CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214665Orig1s000

OTHER REVIEW(S)

MEMORANDUM

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

Date of This Memorandum:	May 21, 2021
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 214665
Product Name and Strength:	Lumakras (sotorasib) Tablets, 120 mg
Applicant/Sponsor Name:	Amgen Inc
OSE RCM #:	2020-1338-1
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on April 26, 2021 for Lumakras. Division of Oncology 2 (DO2) requested that we review the revised container labels and carton labeling for Lumakras (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Stewart J. Label and Labeling Review for Lumakras (NDA 214665). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 22. RCM No.: 2020-1338.

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/s/

JANINE A STEWART
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ASHLEIGH V LOWERY
05/21/2021 03:27:34 PM

Clinical Inspection Summary

Date	May 5, 2021
From	Lee Pai-Scherf, MD Karen Bleich, MD Kassa Ayalew, MD, MPH Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Erica Nakajima, MD Nicole Drezner, MD Harpreet Singh, MD, Division Director Division of Oncology 2 Office of Oncologic Products
NDA #	214665
Applicant	Amgen, Inc.
Drug	Sotorasib
NME (Yes/No)	Yes
Therapeutic Classification	Tyrosine Kinase Inhibitor
Proposed Indication(s)	"Treatment of patients with KRAS G12C-mutated locally advanced or metastatic NSCLC who have disease progression after receiving prior therapy"
Consultation Request Date	January 14, 2021
Summary Goal Date	May 10, 2021
Action Goal Date	May 28, 2021
PDUFA Date	August 16, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study 20170543 were submitted to the Agency in support of a New Drug Application (NDA 214665) for sotorasib for the above proposed indication. Three clinical investigators (Drs. David Hong, Ramaswamy Govindan and Bob Li) were selected for clinical inspection, as well as (b) (4), the central imaging contract research organization (CRO).

The inspections revealed no significant findings at the clinical investigator sites or the imaging CRO site. All inspections were conducted on-site. There was no evidence of underreporting of serious adverse events (SAEs) or significant protocol deviations. Based on the results of these inspections, the Study 20170543 overall appears to have been conducted adequately and the data generated by the inspected clinical investigators and the imaging CRO appear acceptable in support of the proposed indication in the NDA.

II. BACKGROUND

Amgen, Inc. seeks approval for sotorasib for the treatment of patients with KRAS G12C-mutated, locally advanced or metastatic non-small cell lung cancer (NSCLC), who have received at least one prior systemic therapy. Sotorasib is a new molecular entity and was granted Breakthrough Therapy Designation for the proposed indication.

Clinical data from an ongoing, first-in-human, single arm, dose-escalation (phase 1 part) and dose expansion cohort (phase 2 part) study of sotorasib in subjects with KRAS G12C-mutated NSCLC and other solid tumors (Study 20170543) was submitted to support this NDA.

The application includes safety data from 339 patients with various tumor types who received sotorasib 960 mg orally, daily, in Study 20170543. The efficacy population for this application consists of 123 subjects with KRAS G12C-mutated NSCLC enrolled in the phase 2 portion of the study who received sotorasib 960 mg PO QD and had received prior platinum-based chemotherapy. The primary efficacy endpoint is overall response rate (ORR), as determined by a Blinded Independent Central Review (BICR), according to RECIST v 1.1.

Subjects were required to sign an informed consent prior to any screening procedure. Baseline tumor assessment and radiological imaging was performed at screening (within 28 days of initiation of study drug) and every 6 weeks following cycle 1, day 1 for 8 assessments, followed by every 12 weeks until disease progression or end of investigational product, whichever is later.

The first subject was enrolled on August 27, 2018 and the data cutoff date for the NDA is September 1, 2020. At the time of the data cutoff, the study was being conducted at 59 study centers in 11 countries: Australia, Austria, Belgium, Brazil, Canada, France, Germany, Japan, South Korea, Switzerland and United States (51% of the subjects in the phase 2 part were enrolled 27 study centers in the US).

Three clinical investigators were identified for inspection by DO2 and OSI: Dr. David Hong (site # 56928), Dr. Ramaswamy Govindan (site # 28643) and Dr. Bob Li (site # 57631). Clinical site selection used a risk-based approach, taking into consideration the total number of subjects enrolled and safety and efficacy parameters. OSI's Clinical Investigators Site Selection Tool (CISST) was utilized to assist with site selection. (b) (4), the central imaging facility responsible for central review of images, was chosen for evaluation of the conduct of the central imaging review and for evaluation of the primary efficacy endpoint of a larger number of subjects.

III. RESULTS (by site):

1. **Dr. David Hong** (site # 56928)
   1515 Holcombe Boulevard
   Department of Investigational Cancer Therapeutics
   UT MD Anderson Cancer Center
   Houston, TX 77030

   Inspection dates: 03/22/21 – 03/25/21.

   Dr. Hong was inspected as a surveillance inspection for Study 20170543. This investigator has been previously inspected on 05/02/2018 and classified as NAI.

   At the time of the inspection, the site had screened 66 subjects and enrolled 57 subjects (34 were enrolled in the phase 1 part and 23 in the phase 2 part). Of the 57 subjects, 48 had died and 9 subjects withdrew from study.

   Source documents for 24 subjects (12 enrolled in the phase 1 and 12 in the phase 2 part of the study) were reviewed. All subjects met protocol specified inclusion and exclusion criteria and signed informed consent. There was no underreporting of AEs or SAEs or significant protocol deviations. There were no discrepancies or issues with the imaging process when compared to the information submitted to the NDA. There were no scans at the site that were not submitted for central review.

   Other documents reviewed during the inspection include financial disclosure forms, training records, delegation of authority log, investigational drug accountability, electronic medical records, contract research associate (CRA) monitoring records, and other source documents. No discrepancies or regulatory violations were observed.

   The inspection found no regulatory violations at the site. No Form FDA 483 was issued to Dr. Hong at the conclusion of the inspection.

2. **Dr. Ramaswamy Govindan** (site # 20170543)
   Washington University School of Medicine
   660 South Euclid Avenue # 8056
   St. Louis, MO 63110-1093

   Inspection dates: 04/05/21 – 04/09/21.

   Dr. Govindan was inspected as a surveillance inspection for Study 20170543. This was the first FDA inspection for this investigator.

   At the time of the inspection, the investigator had screened 36 subjects and enrolled 27, of which, 8 subjects remain on study drug and 19 subjects were off study.

Source documents for all enrolled subjects were audited, including case report forms, eligibility check lists, AEs and SAEs evaluations, laboratory results, imaging scans, pharmacy and dosing records. All subjects met protocol specified eligibility criteria and signed the informed consent form. There was no evidence of underreporting of AEs or SAEs or protocol deviations.

Other documents reviewed during the inspection include IRB correspondence, monitoring reports, financial disclosure reports, subject questionnaires and diaries, responsibility logs, site training documentation and monitoring plans/ guidelines and reports. No discrepancies or regulatory violations were observed.

The inspection found no regulatory violations at the site. No Form FDA 483 was issued to Dr. Govindan at the conclusion of the inspection.

3. **Dr. Bob Li** (site # 57631)
Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, NY 10065
Inspection dates: 02/17/21 – 02/26-2021

Dr. Li was inspected as a surveillance inspection for Study 20170543. This was the first FDA inspection for this investigator.

At the time of the inspection, the investigator had screened 31 subjects and enrolled 26 subjects. Ten subjects remain on study, with 5 subjects receiving study treatment and 5 subjects in the follow-up phase.

Source documents and electronic medical records for 13 of the enrolled subjects were audited. All subjects met protocol specified eligibility criteria and signed informed consent. In addition, the following areas were reviewed and found to be adequate by the inspector: study required procedures and evaluations, concomitant therapies, monitoring and reporting of AEs and SAEs, investigational product administration and timely communication of SAE findings. There was no evidence of underreporting of serious AE or protocol deviations, however few discrepancies were identified between the submitted data listings and source documents:

Unreported AEs

- **Subject #** (b) (6) **:** experienced 4 episodes of grade 1-2 diarrhea during course of treatment according to the source document. Source records indicate that the subject experienced episodes of grade 1 and 2 diarrhea that were not captured in the eCRF and reported to the NDA: grade 1 diarrhea from 10/11/19 -01/02/20; grade 1 diarrhea from 01/17/20 – 01/31/20, grade 1 diarrhea from 01/31/20 – 01/13/20 and grade 1 diarrhea from 02/13/20 -02/17-20.

Underreported therapy or concomitant medications:

- **Subject #** (b) (6)**:** according to the source document (Toxicity Log), the subject developed grade 3 anemia on 06/27/2019 and received blood transfusion on (b) (6) however the transfusion was not captured in the eCRF and not included in the submitted dataset.

- **Subject #** (b) (6)**:** per source document the subject was prescribed medical marijuana for nausea from (b) (6), but this was not was not captured in the eCRF and not included in the submitted dataset.

- **Subject #** (b) (6) per source document the subject was prescribed diphenoxylate-atropine starting (b) (6) for management of grade 2 diarrhea but this was not was not captured in the eCRF and not included in the submitted dataset.

- **Subject #** (b) (6)**:** per source document subject was prescribed Dilaudid for treatment of intractable chest wall pain from (b) (6) but this was not captured in the eCRF until 10/02/19.

- **Subject #** (b) (6)**:** per source document, the subject was taking supplements probiotic formula oral capsule and vitamin C during the study but was not captured in the eCRF and not included in the submitted dataset.

Reviewer's comment: *The adverse event and concomitant medications were documented in the source record (Toxicity Log) but not entered in the eCRF, thus were not submitted to the NDA. There is no evidence of harm to the study participants related to the unreported episodes of diarrhea, unreported AE and concomitant medications.*

The radiographic scans and related investigator's assessments were performed as specified in the protocol and were de-identified prior to submission to the Sponsor for central review by the imaging CRO (b) (4). All scans performed prior to the NDA data cut-off date were submitted for central review.

Other documents reviewed during the inspection include protocol deviations, Form FDA 1572, financial disclosure and IRB communications. All versions of the protocol were submitted and approved by the IRB. No discrepancies or regulatory violations were observed.

The inspection found no regulatory violations at the site. No Form FDA 483 was issued to Dr. Li at the conclusion of the inspection.

4. (b) (4)

Inspection dates: (b) (4)

(b) (4) was inspected as data audit and surveillance inspection for Study 20170543. This was the first FDA CRO inspection of (b) (4)

The inspection included the review of study files for 60 subjects included in the efficacy population, standard operating procedures (SOPs), independent review charters, contract agreements and correspondence between the Sponsor and (b) (4) Other documents reviewed include training records, data acquisition requirement specification documents, and financial disclosure forms.

For Study 20170543, the radiographic images were electronically transferred from the investigational site by direct transfer into (b) (4) system (AG Mednet-JUDI), through a designated SharePoint site, or via courier service. Images were de-identified by the study site prior to the transfer to (b) (4). All images were uploaded into AG Mednet-JUDI system, which was automatically "pushed" into mint Lesion™, the electronic storage and hardware system for reading. Images were assigned to readers and if warranted, to an adjudicator. (b) (4) final response assessment were transferred to the Amgen via a secure File Transfer Program.

The inspector did not observe deviations from the SOPs or deficiencies in the procedures for image receipt, evaluation and data transfer to Amgen.

During the inspection, the primary endpoint data, consisting of tumor assessment for 60 subjects included in the efficacy population were reviewed. Radiographic scans at multiple time points that stored in the (b) (4) s mint Lesion™ system were compared to those submitted to the NDA. Subject's time point responses from (b) (4) s final data transfer files were compared to the responses submitted to the NDA. No discrepancies were observed in terms of the radiographic scan dates or response assessment.

The inspector confirmed that readers were blinded from each other's evaluation. Once the reader completes a timepoint read, they were required to sign off and not additional changes could be made without unlocking the page and no other person except the assigned reader can update the image evaluation. Reasons to request unlocking and revision of the read are pre-specified in the IRC charter.

To verify that scan re-read revision process followed the pre-specified procedures, the inspector reviewed a sample of 10 scans where the initial assessment was revised by the reader. The inspector confirmed that the reasons to request the revision were in accordance to the SOP and that all procedures were followed.

In addition, the inspector verified that the best overall responses (BOR) were confirmed by a similar or improved response at least 4 weeks after the initial reading.

There were no data discrepancies identified for the primary endpoint assessment. (b) (4) followed all procedures for conducting study related activities. The inspection found no regulatory violations at the site. No Form FDA 483 was issued to (b) (4) at the conclusion of the inspection.

{See appended electronic signature page}

Lee Pai-Scherf, MD
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Karen Bleich, M.D.
Team Leader,
Good Clinical Practice Assessment Branch
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CC:

DARRTS: NDA 214665
Review Division /Project Manager/Sharon Sickafuse
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OSI/DCCE/Branch Chief/Acting Division Director/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Karen Bleich
OSI/DCCE/GCPAB Reviewer/Lee Pai-Scherf
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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/s/

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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: April 28, 2021

To: Idara Udoh
Regulatory Project Manager
Division of Oncology 2 (DO2)

From: Nazia Fatima
Consumer Safety Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kevin Wright, Team Leader, OPDP

Subject: OPDP Labeling Comments for LUMAKRAS™ (sotorasib) tablets, for oral use

NDA: 214665

In response to DO2 consult request dated January 8, 2021, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI) and carton and container labeling for the original NDA submission for LUMAKRAS™ (sotorasib) tablets, for oral use (Lumakras).

OPDP's comment on the proposed labeling are based on the draft labeling received by electronic mail from DO2 on April 14, 2021 and OPDP's comment is listed below.

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 April 26, 2021.

OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on April 23, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Nazia Fatima at 240-402-5041 or nazia.fatima@fda.hhs.gov.

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NAZIA FATIMA
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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:	April 23, 2021
To:	Idara Udoh, MS Senior Regulatory Health Project Manager **Division of Oncology 2 (DO2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nazia Fatima, PharmD, MBA, RAC 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
Applicant:	Amgen Inc.

1 INTRODUCTION

On December 16, 2020, Amgen Inc. submitted for the Agency's review the final submission for a Real-Time Oncology Review (RTOR) for an original New Drug Application (NDA) 214665 for LUMAKRAS (sotorasib) tablets, a New Molecular Entity (NME). The proposed indication for LUMAKRAS (sotorasib) tablets is for the treatment of 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.

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 2 (DO2) on January 8, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for LUMAKRAS (sotorasib) tablets.

2 MATERIAL REVIEWED

- Draft LUMAKRAS (sotorasib) tablets PPI received on December 16, 2020, and received by DMPP and OPDP on April 14, 2021.
- Draft LUMAKRAS (sotorasib) tablets Prescribing Information (PI) received on December 16, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 14, 2021.

3 REVIEW METHODS

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

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

In our collaborative review of the PPI we:

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

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 214665
Submission Number	SDN 007
Submission Date	12/16/2020
Date Consult Received	1/8/2021
Drug Name	Lumakras (sotorasib)
Indication	Treatment of patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) who have received at least one prior systemic therapy.
Therapeutic dose	960 mg once daily with or without food
Clinical Division	DO2

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 1/8/2021 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT protocol review under IND 139023 dated 08/14/2019 in DARRTS;
- Previous IRT protocol review under IND 139023 dated 04/23/2019 in DARRTS;
- Proposed labeling (SN0007); and
- QT Evaluation Report Checklist (Appendix 1) (SN0007; Page 30-33, with links to CSR, SAP, IB, Highlight of Clinical Pharmacology and Cardiac Safety [appendix 2])

1 SUMMARY

No large mean increases in the QTc interval (i.e., >20 msec) were observed in this QT assessment. We are reluctant to draw conclusions of lack of an effect in the absence of a positive control, large exposure margin, or a double-negative finding in an integrated nonclinical safety assessment conduct according to best practices (ICH S7B Q&A 1.1 and 1.2).

The effect of sotorasib was evaluated in Study 20170543. The highest dose tested was the proposed therapeutic dose of 960 mg orally once daily (QD). The data were analyzed using by-timepoint analysis as the primary analysis, which suggested that sotorasib is not associated with large mean increases on the QTc interval (see Table 1 for overall results). The findings of this analysis were further supported by the exposure-response analysis (section 4.5), and categorical analysis (section 4.4).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

Treatment	Time	ΔQTcF (msec)	90% CI (msec)
960 mg QD	Cycle 1 Day 1, 2-hour	8.1	(5.8, 10.5)

The sponsor's dedicated PK studies and population PK analysis suggested that food, age, sex, race, mild organ impairment, and co-administration with strong CYP3A inhibitor do not significantly increase the maximum exposure of sotorasib. The effect of mild and severe hepatic impairment on sotorasib exposure is not known.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

A shallow but positive exposure-response relationship was observed between ΔQTc and sotorasib concentration, and the nonclinical studies do not provide a large safety margin. At the time of this review, the highest exposure scenario is co-administration with strong CYP3A inhibitor which increases Cmax by <10%. If additional studies suggest significant increase in Cmax by moderate/severe hepatic impairment, then we recommend revisiting the labeling language in section 12.2.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SN0007 (link) from the IRT. Our changes are highlighted (addition, ~~deletion~~) for suggestion only and we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4) At the recommended dose of (b) (4) large mean increase in QTc (> 20 msec) in the study.

Reviewer's comment: *We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.*

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Sotorasib (AMG 510) is a small molecule that specifically binds and irreversibly inhibits the KRAS G12C mutant protein. The proposed therapeutic dose is 960 mg QD with or without food for the treatment of patients with KRAS G12C mutated locally advanced or

metastatic non-small cell lung cancer (NSCLC) who have received at least one prior systemic therapy.

Previously the IRT reviewed the QT assessment proposal based on study 20170543 (DARRTS 08/14/2019 and 04/23/2019). The IRT provided recommendations on the statistical analysis method; sample size and dose/exposure were considered review issue.

Study 20170543 is a Phase 1 and 2, multicenter, global, non-randomized, open-label study of sotorasib in patients with KRAS p.G12C mutant advanced solid tumors. Approximately 60 patients (30 in Phase 1 and 30 in Phase 2) receiving the therapeutic dose as a monotherapy were to have intensive ECG assessments and were to be included in the QT assessment. The primary analysis was by-timepoint analysis of QTcF. There are no major changes in dosing regimen, PK/ECG schedule, and primary analysis methods after the previous IRT review.

Highlights of Clinical Pharmacology:

Sotorasib exhibits non-linear PK (less than dose proportional PK) across the dose range studied (180 mg to 960 mg). At the therapeutic dose of 960 mg QD, the mean (%CV) Cmax and AUC_{0-24h} for sotorasib was 8320 ng/mL (59%) and 81500 ng*hour/mL (44%) after a single dose, and was 7180 ng/mL (55%) and 43900 ng*hour/mL (58%) after multiple dosing. Sotorasib is a CYP3A4 inducer and its accumulation at steady state is 0.65 (induction effect). The fraction unbound in human plasma is 0.1. About 75 % of the drug is eliminated fecally (with 53% as unchanged drug) and 6% is renally eliminated. Mean Tmax is 1 hour (range 0.25 - 10 hours) for the parent drug. The mean terminal elimination $t_{1/2}$ of sotorasib is 5 hours. Food decreased Cmax by one-third and increased AUC by 25 % compared to the fasted state. Age, sex, race, and the mildly and moderately impaired renal and hepatic patients showed no effect in the sponsor's population PK analysis. The sponsor considers the co-administration with strong CYP3A4 inhibitor (itraconazole, 4% increase in Cmax) as the highest exposure scenario.

The three metabolites identified are M10 (inactive), M18 (markedly reduced activity and about 4-fold lower Cmax compared to the parent), and M24 (inactive). Mean Tmax is and 4-6 hours for the metabolites on Day 8 of 960 mg QD dosing. Terminal t1/2 was not evaluable for metabolites M10, M18, and M24 in Study 20170543.

Reviewer's comment: *PK and ECG sampling schedule in this QT assessment is expected to capture QT effect around maximum exposure of the parent drug and major metabolites.*

3.1.2 Nonclinical Safety Pharmacology Assessments

No cardiovascular concerns have been identified from nonclinical safety assessment. In the Good Laboratory Practice (GLP) sotorasib human ether-à-gogo-related gene (hERG) assay, the IC50 was 54.8 uM (Study 150431). The free fraction Cmax of sotorasib in human at 960 mg was 1.4~1.6 uM (Study 20170543, Phase 2, mean Cmax: 8320 ng/mL on Day 1, and 7180 ng/mL on Day 8, sotorasib molecular weight: 560.61, free fraction of sotorasib: 0.112); therefore, no clinically significant interaction with the hERG channel is expected over the proposed clinical dose range.

In a GLP cardiovascular safety pharmacology study in telemetered dogs, sotorasib at doses up to 300 mg/kg did not result in changes to electrocardiogram (ECG) or hemodynamic parameters (Study 150458). In 28-day and 3-month GLP repeat-dose toxicology studies in the dog (studies 154029 and 154033), there were no sotorasib-related effects on ECG parameters assessed with modified lead II.

Potential effects of the 3 metabolites, M24, M18 and M10, on hERG channel were also evaluated in vitro (studies 124803 and 153419). The IC50 value was greater than the highest concentration tested (30 uM or 29.9 uM), and clinically significant interactions are not expected, similar to the parent compound.

3.2 SPONSOR'S RESULTS

3.2.1 By Time Analysis

Based on data from Part 1A and Part 2A 960 mg QD group of Study 20170543, the sponsor conducted by-time point analysis using a linear mixed effect model with the change from baseline QTcF as the dependent variable, time (categorical) as factor, baseline QTcF as covariate, and subject as random effect. An unstructured covariance matrix was pre-specified for post-dose measurements within subject. The largest upper bound of 90% CI of ΔQTcF was <20 msec in the sponsor's analysis.

Reviewer's comment: *Results from the reviewer's independent by-time analysis are similar to the sponsor's results (the largest upper bound of 90% CI of ΔQTcF <20 msec for both analyses). Please see section 4.3 for details.*

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were some outliers per the sponsor's analysis for HR (<45 or >100 beats/min), PR (>220 msec and 25% over baseline) and QRS (>120 msec and 25% over baseline). No QTcF >500 msec or QTcF >60 msec over baseline were found in the sponsor's categorical analysis.

Reviewer's comment: *The reviewer's independent categorical analysis results are similar to the sponsor's results. Please see section 4.4 for details.*

3.2.3 Exposure-Response Analysis

All subjects in the safety analysis set (≥1 dose of sotorasib) who received the 960 mg QD dose [fasted], had intensive PK and ECGs collected, and had non-missing QTcF values at baseline and at ≥ 1 hour postbaseline timepoint were included in the concentration-QTc analysis.

Mixed-effect model analysis was conducted with the change from baseline QTcF as the dependent variable. Time-matched concentration was included as predictor variable,

baseline QTcF was included as a covariate in the model, and subject was included as a random effect for intercept and/or slope. The model with mean intercept fixed to 0 (with inter-subject variability) was found to best describe the relationship between pharmacokinetics and change in QTcF from baseline. A shallow trend between concentration and QTcF was observed (slope = 0.00044 msec/(ng/ml), $p < 0.05$). For a 960-mg dose of sotorasib on day 1 under fasted conditions, the model-predicted mean change in QTcF at the observed mean Cmax of 7550 ng/mL was 3.32 milliseconds (90% CI: 2.64, 4.00).

Reviewer's comment: *The reviewer's analysis included patients who had intensive PK/ECG data on all dose levels. The results of the reviewer's analysis are similar to the sponsor's analysis. Please see section 4.5 for details.*

3.2.4 Cardiac Safety Analysis

An integrated analysis of safety of sotorasib monotherapy in the planned marketing application will be provided by the pooled sotorasib monotherapy data from the phase 1 and phase 2 portions of phase 1/2 Study 20170543. The analysis will include an assessment of ECG parameters, and key summary of the data are provided below:

- There were 0 subjects with a QTcF maximum value post-baseline > 500 msec at the proposed indicated dose of 960 mg QD in subjects with NSCLC (n=190). There were 0 subjects with a QTcF maximum value post-baseline >500 msec at the proposed indicated dose of 960 mg QD in any tumor type (n=339).
- There was 1 subject (0.2%) at any tumor type, any dose (n=427) with QTcF maximum value post-baseline > 500 msec. This subject had colorectal cancer and was treated with sotorasib at a dose of 360 mg QD. The subject had a change from baseline QTcF of < 30 msec, with no AEs at time of QTcF increase, and no AEs from the cardiac system organ class (SOC), neuro SOC, or other potential clinical correlation at any time on study.
- There were 0 subjects in any of the groups (NSCLC at 960 mg, any tumor at 960 mg, and any tumor/any dose) with a maximum QTcF increase from baseline of > 60 msec.
- The subject incidence of the AEs as MedDRA preferred terms as noted by the Agency in the instructions at the proposed indicated dose of 960 mg QD in subjects with NSCLC (n=190) was as follows: QT prolongation (1.1%), syncope (0%), seizures (1.1%), ventricular arrhythmias and cardiac arrest MedDRA HLT (1.6%), ventricular tachycardia (0.5%), ventricular fibrillation (0.0%), flutter (0.0%), torsade de pointes (0.0%), and sudden deaths (0.0%).
- The subject incidence of the AEs as MedDRA preferred terms as noted by the Agency in the instructions at the proposed indicated dose of 960 mg QD in subjects with any tumor type (n=339) was as follows: QT prolongation (0.6%), syncope (0.3%), seizures (1.2%), ventricular arrhythmias and cardiac arrest MedDRA HLT (0.9%), ventricular tachycardia (0.3%), ventricular fibrillation (0.0%), flutter (0.0%), torsade de pointes (0.0%), and sudden deaths (0.0%).
- The subject incidence of the AEs as MedDRA preferred terms as noted by the Agency in the instructions at any dose in subjects with any tumor type (n=427) was as follows: QT prolongation (0.7%), syncope (0.5%), seizures (0.9%),

ventricular arrhythmias and cardiac arrest MedDRA HLT (0.7%), ventricular tachycardia (0.2%), ventricular fibrillation (0.0%), flutter (0.0%), torsade de pointes (0.0%), and sudden deaths (0.0%).

- A medical review by Amgen of these and all other cardiac events from the clinical trial ISS dataset did not suggest a risk of potential cardiac toxicity with sotorasib treatment at the intended dose and indication, at the intended dose with any tumor, and/or with any dose with any tumor type.

Reviewer's comment: *The narrative for patient ID* (b) (6)*, who died from cardiac arrest, was reviewed. The subject had a cardiac arrest of approximately 13 days after stopping treatment due to progression of disease. The investigator reported that the cardiac arrest was not related to AMG510 or to the study conduct.*

One subject (ID (b) (6)*) reported a serious TEAE of atrioventricular block second degree. AMG 510 was temporarily withheld for this event. The investigator reported that the event atrioventricular block second degree was not related to AMG 510 or to the study conduct. Previously reported electrocardiogram (ECG) dated 26/MAY/2020 revealed grade 2 intermittent atrioventricular (AV) block. The investigator reported that supraventricular tachycardia (onset dates 22/FEB/2020, 07/APR/2020 and 21/APR/2020) did not meet international conference on harmonization (ICH) seriousness criteria for reporting as separate serious adverse event. Previously reported electrophysiologic intervention was performed on 26/MAY/2020. There was no re-occurrence of the event after restarting of investigational study drug.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable as no large increases or decreases in heart rate (i.e. |mean| < 10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

1304 out of 19336 ECGs (~7%) were found potentially digitized with the ECG viewer inhouse. The digitized ECGs distributed quite evenly across all timepoints, which minimized the impact to overall ECG analysis quality. Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY TIME ANALYSIS

The by-time analyses were based on analysis population of Part 1A and Part 2A (monotherapy 960 QD groups) that had intensive ECG collection. All subjects with a baseline and at least one post-dose ECG were included.

The statistical reviewer used linear mixed model to analyze the drug effect by time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The model includes time (as a

categorical variable) as a fixed effect and baseline as a covariate. The model also includes an unstructured covariance matrix to explain the associated between repeated measures within subject.

4.3.1 QTc

Figure 1 displays the time profile of ΔQTcF for sotorasib 960 mg QD monotherapy. The maximum ΔQTcF values by treatment are shown in Table 2.

Figure 1: Mean and 90% CI of ΔQTcF Time Course (unadjusted CIs).

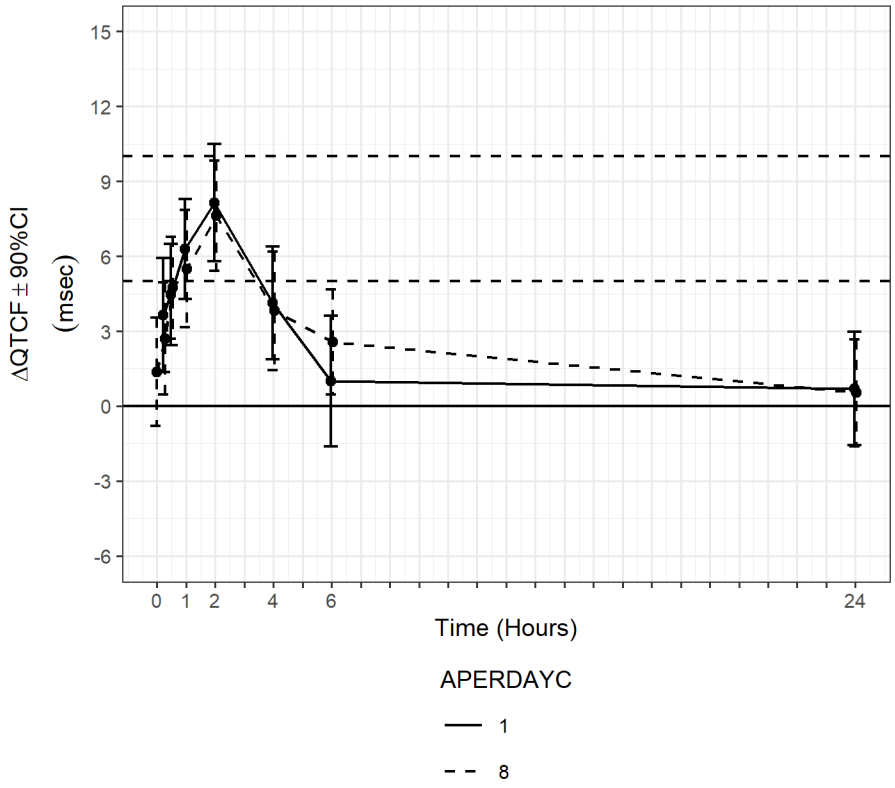


Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔQTcF

Actual Treatment	APERDAYC	N	Time (hours)	ΔQTCF (msec)	90.0% CI (msec)
960 mg QD	1	81	2	8.1	(5.8, 10.5)
	8	77	2	7.6	(5.4, 9.8)

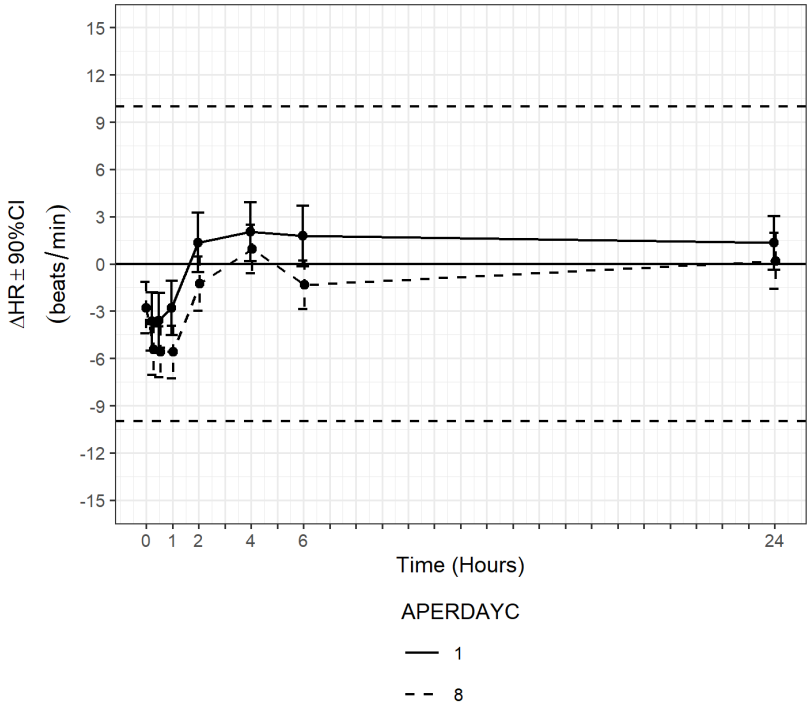
4.3.1.1 Assay sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔHR for sotorasib 960 mg QD monotherapy.

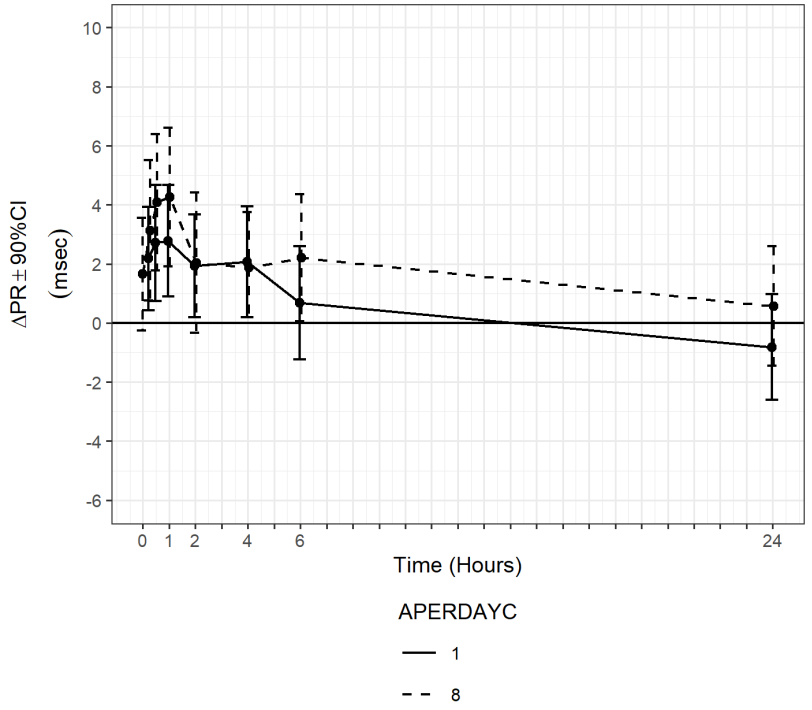
Figure 2: Mean and 90% CI of ΔHR Time Course



4.3.3 PR

Figure 3 displays the time profile of ΔPR for sotorasib 960 mg QD monotherapy.

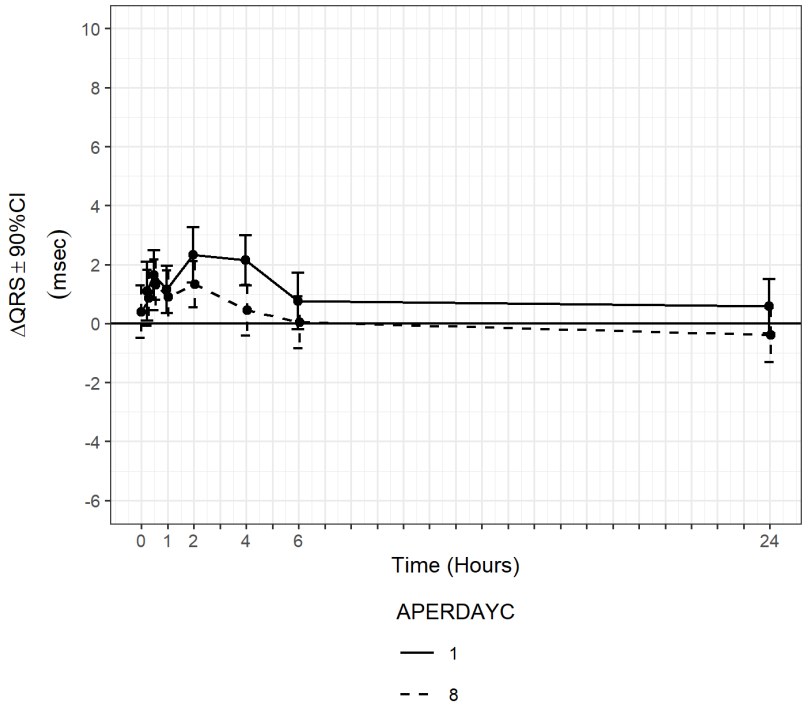
Figure 3: Mean and 90% CI of ΔPR Time Course



4.3.4 QRS

Figure 4 displays the time profile of ΔQRS for sotorasib 960 mg QD monotherapy.

Figure 4: Mean and 90% CI of ΔQRS Time Course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs. All data in safety population of Study 20170543 were included. The doses were pooled to 960 mg QD/480 mg BID group and <960 mg QD/480 mg BID group.

4.4.1 QTc

Table 3 lists the number of subjects and the number of observations whose QTcF values were between 450 and 480 msec, between 480 and 500 msec and greater than 500 msec.

Table 3: Categorical Analysis for QTc (maximum)

Treatment Group	Total N		450<QTcF<=480 msec		480<QTcF<=500 msec		QTcF>500 msec	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	363	363	11 (3.0%)	11 (3.0%)	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
<960 mg QD / 480 mg BID	48	1162	7 (14.6%)	59 (5.1%)	0 (0.0%)	9 (0.8%)	1 (2.1%)	1 (0.1%)
960 mg QD / 480 mg BID	315	4034	24 (7.6%)	133 (3.3%)	1 (0.3%)	2 (0.0%)	0 (0.0%)	0 (0.0%)

Table 4 lists the categorical analysis results for ΔQTcF (less than 30 msec, between 30 and 60 msec). No subjects had ΔQTcF >60 msec in the study.

Table 4: Categorical Analysis for ΔQTcF (maximum)

Treatment Group	Total N		ΔQTcF<=30 msec		30<ΔQTcF<=60 msec	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
<960 mg QD / 480 mg BID	47	1133	41 (87.2%)	1089 (96.1%)	6 (12.8%)	44 (3.9%)
960 mg QD / 480 mg BID	310	4004	278 (89.7%)	3906 (97.6%)	32 (10.3%)	98 (2.4%)

4.4.2 HR

Table 5 lists the categorical analysis results for maximum HR (>100 beats/min and >100 beats/min with >25% increase over baseline) and Table 5 lists the categorical analysis results for minimum HR (>45 beats/min and <=45 beats/min).

Table 5: Categorical Analysis for HR (maximum)

Treatment Group	Total N		HR>100 bpm		HR>100 bpm & Increase >25%	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	363	363	33 (9.1%)	33 (9.1%)		
<960 mg QD / 480 mg BID	48	1162	14 (29.2%)	137 (11.8%)	3 (6.3%)	3 (0.3%)
960 mg QD / 480 mg BID	315	4034	51 (16.2%)	243 (6.0%)	12 (3.8%)	24 (0.6%)

4.4.3 PR

Table 6 lists the categorical analysis results for PR (above 220 msec and above 220 msec with >25% increase over baseline).

Table 6: Categorical Analysis for PR

Treatment Group	Total N		PR>220 msec		PR>220 msec & Increase >25%	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	358	358	3 (0.8%)	3 (0.8%)		
<960 mg QD / 480 mg BID	48	1156	2 (4.2%)	19 (1.6%)	0 (0.0%)	0 (0.0%)
960 mg QD / 480 mg BID	310	3951	12 (3.9%)	77 (1.9%)	1 (0.3%)	1 (0.0%)

4.4.4 QRS

Table 7 lists the categorical analysis results for QRS (above 120 msec and above 120 msec with >25% increase over baseline).

Table 7: Categorical Analysis for QRS

Treatment Group	Total N		QRS>120 msec		QRS>120 msec & Increase >25%	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	363	363	22 (6.1%)	22 (6.1%)		
<960 mg QD / 480 mg BID	48	1162	3 (6.3%)	63 (5.4%)	0 (0.0%)	0 (0.0%)
960 mg QD / 480 mg BID	315	4034	23 (7.3%)	286 (7.1%)	1 (0.3%)	1 (0.0%)

4.5 EXPOSURE-RESPONSE ANALYSIS

The reviewer's concentration-QTc analysis was conducted using Cycle 1 Day 1 and Cycle 1 Day 8 data in patients who received at least one sotorasib dose as a monotherapy in the fasted condition, had intensive PK and ECGs collected, and had non-missing time-matched PK and change-from-baseline ECG data.

4.5.1 QTc

Prior to evaluating the relationship between drug-concentration and QTc using a linear model, the three key assumptions of the model needs to be evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) absence of delay between plasma concentration and ΔQTc and 3) absence of non-linear relationship.

Figure 2 shows the time-course of ΔHR, which shows an absence of significant ΔHR changes. Figure 5 evaluates the time-course of drug-concentration and ΔQTc in NSCLC patients who received 960 mg QD doses only. The figure does not appear to show significant hysteresis. The time profile in QTc changes resemble that of sotorasib. Based on the description of metabolite PK (e.g. lower exposure, Tmax between 4-6 hours), it is unlikely the observed QT effect were driven by metabolites. Figure 6 shows the relationship between drug concentration and ΔQTc and supports the use of a linear model.

Figure 5: Time course of drug concentration (top) and QTc (bottom)

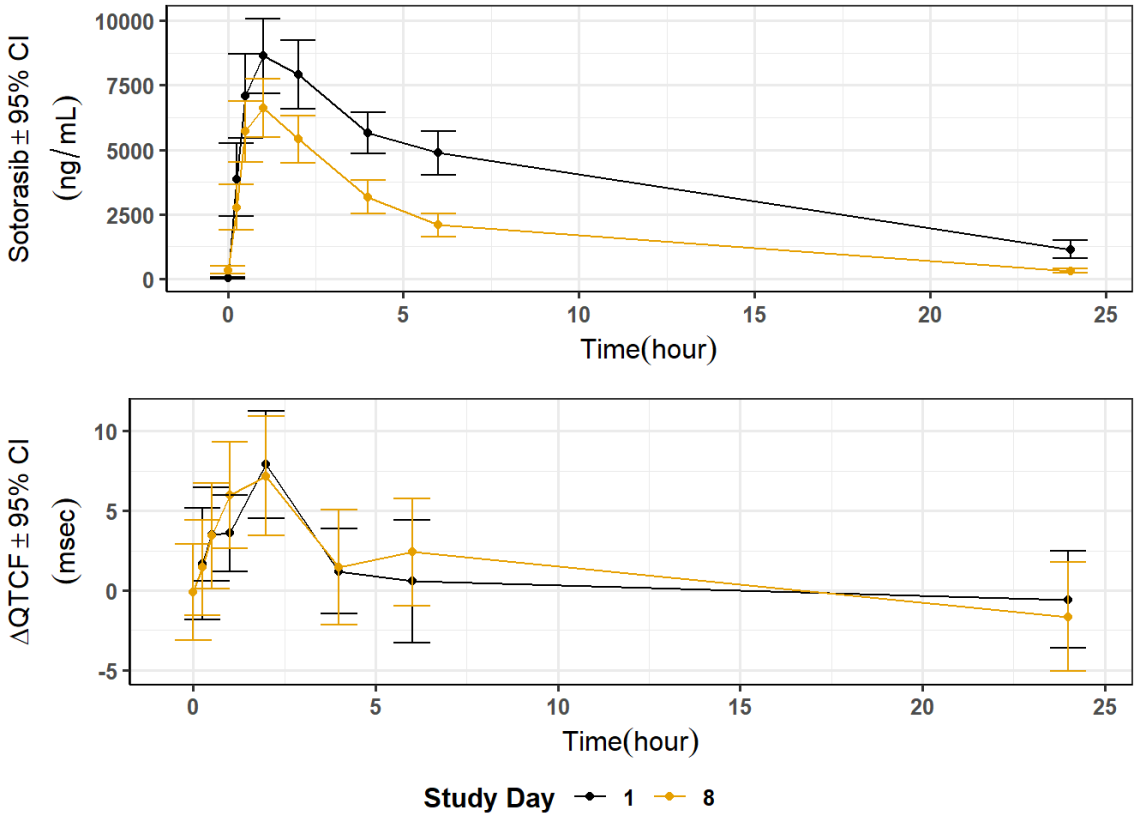
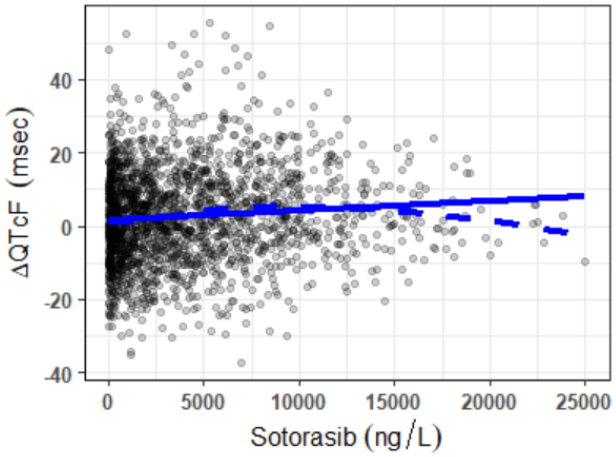


Figure 6: Assessment of linearity of concentration-QTc relationship



Finally, the linear mixed effect model (ΔQTc ~ 1 + CONC + Baseline QTc, with random effect on the slope and intercept) was applied to the data and the goodness-of-fit plot is shown in Figure 7. The model suggested that the concentration-dependent effect on ΔQTc was shallow but statistically significant (slope: 0.46 msec/(ug/mL), p-value: <0.001). Predictions of QTc effect in the subgroup that presented the highest observed concentration in the dataset (n=32) are provide in Table 8.

Figure 7: Goodness-of-fit plot for QTc

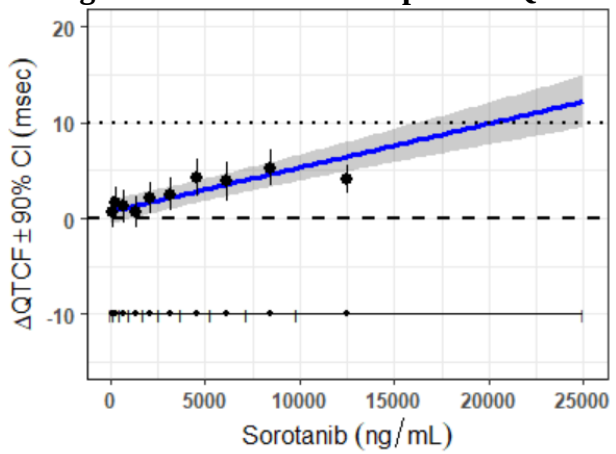


Table 8: Predictions from concentration-QTc model

DOSE	Sotorasib (ng/mL)	ΔQTCF (msec)	90.0% CI (msec)
PHASE 1 NSCLC 960 MG QD, Day 1	8615.2	4.7	(3.4 to 6.0)

Similar results were obtained in the reviewer's analysis that only included intensive PK/ECG data in patients from Part 1A and Part 2A of the study (Phase 1 data only).

4.5.1.1 Assay sensitivity

Not applicable.

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/s/

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
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:	March 22, 2021
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 214655
Product Name, Dosage Form, and Strength:	Lumakras (sotorasib) Tablets, 120 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Amgen Inc
FDA Received Date:	November 12, 2020, December 16, 2020, January 22, 2021, February 4, 2021, February 23, 2021
OSE RCM #:	2020-1338
DMEPA Safety Evaluator:	Janine Stewart, PharmD
DMEPA Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

As part of the approval process for Lumakras (sotorasib) Tablets, the Division of Oncology 2 (DO2) requested that we review the proposed Lumakras prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

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

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

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed PI, container label, and carton labeling for Lumakras (sotorasib) to identify deficiencies that may lead to medication errors and other areas of improvement. We identified areas of the container label and carton labeling that can be modified to improve the clarity of the information presented.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Lumakras PI, container label and, carton labeling can be improved to increase clarity and readability of important information to promote the safe use of the product. We provide a recommendation for the division in Section 4.1 and a recommendation for Amgen Inc in Section 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. Dosage and Administration Section

a. Consider revising the instructions in Section 2.2 pertaining to missed doses and what to do if vomiting occurs after taking the product for clarity and brevity as follows:

i. If a dose of LUMAKRAS is missed by greater than 6 hours, resume treatment as prescribed the next day.

ii. If vomiting occurs after taking LUMAKRAS, do not take an additional dose but resume treatment as prescribed the next day.

2. How Supplied/Storage and Handling Section

a. Consider revising the presentation of information in Section 16: How Supplied/Storage and Handling to improve readability; for example, as follows:

How Supplied

LUMAKRAS (sotorasib) 120 mg tablets, yellow, oblong-shaped, film-coated, debossed with "AMG" on one side and "120" on the opposite side 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]*.

4.2 RECOMMENDATIONS FOR AMGEN INC

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. We are concerned that the prominent strength statement at the top right corner of the principal display panel (PDP) may be misinterpreted as a net quantity statement. Consider relocating the prominent color-blocked strength statement from the top of the PDP to appear next to the proprietary name or below the established name.

2. Relocate the statement on the principal display panel (PDP) that reads "Each tablet contains 120 mg sotorasib" to appear on the back panel.

3. The net quantity statement lacks prominence among other product information. Increase the font size and relocate the net quantity statement to appear away from the strength statement such as in the lower left side of the principal display panel.

4. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for expired drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

5. For consistency with the Prescribing Information (PI) consider revising "Dosage: See Full Prescribing Information" to the following: Recommended dosage: See Prescribing Information.

B. Carton Labeling

1. Remove the statement on the back panel that lists the inactive ingredients and the ingredients of the tablet coating. This information provided in the PI and is not customarily provided on the carton labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Lumakras received on February 23, 2021 from Amgen Inc.

Table 2. Relevant Product Information for Lumakras	
Initial Approval Date	N/A
Active Ingredient	sotorasib
Indication	For the treatment of 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.
Route of Administration	Oral
Dosage Form	Tablets
Strength	120 mg
Dose and Frequency	Recommended dosage: 960 mg (8 tablets) once daily. • 1st dose reduction: 480 mg (4 tablets) once daily • 2nd dose reduction: 240 mg (2 tablets) once daily
How Supplied	• Carton containing 2 bottles of 120 tablets • Carton containing 1 bottle of 240 tablets
Storage	20°C to 25°C (68°F to 77°F). Excursions permitted to 15°C to 30°C (59 to 86°F)
Container Closure	120 cc white high-density polyethylene (HDPE) bottle and a two-piece child resistant (CR) (b) (4) closure with aluminum induction seal.

APPENDIX G. LABELS AND LABELING

G.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.

- Container label received on December 16, 2020
- Carton labeling received on December 16, 2020
- Prescribing Information (Image not shown) received on February 23, 2021, available from \\CDSESUB1\evsprod\nda214665\0017\m1\us\d-sotorasib-us-pi-v1-original-application-c-2020-1202.docx

G.2 Label and Labeling Images

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

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/

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