CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214665Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA OPQ Review and Evaluation

NDA 214665
Review # 01

OPQ RECOMMENDATION: APPROVAL

Drug Substance Retest Period: (b) (4) months retest period, store at or below (b) (4)

FDA Assessment: Retest date of (b) (4) months may be granted when stored at the proposed storage conditions

Drug Product Expiration Dating Period: 24 months shelf-life, store at 20°C to 25°C, excursions permitted 15°C to 30°C.
FDA Assessment: An expiration dating period of 24 months may be granted when stored at the proposed storage conditions.

Drug Name/Dosage Form	Sotorasib / Tablet
Strength	120 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Indication	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
Applicant	Amgen Inc.
US agent, if applicable	N/A

[FDA will complete these sections.]

Submit Date(s)	December 16, 2020
Received Date(s)	December 16, 2020
PDUFA Goal Date	August 16, 2021
Division/Office	Division of Oncology 2/Office of Oncologic Diseases
Review Completion Date	May 7, 2021
Established Name	Sotorasib
(Proposed) Trade Name	LUMAKRAS
Pharmacologic Class	KRAS G12C inhibitor
PSD Recommendation on Regulatory Action	Approval

FDA assessment is indicated in colored fonts

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA Submission	*12/16/2020*	*All*
Quality Amendment	*01/05/2021*	*OPMA*
Quality Amendment	*01/13/2021*	*DS*
Labeling	*01/22/2021*	*DP*
Quality Amendment, Labeling	*02/23/2021*	*DP*
Quality Amendment	*02/24/2021*	*Biopharm*
Quality Amendment	*03/10/2021*	*OPMA*
Quality Amendment	*03/30/2021*	*OPMA*
Quality Amendment	*04/02/2021*	*Biopharm, DS*
Quality Amendment	*04/20/2021*	*DP*
Labeling	*04/23/2021*	*DP*
Labeling	*04/26/2021*	*DP*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Kabir Shahjahan	Paresma Patel
Drug Product	Olen Stephens	Anamitro Banerjee
Process and Facility	Yifan Wang	Rakhi Shah
Microbiology	Yifan Wang	Rakhi Shah
Biopharmaceutics	Min Kang	Banu Zolnik
Regulatory Business Process Manager	Kristine Leahy	
Application Technical Lead	Xing Wang	
Environmental	Olen Stephens	Anamitro Banerjee

ORBIS Partner Agency Quality Review Team ***(To be redacted for FOIA)***

Agency	PRIMARY REVIEWER	SECONDARY REVIEWER
HC Canada (NDQD)		
HC Canada (biopharm)		
TGA Australia		
MHRA		
ANVISA		

RELATED/SUPPORTING DOCUMENTS

DMFs:

[Applicant will complete]				[FDA will complete]	
DMF #	**Type**	**Holder**	**Item Referenced**	**Status**	**Comments**
(b) (4)	III		(b) (4)	Adequate	Active and supporting several A/NDAs
	III			Adequate	Active and supporting several A/NDAs
	III			Adequate	Active and supporting several A/NDAs
	III			Adequate	Active and supporting several A/NDAs
	III			Adequate	Active and supporting several A/NDAs
	III			Adequate	Active and supporting several A/NDAs
	III			Adequate	Active and supporting several A/NDAs

Other Documents: *IND, RLD, or sister applications*
[Applicant will complete this section.]

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	145628	Indication: treatment of advanced *KRAS p.G12C* mutant non-small cell lung cancer
IND	139023	Indication: treatment of advanced solid tumors with *KRAS p.G12C* mutation
IND	145154	Indication: treatment of advanced solid tumors with *KRAS p.G12C* mutation

CONSULTS
None

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Evaluation of the Quality Information

DIFFERENCES IN M3 MODULE IN SUBMISSIONS TO DIFFERENT AGENCIES

#	FDA (US)	Country	Country	Country	Country	Country	Country
1	Proposed Container Closure System - 120 cc Bottle/215 cc Bottle	(b) (4)					

1. EXECUTIVE SUMMARY

[FDA ATL will complete this section.]

Sotorasib is a KRAS G12C Inhibitor. (b) (4)

The proposed impurity levels are qualified. Method validations are found adequate. A retest period of (b) (4) month may be granted when stored in proposed storage conditions. (b) (4)

Sotorasib drug product is formulated as an immediate-release, oral, solid dosage form at a strength of 120 mg. All excipients used are compendial. The drug product manufacturing process consists of (b) (4) The 120-count configuration uses a 120 cc HDPE bottle; the 240-count configuration uses a 215 cc HDPE bottle. The applicant provided a comparison of the moisture vapor transmission rates for the two configurations in order to bridge the lower count configuration to the higher 240-count configuration, which is the commercial presentation. The comparability of this MVTR data and the batch, stability, and stress data that demonstrates the drug product is not appreciably hygroscopic supports this bridging. An expiration dating period of 24 months may be granted when stored at 20°C to 25°C, excursions permitted 15°C to 30°C. The product does not need to be protected from light.

A BCS-IV (low solubility, low permeability) designation is more appropriate classification for sotorasib (rather than BCS-II). The dissolution acceptance criterion is revised to "NLT (Q) (b) (4) % in 15 minutes". The proposed dissolution medium (50 mM Sodium phosphate buf at pH 6.8 with 0.2% SDS and paddle speed (75 rpm) are acceptable. The proposed Physiologically Based Biopharmaceutics Modeling (PBBM) is inadequate to support the proposed DS PSD. The DS PSD specifications are set based on the manufacturing controls and clinical DS batch data.

All facilities are recommended for approval based on acceptable compliancy history and relevant manufacturing experience. No pre-approval inspection is identified.

The claim for an exclusion from an environmental assessment is acceptable.

In conclusion, OPQ recommends APPROVAL of NDA 214665.

Life Cycle Considerations:
[FDA ATL to include any life-cycle considerations here]
None

2. APPLICATION BACKGROUND

IND Applications:
IND 139023 was submitted on 1 June 2018. Study may proceed letter was received on 29 June 2018. Indications for IND 139023 is for treatment of advanced solid tumors with *KRAS p.G12C* mutation.

IND 145154 was submitted on 16 August 2019. Study may proceed letter was received on 13 September 2019. Indication for IND 145154 is for treatment of advanced solid tumors with *KRAS p.G12C* mutation.

IND 145628 was submitted on 26 November 2019. Study may proceed letter was received on 26 December 2019. Indication for IND 145628 is for treatment of advanced *KRAS p.G12C* mutant non-small cell lung cancer.

Request for Fast track designation was submitted on 4 June 2020 to the IND 145628 for the indication, metastatic non-small cell lung cancer (NSCLC) with the *KRAS p.G12C* mutation with disease progression on or after platinum-based chemotherapy. Fast track designation was granted on 5 August 2020.

Orphan drug designation was granted on 1 May 2019 for treatment of *KRAS p.G12C*-positive non-small cell lung cancer.

Breakthrough therapy designation request was submitted to FDA on 8 October 2020 for the proposed Breakthrough Therapy indication of the treatment of patients with *KRAS G12C* mutated locally advanced or metastatic non-small cell lung cancer (NSCLC) who have received at least 1 prior systemic therapy.

Participation in RTOR pilot and Project Orbis requests were submitted to FDA on 12 October 2020. RTOR pilot request was granted on 4 November 2020.

3. SUMMARY OF CMC SPECIFIC PRESUBMISSION AGREEMENTS

The Applicant's Position:

Type C Meeting was held on 30 January 2020. Type C Meeting agreements:

1- FDA agreed tentatively with the designation of (b) (4) as API starting materials for commercial manufacture of the AMG 510 drug substance (DS). FDA stated that it reserves the right to request different (upstream) starting materials upon review of the specifications for each of the proposed starting materials (which according to the briefing package were being finalized) and the review of the complete fate and purge data for impurities originating with the proposed starting materials. FDA agreed that (b) (4) can be designated as a reagent.

2- FDA noted that considering the proposed patient population and indication, it is acceptable to use the clinical drug substance batches for the drug product PPQ campaigns.

3- FDA stated that FDA may consider allowing primary stability data generated using samples of batches manufactured using processes (b) (4) if Amgen provides a detailed analysis and discussion regarding why the differences between (b) (4) would not be expected to result in differences in the drug substance that become observable upon storage. FDA agreed that the presentation provided a clearer explanation and demonstrated equivalence of the reagents. The impurity profile data assisted in clarifying the (b) (4) processes are equivalent to the later processes.

4- FDA stated that FDA would accept 9 months, 6 months and 6 months of long term stability data for the three-primary drug product registration batches at the time of NDA submission with a commitment to provide updated stability data throughout the NDA review period. FDA noted that as per the PDUFA V agreement, stability data submitted 30- days after the original NDA submission may not be reviewed depending on the available FDA resources and review timelines. The data will be evaluated in the context of the available primary stability data and supportive stability data. Shelf -life extrapolation will be considered as per ICH Q1E and on the quality of the available data at the time FDA takes action on the NDA.

5- Amgen agreed that (b) (4) assay will be included in the final drug substance specifications and this will be included in the NDA.

6- Amgen agreed to provide in process control and purging study data in the NDA.

7- FDA provided the minimum data expectations needed for registration of all sites. Amgen planned to register two drug substance manufacturing sites (b) (4) in the initial NDA and third drug substance manufacturing site (b) (4) post-approval. FDA indicated that the proposed plan for submitted the stability data is acceptable.

8- FDA agreed with the concept of controlling impurities according to the principles of ICH S9 and the S9 Q and A document, which reference ICH Q3A for control of drug substance.

9- Amgen agreed to provide requested information related to all manufacturing facilities associated with the application. Amgen included the full corporate name, the address information, FEI number, and specific manufacturing responsibilities for each facility, and the name of the on-site contact person, including phone number, fax number and email address in the Form FDA 356h, 3.2.S.2.1 (Manufacturer(s)) and 3.2.P.3.1 (Manufacturer(s)).

10- Amgen agreed to provide information regarding manufacturing sites used to provide the clinical supply in the expanded access protocol and indicate if the

same sites are used to support the NDA (e.g. PPQ batches used for NDA or previous clinical batches).

Pre-NDA Meeting was held on 15 October 2020. Pre-NDA agreements:

1- FDA agreed that all the data supporting the selection of rotation speed should be included in the dissolution development report in NDA. FDA agreed that n=6 data is sufficient for justification of rotation speed. FDA also recommended that target profile data should be included in the graphs which is utilized to support discriminating ability of dissolution method. Amgen agreed to provide the dissolution method development report. Amgen agreed to provide supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (specificity, precision, accuracy, linearity, stability, etc.) in the NDA. Amgen agreed to provide all individual vessel dissolution profile data for batches tested during method development, assessment of discriminating ability, and validation in Microsoft Excel ".xls or .xlsx" format under Module 5.3.1.3 "In Vitro - In Vivo Correlation Study Reports and Related Information."

2- Per the prior agreement at Type C meeting, the 6-month time point from (b) (4) DP batch will be submitted in the NDA (or during review) and be sufficient for registering (b) (4) as a DS site. Use of one Drug Substance lot from the (b) (4) site to manufacture the two DP stability lots is acceptable.

3- FDA stated that the proposed comparability protocol plan appears to be a reasonable approach to support the CBE-30 reporting category for registration of (b) (4) as a drug substance manufacturing site. The determination of the acceptability of the comparability protocol will be a review issue.

4- FDA noted that the proposed comparability plan appears to be a reasonable approach to support the CBE-0 submission category for the proposed drug substance production scale increase to (b) (4). The final determination on the acceptability of the comparability protocol will be a review issue.

5- FDA agreed to file an original NDA submission for the 240-count supply packaged in a 215 cc HDPE bottle that includes the primary and supportive data described in the meeting package. Acceptability of this configuration will be determined during NDA review. As stated in the meeting package, stability updates are anticipated throughout the review time-line and should be submitted as amendments to the NDA. Shelf life for the proposed product will be determined based on totality of the data available at the time of NDA review based on ICH Q1E recommendations.

6- FDA agreed with the proposed structure and format of Module 3 information as outlined in the Appendix 1. Amgen may submit additional drug product stability data within 30 days after the original NDA submission. Any data submitted beyond this time may be reviewed depending on the internal review timelines and

available resources.

The FDA's Assessment: ***Consistent with FDA's records***

4. ENVIRONMENTAL ASSESSMENT

The Applicant's Position:

Amgen Inc. (Amgen) is requesting a categorical exclusion from the requirement to prepare an environmental assessment (EA) for sotorasib according to 21 CFR §25.31 (b) for the subject NDA application in 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. For the proposed indication, the estimated concentration of sotorasib at the point of entry into the aquatic environment (EIC, Expected Introductory Concentration) is (b) (4) ppb, which is the below the FDA's 1 part per billion (ppb) trigger limit. In addition, Amgen is not aware of any extraordinary circumstances that exist for this product, as referenced in 21 CFR §25.21(a) or 21 CFR §25.21(b) that require submission of an EA.

The FDA's Assessment: ***Adequate***

The applicant submitted a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR 25.31(b), which is for substances that increase in use but result in an expected introduction concentration (EIC) of < 1 ppb. The applicant included use amounts that were consistent with the claim. The required statement of no extraordinary circumstances also was provided, in accordance with 21 CFR 25.15. The applicant also submitted EA data to support the exclusion claim based on recent FDA guidance (USFDA, 2016, Environmental Assessment: Questions and Answers Regarding Drugs with Estrogenic, Androgenic, or Thyroid Activity). The data have been reviewed and found to support the conclusion that approval of this application would not result in a significant environmental impact. Therefore, the claim for an exclusion from an EA is acceptable.

5. FACILITIES

Drug substance manufacturing, packaging and testing facilities are listed below:

---------- [Applicant to fill] ----------			[FDA to fill]
Site/address	**FEI/DUNS**	**Responsibility**	**Recommendation**

(b) (4)	Drug substance manufacturing Drug substance release and stability testing	Approve – Based on previous history
	Drug substance manufacturing - (b) (4)	Approve – Based on previous history
	Drug substance manufacturing Drug substance release and stability testing	Approve – Based on previous history
	Drug substance release testing - elemental impurities only	Approve – Based on previous history

Drug product manufacturing, packaging and testing facilities are listed below:

---------- [Applicant to fill] ----------			[FDA to fill]
Site/address	**FEI/DUNS**	**Responsibility**	**Recommendation**
(b) (4)		Manufacture, primary packaging (bottle), secondary packaging, labeling, storage, release and stability testing	Approve – Based on previous history
Amgen Manufacturing Ltd (Referred to as AML) Carr 31, KM 24.6 Juncos, Puerto Rico 00777 USA	FEI: 1000110364 DUNS: 785800020	Primary packaging (bottle only), secondary packaging, labeling, storage and release	Approve – Based on previous history
Amgen Inc. (Amgen Louisville Distribution Center Referred to as LDC) 12000 Plantside Drive Louisville, Kentucky 40299 USA	FEI: 3003750095 DUNS: 787632801	Storage and distributor	No Evaluation Necessary

Amgen Inc. (Amgen Thousand Oaks Referred to as ATO) One Amgen Center Drive Thousand Oaks, California 91320 USA	FEI: 2026154 DUNS: 039976196	Drug product release	Approve – Based on previous history

The FDA's Assessment: Choose an item. ***Adequate***

All facilities are recommended for approval based on acceptable compliancy history and relevant manufacturing experience. No pre-approval inspection is identified.

6. DRUG SUBSTANCE

(b) (4)

84 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

R. REGIONAL INFORMATION

[To the Applicant: Insert text here]

Not Applicable

The FDA's Assessment: ***Not Applicable***

[FDA will complete this section.]

8. BIOPHARMACEUTICS

a. BCS CLASSIFICATION

Applicant to fill:	FDA assessment (FDA to fill):
BCS Classification: BCS II	Not acceptable

Given its low solubility (0.03 – 1.3 mg/mL between pH 1.2 to 6.8), and high permeability (5.67-11.2 x 10^{-6}) cm/s, AMG 510 is classified as a BCS Class II compound.

Information to support the BCS Class I designation request, if applicable.
Link: Page#:

FDA Comments: Based on the *in vitro* and *in vivo* data, sotorasib does not meet the BCS Class II criteria (low solubility, high permeability) as claimed by the Applicant. A ***BCS-IV (low solubility, low permeability)*** designation is a more appropriate classification for sotorasib.

Solubility: Low

FDA agrees with the Applicant that per BCS criteria, sotorasib is a low solubility drug substance. Based on the drug substance solubility data in Table 1 of 3.2.S.1.3. General Properties, sotorasib shows a pH-dependent solubility at 37°C with highest solubility of 1.3 mg/mL observed at pH 1.2 hydrochloric acid media with subsequent reduction to its solubility at higher pH 0.07 mg/mL at pH 4.5 to 0.03 mg/mL at pH 6.8 – 7.4.

Permeability: *Low*
The proposed labeling states: "(b) (4) 74% of the dose recovered in feces and 6% (1% unchanged) (b) (4) in urine". Therefore, since only about 1% was recovered in urine as unchanged (e.g., <85%) of the administered dose of sotorasib is systemically absorbed, it does not meet the criteria for a high permeability drug substance. Furthermore, based on the available human mass balance study, about 50% of the administered oral dose which is made systemically available (e.g., metabolites M10, M18, M24), only M18 maintains primary pharmacology effects which has a markedly reduced effect compared to the parent drug (>10 fold less potent). Based on the in vivo data, FDA classifies sotorasib as a "low permeability" drug substance.

b. DISSOLUTION TEST

USP Apparatus	Paddle Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion
II	75 rpm	900 ± 9 mL	37°C ± 0.5°C	50 mM Sodium phosphate buffer at pH 6.8 with 0.2% SDS (w/w)	. Q= (b) (4)% in 15 minutes

Biopharmaceutics Figure 1: Dissolution Profiles as a function of:

a. Impact of medium pH on dissolution

Solubility of AMG 510 DS Over the Physiological pH Range:

Solution	Solubility (mg/mL)	Sink Condition[a] (multiples)
(b) (4)		
pH 6.8	0.01	No (0.08)
(b) (4)		

Applicant's comments:

(b) (4)

No degradation was detected in dissolution medium at pH 6.8. Based on the pH solubility data, use of surfactant is required to achieve minimal sink condition (b) (4) After surfactant screening study, 0.2% SDS at pH 6.8 was found to provide suitable sink condition. Complete data set about dissolution medium selection is provided in 3.2.P.2.2 Dissolution Method Development.

FDA Comment: The proposed dissolution medium (50 mM Sodium phosphate buffer at pH 6.8 with 0.2% SDS) is acceptable.

(b) (4)

(b) (4)

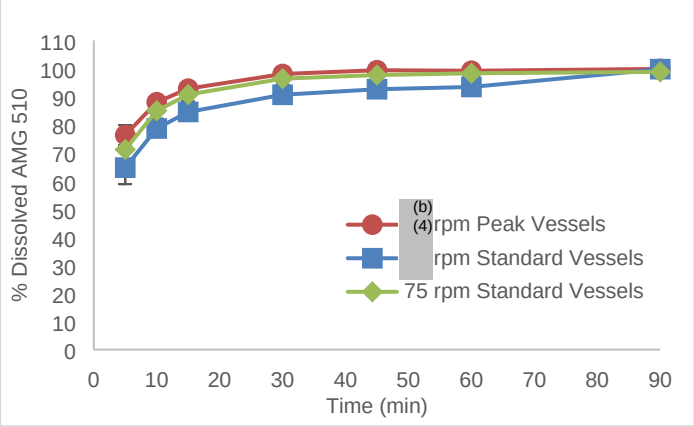
FDA agrees with the Applicant that pH 6.8 is the optimal medium, although it requires the use of surfactant to enhance the solubility and meet the sink condition.

(b) (4)

During one of the IND meetings with the Applicant (IND 145628, Type B CMC Meeting held on 10/15/2020), the Applicant had appropriately justified the selection of 0.2% SDS by providing the dissolution profiles at varied Particle Size Distribution using both 0.2% SDS and 0.5% SDS in pH 6.8 media (Table 5-6 of IND Briefing Package; 10/15/2020). The dissolution results/profiles showed that 0.2% SDS media showed slightly better discriminating ability compared that of (b) (4)% SDS media in pH 6.8. Based on this information, even though 0.2% SDS barely t the sink condition (b) (4) FDA agrees with the Applicant's selection of 0.2% SDS as the final surfactant.

b. Impact of paddle speed on dissolution

Comparison of Dissolution Profile between Dissolution at (b) (4) rpm in Peak Vessels and at (b) (4) rpm and 75 rpm at Standard Vessels



Applicant's comments:

Paddle speeds at (b) (4) and 75 rpm using USP apparatus II were studied using the dissolution medium of 50 mM sodium phosphate buffer at pH 6.8 with 0.2% SDS. The rotation speed of 75 rpm is identified as the lowest speed without coning effect. The figure compares the dissolution profiles obtained from (b) (4) rpm and 75 rpm paddle speed in standard vessels against (b) (4) rpm dissolution data in peak vessels

(b) (4)

(b) (4)

The data supports the selection of 75 rpm. Complete data set about paddle speed selection to maximize the dissolution method discriminating power is provided in 3.2.P.2.2. Dissolution Method Development.

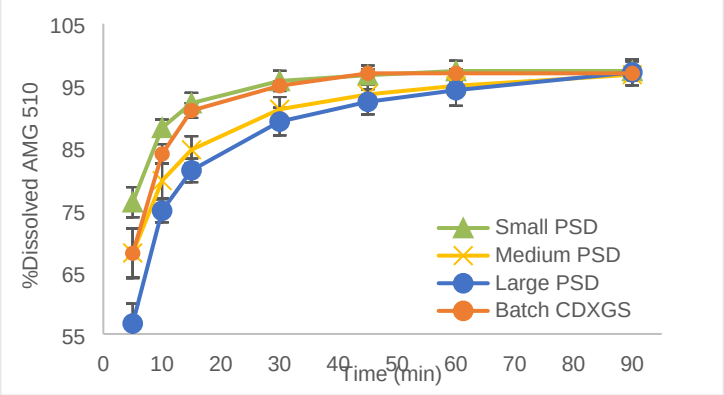
FDA Comment: The proposed paddle speed (75 rpm) is acceptable.

(b) (4)

FDA finds the Applicants' justifications acceptable to support the selection of 75 rpm as the final paddle speed.

c. Impact of DS PSD on dissolution

Dissolution Profiles for AMG 510 120 mg Film-Coated Tablets made with Different DS PSDs, 0.2% SDS (pH 6.8 50 mM Phosphate Buffer, 75 rpm)



Applicant's comments:

DS PSD is found to have impact on dissolution. 3 DS batches engineered with small PSD (b) (4) medium PSD (b) (4) and large PSD (b) (4) were manufactured into DP as part of DP DoE study. The dissolution profile data associated with 3 different DS PSD are shown in the figure together with a representative DP batch made with DS batch with PSD of (b) (4) Even though DS PSD is found to have impact on dissolution, the DS PSD is controlled with (b) (4)

	(b) (4) to ensure consistency of DS PSD.

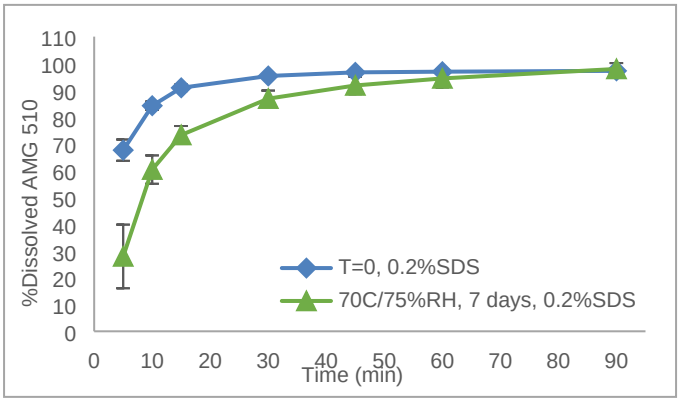
FDA Comment: Of the several Critical Quality Attributes (CQAs: Critical Manufacturing Attributes [CMAs], Critical Formulation Variables [CFVs], Critical Processing Parameters [CPPs]) studied by the Applicant, the proposed dissolution method was shown to have discriminating ability against the varying Particle Size Distribution (PSD) of Sotorasib drug substance as depicted in the figure above (as well as in Table 11 and Figure 12 of M.3.2.P.2.2. Dissolution Method Development Report).

With the dissolution acceptance criterion set at "NLT (Q) = (b) (4)% in 15 minutes", the Applicant's proposed dissolution method is expected to be able to appropriately reject batches that have greater than the target PSD.

d. Impact of tablet stress condition on dissolution (add as appropriate)

Applicant to insert figure here:

Dissolution Profiles of AMG 510 120 mg Film-Coated Tablets at T0 and 7 days at 70°C / 75% RH



Applicant's comments: The method discriminating ability was also assessed with heat and humidity stressed sample, namely AMG 510 120 mg film-coated tablets in an open bottle placed under 70°C / 75%RH for 7 days. DS polymorphic form was confirmed to be the same after stress as DS anhydrous Form (b) (4) There was only minor increase in degradation product DS (b) (4) The disintegration time at T0 and 7 days at 70°C / 75% RH increased from 46.7 seconds to 82.3 seconds. The significant difference in dissolution profile after stress at high temperature and high humidity is shown in figure to the left for its impact on dissolution.

FDA Comment: The discriminating ability of the proposed dissolution method was also assessed by the Applicant with heat and humidity stressed samples (e.g., in an open bottle placed under 70ºC/75%RH for 7 days). It is noted by the Applicant that

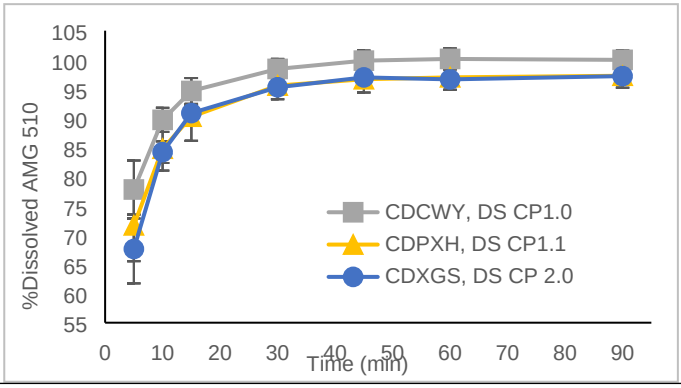
when the AMG 510 120 mg film-coated tablets were placed in an open bottle placed under 70ºC/75%RH for 7 days, the hardness of the tablets decreased (b) (4) and the disintegration time also increased (b) (4) (Page 19 of M.3.2.P.2.2. Dissolution Method Development Report). These changes are captured in the dissolution profile above (as well as in Table 12 and Figure 13 of M.3.2.P.2.2. Dissolution Method Development Report).

"The Applicant's proposed dissolution method is expected to be able to appropriately reject batches that have any changes to the drug product quality as a result of suboptimal storage conditions with the dissolution acceptance criterion set at "Q = (b) (4)% in 15 minutes.

e. Justification for selection of the acceptance criterion

Applicant to insert multipoint dissolution profile in a graphical format from clinical/PK and primary registration batches figure(s) here:

Comparison of Release Profile of AMG 510 120 mg Tablets (Primary Stability Batch CDCWY, and Clinical Batches CDPXH and CDXGS) Tested using 0.2% SDS in pH 6.8 50 mM phosphate buffer



Applicant's comments:

The proposed acceptance criterion is % of labeled amount of AMG 510 dissolved in 15 minutes meets requirements for immediate release dosage forms per USP <711> with Q equal to (b) (4)%.
The accep ce criterion reflects rapidly dissolving immediate release drug product and considers limited batch history data.

FDA Comment: The proposed dissolution acceptance criterion (Q = (b) (4)% in 15 minutes) is acceptable for the reasons described under sections c and d, above.

	Applicant to fill:	FDA assessment:
The dissolution method is discriminating for:		
i) Particle size distribution (PSD) Link[1]: Figure 12 in 3.2.P.2.2 Dissolution Method Development	Discriminating	Agree Page#: 19
ii) Polymorph/solid state form Link[1]:	Not applicable	Not applicable Page#:
iii) Formulation variations Link[1]:	Not discrimitating	Agree Page#:

iv) Manufacturing process variations Link[1]:	Not discrimitating	Agree Page#:
v) Other (specify): Link[1]: Heat and humidity related tablet stress conditions. Figure 13 in 3.2.P.2.2 Dissolution Method Development	Discriminating	Agree Page#: 20

[1]The applicant to provide link to the appropriate section in the submission. FDA reviewer may update the link as needed.

c. BRIDGING THROUGHOUT DRUG PRODUCT DEVELOPMENT (FORMULATION, PROCESS, OR SITE CHANGE)

Link: 3.2.P.2.2 (Formulation Development)	Page#: 2 – 15
3.2.P.2.3 (Process Design) Section 4.1	Page#: 11
3.2.P.3.3 (Description of Manufacturing Process and Process Controls)	Page#: 3
3.2.P.5.4 (Batch Analyses)	Page#: 3 - 7
3.2.P.8.1 (Stability Summary and Conclusion [215 cc Bottle])	Page#: 3 - 7

AMG 510 utilized the same core tablet formulation throughout the clinical studies. Uncoated tablets were used for Phase 1 and early Phase 2 studies and the film-coated tablets, the proposed commercial formulation, have been utilized in on-going Phase 1, 2, and 3 clinical studies. A summary of the AMG 510 120 mg tablet presentations used in clinical studies is presented in Table 8 and compositions of AMG 510 tablets used in clinical studies were summarized in Table 9.

Table 8. Summary of AMG 510 120 mg Tablet Presentations Used in Clinical Studies

Tablet Presentation	Tablet Shape	Tablet Face	Clinical Studies
Uncoated tablet	Round	Plain	Phase 1 and early Phase 2
Yellow film-coated tablet	Oblong	Debossed	Phase 1, Phase 2, and Phase 3

Table 9. Compositions of AMG 510 Tablets Used in Clinical Studies

Component	Function	Percentage (% w/w)	Uncoated 30 mg Quantity (mg/tablet)	Uncoated 120 mg Quantity (mg/tablet)	Film-Coated 120 mg Quantity (mg/tablet)	Reference to Standard
[redacted]						(b) (4)
AMG 510[a]	Active	(b) (4)	(b) (4)	120.0	120.0	In-house Specification
Microcrystalline cellulose						PhEur, NF, JP
Lactose monohydrate						PhEur, NF, JP
Croscarmellose sodium						PhEur, NF, JP
Magnesium stearate, Non-bovine						PhEur, NF, JP
[redacted]						(b) (4)
Film Coating						
[redacted]						(b) (4)
(polyvinyl alcohol)	–	(b) (4)				PhEur, USP, JPE
(titanium dioxide)	–					PhEur, USP, JP
(polyethylene glycol)	–					PhEur, USP, JP
(talc)	–					PhEur, USP, JP
(iron oxide yellow)	–					NF, JPE
[redacted]						(b) (4)

JP - Japanese Pharmacopoeia; JPE - Japanese Pharmaceutical Excipients; NF - National Formulary; PhEur - European Pharmacopoeia; USP - United States Pharmacopeia

[redacted] (b) (4)

The AMG 510 120 mg uncoated tablets were first manufactured for the Phase 1 studies at Amgen Thousand Oaks (ATO) and transferred to the proposed commercial site (b) (4) for Phase 2 and Phase 3 studies. (b) (4) [redacted]

(b) (4)

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Comparability between uncoated and film-coated tablets

The film-coated and uncoated tablets were compared using batch release data, stability data, and dissolution data in multiple media (ie, pH 1.2, 4.5, and 6.8), with or without 0.2% and 0.5% SDS surfactant (Table 10).

The dissolution profiles in multiple media, at pH 1.2, 4.5, and 6.8, with or without presence of 0.2% or 0.5% SDS are similar. Due to limited solubility of sotorasib, comparable but incomplete dissolution was observed in pH 4.5 and pH 6.8 media without SDS. Over 85% of sotorasib was dissolved within 15 minutes in pH 1.2 media and in pH 4.5 and pH 6.8 media with SDS.

No significant differences in product release data and stability profiles were identified between film-coated and uncoated tablets. All test results met acceptance criteria with no obvious trend. Results indicate that the film-coated and uncoated tablets are comparable.

Table 10. Summary of In Vitro Dissolution Studies[a]

Study Ref. No.	Product ID/ Batch No.	Sotorasib Dosage Form	Dissolution Media	No. of Dosage Units	Mean % Dissolved (range)			
					15 minutes	30 minutes	45 minutes	60 minutes
Study 079409-69-06	Batch 0010424907	120 mg uncoated tablet	pH 1.2 without SDS	12	97 (94-99)	96 (94-99)	95 (94-99)	95 (93-98)
			pH 1.2 with 0.5% SDS		88 (83-92)	88 (85-92)	88 (86-90)	87 (86-89)
			pH 4.5 without SDS		12 (12-13)	14 (14-15)	15 (15-15)	16 (15-16)
			pH 4.5 with 0.5% SDS		98 (97-99)	98 (97-100)	98 (96-101)	99 (97-100)
			pH 6.8 without SDS		9 (9-9)	10 (10-10)	10 (10-10)	10 (10-10)
			pH 6.8 with 0.5% SDS		98 (95-100)	98 (96-101)	98 (97-101)	98 (97-101)
	Batch 0010521332	120 mg film-coated tablet	pH 1.2 without SDS	12	97 (96-99)	97 (96-98)	96 (95-98)	95 (94-97)
			pH 1.2 with 0.5% SDS		89 (81-94)	90 (85-93)	89 (86-91)	88 (87-90)
			pH 4.5 without SDS		16 (16-17)	18 (17-18)	18 (17-19)	18 (17-18)
			pH 4.5 with 0.5% SDS		97 (95-99)	98 (95-101)	98 (96-101)	98 (96-101)
			pH 6.8 without SDS		12 (11-13)	13 (12-14)	13 (12-15)	13 (12-14)
			pH 6.8 with 0.5% SDS		97 (96-100)	98 (96-100)	98 (97-100)	98 (97-100)
Study 079409-69-10	Batch 0010424907	120 mg uncoated tablet	pH 1.2 without SDS	12	97 (94-99)	96 (94-99)	95 (93-99)	95 (93-98)
			pH 1.2 with 0.2% SDS		89 (87-91)	87 (86-90)	87 (84-88)	85 (84-87)
			pH 4.5 without SDS		12 (12-13)	14 (14-15)	15 (15-15)	16 (15-16)
			pH 4.5 with 0.2% SDS		98 (96-100)	98 (97-100)	98 (96-100)	98 (96-100)
			pH 6.8 without SDS		9 (9-9)	10 (10-10)	10 (10-10)	10 (10-10)
			pH 6.8 with 0.2% SDS		93 (92-95)	97 (95-98)	98 (96-100)	98 (96-100)
	Batch 0010521332	120 mg film-coated tablet	pH 1.2 without SDS	12	97 (96-99)	97 (96-98)	96 (95-98)	95 (94-97)
			pH 1.2 with 0.2% SDS		88 (86-90)	87 (86-89)	86 (85-88)	85 (84-86)
			pH 4.5 without SDS		16 (16-17)	18 (17-18)	18 (17-19)	18 (17-18)
			pH 4.5 with 0.2% SDS		97 (95-99)	98 (97-100)	99 (97-101)	99 (97-101)
			pH 6.8 without SDS		12 (11-13)	13 (12-14)	13 (12-15)	13 (12-14)
			pH 6.8 with 0.2% SDS		94 (92-96)	98 (96-100)	99 (96-102)	99 (97-102)

SDS = sodium dodecyl sulfate

[a] USP <711> Dissolution Apparatus 2 (USP), 900 mL dissolution media, media temperature 37°C, paddle speed 75 rpm

Source: Table 3 and Table 4 in 3.2.P.2.2 (Formulation Development)

Bridging between 120 cc HDPE bottle and 215 cc HDPE bottle

Both 120 cc and 215 cc HDPE bottles use [redacted] (b) (4) cap closure. The bottle material of construction and wall thickness are the same. A moisture permeability study was conducted per USP <671>. The results demonstrated that on the per tablet basis, the moisture uptake rate for the 215 cc bottle was 1.9 times lower than the 120 cc bottle (Table 11). This is expected as the 215 cc bottle has smaller bottle surface area and head space on per tablet basis. Hence, the stability behavior in the 120 cc bottle represents worst case for shelf-life assignment.

Table 11. Moisture Permeation of the 120 cc and 215 cc HDPE bottles

	120 cc Bottle	215 cc Bottle
Average Permeation (Per Container)	2.1569 mg/day	2.2770 mg/day
Average Permeation (Per Tablet)	0.018 mg/day	0.0095 mg/day

One batch of AMG 510 film-coated tablet in the 215 cc HDPE bottle is placed on stability. Currently, three-month data at 30ºC/65% RH, 30ºC/75% RH, and 40ºC/75% RH is available. Similar to stability results from the 120 cc HDPE bottle, all results (ie, appearance, assay, impurities, dissolution, and moisture content) meet acceptance criteria without significant changes. Tests will continue per stability schedule.

The FDA's Assessment: ***Adequate***

The clinical formulation (AMG 510) is same as the proposed commercial formulation (Sotorasib Tablets). There also were no change to the manufacturing process nor manufacturing site that required bridging. Therefore, no additional in vivo or in vitro bridging studies are needed between the clinical and the commercial formulations.

a. BIOWAIVER REQUEST

The Applicant's Position:

The NDA does not contain a biowaiver request.

Link: 3.2.P.2.2 (Formulation Development) Page#: 2 - 15

A biowaiver request is not required for AMG 510 as the proposed commercial formulation, a 120 mg film-coated tablet, has been utilized in the on-going Phase 1, 2, and 3 clinical studies. While an uncoated 120 mg tablet (core tablet) was initially used to

support the Phase 1 and early Phase 2 studies, it shares the same core tablet formulation with the proposed commercial tablets. In addition, all tablets were manufactured using the similar (b) (4) process and process controls. A comparison of the uncoated and film-coated tablets using batch release, stability, and dissolution data in multiple media (i.e., pH 1.2, 4.5 and 6.8, with or without 0.2% and 0.5% sodium dodecyl sulfate (SDS) surfactant) has demonstrated that the uncoated and film-coated tablets are comparable and no significant differences were observed in dissolution profiles.

The FDA's Assessment: ***Adequate***

The biowaiver request was not applicable as the proposed commercial formulation is a single strength tablet, 120 mg.

b. DATA TO SUPPORT IVIVC AND/OR PHYSIOLOGICALLY BASED BIOPHARMACEUTICS MODELING, IF APPLICABLE.

*Link:*3.2.P.2.2 (Formulation Development) Page#: 25 - 26

(b) (4)

The FDA's Assessment: ***Not Adequate***

The proposed Physiologically-Based Biopharmaceutics Modeling (PBBM) is considered inadequate to support the proposed Particle Size Distribution (PSD) specification for Sotorasib drug substance. Because the proposed PBBM is not acceptable at this time, the PSD specifications for drug substance was evaluated based on the batches used in the clinical studies.

Sotorasib is observed to have a non-linear pharmacokinetics (PK) across the studies of oral doses without a distinct dose-response trend and similar steady-state exposure among the daily doses between 180 mg to 960 mg. Consequently, more t data/ information is

needed to further elucidate a mechanistical understanding of the observed PK non-linearity (e.g., potential factors accounting for the PK non-linearity) in order to support the selection of the model structure and parameters. The Applicant is recommended to justify all assumptions that have been made in the model development ((b) (4) The Applicant is also recommended to provide detailed justification/supporting information on all of the selected input parameters and assumptions.

FDA's comments described above have been conveyed to the Applicant via Information Request on 3/29/21 for the Applicant's considerations in future PBBM model developments.

2. LABELING

[FDA will complete this section.]

USPI

Highlights: ***Adequate***

Includes description of the Lumakras™ (sotorasib) tablets, for oral use, the 120 mg strength available, and recommended dose of 960 mg orally once daily with or without food.

Section 2 (if relevant): ***Adequate***

Includes the option to prepare an extemporaneous dispersion of tablets in 4 oz of non-carbonated, room temperature water without crushing. Includes an in-use period of 2 hours. This preparation and in-use period is supported by developmental data within Module 3.

Section 3 Dosage Forms and Strengths: ***Adequate***

This section is adequately descriptive and terse: "120 mg tablets: yellow, oblong-shaped, immediate release, film-coated, debossed with “AMG” on one side and “120” on the opposite side.”

Section 11 Description: ***Adequate***

If the following excipients used in the drug product, include warning/declaration in the USPI:

- FD&C Yellow No.5 or No.6, as a color additive (21 CFR 201.20) is not used.
- Phenylalanine, as a component of aspartame (21 CFR 201.21) is not used.
- Sulfites (21 CFR 201.22) is not used.

This section includes the molecular formula, molecular weight, chemical name, and structure of sotorasib. The original label did not include a description of chemical or physical properties of the drug substance. The applicant responded to an information request in SDN 0017 to include this information in Section 11 plus the route of administration.

Section 16 How Supplied/Storage and Handling: ***Adequate***

This section includes the strength and dosage form available with identification of the dosage form. NDC numbers associated with the available units and container presentations are provided. The storage conditions listed comport with USP Controlled Room Temperature. No special handling is required for this product, so no special instructions are included.

Manufacturer Information (Name and Address): ***Provided: Adequate***

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

Carton/Container Label ***Adequate***

The container label for the 120-count bottle includes proprietary name, established name, dosage form, dosage strength, route of administration, NDC number, space for lot number and expiration date, storage conditions, bar code, name of manufacturer, and statement to keep out of reach of children.

The label includes “120 film-coated tablets” to designate the net contents of the bottle, but the format may be confused with the strength of the tablets (120 mg). The label includes a website for the patent, which is also not necessary. DMEPA was consulted regarding the information that could be removed or revised for clarity. DMEPA confirmed they would craft comments to the applicant to regarding these issues.

In addition to the information above for the bottle label, the carton for the 120-count configuration includes a statement of containing 2 bottles each containing 120-tablets. Revisions were made to the carton and container label in conjunction with DMEPA to separate tablet-count and strength statements to avoid confusion on the label.

The bottle and carton label for the 240-count configuration is comparable with the change in net contents to “240 film-coated tablets”. All changes recommended through review have been incorporated in the current label being negotiated with the clinical division and the applicant.

Final Risk Assessments

[FDA will complete this section.]

SOLID ORAL

Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	Low	(b) (4)	Low	The DS (b) (4) impurity is limited to NMT (b) (4) % on stability and release. This impurity has not been observed to accumulate in available stability data and the nonclinical reviewer verified it is qualified at this limit. The clinical review team anticipates a PMR to evaluate lower standard dosing regimens. At that time, it may be appropriate to tighten this impurity limit.
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low		Low	
Content Uniformity	• Formulation • Container closure • Raw material • Process Parameters • Scale/equipment • Site	Low		Low	
Moisture content	• Formulation • Container closure • Process parameters • Scale/equipment • Site	Low		Low	

			(b) (4)		
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low		Low	
Dissolution – BCS Class II & IV	• Formulation • Container Closure • Raw materials • Process parameters • Scale/equipment • Site	Low		Low	

Recommendation Page

[FDA will complete this section.]

Drug Substance: Approval

Primary Reviewer: Kabir Shahjahan — Date: May 3, 2021
Secondary Reviewer: Paresma Patel — Date: May 3, 2021

Drug Product: Approval

Primary Reviewer: Olen Stephens — Date: April 21, 2021
Secondary Reviewer: Anamitro Banerjee — Date: April 29, 2021

Process and Facility: Approval

Primary Reviewer: Yifan Wang — Date: April 29, 2021
Secondary Reviewer: Rakhi Shah — Date: April 29, 2021

Biopharmaceutics: Approval

Primary Reviewer: Min (Sammie) Kang — Date: May 3, 2021
Secondary Reviewer Banu Zolnik — Date: May 3, 2021

Application Technical Lead: Approval

Xing Wang — Date: May 7, 2021

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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