + panitumumab and sotorasib monotherapy in previously treated *KRAS p.G12C*-mutated mCRC, a disease state with high unmet medical need.

- Results from Study 20190135 Subprotocol H provided additional evidence of the benefit and supports the use of sotorasib 960 mg + panitumumab as the recommended dose for the treatment of patients with mCRC.

The FDA's Assessment:
See Section 8.1.3.

8.2. **Review of Safety**

Data:
A summary of clinical studies supporting the integrated analyses of safety for sotorasib is provided in Applicant - Table 25.

Applicant - Table 25. Clinical Studies Contributing to the Integrated Analysis of Safety

Study Number	Study Objective(s)	Study Design and Type of Control	Investigational Products; Dosage Regimens; Route of Administration	Number of Subjects Enrolled (Actual/Planned)	Data cut off
20190172 (pivotal)	efficacy, safety, tolerability, PROs, PK	phase 3 multicenter, randomized 1:1:1, open-label, active-controlled	sotorasib (960 or 240 mg) PO QD + panitumumab (6 mg/kg) IV Q2W Control group: investigator's choice (trifluridine and tipiracil or regorafenib)	160/ approximately 153	19 June 2023
20190135	Master Protocol: phase 1b study to evaluate the safety, tolerability, PK, and efficacy of multiple investigational regimens of sotorasib in subjects with advanced solid tumors with *KRAS pG12C* mutation as assessed by molecular testing of tumor biopsy specimens				
Sub-protocol H[a]	safety, tolerability, PK, efficacy	Phase 1b, open-label, nonrandomized	sotorasib PO QD in combination with panitumumab IV Q2W	121/up to 175	23 May 2023
20170543 (phase 1 portion)	safety, tolerability, efficacy, PK, PD	Phase 1, monotherapy, nonrandomized, open-label, dose exploration	sotorasib 180/360/720/960 QD, 480 BID (monotherapy CRC cohorts only)	Phase 1 60 (CRC) / 283 (all tumor types)	01◦April◦2023 (phase 1 CRC cohort only)
20170543 (phase 2 part A portion)	safety, tolerability, efficacy, PK, PD, PRO	monotherapy, multicenter nonrandomized, open-label	960 mg sotorasib PO (recommended phase 2 dose)	62/60 (subjects with CRC)	01◦April◦2023 (phase 2 part A CRC cohort only)

BID = twice daily; CRC = colorectal cancer; CSR = clinical study report; ISS = integrated summary of safety; IV = intravenous; KRAS = Kirsten rat sarcoma viral oncogene homolog; *KRAS p.G12C* = KRAS gene with a mutation resulting in a G12C amino acid substitution; mCRC = metastatic colorectal cancer; PD = pharmacodynamics; PK = pharmacokinetics; PO = administered orally; PRO = patient-reported outcome; QD = once daily; Q3W = every 3 weeks

[a] Subjects from all tumor types who received sotorasib + panitumumab (part 1 cohort A, part 2 cohort A, part 2 cohort B, part 2 cohort C, part 2 cohort D, part 2 cohort H) contributed to the integrated safety analysis.

The Applicant's Position:
Data from these studies allow for an informed assessment of the safety profile of sotorasib in combination with panitumumab and an evaluation of the overall benefit-risk in previously-treated subjects with *KRAS p.G12C*-mutated CRC who received sotorasib in combination with panitumumab. This safety population is also considered appropriate for the detection and characterization of common adverse events and to provide guidance on toxicity management.

The FDA's Assessment:
FDA agrees that the trials presented in Applicant - Table 25 are adequate for the determination of the safety of sotorasib as a single agent and in combination with panitumumab. FDA excluded safety data from site 33013 due to the issue of forgery at that site (see Section 4.1).

8.2.1. Safety Review Approach

Data:
Not applicable.

The Applicant's Position:
Primary support of safety for the indication is based on the data from the pivotal phase 3 Study 20190172 (CodeBreaK 300) and supported by data from the phase 1b Study 20190135 (CodeBreaK 101) Subprotocol H and Study 20170543 (phase 1 and phase 2 part A; CodeBreaK 100). In addition to the safety results presented for Study 20190172, Study 20190135 Subprotocol H, and Study 20170543, an integrated analysis of pooled safety data is provided for sotorasib.

The approach for integrating safety data (Section 1.2.1.1 of Module 2.7.4, Summary of Clinical Safety), was agreed upon with the US FDA.

Demographics, baseline disease characteristics, exposure, adverse events, and other safety assessments were summarized using the safety analysis set, which included all subjects enrolled who received ≥ 1 dose of sotorasib.

The FDA's Assessment:
FDA agrees with the Applicant's description of the safety population. For each patient in the safety population, only the worst grade per treatment emergent adverse event (TEAE) based on MedDRA version 26.0 Preferred Terms, and worse grade per laboratory abnormality were included in the safety analyses. The FDA review used the Treatment Emergent Analysis Flag (TRTEMFL), which was defined as any adverse event that started on or after the first dose of any trial treatment and up to 30 days after the last dose of any trial treatment or the end of trial date, whichever is earlier. Patients from site 33013 were excluded from the FDA safety

analysis as the safety data from that site was determined not to be reliable after investigation of a forgery issue at the site.

8.2.2. Review of the Safety Database

Overall Exposure

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Data:
Exposure to sotorasib and sotorasib + panitumumab in subjects with mCRC is summarized in Applicant - Table 26 and Section 1.4 of Module 2.7.4, Summary of Clinical Safety.

Study 20190172
In the sotorasib 240 mg + panitumumab group, duration on sotorasib (median [range]) was 3.98 (0.9, 10.1) months administered over 5.0 (1, 11) cycles (1 cycle is 4 weeks) and the relative dose intensity (median [range]) was 100% (9.1, 100.0). Duration on panitumumab (median [range]) was 4.14 (0.9, 10.1) months administered over 5.0 (1, 11) cycles and the relative dose intensity (median [range]) was 90% (37.6, 102.6).

In the sotorasib 960 mg + panitumumab group, the duration on sotorasib (median [range]) was 5.52 (1.0, 13.2) months administered over 6.0 (1, 15) cycles and the relative dose intensity was 100% (8.4, 100.0). Duration on panitumumab (median [range]) was 5.29 (0.5, 12.8) months administered over 6.0 (1, 14) cycles and the relative dose intensity (median [range]) was 92% (42.9, 101.2).

Pooled Safety Analysis: Sotorasib Monotherapy
In the sotorasib 960 mg group (median [range]), the duration of treatment (median [range]) was 4.1 (1, 44) months with 26.4% and 9.9% of subjects receiving treatment for ≥ 6 and ≥ 12 months, respectively. The (median [range]) cumulative dose received was 118080.0 (20160, 1272000) mg, the average dose per administration was 960 (466, 960) mg, and the relative dose intensity was 100% (49, 100).

Pooled Safety Analysis: Sotorasib 960 mg + Panitumumab
Subjects with mCRC treated with sotorasib 960 mg + panitumumab received sotorasib in combination with panitumumab treatment for a median of 5.5 months, with 40.9% and 9.8% of subjects receiving treatment for ≥ 6 and ≥ 12 months, respectively. Duration on sotorasib (median [range]) was 5.5 (0, 23) months with 40.2% and 9.8% of subjects receiving treatment for ≥ 6 and ≥ 12 months, respectively. The (median [range]) cumulative dose received was 130560.0 (4800, 632640) mg, the average dose per administration was 960 (80, 960) mg, and the relative dose intensity (median [range]) was 100% (8, 100). Duration on panitumumab (median [range]) was 5.3 (0, 22) months with 40.2% and 9.1% of subjects receiving treatment for ≥ 6 and ≥ 12 months, respectively. The (median [range]) cumulative dose received was 4233.9 (286, 23526) mg, the cumulative weight-adjusted dose was 60.0 (6, 250) mg/kg, the relative dose intensity (median [range]) was 92.7% (40, 106).

Applicant - Table 26. Summary of Sotorasib Exposure (Safety Analysis Set)

	Study 20170543 CRC Sotorasib 960 mg Monotherapy (N = 91)	Study 20170543 CRC Sotorasib Any Dose Monotherapy (N = 122)	Study 20190172 CRC Sotorasib 240 mg + Panitumumab (N = 53)	Study 20190172 CRC Sotorasib 960 mg + Panitumumab (N = 53)	All studies CRC Sotorasib 960 mg + Panitumumab (N = 132)	All studies CRC Sotorasib Any Dose + Panitumumab (N = 185)	All studies Any Tumor Type Sotorasib 960 mg + Panitumumab (N = 174)	All studies Any Tumor Type Sotorasib Any Dose + Panitumumab (N = 227)
Sotorasib cumulative dose (mg)								
n	91	122	53	53	132	185	174	227
Mean	157908.1	143014.9	31938.1	150278.5	168045.5	129052.5	155374.8	126554.8
SD	169603.9	162731.0	16570.4	86705.7	120279.1	119100.3	116817.6	115100.8
Median	118080.0	92430.0	28320.0	140160.0	130560.0	91200.0	122400.0	88320.0
Q1, Q3	79680.0, 179520.0	49920.0, 160200.0	18720.0, 43680.0	81600.0, 205440.0	81600.0, 218880.0	43680.0, 180480.0	72960.0, 214080.0	43680.0, 179520.0
Min, Max	20160, 1272000	3780, 1272000	2640, 73920	14400, 375360	4800, 632640	2640, 632640	3840, 632640	2640, 632640
Sotorasib average dose delivered (mg) per day[a]								
n	91	122	53	53	132	185	174	227
Mean	922.8	863.9	224.3	889.7	893.5	701.8	876.3	724.1
SD	88.3	178.8	40.8	161.1	137.4	325.5	161.5	311.1
Median	960.0	959.5	240.0	960.0	960.0	901.2	951.9	908.9
Q1, Q3	937.0, 960.0	859.9, 960.0	228.9, 240.0	893.1, 960.0	885.1, 960.0	240.0, 960.0	870.0, 960.0	266.7, 960.0
Min, Max	466, 960	180, 960	22, 240	80, 960	80, 960	22, 960	43, 960	22, 960
Sotorasib relative dose intensity[b]								
n	91	122	53	53	132	185	174	227
Mean	96.1	96.5	93.5	92.7	93.1	93.2	91.3	91.8
SD	9.2	8.4	17.0	16.8	14.3	15.1	16.8	16.9
Median	100.0	100.0	100.0	100.0	100.0	100.0	99.2	99.6
Q1, Q3	97.6, 100.0	97.7, 100.0	95.4, 100.0	93.0, 100.0	92.2, 100.0	93.0, 100.0	90.6, 100.0	92.1, 100.0
Min, Max	49, 100	49, 102	9, 100	8, 100	8, 100	8, 100	4, 100	4, 100

Footnotes are defined on the last page of the table.

Applicant - Table 26. Summary of Sotorasib Exposure (Safety Analysis Set)

	Study 20170543 CRC Sotorasib 960 mg Monotherapy (N = 91)	Study 20170543 CRC Sotorasib Any Dose Monotherapy (N = 122)	Study 20190172 CRC Sotorasib 240 mg + Panitumumab (N = 53)	Study 20190172 CRC Sotorasib 960 mg + Panitumumab (N = 53)	All studies CRC Sotorasib 960 mg + Panitumumab (N = 132)	All studies CRC Sotorasib Any Dose + Panitumumab (N = 185)	All studies Any Tumor Type Sotorasib 960 mg + Panitumumab (N = 174)	All studies Any Tumor Type Sotorasib Any Dose + Panitumumab (N = 227)
Panitumumab cumulative dose (mg)								
n	0	0	53	53	132	185	174	227
Mean	-	-	3775.0	4834.2	5259.7	4834.4	5030.0	4737.0
SD	-	-	2056.6	2900.9	3851.5	3494.2	4182.4	3827.1
Median	-	-	3192.0	4428.0	4233.9	3938.0	4002.3	3740.0
Q1, Q3	-, -	-, -	2364.0, 4932.0	2750.0, 6300.0	2421.5, 6759.0	2403.0, 6205.2	2240.0, 6576.0	2240.0, 6126.0
Min, Max	-, -	-, -	840, 9287	286, 14544	286, 23526	286, 23526	286, 30902	286, 30902
Panitumumab cumulative weight-adjusted dose (mg/kg)								
n	0	0	53	53	132	185	174	227
Mean	-	-	55.3	64.0	69.7	65.6	66.0	63.5
SD	-	-	25.7	31.7	42.8	39.2	45.5	41.9
Median	-	-	50.3	63.4	60.0	55.5	54.6	54.0
Q1, Q3	-, -	-, -	37.3, 71.6	42.7, 81.2	39.2, 93.6	38.9, 84.0	35.9, 88.5	36.0, 81.8
Min, Max	-, -	-, -	9, 123	6, 139	6, 250	6, 250	6, 272	6, 272
Panitumumab relative dose intensity[b]								
n	0	0	53	53	132	185	174	227
Mean	-	-	87.6	88.4	88.7	88.4	88.9	88.6
SD	-	-	14.0	13.0	14.1	14.0	15.1	14.8
Median	-	-	90.0	91.7	92.7	92.3	94.2	92.9
Q1, Q3	-, -	-, -	79.6, 99.2	83.6, 99.8	81.1, 99.9	80.8, 99.8	83.6, 100.0	83.1, 100.0
Min, Max	-, -	-, -	38, 103	43, 101	40, 106	38, 106	32, 109	32, 109

Data cut-off date: 01 April 2023 (Study 20170543 Phase 1 and Phase 2), 19 June 2023 (Study 20190172), 23 May 2023 (Study 20190135 Subprotocol H)
CRC = colorectal cancer

[a] Average dose delivered is the cumulative dose divided by the number of days on treatment.
[b] Relative dose intensity = actual dose intensity/planned dose intensity*100, where actual (planned) dose intensity is the actual (planned) cumulative dose (mg) divided by the actual (planned) duration of sotorasib.
All studies include Studies 20190172 and 20190135 Subprotocol H.
Source: Table 6 of Module 2.7.4, Summary of Clinical Safety

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The Applicant's Position:

As of the data cut-off date for this supplemental marketing application, 53 subjects with mCRC in Study 20190172 received sotorasib 240 mg + panitumumab and 53 subjects with mCRC received sotorasib 960 mg + panitumumab. As of the data cut-off dates for the pooled sotorasib monotherapy data from Study 20170543, a total of 122 subjects with mCRC were treated with sotorasib monotherapy across all dose groups. As of the data cut-off for the pooled sotorasib + panitumumab data from Studies 20190172 and 20190135 Subprotocol H, a total of 185 subjects with mCRC were treated with sotorasib + panitumumab across all dose groups. The safety database is considered adequate to assess the safety of sotorasib 960 mg in combination with panitumumab in the mCRC indication.

The FDA's Assessment:

If data from clinical site 33013 is included in the analysis, FDA agrees with the exposure analysis presented in Applicant - Table 26 for Study 20190172, except for some interquartile values, which were slightly different, likely due to slight differences in cutoffs used for first and third quartiles. However, FDA's exposure analysis excludes clinical site 33013 (see Table 27).

The relative dose intensity (RDI) is similar for sotorasib in both sotorasib arms. The RDI is also similar for panitumumab in both sotorasib arms, but the cumulative weight-adjusted dose was numerically higher for panitumumab in the sotorasib 960 mg arm compared to the sotorasib 240 mg arm, likely due to the longer duration of treatment in the sotorasib 960 mg arm. The higher dose of sotorasib did not adversely affect (i.e., lower the RDI) panitumumab and also did not lead to more dose modifications for sotorasib: dose modifications were 60% (30/50) vs. 47% (22/47) for sotorasib 240 mg and sotorasib 960 mg arms, respectively.

Regorafenib had the lowest RDI compared to the other drugs in the trial (i.e., sotorasib, panitumumab, and trifluridine/tipiracil), possibly due to increased toxicity associated with regorafenib: 77% (10/13) vs. 59% (22/37) had dose modifications for regorafenib vs. trifluridine/tipiracil, respectively.

Patients were not administered single-agent panitumumab when sotorasib was withheld, and panitumumab was discontinued when sotorasib was discontinued as per protocol. The protocol permitted continuation of single-agent sotorasib if panitumumab was discontinued and n=3 and n=5 patients continued sotorasib 240 mg daily or sotorasib 960 mg daily, respectively, after panitumumab discontinuation. The mean and median duration of exposure of single-agent sotorasib after panitumumab discontinuation was 13.5 weeks for both arms.

Table 27. FDA's Summary of Exposure in Study 20190172 (excluding site 33013)

	Investigator's choice		Sotorasib 240 mg + Panitumumab		Sotorasib 960 mg + Panitumumab	
	Regorafenib N = 13	Trifluridine/ Tipiracil N = 37	Sotorasib N = 50	Panitumumab N = 50	Sotorasib N = 47	Panitumumab N = 47
Cumulative dose						
Median (25-75 interquartile range)	7840 (3280, 16220) mg	1418 (1353, 2739) mg/m^2	27840 (16500, 43680) mg	49 (36, 71) mg/kg	140160 (67200, 205440) mg	58 (81, 41) mg/kg
Mean (SD)	10385 (8670) mg	2200 (1394) mg/m^2	30706 (15617) mg	53 (24) mg/kg	147649 (88011) mg	62 (31) mg/kg
Average dose delivered per administration						
Median (25-75 interquartile range)	133 (105, 160) mg	34 (33, 35) mg/m^2	240 (240, 240) mg	6 (6, 6) mg/kg	960 (960, 960) mg	6 (6, 6) mg/kg
Mean (SD)	133 (26) mg	34 (1.9) mg/m^2	240 (0.3) mg	6 (0.3) mg/kg	945 (80) mg	6 (0.3) mg/kg
Relative dose intensity (%)						
Median (25-75 interquartile range)	71 (58, 100)	96 (92, 99)	100 (95, 100)	89 (79, 99)	100 (93, 100)	89 (81, 100)
Mean (SD)	76 (22)	95 (8)	93 (17)	87 (14)	93 (17)	88 (13)
Actual dose intensity						
Median (25-75 interquartile range)	83 (66, 116) mg/day	23 (21, 24) mg/m^2/day	240 (227, 240) mg/day	5 (4.8, 6) mg/kg/2 weeks	959 (893, 960) mg/day	5 (4.8, 6) mg/kg/2 weeks
Mean (SD)	88 (26) mg/day	22 (2.6) mg/m^2/day	223 (42) mg/day	5 (0.9) mg/kg/2 weeks	893 (164) mg/day	5 (0.8) mg/kg/2 weeks
Treatment duration (months)						
Median (25-75 interquartile range)	2.3 (1.5, 6)	2.2 (1.9, 4)	4 (3, 6)	4 (3.2, 6)	6 (3.7, 7)	5 (3.7, 7)
Mean (SD)	3.9 (3.2)	3.3 (2.2)	4.5 (2.1)	4.5 (2.1)	5 (3)	5 (2.8)

Abbreviations: SD = standard deviation
Source: ADEXSUM.xpt (SDN 380, submitted April 17, 2024)

Relevant characteristics of the safety population:

Data:

Analysis of disposition, demographic, and baseline characteristics for Study 20190172 and the integrated analysis of pooled sotorasib monotherapy and pooled sotorasib + panitumumab data is presented in Section 1.3 of Module 2.7.4, Summary of Clinical Safety. Baseline demographics and disease characteristics were generally consistent across studies. Subjects in Study 20190172 had similar baseline demographics to the pooled analysis with the exception of geographic region; Study 20190135 Subprotocol H cohort 2A only enrolled in the US and Japan, and cohort 2D was partially enrolled before Europe was added to the study.

The Applicant's Position:

No noteworthy differences, with the exception of geographic region, were observed between the treatment groups. Overall, the clinical studies enrolled subjects with mCRC who were representative of the target patient population.

The FDA's Assessment:

In Study 20190172, three patients who were randomized did not receive treatment and all three patients were randomized to receive trifluridine/tipiracil and were not at site 33013. The reasons for not receiving the trial treatment were different for each patient: patient's request (n=1), ineligibility (n=1), and trial drug not being available and patient's decision to enroll into another trial (n=1). The remaining patients received the drug in the treatment arm to which they were randomized, and excluding the patients from site 33013, the safety population consisted of n=50 in sotorasib 240 mg + panitumumab, n=47 in sotorasib 960 mg + panitumumab, and n=50 in investigator's choice (n=13 regorafenib, and n=37 in trifluridine/tipiracil). Ten patients were excluded from the safety analysis because they were enrolled and treated at site 33013: n=3 in sotorasib 240 mg + panitumumab, n=6 in sotorasib 960 mg + panitumumab, and n=1 in investigator's choice (regorafenib).

The distribution of sex and performance status were generally well-balanced between all three treatment arms, although the number of patients with ECOG performance status of 0 was numerically higher in the sotorasib 960 mg arm compared to the sotorasib 240 mg arm, and numerically higher in the Investigator's choice arm compared to the sotorasib arms (Table 28). The sotorasib 240 mg arm had more patients <65 years old and Asian patients compared to the other two arms. Due to the small sample size of the trial, small numerical differences in demographic characteristics lead to large differences in proportion. These small numerical differences are unlikely to impact FDA's ability to evaluate the safety of the treatment arms in Study 20190172.

Table 28. FDA's Analysis of the Demographic Characteristics of the Safety Population in Study 20190172 Study 20190172 (excluding site 33013)

Demographic Group	Investigator's choice N = 50 n (%)	Sotorasib 240 mg + Panitumumab N = 50 n (%)	Sotorasib 960 mg + Panitumumab N = 47 n (%)
Sex			
Female	27 (54)	26 (52)	23 (49)
Male	23 (46)	24 (48)	24 (51)
Age			

Demographic Group	Investigator's choice N = 50 n (%)	Sotorasib 240 mg + Panitumumab N = 50 n (%)	Sotorasib 960 mg + Panitumumab N = 47 n (%)
18 - 64 Years	25 (50)	37 (74)	29 (62)
65 - 74 Years	22 (44)	8 (16)	14 (30)
75 - 84 Years	3 (6)	5 (10)	4 (9)
ECOG Performance Status			
0	34 (68)	26 (52)	30 (64)
1	15 (30)	22 (44)	15 (32)
2	1 (2)	2 (4)	2 (4.3)
Race			
White	34 (68)	27 (54)	37 (79)
Asian	11 (22)	22 (44)	6 (13)
Black or African American	0 (0)	1 (2)	0
Other	5 (10)	0	4 (9)
Ethnic			
Not Hispanic or Latino	41 (82)	50 (100)	42 (89)
Hispanic or Latino	8 (16)	0	3 (6)
Not reported	1 (2)	0	2 (4.3)
Region			
Western Europe	33 (66)	25 (50)	35 (74)
Asia	10 (20)	19 (38)	6 (13)
North America	7 (14)	5 (10)	5 (11)
Oceania	0 (0)	1 (2)	1 (2.1)

Source: ADSL.xpt (SDN 380, submitted April 17, 2024)

Adequacy of the safety database:

Data:

A summary of clinical studies supporting the integrated analyses of safety is provided in Applicant - Table 25. As of the data cut-off dates for Study 20190172, 53 subjects with mCRC received sotorasib 240 mg + panitumumab and 53 subjects with mCRC received sotorasib 960 mg + panitumumab. As of the data cut-off dates for the pooled sotorasib monotherapy data from Study 20170543, a total of 122 subjects with mCRC were treated with sotorasib monotherapy across all dose groups. As of the data cut-off for the pooled sotorasib + panitumumab data from Studies 20190172 and 20190135 Subprotocol H, a total of 185 subjects with mCRC were treated with sotorasib + panitumumab across all dose groups.

The Applicant's Position:
The safety database is considered adequate to assess the safety of sotorasib and sotorasib + panitumumab in the mCRC indication.

The FDA's Assessment:
FDA agrees that the safety database is adequate to assess the safety of sotorasib and sotorasib with panitumumab in the mCRC indication.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:
The clinical study centers for all clinical studies were monitored by clinical research associates following study-specific monitoring plans for consistency. Data were queried per study-specific data management plans, including 100% source data verification for Study 20190172, automated database edit checks and internal data review by data management, clinical program management, and medical reviewers.

The Applicant's Position:
No issues were identified regarding data integrity or submission quality that had an effect on the safety review.

The FDA's Assessment:
FDA disagrees that there were no issues with data integrity. See Section 4.1 for details regarding the issue of forgery at clinical site 33013.

Categorization of Adverse Event

Data:
Not applicable, please see Applicant's position.

The Applicant's Position:

Standard methodologies were used to categorize adverse events. The analyses used Medical Dictionary for Regulatory Activities (MedDRA) version 26.0 and adverse events were graded using the current version of National Cancer Institute-Common Terminology Criteria for Adverse Events NCI-CTCAE (version 5.0). Events of interest were evaluated based on standardized MedDRA queries, high-level group terms, or high-level terms. The events of interest were selected based on the mechanism of action of sotorasib and panitumumab as well as nonclinical and clinical observations.

The collection of adverse events in the clinical studies was also appropriate. The protocols defined adverse events and serious adverse events, as well as the reporting procedures. Adverse events were collected after enrollment through the safety follow-up visit. All adverse events considered to be related to investigational product and all serious adverse events regardless of relationship were required to be followed until stabilization or reversibility. Treatment-emergent adverse events were defined as any adverse event with an onset date between the date of first dose and up to and including 30 days after the date of last dose of investigational product or the end of study date, whichever was earlier.

Per protocol, investigators were required to report all known signs and symptoms when an adverse event or serious adverse event was due to mCRC, while deaths due to disease progression in the absence of signs and symptoms were required be reported as the primary tumor type. To allow for a more clinically relevant description of safety, a list of select preferred terms that are reflective of the primary tumor and represent disease progression events were excluded from safety analyses of adverse events (excluded disease progression preferred terms are provided in Appendix 1 of Module 2.7.4, Summary of Clinical Safety).

For Studies 20190172 and 20170543, adverse events of interest are defined in the respective study CSRs. In the pooled combination therapy analysis, 4 adverse events of interest were analyzed for sotorasib in combination with panitumumab: hepatotoxicity, which was identified based on data from ongoing clinical studies; renal toxicity, which was identified based on sotorasib nonclinical studies (Module 2.4, Nonclinical Overview) and the panitumumab safety profile (Vectibix USPI 2021); pneumonitis, which was identified based on safety data from ongoing clinical studies and marketing experience with sotorasib and panitumumab; and dermatologic and soft tissue toxicity, which was identified based on the panitumumab safety profile (Vectibix USPI 2021). More details on the adverse events of interest analysis are provided in Section 1.2.1.1.3 of Module 2.7.4, Summary of Clinical Safety.

The FDA's Assessment:

FDA agrees with the Applicant's characterization of the adverse events as described above. FDA analyzed adverse events that occurred after the patient received the investigational agent, i.e., TEAEs, and until 30 days after the last dose of the investigational agent. TEAEs were included

even if they occurred after initiation of subsequent anticancer therapy but were within the 30 days after the last dose of the investigational agent. FDA analysis also excluded adverse event terms related to CRC or progression of CRC, which led to exclusion of 27 Preferred Terms among 18 patients. The Preferred Terms were colon cancer metastatic, colon cancer stage IV, colorectal adenocarcinoma, colorectal cancer, colorectal cancer metastatic, disease progression, metastases to central nervous system, metastases to ovary, metastases to peritoneum, metastases to spine, metastasis, and metastatic neoplasm. Furthermore, differences in incidence rate of TEAEs between the Applicant's and FDA's analysis arose from the FDA's use of composite terms, where Preferred Terms describing the same adverse event are grouped together into one term (e.g., grouping of fatigue and asthenia).

Routine Clinical Tests

Data:
In Studies 20190172, 20190135 Subprotocol H, and 20170543, all protocol-required laboratory assessments, including routine hematology and serum chemistry panels, were to be conducted in accordance with the laboratory manual and the schedule of assessments (Study 20190172 Protocol Table 1-1, Table 1-2, and Table 1-3; Study 20190135 Subprotocol H Protocol Table 1-1; and Study 20170543 Protocol Table 7-1 to Table 7-7). Laboratory values were graded using the current version of NCI-CTCAE (version 5.0). Vital signs, physical measurements, and electrocardiograms (ECGs) were also assessed during study visits as outlined in the schedule of assessments. Clinically significant abnormal vital signs or findings were to be reported as adverse events.

The Applicant's Position:
The clinical monitoring of subject safety was considered adequate for the expected toxicities associated with sotorasib and sotorasib + panitumumab treatment. The time points and analyses of clinical tests were defined in the study protocols.

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

8.2.4. Safety Results

Deaths

Data:
Study 20190172

Four subjects (7.5%) in the sotorasib 240 mg + panitumumab group, 2 subjects (3.8%) in the sotorasib 960 mg + panitumumab group, and 3 subjects (5.9%) in the control group had fatal

adverse events (Applicant - Table 29). Fatal adverse events by preferred term are provided in Table 13 of Module 2.7.4 Summary of Clinical Safety. The only fatal adverse events reported for more than 1 subject in either of the treatment groups were intestinal obstruction reported for 2 subjects (3.8%) in the sotorasib 240 mg + panitumumab group. No fatal adverse events in any group were considered treatment-related.

Applicant - Table 29. Treatment-emergent Fatal Adverse Events by Preferred Term (Safety Analysis Set)

Preferred Term[a]	Trifluridine and Tipiracil or Regorafenib (N = 51) n (%)	Sotorasib 240 mg + Panitumumab (N = 53) n (%)	Sotorasib 960 mg + Panitumumab (N = 53) n (%)	Total Sotorasib + Panitumumab (N = 106) n (%)
Number of subjects reporting treatment-emergent fatal adverse events	3 (5.9)	4 (7.5)	2 (3.8)	6 (5.7)
Cardiac arrest	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.9)
Sepsis	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.9)
Intestinal obstruction	0 (0.0)	2 (3.8)	0 (0.0)	2 (1.9)
Metastases to central nervous system	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.9)
Metastases to peritoneum	0 (0.0)	1 (1.9)	0 (0.0)	1 (0.9)
Cardiac failure acute	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Condition aggravated	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pleuritic pain	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data cut-off date: 19 June 2023.
MedDRA = Medical Dictionary for Regulatory Activities
Coded using MedDRA version 26.0.
Rows are sorted by preferred term in descending order of frequency in the sotorasib 960 mg + panitumumab, then sotorasib 240 mg + panitumumab.
[a] The following preferred terms, if observed, were excluded as they represent disease progression events: adenocarcinoma, adenocarcinoma of colon, cholangiocarcinoma, colon cancer, colon cancer metastatic, colon cancer stage IV, colorectal adenocarcinoma, colorectal cancer, colorectal cancer metastatic, disease progression, lung adenocarcinoma, lung cancer metastatic, malignant neoplasm progression, metastatic neoplasm, ovarian cancer metastatic, rectal adenocarcinoma, rectal cancer, rectal cancer metastatic.
Source: Table 13 of Module 2.7.4, Summary of Clinical Safety

Pooled Safety Analysis: Sotorasib 960 mg Monotherapy

Fatal adverse events were reported for 2 subjects (1.6%) with mCRC treated with sotorasib monotherapy at any dose (Applicant - Table 30). Both subjects were in the sotorasib 960 mg group (2.2%) and had fatal adverse events of small intestinal obstruction. No fatal events were attributed to sotorasib and assessment of individual fatal events found that in all cases the deaths were due to either the underlying cancer or other comorbidities. Fatal adverse events by preferred term for the sotorasib monotherapy groups are provided in Table 14 of Module 2.7.4, Summary of Clinical Safety.

Applicant - Table 30. Treatment-emergent Fatal Adverse Events by Preferred Term (Safety Analysis Set)

Preferred Term[a]	Study 20170543 CRC Sotorasib 960 mg Monotherapy (N = 91) n (%)	Study 20170543 CRC Sotorasib Any Dose Monotherapy (N = 122) n (%)	Study 20190172 CRC Sotorasib 240 mg + Panitumumab (N = 53) n (%)	Study 20190172 CRC Sotorasib 960 mg + Panitumumab (N = 53) n (%)	All studies CRC Sotorasib 960 mg + Panitumumab (N = 132) n (%)	All studies CRC Sotorasib Any Dose + Panitumumab (N = 185) n (%)	All studies Any Tumor Type Sotorasib 960 mg + Panitumumab (N = 174) n (%)	All studies Any Tumor Type Sotorasib Any Dose + Panitumumab (N = 227) n (%)
Number of subjects reporting treatment-emergent fatal adverse events	2 (2.2)	2 (1.6)	4 (7.5)	2 (3.8)	3 (2.3)	7 (3.8)	3 (1.7)	7 (3.1)
Cardiac arrest	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.8)	1 (0.5)	1 (0.6)	1 (0.4)
Intestinal obstruction	0 (0.0)	0 (0.0)	2 (3.8)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.9)
Small intestinal obstruction	2 (2.2)	2 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.5)	1 (0.6)	1 (0.4)
Sepsis	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.8)	1 (0.5)	1 (0.6)	1 (0.4)
Metastases to central nervous system	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.4)
Metastases to peritoneum	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.4)

Data cut-off date: 01 April 2023 (Study 20170543 Phase 1 and Phase 2), 19 June 2023 (Study 20190172), 23 May 2023 (Study 20190135 Subprotocol H)
CRC = colorectal cancer; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities
Grade 5 fatal adverse events may start prior to data cut-off and result in death after cut-off. These events are summarized with grade 5 but the death after data cut-off are not included in analysis.
Adverse events coded using MedDRA version 26.0. Severity graded using CTCAE v5.0.
All studies include Studies 20190172 and 20190135 Subprotocol H.
[a] The following preferred terms, if observed, were excluded as they represent disease progression events: adenocarcinoma, adenocarcinoma of colon, cholangiocarcinoma, colon cancer, colon cancer metastatic, colon cancer stage IV, colorectal adenocarcinoma, colorectal cancer, colorectal cancer metastatic, disease progression, lung adenocarcinoma, lung cancer metastatic, malignant neoplasm progression, metastatic neoplasm, ovarian cancer metastatic, rectal adenocarcinoma, rectal cancer, rectal cancer metastatic.
Source: Table 14 of Module 2.7.4, Summary of Clinical Safety

Pooled Results: Sotorasib 960 mg + Panitumumab

Fatal adverse events were reported for 7 subjects (3.8%) with mCRC in the sotorasib any dose + panitumumab group. Of these, 3 subjects (2.3%) were in the sotorasib 960 mg group + panitumumab group. Fatal adverse events by preferred term for sotorasib + panitumumab groups are provided in Table 14 of Module 2.7.4 Summary of Clinical Safety. In the sotorasib 960 mg + panitumumab group, fatal adverse events of cardiac arrest, hepatic failure, and sepsis (1 subject each [0.8%]) were reported. Hepatic failure was determined by the investigator to be due to progressive disease as shown by computed tomography imaging of worsening liver metastases and concurrent bone metastases. Cardiac arrest was also attributed to disease progression following worsening intestinal obstruction due to colonic stenosis. Similarly, the fatal event of sepsis occurred in the setting of disease progression and was not attributed to study treatment.

The Applicant's Position:

In Study 20190172 and the pooled analyses, no fatal events were attributed to sotorasib or panitumumab, and assessment of individual fatal events found that in all cases the deaths were due to either the underlying cancer or other comorbidities.

The FDA's Assessment:

Study 20190172

FDA agrees with the Grade 5 TEAEs in the Applicant's Table 25 except for the inclusion of metastases to the central nervous system and to the peritoneum since both are related to CRC and the inclusion of "cardiac failure acute" since the patient was in site 33013. Excluding these TEAEs, 2 patients (4-4.2%) in each treatment arm had Grade 5 TEAEs. Intestinal obstruction (n=2, 3.8%) was the only Grade 5 TEAE that occurred in more than one patient, and it occurred in the sotorasib 240 mg arm.

Pooled Analysis

FDA notes that there is a typographical error in the Applicant - Table 30; it states that no patients died of hepatic failure in the sotorasib 960 mg + panitumumab arm in Study 20190172 when in fact one patient died from hepatic failure in this arm. Otherwise, FDA agrees with the Grade 5 TEAEs in the Applicant - Table 30 except for the inclusion of metastases to the central nervous system and to the peritoneum since both are related to CRC. In the pooled analysis that included patients with KRAS G12C mutated advanced solid tumors, including CRC, all 7 patients who died had CRC, where 2 patients received single-agent sotorasib 960 mg and 5 patients received sotorasib + panitumumab (n=2 sotorasib 240 mg, and n=3 sotorasib 960 mg). Intestinal obstruction was again the only Grade 5 TEAE that occurred in more than one patient (n=4/307, 1.3%) among patients who received sotorasib with or without panitumumab.

Overall FDA Assessment of Deaths

Intestinal obstruction was the only Grade 5 TEAE that occurred in more than one patient in the analysis of Grade 5 TEAEs in Study 20190172 and the pooled safety analysis and it occurred in sotorasib-containing regimens. Even though intestinal obstruction is a common complication of CRC and its incidence was low in the analysis, this is a clinically significant event that warrants awareness among health care providers treating patients with KRAS G12C mutated mCRC with sotorasib in combination with panitumumab.

Serious Adverse Events

Data:

Study 20190172

Serious adverse events were reported for 17 subjects (32.1%) in the sotorasib 240 mg + panitumumab group, 14 subjects (26.4%) in the sotorasib 960 mg + panitumumab group, and 15 subjects (29.4%) in the control group (Applicant - Table 31). Across the sotorasib 240 mg + panitumumab, sotorasib 960 mg + panitumumab, and control groups respectively, the most frequently reported serious adverse events (≥ 3 subjects in any group) were sepsis (0 subjects [0%], 3 subjects [5.7%], and 0 subjects [0.0%]), intestinal obstruction (3 subjects [5.7%], 2 subjects [3.8%], and 0 subjects [0.0%]), and small intestinal obstruction (3 subjects [5.7%], 0 subjects [0.0%], and 0 subjects [0.0%]).

Applicant - Table 31. Treatment-emergent Serious Adverse Events by Preferred Term Reported for > 2% of Subjects in Any Treatment Group (Safety Analysis Set)

Preferred Term[a]	Trifluridine and Tipiracil or Regorafenib (N = 51) n (%)	Sotorasib 240 mg + Panitumumab (N = 53) n (%)	Sotorasib 960 mg + Panitumumab (N = 53) n (%)	Total Sotorasib + Panitumumab (N = 106) n (%)
Number of subjects reporting treatment-emergent serious adverse events	15 (29.4)	17 (32.1)	14 (26.4)	31 (29.2)
Sepsis	0 (0.0)	0 (0.0)	3 (5.7)	3 (2.8)
Intestinal obstruction	0 (0.0)	3 (5.7)	2 (3.8)	5 (4.7)
Small intestinal obstruction	0 (0.0)	3 (5.7)	0 (0.0)	3 (2.8)
Pyrexia	0 (0.0)	2 (3.8)	0 (0.0)	2 (1.9)
Urinary tract infection	0 (0.0)	2 (3.8)	0 (0.0)	2 (1.9)
Vomiting	0 (0.0)	2 (3.8)	0 (0.0)	2 (1.9)
Pulmonary embolism	2 (3.9)	1 (1.9)	0 (0.0)	1 (0.9)
Dyspnoea	2 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)

MedDRA = Medical Dictionary for Regulatory Activities
Data cut-off date: 19 June 2023.
Coded using MedDRA version 26.0.
Rows are sorted by preferred term in descending order of frequency in the sotorasib 960 mg + panitumumab, then sotorasib 240 mg + panitumumab.

[a] The following preferred terms, if observed, were excluded as they represent disease progression events: adenocarcinoma, adenocarcinoma of colon, cholangiocarcinoma, colon cancer, colon cancer metastatic, colon cancer stage IV, colorectal adenocarcinoma, colorectal cancer, colorectal cancer metastatic, disease progression, lung adenocarcinoma, lung cancer metastatic, malignant neoplasm progression, metastatic neoplasm, ovarian cancer metastatic, rectal adenocarcinoma, rectal cancer, rectal cancer metastatic .
Source: Table 15 of Module 2.7.4, Summary of Clinical Safety

Pooled Results: Sotorasib 960 mg Monotherapy

Serious adverse events were reported for 34 subjects (27.9%) with mCRC treated with sotorasib monotherapy at any dose (Applicant - Table 32). Of these, 24 subjects (26.4%) in the sotorasib 960 mg monotherapy group reported serious adverse events. In the sotorasib 960 mg group, the most common serious adverse events (≥ 2% subjects) were small intestinal obstruction (6 subjects, 6.6%), large intestinal obstruction (2 subjects, 2.2%), cholangitis (3 subjects, 3.3%), acute kidney injury (2 subjects, 2.2%), and pleural effusion (2 subjects, 2.2%).

Pooled Results: Sotorasib 960 mg + Panitumumab

Serious adverse events were reported for 57 subjects (30.8%) with mCRC in the sotorasib any dose + panitumumab group (Applicant - Table 32). Of these, 40 subjects (30.3%) in the sotorasib 960 mg + panitumumab group reported serious adverse events. In the sotorasib 960 mg + panitumumab group, the most common serious adverse events (≥ 2% subjects) were intestinal obstruction (4 subjects, 3.0%), and abdominal pain, pain, and sepsis (3 subjects each, 2.3%).

Applicant - Table 32. Treatment-emergent Serious Adverse Events by Preferred Term (Reported for ≥ 2% Subjects in Any Treatment Group) (Safety Analysis Set)

Preferred Term[a]	Study 20170543 CRC Sotorasib 960 mg Monotherapy (N = 91) n (%)	Study 20170543 CRC Sotorasib Any Dose Monotherapy (N = 122) n (%)	Study 20190172 CRC Sotorasib 240 mg + Panitumumab (N = 53) n (%)	Study 20190172 CRC Sotorasib 960 mg + Panitumumab (N = 53) n (%)	All studies CRC Sotorasib 960 mg + Panitumumab (N = 132) n (%)	All studies CRC Sotorasib Any Dose + Panitumumab (N = 185) n (%)	All studies Any Tumor Type Sotorasib 960 mg + Panitumumab (N = 174) n (%)	All studies Any Tumor Type Sotorasib Any Dose + Panitumumab (N = 227) n (%)
Number of subjects reporting treatment-emergent serious adverse events	24 (26.4)	34 (27.9)	17 (32.1)	14 (26.4)	40 (30.3)	57 (30.8)	57 (32.8)	74 (32.6)
Intestinal obstruction	0 (0.0)	0 (0.0)	3 (5.7)	2 (3.8)	4 (3.0)	7 (3.8)	4 (2.3)	7 (3.1)
Abdominal pain	1 (1.1)	2 (1.6)	0 (0.0)	0 (0.0)	3 (2.3)	3 (1.6)	5 (2.9)	5 (2.2)
Vomiting	0 (0.0)	0 (0.0)	2 (3.8)	0 (0.0)	2 (1.5)	4 (2.2)	3 (1.7)	5 (2.2)
Small intestinal obstruction	6 (6.6)	7 (5.7)	3 (5.7)	0 (0.0)	1 (0.8)	4 (2.2)	3 (1.7)	6 (2.6)
Large intestinal obstruction	2 (2.2)	2 (1.6)	1 (1.9)	0 (0.0)	1 (0.8)	2 (1.1)	1 (0.6)	2 (0.9)
Pain	0 (0.0)	0 (0.0)	1 (1.9)	1 (1.9)	3 (2.3)	4 (2.2)	3 (1.7)	4 (1.8)
Pyrexia	0 (0.0)	1 (0.8)	2 (3.8)	0 (0.0)	2 (1.5)	4 (2.2)	2 (1.1)	4 (1.8)
Cholangitis	3 (3.3)	3 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sepsis	1 (1.1)	1 (0.8)	0 (0.0)	3 (5.7)	3 (2.3)	3 (1.6)	3 (1.7)	3 (1.3)
Urinary tract infection	0 (0.0)	0 (0.0)	2 (3.8)	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.9)
Back pain	1 (1.1)	1 (0.8)	1 (1.9)	1 (1.9)	1 (0.8)	2 (1.1)	4 (2.3)	5 (2.2)
Acute kidney injury	2 (2.2)	3 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pleural effusion	2 (2.2)	2 (1.6)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.5)	2 (1.1)	2 (0.9)
Dyspnoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.3)	4 (1.8)

MedDRA = Medical Dictionary for Regulatory Activities
Data cut-off date: 01 April 2023 (Study 20170543 Phase 1 and Phase 2), 19 June 2023 (Study 20190172), 23 May 2023 (Study 20190135 Subprotocol H)
Adverse events coded using MedDRA version 26.0.
All studies include Studies 20190172 and 20190135 Subprotocol H.

[a] The following preferred terms, if observed, were excluded as they represent disease progression events: adenocarcinoma, adenocarcinoma of colon, cholangiocarcinoma, colon cancer, colon cancer metastatic, colon cancer stage IV, colorectal adenocarcinoma, colorectal cancer, colorectal cancer metastatic, disease progression, lung adenocarcinoma, lung cancer metastatic, malignant neoplasm progression, metastatic neoplasm, ovarian cancer metastatic, rectal adenocarcinoma, rectal cancer, rectal cancer metastatic.
Source: Table 16 of Module 2.7.4, Summary of Clinical Safety

The Applicant's Position:

In Study 2019172 and the pooled analyses, the subject incidences of serious adverse events were similar across the treatment groups and review of individual serious adverse events did not identify any new safety concerns. Most serious adverse events were due to either the underlying cancer or other cancer-related comorbidities.

The FDA's Assessment:

Study 2019172

In this review, the FDA clinical reviewer defined a >2% difference in incidence among serious TEAEs (SAEs) to indicate a potential difference in toxicity profile between the treatment arms. Based on this cutoff, among SAEs that occurred in ≥2 patients in any treatment arm, serious infections and gastrointestinal disorders were more common in the sotorasib-containing arms, and dyspnea was more common in the control arm, but the overall incidence of these events was low (Table 33). The higher dose of sotorasib was not associated with an increase in SAEs except for sepsis. Sepsis in the sotorasib 960 mg arm and intestinal obstruction in the sotorasib 240 mg arm were the only SAEs with an incidence ≥5% in Study 2019172; no SAEs had an incidence ≥5% in the control arm. It is difficult to make conclusions regarding the dose-toxicity relationship based on these small differences in incidence of SAEs in a small study.

One SAE was reported in the site that was excluded from the safety analysis (i.e., 33013), and it was a case of urinary tract stoma complication in a patient in the sotorasib 960 mg arm. Thus, the exclusion of this site did not alter the conclusion of the safety analysis based on SAEs.

Table 33. FDA's Analysis of SAEs in ≥2 Patients in Study 20190172 (excluding site 33013)

	Trifluridine/Tipiracil or Regorafenib (N = 50) n (%)	Sotorasib 240 mg + Panitumumab (N = 50) n (%)	Sotorasib 960 mg + Panitumumab (N = 47) n (%)	Total Sotorasib + Panitumumab (N = 97) n (%)
Patients with SAEs	**13 (26)**	**14 (28)**	**12 (26)**	**26 (27)**
Infections and Infestations				
Sepsis	0	0	3 (6)	3 (3.1)
Urinary Tract Infection [a]	1 (2)	2 (4)	0	2 (2.1)
Gastrointestinal Disorders				
Intestinal Obstruction [b]	0	5 (10)	2 (4.3)	7 (7)
Vomiting	0	2 (4)	0	2 (2.1)
Ileus [c]	0	2 (4)	0	2 (2.1)
General Disorders and Administration Site Conditions				
Pyrexia	0	2 (4)	0	2 (2.1)
Vascular Disorders				

Pulmonary Embolism	2 (4)	1 (2)	0	1 (1)
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea	2 (4)	0	0	0

[a] includes urinary tract infection, urosepsis
[b] includes intestinal obstruction, small intestinal obstruction, large intestinal obstruction
[c] includes ileus, subileus
Source: ADAE.xpt (SDN 380, submitted April 17, 2024)

Pooled Analysis

The incidence of SAEs was low in the pooled analysis, which limits the ability to adequately compare the safety based on SAEs of sotorasib as a single agent and in combination with panitumumab, and of different doses of sotorasib (Table 34). This also limits that ability to make any conclusions regarding relationships between dose and toxicity. With this limitation in mind, FDA noted the following:

- The 960 mg dosage of sotorasib (both as single-agent and in combination with panitumumab) was associated with more infections, including cholangitis.
- The only SAE with an incidence of ≥5% was intestinal obstruction, which was more common with the sotorasib 960 mg dosage compared to the lower dosages in the single-agent groups, and it was more common in the sotorasib 240 mg dosage than the sotorasib 960 mg dosage in the sotorasib with panitumumab groups. Thus, it is unclear if increasing dosages of sotorasib is associated with serious intestinal obstruction. The addition of panitumumab did not appear to increase the risk of intestinal obstruction in patients with CRC (8% with any dose single agent sotorasib, and 6% with any dose sotorasib with panitumumab). Not surprisingly, the incidence of intestinal obstruction is lower in the non-CRC cohort (4.8%) compared to the CRC cohorts.

Table 34. FDA's Pooled Analysis of SAEs in ≥2 Patients in Any Cohort (excluding site 33013)

	CRC Sotorasib single-agent any dose (N = 122) n (%)	CRC Sotorasib single-agent any dose excluding 960 mg (N = 31) n (%)	CRC Sotorasib 960 mg (N = 91) n (%)	CRC Sotorasib 240 mg + Panitumumab (N = 50) n (%)	CRC Sotorasib 960 mg + Panitumumab (N = 126) n (%)	CRC Sotorasib any dose + Panitumumab (N = 176) n (%)	All tumors Sotorasib any dose + Panitumumab (N = 218) n (%)	Any non-CRC tumors Sotorasib 960 mg + Panitumumab (N = 42) n (%)
Patients with SAEs	**34 (28)**	**10 (32)**	**24 (26)**	**14 (28)**	**37 (29)**	**51 (29)**	**68 (31)**	**17 (40)**
Gastrointestinal Disorders								
Intestinal or GI Obstruction [a]	10 (8)	1 (3.2)	9 (10)	5 (10)	6 (4.5)	11 (6)	13 (6)	2 (4.8)
Abdominal Pain [b]	2 (1.6)	1 (3.2)	1 (1.1)	0	4 (3.0)	4 (2.3)	6 (2.8)	2 (4.8)
Vomiting	0	0	0	2 (4)	2 (1.5)	4 (2.3)	5 (2.3)	1 (2.4)
Constipation	0	0	0	0	2 (1.5)	2 (1.1)	2 (0.9)	0
General Disorders and Administration Site Conditions								
Pyrexia	1 (0.8)	1 (3.2)	0	2 (4)	3 (2.3)	5 (2.8)	5 (2.3)	0
Pain	0	0	0	1 (2)	3 (2.3)	4 (2.3)	4 (1.8)	0

Edema Peripheral	0	0	0	0	2 (1.5)	2 (1.1)	2 (0.9)	0
Infections and Infestations								
Sepsis [c]	2 (1.6)	0	2 (2.2)	0	3 (2.3)	3 (1.7)	3 (1.4)	0
Enteritis Infectious [d]	0	0	0	0	2 (1.5)	2 (1.1)	2 (0.9)	0
Urinary Tract Infection [e]	2 (1.6)	0	2 (2.2)	2 (4)	0	2 (1.1)	2 (0.9)	0
Pneumonia	2 (1.6)	1 (3.2)	1 (1.1)	0	0	0	0	0
Musculoskeletal and Connective Tissue Disorders								
Musculoskeletal Pain [f]	2 (1.6)	0	2 (2.2)	1 (2)	3 (2.3)	4 (2.3)	7 (3.2)	3 (7)
Muscular Weakness	0	0	0	0	0	0	2 (0.9)	2 (4.8)
Nervous System Disorders								
Seizure	3 (2.5)	1 (3.2)	2 (2.2)	0	2 (1.5)	2 (1.1)	2 (0.9)	0
Syncope	1 (0.8)	0	1 (1.1)	0	2 (1.5)	2 (1.1)	2 (0.9)	0
Injury, Poisoning and Procedural Complications								
Fracture [g]	0	0	0	0	2 (1.5)	2 (1.1)	2 (0.9)	0
Skin and Subcutaneous Tissue Disorders								
Dermatitis Acneiform	0	0	0	0	2 (1.5)	2 (1.1)	2 (0.9)	0
Vascular Disorders								
Thromboembolism [h]	1 (0.8)	0	1 (1.1)	2 (4)	1 (0.8)	3 (1.7)	5 (2.3)	2 (4.8)
Hemorrhage [i]	1 (0.8)	0	1 (1.1)	0	1 (0.8)	1 (0.6)	2 (0.9)	1 (2.4)
Hematoma [j]	0	0	0	0	1 (0.8)	1 (0.6)	2 (0.9)	1 (2.4)
Respiratory, Thoracic and Mediastinal Disorders								
Pleural Effusion [k]	2 (1.6)	0	2 (2.2)	0	1 (0.8)	1 (0.6)	2 (0.9)	1 (2.4)
Dyspnea	0	0	0	0	0	0	4 (1.8)	4 (10)
Hepatobiliary Disorders								
Biliary Obstruction [l]	3 (2.5)	2 (6)	1 (1.1)	0	1 (0.8)	1 (0.6)	1 (0.5)	0
Cholangitis	3 (2.5)	0	3 (3.3)	0	0	0	0	0
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)								
Tumor Pain	2 (1.6)	0	2 (2.2)	0	1 (0.8)	1 (0.6)	1 (0.5)	0
Cardiac Disorders								
Sinus Tachycardia	0	0	0	0	0	0	2 (0.9)	2 (4.8)
Renal and Urinary Disorders								
Acute Kidney Injury	3 (2.5)	1 (3.2)	2 (2.2)	0	0	0	0	0

[a] includes small intestinal obstruction, intestinal obstruction, large intestinal obstruction, gastrointestinal obstruction, obstruction gastric
[b] includes abdominal pain, abdominal pain upper
[c] includes sepsis, staphylococcal sepsis
[d] includes enteritis infectious, bacterial diarrhea
[e] includes urinary tract infection, bacterial pyelonephritis, urosepsis, urinary tract infection pseudomonal
[f] includes back pain, musculoskeletal chest pain, musculoskeletal pain, pain in extremity
[g] includes humerus fracture, femoral neck fracture

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

[h] includes pulmonary embolism, embolism, thrombosis, pelvic venous thrombosis, vena cava thrombosis
[i] includes gastrointestinal hemorrhage, hematuria, gastric hemorrhage
[j] includes hematoma, traumatic hematoma
[k] includes pleural effusion, malignant pleural effusion
[l] includes biliary obstruction, malignant biliary obstruction
Source: ADAE.xpt (SDN 380, submitted April 17, 2024) – Integrated Summary of Safety - CRC, Module 5.3.5.3

Overall FDA Assessment of SAEs

Gastrointestinal disorders and infections were more common in the sotorasib-containing groups in Study 20190172. Based on SAEs in both Study 20190172 and the Pooled Analysis, infection risk may be increased with increasing dosages of sotorasib, but this observation is limited by the low incidence of SAEs in the submitted datasets. Intestinal obstruction remains a concern in patients with CRC treated with sotorasib, compared to treatment with trifluridine/tipiracil or regorafenib. However, the risk of intestinal obstruction does not appear to increase with sotorasib dosage. See Significant Adverse Events section for a discussion about intestinal obstruction.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Study 20190172

In the sotorasib 240 mg + panitumumab group, 3 subjects (5.7%) had an adverse event leading to the discontinuation of both sotorasib and panitumumab, and 1 subject (1.9%) had an adverse event leading to the discontinuation of sotorasib only. In the sotorasib 960 mg + panitumumab group, 3 subjects (5.7%) had an adverse event leading to the discontinuation of both sotorasib and panitumumab. In the control group, 3 subjects (5.9%) had adverse events leading to the discontinuation of investigational product. No adverse event type was reported for more than 1 subject in any group.

Pooled Results: Sotorasib 960 mg Monotherapy

Adverse events leading to sotorasib treatment discontinuation were reported for 2 subjects (1.6%) treated with sotorasib monotherapy at any dose. Both of these subjects were in the sotorasib 960 mg monotherapy group (2.2%). One subject each (0.8%) had adverse events of back pain and invasive ductal breast carcinoma that led to sotorasib discontinuation.

Pooled Results: Sotorasib 960 mg + Panitumumab

In the sotorasib 960 mg + panitumumab group, 3 subjects (2.3%) with mCRC had an adverse event leading to the discontinuation of both sotorasib and panitumumab, and 3 subjects (2.3%) had an adverse event leading to the discontinuation of sotorasib and 4 subjects (3.0%) had an adverse event leading to the discontinuation of panitumumab only. No preferred term was reported for more than 1 subject in these groups.

The Applicant's Position:

In Study 20190172 and across the pooled analysis, the subject incidence of adverse events leading to treatment discontinuation was low: no preferred term led to discontinuation of

sotorasib ≥ 2 subjects, and only hypomagnesemia led to discontinuation of panitumumab in ≥ 2 subjects. Overall, sotorasib in combination with panitumumab was well tolerated based on the low incidence of discontinuation due to adverse events. More detailed results for discontinuation due to adverse events are provided in Section 2.1.5.2 of Module 2.7.4, Summary of Clinical Safety.

The FDA's Assessment:

Study 20190172

Table 35 summarizes the TEAEs that led to dose modifications in Study 20190172. The FDA analysis has different values from the Applicant's analysis because FDA excluded patients from site 33013 and did not include CRC-related Preferred Terms. Patients in the sotorasib with panitumumab arms had less dose modifications than the patients in the control arm. In all three arms, more patients had dose interruption to manage the TEAEs than dose reduction. Permanent discontinuation was infrequently used to manage toxicity (3.1% in the sotorasib containing arms, 4% in the control arm). It is notable that there were more dose reductions or interruptions of panitumumab than sotorasib among patients in the sotorasib with panitumumab arms. If sotorasib was modified, dosing was more often interrupted rather than reduced; only 1 patient in the sotorasib 960 mg with panitumumab arm had sotorasib dose reduced and dose reduction was not permitted for the sotorasib 240 mg with panitumumab arm. Patients in the sotorasib 960 mg with panitumumab arm underwent less dose interruption of sotorasib than the patients in the sotorasib 240 mg with panitumumab arm. Furthermore, the difference in dose modifications rates between the two sotorasib arms were seen across clinical sites. In both arms, most sites which had a dose modification modified the dose of only one patient, and three was the maximum number of patients who had a dose modification at a given site (n=3 in only one site per sotorasib-containing arm). In conclusion, the patients in the sotorasib 240 mg with panitumumab arm experienced more dose modifications than the patients in the sotorasib 960 mg with panitumumab arm.

Overall, the summary of dose modification data suggests that sotorasib with panitumumab regimens were at least as tolerable, if not slightly more tolerable than the control arm regimens, and that sotorasib 960 mg with panitumumab is at least as tolerable as the sotorasib 240 mg with panitumumab regimen. Furthermore, investigators were more likely to modify panitumumab dosing than sotorasib among patients who received sotorasib with panitumumab.

Table 35. FDA's Analysis of Dose Modifications in Study 20190172 (excluding site 33013)

	Trifluridine/Tipiracil or Regorafenib (N = 50) n (%)	Sotorasib 240 mg + Panitumumab (N = 50) n (%)	Sotorasib 960 mg + Panitumumab (N = 47) n (%)	Total Sotorasib + Panitumumab (N = 97) n (%)
TEAEs that led to any drug modification	32 (64)	30 (60)	22 (47)	52 (54)

Trifluridine/Tipiracil or Regorafenib	32 (64)	-	-	-
Sotorasib only	-	8 (16)	6 (13)	14 (14)
Panitumumab only	-	17 (34)	14 (30)	31 (32)
Both Sotorasib and Panitumumab		17 (34)	9 (19)	
TEAEs that led to any drug discontinuation	2 (4)	2 (4)	1 (2)	3 (3.1)
Trifluridine/Tipiracil or Regorafenib	2 (4)	-	-	-
Sotorasib only or Panitumumab only	-	0	0	0
Both Sotorasib and Panitumumab	-	2 (4)	1 (2)	3 (3.1)
TEAEs that led to any dose reduction	11 (22)	9 (18)	9 (19)	18 (19)
Trifluridine/Tipiracil or Regorafenib	11 (22)	-	-	-
Sotorasib only	-	0	1 (2.1)	1 (1)
Panitumumab only	-	9 (18)	8 (17)	17 (18)
Both Sotorasib and Panitumumab	-	0	0	0
TEAEs that led to any dose interruption	28 (56)	28 (56)	21 (45)	49 (51)
Trifluridine/Tipiracil or Regorafenib	28 (56)	-	-	-
Sotorasib only	-	8 (16)	6 (13)	14 (14)
Panitumumab only	-	13 (26)	14 (30)	27 (29)
Both Sotorasib and Panitumumab		17 (34)	8 (17)	25 (26)
TEAEs that led to any dose increase	0	1 (2)	0	1 (1)
Trifluridine/Tipiracil or Regorafenib increased	0	-	-	-
Sotorasib only	-	0	0	0
Panitumumab only	-	1 (2)[a]	0	1 (1)
Both Sotorasib and Panitumumab	-	0	0	0

[a] Panitumumab dose increased due to weight increase.
Source: ADAE.xpt (SDN 380, submitted April 17, 2024)

Table 36 summarizes the TEAEs that led to treatment discontinuation. In the sotorasib-containing arms, both sotorasib and panitumumab were discontinued concurrently. Two patients who discontinued trial drugs died from the adverse event a few days later – one patient was in the control arm and the other patient was in the sotorasib 240 mg arm. The patient who developed Grade 4 dyspnea in the control arm (received regorafenib) died of Grade 5 pleuritic pain seven days later on Trial Day 62. The patient who developed Grade 3 small intestine obstruction died from Grade 5 bowel obstruction five days later on Trial Day 75. The drug discontinuation data does not suggest a safety signal, however any conclusions are limited because of the overall low incidence of TEAEs that led to treatment discontinuation.

Table 36. FDA's Analysis of Patients with TEAEs that led to Treatment Discontinuation in Study 20190172 (excluding site 33013)

	Trifluridine/Tipiracil or Regorafenib (N = 50) n (%)	Sotorasib 240 + Panitumumab (N = 50) n (%)	Sotorasib 960 + Panitumumab (N = 47) n (%)
Number of patients	2 (4) [a]	2 (4)	1 (2.1)
TEAEs	Grade 4 dyspnea	Grade 2 nausea [b]	Grade 4 hypocalcemia [b]
	Grade 3 hepatic failure	Grade 3 small intestinal obstruction [b]	

[a] Both patients received regorafenib.
[b] All three patients discontinued both sotorasib and panitumumab.
Source: ADAE.xpt (SDN 380, submitted April 17, 2024)

Dose Interruption/Reduction Due to Adverse Effects

Data:
Study 20190172
Dose Reduction

In the sotorasib 240 mg + panitumumab group, the protocol specified no dose reduction for sotorasib (only dose hold was allowed), and 10 subjects (18.9%) had an adverse event leading to dose reduction of panitumumab. In the sotorasib 960 mg + panitumumab group, 3 subjects (5.7%) had an adverse event leading to dose reduction of sotorasib only and 8 subjects (15.1%) had an adverse event leading to dose reduction of panitumumab only. None of the patients in the sotorasib 960 mg + panitumumab group had TEAEs that led to dose reduction of both sotorasib and panitumumab simultaneously. In the control group, 11 subjects (21.6%) had adverse events leading to dose reduction of investigational product.

The TEAEs that led to dose reduction of panitumumab in ≥2 patients were rash (3 patients [3.8%]), hypomagnesemia (2 patients [3.8%]), and weight decreased (2 patients [3.8%]) in the sotorasib 240 mg + panitumumab group, and rash (7 patients [3.8%]) in the sotorasib 960 mg + panitumumab group. Rash is a composite term that includes dermatitis acneiform, dermatosis, palmar-plantar erythrodysesthesia syndrome, rash, and skin toxicity.

Three TEAEs (anemia, transaminitis, and nausea) led to dose reduction of sotorasib in the sotorasib 960 mg + panitumumab group. The TEAEs that led to dose reduction of the investigational product in the control group in ≥2 patients were palmar-plantar erythrodysesthesia syndrome (3 patients [5.9%]), anemia (2 patients [3.9%]), and hypertension (2 patients [3.9%]).

Dose Interruption

In the sotorasib 240 mg + panitumumab group, 19 subjects (35.8%) had an adverse event leading to the interruption of both sotorasib and panitumumab. In the sotorasib 960 mg + panitumumab group, 11 subjects (20.8%) had an adverse event leading to interruption of both sotorasib and panitumumab. In the control group, 29 subjects (56.9%) had adverse events leading to the interruption of any investigational product.

The most frequently reported adverse events that led to dose interruption of panitumumab (≥ 5% in any group) were hypomagnesaemia (5 subjects [9.4%]), and diarrhea and nausea (3 subjects each [5.7%]) in the sotorasib 240 mg + panitumumab group, and dermatitis acneiform (4 subjects [7.5%]) in the sotorasib 960 mg + panitumumab group.

The most frequently reported adverse events that led to dose interruption of sotorasib (≥ 5% in any group) were nausea, vomiting, and small intestinal obstruction (3 subjects each [5.7%]) in the sotorasib 240 mg + panitumumab group. There were no event types leading to dose interruption of sotorasib observed at a rate of greater than 5% in the sotorasib 960 mg + panitumumab group.

The most frequently reported adverse events that led to dose interruption of investigational product in the control group (≥ 5%) were neutropenia (9 subjects [17.6%]), neutrophil count decreased (3 subjects [5.9%]), and palmar-plantar erythrodysesthesia syndrome (3 subjects [5.9%]).

Pooled Results: Sotorasib 960 mg Monotherapy

Adverse events leading to dose interruption and/or reduction of sotorasib were reported in 34 subjects (27.9%) with mCRC treated with sotorasib monotherapy at any dose. Of these, 26 subjects (28.6%) in the sotorasib 960 mg monotherapy group reported adverse events leading to dose interruption and/or reduction of sotorasib. In the sotorasib 960 mg group, the most frequently reported adverse events leading to dose interruption and/or reduction of sotorasib (reported in ≥ 5% of subjects) were diarrhea and nausea (5 subjects each, 5.5%), and increased alanine aminotransferase (ALT) and increased aspartate aminotransferase (AST) (6 subjects each, 6.6%).

Pooled Results: Sotorasib 960 mg + Panitumumab

Adverse events that led to dose interruption and/or reduction of both sotorasib and panitumumab were reported for 44 subjects (23.8%) with mCRC in the sotorasib any dose + panitumumab group. Of these, 25 subjects (18.9%) in the sotorasib 960 mg group + panitumumab group reported adverse events that led to dose interruption and/or reduction of both sotorasib and panitumumab. In the sotorasib 960 mg group + panitumumab group, the most frequently reported adverse events that led to dose interruption and/or reduction of both sotorasib and panitumumab (≥ 2% subjects) were vomiting, and COVID-19 (3 subjects each, [2.3%]).

Adverse events that led to dose interruption and/or reduction of sotorasib were reported for 66 subjects (35.7%) with mCRC in the sotorasib any dose + panitumumab group. Of these,

41 subjects (31.1%) in the sotorasib 960 mg group + panitumumab group reported adverse events that led to dose interruption and/or reduction of sotorasib. In the sotorasib 960 mg group + panitumumab group, the most frequently reported adverse events that led to dose interruption and/or reduction of sotorasib (≥ 2% subjects) were vomiting, intestinal obstruction, diarrhea, abdominal pain, and fatigue (3 subjects each [2.3%]), and COVID-19 (4 subjects [3.0%]).

Adverse events that led to dose interruption and/or reduction of panitumumab were reported for 84 subjects (45.4%) with mCRC in the sotorasib any dose + panitumumab group. Of these, 55 subjects (41.7%) in the sotorasib 960 mg group + panitumumab group reported adverse events that led to dose interruption and/or reduction of panitumumab. In the sotorasib 960 mg group + panitumumab group, the most frequently reported adverse events that led to dose interruption and/or reduction of panitumumab (≥ 5% subjects) were rash and dermatitis acneiform (10 subjects each [7.6%]).

The Applicant's Position:

In Study 20190172, the subject incidences of dose interruption and/or reduction were similar between the control group and the sotorasib groups. In the pooled analyses, the types of adverse events leading to dose interruption and/or reduction of sotorasib reported in the 960 mg dose monotherapy group were consistent with safety profile of sotorasib. The subject incidences of dose interruption and/or reduction were higher in the combination regimen compared with the sotorasib monotherapy; and consistent with the known safety profile of panitumumab.

The FDA's Assessment:

Study 20190172

Dose reduction

The rate of dose reduction was similar across all three arms: 18% (n=9) in the sotorasib 240 mg with panitumumab arm, 19% (n=9) in the sotorasib 960 mg with panitumumab arm, and 22% (n=11) in the control arm. Differences in FDA's analysis from the Applicant's analysis are due to FDA's exclusion of site 33013.

FDA agrees with the Applicant that panitumumab was the only drug that was dose reduced (n=9, 18%) in the sotorasib 240 mg + panitumumab arm. Based on composite terms, the most common TEAEs that led to dose reduction of panitumumab were the expected skin and nail toxicities (rash [n=3], and nail disorder [n=1]), hypomagnesemia (n=2), and diarrhea (n=1). The other TEAE that led to panitumumab dose reduction were weight decreased (n=2) likely due to its weight-based dosing.

In the sotorasib 960 mg + panitumumab arm, 1 patient (2.1%) and 8 patients (17%) had dose reductions of sotorasib and panitumumab, respectively. Sotorasib was reduced for nausea (n=1, 2.1%). Similar to the sotorasib 240 mg + panitumumab arm, the TEAEs that led to dose reduction of panitumumab were the expected skin and nail toxicities (n=7, 15%), and

hypomagnesemia (n=1, 2.1%). The skin and nail toxicities were rash (n=7), palmar-plantar erythrodysesthesia syndrome (n=1), and paronychia (n=1).

The TEAEs that led to a dose reduction of the drugs in the control arm in more than one patient were palmar-plantar erythrodysesthesia syndrome (n=3), anemia (n=2), hypertension (n=2), and platelet count decreased (n=2).

In summary, the rate of dose reduction was similar between the experimental and control arms, and most dose reductions in the sotorasib + panitumumab arms were due to toxicities attributed to panitumumab. Only one drug was reduced per TEAE in the sotorasib-containing arms, suggesting that the drugs' toxicity profiles were distinct facilitating attribution of causality. The incidences of TEAEs based on sotorasib dose reduction data were too low to suggest a safety signal.

Dose interruption
Because FDA excluded TEAEs that were related to CRC, including metastases, and excluded safety data from site 33013, the FDA analysis had slightly different values for dose interruption. FDA's use of composite terms also led to slight differences in incidences of TEAEs between FDA's and the Applicant's analyses.

The rate of dose interruption was numerically higher in the sotorasib 240 mg with panitumumab and control arms compared to the sotorasib 960 mg with panitumumab arm (56% vs. 56% vs. 45%, respectively).

Dose interruption of both sotorasib and panitumumab due to a TEAE was higher in the sotorasib 240 mg with panitumumab arm (n=17, 34%) compared to the sotorasib 960 mg with panitumumab arm (n=8, 17%). Dose interruption of only panitumumab or only sotorasib was similar between the sotorasib 240 mg with panitumumab and sotorasib 960 mg with panitumumab arms: n=13 (26%) vs. n=14 (30%), respectively, and n=8 (16%) vs. n=6 (13%), respectively. Note that based on the exposure dataset (ADEX), panitumumab was not administered as a single agent when sotorasib was interrupted for any of the patients. Thus, patients who had only sotorasib interrupted (n=8 [16%] in the sotorasib 240 mg with panitumumab arm and n=6 [13%] in the sotorasib 960 mg with panitumumab) likely also had the dose interrupted between the every 2-week administration of panitumumab.

The TEAEs that led to dose interruption of both sotorasib and panitumumab in more than 1 patient in the sotorasib 240 mg with panitumumab arm were rash, nausea (each n=3, 6%), pyrexia, and vomiting (each n=2, 4%). The TEAEs that led to only panitumumab interruption in more than 1 patient in the sotorasib 240 mg with panitumumab arm were skin and nail toxicities (n=5, 10%: rash [n=4] and paronychia [n=1]), hypomagnesemia (n=4, 8%), and diarrhea (n=2, 4%). The other TEAEs the led to interruption of panitumumab only in the

sotorasib 240 mg with panitumumab arm occurred in 1 patient each (2%): abdominal pain, COVID-19 test positive, dizziness, and ileus. The TEAE that led to only sotorasib interruption in more than 1 patient in the sotorasib 240 mg with panitumumab arm was intestinal obstruction (n=4, 8%). The other TEAEs that led to interruption of sotorasib only in the sotorasib 240 mg with panitumumab arm occurred in 1 patient each (2%): decreased appetite, diarrhea hemorrhagic, inguinal hernia, malaise, nausea, and vomiting.

The TEAEs that led to dose interruption of both sotorasib and panitumumab in more than 1 patient in the sotorasib 960 mg with panitumumab arm was rash (n=3, 6%). The TEAEs that led to only panitumumab interruption in more than 1 patient in the sotorasib 960 mg with panitumumab arm were skin toxicity (n=9, 47%: rash [n=9] and palmar-plantar erythrodysesthesia syndrome [n=1]), hypomagnesemia, and keratitis (n=2 each, 4.3%). The other TEAEs that led to interruption of panitumumab only in the sotorasib 960 mg with panitumumab arm occurred in 1 patient each (2.1%): COVID-19, pyrexia, and renal tubular disorder. The TEAEs that led to only sotorasib interruption in more than 1 patient in the sotorasib 960 mg with panitumumab arm was rash (n=2, 4.3%). The other TEAEs that led to interruption of only sotorasib in the sotorasib 960 mg with panitumumab arm occurred in 1 patient each (2.1%): abdominal pain, alanine aminotransferase increased, blood bilirubin increased, COVID-19, diarrhea, intestinal obstruction, and nausea.

Across the two sotorasib arms, 14 patients (14%) had only sotorasib interrupted, and the TEAEs that occurred in more than 1 patient were intestinal obstruction (n=5, 5%), diarrhea or diarrhea hemorrhagic, rash, and vomiting (n=2 each, 2.1%).

The TEAEs that led to dose interruption of any drug in more than 1 patient in the control arm were neutropenia (n=11, 22%), skin toxicity (n=4, 8%: palmar-plantar erythrodysesthesia syndrome [n=3] and skin toxicity [n=1]), abdominal pain upper, asthenia, decreased appetite, gastroenteritis, leukopenia, nausea, proteinuria, and vomiting (each n=2; 4%).

Overall, the incidence of TEAEs leading to dose interruption was low. The higher dose of sotorasib did not lead to more dose interruptions of either drug in the sotorasib with panitumumab regimen. TEAEs that led to dose interruption of panitumumab were the expected toxicities of skin and nail toxicity, hypomagnesemia, keratitis, and toxicities of the GI tract such as nausea, vomiting, and diarrhea. A relatively high incidence of intestinal obstruction (5%) led to sotorasib interruption. The other common TEAEs that led to sotorasib interruption were expected toxicities of sotorasib (e.g., GI tract toxicities) or possibly due to concomitant administration with panitumumab (e.g., rash).

Pooled Results
TEAEs that led to dose modifications were comparable between Study 20190172 and the pooled analysis for sotorasib 960 mg + panitumumab arms.

Table 37. FDA's Pooled Analysis of Patients with TEAEs that led to Treatment Modification (excluding site 33013)

	CRC Sotorasib monotherapy any dose (N = 122) n (%)	CRC Sotorasib any dose excluding 960 mg (N = 31) n (%)	CRC Sotorasib 960 mg (N = 91) n (%)	CRC Sotorasib 240 mg + Panitumumab (N = 50) n (%)	CRC Sotorasib 960 mg + Panitumumab (N = 126) n (%)	CRC Sotorasib any dose + Panitumumab (N = 176) n (%)	All tumors Sotorasib any dose + Panitumumab (N = 218) n (%)	Any non-CRC tumors Sotorasib 960 mg + Panitumumab (N = 42) n (%)
TEAEs that led to any drug modification	35 (29)	8 (26)	27 (30)	30 (60)	65 (52)	95 (54)	119 (54)	24 (57)
Sotorasib only	35 (29)	8 (26)	27 (30)	8 (16)	22 (17)	30 (17)	48 (22)	18 (43)
Panitumumab only	-	-	-	17 (34)	38 (30)	55 (31)	64 (29)	9 (21)
Sotorasib + Panitumumab	-	-	-	17 (34)	26 (21)	43 (24)	56 (26)	13 (31)
TEAEs that led to any drug discontinuation	2 (1.6)	0	2 (2.2)	2 (4)	4 (3.2)	6 (3.4)	10 (4.6)	4 (9.5)
Sotorasib only	2 (1.6)	0	2 (2.2)	0	0	0	0	0
Panitumumab only	-	-	-	0	1 (0.8)	1 (0.6)	3 (1.4)	2 (4.8)
Sotorasib + Panitumumab	-	-	-	2 (4)	3 (2.4)	5 (2.8)	7 (3.2)	2 (4.8)
TEAEs that led to any dose reduction	0	0	0	9 (18)	21 (17)	30 (17)	37 (17)	7 (17)
Sotorasib only	0	0	0	0	4 (3.2)	4 (2.3)	10 (4.6)	6 (14)
Panitumumab only	-	-	-	9 (18)	18 (14)	27 (15)	29 (13)	2 (4.8)
Sotorasib + Panitumumab	-	-	-	0	1 (0.8)	1 (0.6)	1 (0.5)	0
TEAEs that led to any dose interruption	34 (28)	8 (26)	26 (29)	28 (56)	60 (48)	88 (50)	111 (51)	23
Sotorasib only	34 (28)	8 (26)	26 (29)	8 (16)	20 (16)	28 (16)	43 (20)	15
Panitumumab only	-	-	-	13 (26)	34 (27)	47 (27)	54 (25)	7
Sotorasib + Panitumumab	-	-	-	17 (34)	21 (17)	38 (22)	51 (23)	13
TEAEs that led to any dose increase	0	0	0	1 (2)	0	1 (0.6)	1 (0.5)	0
Sotorasib only	0	0	0	0	0	0	0	0
Panitumumab only	-	-	-	1 (2)	0	1 (0.6)	1 (0.5)	0
Sotorasib + Panitumumab	-	-	-	0	0	0	0	0

Source: ADAE.xpt (SDN 380, submitted April 17, 2024)

Significant Adverse Events

Data:
Study 20190172

Grade ≥ 3 adverse events were reported for 32 subjects (60.4%) in the sotorasib 240 mg + panitumumab group, 29 subjects (54.7%) in the sotorasib 960 mg + panitumumab group, and 31 subjects (60.8%) in the control group (Table 11 of Module 2.7.4, Summary of Clinical Safety).

Across the sotorasib 240 mg + panitumumab, sotorasib 960 mg + panitumumab, and control groups, respectively, the most common grade ≥ 3 adverse events occurring in ≥ 5% of any group were dermatitis acneiform (3.8%, 11.3%, 0.0%), hypomagnesaemia (13.2%, 7.5%, 0.0%), diarrhea (5.7%, 5.7%, 0.0%), rash (1.9%, 5.7%, 0.0%), sepsis (0.0%, 5.7%, 0.0%), intestinal obstruction (5.7%, 3.8%, 0.0%), small intestinal obstruction (5.7%, 0.0%, 0.0%), anemia (3.8%, 1.9%, 9.8%), hypertension (0.0%, 1.9%, 5.9%), and neutropenia (0.0%, 0.0%, 25.5%) (Table 11 of Module 2.7.4, Summary of Clinical Safety).

Pooled Results: Sotorasib 960 mg Monotherapy

Grade ≥ 3 adverse events were reported for 49 subjects (40.2%) with mCRC treated with sotorasib monotherapy at any dose. Of these, 34 subjects (37.4%) in the sotorasib 960 mg monotherapy group reported grade ≥ 3 adverse events (Table 12 of Module 2.7.4, Summary of Clinical Safety). In the sotorasib 960 mg group, the most frequently reported grade ≥ 3 adverse events (≥ 5% subjects) were anemia (6 subjects, 6.6%), and small intestinal obstruction (5 subjects, 5.5%).

Pooled Results: Sotorasib 960 mg + Panitumumab

Grade ≥ 3 adverse events were reported for 99 subjects (53.5%) with mCRC in the sotorasib any dose + panitumumab group. Of these, 67 subjects (50.8%) in the sotorasib 960 mg + panitumumab group reported grade ≥ 3 adverse events (Table 12 of Module 2.7.4 Summary of Clinical Safety). In the sotorasib 960 mg + panitumumab group, the most frequently reported grade ≥ 3 adverse events (≥ 5% in subjects) were anemia (7 subjects, 5.3%), hypomagnesemia (10 subjects, 7.6%), dermatitis acneiform (8 subjects, 6.1%), and rash (8 subjects, 6.1%).

The Applicant's Position:

The subject incidences of grade ≥ 3 adverse events were generally consistent with the safety profiles of sotorasib and panitumumab. The observed subject incidence of some adverse events (eg, hypokalemia and skin toxicity) were lower in Study 20190172 than would be expected from the known safety profile of panitumumab as monotherapy. With the exception of hypomagnesemia, which was more frequent (> 5% difference) in the 240 mg combination regimen; and dermatitis acneiform and sepsis, which were more frequent in the 960 mg combination regimen, there were no other notable numerical differences (> 5%) by sotorasib dose groups. Investigator causality assessment reported that sepsis was not related to sotorasib or panitumumab. Across the pooled analyses, the subject incidences of the majority of grade ≥ 3 adverse events were higher in the combination regimen group compared with the sotorasib monotherapy group; and these differences were driven by the known safety profile of panitumumab. Select grade ≥ 3 adverse events were higher in the monotherapy arm compared to the combination regimen (Table 12 of Module 2.7.4, Summary of Clinical Safety) and most

were due to the underlying cancer and/or other comorbidities.

The FDA's Assessment:

For significant TEAEs, FDA focused on GI obstruction, including ileus, subileus, and intussusception. FDA analyzed the incidence of GI obstruction by pooling the following Preferred Terms: gastrointestinal obstruction, ileus, intestinal obstruction, intestinal pseudo-obstruction, intussusception, large intestinal obstruction, obstruction gastric, small intestinal obstruction, and subileus.

Study 20190172

Based on this analysis of pooled Preferred Terms, eight patients experienced intestinal obstruction in Study 20190172, and all 8 patients were in the sotorasib-containing arms: n=6 in sotorasib 240 mg arm, and n=2 in sotorasib 960 mg arm. In the sotorasib 240 mg arm, four patients had Grade 3 and two patients had Grade 5 as the maximum severity of intestinal obstruction. In the sotorasib 960 mg arm, two patients had Grade 3 as the maximum severity.

The investigators determined that both Grade 5 intestinal obstructions (in sotorasib 240 mg arm) and three of the six Grade 3 intestinal obstructions (n=1 in sotorasib 240 mg arm, and n=2 in sotorasib 960 mg arm) were due to disease progression. However, there is inadequate data in the submitted narratives and datasets for FDA to determine if the higher rate of intestinal obstruction in the sotorasib 240 mg arm was due to progression at the site intestinal obstruction. FDA did not find a clear difference in pattern of progression between the two dosages, i.e., patients in both arms had progressed and intestinal obstruction within a day or a few months of each event.

Table 38. FDA's Analysis of Patients with Intestinal Obstruction (Maximum Grade) in Study 20190172 (excluding site 33013)

	Trifluridine/Tipiracil or Regorafenib (N = 51) n (%)	Sotorasib 240 mg + Panitumumab (N = 50) n (%)	Sotorasib 960 mg + Panitumumab (N = 47) n (%)	Total Sotorasib + Panitumumab (N = 97) n (%)
Intestinal obstruction or ileus [a]				
Grades 1-2	0	0	0	0
Grades 3-4	0	4 (8)	2 (4.3)	5 (5)
Grade 5	0	2 (4)	0	2 (2.1)

[a] includes intestinal obstruction, large intestinal obstruction, small intestinal obstruction
Source: ADAE.xpt (SDN 380, submitted April 17, 2024)

Pooled Analysis

Based on this analysis of pooled Preferred Terms, rates of GI obstruction were observed in both single-agent sotorasib and sotorasib with panitumumab arms in patients with CRC (Table 39).

As expected, GI obstruction is less common in non-CRC cancers. In patients with CRC, the rates of obstruction were highest in the single-agent sotorasib and sotorasib 240 mg with panitumumab arms, compared to the sotorasib 960 mg with panitumumab arm. Given that the rates are higher in the less effective therapies (i.e., single-agent sotorasib and lower dose sotorasib with panitumumab), it is plausible that disease progression may play a role in development of obstruction. However, as previously mentioned, the submitted data is not adequate to verify this hypothesis and the sample size of some of the treatment arms are small.

Table 39. FDA's Pooled Analysis of Patients with Intestinal Obstruction (Maximum Grade; excluding site 33013)

	CRC Sotorasib monotherapy any dose (N = 122) n (%)	CRC Sotorasib any dose excluding 960 mg (N = 31) n (%)	CRC Sotorasib 960 mg (N = 91) n (%)	CRC Sotorasib 240 mg + Panitumumab (N = 50) n (%)	CRC Sotorasib 960 mg + Panitumumab (N = 126) n (%)	CRC Sotorasib any dose + Panitumumab (N = 176) n (%)	All tumors Sotorasib any dose + Panitumumab (N = 218) n (%)	Any non-CRC tumors Sotorasib 960 mg + Panitumumab (N = 42) n (%)
Intestinal obstruction or ileus [a]								
Grades 1-2	2 (1.6)	1 (3.2)	1 (1.1)	0	1 (0.8)	1 (0.6)	1 (0.5)	0
Grades 3-4	7 (6)	1 (3.2)	6 (7)	4 (8)	6 (4.8)	10 (5)	12 (6)	2 (4.8)
Grade 5	2 (1.6)	0	2 (2.2)	2 (4)	0	2 (1.1)	2 (0.9)	0
Total	11 (9)	2 (6)	9 (10)	6 (12)	7 (6)	13 (7)	15 (7)	2 (4.8)

[a] includes gastrointestinal obstruction, ileus, intestinal obstruction, intestinal pseudo-obstruction, intussusception, obstruction gastric, large intestinal obstruction, small intestinal obstruction, subileus
Source: ADAE.xpt (SDN 380, submitted April 17, 2024) – Integrated Summary of Safety - CRC, Module 5.3.5.3

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Study 20190172

A total of 53 subjects (100%) in the sotorasib 240 mg + panitumumab group, 53 subjects (100.0%) in the sotorasib 960 mg + panitumumab group, and 49 subjects (96.1%) in the control (trifluridine and tipiracil or regorafenib) group had at least 1 adverse event. An overall summary of the incidence of adverse events is provided in Applicant - Table 40. Overall, the subject incidences of adverse events were similar between the control group and the sotorasib groups. There were no clinically meaningful differences by sotorasib dose groups.

Applicant - Table 40. Summary of Subject Incidence of Treatment-emergent Adverse Events in Study 20190172 (Safety Analysis Set)

	Trifluridine and Tipiracil or Regorafenib (N = 51) n (%)	Sotorasib 240 mg + Panitumumab (N = 53) n (%)	Sotorasib 960 mg + Panitumumab (N = 53) n (%)	Total Sotorasib + Panitumumab (N = 106) n (%)
Treatment-emergent adverse events excluding disease-progression related terms[a]	49 (96.1)	53 (100.0)	53 (100.0)	106 (100.0)
Grade ≥ 2	45 (88.2)	47 (88.7)	49 (92.5)	96 (90.6)
Grade ≥ 3	31 (60.8)	32 (60.4)	29 (54.7)	61 (57.5)
Grade ≥ 4	7 (13.7)	6 (11.3)	4 (7.5)	10 (9.4)
Serious adverse events	15 (29.4)	17 (32.1)	14 (26.4)	31 (29.2)
Leading to discontinuation of any investigational product	2 (3.9)	3 (5.7)	1 (1.9)	4 (3.8)
Leading to dose reduction of any investigational product	11 (21.6)	10 (18.9)	11 (20.8)	21 (19.8)
Leading to interruption of any investigational product	29 (56.9)	29 (54.7)	25 (47.2)	54 (50.9)
Fatal adverse events	3 (5.9)	4 (7.5)	2 (3.8)	6 (5.7)

Data cut-off date: 19 June 2023.
CRC = colorectal cancer; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic case report form; MedDRA = Medical Dictionary for Regulatory Activities
Coded using MedDRA version 26.0. Graded using CTCAE version 5.0.
A treatment-related adverse event is any treatment-emergent adverse event with the relationship flag on the Events eCRF indicating there is a reasonable possibility that the event may have been caused by investigational medicinal product. In the unlikely event that the relationship is missing, the treatment-emergent event is considered treatment-related.
For subjects with multiple events under the same category, only the worst grade is reported.
[a] The following preferred terms were excluded as treatment-emergent adverse events as they represent disease progression events: colon cancer metastatic, colon cancer stage IV, colorectal adenocarcinoma, colorectal cancer, colorectal cancer metastatic, disease progression, metastatic neoplasm
Source: Table 7 of Module 2.7.4, Summary of Clinical Safety

Pooled Results: Sotorasib 960 mg Monotherapy

A total of 122 subjects were treated with sotorasib monotherapy at any dose. Of these, 91 subjects received sotorasib 960 mg monotherapy. In the sotorasib 960 mg group, 87 subjects (95.6%) had at least 1 adverse event. An overall summary of the incidence of adverse events is provided in Applicant - Table 41.

Pooled Results: Sotorasib 960 mg + Panitumumab

A total of 185 subjects with mCRC were treated with sotorasib any dose + panitumumab. Of these, 132 subjects received sotorasib 960 mg + panitumumab. In the sotorasib 960 mg + panitumumab group, 131 subjects (99.2%) had at least 1 adverse event. An overall summary of the incidence of adverse events is provided in Applicant - Table 41. Subject incidences of most adverse event categories were higher in the combination regimen compared to sotorasib monotherapy, and this was driven by the panitumumab safety profile; sotorasib dosage interruption and treatment discontinuation rates due to adverse events were similar in both the monotherapy and combination regimen groups, supporting that the combination regimen is tolerable.

Applicant - Table 41. Summary of Treatment-emergent Adverse Events (Safety Analysis Set)

	Study 20170543 CRC Sotorasib 960 mg Monotherapy (N = 91) n (%)	Study 20170543 CRC Sotorasib Any Dose Monotherapy (N = 122) n (%)	Study 20190172 CRC Sotorasib 240 mg + Panitumumab (N = 53) n (%)	Study 20190172 CRC Sotorasib 960 mg + Panitumumab (N = 53) n (%)	All studies CRC Sotorasib 960 mg + Panitumumab (N = 132) n (%)	All studies CRC Sotorasib Any Dose + Panitumumab (N = 185) n (%)	All studies Any Tumor Type Sotorasib 960 mg + Panitumumab (N = 174) n (%)	All studies Any Tumor Type Sotorasib Any Dose + Panitumumab (N = 227) n (%)
All treatment-emergent adverse events	87 (95.6)	117 (95.9)	53 (100.0)	53 (100.0)	131 (99.2)	184 (99.5)	173 (99.4)	226 (99.6)
Grade ≥ 2	63 (69.2)	87 (71.3)	47 (88.7)	49 (92.5)	120 (90.9)	167 (90.3)	157 (90.2)	204 (89.9)
Grade ≥ 3	34 (37.4)	49 (40.2)	32 (60.4)	29 (54.7)	67 (50.8)	99 (53.5)	92 (52.9)	124 (54.6)
Grade ≥ 4	3 (3.3)	3 (2.5)	6 (11.3)	4 (7.5)	9 (6.8)	15 (8.1)	12 (6.9)	18 (7.9)
Serious adverse events	24 (26.4)	34 (27.9)	17 (32.1)	14 (26.4)	40 (30.3)	57 (30.8)	57 (32.8)	74 (32.6)
Fatal adverse events	2 (2.2)	2 (1.6)	4 (7.5)	2 (3.8)	3 (2.3)	7 (3.8)	3 (1.7)	7 (3.1)
Leading to discontinuation of sotorasib	2 (2.2)	2 (1.6)	3 (5.7)	1 (1.9)	3 (2.3)	6 (3.2)	5 (2.9)	8 (3.5)
Leading to discontinuation of panitumumab	0	0	2 (3.8)	1 (1.9)	4 (3.0)	6 (3.2)	8 (4.6)	10 (4.4)
Leading to both sotorasib and panitumumab discontinuation	0	0	2 (3.8)	1 (1.9)	3 (2.3)	5 (2.7)	5 (2.9)	7 (3.1)
Leading to sotorasib or panitumumab discontinuation	2 (2.2)	2 (1.6)	3 (5.7)	1 (1.9)	4 (3.0)	7 (3.8)	8 (4.6)	11 (4.8)
Leading to dose interruption and/or reduction of sotorasib	26 (28.6)	34 (27.9)	25 (47.2)	16 (30.2)	41 (31.1)	66 (35.7)	61 (35.1)	86 (37.9)
Leading to dose interruption of sotorasib	26 (28.6)	34 (27.9)	25 (47.2)	16 (30.2)	39 (29.5)	64 (34.6)	58 (33.3)	83 (36.6)
Leading to dose reduction of sotorasib	0	0	0	3 (5.7)	7 (5.3)	7 (3.8)	13 (7.5)	13 (5.7)
Leading to dose interruption and/or reduction of panitumumab	0	0	29 (54.7)	21 (39.6)	55 (41.7)	84 (45.4)	73 (42.0)	102 (44.9)
Leading to dose interruption of panitumumab	0	0	26 (49.1)	21 (39.6)	51 (38.6)	77 (41.6)	69 (39.7)	95 (41.9)
Leading to dose reduction of panitumumab	0	0	10 (18.9)	8 (15.1)	18 (13.6)	28 (15.1)	20 (11.5)	30 (13.2)

Footnotes are defined on the last page of the table.

Applicant - Table 41. Summary of Treatment-emergent Adverse Events (Safety Analysis Set)

	Study 20170543 CRC Sotorasib 960 mg Monotherapy (N = 91) n (%)	Study 20170543 CRC Sotorasib Any Dose Monotherapy (N = 122) n (%)	Study 20190172 CRC Sotorasib 240 mg + Panitumumab (N = 53) n (%)	Study 20190172 CRC Sotorasib 960 mg + Panitumumab (N = 53) n (%)	All studies CRC Sotorasib 960 mg + Panitumumab (N = 132) n (%)	All studies CRC Sotorasib Any Dose + Panitumumab (N = 185) n (%)	All studies Any Tumor Type Sotorasib 960 mg + Panitumumab (N = 174) n (%)	All studies Any Tumor Type Sotorasib Any Dose + Panitumumab (N = 227) n (%)
Leading to dose interruption and/or reduction of both sotorasib and panitumumab	0	0	19 (35.8)	11 (20.8)	25 (18.9)	44 (23.8)	38 (21.8)	57 (25.1)
Leading to dose interruption and/or reduction of sotorasib or panitumumab	26 (28.6)	34 (27.9)	32 (60.4)	25 (47.2)	67 (50.8)	99 (53.5)	91 (52.3)	123 (54.2)

Data cut-off date: 01 April 2023 (study 20170543 Phase 1 and Phase 2), 19 June 2023 (study 20190172), 23 May 2023 (Study 20190135-H)
CRC = colorectal cancer; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities
If relationship to the treatment is missing, the event is assumed to be treatment-related.
For subjects with multiple events under the same category, only the worst grade is reported.
Adverse events coded using MedDRA version 26.0. Severity graded using CTCAE v5.0
All studies include Studies 20190172 and 20190135 Subprotocol H.
The following preferred terms, if observed, were excluded as they represent disease progression events: adenocarcinoma, adenocarcinoma of colon, cholangiocarcinoma, colon cancer, colon cancer metastatic, colon cancer stage IV, colorectal adenocarcinoma, colorectal cancer, colorectal cancer metastatic, disease progression, lung adenocarcinoma, lung cancer metastatic, malignant neoplasm progression, metastatic neoplasm, ovarian cancer metastatic, rectal adenocarcinoma, rectal cancer, rectal cancer metastatic.
Source: Table 8 of Module 2.7.4, Summary of Clinical Safety

Adverse Drug Reactions

To provide a robust dataset and to maximize the potential for identifying adverse events that were related to the use of sotorasib in combination with panitumumab, adverse drug reactions were evaluated based on the totality of the safety data of the combination treatment, with a focus on the 132 subjects with mCRC who were treated with sotorasib at 960 mg QD and panitumumab 6 mg/kg once every 2 weeks in Study 20190172 and Study 20190135 Subprotocol H. Medical review was based on a broad evaluation of all adverse events (including their severity, onset, duration, and outcome), changes in laboratory values, and vital signs, with special attention to common events, grade ≥ 3 events, serious adverse events, adverse events leading to dose interruption/reduction or treatment discontinuation, and events that occurred at higher frequency in the sotorasib and panitumumab treatment arms versus the comparator arm in Study 20190172. The review considered events and clinical findings expected to occur in the context of the underlying disease or in the patient population independent of drug exposure. Additional considerations such as temporal association, biological plausibility, and medical judgment were then applied for a probable causal drug event association to determine the final adverse drug reactions for the combination treatment.

The resulting list of adverse drug reactions for sotorasib 960 mg + panitumumab are summarized in Applicant - Table 42.

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Applicant - Table 42. Adverse Reactions Reported for Sotorasib 960 mg in Combination with Panitumumab

Adverse Reaction	Frequency	All Grades (N=132) n (%)	Grade 3 or 4 (N=132) n (%)
Skin and subcutaneous tissue disorders			
Rash including dermatitis acneiform[a]	Very common	116 (87.9)	20 (15.2)
Dry skin[b]	Very common	54 (40.9)	1 (0.8)
Pruritis[c]	Very common	40 (30.3)	1 (0.8)
Nail disorder[d]	Very common	27 (20.5)	0
Palmar-plantar erythrodysesthesia syndrome	Common	10 (7.6)	0
Skin fissures	Common	9 (6.8)	0
Gastrointestinal disorders			
Diarrhea	Very common	40 (30.3)	4 (3.0)
Nausea	Very common	38 (28.8)	1 (0.8)
Vomiting	Very common	23 (17.4)	3 (2.3)
Abdominal pain[e]	Very common	23 (17.4)	5 (3.8)
Constipation	Very common	20 (15.2)	2 (1.5)
Stomatitis[f]	Very common	25 (18.9)	0
General disorders			
Fatigue[g]	Very common	41 (31.1)	3 (2.3)
Investigations			
Alanine aminotransferase increased	Common	6 (4.5)	0
Aspartate aminotransferase increased	Common	6 (4.5)	0
Metabolism and Nutritional Disorders			
Hypomagnesaemia[h]	Very common	51 (38.6)	10 (7.6)
Hypokalemia[i]	Very common	20 (15.2)	6 (4.5)
Decreased appetite	Very common	17 (12.9)	1 (0.8)
Hypocalcemia	Common	12 (9.1)	1 (0.8)
Nervous system disorder			
Headache	Very common	14 (10.6)	1 (0.8)
Ocular disorders			
Conjunctivitis	Common	8 (6.1)	0
Keratitis[j]	Common	2 (1.5)	0

[a] Rash including dermatitis acneiform includes rash, rash maculo-papular, rash erythematous, rash papular, rash pruritic, rash pustular, dermatitis acneiform, folliculitis, and skin toxicity.

[b] Dry skin includes dry skin and xerosis
[c] Pruritis includes pruritus and ear pruritus.
[d] Nail disorder includes nail disorder, paronychia, nail cuticle fissure, nail avulsion, and nail toxicity.
[e] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain, and abdominal discomfort.
[f] Stomatitis includes stomatitis and mouth ulceration.
[g] Fatigue includes fatigue, asthenia and malaise.
[h] Hypomagnesemia includes hypomagnesaemia and blood magnesium decreased.
[i] Hypokalemia includes hypokalemia and blood potassium decreased
[j] Keratitis includes keratitis and ulcerative keratitis

The Applicant's Position:

Overall, in Study 20190172 and the pooled analyses, the types of adverse events observed were largely consistent with those previously observed with sotorasib or panitumumab monotherapy treatment, or with events expected to occur in the study population independent of drug exposure. There were no new safety findings specific to sotorasib in combination with panitumumab.

Adverse events that have been determined by the Sponsor to be associated with sotorasib 960 mg + panitumumab, based on the totality of data, are considered to be adverse drug reactions. The identified adverse drug reactions are rash including dermatitis acneiform, dry skin, pruritis, nail disorder, palmar-plantar erythrodysesthesia syndrome, skin fissures, diarrhea, nausea, vomiting, abdominal pain, constipation, stomatitis, fatigue, ALT increased, AST increased, hypomagnesaemia, hypokalemia, decreased appetite, hypocalcemia, headache, conjunctivitis, and keratitis.

The FDA's Assessment:

All Grade TEAEs in Study 20190172

FDA generally agrees with the Applicant's summary safety tables, but FDA had slightly different values because FDA excluded more Preferred Terms related to CRC adverse events or progression, and FDA excluded safety data from site 33013. FDA excluded the following Preferred Terms related to the underlying disease that the Applicant did not: metastases to central nervous system, metastases to ovary, metastases to peritoneum, metastases to spine, and metastasis. Table 43 shows the summary safety information for Study 20190172, which suggests that sotorasib with panitumumab is at least as tolerable as the control regimen. In addition, based on the summary safety data, the regimen with the higher dose of sotorasib (i.e., sotorasib 960 mg with panitumumab) does not appear to be more toxic than the regimen with the lower dose.

Table 43. FDA's Summary Safety Information for Study 20190172 (excluding site 33013)

	Trifluridine/Tipiracil or Regorafenib (N = 50) n (%)	Sotorasib 240 mg + Panitumumab (N = 50) n (%)	Sotorasib 960 mg + Panitumumab (N = 47) n (%)	Total Sotorasib + Panitumumab (N = 97) n (%)
Had any TEAE	48 (96)	50 (100)	47 (100)	97 (100)
Grade 5 TEAEs*	2 (4)	2 (4)	2 (4.3)	4 (4.1)

Grade 3-4 TEAEs*	30 (60)	29 (58)	26 (55)	55 (57)
Serious TEAEs	13 (26)	14 (28)	12 (26)	26 (27)
TEAEs that led to any drug modification	32 (64)	30 (60)	22 (47)	52 (54)
TEAEs that led to any drug discontinuation	2 (4)	2 (4)	1 (2)	3 (3.1)
TEAEs that led to any dose reduction	11 (22)	9 (18)	9 (19)	18 (19)
TEAEs that led to any dose interruption	28 (56)	28 (56)	21 (45)	49 (51)
TEAEs that led to any dose increase	0	1 (2)	0	1 (1)

*Only the maximum severity is included for a given TEAE for each patient.
Source: ADAE.xpt (SDN 380, submitted April 17, 2024)

In this review, the FDA clinical reviewer defined a >10% difference in incidence among the most common TEAEs to indicate a potential difference in toxicity profile between the treatment arms. Based on this cutoff, among TEAEs that occurred in ≥10% of any of the treatment arms, some skin and mucosal toxicities (i.e., skin wound, and stomatitis) were more common in the sotorasib 960 mg arm than the sotorasib 240 mg arm, and nausea, and vomiting were more common in the sotorasib 240 mg arm than the sotorasib 960 mg arm. Using a >10 incidence/100 patient-year difference in exposure-adjusted TEAE incidence rate to indicate a potential difference in toxicity profile between the treatment arms, these findings persisted with some skin and mucosal toxicities (i.e., folliculitis, skin wound, and stomatitis) being higher in the sotorasib 960 mg arm, and of some GI toxicities (i.e., abdominal pain, nausea, and vomiting), and dyspnea being higher in the in the sotorasib 240 mg arm. The following toxicities are also higher in the sotorasib 240 mg arm based on an exposure-adjusted incidence rate: anemia, fatigue, hypomagnesemia, and pyrexia.

Compared to the control arm, patients in the sotorasib with panitumumab arms were more likely to experience skin and nail toxicities, hypomagnesemia, and hemorrhage. Compared to the sotorasib + panitumumab arms, patients in the control arm were more likely to experience nausea, anemia, and neutropenia.

In summary, compared to the sotorasib 240 mg arm, the sotorasib 960 mg arm was associated with an increase in TEAEs that were associated with panitumumab rather than sotorasib, even when adjusted for exposure, which is an unexpected finding because the dose of panitumumab was the same in the two sotorasib arms. The different toxicities experienced by the patients between the control arm and the sotorasib were consistent with the known toxicity profiles of the drugs.

Table 44. FDA's Analysis of All Grades Maximum Severity TEAEs in Study 20190172 (excluding site 33013)

	Trifluridine/Tipiracil or Regorafenib (N = 50) n (%)	Sotorasib 240 mg + Panitumumab (N = 50) n (%)	Sotorasib 960 mg + Panitumumab (N = 47) n (%)	Total Sotorasib + Panitumumab (N = 97) n (%)
Patients with TEAEs	48 (96)	50 (100)	47 (100)	97 (100)
Skin and Subcutaneous Tissue Disorders				
Rash [a]	8 (16)	40 (80)	41 (87)	81 (84)
Dry Skin [b]	1 (2)	14 (28)	13 (28)	27 (28)
Skin Wound [c]	0	4 (8)	9 (19)	13 (13)
Nail Disorder [d]	0	8 (16)	8 (17)	16 (16)
Pruritus	2 (4)	9 (18)	8 (17)	17 (18)
Metabolism and Nutrition Disorders				
Hypomagnesemia [e]	1 (2)	17 (34)	18 (38)	35 (36)
Decreased Appetite	6 (12)	5 (10)	3 (6)	8 (8)
Gastrointestinal Disorders				
Diarrhea [f]	13 (26)	13 (26)	13 (28)	26 (27)
Stomatitis [g]	7 (14)	5 (10)	12 (26)	17 (18)
Nausea	18 (36)	16 (32)	8 (17)	24 (25)
Abdominal pain [h]	9 (18)	10 (20)	7 (15)	17 (18)
Constipation	5 (10)	5 (10)	7 (15)	12 (12)
Vomiting	5 (10)	12 (24)	6 (13)	18 (19)
Intestinal obstruction [i]	0	5 (10)	2 (4.3)	7 (7)
General Disorders and Administration Site Conditions				
Fatigue [j]	17 (34)	13 (26)	10 (21)	23 (24)
Pyrexia	8 (16)	5 (10)	2 (4.3)	7 (7)
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain [k]	7 (14)	8 (16)	10 (21)	18 (19)
Infections and Infestations				
Conjunctivitis [l]	1 (2)	3 (6)	5 (11)	8 (8)
Blood and Lymphatic System Disorders				
Anemia [m]	13 (26)	9 (18)	4 (9)	13 (13)
Thrombocytopenia [n]	6 (12)	2 (4)	3 (6)	5 (5)
Leukopenia [o]	5 (10)	1 (2)	2 (4.3)	3 (3.1)
Neutropenia [p]	20 (40)	4 (8)	1 (2.1)	5 (5)
Vascular Disorders				
Hemorrhage [q]	1 (2)	5 (10)	6 (13)	11 (11)
Hypertension [r]	6 (12)	2 (4)	2 (4.3)	4 (4.1)
Hepatobiliary Disorders				
Hypertransaminasemia [s]	2 (4)	6 (12)	3 (6)	9 (9)

Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea [t]	3 (6)	5 (10)	0	5 (5)

[a] includes rash, dermatitis acneiform, palmar-plantar erythrodysesthesia syndrome, rash maculo-papular, skin toxicity, eczema, rash erythematous, erythema, rash papular, rash pustular, hand dermatitis, drug eruption, dermatosis, rash pruritic, dermatitis bullous
[b] includes dry skin, xerosis, xeroderma
[c] includes skin wound, skin fissures, skin ulcer, skin laceration, skin abrasion
[d] includes nail disorder, paronychia, onychoclasis, nail toxicity, nail cuticle fissure, nail avulsion
[e] includes hypomagnesemia, blood magnesium decreased
[f] includes diarrhea, gastroenteritis, diarrhea hemorrhagic
[g] includes mucosal inflammation, stomatitis, mouth ulceration, angular cheilitis, cheilitis
[h] includes abdominal pain, abdominal pain upper, abdominal pain lower, hepatic pain, abdominal discomfort
[i] includes intestinal obstruction, large intestinal obstruction, small intestinal obstruction
[j] includes fatigue, asthenia
[k] includes arthralgia, back pain, myalgia, musculoskeletal chest pain, bone pain, pain in extremity
[l] includes conjunctivitis, conjunctival hyperemia, conjunctivitis allergic
[m] includes anemia, normocytic anemia, iron deficiency anemia, normochromic normocytic anemia
[n] includes thrombocytopenia, platelet count decreased
[o] includes white blood cell count decreased, leukopenia
[p] includes neutrophil count decreased, neutropenia
[q] includes hematuria, epistaxis, gastrointestinal hemorrhage, vaginal hemorrhage, rectal hemorrhage, hematochezia, hemorrhage, hemorrhage urinary tract, hematospermia
[r] includes hypertension, diastolic hypertension
[s] includes alanine aminotransferase increased, hypertransaminasemia, aspartate aminotransferase increased, transaminases increased
[t] includes dyspnea, dyspnea exertional
Source: ADAE.xpt (SDN 380, submitted April 17, 2024)

All Grade TEAEs in Pooled Analysis

FDA pooled analysis of TEAEs yielded similar results to those observed in Study 20190172.

Grade 3-4 TEAEs in Study 2019172

In this review, the FDA clinical reviewer defined a >5% difference in incidence among Grade 3-4 TEAEs to indicate a potential difference in toxicity profile between the treatment arms. Based on this cutoff, among Grade 3-4 TEAEs that occurred in ≥2 patients in any treatment arm, TEAEs known to be associated with panitumumab (i.e., rash, and hypomagnesemia) and GI TEAEs (i.e., diarrhea, and intestinal obstruction) were more common in the sotorasib with panitumumab arms, and anemia and neutropenia were more common in the control arm. The higher dose of sotorasib was not associated with increase Grade 3-4 TEAEs among patients compared to the lower dose (55% vs. 58% for sotorasib 960 mg arm vs. sotorasib 240 mg arm, respectively). The TEAEs with an incidence of ≥5% in the sotorasib 960 mg arm were rash, hypomagnesemia, and diarrhea, and in the sotorasib 240 mg arm were rash, hypomagnesemia, diarrhea, and intestinal obstruction. Among the Grade 3-4 TEAEs with an incidence of ≥5% in either sotorasib arm, rash was the only TEAE that occurred more frequently in the sotorasib 960 mg arm, and hypomagnesemia and intestinal obstruction were TEAEs that occurred more frequently in the sotorasib 240 mg arm.

Table 45. FDA's Analysis of Grades 3-4 as Maximum Severity TEAEs in ≥2 Patients in Any Treatment Group in Study 20190172 (excluding site 33013)

	Trifluridine/Tipiracil or Regorafenib (N = 50) n (%)	Sotorasib 240 mg + Panitumumab (N = 50) n (%)	Sotorasib 960 mg + Panitumumab (N = 47) n (%)	Total Sotorasib + Panitumumab (N = 97) n (%)
Patients with Grade 3-4 TEAEs	**30 (60)**	**29 (58)**	**26 (55)**	**55 (57)**
Skin and Subcutaneous Tissue Disorders				
Rash [a]	3 (6)	5 (10)	12 (26)	17 (18)
Metabolism and Nutrition Disorders				
Hypomagnesemia	0	6 (12)	3 (6)	9 (9)
Hypokalemia [b]	2 (3.9)	0	2 (4.3)	2 (2.1)
Decreased Appetite	1 (2)	2 (4)	0	2 (2.1)
Gastrointestinal Disorders				
Diarrhea	0	3 (6)	3 (6)	6 (6)
Intestinal Obstruction [c]	0	3 (6)	2 (4.3)	5 (5)
Nausea	2 (4)	2 (4)	1 (2.1)	3 (3.1)
Ileus [d]	0	2 (4)	0	2 (2.1)
Vascular Disorders				
Hypertension [e]	3 (6)	0	2 (4.3)	2 (2.1)
Embolism [f]	2 (4)	1 (2)	1 (2.1)	2 (2.1)
Infections and Infestations				
Sepsis	0	0	2 (4.3)	2 (2.1)
Urinary Tract Infection [g]	1 (2)	2 (4)	1 (2.1)	3 (3.1)
Investigations				
Blood Bilirubin Increased [h]	0	1 (2)	2 (4.3)	3 (3.1)
Blood and Lymphatic System Disorders				
Anemia	5 (10)	2 (4)	0	2 (2.1)
Leukocytosis	0	2 (4)	0	2 (2.1)
Neutropenia [i]	14 (28)	0	0	0
Renal And Urinary Disorders				
Acute Kidney Injury	2 (4)	0	0	0

[a] includes dermatitis acneiform, dermatosis, rash, rash maculo-papular, skin toxicity, palmar-plantar erythrodysaesthesia syndrome
[b] includes hypokalemia, blood potassium decreased
[c] includes intestinal obstruction, small intestinal obstruction, large intestinal obstruction
[d] includes ileus, subileus
[e] includes hypertension, diastolic hypertension
[f] includes pulmonary embolism, embolism
[g] includes urinary tract infection, urosepsis
[h] includes blood bilirubin increased, hyperbilirubinemia
[i] includes neutropenia, neutrophil count decreased

Source: ADAE.xpt (SDN 380, submitted April 17, 2024)

Pooled Analysis

Among the Grade 3-4 TEAEs with incidence ≥5% in patients with CRC who received single agent sotorasib, patients who did not receive sotorasib 960 mg had a higher incidence of abdominal pain compared to patients who received sotorasib 960 mg. The addition of panitumumab to sotorasib increased rash and hypomagnesemia among Grade 3-4 TEAEs with incidence ≥5% in patients with CRC. Overall, the results of the pooled analysis were consistent with Study 20190172 for patients with CRC.

Table 46. FDA's Pooled Analysis of Grades 3-4 as Maximum Severity TEAEs with Incidence of ≥5% in Any Cohort (excluding site 33013)

	CRC Sotorasib monotherapy any dose (N = 122) n (%)	CRC Sotorasib any dose excluding 960 mg (N = 31) n (%)	CRC Sotorasib 960 mg (N = 91) n (%)	CRC Sotorasib 240 mg + Panitumumab (N = 50) n (%)	CRC Sotorasib 960 mg + Panitumumab (N = 126) n (%)	CRC Sotorasib any dose + Panitumumab (N = 176) n (%)	All tumors Sotorasib any dose + Panitumumab (N = 218) n (%)	Any non-CRC tumors Sotorasib 960 mg + Panitumumab (N = 42) n (%)
Patients with Grade 3-4 TEAEs	**45 (37)**	**15 (48)**	**34 (37)**	**30 (60)**	**63 (50)**	**93 (53)**	**118 (54)**	**25 (60)**
Skin and Subcutaneous Tissue Disorders								
Rash [a]	1 (0.8)	0	1 (1.1)	5 (9)	21 (16)	26 (14)	29 (13)	3 (7)
Metabolism and Nutrition Disorders								
Hypomagnesemia	2 (1.6)	0	2 (2.2)	6 (12)	9 (7)	15 (9)	18 (8)	3 (7)
Blood and Lymphatic System Disorders								
Anemia	10 (8)	3 (10)	7 (8)	2 (3.8)	6 (4.8)	8 (4.5)	9 (4.1)	1 (2.4)
Gastrointestinal Disorders								
Intestinal Obstruction [b]	7 (6)	1 (3.2)	6 (7)	3 (6)	5 (3.8)	8 (4.3)	10 (4.4)	2 (4.8)
Abdominal Pain [c]	5 (4.1)	4 (13)	1 (1.1)	0	5 (3.8)	5 (2.7)	7 (3.1)	2 (4.8)
General Disorders and Administration Site Conditions								
Fatigue [d]	3 (2.5)	1 (3.2)	2 (2.2)	1 (1.9)	3 (2.3)	4 (2.2)	8 (3.5)	4 (10)
Cardiac Disorders								
Arrhythmia [e]	0	0	0	0	0	0	3 (1.3)	3 (7)
Hepatobiliary Disorders								
Hypertransaminasemia [f]	3 (2.5)	1 (3.2)	2 (2.2)	1 (1.9)	1 (0.8)	2 (1.1)	8 (3.7)	6 (14)
Biliary Obstruction [g]	3 (2.5)	2 (6)	1 (1.1)	0	1 (0.8)	1 (0.5)	1 (0.4)	0
Respiratory, Thoracic and Mediastinal Disorders								
Dyspnea	1 (0.8)	1 (3.2)	0	0	0	0	5 (2.2)	5 (12)

[a] includes dermatitis acneiform, rash, skin toxicity, rash maculo-papular, rash pustular, dermatosis
[b] includes small intestinal obstruction, intestinal obstruction, large intestinal obstruction, gastrointestinal obstruction, obstruction gastric
[c] includes abdominal pain, abdominal pain upper
[d] includes fatigue, asthenia

[e] includes sinus tachycardia, electrocardiogram qt prolonged
[f] includes aspartate aminotransferase increased, alanine aminotransferase increased, hypertransaminasaemia, hepatic enzyme increased
[g] includes biliary obstruction, malignant biliary obstruction
Source: ADAE.xpt (SDN 380, submitted April 17, 2024) – Integrated Summary of Safety - CRC, Module 5.3.5.3

Overall FDA Assessment of Grade 3-4 TEAEs

Compared to trifluridine and tipiracil or regorafenib, sotorasib with panitumumab was associated with increased incidence of Grade 3-4 TEAEs known to be associated with panitumumab (i.e., rash, and hypomagnesemia) and GI TEAEs in Study 20190172. As expected, the Pooled Analysis demonstrated that the addition of panitumumab to sotorasib increased the incidence of rash and hypomagnesemia. Based on the analysis of Study 20190172 and the Pooled Analysis, rash was the only Grade 3-4 TEAE that was notably increased in the sotorasib 960 mg and panitumumab arm compared to the sotorasib 240 mg and panitumumab arm.

Laboratory Findings

Data:

Hepatotoxicity

Increased ALT and increased AST are known adverse drug reactions for sotorasib. Hepatotoxicity adverse events of interest are discussed in Section 8.2.5. In Study 20190172 and across the pooled analysis data, the subject incidence of hepatotoxicity in subjects with mCRC appears to be lower than what has been observed in subjects with NSCLC who received sotorasib. Across the pooled analysis data, increases in ALT, AST, total bilirubin, and ALP were consistent with those previously observed in the sotorasib program and described in the product labeling.

Hepatotoxicity was also evaluated by reviewing subject incidence of chemistry laboratory criteria potentially consistent with Hy's Law cases (ALT or AST > 3 x upper limit of normal [ULN] and total bilirubin > 2 x ULN and ALP < 2 x ULN); to identify all potential Hy's law cases, subjects with any of the laboratory components occurring within ± 7 days of each other were included. One subject in the sotorasib monotherapy 960 mg dose group had laboratory values that met the Hy's Law criteria. However, these laboratory results were observed while the subject was in the long term follow-up period and had enrolled in a new clinical study. No subjects in any other treatment groups had laboratory values that met the Hy's Law criteria.

Laboratory Toxicity

A summary of the worst clinical chemistry laboratory toxicity changes from baseline (ie, changes of 3 or more grades from baseline) is provided in Table 21 of Module 2.7.4, Summary of Clinical Safety.

In subjects with mCRC, shifts of 3 or more grades from baseline (≥ 10% of subjects in either group) were observed for magnesium (decrease) in 18.9% subjects in the sotorasib 240 mg + panitumumab and 17.0% subjects in the sotorasib 960 mg + panitumumab group in Study 20190172, 12.1% subjects in the sotorasib 960 mg + panitumumab group and 14.1%

subjects in the sotorasib any + panitumumab group in all studies CRC and 10.3% subjects in the sotorasib 960 mg + panitumumab group and 12.3% subjects in the sotorasib any dose + panitumumab group in all studies any tumor type.

Other Laboratory Parameters

No meaningful trends were identified in changes from baseline in any other laboratory parameter and no meaningful differences were observed in subjects treated with combination therapy and sotorasib monotherapy.

The Applicant's Position:

In Study 20190172 and across the pooled analysis data, the subject incidence of hepatotoxicity in subjects with mCRC appears to be lower than what has been observed in subjects with NSCLC who received sotorasib. Otherwise, there were no notable trends in clinical laboratory evaluations and the results were consistent with the known safety profile of sotorasib and panitumumab.

The FDA's Assessment:

In this review, FDA clinical reviewer defined a >10% difference in incidence among Grade 1-4 laboratory abnormalities to indicate a potential difference in toxicity profile between the treatment arms. Based on this cutoff, among laboratory abnormalities with incidence ≥10% in any treatment arm, patients in the sotorasib 960 mg with panitumumab arm experienced more laboratory abnormalities than the patients in the sotorasib 240 mg with panitumumab arm which consisted of electrolyte abnormalities (decreased magnesium, calcium, and potassium), increased aspartate amino transferase (AST), and increased creatine kinase 2 (CK2, Table 47). The patients in the sotorasib 240 mg arm experienced more increased urine protein. The patients in the sotorasib-containing arms experienced more electrolyte abnormalities (except for sodium decreased), transaminitis, increased CK2, increased urine protein, and increased activated partial thromboplastin time (aPTT) compared to the control arm. The patients in the control arm experienced more decreased sodium, increased total bilirubin, and cytopenias compared to the sotorasib-containing arms.

Table 47. FDA's Analysis of Laboratory Abnormalities in Study in Study 20190172 (excluding site 33013)

	Trifluridine/Tipiracil or Regorafenib		Sotorasib 240 mg + Panitumumab		Sotorasib 960 mg + Panitumumab		Total Sotorasib + Panitumumab	
	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 (%)	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)
Chemistry								

	Trifluridine/Tipiracil or Regorafenib		Sotorasib 240 mg + Panitumumab		Sotorasib 960 mg + Panitumumab		Total Sotorasib + Panitumumab	
	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 (%)	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)
MAGNESIUM (MMOL/L) - Decreased	4/49 (8)	0/49 (0)	32/49 (65)	10/49 (20)	35/46 (76)	11/46 (24)	67/95 (71)	21/95 (22)
CALCIUM (CORRECTED) (MMOL/L) - Decreased	23/50 (46)	0/50 (0)	27/50 (54)	1/50 (2)	34/46 (74)	2/46 (4.3)	61/96 (64)	3/96 (3.1)
CREATINE KINASE 2 (U/L) - Increased	3/41 (7)	0/41 (0)	5/46 (11)	1/46 (2.2)	13/44 (30)	1/44 (2.3)	18/90 (20)	2/90 (2.2)
POTASSIUM (MMOL/L) - Decreased	6/50 (12)	0/50 (0)	9/50 (18)	0/50 (0)	12/46 (26)	3/46 (7)	21/96 (22)	3/96 (3.1)
URINE PROTEIN - Increased	4/18 (22)	1/18 (6)	22/49 (45)	2/49 (4.1)	10/44 (23)	0/44 (0)	32/93 (34)	2/93 (2.2)
POTASSIUM (MMOL/L) - Increased	3/50 (6)	0/50	9/50 (18)	1/50 (2)	10/46 (22)	2/46 (4.3)	19/96 (20)	3/96 (3.1)
GLUCOSE (MMOL/L) - Decreased	1/50 (2)	0/50	9/49 (18)	0/49 (0)	10/46 (22)	0/46 (0)	19/95 (20)	0/95 (0)
CREATININE (UMOL/L) - Increased	6/50 (12)	2/50 (4)	5/50 (10)	1/50 (2)	6/46 (13)	0/46 (0)	11/96 (11)	1/96 (1)
SODIUM (MMOL/L) - Decreased	15/50 (30)	1/50 (2)	8/50 (16)	0/50 (0)	6/46 (13)	0/46 (0)	14/96 (15)	0/96 (0)
SODIUM (MMOL/L) - Increased	5/50 (10)	0/50 (0)	5/50 (10)	0/50 (0)	3/46 (7)	0/46 (0)	8/96 (8)	0/96 (0)
Liver Function Tests								
ASPARTATE AMINO TRANSFERASE (U/L) - Increased	11/50 (22)	1/50 (2)	14/50 (28)	0/50	18/46 (39)	0/46 (0)	32/96 (33)	0/96 (0)
ALKALINE PHOSPHATASE (U/L) - Increased	16/49 (33)	0/49 (0)	15/50 (30)	1/50 (2)	15/46 (33)	1/46 (2.2)	30/96 (31)	2/96 (2.1)
ALANINE AMINO TRANSFERASE (U/L) - Increased	8/50 (16)	1/50 (2)	11/50 (22)	0/50 (0)	13/46 (28)	0/46 (0)	24/96 (25)	0/96 (0)
ALBUMIN (G/L) - Decreased	11/50 (22)	0/50 (0)	15/50 (30)	1/50 (2)	12/46 (26)	1/46 (2.2)	27/96 (28)	2/96 (2.1)
TOTAL BILIRUBIN (UMOL/L) - Increased	15/50 (30)	0/50 (0)	4/50 (8)	2/50 (4)	6/46 (13)	1/46 (2.2)	10/96 (10)	3/96 (3.1)
Hematology								
HEMOGLOBIN (G/L) - Decreased	29/50 (58)	3/50 (6)	12/50 (24)	1/50 (2)	14/46 (30)	0/46 (0)	26/96 (27)	1/96 (1)

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

	Trifluridine/Tipiracil or Regorafenib		Sotorasib 240 mg + Panitumumab		Sotorasib 960 mg + Panitumumab		Total Sotorasib + Panitumumab	
	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 (%)	Grades 1-4 n/N evaluable (%)	Grades 3-4 n/N evaluable (%)
LYMPHOCYTES (10^9/L) - Decreased	28/50 (56)	4/50 (8)	14/50 (28)	2/50 (4)	12/46 (26)	1/46 (2.2)	26/96 (27)	3/96 (3.1)
WHITE BLOOD CELLS (10^9/L) - Decreased	24/50 (48)	7/50 (14)	9/50 (18)	0/50 (0)	11/46 (24)	0/46 (0)	20/96 (21)	0/96 (0)
PLATELETS (10^9/L) - Decreased	12/50 (24)	2/50 (4)	3/50 (6)	0/50 (0)	7/46 (15)	1/46 (2.2)	10/96 (10)	1/96 (1)
TOTAL NEUTROPHILS (10^9/L) - Decreased	22/49 (45)	12/49 (24)	3/43 (7)	0/43 (0)	4/45 (9)	0/45 (0)	7/88 (8)	0/88 (0)
Coagulation Panel								
ACTIVATED PARTIAL THROMBOPLASTIN TIME (S) - Increased	1/19 (5)	0/19 (0)	6/43 (14)	0/43 (0)	6/41 (15)	1/41 (2.4)	12/84 (14)	1/84 (1.2)

Abbreviations: AST = aspartate amino transferase, ALT = alanine amino transferase, PTT = partial thromboplastin time
Source: ADLB.xpt (SDN 380, submitted April 17, 2024)

Pooled Analysis

In the pooled analysis, the laboratory abnormalities between the sotorasib 960 mg with panitumumab and the sotorasib 240 mg with panitumumab arms were comparable, except the former having a higher incidence of some cytopenias (hemoglobin, leucocytes, and platelets), decreased CK2, and aPTT increased. As expected, the addition of panitumumab to sotorasib increased electrolyte abnormalities (decreased magnesium, calcium, and potassium).

Vital Signs

Data:

The assessments of vital signs and ECGs for the integrated safety analysis set are provided in Section 4 of Module 2.7.4, Summary of Clinical Safety. Adverse events associated with vital signs and ECGs are presented in Section 2.1 of Module 2.7.4, Summary of Clinical Safety.

No notable trends in vital signs, physical findings, and other observations related to safety were identified, and the results were consistent with the known safety profile of sotorasib and panitumumab.

The Applicant's Position:

There were no notable trends in vital signs, physical findings, and other observations related to safety and the results were consistent with the known safety profile of sotorasib and panitumumab.

The FDA's Assessment:

FDA agrees with the Applicant.

Electrocardiograms (ECGs)

Data:
Not applicable. No new ECG-related data were submitted in this supplemental marketing application other than routine monitoring as specified in the protocol.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
No concerning safety signals were identified on submitted EKG-related data.

QT

Data:
Not applicable.

The Applicant's Position:
No dedicated QT studies were conducted.

The FDA's Assessment:
No patient in Study 20190172 had QTc >500 ms. The median QTc was 415 ms (range 321 – 479).

Immunogenicity

Data:
Not applicable.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
See Section 6.3.1 for FDA Clinical Pharmacology review.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1 Dermatologic and Soft Tissue Toxicity

Data:

Study 20190172

Dermatologic and soft tissue toxicity events of interest (EOIs) were reported for 10 subjects (18.9%) in the sotorasib 240 mg + panitumumab group, for 14 subjects (26.4%) in the sotorasib 960 mg + panitumumab group, and for 8 subjects (15.7%) in the control group. The most common dermatologic and skin tissue toxicity EOIs reported in both sotorasib + panitumumab groups (total N = 106) were skin toxicity (10 subjects [9.4%]), stomatitis (8 subjects [7.5%]) and conjunctivitis (6 subjects [5.7%]) (Table 12 of Module 2.5, Clinical Overview). The most commonly reported dermatologic and skin tissue toxicity EOIs in the control group was stomatitis (6 subjects [11.8%]).

Grade ≥ 3 dermatologic and soft tissue toxicity EOIs were reported for 1 subject (1.9%) in the sotorasib 240 mg + panitumumab group, for 2 subjects (3.8%) in the sotorasib 960 mg + panitumumab group, and for 1 subject (2.0%) in the control group (all grade ≥ 3 dermatologic and soft tissue toxicity events were preferred term skin toxicity events). No serious or fatal adverse events were identified as dermatologic and soft tissue toxicity EOIs.

No subjects discontinued any investigational product due to dermatologic and soft tissue toxicity EOIs. One subject (1.9%) in the sotorasib 240 mg + panitumumab group and 1 subject (1.9%) in the sotorasib 960 mg + panitumumab group had dermatologic and soft tissue toxicity EOIs (skin toxicity) that led to reduction of panitumumab dose. No subjects in either sotorasib + panitumumab group had dermatologic and soft tissue toxicity EOIs (skin toxicity) that led to reduction of sotorasib dose. No subjects in the control group reported dermatologic and soft tissue toxicity EOIs leading to reduction of investigational product dose. One subject (1.9%) in the sotorasib 240 mg + panitumumab group and 1 subject (1.9%) in the sotorasib 960 mg + panitumumab group had dermatologic and soft tissue toxicity EOIs (skin toxicity) that led to interruption of both sotorasib and panitumumab doses. In the sotorasib 960 mg + panitumumab group, dermatologic and soft tissue toxicity EOIs (skin toxicity) led to interruption of sotorasib dose for 1 subject (1.9%) and interruption of panitumumab dose for 2 subjects (3.8%). One subject (2.0%) in the control group reported a dermatologic and soft tissue toxicity EOI leading to interruption of investigational product dose (skin toxicity).

The median (range) time to first onset of a dermatologic and soft tissue toxicity EOI was 29.5 (13, 274) days in the sotorasib 240 mg + panitumumab group, 75.0 (4, 266) days in the sotorasib 960 mg + panitumumab group, and 23.0 (4, 57) days in the control group. For 6 subjects (11.3%) in the sotorasib 240 mg + panitumumab group and 10 subjects (18.9%) in the sotorasib 960 mg + panitumumab group, the dermatologic and soft tissue toxicity EOIs were resolved, and the median (range) duration of the events was 35.0 (7, 195) days and

60.5 (11, 314) days, respectively. For 6 subjects (11.8%) in the control group, the dermatologic and soft tissue toxicity EOIs were resolved, and the median (range) duration of the events was 18.0 (8, 148) days. Seven subjects (13.2%), 8 subjects (15.1%) and 2 subjects (3.9%) had ongoing dermatologic and soft tissue toxicity EOIs at the time of data cut-off in the sotorasib 240 mg + panitumumab group, the sotorasib 960 mg + panitumumab group, and the control group, respectively. One of these ongoing events was considered grade 3 or higher, reported in the sotorasib 240 mg + panitumumab group.

Pooled Results: Sotorasib 960 mg Monotherapy

Dermatologic and soft tissue toxicity EOIs were reported for 2 subjects treated with sotorasib monotherapy at any dose (stomatitis and skin exfoliation in 1 subject each, [0.8%]). Of these, 1 subject in the sotorasib 960 mg monotherapy group had a dermatologic and soft tissue toxicity EOI of stomatitis. Neither of the events were considered serious or grade ≥ 3, and did not result in discontinuation, dose reduction, or interruption of any investigational product. In the sotorasib 960 mg group, the time to first onset of stomatitis event was 10 days, and it was reported resolved with a duration of 4 days.

Pooled Results: Sotorasib 960 mg + Panitumumab

Dermatologic and soft tissue toxicity EOIs were reported for 40 subjects (21.6%) with mCRC in the sotorasib any dose + panitumumab group. Of these, 30 subjects (22.7%) reported dermatologic and soft tissue toxicity EOIs in the sotorasib 960 mg + panitumumab group.

In the sotorasib 960 mg + panitumumab group, the most common dermatologic and skin tissue toxicity EOIs reported in (≥ 5 % of subjects) were stomatitis (14 subjects, 10.6%), conjunctivitis (8 subjects, 6.1%), and skin toxicity (7 subjects, 5.3%). Grade ≥ 3 dermatologic and soft tissue toxicity EOIs were reported for 2 subjects (1.5%) (skin toxicity events). No serious adverse events were identified as dermatologic and soft tissue toxicity EOIs. No subjects discontinued any investigational product due to dermatologic and soft tissue toxicity EOIs.

Three subjects (skin toxicity in 2 subjects [1.5%] and conjunctivitis in 1 subject [0.8%]) had dermatologic and soft tissue toxicity EOIs that led to interruption and/or reduction of panitumumab dose, and 1 subject (0.8%) had dermatologic and soft tissue toxicity EOIs (skin toxicity) that led to interruption and/or reduction of sotorasib dose. One subject (0.8%) had dermatologic and soft tissue toxicity EOIs (skin toxicity) that led to interruption and/or reduction of both sotorasib and panitumumab.

The median (range) time to first onset of a dermatologic and soft tissue toxicity EOI was 61.0 (4, 365) days. For 20 subjects (15.2%), the dermatologic and soft tissue toxicity EOIs were resolved, and the median (range) duration of the events was 33.5 (3, 314) days. Sixteen subjects (12.1%) had ongoing dermatologic and soft tissue toxicity EOIs at the time of data cut-off.

The Applicant's Position:
In the Study 20190172 and across the pooled analysis data, the incidence of dermatologic and soft tissue toxicity was consistent with panitumumab safety profile. Using the severe cutaneous adverse reactions Standardized MedDRA Query broad search strategy, there were no adverse events that were fatal, serious, and none led to treatment discontinuation.

The FDA's Assessment:
Overall, the incidence of dermatological TEAEs, including those that led to dose modifications, were higher in the sotorasib 960 mg with panitumumab arm compared to the other two arms. The difference between the sotorasib arms persisted after exposure-adjusted TEAEs analysis; thus, the reason for the difference is. The finding may be due to chance given the small sample size of Study 20190172, however the difference persisted for some dermatological TEAEs in the pooled analysis (albeit the sample size of the sotorasib 240 mg with panitumumab did not increase in the pooled analysis). Use of concomitant medications for dermatological conditions (Section 8.1.2) was similar across the two sotorasib arms, suggesting that the rate of dermatological conditions may have been similar across the two arms and perhaps some cases were not captured during AE assessment.

No patients died from dermatologic TEAEs in Study 20190172. One patient was considered to have a serious dermatologic TEAE in the sotorasib arm (dermatitis acneiform in sotorasib 960 mg with panitumumab arm) and one patient in the control arm (palmar-plantar erythrodysesthesia syndrome in regorafenib cohort).

Sotorasib was not dose reduced for dermatologic TEAEs. Panitumumab was dose reduced for dermatologic TEAEs in both sotorasib 240 mg (8%) and sotorasib 960 mg arms (15%). In the control arm, regorafenib was dose reduced for palmar-plantar erythrodysesthesia syndrome (6%). In both sotorasib with panitumumab arms, 6% of patients had sotorasib and panitumumab interrupted concurrently for dermatological TEAEs. Only panitumumab was interrupted (and sotorasib continued) for dermatological TEAEs in 10% and 19% of the patients in the sotorasib 240 mg and sotorasib 960 mg arms, respectively. Only sotorasib was interrupted (and panitumumab continued) for dermatological TEAEs in 0% and 4.3% of patients in the sotorasib 240 mg and sotorasib 960 mg arms, respectively; note that the exposure dataset (ADEX) indicated that no patients in Study 20190172 were exposed to panitumumab as a single agent during sotorasib interruption, so patients likely had sotorasib briefly held in between the every 2-week dosing of panitumumab. Drugs in the control arm (more often regorafenib than trifluridine/tipiracil) were interrupted for dermatologic TEAEs in 8% of the patients. Certain dermatologic TEAEs were more common in the sotorasib 960 mg arm compared to the sotorasib 240 mg and control arms: skin wound – 19%, 8%, and 0%, respectively; and stomatitis – 26%, 10%, and 14%, respectively. Grade 3-4 rashes were also more common in the sotorasib 960 mg arm compared to the sotorasib 240 mg and control arms: 26%, 10%, and 6%, respectively. This finding persisted with some skin and mucosal

toxicities being higher in the sotorasib 960 mg arm in the exposure-adjusted TEAEs analysis of Study 20190712 and in the pooled analysis.

8.2.5.2 Hepatotoxicity

Data:

In Study 20190172 and across the pooled analysis data, the subject incidence of hepatotoxicity in subjects with mCRC appears to be lower than what has been observed in subjects with NSCLC who received sotorasib. Observed hepatotoxicity adverse events were similarly mostly related to laboratory results, but rarely led to discontinuation of sotorasib or panitumumab. Hepatotoxicity events were driven by transaminase elevations. Most of these events were grade 1 or grade 2 in severity, non-serious, and rarely led to permanent discontinuation of sotorasib or panitumumab. Hepatotoxicity was manageable with dose modification, and no severe sequelae of liver dysfunction were observed. Subject incidence of hepatotoxicity EOIs using the drug related hepatic disorders - comprehensive Standardized MedDRA Query narrow search strategy are presented in this section.

Study 20190172

Hepatotoxicity EOIs were reported for 7 subjects (13.2%) in the sotorasib 240 mg + panitumumab group, for 7 subjects (13.2%) in the sotorasib 960 mg + panitumumab group, and for 6 subjects (11.8%) in the control group (Table 13 of Module 2.5, Clinical Overview). The most common hepatotoxicity EOIs reported in both sotorasib + panitumumab groups (total N = 106) were increased ALT (5 subjects [4.7%]), increased AST (5 subjects [4.7%]), hypertransaminasemia (3 subjects [2.8%]), hyperbilirubinemia (3 subjects [2.8%]), transaminases increased (3 subjects [2.8%]), ascites (2 subjects [1.9%]), and increased blood bilirubin (2 subjects [1.9%]). In the control group, the 4 reported hepatotoxicity EOIs were increased blood bilirubin (2 subjects [3.9%], and increased ALT, increased AST, hypertransaminasemia, hyperbilirubinemia, and hepatic failure (1 subject [2.0%] reporting each).

Grade ≥ 3 hepatotoxicity EOIs were reported for 1 subject (1.9%) in the sotorasib 240 mg + panitumumab group, for 3 subjects (5.7%) in the sotorasib 960 mg + panitumumab group, and for 1 subject (2.0%) in the control group. One hepatotoxicity EOI in the sotorasib 240 mg + panitumumab group (ascites) and 1 hepatotoxicity EOI in the sotorasib 960 mg + panitumumab group, a blood bilirubin increased adverse event, was considered serious. One hepatic toxicity EOI in the control group, a hepatic failure event, was considered serious.

No subjects in either sotorasib + panitumumab group and 1 subject (2.0%) in the control group (hepatic failure event) discontinued investigational product due to a hepatotoxicity EOI. No subjects in the sotorasib 240 mg + panitumumab group and 1 subject (1.9%) in the sotorasib 960 mg + panitumumab group had a hepatotoxicity EOI (hypertransaminasemia) that

led to reduction of sotorasib dose. No subjects in the control group reported hepatotoxicity EOIs leading to reduction of investigational product dose.

One subject (1.9%) in the sotorasib 240 mg + panitumumab group (transaminases increased) and 2 subjects (3.8%) in the sotorasib 960 mg + panitumumab group had hepatotoxicity EOIs (hypertransaminasemia [2 subjects] and hyperbilirubinemia [1 subject]) that led to interruption of both sotorasib and panitumumab doses. In the sotorasib 960 mg + panitumumab group, hepatotoxicity EOIs that led to reduction of sotorasib dose only were increased ALT (2 subjects [3.8%]), increased AST (1 subject [1.9%]), and increased blood bilirubin (1 subject [1.9%]). One subject (2.0%) in the control group reported a hepatotoxicity EOI leading to interruption of investigational product dose (hypertransaminasemia).

The median (range) time to first onset of a hepatotoxicity EOI was 113.0 (1, 183) days in the sotorasib 240 mg + panitumumab group,70.0 (1, 153) days in the sotorasib 960 mg + panitumumab group, and 22.0 (15, 49) days in the control group. For 4 subjects (7.5%) in the sotorasib 240 mg + panitumumab group and 7 subjects (13.2%) sotorasib 960 mg + panitumumab group, the hepatotoxicity EOIs were resolved, and the median (range) duration across the events per subject was 26.5 (14, 57) days and 41.0 (15, 57) days, respectively. For 6 subjects (11.8%) in the control group, the hepatotoxicity EOIs were resolved, and the median (range) duration across the events per subject was 15.5 (15, 49) days. Four subjects (7.5%), 1 subject (1.9%) and 0 subjects had ongoing hepatotoxicity EOIs at the time of data cut-off in the sotorasib 240 mg + panitumumab group, the sotorasib 960 mg + panitumumab group, and the control group, respectively. Two of these ongoing events were considered grade 3 or higher, both reported in 1 subject in the sotorasib 240 mg + panitumumab group.

Pooled Results: Sotorasib 960 mg Monotherapy

Hepatotoxicity EOIs were reported for 24 subjects (19.7%) treated with sotorasib monotherapy at any dose. Of these, 19 subjects (20.9%) in the sotorasib 960 mg monotherapy group had hepatotoxicity EOIs. In the sotorasib 960 mg group, the most common hepatotoxicity EOIs reported in (≥ 5 % of subjects) were increased AST (9 subjects, 9.9%), increased ALT (7 subjects, 7.7%) and increased blood bilirubin (5 subjects, 5.5%). Grade ≥ 3 hepatotoxicity EOIs were reported for 4 subjects (4.4%). None of the hepatotoxicity EOIs were considered serious. No subjects in either dose groups discontinued sotorasib due to a hepatotoxicity EOI. A total of 7 subjects (7.7%) had hepatotoxicity EOIs that led to reduction and/or interruption of sotorasib dose.

The median (range) time to first onset of a hepatotoxicity EOI was 77.0 (8, 246) days in the 960 mg group. For 13 subjects (14.3%) hepatotoxicity EOIs were resolved, and the median (range) duration across the events per subject was 30.0 (6, 78) days. Eight subjects had ongoing hepatotoxicity EOIs at the time of data cut-off. One ongoing event was considered grade 3 or higher.

Pooled Results: Sotorasib 960 mg + Panitumumab

Hepatotoxicity EOIs were reported for 26 subjects (14.1%) with mCRC in the sotorasib any dose + panitumumab group. Of these, 19 subjects (14.4%) in the sotorasib 960 mg + panitumumab group had hepatotoxicity EOIs.

In the sotorasib 960 mg + panitumumab group, the most common hepatotoxicity EOIs reported (≥ 2 % of subjects) were increased AST and increased ALT (6 subjects each, 4.5%) and hyperbilirubinemia (3 subjects, 2.3%). Grade ≥ 3 hepatotoxicity EOIs were reported for 6 subjects (4.5%). Two subjects had hepatotoxicity EOIs (1 subject each: increased blood bilirubin and hepatic failure), which were considered serious. One subject discontinued investigational product due to a hepatotoxicity EOI (hepatic failure).

Two subjects had hepatotoxicity EOIs (hypertransaminasemia [2 subjects] and hyperbilirubinemia [1 subject]) that led to interruption and/or reduction of both sotorasib and panitumumab doses, and interruption and/or reduction of panitumumab dose only. Four subjects had a hepatotoxicity EOIs (hypertransaminasemia and increased ALT [2 subjects each], increased AST, increased blood bilirubin, hyperbilirubinemia, increased hepatic enzyme [1 subject each]) that led to interruption and/or reduction of sotorasib dose only (either because panitumumab was already discontinued, or because the sotorasib dose interruption was between panitumumab doses).

The median (range) time to first onset of a hepatotoxicity EOI was 71.0 (1, 153) days. For 17 subjects (12.9%), the hepatotoxicity EOIs were resolved, and the median (range) duration across the events per subject was 20.0 (4, 141) days. Four subjects had ongoing hepatotoxicity EOIs at the time of data cut-off. Two of ongoing events were considered grade 3 or higher.

The Applicant's Position:

In Study 20190172 and across the pooled analysis data, the subject incidence of hepatotoxicity in subjects with mCRC appears to be lower than what has been observed in subjects with NSCLC who received sotorasib. In NSCLC and mCRC, the observed hepatotoxicity adverse events were mostly related to laboratory results, but in mCRC, the hepatotoxicity events rarely led to discontinuation of sotorasib or panitumumab. Serious hepatotoxicity adverse events were observed in ≤ 2 subjects in the pooled analysis.

The FDA's Assessment:

Most hepatotoxic TEAEs in the sotorasib arms in Study 20190172 were not severe and were comparable to rates in the control arm. The rate of hepatotoxicity did not increase with increasing dose of sotorasib in Study 20190172. The pooled analysis was consistent in Study 20190172.

No patients died from hepatotoxicity and there were no dose reductions for hepatotoxicity in Study 20190172. One patient each was considered to have experienced a serious hepatotoxic TEAE in the sotorasib 960 mg arm (Grade 3 blood bilirubin increased) and in the control arm (Grade 3 hepatic failure). No patients in either of the sotorasib arms discontinued trial therapy

for hepatotoxicity. One patient discontinued a control arm drug due to hepatotoxicity (Grade 3 hepatic failure). One patient each in the sotorasib arms interrupted sotorasib and panitumumab concurrently for hepatotoxicity. One patient in the sotorasib 960 mg arm interrupted only sotorasib for hepatotoxicity. One patient in the control arm interrupted therapy for hepatotoxicity. The incidence of all grade and Grade 3-4 hepatotoxic TEAEs were comparable between all three treatment arms (Table 48 and Table 49). Five hepatotoxic TEAEs did not resolve in five patients– all were in sotorasib 240 mg arm: Grade 1 transaminitis (n=3), Grade 3 transaminitis (n=1), Grade 2-3 blood alkaline phosphatase increased (n=1 for each grade), and Grade 4 hyperbilirubinemia (n=1).

Based on the pooled analysis, the addition of panitumumab to sotorasib did not increase incidence of hepatotoxic TEAEs and the sotorasib 960 mg dosage does not appear to be more hepatotoxic than sotorasib 240 mg dosage in the patients with CRC. However, patients with non-CRC had higher rates of hepatoxicity than patients with CRC, particularly for transaminitis (for both all grades and Grade 3-4).

Table 48. FDA's Analysis of All Grade Hepatotoxic TEAEs in Study 20190172 (excluding site 33013)

	Trifluridine/Tipiracil or Regorafenib (N = 50) n (%)	Sotorasib 240 mg + Panitumumab (N = 50) n (%)	Sotorasib 960 mg + Panitumumab (N = 47) n (%)	Total Sotorasib + Panitumumab (N = 97) n (%)
Patients with hepatotoxic TEAEs	**7 (14)**	**7 (14)**	**6 (13)**	**13 (13)**
Hypertransaminasemia [a]	2 (4)	6 (12)	3 (6)	9 (9)
Hyperbilirubinemia [b]	3 (6)	1 (2)	3 (6)	4 (4.1)
Blood alkaline phosphatase increased	1 (2)	3 (6)	1 (2.1)	4 (4.1)
Hepatic pain	0	0	1 (2.1)	1 (1)
Hepatic failure	1 (2)	0	0	0

[a] alanine aminotransferase increased, aspartate aminotransferase increased, hypertransaminasemia, transaminases increased
[b] blood bilirubin increased, hyperbilirubinemia
Source: ADLB.xpt (SDN 380, submitted April 17, 2024)

Table 49. FDA's Analysis of Grade 3-4 Hepatotoxic TEAEs in Study 20190172 (excluding site 33013)

Patients with Grade 3-4 hepatotoxic TEAEs	Trifluridine/Tipiracil or Regorafenib (N = 50) n (%)	Sotorasib 240 mg + Panitumumab (N = 50) n (%)	Sotorasib 960 mg + Panitumumab (N = 47) n (%)	Total Sotorasib + Panitumumab (N = 97) n (%)
	1 (2)	2 (4)	2 (4.3)	4 (4.1)
Hypertransaminasemia [a]	0	1 (2)	1 (2.1)	2 (2.1)
Hyperbilirubinemia [b]	0	1 (2)	2 (4.3)	3 (3.1)
Blood alkaline phosphatase	0	1 (2)	0	0

increased				
Hepatic failure	1 (2)	0	0	0

[a] alanine aminotransferase increased, aspartate aminotransferase increased, hypertransaminasemia, transaminases increased
[b] blood bilirubin increased, hyperbilirubinemia
Source: ADLB.xpt (SDN 380, submitted April 17, 2024)

Table 50. FDA's Pooled Analysis of All Grade Hepatotoxic TEAEs (excluding site 33013)

	CRC Sotorasib monotherapy any dose (N = 122) n (%)	CRC Sotorasib any dose excluding 960 mg (N = 31) n (%)	CRC Sotorasib 960 mg (N = 91) n (%)	CRC Sotorasib 240 mg + Panitumumab (N = 50) n (%)	CRC Sotorasib 960 mg + Panitumumab (N = 126) n (%)	CRC Sotorasib any dose + Panitumumab (N = 176) n (%)	All tumors Sotorasib any dose + Panitumumab (N = 218) n (%)	Any non-CRC tumors Sotorasib 960 mg + Panitumumab (N = 42) n (%)
Patients with hepatotoxic TEAEs	**19 (16)**	**5 (16)**	**14 (15)**	**7 (14)**	**19 (15)**	**26 (15)**	**36 (17)**	**10 (24)**
Hypertransaminasemia [a]	15 (12)	5 (16)	10 (11)	6 (12)	9 (7)	15 (9)	23 (11)	8 (19)
Blood alkaline phosphatase increased	5 (4)	0	5 (5)	3 (6)	7 (6)	10 (6)	13 (6)	3 (7)
Hyperbilirubinemia [b]	6 (4.9)	1 (3.2)	5 (5)	1 (2)	4 (3.2)	5 (2.8)	8 (3.7)	3 (7)
GGT increased	2 (1.6)	0	2 (2.2)	0	1 (0.8)	1 (0.6)	3 (1.4)	2 (4.8)
Hepatic failure	0	0	0	0	1 [c] (0.8)	1 (0.6)	1 (0.5)	0
Hepatic function abnormal	1 (0.8)	0	1 (1.1)	0	1 (0.8)	1 (0.6)	1 (0.5)	0

Abbreviations: GGT = gamma-glutamyltransferase increased
[a] alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, hypertransaminasemia, transaminases increased
[b] blood bilirubin increased, hyperbilirubinemia
[c] Patient experienced a Grade 3 and Grade 5 hepatic failure, which was attributed to CRC liver metastasis progression based on imaging findings.
Source: ADLB.xpt (SDN 380, submitted April 17, 2024) – Integrated Summary of Safety - CRC, Module 5.3.5.3

Table 51. FDA's Pooled Analysis of Grade 3-4 Hepatotoxic TEAEs (excluding site 33013)

	CRC Sotorasib monotherapy any dose (N = 122) n (%)	CRC Sotorasib any dose excluding 960 mg (N = 31) n (%)	CRC Sotorasib 960 mg (N = 91) n (%)	CRC Sotorasib 240 mg + Panitumumab (N = 50) n (%)	CRC Sotorasib 960 mg + Panitumumab (N = 126) n (%)	CRC Sotorasib any dose + Panitumumab (N = 176) n (%)	All tumors Sotorasib any dose + Panitumumab (N = 218) n (%)	Any non-CRC tumors Sotorasib 960 mg + Panitumumab (N = 42) n (%)
Patients with Grade 3-4 hepatotoxic TEAEs	**6 (4.9)**	**1 (3.2)**	**5 (5.5)**	**2 (4)**	**6 (4.8)**	**8 (4.5)**	**14 (6.4)**	**6 (14)**
Hypertransaminasemia [a]	3 (2.5)	1 (3.2)	2 (2.2)	1 (2)	1 (0.8)	2 (1.1)	8 (3.7)	6 (14)
Blood alkaline phosphatase increased	1 (0.8)	0	1 (1.1)	1 (2)	1 (0.8)	2 (1.1)	3 (1.4)	1 (2.4)
Hyperbilirubinemia [b]	1 (0.8)	0	1 (1.1)	1 (2)	3 (2.4)	4 (2.3)	5 (2.3)	1 (2.4)
GGT increased	1 (0.8)	0	1 (1.1)	0	0	0	0	0
Hepatic function abnormal	0	0	0	0	1 (0.8)	1 (0.6)	1 (0.5)	0

Abbreviations: GGT = gamma-glutamyltransferase increased
[a] alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, hypertransaminasemia,

transaminases increased
[b] blood bilirubin increased, hyperbilirubinemia
Source: ADLB.xpt (SDN 380, submitted April 17, 2024) – Integrated Summary of Safety - CRC, Module 5.3.5.3

8.2.5.3 Renal Toxicity

Data:

Study 20190172

One subject (1.9%) in the sotorasib 240 mg + panitumumab group, 0 subjects in the sotorasib 960 mg + panitumumab group, and 2 subjects (3.9%) in the control group reported renal toxicity EOIs (Table 14 of Module 2.5, Clinical Overview). All 3 events were acute kidney injury adverse events. In the sotorasib 240 mg + panitumumab group, the single renal toxicity EOI was considered grade 1 and non-serious, and did not lead to discontinuation, dose reduction, or interruption of investigational product. The time to first onset of this event was 167.0 days, and it was reported as resolved with a duration of 37.0 days.

In the control group, both renal toxicity EOIs were reported as grade 3 events, with one event reported as a serious adverse event. No renal toxicity EOI led to discontinuation of investigational product, while 1 event (2.0%) led to dose reduction and 1 event (2.0%) led to interruption of investigational product. In the control group, 2 subjects experienced total of 3 resolved renal toxicity events, with a median (range) time to first onset of 66.0 (16, 116) days and a median (range) duration across events per subject was 19.5 (4, 35) days.

Pooled Results: Sotorasib 960 mg Monotherapy

Four subjects (3.3%) treated with sotorasib monotherapy at any dose reported renal toxicity EOIs. Of these, 3 subjects (3.3%) in the sotorasib 960 mg monotherapy group reported renal toxicity EOIs of acute kidney injury.

In the sotorasib 960 mg group, grade ≥ 3 renal toxicity EOIs were reported for 3 subjects (3.3%). Two subjects (2.2%) had renal toxicity EOIs of acute kidney injury which were considered serious. No subjects discontinued sotorasib due to a renal toxicity EOI. Two subjects (2.2%) had renal toxicity EOI of acute kidney injury that led to reduction and/or interruption of sotorasib doses.

The median (range) time to first onset of a renal toxicity EOI was 129.0 (8, 312) days. For 3 subjects (3.3%), the renal toxicity EOIs were resolved, and the median (range) duration across the events per subject was 11.0 (4, 15) days. None of the subjects had ongoing renal toxicity EOIs at the time of data cut-off.

Pooled Results: Sotorasib 960 mg + Panitumumab

Renal toxicity EOIs were reported for 2 subjects (1.1%) with mCRC in the sotorasib any dose + panitumumab group. Of these, 1 subject (0.8%) in the sotorasib 960 mg + panitumumab group had renal toxicity EOI of acute kidney injury.

In the sotorasib 960 mg + panitumumab group, grade ≥ 3 renal toxicity EOIs of acute kidney injury was reported for 1 subject (0.6%). This event was not considered serious, and did not result in discontinuation, dose reduction, or interruption of any investigational product.

The time to first onset of the renal toxicity EOI was 120 days. The event resolved, with an event duration of 198 days.

The Applicant's Position:

In Study 20190172 and the pooled sotorasib + panitumumab results, there was no increase in incidence of renal toxicity events compared to those previously observed in either the sotorasib or panitumumab program. Overall, review of individual events did not find evidence of direct renal toxicity attributable to sotorasib or the combination regimen.

The FDA's Assessment:

FDA's analysis of renal toxicity included composite terms for acute kidney injury, and included other terms related to renal toxicity (see Table 52). The incidence of renal toxicity is not high enough to be a concerning safety signal. The rates of renal toxicity were comparable between the sotorasib and control arms and did not increase with increasing dosage of sotorasib in Study 20190172. Most renal toxicities recovered except for one patient each in the sotorasib 240 mg arm and the control arm, and recovery was unknown for one patient in the sotorasib 960 mg arm.

Table 52. FDA's Analysis of All Grade Renal TEAEs in Study 20190172 (excluding site 33013)

	Trifluridine/Tipiracil or Regorafenib (N = 50) n (%)	Sotorasib 240 mg + Panitumumab (N = 50) n (%)	Sotorasib 960 mg + Panitumumab (N = 47) n (%)	Total Sotorasib + Panitumumab (N = 97) n (%)
Patients with renal toxic TEAEs	**4 (8)**	**3 (6)**	**3 (6)**	**6 (6.2)**
Acute kidney injury [a]	2 (4)	1 (2)	2 (4.3)	4 (4.1)
Proteinuria [b]	2 (4)	2 (4)	0	2 (2.1)
Renal tubular disorder	0	0	1 (2.1)	1 (1)

[a] includes acute kidney injury, blood creatinine increased, hypercreatininemia
[b] includes albumin urine present, proteinuria, protein urine present
Source: ADLB.xpt (SDN 380, submitted April 17, 2024)

Table 53. FDA's Analysis of Grade 3-4 Renal TEAEs in Study 20190172 (excluding site 33013)

	Trifluridine/Tipiracil or Regorafenib (N = 50)	Sotorasib 240 mg + Panitumumab (N = 50)	Sotorasib 960 mg + Panitumumab (N = 47)	Total Sotorasib + Panitumumab (N = 97)

	n (%)	n (%)	n (%)	n (%)
Patients with renal toxic TEAEs	**2 (4)**	**1 (2)**	**0**	**1 (1)**
Acute kidney injury	2 (4)	0	0	0
Proteinuria	0	1 (2)	0	1 (1)

Source: ADLB.xpt (SDN 380, submitted April 17, 2024)

Table 54. FDA's Pooled Analysis of All Grade Renal TEAEs (excluding site 33013)

	CRC Sotorasib monotherapy any dose (N = 122) n (%)	CRC Sotorasib any dose excluding 960 mg (N = 31) n (%)	CRC Sotorasib 960 mg (N = 91) n (%)	CRC Sotorasib 240 mg + Panitumumab (N = 50) n (%)	CRC Sotorasib 960 mg + Panitumumab (N = 126) n (%)	CRC Sotorasib any dose + Panitumumab (N = 176) n (%)	All tumors Sotorasib any dose + Panitumumab (N = 218) n (%)	Any non-CRC tumors Sotorasib 960 mg + Panitumumab (N = 42) n (%)
Patients with renal toxic TEAEs	**8 (7)**	**2 (6)**	**6 (7)**	**3 (6)**	**4 (3.2)**	**7 (0.6)**	**10 (4.6)**	**3 (7)**
Acute kidney injury [a]	8 (7)	2 (6)	6 (7)	1 (2)	3 (2.4)	4 (2.3)	6 (2.8)	2 (4.8)
Proteinuria [b]	0	0	0	2 (4)	1 (0.8)	3 (1.7)	4 (1.8)	1 (2.4)
Renal tubular disorder	0	0	0	0	1 (0.8)	1 (0.6)	1 (0.5)	0

[a] includes acute kidney injury, blood creatine increased, blood creatinine increased, hypercreatininemia
[b] includes albumin urine present, proteinuria
Source: ADLB.xpt (SDN 380, submitted April 17, 2024) – Integrated Summary of Safety - CRC, Module 5.3.5.3

Table 55. FDA's Pooled Analysis of Grade 3-4 Renal TEAEs (excluding site 33013)

	CRC Sotorasib monotherapy any dose (N = 122) n (%)	CRC Sotorasib any dose excluding 960 mg (N = 31) n (%)	CRC Sotorasib 960 mg (N = 91) n (%)	CRC Sotorasib 240 mg + Panitumumab (N = 50) n (%)	CRC Sotorasib 960 mg + Panitumumab (N = 126) n (%)	CRC Sotorasib any dose + Panitumumab (N = 176) n (%)	All tumors Sotorasib any dose + Panitumumab (N = 218) n (%)	Any non-CRC tumors Sotorasib 960 mg + Panitumumab (N = 42) n (%)
Patients with Grade 3-4 renal toxic TEAEs	**4 (3.3)**	**1 (3.2)**	**3 (3.3)**	**1 (2)**	**1 (0.8)**	**2 (1.1)**	**2 (0.9)**	**0**
Acute kidney injury	4 (3.3)	1 (3.2)	3 (3.3)	0	1 (0.8)	1 (0.6)	1 (0.5)	0
Proteinuria	0	0	0	1 (2)	0	1 (0.6)	1 (0.5)	0

Source: ADLB.xpt (SDN 380, submitted April 17, 2024) – Integrated Summary of Safety - CRC, Module 5.3.5.3

8.2.5.4 Pneumonitis

Data:

Study 20190172

Across all groups, 1 subject (1.9%) reported 1 pneumonitis EOI (adverse event of pneumonitis in the sotorasib 240 mg + panitumumab group) (Table 15 of Module 2.5, Clinical Overview). This event was not considered serious or grade ≥ 3, and did not result in discontinuation, dose reduction, or interruption of any investigational product. This event was considered ongoing at the time of data cut-off with a time to first onset of 171 days.

Pooled Results: Sotorasib 960 mg Monotherapy
None of the subjects in the sotorasib monotherapy groups had pneumonitis EOI.

Pooled Results: Sotorasib 960 mg + Panitumumab
Pneumonitis EOIs were reported for 2 subjects (1.1%) with mCRC in the sotorasib any dose + panitumumab group. Of these,1 subject (0.8%) in the sotorasib 960 mg + panitumumab group had pneumonitis EOI (pneumonitis). This event was not considered serious or grade ≥ 3, and did not result in discontinuation, dose reduction, or interruption of any investigational product.

The time to first onset of the pneumonitis EOI was 143 days, the event resolved, and the duration of the event was 28 days.

The Applicant's Position:
In Study 20190172 and across the pooled analysis data, pneumonitis events were rare and there were no serious adverse events of pneumonitis.

The FDA's Assessment:
The incidence of pneumonitis was very low and does not appear to be a concerning safety signal in clinical trials of sotorasib with panitumumab. There was one case of pneumonitis in Study 20190172 (Grade 1 in sotorasib 240 mg with panitumumab which has not recovered) and an additional case in the pooled analysis (Grade 1 in sotorasib 960 mg with panitumumab which recovered).

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

Data:
Patient-reported outcomes are discussed in Section 8.1.2.

The Applicant's Position:
Patient-reported outcomes are discussed in Section 8.1.2.

The FDA's Assessment:
FDA did not review the COAs as the results of the COA analysis are considered exploratory. There were adequate efficacy and safety data to determine that the benefit-risk was favorable for the sotorasib 960 mg with panitumumab regimen.

8.2.7. Safety Analyses by Demographic Subgroups

Data:
Adverse events were analyzed by intrinsic and extrinsic factor subgroups of race, age, sex, and region. Overall summaries of adverse events by subgroup are provided in Sections 5.1 and 5.2

of Module 2.7.4, Summary of Clinical Safety. No meaningful differences were observed in the types of adverse events reported across subgroups. Results were generally similar for subjects with mCRC treated with sotorasib monotherapy and sotorasib in combination with panitumumab.

The Applicant's Position:
No meaningful differences were observed in the types of adverse events reported across subgroups of race, age, sex, or region, across the pooled analysis of data. Results were generally similar for subjects with mCRC treated with sotorasib monotherapy and sotorasib in combination with panitumumab.

The FDA's Assessment:
In general, the toxicity profile of sotorasib 960 mg with panitumumab appears similar between patients who were <65 years old and patients who were ≥65 years older, but this observation is limited by the small number of older patients in the pooled analysis.

8.2.8. Specific Safety Studies/Clinical Trials

Data:
Not applicable as no studies were conducted to evaluate a specific safety concern.

The Applicant's Position:
Not applicable.

The FDA's Assessment:
Not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development
Data:
Not applicable.

The Applicant's Position:
See Pharmacology/Toxicology review.

The FDA's Assessment:
Not applicable.

Human Reproduction and Pregnancy

Data:
No clinical studies of sotorasib + panitumumab have been conducted in pregnant or breastfeeding women.

One pregnancy case was reported from study source in which a man was administered sotorasib during his partner's pregnancy. There were no adverse events reported, and the birth outcome for this paternal exposure case was lost to follow-up. No pregnancy or lactation cases in women exposed to sotorasib have been reported.

Nine pregnancy cases have been reported for panitumumab. These include a total of 4 pregnancies from study sources and 5 pregnancies from non-study sources; 2 cases described maternal exposure and 7 cases described paternal exposure. No lactation cases were reported from study and non-study sources. A review of all pregnancy cases, including pregnancy outcomes and adverse events, received from the Amgen Global Safety Database did not reveal any patterns suggestive of a safety concern.

There are no clinical studies to evaluate the effect of sotorasib + panitumumab on fertility.

The Applicant's Position:
There are no available data on sotorasib + panitumumab use in pregnant women.
There are no data on the presence of sotorasib or its metabolites in human milk, the effects on the breastfed child, or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with sotorasib and for 1 week after the final dose.
There are no data on the presence of panitumumab in human milk or the effects of panitumumab on the breastfed infant or on milk production. Human immunoglobulin G is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because of the potential for serious adverse reactions in breastfed infants from panitumumab, advise women not to breastfeed during treatment with panitumumab and for 2 months after the final dose.
There are no clinical studies to evaluate the effect of sotorasib + panitumumab on fertility.

The FDA's Assessment:
There is inadequate data for FDA to assess the impact of sotorasib with panitumumab on human reproduction, pregnancy, and lactation.

Pediatrics and Assessment of Effects on Growth
Data:
Not applicable.

The Applicant's Position:
Safety and effectiveness of sotorasib + panitumumab in pediatric patients have not been

established.

Sotorasib was not studied in pediatric subjects. Amgen intends to request a full waiver for studies in the pediatric population with *KRAS p.G12C*-mutated mCRC based on the grounds that the necessary studies are impossible or highly impracticable to conduct as CRC occurs rarely in the pediatric population and *KRAS p.G12C*-mutated CRC occurs even more rarely. Additionally, the *KRAS p.G12C* mutation does not represent a relevant molecular target to pediatric cancer.

The safety and effectiveness of panitumumab have not been established in pediatric patients.

The PK of panitumumab at doses ranging from 2.5 mg/kg IV weekly, 6 mg/kg every 2 weeks, or 9 mg/kg IV every 3 weeks were evaluated in 28 pediatric patients. Panitumumab exposures were comparable in the adult and adolescent patients 12 to 17 years of age. Limited data suggested that pediatric patients of 2 to $<$ 12 years of age had lower panitumumab exposure and higher clearance than that in adolescent patients following 6 mg/kg IV administration of panitumumab. There was no evidence of an anti-tumor treatment effect in these patients.

The FDA's Assessment:
There is inadequate data for FDA to assess the effect of sotorasib with panitumumab in the pediatric population.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
Data:
Not applicable.

The Applicant's Position:
There is no clinical experience with overdose with sotorasib.
Doses up to approximately twice the recommended therapeutic dose of panitumumab (12 mg/kg) resulted in adverse reactions of skin toxicity, diarrhea, dehydration, and fatigue.

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

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience
Data:
Sotorasib
As of 27 November 2023, Amgen received a total of 3582 adverse drug reactions from medically confirmed and unconfirmed spontaneous sources, of which 1485 were serious and 2097 were nonserious (Section 6.3 of Periodic Benefit Risk Evaluation Report [PBRER] No. 05).

Sotorasib was considered to be used off-label in (b) (4) cases out of a grand total of (b) (4). About 27% of indications that were not NSCLC were coded as off-label use, whereas the other most commonly reported off-label indications (≥ 5%) were colon cancer (11%), unspecified malignant neoplasm (10%), pancreatic carcinoma (7%), and metastatic colorectal cancer (6%). A comparison of adverse events between off-label use and on-label use revealed no difference in the pattern of adverse event occurrence (Amgen Global Safety Database).

Amgen also received a total of 1719 serious adverse reactions from noninterventional postmarketing sources and other solicited sources. The most frequently reported adverse events (≥ 20 events) from spontaneous sources were diarrhea (320 events), disease progression (278 events), off-label use (207 events), NSCLC (133 events), death (96 events), nausea (85 events), hepatotoxicity (79 events), fatigue (71 events), adverse event (68 events), increased ALT (56 events), increased liver function test (54 events), increased AST and increased hepatic enzymes (52 events each), metastatic NSCLC (48 events), hepatic cytolysis and decreased appetite (45 events each), abnormal hepatic function (43 events), vomiting (37 events), dyspnea and adverse drug reaction (28 events each), liver disorder (27 events), malignant lung neoplasms and malaise (25 events each), ineffective drug (24 events), myalgia, asthenia, and pyrexia (22 events each), cough and hepatitis (21 events each), anemia and pneumonitis (20 events each).

The most frequently reported serious adverse events (≥ 20 events) from noninterventional postmarketing sources and other solicited sources (eg, expanded access programs and patient support programs) were death (445 events), NSCLC (179 events), hospitalization (73 events), malignant lung neoplasm (60 events), hepatotoxicity (57 events), hepatic cytolysis (55 events), pneumonia (35 events), diarrhea (33 events), unevaluable event (30 events), disease progression (26 events), and hepatitis (23 events).

Overall, the most frequently reported adverse events were consistent with expected adverse events in the target patient population independent of sotorasib exposure or with previously identified adverse drug reactions associated with sotorasib use.

<u>Panitumumab</u>

As of 30 September 2023, Amgen received a total of 33 621 adverse drug reactions from medically confirmed and unconfirmed spontaneous sources, of which 10 986 were serious and 22 635 were nonserious (Section 6.3 of PBRER No. 23). Amgen also received a total of 8608 serious adverse reactions cumulatively from noninterventional postmarketing sources and other solicited sources. The most frequently reported adverse events (≥ 300 events) from spontaneous sources were rash (2182 events), dermatitis acneiform (1713 events), hypomagnesaemia (1487 events), skin disorder (1439 events), paronychia (942 events), skin toxicity (765 events), diarrhea (739 events), stomatitis (537 events), dry skin (536 events), disease progression (509 events), off-label use (479 events), erythema (460 events), pruritus (452 events), death (428 events), skin reaction (356 events), acne (337 events), rash pustular (311 events), nausea (311 events), and neutropenia (305 events). The most frequently

reported serious adverse events (≥ 100 events) from noninterventional postmarketing sources and other solicited sources (eg, expanded access programs and patient support programs) were death (1045 events), mCRC (476 events), rash (194 events), diarrhea (177 events), disease progression (153 events), dermatitis acneiform (124 events), metastases to liver (119 events), and vomiting (109 events).

Overall, the most frequently reported adverse events were consistent with expected adverse reactions in the target patient population independent of panitumumab exposure or with previously identified adverse drug reactions associated with panitumumab use.

The Applicant's Position:
Overall, the most frequently reported adverse events in the clinical trials were consistent with expected adverse events in the target patient population independent of sotorasib or panitumumab exposure or with previously identified adverse drug reactions associated with sotorasib or panitumumab use.

Cumulatively, since the International Birth Date of sotorasib up to the end of the PBRER No. 05 reporting period, there was an estimated (b) (4) patient-years of exposure to sotorasib in the marketed setting. Based on evaluation of postmarketing data received through 27 November 2023, the overall benefit-risk balance of sotorasib for its approved indication remains favorable.

Cumulatively, since the International Birth Date of panitumumab up to the end of the PBRER No. 23 reporting period, there was an estimated (b) (4) patient-years of exposure to panitumumab in the marketed setting. Based on evaluation of postmarketing data received through 30 September 2023, the overall benefit-risk balance of panitumumab for its approved indication remains favorable.

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

Expectations on Safety in the Postmarket Setting
Data:
Not applicable.

The Applicant's Position:
Toxicities appear to have been adequately represented in the sotorasib + panitumumab safety database for this submission. Routine pharmacovigilance will be conducted to monitor for unexpected adverse events. The ongoing and planned clinical studies will contribute additional safety information to further characterize the safety profile of sotorasib + panitumumab.

The FDA's Assessment:
FDA expects the safety profile in the post-marketing setting to be as observed in Study

20190172 and the pooled analysis. Risks outside of those identified in clinical trials and conveyed in the proposed labeling are not expected. Routing pharmacovigilance will be conducted to monitor for unexpected adverse events.

8.2.11. Integrated Assessment of Safety

Data:

Adverse drug reactions for sotorasib 960 mg + panitumumab are described in Section 8.2.4.

The Applicant's Position:

The pivotal safety data in this supplemental marketing application supporting approval are obtained from Study 20190172:

- In Study 20190172, crude subject incidences of grade ≥ 3 adverse events and serious events were comparable between the sotorasib and control groups.
- After excluding deaths due to disease progression-related preferred terms, rates of fatal adverse events were comparable across all groups. No fatal events were attributed to sotorasib or panitumumab.
- Sotorasib + panitumumab combination treatment was well tolerated based on the low incidence of discontinuation and dose reduction/interruption due to adverse events.
- The toxicity of panitumumab was consistent with its known safety profile, with dermatologic toxicities being the most frequent adverse events.
- No new risks of sotorasib were identified in this population of subjects with CRC . The known risks of diarrhea, hepatotoxicity, and interstitial lung disease were observed at lower incidences than previously observed in the population of subjects with NSCLC.
- The safety profile of sotorasib in combination with panitumumab was consistent with the known safety profiles of each agent. No overlapping toxicity (increased incidence or severity of diarrhea, interstitial lung disease/pneumonitis) was observed with the combination treatment.
- The incidence of elevated transaminases was less frequent than what has been observed in the sotorasib safety profile.
- There were no clinically relevant changes in laboratory values or vital signs.

Safety data supporting this supplemental marketing application are obtained from Studies 20190135 Subprotocol H and 20170543:

- In Study 20190135 Subprotocol H, no new safety concerns were identified.
- Sotorasib and panitumumab combination had an acceptable safety profile, with few events leading to discontinuation of study treatment.
- The safety profile of sotorasib in combination with panitumumab was consistent with the known safety profiles of each agent. No overlapping toxicity (increased incidence or severity of diarrhea, interstitial lung disease/pneumonitis) was observed with the combination treatment.
- Dermatologic toxicities were the most frequent adverse events observed and were consistent with the known safety profile of panitumumab. The incidence of elevated

transaminases was less frequent than what has been observed in the sotorasib safety profile.

- There were no clinically relevant changes in laboratory values or vital signs.
- Post-hoc analyses of adverse events excluding select disease progression preferred terms (those consistent with the primary tumor) were generally aligned with the findings in the prespecified analysis. For fatal events, there was only 1 event with a preferred term not related to disease progression (hepatic failure; not related to study treatment).
    - In the phase 1 CRC portion of Study 20170543, No dose-limiting toxicities were observed in any cohort.
    - The toxicity profile was consistent with the known sotorasib safety profile. Sotorasib had acceptable tolerability across dose levels tested.
    - No treatment-related deaths were reported.
    - Ad hoc analysis of adverse events excluding select disease progression preferred terms (those consistent with the primary tumor) were generally aligned with the findings in the prespecified analysis except for serious events (3 events less) and fatal events (6 events less). For fatal events, there was only 1 event with a preferred term not related to disease progression (small intestinal obstruction, not related to study treatment).
    - In the phase 2 portion of Study 2017543, the safety profile was consistent with that observed in Interim Analysis 1 for the phase 2 CRC portion of the study. Sotorasib had acceptable tolerability among subjects with CRC.
    - No safety concerns were observed.

Further support comes from safety analysis of integrated sotorasib monotherapy and sotorasib in combination with panitumumab in subjects with mCRC:

- In this integrated safety dataset, the most common adverse events were generally consistent with the known safety profiles of the individual study drugs or with events occurring in the subject population independent of drug exposure. Across the pooled analyses, the subject incidences of the most common adverse events were higher for the combination regimen compared with sotorasib monotherapy; and these differences were driven by the known safety profile of panitumumab.
- The safety profile of sotorasib monotherapy and sotorasib + panitumumab combination therapy was consistent across subgroups (age, gender, race, region).
- Routine risk minimization activities (ie, risk communications through prescribing information or product packaging, including dose modification guidance) are considered adequate to address the safety concerns associated with the use of sotorasib in combination with panitumumab.

The FDA's Assessment:

Sotorasib 960 mg with panitumumab is a safe and tolerable regimen for the third-line treatment of patients with mCRC. It was at least as tolerable, if not more tolerable based on analysis of dose modifications, as sotorasib 240 mg with panitumumab and the control

regimens. The TEAEs reported in Study 20190172 for the sotorasib with panitumumab regimens were consistent with the known toxicity profiles of sotorasib and panitumumab. Most of the common TEAEs (≥20%) in the sotorasib 960 mg arm were toxicities associated with panitumumab (i.e., rash, hypomagnesemia, dry skin, stomatitis), or common in patients with cancer (i.e., fatigue, and musculoskeletal pain); diarrhea was the only common TEAE commonly seen in patients exposed to sotorasib. The most common Grade 3-4 TEAEs (≥5%) in the sotorasib 960 mg arm were rash, hypomagnesemia, and diarrhea. GI obstruction was a potential safety signal for the sotorasib with panitumumab regimen, but the incidence of this toxicity was low in the pooled analysis of non-CRC cancers; this increased incidence of GI obstruction was likely due to the disease process of CRC itself than exposure sotorasib with panitumumab therapy.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

The primary trial supporting the statistical review of this application is Study 20190172, a global, open-label, randomized, active-controlled clinical trial in patients with KRAS G12C mutated mCRC comparing third-line treatment with sotorasib in combination with panitumumab to investigator's choice of regorafenib or trifluridine and tipiracil. Patients were randomized equally to 3 arms, sotorasib 960 mg PO QD with panitumumab 6 mg/kg IV Q2W, sotorasib 240 mg PO QD with panitumumab 6 mg/kg IV Q2W, or investigator's choice control (trifluridine and tipiracil or regorafenib which was chosen prior to randomization). The primary endpoint was PFS per central review, comparing each treatment arm to control, with secondary endpoints of OS and ORR. The study-wise Type I error rate for multiple comparisons and multiple endpoints was controlled by splitting the Type I error rate across primary comparisons and by using a graphical approach to subsequent planned comparisons of key secondary endpoints.

The results of the primary endpoint of PFS by central review were statistically significant for the comparison of sotorasib 960 mg with panitumumab (median PFS: 5.6 months, 95% CI: 4.2, 6.3 months) to control (median PFS: 2.0 months, 95% CI: 1.9, 3.9 months) with a hazard ratio of 0.48 (95% CI: 0.30,0.78). The comparison of the sotorasib 240 mg with panitumumab treatment arm to control resulted in a numerical but not statistically significant improvement in PFS per central review. The key secondary endpoint of OS was not powered to detect a statistical difference between the arms. The OS HR was 0.70 (95% CI: 0.41, 1.18) comparing sotorasib 960 mg with panitumumab to control (2-sided p-value: 0.20) and 0.83 (95% CI: 0.49, 1.39) comparing sotorasib 240 mg with panitumumab to control (2-sided p-value: 0.20). ORR was not tested formally due to the pre-specified hierarchical order.

There was a forgery reported at one site that impacted safety data only. Efficacy data was determined to not be affected by this forgery, and no other statistical review issues were encountered during the efficacy review of this application. FDA performed additional sensitivity analyses to assess the impact this site may have had on the efficacy and did not identify any clinically meaningful differences.

8.4. **Conclusions and Recommendations**

The FDA's Assessment:

The data submitted has provided substantial evidence of effectiveness of sotorasib 960 mg once daily in combination with panitumumab for the treatment of adult patients with *KRAS G12C*-mutated mCRC who have received prior fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. Study 20190172 demonstrated that sotorasib 960 mg with panitumumab had a statistically significant and clinically meaningful improvement in PFS compared to investigator's choice of SOC therapy (HR 0.48 (95% CI 0.3, 0.78; p-value = 0.005). The response rate was also substantially better in patients treated with sotorasib 960 mg in combination with panitumumab at 26% (95% CI 15, 40) compared to 0% (95% CI 0, 7) in patients treated with investigator's choice therapy. In the same trial, based on updated data submitted to the application, sotorasib 240 mg with panitumumab did not meet statistical significance for PFS based on the pre-specified p-value boundary compared to investigator's choice. The ORR was numerically higher in the sotorasib 960 mg with panitumumab arm compared to the sotorasib 240 mg with panitumumab arm (ORR 6%; 95% CI: 1, 16). However, this study was not designed to conduct a statistical comparison between the two sotorasib regimens.

There were no new safety signals identified during the review and the adverse events associated with sotorasib 960 mg in combination with panitumumab are adequately described in the USPI. The safety profile of sotorasib 960 mg with panitumumab was consistent with the known safety profile of the individual drugs, and the combination regimen was tolerable and safe. Sotorasib 960 mg with panitumumab was not more toxic, nor less tolerable compared to sotorasib 240 mg with panitumumab.

Based on the comparable safety profile, the PK profile which demonstrated overlapping exposures between the sotorasib 240 mg and sotorasib 960 mg group, and superior efficacy demonstrated with sotorasib 960 mg with panitumumab in Study 20170192, the review team has concluded that the benefit-risk profile of sotorasib 960 mg in combination with panitumumab is favorable and supports approval.

The review division recommends traditional approval of sotorasib 960 mg with panitumumab for the treatment of KRAS G12C-mutated mCRC who have received prior fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy.

8.4.1. Approach to Substantial Evidence of Effectiveness

1. Verbatim indication

   LUMAKRAS, in combination with panitumumab, is indicated for the treatment of adult patients with *KRAS G12C*-mutated metastatic colorectal cancer (mCRC), as determined by an FDA-approved test, who have received prior fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy.

2. SEE was established with *(check **one** of the options for traditional or accelerated approval pathways)*
   a. Adequate and well-controlled clinical investigation(s):
      i. ☐ At least two adequate and well-controlled clinical investigations, **OR**
      ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

      OR

   b. ☒ One adequate and well-controlled clinical investigation supported by confirmatory evidence[1,2,3]

      OR

   c. ☐ Evidence that supported SEE from a prior approval of the drug and was determined, through extrapolation, to provide SEE for the new use/indication *(e.g., 505(b)(2) application relying only on a previous determination of effectiveness; pediatric extrapolation; extrapolation of data from immediate-release dosage form to new extended-release dosage form; over-the-counter switch)*[2]

[1] FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (2019)
[2] FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (1998)
[3] Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence (2023)]

X X

Primary Statistical Reviewer Statistical Team Leader

X	X
Primary Clinical Reviewer	Clinical Team Leader

APPEARS THIS WAY ON ORIGINAL

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:
There was no advisory committee meeting or request for external consultation for this application because the application did not raise significant review issues regarding the role of sotorasib with panitumumab for this indication.

APPEARS THIS WAY ON ORIGINAL

10 Pediatrics

The Applicant's Position:

Sotorasib was not studied in pediatric subjects. As described in the agreed Initial Pediatric Study Plan (Agreed iPSP Agreement letter dated 21 April 2020; Reference ID: 4571203), Amgen plans to request a full waiver for the development of AMG 510 for the treatment of previously treated, locally advanced and mCRC with *KRAS p.G12C* mutation in all pediatric age groups because the necessary studies are impossible or highly impracticable to conduct as the disease occurs primarily in the adult population (FDARA Section 504 and Section 505B(a)(4)(A)(i) of the FD&C Act). Additionally, the *KRAS p.G12C* mutation does not represent a relevant molecular target to pediatric cancer.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. The Applicant was granted a full waiver of the requirement to conduct pediatric studies under PREA.

APPEARS THIS WAY ON ORIGINAL

11 Labeling Recommendations

Data:
This is a supplemental application, please see annotated label in Module 1 for proposed labeling.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
1 Indications and Usage	(b) (4) [redacted]	1.2 Metastatic Colorectal Cancer (mCRC) LUMAKRAS, in combination with panitumumab, is indicated for the treatment of adult patients with *KRAS G12C*-mutated metastatic colorectal cancer (mCRC), as determined by an FDA-approved test, who have received prior fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy
2 Dosage and Administration	2.1 Patient Selection Included patient selection for KRAS G12C-mutated mCRC	FDA agreed
5 Warnings and Precautions	(b) (4) [redacted] 5.1 Hepatotoxicity 5.2 Interstitial Lung Disease (ILD)/ Pneumonitis	Statement deleted per labeling practices. 5.1 Updated to include hepatotoxicity events from CodeBreaK 300 and CodeBreaK 100 5.2 Updated to include ILD from CodeBreaK 300 and CodeBreak 100
6 Adverse Reactions	6.1 Clinical Trial Experience Metastatic Colorectal Cancer CodeBreaK 300 study	FDA generally agrees; minor edits to align with current format.
8 Use in Specific Populations	8.1 Pregnancy Risk Summary	8.1 Added to Risk Summary: Refer to the Full Prescribing Information of panitumumab for pregnancy risk information and contraception recommendations when LUMAKRAS is administered in combination with panitumumab.

8.5 Geriatric Use	Included statement on geriatric population receiving combination Lumakras 960 mg in combination with panitumumab	FDA agrees.
12 Clinical Pharmacology	12.1 Mechanism of Action (b) (4) (b) (4)	12.1 Mechanism of Action In the setting of *KRAS G12C*-mutant CRC, EGFR activation has been identified as a mechanism of resistance to $KRAS^{G12C}$ inhibition. In a murine patient-derived colorectal tumor xenograft model, the combination of sotorasib and panitumumab, an epidermal growth factor receptor (EGFR) antagonist, had increased antitumor activity compared to either sotorasib or panitumumab alone. (b) (4)
14 Clinical Studies	14.2 Metastatic Colon Cancer Description and efficacy of CodeBreaK-300 study added	FDA generally agreed; minor edits to include the following statements: • Final analysis of OS was not statistically significant. • PFS was not statistically significant for patients receiving 240 mg sotorasib in combination with panitumumab.

The Applicant's Position:
The draft USPI is provided with this marketing application.

The FDA's Assessment:
See table above entitled "Summary of Significant Labeling Changes."

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:
There are no safety issues identified at this time requiring Risk Evaluation and Mitigations Strategies. The medical community has experience with the management of adverse reactions observed with this regimen. Recommendations for the safe and effective use of sotorasib in combination with panitumumab are provided in the US prescribing information as well as in the medication guide.

APPEARS THIS WAY ON ORIGINAL

13 Postmarketing Requirements and Commitment

The FDA's Assessment:
There are no postmarketing requirements or commitments for this application.

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed? No. Although the patient population in the pivotal trial consisted primarily of patients with reported races of White and Asian, there is limited available data regarding the racial and ethnic distribution of *KRAS G12C*-mutated CRC to inform target enrollment of REM patients.
□	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	__ Yes _x_ No
□	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	__ Yes _x_ No
□	Other considerations (e.g.: PK/PD), if applicable:	__ Yes _x_ No

14 Division Director (DHOT) (NME ONLY)

X

APPEARS THIS WAY ON ORIGINAL

15 Division Director (OCP)

X

APPEARS THIS WAY ON ORIGINAL

16 Deputy Division Director (OB)

X

APPEARS THIS WAY ON ORIGINAL

17 Division Director (Clinical)

X

APPEARS THIS WAY ON ORIGINAL

18 Office Director (or designated signatory authority)

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

X _____

APPEARS THIS WAY ON ORIGINAL

19 Appendices

19.1. References

The Applicant's References:

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The FDA's References:

1. NCI Surveillance, Epidemiology, and End Results Program. https://seer.cancer.gov/statfacts/html/colorect.html (accessed January 2, 2025).

2. Teo MYM, Fong JY, Lim WM, and In LLA. Current Advances and Trends in KRAS Targeted Therapies for Colorectal Cancer. *Molecular Cancer Research.* 2022; 20 (1): 30–44.

3. Nassar AH, Adib E, and Kwiatkowski DJ. Distribution of KRASG12C Somatic Mutations across Race, Sex, and Cancer Type. *New England Journal of Medicine.* 2021; 384: 185-187.

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5. Habashy P, Lea V, Wilkinson K, et al. KRAS and BRAF Mutation Rates and Survival Outcomes in Colorectal Cancer in an Ethnically Diverse Patient Cohort. *International Journal of Molecular Sciences*. 2023; 24 (24): 17509.

6. Nfonsam V, Wusterbarth E, Gong A, and Vij P. Early-Onset Colorectal Cancer. *Surgical Oncology Clinics of North America*. 2022;31(2): 143-155.

19.2. Financial Disclosure

The Applicant's Position:
[To the Applicant: Insert text here.]

Covered Clinical Study (Name and/or Number):* Study 20190172

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 824		
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): 3		
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: _____ Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
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): n/a		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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

Covered Clinical Study (Name and/or Number):* Study 20191035 Subprotocol H

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1173		
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): 0		
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: _____ Significant payments of other sorts:_____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study:_____ Sponsor of covered study: _____		
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): n/a		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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

Covered Clinical Study (Name and/or Number):* Study 20170543

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1211		
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): 3		
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: _____ Significant payments of other sorts: 2		

Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: 1 Sponsor of covered study: _____		
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): n/a		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

The FDA's Assessment:
FDA focused the assessment of financial disclosure to Study 20180172 because the efficacy results from this trial served as the basis for the review of this supplemental application. Three investigators reported disclosable financial interests; (b) (4)

Ten investigators in Study 20190172 did not provide financial disclosures and all ten investigators ended site affiliation prior site activation.

The FDA clinical review team determined that the financial interests of the two investigators did not impact the interpretation of safety or efficacy of sotorasib 960 mg with panitumumab regimen given that (b) (4)

19.3. Nonclinical Pharmacology/Toxicology

Data:
All data presented in Section 5, Nonclinical Pharmacology/Toxicology.

The Applicant's Position:
Not applicable.

The FDA's Assessment:

Not applicable.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Population PK Analysis

19.4.1.1. Executive Summary

The FDA's Assessment:
Model performance and predictivity of the previously developed popPK model is considered acceptable to predict individual PK for subsequent E-R analysis.

19.4.1.2. PPK Assessment Summary

The Applicant's Position:
[Highlight the key findings in the white cells.]

General Information		
Objectives of PPK Analysis		The objectives of the analysis were to evaluate sotorasib population pharmacokinetics (PK) in patients with previous treated advanced colorectal cancer (CRC) with KRASG12C mutation using the previously developed population PK model in healthy subjects and patients with advanced solid tumors with KRASG12C mutation (reference model), and evaluate model performance and predictability by several diagnosis methods
Study Included		The population pharmacokinetic (popPK) analysis evaluated concentration-time data from one phase 1/2 study 20170543, one phase 1b study 20190135, and one phase 3 study 20190172 in subjects with CRC. Study numbers are listed below: 20170543, 20190135 and 20190172
Dose(s) Included		Sotorasib was administered orally at doses of 180 mg, 240mg, 360 mg, 720 mg, 960 mg QD or 480 mg twice-daily (BID). Majority of subjects received a 960 mg QD dose.
Population Included		Patients with previously treated advanced colorectal cancer (CRC) with KRASG12C mutation
	General	Age median (range): 57.8 (30-85)

Population Characteristics (Table1)		Weight median (range): 72.6 (37.1-157.9) 140 (46.1%) male 204 (67.1%) in White 76 (25.0%) in Asian 9 (3.0%) in Black 15 (4.9%) in Other
	Organ Impairment	Hepatic (NCI): 208 (68.4%) in Normal 91 (29.9%) in Mild liver dysfunction 5 (1.6%) in Moderate liver dysfunction 0 (0.0%) in Severe liver dysfunction Renal (CKD): 142 (46.7%) in Normal 143 (47.0%) in Mild CKD 19 (6.2%) in Moderate CKD 0 (0.0%) in Severe CKD
	Pediatrics (if any)	None
No. of Patients, PK Samples, and BLQ		304 patients, 4455 PK samples, 10 (0.22%) predose and 89 (2%) postdose BLQ samples
Sampling Schedule	Rich Sampling	Intensive sotorasib PK samples were nominally defined to be collected on study day 1 and day 15 over a 24-hour period (pre-dose, 1, 2, 4 hours post-dose and pre-dose before next dose) and sparse pre-dose PK samples were collected on the Day 1 of cycle 2 to cycle 5 and at the end-of-treatment from all subjects
	In ITT Population	Intensive sotorasib PK samples were nominally defined to be collected on study day 1 and day 15 over a 24-hour period (pre-dose, 1, 2, 4 hours post-dose and pre-dose before next dose) and sparse pre-dose PK samples were collected on the Day 1 of cycle 2 to cycle 5 and at the end-of-treatment from all subjects
Covariates Evaluated	Static	Reference model used bodyweight, age, sex, race, country, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, albumin (ALB), chronic kidney disease stage (CKD) score based on eGFR evaluated by Modification of Diet in Renal Disease (MDRD) formula, overall hepatic impairment scores evaluated by National Cancer Institute Organ Dysfunction Working Group criteria (NCI), ECOG score (ECOGBL), the

<table>
<tr><td></td><td></td><td>number of prior anticancer therapies (NHXACTHR), disease stage at screening (DSSTGSCR), population (healthy, NSCLC patients, colorectal cancer (CRC) patients, or patients other types of cancers)</td><td></td></tr>
<tr><td></td><td>Time-varying</td><td>Use of CYP3A4 inhibitors/inducers, use of P-glycoprotein (P-gp) inhibitors/inducers, use of proton pump inhibitors (PPI), use of histamine-2 receptor (H2) antagonists, use of antacids, drug administration with/without food, and drug administration with/without high-fat meal</td><td></td></tr>
<tr><td colspan="2">Final Model</td><td>Summary</td><td>Acceptability [FDA's comments]</td></tr>
<tr><td colspan="2">Software and Version</td><td>NONMEM 7.4</td><td>Yes</td></tr>
<tr><td colspan="2">Model Structure</td><td>Three-compartment disposition pharmacokinetic model with 2 transit compartments and first order elimination</td><td>Yes</td></tr>
<tr><td colspan="2">Model Parameter Estimates</td><td>The data from patients with CRC fit the reference model with parameters listed below:
<table>
<tr><th>Parameter Description (unit)</th><th>Parameter</th><th>Mean</th><th>%RSE</th></tr>
<tr><td>1st order absorption parameter in between transit compartments and the last transit compartment to the central compartment (1/hour)</td><td>KA</td><td>5.2</td><td>3.5</td></tr>
<tr><td>Clearance at baseline (L/hr)</td><td>CLBS</td><td>3.94</td><td>6.5</td></tr>
<tr><td>Clearance at steady state (L/hr)</td><td>CLSS</td><td>8.08</td><td>6.7</td></tr>
<tr><td>Induction rate coefficient (1/hr)</td><td>KIND</td><td>0.00585</td><td>5.5</td></tr>
<tr><td>Apparent volume of distribution of central compartment (L)</td><td>V2</td><td>45.9</td><td>6.4</td></tr>
<tr><td>Rate from central to peripheral compartment 1 (1/hour)</td><td>K23</td><td>0.0317</td><td>8.7</td></tr>
<tr><td>Rate from peripheral 1 to central compartment (1/hour)</td><td>K32</td><td>0.0777</td><td>10</td></tr>
<tr><td>Rate from central to peripheral compartment 2 (1/hour)</td><td>K24</td><td>0.0152</td><td>11</td></tr>
<tr><td>Rate from peripheral 2 to central compartment (1/hour)</td><td>K42</td><td>0.00132</td><td>15</td></tr>
<tr><td>Relative bioavailability at baseline (ratio to F1BS_DG1):</td><td></td><td></td><td></td></tr>
<tr><td>• Dose:240mg or lower</td><td>F1BS_DG1</td><td>1</td><td>Fixed</td></tr>
<tr><td>• Dose:360mg</td><td>F1BS_DG2</td><td>0.765</td><td>8.6</td></tr>
<tr><td>• Dose:480mg</td><td>F1BS_DG3</td><td>0.591</td><td>12</td></tr>
<tr><td>• Dose:720mg and 840mg</td><td>F1BS_DG4</td><td>0.542</td><td>13</td></tr>
<tr><td>• Dose:960 mg or higher</td><td>F1BS_DG5</td><td>0.358</td><td>6.3</td></tr>
<tr><td>Relative bioavailability at steady state (ratio to F1BS_DG1):</td><td></td><td></td><td></td></tr>
<tr><td>• Dose:240mg or lower</td><td>F1SS_DG1</td><td>0.755</td><td>6.1</td></tr>
<tr><td>• Dose:360mg</td><td>F1SS_DG2</td><td>0.566</td><td>9</td></tr>
<tr><td>• Dose:480mg</td><td>F1SS_DG3</td><td>0.321</td><td>11</td></tr>
<tr><td>• Dose:720mg and 840mg</td><td>F1SS_DG4</td><td>0.312</td><td>9</td></tr>
</table></td><td>Yes

PopPK modeling was not conducted in this application.</td></tr>
</table>

	• Dose:960 mg or higher F1SS_DG5 0.228 6.6 Covariate Effects Cancer Type on CL (proportional change) • NSCLC (reference) • CRC vs. NSCLC CLPRIM1 0.219 24 • Other Cancers vs. NSCLC CLPRIM2 0.0856 64 • Healthy vs. NSCLC CLPRIM3 0.492 96 SEX on V2 (proportional change) • Male (reference) • Female CLSEX1 -0.0988 29 Baseline tumor size on CL (proportional change) • >70mm (reference) • ≤70mm CLTUM_BS1 0.152 23 • Healthy (0mm) CLTUM_BS2 0.41 100 ALB on CL ((L/hr)/(g/dL)) CLALB 0.0315 6.8	
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	For the reference model RSE and IIV shrinkage can be found in the Table above. All eta and epsilon shrinkage values were <10%. The estimated model parameters fell within the distribution of 1,000 bootstrap replicates. These results confirmed stability of the model developed and quantified precision of the parameter estimates. Hence, the reference model was appropriately validated and deemed adequate to analyze the patients with CRC population dataset.	Yes
BLQ for Parameter Accuracy	2% of PK samples below the limit of quantification were excluded from the analysis.	Yes
GOF, VPC	pcVPC: Figure 12-4 GOF: Figure 12-5, Figure 12-6, Appendix 2	Yes
Significant Covariates and Clinical Relevance	None of the covariates evaluated in the reference model resulted in clinically meaningful changes in exposure and therefore do not warrant a dose adjustment. Impact of covariates on sotorasib exposure using the final model: · Age, body weight, liver and renal function did not show	Yes Covariate modeling was not conducted in this application.

	significant effects on sotorasib PK · Females had +8.6% $C_{max,ss}$ and +0.29% $AUC_{tau,ss}$ compared to males · Asians had -4.8% $C_{max,ss}$ and -22% $AUC_{tau,ss}$ compared to Caucasians · Low albumin levels resulted in +8.8% $C_{max,ss}$ and +37% $AUC_{tau,ss}$ · Healthy subjects had lower sotorasib exposure, with -11% $C_{max,ss}$ and -48% $AUC_{tau,ss}$ · Patients with lower baseline tumors (≤70 mm) had -2.8% $C_{max,ss}$ and -13% $AUC_{tau,ss}$ sotorasib exposure These covariates while significant in the reference model building did not result in clinically meaningful changes to sotorasib exposure and do not necessitate dose adjustments.	
Analysis Based on Simulation (optional)		
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.3 PK		Yes. No update from the previous labeling.

The FDA's Assessment:

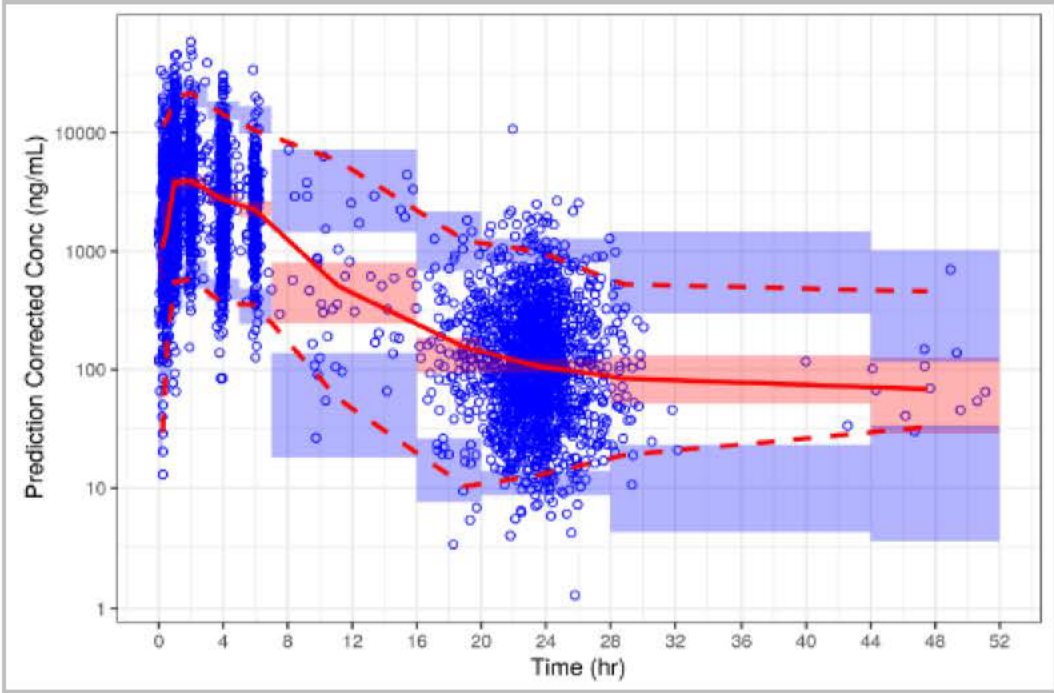
The PK data of CRC patients with KRAS p.G12C mutation who received sotorasib alone or in combination with panitumumab can be reasonably described by the previously developed popPK model. The individual exposure predicted by the popPK model is appropriate to be used in the E-R analysis.

19.4.1.3. PPK Review Issues

Figure/table numbers in Section 19.4.1.2 PPK Assessment Summary were referenced from Applicant popPK report 157509. The key figures/tables were hereby attached by the Reviewer below.

The model performance and predictability are evaluated by pcVPC (**Figure 7**), which showed good agreement between PK observations in CRC patients receiving sotorasib as monotherapy or in combination with panitumumab and the previously developed popPK model.

Figure 11. pcVPC of the CRC patients in studies 2017543, 2019135 and 2019172



Source: Applicant popPK report 157509 Figure 2-1. Blue opened circles represent the observed prediction-corrected concentrations over the time post the most recent dose. Red solid line represents the median observed sotorasib serum concentrations (4356 plasma samples from 304 subjects) and red dashed lines represent the 2.5 and 97.5 percentiles of the observed concentrations over the median times in the bins. Shaded areas constitute the model-projected 95% confidence interval (CI) for the median, 2.5th and 97.5th percentiles computed for each bin across time and replicates based on the previously developed popPK model (Report 157092).

19.4.1.4. Reviewer's Independent Analysis

None.

19.4.2. Exposure-Response Analysis

19.4.2.1. ER (efficacy) Executive Summary

The FDA's Assessment:

E-R analysis for efficacy is inconclusive due to confounding effect (e.g., baseline disease) and could not inform dose selection for the narrow and comparable exposure range achieved with 240 mg and 960 mg QD.

19.4.2.2. ER (efficacy) Assessment Summary

The Applicant's Position:
[Highlight the key findings in the white cells.]

General Information		
Goal of ER analysis		To characterize the exposure response (ER) relationships between sotorasib exposures and study efficacy endpoints, including progression-free survival (PFS), overall survival (OS), duration of response (DOR), objective response rate (ORR), disease control rate (DCR), time to response (TTR), and best tumor size response (BTSR)
Study Included		The full analysis dataset for ER analysis consisted of 164 patients with previous treated advanced colorectal cancer (CRC) with KRAS p.G12C mutation receiving sotorasib with panitumumab and having sotorasib exposure measured in a phase 1b study 20190135 and phase 3 study 20190172.
Endpoint		Primary: 20190135: safety/tolerability 20190172: PFS Secondary: 20190135: OS, ORR, PRO, DOR, TTR, DCR and PK 20190172: OS, ORR, PRO, DOR, TTR, DCR, safety, tolerability and PK
No. of Patients (total, and with individual PK)		164
Population Characteristics (Table 1)	General	Age median (range): 59 (30-82) Weight median (range): 66.0 (39, 146) 74 (45.1%) male

		105 (64%) White 4 (2.44%) Black or African American 46 (28%) Asian 9 (5.49%) Others	
	Pediatrics (if any)	None	
Dose(s) Included		240 mg and 960 mg QD	
Exposure Metrics Explored (range)		The sotorasib exposure metrics evaluated as predictors of ER were model predicted AUC_{tau}, C_{max}, and C_{trough}, at steady-state, generated using the reference sotorasib population pharmacokinetic model depending on the respective subjects planned sotorasib dose, regimen, and PK covariates.	
Covariates Evaluated		Covariates included in the ER analyses were country, age, weight, race, ethnicity, Eastern Clinical Oncology Group (ECOG) performance status, smoking status (never, current, or former), number of prior anticancer therapies, sum of target lesion diameters, chronic kidney disease, glomerular filtration rate, liver function, ALT, AST, total bilirubin (TBIL) and albumin level at baseline	
Final Model Parameters		**Summary**	**Acceptability [FDA's comments]**
Model Structure		Cox proportional hazard: PFS, OS, DOR Logistic regression: ORR, DCR Linear regression: TTR, BTSR	Yes
Model Parameter Estimates		Univariate: Appendix 3 Table 1 Multivariate: Appendix 3 Table 2	Yes
Model Evaluation		A stepwise method was used for model selection based on Bayesian Information Criterion (BIC) for adequate parsimony. Exposure metrics and/or covariates not reducing BIC were excluded from the model in a stepwise variable selection process. P-values in models attempted were assessed by Wald test. Associations were considered significant if the p-value was less than 0.05.	Yes

Covariates and Clinical Relevance	Baseline sum of lesion diameters, body weight and liver function were significant covariates for the relationship of $C_{trough,ss}$ with the tested efficacy endpoints. The independent effect of baseline disease burden on both pharmacokinetics and efficacy outcomes (OS, PFS, ORR, DCR, and BTSR) limited the ability to interpret the results from multivariate regression analyses.	Yes
Simulation for Specific Population	N/A	N/A
Visualization of E-R relationships	Main text Figures 2 - 7 Appendix 2 Figures 3 - 9	Yes
Overall Clinical Relevance for ER	Higher baseline disease burden was independently associated with higher sotorasib exposure and poorer clinical response. The independent effect of baseline disease burden on pharmacokinetics and efficacy outcomes (PFS, OS, DOR, ORR, DCR, TTR and BTSR) limited the ability to interpret the ER relationships for sotorasib. This effect of baseline disease status on both sotorasib PK and efficacy makes the ER relationship uninformative.	Yes
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics		Yes. No update from the previous labeling

19.4.2.3. ER (safety) Executive Summary

The FDA's Assessment:

E-R analysis for safety is inconclusive due to confounding effect (e.g., baseline disease) and could not inform dose selection for the narrow and comparable exposure range achieved with 240 mg and 960 mg QD.

19.4.2.4. ER (safety) Assessment Summary

The Applicant's Position:
[Highlight the key findings in the white cells.]

General Information		
Goal of ER analysis		To characterize the ER relationships between sotorasib exposures and selected safety events: Grade 3+ overall treatment-related adverse events (TRAEs), Grade 3+ overall treatment-emergent adverse events (TEAEs), and specific Grade 3+ TEAEs of interest, including GI disorders, diarrhea, ALT increase, AST increase, hepatotoxicity based on standardized MedDRA queries (SMQ) narrow and explore factors that could impact ER relationship for safety in the CRC patient population.
Study Included		Phase 1b study 20190135 and Phase 3 study 20190172 which included the population of interest
Population Included		Patients with previous treated advanced colorectal cancer (CRC) with KRAS p.G12C mutation
Endpoint		Grade 3+ overall treatment-related adverse events (TRAEs), Grade 3+ overall treatment-emergent adverse events (TEAEs), and specific Grade 3+ TEAEs of interest, including GI disorders, diarrhea, ALT increase, AST increase, hepatotoxicity based on standardized MedDRA queries (SMQ) narrow
No. of Patients (total, and with individual PK)		164
Population Characteristics (Table XX)	General	Age median (range): 59 (30-82) Weight median (range): 66.0 (39, 146) 74 (45.1%) male 105 (64%) White 4 (2.44%) Black or African American 46 (28%) Asian 9 (5.49%) Others
	Organ impairment	Hepatic function (NCI); Mild: n=44 (26.8%)

		Moderate: n=4 (2.44%) Renal function (CKD on eGFR); GFR C ≥60: n=80 (48.8%) GFR C ≥30: n=13 (7.93%)
	Pediatrics (if any)	None
	Geriatrics (if any)	Age ≥ 75; n = 16 (9.76)
Dose(s) Included		240 mg and 960 mg QD
Exposure Metrics Explored (range)		The sotorasib exposure metrics evaluated as predictors of ER were model predicted AUC_{tau}, C_{max}, and C_{trough}, at steady-state, generated using the reference sotorasib population pharmacokinetic model depending on the respective subjects planned sotorasib dose, regimen, and PK covariates.
Covariates Evaluated		Covariates included in the ER analyses were country, age, weight, race, ethnicity, Eastern Clinical Oncology Group (ECOG) performance status, smoking status (never, current, or former), number of prior anticancer therapies, sum of target lesion diameters, chronic kidney disease, glomerular filtration rate, liver function, ALT, AST, total bilirubin (TBIL) and albumin level at baseline.
Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	Logistic regression: binary AE endpoints	Yes
Model Parameter Estimates	Univariate: Appendix 5 Table 3 Multivariate: Appendix 5 Table 4	Yes
Model Evaluation	A stepwise method was used for model selection based on Bayesian Information Criterion (BIC) for adequate parsimony. Exposure metrics and/or covariates not reducing BIC were excluded from the model in a stepwise variable selection process. P-values in models attempted were assessed by Wald test. Associations were considered significant if the p-value was less than 0.05.	Yes

Covariates and Clinical Relevance	In the multivariate regression analysis, smoking status emerged as a significant factor for grade 3+ TEAEs related to gastrointestinal disorders. However, the clinical relevance of this finding is considered low due to the small number of subjects and events involved	Yes
Simulation for Specific Population	N/A	Yes
Visualization of E-R relationships	Main text: Figures 8 – 13 Appendix 4: Figures 10 – 15	Yes
Overall Clinical Relevance for ER	Significantly positive ER relationships were only identified for grade ≥ 3 adverse events and grade ≥ 3 GI adverse events. No significant ER relationship was found for overall grade ≥ 3 treatment-related adverse events, including specific grade ≥ 3 treatment-emergent adverse events of interest such as diarrhea and hepatotoxicity. Due to the small number of observations (event number ≤ 1) for grade ≥ 3 AST or ALT increase, no positive ER relationships for these events were observed. Ability to assess ER relationships was limited by the independent effects of baseline disease severity (quantified by baseline tumor size, ECOG status) on sotorasib exposure and safety	Yes
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics		Yes. No update from the previous labeling.

The FDA's Assessment:
FDA agrees with the E-R analysis conducted by Applicant.

19.4.2.5. ER Review Issues

Figure/table numbers in Section 19.4.2.2 ER (efficacy) Assessment Summary or 19.4.2.4 ER (safety) Assessment Summary were referenced from the Applicant's E-R report 157508. The key figures/tables were hereby attached by the Reviewer below.

In multivariate regression analysis for efficacy (Table 56), ORR, PFS, OS, and best tumor response were found to have an inverse relationship with steady-state C_{trough}, suggesting that efficacy improvement is not associated with exposure increase in patients receiving 240 mg or 960 mg QD dosages. In multivariate regression analysis for safety (Table 56), Gr≥3 TEAE and Gr≥3 GI disorders were found to have a positive relationship with steady-state C_{trough}, while other safety endpoints, Gr≥3 TRAE and Gr≥3 TEAE of interest (i.e., diarrhea, hepatotoxicity, AST/ALT elevation), were not observed to increase with exposure. Due to similar exposures between the two dosages, E-R analysis is not informative for dosage optimization.

Table 56. Results of univariate regression analyses for efficacy.

Response Variable	Predictor Variable	Estimate	Standard Error	P-value
	Multivariate Cox Regression Analysis			
Progression Free Survival, PFS	LN($C_{trough,ss}$)	0.422	0.0994	2.21E-05
	NCIODWG Mild vs. Normal	0.770	0.221	0.000498
	NCIODWG Moderate vs. Normal	-0.641	1.01	0.527
Overall Survival, OS	LN($C_{trough,ss}$)	0.631	0.124	3.73E-07
	WTKG	-0.0293	0.00732	6.33E-05
	Sum of Target Lesion Diameters	0.00659	0.00206	0.00136
	Multivariate Logistic Regression Analysis			
Overall Response Rate, ORR	WTKG	0.0258	0.00979	0.00849
Disease Control Rate, DCR	LN($C_{trough,ss}$)	-0.635	0.233	0.00646
	Multivariate Linear Regression Analysis			
Best Tumor Size Response, BTSR	LN($C_{trough,ss}$)	7.46	2.92	0.0117

Source: Applicant E-R report 157508 Appendix 3 Table 2.

Table 57. Results of multivariate regression analyses for safety.

Response Variable	Predictor Variable	Estimate	Standard Error	P-value
	Multivariate Logistic Regression Analysis			
All Grade 3+ TEAE	LN($C_{trough,ss}$)	0.443	0.199	0.0259
Grade 3+ TEAE of GI-disorders	LN($C_{trough,ss}$)	0.751	0.265	0.00455
	SMCATSCR: Former smoker vs. Current smoker	-2.67	0.878	0.00234
	SMCATSCR: Never smoke vs. Current smoker	-1.33	0.688	0.0529

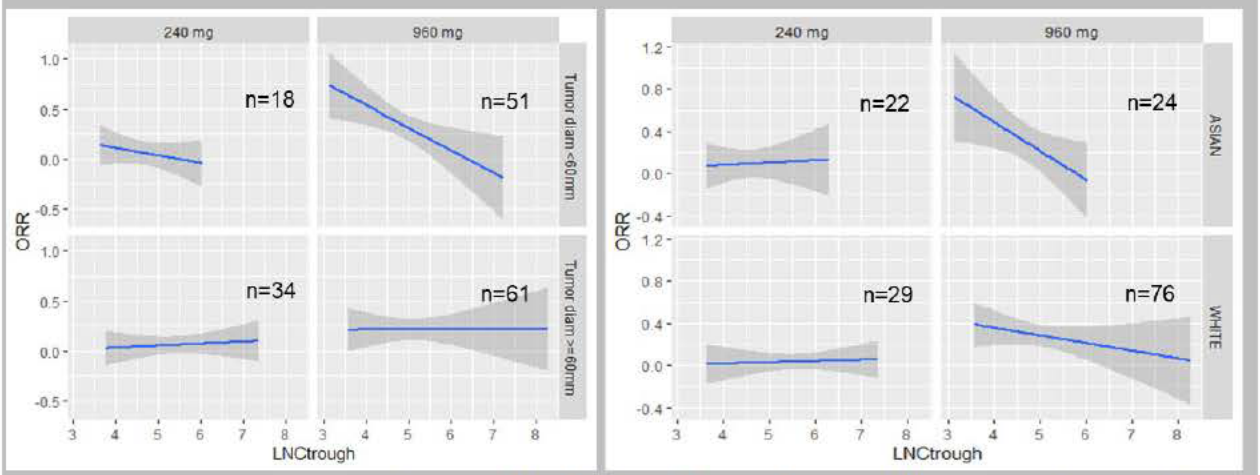
Source: Applicant E-R report 157508 Appendix 5 Table 4.

19.4.2.6. Reviewer's Independent Analysis

A large difference in ORR was observed between 240 mg and 960 mg in CodeBreak 300 (ORR: 6% vs 26%) that could not be attributed to exposure difference. Therefore, apart from multivariate analysis that evaluates the main effect with linear combination, the possible interaction between exposure and specific factors of interest was further examined via graphical exploration. The two factors of interest are baseline tumor size, a confounder that impacts both sotorasib's clearance and clinical efficacy, and Asian race which is found imbalanced between the randomized arms of two sotorasib dosages.

As shown in Figure 12, there was no apparent positive E-R relationship observed in any of the subgroups dichotomized by baseline tumor size or categorized by race. The probability of ORR is generally higher in 960 mg arm than 240 mg arm especially at lower exposures. This suggests the higher ORR observed in 960 mg arm is unlikely to be related to higher exposure, regardless of patients' baseline tumor size or whether they are Asian or White. The subgroups that showed a prominent inverse trend are those with baseline tumor size <60mm and/or Asian who were treated with 960 mg sotorasib. The factors that contribute to the ORR difference between the two dosages are unknown.

Figure 12. Relationship between ORR and Ctrough by baseline tumor size or race.



Source: Reviewer's analysis. Linear trend was plotted. Races other than Asian and White were not included due to small sample size

19.4.2.7. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

Overall, sotorasib PK and ER relationships were consistent with those observed in data that supported the original marketing application for the treatment of patients with previously treated *KRAS p.G12C*-mutated NSCLC.

Higher baseline disease burden was independently associated with higher sotorasib exposure and poorer clinical response. Significantly positive ER relationships were identified for overall grade 3+ treatment-emergent adverse events and grade 3+ GI treatment-emergent adverse events. No significant ER relationships were found for overall grade 3+ treatment-emergent adverse events or specific grade 3+ treatment emergent adverse events of interest such as diarrhea and hepatotoxicity. Due to the small number of observations (event number ≤ 1) for grade ≥ 3 AST or ALT increase, positive ER relationships for those events were not observed. Ability to assess ER relationships was limited by the independent effects of baseline disease severity (quantified by baseline tumor size, ECOG performance status) on sotorasib exposure, efficacy, and safety.

Therefore, the ER analysis supports the current approved sotorasib 960 mg dose for patients with *KRAS p.G12C*-mutated mCRC.

The FDA's Assessment:
The PK and ER relationship in general support the approval of the 960 mg QD dose of sotorasib but could not differentiate 960 mg from 240 mg. The acceptability of 960 mg is primarily based on the clinical benefit-risk analysis.

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:
None.

Signatures, NDA 214665/S-009/ Lumakras (sotorasib), BLA 125147 S-213/Vectibix (panitumumab)

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Yue Xiang, PharmD	CDER/OTS/OCP/DCPI	Sections: 6	**Select one:** x Authored _Approved
	Signature: Yue Xiang -S Digitally signed by Yue Xiang -S Date: 2025.01.14 08:25:56 -05'00'			
Clinical Pharmacology Team Leader	Jason Moore, PharmD	CDER/OTS/OCP/DCPII	Sections: 6	Select one: _Authored x Approved
	Signature: JASON N. MOORE JR -S Digitally signed by JASON N. MOORE JR -S Date: 2025.01.14 11:57:54 -05'00'			
Pharmacometrics Reviewer	Ye Xiong, PhD	CDER/OTS/OCP/DPM	Sections: 6, 19.4	**Select one:** x Authored _Approved
	Signature: Ye Xiong -S Digitally signed by Ye Xiong -S Date: 2025.01.14 12:32:13 -05'00'			
Pharmacometrics Reviewer Team Leader	Youwei Bi, PhD	CDER/OTS/OCP/DPM	Sections: 6, 19.4	**Select one:** x Authored _Approved
	Signature: Youwei Bi -S Digitally signed by Youwei Bi -S Date: 2025.01.14 12:40:06 -05'00'			
Division Director	Nam Atiqur Rahman, PhD	CDER/OTS/OCP/DCPII	Sections: 6	**Select one:** x Approved
	Signature: NAM A. RAHMAN -S Digitally signed by NAM A. RAHMAN -S Date: 2025.01.15 11:23:25 -05'00'			
Pharmacology/ Toxicology Reviewer/TL	Matthew Thompson, PhD	CDER/DHOT	Sections: 5	**Select one:** x Authored x Approved
	Signature: Matthew D. Thompson -S Digitally signed by Matthew D. Thompson -S Date: 2025.01.14 14:16:24 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Reviewer	Sirisha Mushti, PhD	CDER/OTS/OB/DBV	Sections: 7, 8.1, 8.3 and 1, 8.4	**Select one:** x Authored x Approved
	Signature: Sirisha Mushti -S Digitally signed by Sirisha Mushti -S Date: 2025.01.14 14:50:13 -05'00'			
Statistical Team Leader	Chi Song, PhD	CDER/OTS/OB/DBV	Sections: 1, 7, 8.1, 8.3 and 8.4	**Select one:** _Authored x Approved
	Signature: Chi Song -S Digitally signed by Chi Song -S Date: 2025.01.14 14:55:19 -05'00'			
Deputy Division Director (OB)	Pallavi Mishra-Kalyani, PhD	CDER/OTS/OB/DBV	Sections: 1, 7, 8.1, 8.3 and 8.4	**Select one:** x Approved
	Signature: Pallavi S. Mishra-kalyani -S Digitally signed by Pallavi S. Mishra-kalyani -S Date: 2025.01.14 14:59:06 -05'00'			
Clinical Reviewer	May Tun Saung, MD	CDER/OND/OOD/DO3	Sections: 2, 3, 4.1, 4.4, 7, 8, 9, 10, 12, 13, 19.1, 19.2	**Select one:** x Authored _Approved
	Signature: May Tun Saung -S Digitally signed by May Tun Saung -S Date: 2025.01.14 16:41:20 -05'00'			
Clinical Team Leader	Jamie Brewer, MD	CDER/OND/OOD/DO3	Sections:	**Select one:** x Authored x Approved
	Signature:			
Associate Director for Labeling (ADL)	Doris Auth, Pharm D	OCE	Sections: All	**Select one:** _Authored x Approved

	Signature: Doris Auth -S Digitally signed by Doris Auth -S Date: 2025.01.14 19:02:04 -05'00'			
Cross-Disciplinary Team Leader (CDTL)	Jamie Brewer, MD	CDER/OND/OOD/DO3	Sections: All	**Select one:** x Authored x Approved
	Signature:			
Deputy Division Director (Clinical)	Chana Weinstock, MD	CDER/OND/OOD/DO3	Sections: All	**Select one:** x Approved
	Signature:			

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/s/

JAMIE R BREWER
01/15/2025 05:21:48 PM

CHANA WEINSTOCK
01/15/2025 05:40:33 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214665Orig1s009

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-214665-SUPPL-009
   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	04/17/2024	04/17/2024	04/24/2024	10/17/2024	08/05/2024

3. **Provides For:**
   - to propose an indication of (b) (4)

4. **Review #**: 01

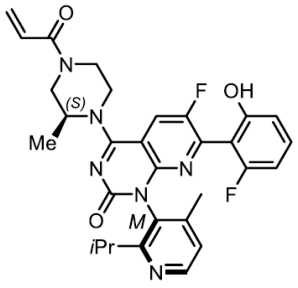
5. **Clinical Review Division**: OOD/DO2

6. **Name and Address of Applicant**:
   AMGEN INC.
   One Amgen Center Drive
   Mail Stop: 27-3-A
   Thousand Oaks, CA 91320-1799
   Contact: Stephanie Hansen
   PH: (805) 234-7002
   Email: shanse01@amgen.com

7. **Drug Product**:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product	Orphan Designation
LUMAKRAS (sotorasib) tablets	Tablets	120 mg, 320 mg	oral	Rx	Yes	18-6549

8. Chemical Name and Structure of Drug Substance:

	**USAN**: sotorasib **Chemical name**: 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1M)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2S)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]pyrido[2,3-d]pyrimidin-2(1H)-one **Molecular formula**: $C_{30}H_{30}F_2N_6O_3$ **MW**: 560.6

9. Indication: [redacted] (b) (4)

10. Supporting/Related Documents: None.

11. Disciplines/Consults: none

12. Executive Summary:

This supplement is Real Time Oncology Review PRE-SUBMISSION NO. 3 and the final submission. This submission therefore includes documents and datasets previously submitted as part of Real-Time Oncology Review (RTOR) Pre-submission No. 1 (SN0143) and Pre-submission No. 2 (SN0146), which have been revised with the PFS and safety re-analysis.

This efficacy supplement is submitted to propose an indication of sotorasib in combination with panitumumab for [redacted] (b) (4)

The applicant has claimed categorical exclusion from the determination of an environmental assessment. As per the applicant, for the approved indication, the revised estimated concentration of sotarasib, the active ingredient, at the point of entry into the aquatic environment (EIC, Expected Introductory Concentration) is below 1 part per billion (ppb). Amgen is not aware of any extraordinary circumstances that exist for this product, as referenced in 21 CFR §25.21(a) or 21 CFR §25.21(b) that require submission of an EA. Based on the calculation provided in the FDA (1998) Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications, the revised EIC for sotarasib was updated and recalculated from the highest annual amount projected to be produced in the next five years for the treatment of advanced solid tumors. The EIC (aquatic) = [redacted] (b) (4) ppb which is significantly less than 1 ppb. Therefore, the request for categorical exclusion may be granted as per 21 CFR Part 25.31 (b).

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

From a CMC perspective the changes proposed in S009 are acceptable.

13. Conclusions & Recommendations:

This supplement is recommended for approval.

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

15. Primary Reviewer:
Qi Liu, Ph.D., CMC reviewer, Branch 1, DPMAI, OLDP, OPQ

16. Secondary Reviewer:
Rohit Kolhatkar, Ph.D., SPQA, Branch 1, DPMAI, OLDP, OPQ

Qi Charles Liu

Digitally signed by Qi Charles Liu
Date: 8/05/2024 01:24:57PM
GUID: 53b4299e000120abe375af2240eda3f5

Rohit Kolhatkar

Digitally signed by Rohit Kolhatkar
Date: 8/06/2024 02:26:00PM
GUID: 57bf531500b52a2eccd5395bec77ebc2
Comments: concur with approval recommendation

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214665Orig1s009

OTHER REVIEW(S)

Clinical Inspection Summary

Date	October 16, 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	May Tun Saung, MD, Clinical Reviewer Jamie Brewer, MD, Clinical Team Leader Nataliya Fesenko, Regulatory Project Manager Division of Oncology 3 (DO3)
NDA #	sNDA 214665, Supplement 9
Applicant	Amgen Inc.
Drug	Sotorasib
NME (Yes/No)	No
Therapeutic Classification	KRAS p.G12C inhibitor
Proposed Indication	(b) (4) [redacted]
Consultation Request Date	May 15, 2024
Summary Goal Date	November 7, 2024
Action Goal Date	January 17, 2024
PDUFA Date	January 17, 2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The Applicant, Amgen, Inc., submitted clinical data from Study 20190172 (NCT05198934) to the Agency in support of a supplemental New Drug Application (sNDA 214665, S9) for sotorasib in combination with panitumumab. The proposed indication is (b) (4) [redacted]

The imaging contract research organization (CRO), (b) (4), and two foreign clinical investigators (CIs), Drs. Meriggi and Salvatore, were inspected.

The inspection of the imaging CRO, (b) (4), revealed no significant discrepancies, regulatory violations, or Good Clinical Practice (GCP) noncompliance. The inspection of Dr Meriggi identified enrollment of two ineligible subjects, including one that received exclusionary prior chemotherapy (i.e., trifluridine and tipiracil and intermittent regorafenib). Apart from this finding, based on the results of these inspections, data generated by Dr. Meriggi and by the imaging CRO and submitted by the Applicant appear acceptable in support of the proposed indication.

At the site of Dr. Salvatore, the efficacy data appear acceptable. The safety data, however, are deemed unreliable due to multiple fraudulent activities committed by a clinical research associate (CRA). OSI recommends removal of the entire safety data obtained at Dr. Salvatore's site from the study analysis. See below for details.

On July 15, 2024, the Sponsor informed the FDA of an investigation into GCP violations, specifically fraudulent activities, at Dr. Salvatore's site that were identified in preparation for FDA's onsite CI inspection. To obtain more information, OSI sent four information requests (IRs), and received responses from the Sponsor on July 22, July 31, August 14, and September 16, 2024. The totality of the inspection findings and IR responses identified three types of fraud committed by a CRA employed by a CRO, who was responsible for study monitoring at Dr. Salvatore's site: (1) signature and document forgery on paper source documents, (2) unauthorized access to 3 study electronic systems using fraudulent user accounts created with fake email addresses. These study electronic systems accessed by the CRA included the Medidata RAVE Electronic Data Capture system (Medidata) and (b) (4) system, which housed the imaging data for the primary efficacy endpoint assessment, and (3) unauthorized access to the (b) (4) system through stolen/borrowed login credentials of a site radiology technician.

OSI reviewed the imaging data flow and audit trail summaries for the (b) (4) system submitted by the Sponsor and determined that the imaging data in the (b) (4) system, which were rated by the Blinded Independent Central Review (BICR), appear unimpacted by the fraudulent email accounts. However, because this CRA also used existing legitimate credentials and accessed the (b) (4) system at the site level, audit trails cannot distinguish his actions from those conducted by the legitimate user. To assess the potential impact, OSI reviewed additional findings from the Sponsor-conducted site data audit and identified no apparent discrepancies in the imaging data transferred from the site to the central imaging CRO or the quality control (QC) responses that would impact the overall interpretation of efficacy. Therefore, the efficacy data generated by Dr. Salvatore's site appear acceptable in support of the proposed indication.

However, the safety data generated at Dr. Salvatore's site are deemed unreliable. Specifically, the signature and document forgery impacted 6 enrolled subjects over approximately 2 years, with the majority of impacted records consisting of complete electronic medical record (EMR) visit notes documenting safety data such as adverse events

(AE), vital signs, physical examinations as well as concomitant medications. Since the EMR used by the site is unvalidated, there is no way to verify the forged records, and therefore, these safety data are unverifiable. In addition, the two fraudulent accounts conducted 6,228 audit actions in the Medidata system impacting 11 subjects at this site across a range of Case Report Form (CRF) domains (i.e., screening assessments, commitment medications, safety assessments, etc.). All source records impacted by forgeries cannot be used to verify these altered EDC data entries. Finally, while OSI did not have evidence that the site's EMR was also breached, because the site's unvalidated EMR lacks both an audit trail and timestamped signatures, we cannot exclude the possibility of additional unauthorized access to the EMR, potentially making all paper source documents unverifiable. Therefore, based on the extent of these fraudulent activities, OSI recommends removal of safety data obtained at Dr. Salvatore's site from the study analysis.

II. BACKGROUND

Lumakras (sotorasib) was granted accelerated approval by FDA for treatment of adult patients with *KRAS p.G12C*- mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) who have received at least 1 prior systemic therapy. On April 17, 2024, Amgen submitted sNDA 214665/S9 seeking full approval of sotorasib in combination with panitumumab for the treatment of (b) (4) based on the safety and efficacy results from Study 20190172.

Study Design

Study 20190172 is an ongoing, phase 3, multicenter, randomized, open-label, active-controlled study evaluating efficacy and safety of sotorasib and panitumumab in previously treated mCRC subjects with prospectively identified *KRAS p.G12C* mutation.

The study consisted of a screening period, a treatment period, a safety follow-up (SFU), and a long-term follow-up (LTFU) period. Following the 28-day screening period, the study equally randomized eligible subjects (1:1:1) to one of the following 3 treatment arms:

1. Sotorasib 960 mg once daily (QD) + panitumumab (Soto960 + Pmab)
2. Sotorasib 240 mg QD + panitumumab (Soto240 + Pmab)
3. Investigators' choice chemotherapy (trifluridine/tipiracil, or regorafenib), with the choice declared prior to randomization (ICC).

Randomization was stratified by prior anti-angiogenic therapy (yes or no), time from initial diagnosis of metastatic disease to randomization (≥ 18 months, <18 months), and Eastern Cooperative Oncology Group (ECOG) status (0 or 1 vs 2). Subjects received study treatment until blinded independent central review (BICR) assessed progression, start of another anticancer therapy, withdrawal of consent, loss to follow-up, or death, whichever occurred

first. Subjects were allowed to continue sotorasib alone upon panitumumab discontinuation if the patient was considered to be deriving clinical benefit by the investigator, but if sotorasib was discontinued for any reason, panitumumab was also discontinued.

Endpoints

- *Primary endpoint*: PFS assessed using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 per BICR.
- *Key secondary efficacy endpoints*: Overall survival, Objective response rate (ORR)
- *Other secondary efficacy endpoints:* Duration of response (DOR), time to response (TTR), disease control rate (DCR)

The final analysis of efficacy was based on BICR of tumor scans.

Study Status
As of the data cut-off of June 19, 2023, the study enrolled the following subjects across 67 study centers, across countries in Asia, Europe, North America, and Australia.

Safety population:	N= 157
Efficacy population:	N= 160

Dr. Fausto Meriggi (Site 33002 / 12500), Dr. Lisa Salvatore (Site 33013 / 64380), and the imaging CRO (b) (4) were inspected.

III. RESULTS

1. **Dr. Fausto Meriggi (Site 33002 / 12500)**
   Via Bissolati 57
   Unità Operativa Oncologia Medica
   Brescia, NA 25124
   Italy

Inspection Dates: July 29 to August 2, 2024

The investigator was inspected as a routine PDUFA inspection for Study 20190172. This was the first FDA inspection for this investigator.

As of the data cutoff date (June 19, 2023), the site screened 10 subjects, and 9 subjects were enrolled and received treatment. At the time of the inspection, one subject remained on treatment and 2 subjects were in long-term follow-up.

The inspection reviewed the following subject-related source documents, as applicable, for all 9 enrolled subjects: ICFs, medical history records, laboratory results, printed visit notes, electronic diary entries, and infusion records.

The inspection reviewed the following study-related documents: site training, site delegation log, ethics committee approvals, screening and enrollment log, protocol, and amendments, ICFs, protocol deviations, site monitoring log and correspondences, safety reporting, calibration and temperature records, financial disclosures, IP accountability, electronic systems, and records retention.

The inspection verified that CT scans for the primary efficacy endpoint were performed at the protocol specified time points and uploaded to the imaging portal for central review.

Comparison of source records to the data listings (i.e., AEs, concomitant medications, subject disposition, treatment received, vital signs, and laboratory results) for all enrolled subjects identified no discrepancies.

The inspection identified two subjects that were enrolled but did not meet enrollment criteria:

1) Subject (b) (6) was enrolled and randomized to the Soto960 + Pmab arm despite meeting exclusion criterion 212, "Subjects have received Trifluridine and Tipiracil or Regorafenib in the past."

   Reviewer comment. *Subject (b) (6) received both trifluridine and tipiracil in (b) (6) and (b) (6), and intermittent regorafenib beginning in (b) (6). Despite the prior treatments, the subject was randomized to the study on (b) (6), and the protocol deviation was not identified nor reported prior to the data cutoff (documented as a protocol deviation on (b) (6)).*

   In response to the observation, dated August 2, 2024, Dr. Meriggi stated that he did not consider the duration and dosage of regorafenib therapy sufficient for exclusion (i.e., 1-month supply taken intermittently over a 4-month period due to AEs). As Subject (b) (6) was randomized to the Soto960 + Pmab arm, the prior therapies were unlikely to impact the safety evaluation for this subject. OSI defers to the Review Division regarding the potential impact of the prior therapies on the subject's eligibility and the interpretation of efficacy. The site's proposed root cause analysis and corrective / preventive actions are acceptable.

2) Subject (b) (6) was randomized and received study drug prior to the investigator's review of all screening lab results. The subject was ineligible due to an exclusionary screening bilirubin level per Inclusion Criterion 109.

   Reviewer comment. *The subject had Gilbert's disease and a screening total bilirubin level of 2.4 mg/dL (2.0 x ULN), which did not meet Inclusion Criterion 109 specifications for subjects with Gilbert's disease. After identification of the abnormal lab, the site reported the deviation and obtained permission from the Sponsor to keep the subject in the study. The site's response to the observation dated August 2, 2024,*

appears reasonable, and overall, this protocol deviation did not appear to impact subject safety, as the remainder of the bilirubin lab tests remained <ULN with the exception of mild elevation on Cycle 8 Day 1 (1.4 mg/dL).

Based on the results of the inspection, Study 20190172 data generated at Dr. Meriggi's site appear acceptable in support of the proposed indication in the sNDA.

2. Dr. Lisa Salvatore (Site 33013 / 64380)
Largo Gemelli, 8, Unita Operativa Complessa
Oncologia Medica
Roma, NA 168
Italy

Inspection Dates: July 22, 2024, to July 26, 2024

This investigator was inspected as a routine PDUFA inspection for Study 20190172. This was the first FDA inspection for this investigator.

As of the data cut-off (June 19, 2023), there were 13 subjects screened and 10 subjects enrolled and treated with IP. At the time of the data cutoff, 5 subjects were on treatment and 1 was on treatment beyond progression. The site currently has 2 active subjects on treatment.

The inspection reviewed subject-related source documents for all 10 subjects, including informed consents, medical history notes, study visit notes, laboratory results, CT reports, infusion, and PK records.

Study-related records reviewed included the protocol and amendments, protocol signature pages, screening and enrollment log, site delegation log, CVs, ICFs and amendments, ethics committee approvals, storage and maintenance of IP, electronic systems, Financial Disclosures, clinical site training records, records custody, and monitoring log. Additional study-related processes reviewed included central submission of scans, electronic records system access, and AE reporting.

***Reviewer comment**. The clinic site EMR, TrackCare, is an electronic system that allows clinical reports to be written in digital format and printed for signature, including the following information: concomitant medications, vital signs, weight, physical examinations, and AEs. Additional information including lab and imaging data are read only in the TrackCare EMR. The TrackCare is an unvalidated EMR due to absence of audit trails, absence of electronic / digital signatures, and lack of ability to create certified copies of the EMR. To address this issue, the Sponsor's standard operating procedure (SOP) for source document record keeping relied on creation of certified paper copies created by principal investigator (PI)/Sub-investigator (SI) handwritten signature and date of printed EMR pages, certifying that all pages are an accurate representation of the patient data. The printed EMR pages required the signature of the PI or SI creating them to verify that the printed record is an accurate representation of the data. This approach appears acceptable for the creation of a certified copy for the*

purpose of record retention (see FDA Guidance: Part 11, Electronic Records; Electronic Signatures - Scope and Application).

The inspection verified all CT scans were performed and uploaded for central review for all subjects. No unreported protocol deviations were identified.
The inspection, however, identified discrepancies in AEs (Table 1):

Table 1. AE Discrepancies Identified During Inspection at Site 33013 / 64380

Subject ID	AE Discrepancy	Grade	Description
(b) (6)	unreported	1	folliculitis, related to panitumumab
	unreported	1	hypomagnesemia on lab results from (b) (6)
	incorrect start date	2	anemia ((b) (6) → (b) (6)).
	incorrect start date	2	hypomagnesemia ((b) (6) → (b) (6)).
	unreported	3	hypokalemia on lab results from (b) (6)
		2	hypocalcemia on lab results from (b) (6)
	unreported	2	anemia on visit notes from (b) (6) to (b) (6)
Gray: unreported, new incident AE for subject			

Reviewer comment. *Four additional unreported AEs were identified that represent new incident AEs for the respective subjects in the AE dataset. However, the AEs related to laboratory events were captured in the laboratory dataset.*

Fraudulent Activities

On July 15, 2024, the Sponsor informed the FDA of an ongoing investigation into GCP violations, specifically fraudulent activities, at Site 33013 that were identified in preparation for the FDA's onsite CI inspection. Subsequently, OSI sent the following four IRs to obtain more information regarding the fraudulent activities at Site 33013.

Table 2. Dates of FDA Information Requests and Sponsor's Responses

FDA IR	Date IR Sent	Date Response First Received (Email)
#1	7/18/2024	7/22/2024
#2	7/26/2024	7/31/2024
#3	8/7/2024	8/14/2024
#4	8/27/2024	9/16/2024
#5	10/8/2024	10/11/2024
IR: information request		

Additionally, OSI and the Review Division had a teleconference with the Sponsor on August 26, 2024.

The totality of the inspection findings and IR responses identified three types of fraud committed by a CRA employed by the CRO who was responsible for clinical site monitoring at Site 33013:

- Fraud 1: Signature and document forgery for 3 sub-investigators (SIs) on paper source documents (i.e., signed printed EMR documents) impacting a total of 6 subjects.

- Fraud 2: Unauthorized access to 3 study electronic systems using fraudulent user accounts created with fake email addresses impersonating 2 site SIs: (b) (4) , Medidata RAVE Electronic Data Capture system (Medidata), and Signant Health Trial Manager (Signant Health).

- Fraud 3: Unauthorized access to (b) (4) system using stolen/borrowed login credentials of a radiology technician.

The following section discusses OSI's review of each fraudulent activity.

> ***Reviewer comment***. *CRA monitored two additional sites (Sites 33010 and 33020) in the same trial that enrolled a total of 5 subjects. While the FDA did not conduct CI inspections for these sites, in light of the fraudulent activities at Site 33013, OSI requested the Sponsor to conduct source document and imaging data audits at these sites to investigate for potential evidence of fraud.* [1] *OSI reviewed the Sponsor's data audit, and the following section briefly discusses these findings for Sites 33010 and 33020 under the relevant discussions below.*

Fraud 1: Signature and Document Forgery

On June 14, 2024, the CI notified the Sponsor and CRO after discovering forged signatures on final paper source documents for two subjects ((b) (6) and (b) (6)). Additional review of all paper source records at Site 33013 determined that signature forgery impacted 6 subjects, of which 4 cases also included document forgery (i.e., written data entries) by the individual portraying to be a SI (Table 3):

[1] Response to IR #4, see Table 2

Table 3. Summary of Forged Subject Records at Site 33013

Subject ID (arm)	Date	Description of Impacted Data	Forgery Type
(b) (6)		All C2D1 visit data printed from EMR	Signature
		All C3D1 visit data printed from EMR	Signature
		All C3D15 visit data printed from EMR	Signature
		All visit C4D15 data printed from EMR	Signature
		Corrected VS body position	Signature + data entry
		All C5D1 visit data printed from EMR	Signature
		All C7D1visit data printed from EMR	Signature
		Time of sotorasib administration, C7D15	Signature + data entry
		All C8D1 visit data printed from EMR	Signature
		All C8D15 visit data printed from EMR	Signature
		All C19D1 visit data printed from EMR	Signature
		All C21D15 visit data printed from EMR	Signature
		Entered grade (2) for thrombocytopenia AE	Signature + data entry
		Entered eligibility confirmation	Signature + data entry
		All C3D1 visit data printed from EMR	Signature
		GCP correction for typo at C3D15	Signature + data entry
		All EOT visit data printed from EMR	Signature
		All C7D1 visit data printed from EMR	Signature
		All C3D15 visit data printed from EMR	Signature
		Addendum to accounting C6D1	Signature + data entry
		GCP correction to accounting C6D15	Signature + data entry
		Entered AE mild dyspnea (incorrect stop date)	Signature + data entry
		Entered AE correlation with panitunumab	Signature + data entry
		All C13D15 visit data printed from EMR	Signature
		IP accountability C3D1	Signature + data entry
		IP accountability C5D1	Signature + data entry

C: cycle; D: day; EMR: electronic medical record; GCP: good clinical practice; ID: identification; IP: investigational product
Shaded red: unverifiable.
Source: Data from Appendix 1, IR response #1 and Table 4 of IR response #3, see Table 2

Reviewer comment. *The forgery impacted 6 of 9 enrolled subjects at Site 33013 over approximately 2 years. A majority of the impacted records included visit notes consisting of safety data such as concomitant medications, vital signs, AEs, and physical examinations. In response to the forgery, the site attempted to verify all data on the paper source documents by leveraging additional available records (i.e., site EMR, IP accountability logs, laboratory reports). However, because the site EMR is unvalidated, the EMR cannot be leveraged as a "source document" to verify the accuracy of these*

data. Therefore, any safety data relying on the EMR for verification are deemed unreliable (i.e., all rows shaded red in Table 3).

Addendum for Sites 33010 and 33020:

In response to FDA IR #4, the Sponsor conducted an audit of Sites 33010 and 33020, on September 3-4, 2024, and August 29-30, 2024, respectively.[2] The Sponsor's audit of paper source records did not identify evidence of signature or document forgery for the 5 subjects enrolled at these two sites. However, the Sponsor's Source Data Verification (SDV) identified 27 discrepancies with the eCRF across 3 enrolled subjects at Site 33020:

Table 4. Summary of Data Discrepancies by Subject at Site 33020

Subject ID (arm)	Data Category	High Level Description of Audit Trail Action
(b) (6)	AE	• **Periungual toxicity, G1, nonserious, (b) (6) to (b) (6)** • Rash face, G1, nonserious, (b) (6) to (b) (6) **(corrected end date)**
	Screening	• Cancer Hx: correction colorectal cancer diagnosis date of (b) (6), pT4a N2bM1c
	CM	• Prophylaxis medications for panitumumab (dexamethasone, pantoprazole, chlorphenamine)
	AE	• **Constipation, G3, (b) (6) to (b) (6)** • **Pain, G3, (b) (6) to (b) (6)** • **Ascites, G3, (b) (6) to (b) (6)** • **Nail fissure, G1, (b) (6) to (b) (6)** • **Emesis, G1, (b) (6) to (b) (6)**
	Screening	• Med Hx: Allergy to CT scan contrast media • Med Hx: Chronic arterial disease treated with 3 stents
	CM	• Pre-medications before CT scan contrast (deltacortene, cetirizine) • Prophylaxis medications for panitumumab (dexamethasone, pantoprazole, chlorphenamine)
	Screening	• Med Hx: hemorrhoidal prolapse
	CM	• Prophylaxis medications for panitumumab (dexamethasone, pantoprazole, chlorphenamine)

AE: adverse event, G: severity grade, Hx: history, CM: concomitant medication
Bold: unreported AE incident events for subject.
Source: Appendix 5, IR response #4, see Table 2.

Reviewer comment. *The SDV identified 6 unreported AEs that represent new incident AEs for the respective subjects in the AE dataset. The seriousness of the newly identified AEs for Subject (b) (6) was not documented. OSI recommends the Review Division include these unreported AEs in the safety analysis.*

2 IR response #4, see Table 2

Fraud 2: Fraudulent account access using fake email accounts.

The Sponsor's query of vendor electronic systems for the study determined that 2 fake email addresses created fraudulent accounts on the following 3 systems by impersonating 2 SIs: (b) (4), Medidata, and Signant Health.[3] However, the Sponsor's review of audit trails and account privileges on the (b) (4) system concluded that a single fraudulent account was created, but the identified account did not perform any data-related activities through the time of deactivation on July 11, 2024.

Reviewer comment. *Based on the review of the imaging data flow and audit trail summaries, OSI agrees that the (b) (4) system used for BICR appears to be unimpacted by the fraudulent email accounts. Therefore, the following discussion focuses on the Medidata and Signant Health systems. Refer to Incident 3 for a separate discussion of unauthorized site user access to the (b) (4) system. Finally, the Sponsor identified no evidence of fraudulent account access for Sites 33010 and 33020.*[4]

A. Medidata System

The Sponsor's query of the Case Report Form (CRF) audit history demonstrated that CRA completed 6,228 audit actions in the Medidata system under 2 fraudulent accounts including but not limited to data entry, revision, and answering queries, impacting CRF data for 11 subjects[5] at Site 33013 between 11/28/22 and 5/28/24. The audit actions impacted a range of CRF domains including but not limited to screening assessments (anti-cancer therapies, cancer diagnosis, medical history, demographics, electrocardiograms, procedures, etc.), commitment medications, safety assessments (adverse events, labs, vital signs, electrocardiograms, etc.), and documentation of IP administration.

To address the impact of these actions on the safety and efficacy data from Site 33013, the Sponsor/CRO assigned new CRAs to conduct repeat "SDV" for 2 subjects exclusively monitored by CRA (Subjects (b) (6) and (b) (6)). This process identified multiple discrepancies between data in the source documents and the Medidata system that were not captured in the datasets submitted with the sNDA application. The Sponsor did not conduct repeat "SDV" for the remaining 8 enrolled subjects at Site 33013 after identification of the fraudulent accounts because other CRAs (i.e., not the CRA who committed fraud) had monitored these 8 subjects during the trial and already conducted a full "SDV" prior to the sNDA 214665 S9 submission.

Reviewer comment. *While the Sponsor proposed to leverage repeat "SDV" to analyze the impact of the fraudulent accounts, any source records impacted by fraudulent activities (e.g., forged signatures [see Incident 1], potential unauthorized EMR access*

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3 Response to IR #2, see Table 2
4 Response to IR #4, see Table 2
5 Subject IDs: (b) (6), (b) (6) (screen fail), (b) (6), (b) (6), (b) (6), (b) (6), (b) (6), (b) (6), (b) (6), (b) (6), (b) (6), (b) (6), (b) (6) and (b) (6).

[see Incident 3]), cannot be used as source documents to verify altered data entries in the Medidata system. Acknowledging the limitations of the Sponsor's "SDV" methodology, OSI conducted a review of audit trails and the Sponsor's analyses in order to characterize the audit actions. From a safety perspective, while the impacted safety data do not appear to change the overall interpretation of safety for Soto960 + Pmab, the number of audit trail actions and range of CRF domains suggest that CRA's actions were diffuse within the Medidata system, raising significant concerns with the reliability of the safety data at Site 33013. From an efficacy perspective, the BICR process provides additional confidence in the efficacy evaluation. Therefore, the following high-level discussion is limited to the potential impact of the audit actions on the interpretation of efficacy.

OSI's review of the audit trails[6] (all 10 subjects) and reported data discrepancies[7] (Subjects (b) (6) and (b) (6) only) identified the following data with the potential to impact the interpretation of efficacy:

Screening Assessments:

The Sponsor identified additions and minor corrections to the screening assessments across a range of CRF categories including cancer histopathology sub-type, medical history, surgical procedures, and anti-cancer therapies (Table 5).

Table 5. Screening History Changes by Subject at Site 33013

Subject ID (arm)	CRF Category	Change
(b) (6)	Prior radiotherapy for current malignancy	-Added history of radiotherapy (b) (6) to 1 (b) (6) at left iliac axis (18 months before enrollment) -Unverified history of partial response
	Prior surgical procedures	-Added pleural biopsies, atypical resection of LLL, and chemical pleurodesis in VATS ((b) (6)) -Added Proctoscopy ((b) (6)) -Added colonoscopy ((b) (6)) -Added Intestinal recanalization ((b) (6))
	Medical history	-Added elevated creatinine (Grade 1, (b) (6))
	Anti-cancer therapies (prior)	-Correction: **irotecan stopped for toxicity not PD** -Correction: regorafenib dosage (BID to QD)
	Physical measurement	-Non-verification of BSA at Screening, but height and weight measurements verified
	Anti-cancer therapies (prior)	-Correction of category (i.e., targeted biologic)
	Anti-cancer therapies (prior)	-Data entry for oxaliplatin
	Anti-cancer therapies (prior)	-Correction of categories of prior anti-cancer therapies

6 Appendix 3, Response to IR #1, see Table 2
7 Appendix 18, Response to IR #2, see Table 2

Subject ID (arm)	CRF Category	Change
(b) (6)		
	Medical history	-Queries / data entry for nausea, hypomagnesemia
	Anti-cancer therapies (prior)	-Correction of category
	Medical history	-Queries / data entry for weakness and hypothesia of right lower limb
	Medical history	-Added juvenile glaucoma and lactose intolerance
	Substance Use	-Correction: tobacco use (1 unit, not 15 units)
	Cancer diagnosis	-Addition of non-mucinous
	Medical history	-Queries / data entry for vein thrombosis
	Anti-cancer therapies (prior)	-Data entry of therapies, including multiple descriptive variables
	Procedures	-Data entry for colon surgery
	Cancer diagnosis	-Data entry for TNM overall and components
Source: Appendix 3, Response to IR #1, and Appendix 18, Response to IR #2, see Table 2		

Reviewer comment. *Many entries included limited information and/or appear largely related to modifying nomenclature. Because Subject* (b) (6) *discontinued irinotecan for toxicity rather than progressive disease, OSI defers to the review division regarding the interpretation of the subject's eligibility as it relates to Inclusion Criterion 104. Independent of the ability to verify these data, OSI notes that the remaining changes do not appear to impact subject eligibility.*

Concomitant medications:

The Sponsor identified several underreported concomitant medications as well as multiple minor discrepancies in data variables describing previously reported concomitant medications such as start/stop dates, indication, dosage, units, route of administration, or drug name (Table 6).

Table 6. Concomitant Medication Changes by Subject at Site 33013

Subject ID (arm)	Medication Name	Description of Change
(b) (6)	doxycycline	-Correction of frequency (daily) -Addition of stop date ((b) (6))
	mometasone furoate	-Added prophylaxis categorization -Unverified dose and units
	eflornithine (topical)	-Updated dosing units (1 application)
	furosemide	-Added stop date ((b) (6))
	atorvastatin	-Updated start date ((b) (6) to (b) (6))
	deltacortene	-Correction of name (prednisone to deltacortene) -Removal of stop date -Updated indication (folliculitis to dyspnea)

Subject ID (arm)	Medication Name	Description of Change
(b) (6)	rivaroxaban	-Correction of dosing units (1 unit to 1 tablet)
	olmesartan/ hydrochlorothiazide	-Correction stop date ((b) (6) to (b) (6))
	n-acetylcysteine	-Correction start date ((b) (6) to (b) (6)) -Updated dose
	chlorphenamine	-Added as new CM for premedication for panitumumab since beginning of treatment
	Undisclosed anesthetic agents and analgesics	-Addition as new CM for surgical procedure (b) (6) and during hospitalization of (b) (6)
	Fucimix, Augmentin	-Query and data entry
	mycostatin	-Query regarding indication
	Unknown med	-Updated for indication for unknown med to "AST increased"
	Fucimix	-Query and data entry
	Arixtra (fondaparinux)	-Removal of stop date -Change in route of administration (IM → SubQ)
	doxycycline	-Update units (mcg → milligram) -Addition of a second course of CM ((b) (6) x 20 days)
	Fucidin	-Addition of new CM ((b) (6) to (b) (6))
	cetirizine	-Added as new CM, premedication for panitumumab with start date ((b) (6))*
	iron/vitamin C	-Added as new CM with start date ((b) (6))
	chlorphenamine	-Added as new CM biweekly from (b) (6) to (b) (6)
	unknown med	-Query regarding medication for folliculitis

CM: concomitant medication, mcg: microgram, IP: investigational product
Shaded: unreported, incident CM for subject
*After primary endpoint (PFS) database lock (6/19/2023)
Source: Appendix 3, Response to IR #1, and Appendix 18, Response to IR #2, see Table 2

Reviewer comment. *Many entries included limited information and/or were largely related to modifying nomenclature or indications. Independent of the ability to verify these data, while multiple new concomitant medications were reported for each subject, the reported concomitant medications do not reflect prohibited medications and are unlikely to impact the interpretation of efficacy data.*

B. Signant Health System

The Signant Health system is an online, internet-based web portal used by study personnel to review data and reports for Electronic Clinical Outcome Assessment (eCOA) and eDiary data, and to manage Data Clarification Forms (DCF). The Sponsor's query of the system's audit history demonstrated that 1 fraudulent account created 67 DCFs for eCOA and/or

eDiary data across 10 subjects[8] between February 23, 2023, and June 20, 2024. The DCFs spanned a range of reasons such as visit names, day/time of administration, pill counts, paper PRO forms, subject status, patient deactivation, deletion for paper diary, and duplicate data.

Reviewer comment. *The study data from the eCOA supported secondary and exploratory endpoints and do not impact the primary endpoint (PFS) or key secondary efficacy endpoints (OS, ORR) proposed for inclusion in the drug prescribing information. The eDiary was a daily electronic dosing diary for recording adherence to oral medications at home (i.e., sotorasib, regorafenib, or trifluridine and tipiracil administered). However, the study also monitored treatment compliance by documentation in the EMR, review of pill counts, and PK assessments (sotorasib).*

Fraud 3: Unauthorized access to (b) (4) using stolen/borrowed login credentials.

On August 14, 2024, the Sponsor informed the FDA that on July 12, 2024, they were made aware by the CRO that the CRA had also accessed the (b) (4) system through an existing, legitimate site user account belonging to a radiology technician (hereafter, referred to as "RT") on March 6, 2023.[9] The Sponsor's review of the audit trail for this site user on March 6, 2023, indicated that there were no queries responded to and no image uploads by that user account.

Reviewer comment. (b) (4) *system is used by site users (i.e., authorized radiologists and technicians) to electronically upload / transfer tumor images to the CRO database for BICR and to respond to quality control (QC) queries from the CRO. While CRA admitted to accessing the* (b) (4) *system on only a single date, OSI cannot verify that his access was limited to a single occurrence; because CRA used existing, legitimate credentials belonging to a radiology technician, audit trails of the* (b) (4) *system cannot distinguish his actions from those conducted by the legitimate user account. Further, OSI cannot determine whether CRA also obtained unauthorized access to other unvalidated systems (i.e., systems lacking audit trails) such as the EMR. OSI informed the Review Division of these concerns by email and verbal communication on August 20, 2024. To verify efficacy data from this site, the Review Division did request additional verification of imaging data and key QC queries.*[10]

A. Imaging Data Audit (Site 33013)

In response to an FDA IR #4, the Sponsor subsequently conducted an audit to compare the imaging dates, times, subject identifiers, number of series and imaging slices per series for all

8 Subject IDs: (b) (6), (b) (6), (b) (6), (b) (6), (b) (6), (b) (6), (b) (6), (b) (6), (b) (6) & (b) (6)
9 Response to IR #3, see Table 2
10 IR #4, see Table 2

imaging at Site 33013 with that of the imaging uploaded to [redacted] database. OSI review of the submitted Imaging Metadata File[11] for Site 33013 noted the following key discrepancies:

- Subject [redacted] (Soto960 + Pmab): At Week 40, a series of the abdomen imaging with contrast was not uploaded.

  Reviewer comment. *Week 40 imaging was a delayed venous phase and not required to be uploaded to* [redacted] *per the image acquisition guidelines (i.e., only portal venous phase for abdomen and pelvis).*

- Subject [redacted] (Soto960 + Pmab): At the Week 24 timepoint, a series covering chest anatomy was partially uploaded, and a cranium imaging series was not uploaded.

  Reviewer comment. *The absence of the Week 24 images appears secondary to a malfunction during the upload process. The imaging read by* [redacted] *included complete chest anatomy from another concurrently uploaded series Week 24 image, but no cranium / brain imaging. While the imaging charter required upload of imaging from other anatomical locations if clinically indicated (i.e., brain / cranium), as the RECIST assessment was progressive disease (PD) at Week 24 due to new lesions (right chest wall and subcarinal lymph nodes), this discrepancy does not change the interpretation of efficacy for this subject.*

- Subject [redacted] (Soto960 + Pmab)- Unscheduled MRI of the abdomen from [redacted] was not transferred to [redacted] but per Sponsor, entered in RAVE EDC as a procedure.

  Reviewer comment. *While OSI review of the ADPR (procedure) dataset did not identify an MRI for Subject* [redacted] *at any timepoint, the RAVE Audit Trail[12] identified an abdominal MRI dated* [redacted]*, entered on* [redacted] *as a procedure. The absence of a central read for the abdominal MRI was unlikely to impact efficacy as the RECIST assessments were complete response (CR) at subsequent visits (Week 16 and Week 24), inclusive of abdominal imaging.*

- Subject [redacted] (Soto960 + Pmab)- Unscheduled brain CT (x2) and one MRI (anatomic location unknown) obtained in [redacted] were not uploaded.

  Reviewer comment. *The imaging acquisition guidelines required upload of CT scans / MRIs of other known sites of disease or if clinically indicated until BICR assessed progression. There was a RECIST assessment of PD for an unscheduled Brain MRI on* [redacted]*, with BICR read on* [redacted]*. Therefore, this discrepancy does not change the interpretation of efficacy for this subject, as the subject had already progressed on* [redacted].

The following additional categories of imaging data were not transferred to [redacted] scout images, contrast or radiation dosage details, contrast monitoring protocols, key images

11 Appendix 10, Response to IR #4, see Table 2
12 Appendix 3, Response to IR #1, see Table 2

identified by the site radiologist (series containing a selection of images already uploaded as part of other series), image reconstructions, and non-contrast images.

Reviewer Comment. The listed images do not contribution to the RECIST assessment supporting the PFS endpoint, and therefore do not have an impact on efficacy.

B. Image Quality Control Audit (Site 33013)

Review of the Image Quality Control (QC) Process audit trails identified 31 queries for Site 33013 completed under site user RT including the following notable responses with image modification:

- Two imaging assessments performed at Site 33013 were incorrectly uploaded to Site 33012 and subsequently removed from (b) (4) database on October 26, 2022.
- Subject (b) (6) (Soto960 + Pmab)- (b) (4) removed MRI images on July 4, 2023, following a Site User query response indicating that the images were uploaded in error on June 19, 2023, for the Week 16 timepoint.

  Reviewer comment*. Subject (b) (6) 's Week 24 CT images from the same date ((b) (6)) were read as complete response (CR) (BICR). In the response to IR #5, the Sponsor indicated that a brain MRI belonging to a different subject on (b) (6), was erroneously uploaded for Subject (b) (6) and then removed. As such, the removed MRI images do not appear to impact the efficacy for this subject.*

  The image acquisition guidelines required the site to respond to QC queries in 3-days, but the audit trails revealed multiple instances of repeated QC queries due to lack of initial response from Site 33013.

  Overall, the Image QC query responses do not appear to impact the interpretation of the primary efficacy endpoint at Site 33013.

Addendum for Sites 33010 and 33020:

OSI review of the submitted Imaging Metadata Files[13] for Site 33010 and 33020 noted the following discrepancy at Site 33020:

- Subject: (b) (6) (Soto960 + Pmab): Week 8 series containing contrast-enhanced images not uploaded to (b) (4) by the site.

  Reviewer comment*. The image was a delayed venous phase not required by the imaging acquisition charter and did not add to the complete anatomy already uploaded to (b) (4) for the same timepoint. The RECIST assessment was progressive disease (PD) at Week 8, and this discrepancy does not change the interpretation of efficacy for this subject.*

13Appendices 8 and 9, Response to IR #4, see Table 2

For both sites, similar to Site 33013, additional categories of imaging data were not transferred to (b) (4) such as scout images, pre-contrast medium, contrast or radiation dosage details, contrast monitoring protocols, image reconstructions, summary of images, and non-contrast images.

> ***Reviewer Comment***. *The listed imaging data do not contribute to the RECIST assessment supporting the PFS endpoint, and therefore do not have an impact on efficacy.*

OSI review of the Sponsor's additional imaging audit identified no QC responses that impact the overall interpretation of efficacy.

OSI Summary Recommendations:

Based on the totality of the inspection findings and communications regarding Site 33013, OSI has significant concerns with the safety data obtained at Site 33013. There were clear data integrity concerns resulting from the CRA committing at least 3 types of fraudulent activities, spanning a period of approximately 2 years. In addition, there appeared to be an initial lack of transparency from the Sponsor as evidenced by the delayed notification of the third type of fraud until well after the CI inspection and overall challenges obtaining complete information requiring multiple information requests (Table 7):

Table 7. Summary of Timeline for Fraudulent Activity Discovery and Notification

Date	Event
June 14, 2024	PI notified Sponsor/CRO of initial discovery of forged signatures for 2 subjects (Fraud 1).
June 20, 2024	CRO removed the CRA from all studies and systems.
July 4, 2024	PI informed Sponsor of fraudulent accounts in Medidata and Signant Health (Fraud 2).
July 11, 2024	3rd fraudulent user account identified and deactivated on (b) (4) system (Fraud 2).
July 12, 2024	CRO informed Sponsor of additional unauthorized access to (b) (4) Imaging Portal using existing site user credentials (Fraud 3).
July 15, 2024	Sponsor first notified FDA of investigation into GCP violations at Site 33013 (Fraud 1 and 2).
July 22-26, 2024	FDA Inspection included queries regarding Fraud 1 and 2
July 23, 2024	Response to FDA IR #1 updated findings for Fraud 1 and 2 with audit trails: forged signatures impacted 6 subjects and fraudulent accounts identified on 3 electronic systems.
July 26, 2024	Response to FDA IR #2 states absence of additional fraudulent accounts and provides Medidata "inconsistency" analysis for Subjects (b) (6) and (b) (6) in reference to Fraud 2.
August 14, 2024	Response to FDA IR #3 first notifying FDA of third type of fraud (Fraud 3)

From an efficacy perspective, minor discrepancies in concomitant medications and screening assessments do not appear to impact subject eligibility for enrollment or the overall interpretation of efficacy. OSI review of the Sponsor's additional imaging audit identified no apparent discrepancies in the imaging data transferred to the central imaging CRO or the QC responses that would impact the overall interpretation of efficacy. Overall, the use of a BICR

process provides additional confidence in the efficacy evaluation, and the separate (b) (4) inspection included imaging data verification for all 6 subjects enrolled in the Soto960 + Pmab arm at Site 33013 (see Table 8). Therefore, the efficacy data generated by Dr. Salvatore appear acceptable in support of the proposed indication.

From the safety perspective, the safety data at Site 33013 are deemed unreliable. Specifically, all data originating in forged source documents cannot be verified against the unvalidated EMR, and in turn, these forged source documents cannot be used to verify altered eCRF data entries. Further, while OSI did not have evidence that the TrackCare EMR was also breached, because the unvalidated EMR lacks both an audit trail and timestamped signatures, we cannot exclude that the possibility of unauthorized access to the EMR (i.e., similar to Fraud 3), potentially making all paper source records unverifiable. OSI recommends removal of Site 33013 safety data from the analysis.

Regarding Sites 33010 and 33020, the safety and efficacy data appear acceptable in support of the sNDA.

3. (b) (4) **(Imaging CRO)**
(b) (4)

Inspection dates: (b) (4), to (b) (4)

(b) (4) was inspected as a routine PDUFA inspection for Study 20190172. The firm was previously inspected in (b) (4) and there were no observations.

This inspection reviewed (b) (4) responsibilities to perform an independent central imaging review for Study 20190172, with a focus on data reliability. Records reviewed included organizational charts, financial disclosures, SOPs, agreements with the Sponsor (Amgen) and other venders, electronic records and systems utilized in analyzing/marking the scans, quality assurance activities, records retention, and financial disclosures. (b) (4) data collection, handling and transfer procedures, blinding procedures, adherence to the protocol and imaging review charter, and adjudication procedures were also reviewed and found to be adequate. There were no changes to the quality assurance activities or SOPS from the last inspection in (b) (4).

The inspection verified the primary efficacy endpoint (PFS) for 48 subjects by comparison of data for tumor response/progression and objective tumor responses in source records with data line listings at all timepoints, including when applicable, objective response confirmation. There were no discrepancies. The following table lists the subjects whose tumor measurements were verified (Table 8):

Table 8. List of Unique Subject IDs* for Verified Measurements

(b) (6)

*46 subjects selected based on their efficacy response (i.e., PR/CR in the active arms and early PD in the ICC arms) and 2 additional subjects selected at random.
Shaded: Subjects enrolled at Site 33013 / 64380, CI: Dr. Salvatore

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

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cc:
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Review Division/Deputy Division Director acting/Chana Weinstock
Review Division/Project Manager/ Nataliya Fesenko
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: **September 24, 2024**

To: Nataliya Fesenko, Senior Regulatory Health Project Manager, DO3

Doris Auth, Associate Director for Labeling, DO3

From: Mispa Ajua-Alemanji, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, Team Leader, OPDP

Subject: OPDP Labeling Comments for LUMAKRAS® (sotorasib) tablets, for oral use

NDA: 214665-009

Background:
In response to DO3's consult request dated April 30, 2024, OPDP has reviewed the proposed Prescribing Information (PI), and Patient Package Insert (PPI) for LUMAKRAS® (sotorasib) tablets, for oral use. This supplement proposes to include a new indication for sotorasib in combination with panitumumab for (b) (4)

PI:
OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DO3 on September 10, 2024, and revised labeling received on September 16, 2024. Our comments are below.

PPI:
A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed and comments on the proposed PPI were sent under separate cover on September 16, 2024.

Thank you for your consult. If you have any questions, please contact Mispa Ajua-Alemanji at Mispa.Ajua-Alemanji@fda.hhs.gov.

PI:

Section	Statement from Draft (if applicable)	OPDP Comment
HIGHKIGHTS OF PRESCRIBING INFORMATION: Adverse reactions	(b) (4) 	We note that the HIGHLIGHTS (b) (4) while section 6 of the FPI lists the most common Grade 3-4 laboratory abnormalities (b) (4). We defer to DO3 to determine the cutoff rates for the most common laboratory abnormalities. We recommend updating this information in the HIGHLIGHTS and section 6 so that they are consistent with one another and throughout the PI. Additionally, once the values in the tables are updated, we recommend revising the order of the most common laboratory abnormalities so that they are presented in decreasing order of frequency.

WARNING AND PRECAUTION: 5.1 Hepatotoxicity	(b) (4) [redacted]	We note that in recent labels, for example KRAZATI, the individual incident rates are separated out for the serious risks (e.g., Grade 3 (X%), and Grade 4 (X%). OPDP is concerned that combining this risk presentation, may minimize the more serious risks in the group (i.e., Grade 4 adverse reactions or higher). We recommend revising the risk presentation to individually present the incident rates for each grade observed in this section, if the data is available, to avoid minimizing the presentation of the more serious risk.
ADVERSE REACTIONS: Clinical Trial Experience 6.1	"Metastatic Colorectal Cancer: The most common Grade 3-4 laboratory abnormalities (b) (4) [redacted]	As earlier noted, please revise cutoff rates for the most common Grade 3-4 laboratory abnormalities so that this information is consistent with the HIGHLIGHTS.
USE IN SPECIFIC POPULATIONS: Geriatric Use 8.5	"In a pooled analysis of 132 patients who received LUMAKRAS 960 mg in combination with panitumumab for (b) (4) 30% were 65 and over while 9% were 75 and over."	We recommend revising "(b) (4)" to "***KRAS* G12C-mutated mCRC**" so that it is consistent with section 8.5 of the panitumumab PI.

CLINICAL STUDIES: *KRAS G12C*-mutated Metastatic Colorectal Cancer 14.2	*"*LUMAKRAS discontinuation required panitumumab discontinuation, however, patients could continue to receive LUMAKRAS if panitumumab was discontinued *[see Dosage and Administration (2.3)]."*	OPDP is concerned about the inclusion of the statement that "patients could continue to receive LUMAKRAS if paninumumab was discontinued" without additional context, because it suggests that LUMAKRAS can be used as monotherapy for treatment of *KRAS G12C* mCRC when such information for use is not currently included in section 2 of the PI. While we acknowledge that this information may be consistent with the study protocol, we note that per the *Labeling Review Tool*, the clinical CLINICAL STUDIES section must not include any information that implies or suggests indications or uses or dosing regimens not stated in the INDICATIONS AND USAGE or DOSAGE AND ADMINISTRATION sections. OPDP recommends one of the following approaches: 1) Revising the CLINICAL STUDIES section to provide additional context which clarifies that although patients in the CodeBreaK trial were allowed to receive LUMAKRAS alone as part of a dosage modification in the study protocol, LUMAKRAS has not been approved as monotherapy for the mCRC indication and that it is not recommended to continue LUMAKRAS after discontinuation of panitumumab. 2) Revising the DOSAGE AND INDICATION section to state that treatment with LUMAKRAS as a single agent may be continued if panitumumab is permanently discontinued. We note that a similar recommendation is included in section 2 of the Krazati label (i.e., "Treatment with KRAZATI as a single agent may be continued if cetuximab is permanently discontinued.")

CLINICAL STUDIES: *KRAS G12C*-mutated Metastatic Colorectal Cancer	"Among the 107 patients, 100% received prior fluoropyrimidine, 99% received prior oxaliplatin, 93% received prior irinotecan and 18% of patients had received prior trifluridine and tipiracil, or regorafenib."	We note that when describing prior therapies of the patients in the approved dosing regimen, in the panitumumab label (b) (4) Additionally, we note that in the Lumakras label (b) (4) % of patients had received prior trifluridine and tipiracil, or regorafenib meanwhile in the vectibix label, only 18% of patients were identified to have received prior trifluridine and tipiracil, or regorafenib. We defer to DO3 regarding what the proper percentages of prior therapies should be and recommend that this information be consistent in both labels.

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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:	September 16, 2024
To:	Nataliya Fesenko, PharmD 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:	Helen Young, MSN, MPH, CRRN, PHN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Mispa Ajua-Alemanji, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	LUMAKRAS (sotorasib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 214665
Supplement Number:	S-009
Applicant:	Amgen Inc.

1 INTRODUCTION

On April 17, 2024, Amgen Inc. submitted for the Agency's review a Prior Approval Supplement (PAS) – Efficacy to their approved New Drug Application (NDA) 211665/S-009 for LUMAKRAS (sotorasib) tablets. With this submission, the Applicant proposes the following new indication:

(b) (4)

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 April 30, 2024 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) LUMAKRAS (sotorasib) tablets.

2 MATERIAL REVIEWED

- Draft LUMAKRAS (sotorasib) tablets PPI received on April 17, 2024, and received by DMPP and OPDP on September 11, 2024.
- Draft LUMAKRAS (sotorasib) tablets Prescribing Information (PI) received on April 17, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 11, 2024.
- Approved LUMAKRAS (sotorasib) labeling dated January 20, 2023.
- Approved KRAZATI (adagrasib) tablets comparator labeling dated June 21, 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. In our review of the PPI the target reading level is at or below an 8th grade 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)
- ensured that the PPI is consistent with the approved comparator labeling where applicable

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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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:	September 3, 2024
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 214665/S-009
Product Name, Dosage Form, and Strength:	Lumakras (sotorasib) tablets, 120 mg and 320 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Amgen Inc.
FDA Received Date:	April 17, 2024
TTT ID #:	2024-9328
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Acting Team Leader:	Tingting Gao, PharmD

1 INTRODUCTION

Amgen Inc. submitted an Efficacy Supplement for Lumakras (sotorasib) tablets to support full approval of sotorasib for the following proposed indication:

> Lumakras (sotorasib) in combination with panitumumab, is indicated for (b) (4) [redacted]

Subsequently, the Division of Oncology 2 (DO2) requested that we review the proposed Lumakras Prescribing Information (PI) and Patient Package Insert (PPI) for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 214665/S-009.

Table 1. Materials Considered for this Label and Labeling Review	
Material(s) Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 CONCLUSION

We evaluated the proposed Lumakras Patient Package Insert (PPI) and determined that it is acceptable from a medication error perspective.

However, the proposed Lumakras Prescribing Information (PI) may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Oncology 2 (DO2) in Section 4.

4 RECOMMENDATIONS FOR THE DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. Highlights of Prescribing Information

a. Consider revising the format of the information in the Dosage and Administration section for improved readability as follows:

<u>NSCLC</u>

- Recommended dosage: 960 mg orally once daily.

<u>mCRC</u>

- Recommended dosage: 960 mg orally once daily, in combination with panitumumab.

Swallow tablets whole. Take with or without food.

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APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Lumakras received on April 17, 2024 from Amgen Inc.

Table 2. Relevant Product Information for Lumakras	
Initial Approval Date	May 28, 2021
Active Ingredient	sotorasib
Indication	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. Proposed: Lumakras (sotorasib) in combination with panitumumab for (b) (4)
Route of Administration	Oral
Dosage Form	tablets
Strength	120 mg and 320 mg
Dose and Frequency	960 mg (three 320 mg tablets or eight 120 mg tablets) orally once daily until disease progression or unacceptable toxicity
How Supplied	120 mg tablets • Carton containing 2 bottles of 120 tablets. • Carton containing 1 bottle of 240 tablets. 320 mg tablets • Carton containing 1 bottle of 90 tablets.
Storage	20°C to 25°C (68°F to 77°F). Excursions permitted to 15°C to 30°C (59 to 86°F) [see USP Controlled Room Temperature].
Container Closure	(b) (4)

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

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

- Prescribing Information received on April 17, 2024, available from \\CDSESUB1\EVSPROD\nda214665\0161\m1\us\114-labeling\draft\annotated\d-sotorasib-us-pi-vx-sotorasib-mcrc-new-indication-with-pan.docx
- Patient Package Insert received on April 17, 2024, available from \\CDSESUB1\EVSPROD\nda214665\0161\m1\us\114-labeling\draft\annotated\d-sotorasib-us-ppi-vx-sotorasib-mcrc-new-indication-with-pa.docx

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

APPENDIX C. PREVIOUS DMEPA REVIEWS

On August 26, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, Lumakras. Our search identified 2 previous review(s)[b,c] since the date of our last search on May 13, 2024, and we considered our previous recommendations to see if they are applicable for this current review.

APPEARS THIS WAY ON ORIGINAL

[b] Stewart, J. Label and Labeling Review for Lumakras (NDA 214665/s-011). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 Jun 11 . TTT ID No.: 2024-8669-1.

[c] Stewart, J. Label and Labeling Review for Lumakras (NDA 214665/s-011). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 May 20 . TTT ID No.: 2024-8669.

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