CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214665Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	145628
Request Receipt Date	10/8/2020
Product	Sotorasib (AMG 510)
Indication	Sotorasib is indicated for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with KRAS p.G12C mutation, as determined by an FDA-approved test, following at least one prior systemic therapy.
Drug Class/Mechanism of Action	Sotorasib is a small molecular inhibitor that binds irreversibly to KRAS p.G12C.
Sponsor	Amgen
ODE/Division	OCE DO2
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	12/7/2020

Note: This document must be uploaded into CDER's electronic document archival system as a ***clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes and*** *will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR).* ***Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.***

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 4a is checked "No," please provide the rationale in a brief paragraph below, and send the completed BTDDRT to Miranda Raggio for review so that the BTDR can be denied without MPC review. Once reviewed and cleared by Miranda this BTDR will be removed from the MPC calendar and you can skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Drug Description

Sotorasib is a novel, small molecule inhibitor that binds irreversibly to the KRAS p.G12C cysteine residue, thereby locking the kinase receptor in an inactive conformation.

Disease Background: KRAS p.G12C mutated non-small cell lung cancer

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Approximately 13% of patients with metastatic NSCLC harbor a Kirsten rat sarcoma proto-oncogene (KRAS) p.G12C mutation. This mutation leads to persistent downstream signaling from KRAS to pathways promoting cell growth and division including the RAF-MEK-ERK pathway. KRAS mutations are most commonly found in patients with a smoking history, a distinction from other mutations found in NSCLC patients such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) (Canon 2019). Other unique features of KRAS-mutated NSCLC are an increased programmed death-ligand1 (PD-L1) expression, high tumor mutational burden (TMB), and responsiveness to immunotherapy (Karatrasoglou 2020; Jeanson 2019). The median overall survival of KRAS p.G12C NSCLC patients treated with immunotherapy has improved to 21-28 months from 10-20 months with chemotherapy alone (Herbst 2019; Gadgeel 2019).

Regulatory history
Sotorasib is not approved in the US for any indication.

8. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

Amgen considers ORR, as assessed by a blinded, independent central review according to RECIST v1.1, to be a clinically meaningful, primary endpoint supporting the BTDR. Duration of response (DOR), progression free survival (PFS), and overall survival (OS) are secondary endpoints.

In confirmatory trial comparing sotorasib with docetaxel as second-line therapy for KRAS p.G12C mutated NSCLC, Amgen plans to assess PFS as the primary endpoint to support their application for sotorasib. OS and ORR will be secondary endpoints.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

The Division accepts endpoints as clinically significant outcome measures for patients with metastatic NSCLC and considered adequate to support traditional approval include an improvement in OS or a large, clinically meaningful improvement in PFS. ORR of large magnitude and long duration is considered to be an endpoint reasonably likely to predict clinical benefit in NSCLC and has been considered adequate to support accelerated approval for the treatment of patients with NSCLC (Blumenthal 2015).

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*

- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

There are currently no FDA-approved therapies specifically targeting KRAS mutations in NSCLC. Patients with KRAS p.G12C are treated with standard therapies approved for NSCLC that does not harbor a targetable mutation (such as EGFR, ALK). First-line standard therapies include immunotherapy alone or in combination with platinum-based chemotherapy. The vast majority of KRAS p.G12C patients will progress on upfront chemo-immunotherapy. After chemo-immunotherapy, second-line options are limited to docetaxel monotherapy or docetaxel with ramucirumab. The latter combination is toxic and rarely used clinically, while docetaxel monotherapy has a dismal ORR of about 6%.

The following table summarizes available therapies for NSCLC in the second-line setting:

- **Table 1. Available second line therapies for NSCLC**

Regimen	Intended population	Approval	n	ORR (95% Confidence Interval [CI])	Median DoR, months (95% CI)
Docetaxel	NSCLC after platinum therapy failure	Regular Primary endpoint: OS[1]	104 (TAX317)	5.5% (1.1, 15.1)	Not provided
			373 (TAX320)	5.7% (2.3, 11.3)	Not provided
Docetaxel +Ramucirumab	NSCLC after platinum therapy failure	Regular Primary endpoint: OS[2]	628	23% (20, 26)	Not provided
Pemetrexed	NSCLC (excluding squamous cell histology)	Regular Primary endpoint: OS[3]	283	8.5% (5.2, 11.7)	Not provided
Nivolumab	NSCLC after platinum therapy failure	Regular Primary endpoint: OS	286 (non-squamous)	19% (15, 24)	17 (8.4, NR)
			135 (squamous)	20% (14, 28)	NR (9.8, NR)
Atezolizumab	NSCLC after platinum therapy failure	Regular Primary endpoint: OS	425	14% (11, 17)	16.3 (10.0, NE)
Pembrolizumab	NSCLC, PD-L1 ≥1%	Regular Primary endpoint: OS	344	18% (14, 23)	NR (0.7, 20.1)

10. A brief description of any drugs being studied for the same indication, or very similar indication, that

requested breakthrough therapy designation[3].

There are no additional KRAS inhibitors being considered for BTD.

11. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

Table 2: Clinical Trial Supporting the BTDR

Study ID	Trial Design	Treatment Group	Patient Group	Trial Endpoints
CodeBreaK (Study 20170543)	Single arm study with two portions: dose escalation (n = 25) and dose expansion (n = 126)	Sotorasib 960mg daily for 21 day cycles.	Locally advanced or metastatic NSCLC with KRAS p.G12C mutation previously treated with ≥1 systemic therapy	Dose escalation: safety and tolerability Dose expansion: objective response rate (ORR) and duration of response (DOR)

Table 3. Anti-tumor efficacy of sotorasib

Efficacy parameter	Primary efficacy population N=123	Prior treatment with platinum-based chemo and immunotherapy N=99
ORR by BICR, n (%)	**46 (37)**	**32 (32)**
95% CI	(29, 47)	(23, 43)
Complete response	2 (1.6)	NR
Partial response	44 (36)	NR
Median DOR (mos)	8.4	NE
95% CI	(6.9, 8.4)	(6.9, NE)
% response ≥ 6mos	50	NR

NR: not reported; NE: not estimable

b. Include any additional relevant information. Consider the following in your response:

CodeBreaK is an ongoing study of sotorasib in patients with locally advanced or metastatic KRAS p.G12C-positive malignancies, including NSCLC (Table 2). Key eligibility criteria for study enrollment included confirmation of KRAS p.G12C mutation by central testing using the Qiagen *therascreen*® KRAS RGQ PCR kit, and receipt of prior standard chemotherapy and/or immunotherapy. Patients with active CNS metastasis were excluded from the study.

Top-line results from CodeBreaK are shown in Table 3. As of the data cutoff date of September 1, 2020, 41 of the 46 responders (89%) have had ≥6 months of response follow-up. At next planned data cutoff of December 1, 2020, all responders will have had at least 6 months of response follow-up at that time.

The reported ORR of 32% in a refractory KRAS p.G12C population represents an improvement over available second-line therapies that have ORRs ranging from 6-23%.

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*

- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*

- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

  The safety profile of sotorasib is acceptable based upon the available data from 126 patients. 99% of patients experienced treatment-emergent adverse events (TEAEs); of these, the most common (≥20%) were diarrhea (49%), nausea (29%), fatigue (25%), increased aspartate aminotransferase (21%), and increased alanine aminotransferase. Serious adverse events were reported for 63 of patients (50%). Eleven patients (8.7%) discontinued sotorasib due to an adverse event. Of the 18 fatal adverse events on study, none were considered related to sotorasib by the investigator.

12. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Provide brief summary of rationale for granting: The ORR and DoR observed in the CodeBreaK study demonstrate an improvement overcurrently available second-line therapy for patients with KRAS G12C mutant NSCLC who have progressed on prior platinum-based chemotherapy and immunotherapy. ORR and DoR are accepted endpoints in NSCLC as being predictive of clinical benefit and have been used to support accelerated approvals.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

13. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

   The Division met with Amgen in November 2020 to discuss modifications to their confirmatory trial comparing sotorasib versus docetaxel in patients with KRAS p.G12C who have already received chemotherapy and immunotherapy. We are recommending changes to the powering of the study so that fewer patients are randomized to docetaxel given the very low ORR (6%) of docetaxel in this setting.

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

14. List references, if any:

1. Blumenthal GM, et al. Overall response rate, progression-free survival, and overall survival with targeted and standard therapies in advanced non-small-cell lung cancer: US Food and Drug Administration trial-level and patient-level analyses. J Clin Oncol. 2015 Mar 20;33(9):1008-14.
2. .Canon, J., Rex, K., Saiki, A.Y. *et al.* The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. *Nature* **575,** 217–223 (2019).
3. Herbst RS, Lopes G, Kowalski DM, *et al.* Association of KRAS mutational status with response to pembrolizumab monotherapy given as first-line therapy for PD-L1-positive advanced non-squamous NSCLC in KEYNOTE-042. ESMO Immuno-Oncology Congress 2019.
4. Gadgeel, S. et al. KRAS mutational status and efficacy in KEYNOTE-189: Pembrolizumab (pembro) plus chemotherapy (chemo) vs placebo plus chemo as first-line therapy for metastatic non-squamous NSCLC. ESMO Immuno-Oncology Congress 2019.
5. Karatrasoglou, E.A., Chatziandreou, I., Sakellariou, S. *et al.* Association between PD-L1 expression and driver gene mutations in non-small cell lung cancer patients: correlation with clinical data. *Virchows Arch* **477,** 207–217 (2020).
6. Jeanson A, et al. Efficacy of Immune Checkpoint Inhibitors in KRAS-Mutant Non-Small Cell Lung Cancer (NSCLC). J Thorac Oncol. 2019 Jun;14(6):1095-1101.

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 10/13/20 /M. Raggio

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/

ERICA C NAKAJIMA
12/02/2020 08:26:58 AM

B HARPREET SINGH
12/03/2020 04:14:59 PM

NICOLE L DREZNER
12/04/2020 09:47:06 AM

IND 145628

MEETING MINUTES

Amgen, Inc.
Attention: Vandana Pathak, M.Sc., RAC
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop: 27-3-A
Thousand Oaks, CA 91320-1799

Dear Ms. Pathak:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for sotorasib (AMG510).

We also refer to the teleconference between representatives of your firm and the FDA on November 10, 2020. The purpose of the meeting was to discuss and reach agreement on the clinical and nonclinical aspects of the sotorasib program in advance of a planned NDA.

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

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

If you have any questions, call me at 301-796-3074.

Sincerely,

{See appended electronic signature page}

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	November 10, 2020; 12:00 PM – 1:00 PM, EST
Meeting Location:	Teleconference
Application Number:	IND 145628
Product Name:	sotorasib (AMG510)
Indication:	Sotorasib is indicated for the treatment of patients with *KRAS G12C*-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by a Food and Drug Administration (FDA)-approved test, who have received at least one prior systemic therapy
Sponsor Name:	Amgen, Inc.
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetics Act
Meeting Chair:	Nicole Drezner
Meeting Recorder:	Idara Udoh

FDA ATTENDEES

Harpreet Singh, Director, Division of Oncology 2 (DO2)
Nicole Drezner, Clinical Team Lead, DO2
Erin Larkins, Clinical Team Lead, DO2
Erica Nakajima, Clinical Reviewer, DO2
Luckson Mathieu, Clinical Reviewer, DO2
Katie Chon, Clinical Reviewer, DO2
Liza Stapleford, Clinical Reviewer, DO2
Whitney Helms, Nonclinical Team Leader, Division of Hematology, Oncology, and Toxicology Products (DHOT)
Sachia Khasar, Nonclinical Reviewer, DHOT
Xing Wang, Product Quality Team Lead, Office of New Drug Products
Hong Zhao, Clinical Pharmacology Team Lead, Office of Clinical Pharmacology (OCP)
Guoxiang (George) Shen, Clinical Pharmacology Reviewer, OCP
Xinyuan Zhang, Clinical Pharmacology Reviewer, OCP
Rosane Charlab Orbach, Genomics Team Lead, OCP
Pallavi Mishra-Kalyani, Statistics Team Lead, Division of Biometrics (DB)
Somak Chatterjee, Statistics Reviewer, DB
Missiratch Biable, Chief, Division of Regulatory Operations (DORO)
Idara Udoh, Senior Regulatory Health Project Manager, DORO
Emily Pak, Regulatory Health Project Manager, DORO

Gregory Reaman, Associate Director for Pediatric Oncology, Office of Oncologic Diseases

SPONSOR ATTENDEES
Monica Batra, Director, Global Regulatory Affairs
Sandeep Dutta, Executive Director, Clinical Pharmacology Modeling & Simulation
Greg Friberg, Vice President, Global Development
Michelle Geller, Executive Medical Director, Global Safety
Brett Houk, Director, Clinical Pharmacology Modeling & Simulation
Jacqueline Kline, Executive Director, Global Regulatory Affairs
Julie Lepin, Vice President, Global Regulatory Affairs
Omar Mather, Medical Director, Global Safety
Gift Ngarmchamnanrith, Executive Medical Director, Global Development
Eric Ng, Medical Director, Global Safety
Vandana Pathak, Senior Manager, Global Regulatory Affairs
Ramachandran Suresh, Executive Director, Global Biostatistics
Xuena Wang, Director, Global Biostatistics

BACKGROUND

Meeting Purpose

On September 16, 2020, Amgen, Inc. submitted a request for a type B, pre-New Drug Application (NDA) meeting to discuss to discuss and reach agreement on the clinical and nonclinical aspects of the sotorasib program in advance of a planned NDA. FDA granted the meeting on September 28, 2020.

The briefing package was received on October 14, 2020.

FDA sent Preliminary Comments to Amgen on November 4, 2020.

Regulatory

On June 6, 2018, IND 139023 was initiated with submission of Study 20170543, a first-in-human, dose escalation and dose expansion study of AMG 510 in patients with advanced solid tumors with KRAS G12C-mutation.

On August 16, 2019, Fast Track Designation was granted under IND 139023 for AMG 510 for the treatment of metastatic non-small cell lung cancer (NSCLC) with KRAS pG12C mutation with disease progression on or after platinum-based chemotherapy.

On August 30, 2019, Amgen requested a pre-IND meeting (PIND 145628) to discuss the design of a proposed clinical trial, Study 20190009, a randomized, open-label study of sotorasib versus docetaxel in patients with previously treated locally advanced and unresectable or metastatic KRAS G12C-mutated NSCLC.

On January 8, 2020, an Initial Pediatric Study Plan (iPSP) was submitted for AMG 510 for treatment of previously treated locally advanced and metastatic NSCLC with KRAS p.G12C mutation; and a Written Response letter issued on February 27, 2020. Amgen submitted its Agreed iPSP on March 13, 2020, and the Agreement letter issued on April 7, 2020.

On October 8, 2020, a request for Breakthrough Therapy Designation was received, and is currently under review.

Nonclinical

AMG 510 is an irreversible small molecule inhibitor of $KRAS^{G12C}$. Amgen has completed in vitro and in vivo pharmacology studies with AMG 510 to assess its mechanism of action and activity; safety pharmacology studies assessing CNS and cardiovascular endpoints; GLP-compliant toxicology studies of up to 3 months duration in Sprague-Dawley rats and Beagle dogs; as well as embryo-fetal development studies in rats and rabbits. Amgen does not plan to conduct carcinogenicity studies.

Clinical Pharmacology

Per Amgen, after single and multiple doses, sotorasib is absorbed rapidly after oral administration with median tmax values between 0.75 to 2 hours. In patients with KRAS p.G12C-mutated advanced solid tumors, increases in sotorasib exposure from 180 to 960 mg once-daily were less than dose proportional based on preliminary data. Sotorasib does not accumulate with multiple oral once daily dosing. Mean half-life ranged from 5 to 7 hours. In a human mass balance study 20190321, after a 720-mg dose, the geometric mean cumulative recovery of radioactivity over the collection period (0 to 312 hours) was 80.6%, with 74.4% being excreted in the feces and 5.81% excreted in the urine. Dose excreted unchanged in urine was only 1.5%. When sotorasib was coadministered with a high-fat meal, AUC_{inf} and C_{max} were 1.38- and 1.03-fold of sotorasib administered under fasted conditions, respectively.

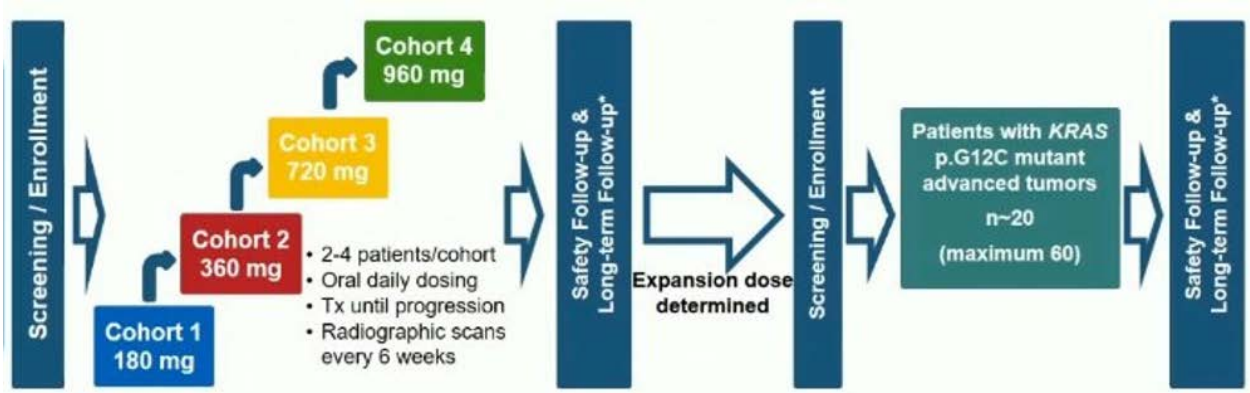
The completed drug-drug interaction studies suggest that there was no significant change of sotorasib pharmacokinetics (PK) exposure when coadministered with metformin (MATE1 competitive inhibition). There was a 4% increase in C_{max} and 26% increase in AUC of sotorasib when coadministered with a strong CYP3A4 inhibitor itraconazole. Coadministration of a single dose rifampin (an OATP1B1/3 inhibitor) decreased sotorasib C_{max} by 16% and AUC by 24%, while multiple-dose rifampin (strong CYP3A inducer) decreased sotorasib C_{max} by 35% and AUC by 51%. Coadministration of a proton pump inhibitor omeprazole decreased sotorasib C_{max} by 57% and AUC by 42%. Coadministration of sotorasib increased P-gp substrate digoxin C_{max} by 91% and AUC by 21%. Coadministration of sotorasib has no significant effect on PK of metformin, a sensitive substrate of MATE1/MATE2-K.

Clinical

There are no approved therapies targeting KRAS mutations in lung cancer. KRAS mutations are found in approximately 20-30% of non-small cell lung cancer (NSCLC),

and the point mutation KRAS p.G12C is found in about 13% of NSCLC patients. Amgen intends to submit an NDA for sotorasib for the treatment of patients with KRAS p.G12C-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least one prior systemic therapy.

Study 20170543: Single arm study of sotorasib in KRAS p.G12C mutant solid tumors
CodeBreaK (Study 20170543) is an ongoing, multi-center, non-randomized, dose escalation and dose expansion study of sotorasib in patients with locally advanced or metastatic KRAS p.G12C-positive malignancies, including NSCLC. The primary objective of the dose escalation portion is to assess the safety and tolerability of sotorasib and to establish a recommended phase 2 dose (RP2D). The primary objective of the dose expansion portion is to evaluate the antitumor activity of sotorasib by overall response rate (ORR) assessed by blinded independent central review (BICR) per RECIST v1.1. Key eligibility criteria for study enrollment included confirmation of KRAS p.G12C mutation by central testing using the Qiagen *therascreen*® KRAS RGQ PCR kit, and receipt of prior standard chemotherapy and/or immunotherapy. Patients with active CNS metastasis were excluded from the study. A study schema is provided below.



Meeting package, Appendix 8

Summary of efficacy
The data cut-off date for the analysis of the dose expansion portion of the study, in which all patients received sotorasib at the RP2D of 960 mg once daily, was September 1, 2020 with a median follow-up of 6.9 months. A total of 126 patients with previously treated KRAS p.G12C mutated NSCLC were enrolled and of these, 123 patients were evaluable for response by the data cutoff date. Of these, 99 patients (80%) received prior treatment with both platinum-based chemotherapy and an anti-PD-(L)1 agent. A summary of the efficacy results is provided in the table below.

Efficacy parameter	Primary efficacy population N=123	Prior treatment with chemo and IO N=99
ORR by BICR, n (%)	46 (37%)	32 (32%)
95% CI	(29, 47)	(23, 43)
Complete response	2 (1.6)	NR
Partial response	44 (36)	NR
Median DOR (mos)	8.4	NE
95% CI	(6.9, 8.4)	(6.9, NE)
% response ≥ 6mos	50	NR

NR: not reported; NE: not estimable

Amgen states that as of the data cutoff date of September 1, 2020, 41 of the 46 responders (89%) have had at least 6 months of response follow-up. The next planned data cutoff will be on December 1, 2020, and all responders will have had at least 6 months of response follow-up at that time.

Summary of Safety
The primary safety population supporting the proposed indication will include all patients with NSCLC who received sotorasib 960 mg QD across both the dose escalation and dose expansion portion of the study. The meeting package provides safety data from the126 NSCLC patients from the dose expansion portion of Study 20170543. A total of 99% of patients experienced treatment-emergent adverse events (TEAE); of these, the most common (≥20%) were diarrhea (49%), nausea (29%), fatigue (25%), increased aspartate aminotransferase (21%), and increased alanine aminotransferase (21%). Serious adverse events (SAE) were reported in 63 patients (50%). Eleven patients (8.7%) discontinued sotorasib due to an adverse event. There were 18 fatal adverse events; none were considered related to study therapy by the investigator.

Treatment-emergent adverse events of interest included hepatotoxicity, observed in 32% of NSCLC patients, and renal toxicity, observed in 21% of patients. Sotorasib was discontinued for 6% of patients with hepatotoxicity. No patients with renal toxicity discontinued sotorasib.

Proposed contents of the NDA:

- The Summary of Clinical Efficacy (SCE) will contain the narrative description of efficacy results from the dose expansion portion of Study 20170543 involving 123 patients with NSCLC in the primary efficacy population. A brief summary of efficacy data from the phase 1 portion of Study 20170543 will also be provided in the SCE but will not be pooled with the phase 2 data. An Integrated Summary of Efficacy (ISE) will not be included in the submission.
- The primary safety population will include patients with NSCLC who received sotorasib as a single agent at the RP2D across both the dose escalation and dose expansion portions of Study 20170543.

- In the Summary of Clinical Safety (SCS), pooled data will be presented from patients with KRAS p.G12C mutated NSCLC, colon cancer, and other solid tumors who received at least one dose of sotorasib 960mg.
- The Integrated Summary of Safety (ISS) will provide tables summarizing safety data across dose regimens, tumor types, and fed/fasted status.

DISCUSSION

Nonclinical

1) Does the Agency agree with the planned nonclinical package in support of the NDA submission for the proposed indication?

FDA Response: Based on the table of completed studies in Appendix 6 of the meeting package, the planned nonclinical package appears acceptable; however, FDA will determine the adequacy of the data to support the approval of a marketing application during the review of the package submitted to the NDA.

Amgen's Response (received via email on November 6, 2020): Amgen acknowledges the Agency's feedback.

Discussion During Meeting: No discussion occurred.

Clinical

2) Does the Agency agree that clinical data from the pivotal phase 2 portion of Study 20170543 and the supporting studies provide an adequate basis for NDA submission under accelerated approval regulations (21 CFR 314 Subpart H) for sotorasib monotherapy for the proposed indication of the treatment of patients with *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC who have received at least 1 prior systemic therapy?

FDA Response: FDA agrees that the study results from the dose expansion portion of Study 20170543 proposed for inclusion in an NDA may provide sufficient evidence to characterize the benefits and risks of sotorasib for the proposed indication. The proposed data may be adequate to support accelerated or regular approval; this will be determined during review of the NDA.

Since Study 20190009 is being conducted in the same patient population as the subgroup of patients with NSCLC enrolled in the dose expansion portion of Study 20170543 who received prior treatment with both chemotherapy and an anti-PD-(L)1 agent (n=99), FDA suggests implementing an early stopping rule for futility in the docetaxel arm and/or a 2:1 randomization scheme to maximize the number of patients with KRAS p.G12C mutated NSCLC who receive sotorasib.

Amgen's Response (received via email on November 6, 2020): The Study 20190009 is overseen by an independent data monitoring committee (DMC) which will act in an advisory capacity to the sponsor with respect to safeguarding the interests of study subjects, assessing interim safety and efficacy data, monitoring the overall conduct of the study, and providing with recommendations relating to continuing, modifying, or stopping the study based on these findings. An interim analysis (IA) is planned (when approximately 66.7% of the total PFS events have been observed, or when the enrollment is finished. At that time, DMC may recommend an early stopping or consideration of crossover depending on the interim IA result.

Discussion During Meeting: FDA clarified that Study 20190009 should not be used solely as a confirmatory trial for conversion to regular approval given the issues described using docetaxel as a comparator in the US population. FDA acknowledged Amgen's response describing an early analysis for futility and that the trial is already undergoing enrollment.

Clinical Safety

3) Does the Agency agree with Amgen's approach for overall safety evaluation to support the NDA submission for the proposed indication?

FDA Response: FDA agrees.

Amgen's Response (received via email on November 6, 2020): Amgen acknowledges the Agency's feedback.

Discussion During Meeting: No discussion occurred.

4) Does the Agency agree with the submission of the 90-day safety update report with the proposed additional months of safety data?

FDA Response: FDA agrees.

Amgen's Response (received via email on November 6, 2020): Amgen acknowledges the Agency's feedback.

Discussion During Meeting: No discussion occurred.

Does the Agency agree with the proposal to submit updated efficacy data with the 90-day safety update report and that updated efficacy data will not impact the NDA review timelines and the PDUFA action date?

FDA Response: Yes, FDA agrees.

Amgen's Response (received via email on November 6, 2020): Amgen acknowledges the Agency's feedback.

Discussion During Meeting: No discussion occurred.

5) Does the Agency agree that a Risk Evaluation and Mitigation Strategy or Medication Guide would not be considered necessary to support the NDA submission for the proposed indication?

FDA Response: The necessity of REMs will be determined at the time of NDA review.

Amgen's Response (received via email on November 6, 2020): Amgen acknowledges the Agency's feedback.

Discussion During Meeting: No discussion occurred.

Clinical Pharmacology

6) Does the Agency agree that clinical pharmacology studies and the key conclusions are sufficient to support the planned NDA?

FDA Response: The proposed clinical pharmacology package appears sufficient to support the planned NDA. However, Amgen should evaluate whether sotorasib is a substrate of human uptake transporters. In addition, a dedicated hepatic impairment study should be initiated as soon as possible with the inclusion of patients with moderate and severe hepatic impairment. The selection of the dose for patients with severe hepatic impairment should be based on emerging pharmacokinetics (PK) and safety (such as liver toxicity) data from patients with moderate hepatic impairment. Submit the full protocol to obtain FDA's agreement on the study design.

FDA has the following comments regarding the utility of the PBPK approach to evaluate the effect of sotorasib on the PK of a CYP2D6 substrate:

- The inhibition constant (Ki) value towards CYP2D6 should be corrected for protein binding when it is used in the PBPK analysis.
- If sensitivity analysis is conducted for the Ki value, provide a table comparing the in vitro Ki,u values and the Ki,u values used in PBPK modeling to recover the observed DDIs for known CYP2D6 inhibitors.
- Include the major metabolite, M24, in the model as a CYP2D6 perpetrator. If not, provide justification.

It appears reasonable to use Study 20170543 to support the QT assessment of sotorasib for the proposed indication. The adequacy of dose selection and sample size will be a review issue.

Additionally, we have the following comments for you to consider:

- When you submit your QT evaluation report, please include a completed version of the "QT Evaluation Report Submission Checklist" located at the IRT website (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/interdisciplinaryreview-team-cardiac-safety-studies-formerly-qt-irt).

- For each study included in your QT evaluation report, submit the related digital ECGs with annotations in electronic format (XML) following the HL7 annotated ECG (aECG) standard to the ECG warehouse (www.ecgwarehouse.com). Scan paper ECGs into PDF and submit to FDA only if digital ones are not available.

- FDA is currently testing our capability to receive aECG HL7 files directly through the FDA electronic submission gateway. If you would like to volunteer to test this capability, you are welcome to perform an additional submission of the aECG HL7 files directly through FDA electronic submission gateway. We recommend placing the aECG file in an aecg folder under the misc folder (e.g., m5 -> datasets -> [study-id] -> misc -> aecg).

Amgen's Response (received via email on November 6, 2020):

Hepatic Impairment Study

Amgen will submit the full protocol for a hepatic impairment study for the Agency's review for obtaining agreement on the study design.

PBPK Approach and QT Assessment of Sotorasib

Amgen will include the requested information in the planned NDA as advised.

Discussion During Meeting: No discussion occurred.

Regulatory

7) Does the Agency concur that with the agreed initial pediatric study plan, pre-filing pediatric requirements per the amendments made by FDA

Reauthorization Act of 2017 (FDARA) Section 504 to Section 505B of the Federal Food, Drug, and Cosmetic Act regarding molecularly targeted oncology drugs have been met?

FDA Response: FDA does not agree. Because your planned marketing application was not submitted prior to August 18, 2020 and consistent with the advice in our April 7, 2020 letter indicating agreement with your iPSP, you will need to amend the iPSP to address the new PREA requirements, as amended by FDARA section 504 to section 505B of the FD&C Act regarding molecularly targeted oncology drugs. This amended iPSP should addresses the target of this product (KRAS p.G12C) and its potential relevance to one or more pediatric cancers and describe the molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach) and/or any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation and justification for this approach.

Amgen's Response (received via email on November 6, 2020): Amgen acknowledges the Agency's feedback. Amgen kindly refers the Agency to the Agreed Initial Pediatric Study Plan (Reference ID: 4588278) which provided evidence to support a full waiver of sotorasib based lack of relevance of *KRAS pG12C* molecular target in pediatric cancers.

(b) (4)

(b) (4)

Discussion During Meeting: FDA agreed in principle with Amgen's planned request for a waiver and recommends revision of Section 4 to clarify the justification based specifically on the lack of relevance of the target KRAS *p.G12C* in childhood cancers.

8) **Given the top-line results from the pivotal phase 2 portion of Study 20170543, Amgen intends to apply for Priority Review Designation.**

a. **Does the Agency have any comments on Amgen's proposal to apply for Priority Review Designation in the initial NDA?**

FDA Response: The proposal is acceptable. The final decision regarding Priority Review Designation will be made at the time of NDA review.

Discussion During Meeting: No discussion occurred.

b. **In case the planned NDA is not selected for the Real-Time Oncology Review (RTOR) Pilot Program, does the Agency agree with the rolling review based on the proposed plan and schedule of submission of NDA components given sotorasib has been granted fast track designation for the NSCLC indication?**

FDA Response: Yes, FDA agrees with the rolling review based upon the proposed plan.

We also agree with your request for RTOR.

Amgen's Response (received via email on November 6, 2020): Amgen acknowledges the Agency's agreement regarding Amgen's participation in the RTOR pilot program for the review of its initial NDA for sotorasib monotherapy for the proposed indication of treatment of patients with *KRAS p.G12C*-mutated NSCLC.

Amgen included a plan for submission of proposed NDA components and timelines for the pre-submission batches in the RTOR request submitted on 12 October 2020 (IND 145628; Serial No. 0045). In order to initiate the submission of NDA components, Amgen hereby proposes to submit the first pre-submission batch on 12 November 2020.

As the initial RTOR request submitted on 12 October 2020 included the proposal for submission of NDA components starting from 21 October 2020, Amgen has now merged the first and second pre-submission batches (from the initial RTOR request) as first pre-submission batch for submission on 12 November 2020. No changes to the NDA components of the subsequent batches have been made. A detailed submission plan of the NDA components and timelines for the pre-submission batches is included as Appendix 2.

Does the Agency agree with the proposed schedule and plan of submission of NDA components under the RTOR pilot program?

Discussion During Meeting: FDA will clarify whether it is acceptable to begin submitting the NDA components on November 12th and will follow-up with Amgen.

Post-Meeting Response: FDA notified Amgen that submission of its RTOR NDA components before receipt of the November 10th meeting minutes was acceptable. Refer to the attached "Appendix 2_Sotorasib RTOR Pre-submission Plan for submission timelines."

9) Based on the data presented herein and considering the totality of evidence, can the Agency advise if they intend to convene an Oncologic Drug Advisory Committee meeting for the planned NDA?

FDA Response: FDA does not plan to convene an ODAC for the planned NDA at this time.

Amgen's Response (received via email on November 6, 2020): Amgen acknowledges the Agency's feedback.

Discussion During Meeting: No discussion occurred.

Multidisciplinary

10) Based on the high-level summary of the data from clinical, clinical pharmacology, and nonclinical studies, does the Agency have any preliminary feedback on the overall content of the sotorasib full prescribing information and draft carton and container labels that Amgen can consider at the time of its inclusion in the NDA?

FDA Response: FDA cannot comment on the full prescribing information, draft carton, or container labels until full study data is provided.

Amgen's Response (received via email on November 6, 2020): Amgen acknowledges the Agency's feedback.

Discussion During Meeting: No discussion occurred.

11) Can the Agency provide advice on the timing and process for Bioresearch Monitoring Program (BIMO) site audits to support the planned NDA?

FDA Response: Decisions regarding BIMO site audits are made at the time that inspections are determined to be necessary to the review of an application. We will provide advice regarding timing, scope, and processes at that time.

Amgen's Response (received via email on November 6, 2020): Amgen acknowledges the Agency's feedback.

Discussion During Meeting: No discussion occurred.

12) Given the COVID-19 pandemic, can the Agency confirm that the approach of documenting the affected procedures is acceptable to describe the actions taken as a result of the COVID-19 pandemic?

FDA Response: Yes, FDA agrees that the documentation of procedures affected by COVID-19 is acceptable.

Amgen's Response (received via email on November 6, 2020): Amgen appreciates the Agency for its response.

Discussion During Meeting: No discussion occurred.

ADDITIONAL FDA COMMENTS

Clinical Pharmacology

13) The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products –Content and Format" (available at: https://www.fda.gov/media/74346/download). Consider strategies to enhance clarity, readability, and comprehension of this information for health

care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

Amgen's Response (received via email on November 6, 2020): Amgen acknowledges the FDA's comments

Discussion During Meeting: No discussion occurred.

14) Address the following questions in the Summary of Clinical Pharmacology:

a. What is the basis for selecting the doses and dosing regimen used in the trials intended to support your marketing application? Identify individuals who required dose modifications, and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.
b. What are the exposure-response relationships for efficacy, safety and biomarkers?
c. What is the effect of sotorasib on the QT/QTc interval?
d. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?
e. What are the effects of food on the bioavailability? What are the dosing recommendations with regard to meals or meal types? Provide justification for recommendation with regard to meals or meal types.
f. How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?

Amgen's Response (received via email on November 6, 2020): Amgen acknowledges the FDA's comments

Discussion During Meeting: No discussion occurred.

15) Apply the following advice in preparing the clinical pharmacology sections of the original submission:

a. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
b. Provide the final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with minimum and maximum values as appropriate.
c. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
    - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of

each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

- Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.

d. Submit the following for the population pharmacokinetic analysis reports:

- Standard model diagnostic plots
- Individual plots for a representative number of subjects.

Each individual plot should include observed concentrations, the individual prediction line and the population prediction line

- Model parameter names and units in tables.
- Summary of the report describing the clinical application of modeling results. Refer to the following pharmacometric data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

e. Submit the following information and data to support the population pharmacokinetic analysis:

- SAS transport files (*.xpt) for all datasets used for model development and validation
- A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
- Model codes or control streams and output listings for all major model building steps (e.g., base structural model, covariates models, final model, and validation model). Submit these files as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt)

f. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to Guidance for Industry at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf for population PK, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for exposure-response relationships.

Amgen's Response (received via email on November 6, 2020): Amgen acknowledges the FDA's comments

Discussion During Meeting: No discussion occurred.

16) Include the purpose of the simulations, assumptions, detailed process of PBPK model building and verification, summary of model input parameters, version of software, simulation results, and conclusions in the study report.

a. Provide the study report as PDF files (screenshots can be incorporated if required).
b. Include the model files used to generate the final PBPK simulations. These files should be executable by FDA reviewers using the specified software.
c. Include appropriate supporting documentations such as any special instructions and file definitions.
d. Refer to the Guidance for Industry "Physiologically Based Pharmacokinetic Analyses–Format and Content at https://www.fda.gov/media/101469/download.

Amgen's Response (received via email on November 6, 2020): Amgen acknowledges the FDA's comments

Discussion During Meeting: No discussion occurred.

Statistics

17) Please confirm that the proposed NDA will contain a define file to show the variables which will be included in the derived datasets for the primary and key secondary efficacy analyses including, but not limited to, the variables for reasons of censoring, dates of ICR determined progression or censoring and variables for subgroup analyses, etc. Please include in your submission
a. SAS programs that produced all efficacy results,
b. All raw as well as derived variables in.xpt format,
c. SAS programs by which the derived variables were produced from the raw variables, and results of any interim analysis if ever performed.

Amgen's Response (received via email on November 6, 2020): Amgen confirms that a define file will be included in the planned NDA. In addition, the requested SAS programs for producing derived variables and phase 2 key efficacy results, .xpt datasets with raw and derived variables will be also included in the submission. Only one administrative interim analysis was performed on the NSCLC subjects enrolled in the phase 2 portion of Study 20170543 at the time of a pre-planned Data Review Team (DRT) assessment using data cutoff of 25 March 2020. The results of this interim were blinded to the study team and was only used to inform decisions for the development of future studies. The results from this interim analysis will be included in the submission.

Discussion During Meeting: No discussion occurred.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed; Amgen intends to submit the last RTOR component on December 16, 2020.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- FDA stated that an inclusion of a REMS is not required for filing of the planned NDA. FDA will make a final determination regarding whether a REMS will be required during the NDA review.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, we note that a CMC-only pre-submission meeting was held on October 15, 2020. We refer you to the November 12, 2020 minutes of that meeting for any additional agreements that may have been reached.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

FDA acknowledges receipt of your Agreed Initial Pediatric Study Plan (iPSP) submitted on March 13, 2020, and also refers to our April 7, 2020, letter confirming our agreement with this iPSP; however, (b) (4) in addition to your stated plan to seek an indication-based full waiver for the conduct of a study in pediatric patients in patients with locally advanced and metastatic non-small cell lung cancer with KRAS p.G12C mutations. Please refer to the Agreement letter for additional information regarding amending your iPSP and FDARA requirements

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[2]

FDARA REQUIREMENTS

Sponsors may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology

that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided.

Meeting requests should be sent to the appropriate review division with the cover letter clearly stating, "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and

[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for

inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[6]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[7]

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

[6] http://www.fda.gov/ectd
[7] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[8] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[9]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

[8] https://www.fda.gov/media/84223/download

[9] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[10]

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[11]: In general, the data submission should be fully CDISC-compliant to

[10] https://www.fda.gov/media/85061/download
[11] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program

facilitate efficient review.

Assessment Aid[12]

ISSUES REQUIRING FURTHER DISCUSSION
No issues requiring further discussion.

ACTION ITEMS
No action items.

ATTACHMENTS AND HANDOUTS
Appendix 2_Sotorasib RTOR Pre-submission Plan for submission timelines

9 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

[12] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

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/s/

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