CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215358Orig1s000
215358Orig2s000

PRODUCT QUALITY REVIEW(S)

NDA OPQ Review and Evaluation

NDA 215358
Review # 1

OPQ RECOMMENDATION: APPROVAL

Drug Substance Retest Period: Proposed retest period is [redacted] (b) (4) and storage condition is [redacted] (b) (4).

FDA Assessment: A retest period of [redacted] (b) (4) may be granted when stored at the proposed storage conditions.

Drug Product Expiration Dating Period: Proposed shelf life is **24** months and storage condition is ", Store at 20°C to 25°C (68^{0}F to 77^{0}F); excursions permitted between 15^{0}C and 30^{0}C (59^{0}F and 86^{0}F); store in the original package in order to protect from moisture".

FDA Assessment: An expiration dating period of 24 months may be granted when stored at the proposed storage conditions.

Drug Name/Dosage Form	Asciminib/Film-Coated Tablets
Strength	20 mg and 40 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Indication	• Philadelphia chromosome-positive Chronic Myeloid Leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs). • Ph+ CML in CP harboring the T315I mutation.
Applicant	Novartis Pharmaceuticals Corporation
US agent, if applicable	N/A

[FDA will complete these sections.]

Submit Date(s)	March 31, 2021
Received Date(s)	June 24, 2021
PDUFA Goal Date	October 29, 2021
Division/Office	Division of Hematology Malignancies 1/Office of Oncologic Diseases
Review Completion Date	September 27, 2021
Established Name	Asciminib
(Proposed) Trade Name	Scemblix (Asciminib)

FDA assessment is indicated in colored fonts

Pharmacologic Class	
Recommendation on Regulatory Action	Approval

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	*3/31/2021*	*All*
Amendment	*7/20/2021*	
Amendment	*7/30/2021*	
Amendment	*8/13/2021*	
Amendment	*8/24/2021*	
Amendment	*9/1/2021*	
Amendment	*9/9/2021*	
Amendment	*9/16/2021*	
Amendment	*9/30/2021*	

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Rajan Pragani	Paresma Patel
Drug Product	Rajiv Agarwal	Anamitro Banerjee
Process and Facility	Yifan Wang	Bogdan Kurtyka
Microbiology	N/A	N/A
Biopharmaceutics	Gerlie Gieser	Om Anand
Regulatory Business Process Manager	Dahlia Walters	N/A
Application Technical Lead	Sherita McLamore	N/A
ORA Lead	Caryn McNab	N/A
Environmental	Raanan Bloom	N/A

RELATED/SUPPORTING DOCUMENTS

DMFs:

[Applicant will complete]				[FDA will complete]	
DMF #	**Type**	**Holder**	**Item Referenced**	**Status**	**Comments**
(b) (4)	Type III		(b) (4)	Adequate	Adequate information provided in the NDA
	Type III			Adequate	Adequate information provided in the NDA
	Type III			Adequate	Adequate information provided in the NDA
	Type III			Adequate	Adequate information provided in the NDA
	Type III			Adequate	Adequate information provided in the NDA

Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	119,257	asciminib (ABL001) IND cross-reference

CONSULTS

N/A

TABLE OF CONTENTS

Evaluation of the Quality Information

1. EXECUTIVE SUMMARY

OPQ recommends **APPROVAL** of NDA 215358 for SCEMBLIX® (asciminib) tablets, 20 and 40 mg. A comprehensive evaluation of the facilities associated with this application confirms that all sites are acceptable for the responsibility listed in the application. There are no outstanding issues and no post-approval quality agreements to be conveyed to the applicant.

The active pharmaceutical ingredient Asciminib Hydrochloride is a small chiral molecule. The molecule has a single chiral center that is produced in the enantiopure (R)-configuration. Asciminib Hydrochloride is a white to slightly yellow, non-hygroscopic powder with a melting point of 230°C. Asciminib Hydrochloride is slightly soluble in water, ethanol and isopropanol, practically insoluble in TBME and acetone and soluble in methanol. The molecule exhibits pH dependent solubility that slightly increases in solubility at low pH but is overall relatively poor in aqueous solutions.

Asciminib Hydrochloride is manufactured by Novartis Pharma Schweizerhalle AG of Switzerland in the enantiopure (R)-configuration. (b) (4) In the October 18, 2017 Type C meeting, FDA did not agree to the proposed starting materials (b) (4) because the commercial manufacturing development and supporting data was not available at the time. Upon evaluation of the tightening of the acceptance criteria for impurities (b) (4), in addition to the additional supporting information, the starting material (b) (4) was deemed justified as per ICH Q11. The final stage of the manufacturing process includes (b) (4) Polymorph screenings for the drug substance were performed and revealed that (b) (4) is the form to be used for commercialization.

The drug substance specification includes tests and acceptance criteria for appearance, particle size, identity, enantiomeric purity, residual solvents, loss on drying, sulfated ash, heavy metals, related substances, assay, and microbial enumeration tests (TAMC and TYMC). The specification and available stability data were deemed acceptable to ensure the identity, purity, and strength of the drug substance and to support the proposed (b) (4) month retest date for the drug substance when stored under the proposed storage conditions.

The drug product, Asciminib 20 mg and 40 mg film-coated tablets, is an immediate-release, film-coated tablet for oral administration. The drug product formulation includes the active, lactose monohydrate, microcrystalline cellulose, hypromellose, croscarmellose sodium, polyvinyl alcohol, titanium dioxide, colloidal silicon dioxide, lecithins, magnesium stearate, iron oxide yellow, xanthan gum, iron oxide red, (b) (4) and

(b) (4). All drug product excipients including the excipients used in the (b) (4) film-coat are commonly used in solid oral dosage forms and fall below the limits specified in the FDA Inactive Ingredient Database for this route of administration. The 20 mg drug product is presented as a as a pale-yellow, unscored, round, biconvex film-coated tablet with beveled edges. They are 6.2 mm in diameter debossed with "20" on one side and "Novartis Logo" on the other. The 40 mg drug product is presented as a as a (b) (4), unscored, round, biconvex film-coated tablet with beveled edges. They are 8.2 mm in diameter debossed with "40" on one side and "Novartis Logo" on the other.

Asciminib hydrochloride exhibits the characteristics of a low solubility (BCS-II or BCS-IV) drug substance. The biopharmaceutics review focused on the need for bridging of the pivotal clinical and commercial formulations and the acceptability of the proposed in-vitro dissolution method and acceptance criterion for the routine quality control testing of the proposed drug product.

The proposed dissolution method (USP Apparatus 2 at 60 rpm, 900 mL pH 3.0 citrate buffer, 37 °C) and proposed dissolution acceptance criterion (Q = (b) (4)% in 20 min) are acceptable for QC testing of asciminib hydrochloride film-coated tablets. The 20 mg and 40 mg strengths of the proposed commercial asciminib hydrochloride formulation were used in the pivotal clinical trials and primary stability studies. Overall, there were adequate *in vitro* dissolution and *in vivo* PK data to bridge the products used in clinical and stability studies to the final proposed to-be-marketed drug product.
For additional details of the Biopharmaceutics assessment, refer to Section 8 of this Assessment Aid

The drug product is manufactured by Novartis Pharma Stein AG of Switzerland at a commercial batch size of (b) (4) for the 20 and 40 mg tablets, respectively. The drug product is manufactured (b) (4) Hold time of the film-coated tablet is (b) (4) months. No PAIs triggered. All facilities are recommended for approval.

The drug product specification includes controls for all critical quality attributes for the intended dosage form and comply with compendial standards. The drug product specification includes tests and acceptance criteria for: appearance, identification, purity, dissolution, assay, related substances, (b) (4), uniformity of dosage form, and microbial enumeration tests. The applicant proposed real-time release testing for Identity, Assay, and CU based on NIRS methods. For Identity testing, the same NIRS method for ID is used for both 20 mg and 40 mg tablet cores. For Assay and CU, separate

NIR models are developed for the two strengths. The sample selection, method development, and method validation with the associated acceptance criteria are adequate. The model will be systematically monitored, which includes trend analysis and routine comparative testing. The routine maintenance is managed under the firms QMS. In the comparability protocol, the applicant provided reporting category of CBE 30 for the (b) (4) . The drug product specifications are adequate to establish the drug product identity, potency, and purity, and provide adequate controls to ensure the quality of the drug product throughout the product expiry.

The applicant requested a 24-month expiry for the drug product when stored under controlled room temperature (25°C/60%RH). In support of the proposed 24-month expiry the applicant included up to 18 months of long term (25°C/60% RH) and 6 months of accelerated (40°C/75% RH) data for three pilot scale batches each of the 20 and 40 mg drug product. These batches are representative of the proposed commercial product with respect to formulation, manufacturing process, and manufacturing equipment. The primary packaging is representative of the proposed commercial container closure system for both, the commercial pack and physician pack with minor differences detailed in the Pharmaceutical Development section and in Section 7 of this Assessment Aid. Stability studies were conducted in accordance with the ICH 1A and Q1B. The available stability data shows consistency over time and supports the proposed expiry. Therefore, based on the available stability data, the applicant proposed, and the OPQ accepts the expiration dating period of **24-months** for the drug product when stored at stored under controlled room temperature.

Life Cycle Considerations:
N/A

2. APPLICATION BACKGROUND

The purpose of this NDA submission is to obtain marketing authorization for asciminib film-coated tablets for the treatment of adult patients with:

- Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs)
- Ph+ CML in CP harboring the T315I mutation.

Asciminib is a new chemical entity and has been in clinical development as an investigational drug for chronic myeloid leukemia (CML) (b) (4) Asciminib's clinical development was

initiated by Novartis under the Investigational New Drug (IND) 119,257 submitted to FDA on December 17, 2013 with the compound code ABL001. The "Study May Proceed" letter was issued by the Agency on January 16, 2014.

Asciminib is not approved or marketed in any country at the time of this submission.

On February 27, 2017, the Agency granted Orphan Drug Designation for asciminib for "treatment of chronic myelogenous leukemia" (#16-5564). This Orphan Drug Designation population includes the proposed marketing indication described in the proposed USPI of this New Drug Application (NDA).

On August 24, 2020, the Agency granted the asciminib development program as Fast Track Designation for the investigation of asciminib for the treatment of patients with:

- Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs).
- Ph+ CML in CP harboring the T315I mutation.

On February 2, 2021, two Breakthrough Therapy Designations were granted for asciminib for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs) and for the treatment of adult patients with Ph+ CML in CP harboring the T315I mutation.

3. SUMMARY OF CMC SPECIFIC PRESUBMISSION AGREEMENTS

The Applicant's Position:

Date	Description	Pre-NDA agreements
18-Oct-2017	Type C CMC meeting to obtain agreement on proposed starting materials for the synthesis of ABL001 Hydrochloride drug substance; meeting was cancelled after preliminary comments were received	Based on the FDA recommendation for proposed starting material (b) (4) , the acceptance criteria for the impurities (b) (4)
25-Feb-2020	Type C CMC meeting (Written Responses Only) to propose anew dissolution method	Based on the FDA advice, a new dissolution method with (b) (4) was developed and

		demonstration of discriminatory power with regard to the critical quality attribute was performed.

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

4. ENVIRONMENTAL ASSESSMENT

The Applicant's Position:

As set forth in 21 CFR Part 25.31(b), action on a New Drug Application (NDA) is categorically excluded from the requirement to prepare an Environmental Assessment (EA) or an Environmental Impact Statement (EIS) if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be less than 1 part per billion (ppb). "Increased use", as defined in 21 CFR Part 25.5(a), will occur if the drug is "administered at higher dosage levels, for longer duration or for different indications than were previously in effect, or if the drug is a new molecular entity."

Novartis Pharmaceuticals Corporation is filing a New Drug Application (NDA 215,358) for asciminib. Asciminib is a potent, orally bioavailable BCR-ABL1 tyrosine kinase inhibitor with a novel mechanism of action that potently and specifically inhibits the proliferation of chronic myeloid leukemia (CML), that are dependent on BCR-ABL1. In some patients treated with the current generation of ATP binding site targeted inhibitors, resistance to therapy can merge, commonly as a result of point mutations in the ATP-site of the ABL1 kinase SH1 domain that effect the ability of these inhibitors to bind to the enzyme. Asciminib may act as a potent BCR-ABL1 tyrosine kinase inhibitor in combination with an ATP-site inhibitor to prevent the emergence of resistance due to point mutations being acquired in one of the binding sites.

Asciminib is indicated for treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs) (Ph+ CML-CP) and for Ph+ CML in CP harboring the T315I mutation (Ph+ CML-CP with T315I).

Novartis certifies that this submission for asciminib qualifies for a categorical exclusion in accordance with 21 CFR Part 25.31(b) as the estimated environmental intake concentration of the active moieties, asciminib, will be significantly less than 1 ppb, based on the peak production estimates within the next five years.

Further, Novartis states that, to the best of its knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment and would thus require the preparation of at least an Environmental Assessment.

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

The yearly API production level for this NDA is (b) (4) At this level, significant environmental impacts are not expected, and a full EA review is not required.

The applicant has submitted a claim of categorical exclusion. The categorical exclusion cited at 21 CFR 25.31(b) is appropriate for the estimated amount of drug to be produced for direct use. A statement of no extraordinary circumstances has been submitted. The claim of categorical exclusion is acceptable.

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Immediately Following this Page

(b) (4)

8. BIOPHARMACEUTICS

a. BCS CLASSIFICATION

Applicant to fill:	FDA assessment (FDA to fill):
BCS Classification: BCS II	*BCS-II or BCS-IV*

Information to support the BCS Class II designation request, if applicable.
Link: Summary of biopharmaceutics is available CTD 2.7.1. Page#:

FDA Comments:

The Applicant classifies asciminib as a BCS-II (low solubility, high permeability) drug substance. FDA agrees that asciminib hydrochloride is a low solubility drug substance, and can be classified as either a BCS-II or a BCS-IV drug substance.

Drug Substance Solubility - Low
The drug substance (asciminib hydrochloride (b) (4) exhibits distinct pH-dependent solubility, i.e., lower solubility in higher pH (>2) media. Based on the pH-solubility at 37°C data in Table 2-1 of the Dissolution Method Development Report (DMDR) or the table in Section 6.a above, and Table 3-1 of the PDR-Dissolution Comparability Report/DCR, (b) (4) mg/mL of the salt is soluble in aqueous media across the physiologic pH range, including in biorelevant media.

Additionally, based on the pH-solubility data presented in Table 1-2 of 3.2.S.1.3 Drug Substance General Properties (or in Section 6 above of this Assessment Aid), asciminib hydrochloride solubility at 37°C is substantially higher in fasted simulated gastric fluid (FaSSGF; pH ~1.6) than in both fed simulated gastric fluid (FeSSGF; pH ~4.9) and in fasted simulated small intestinal fluid (FaSSIF pH 5.4). Note that the asciminib hydrochloride film-coated tablets contain the equivalent of 20 mg and 40 mg asciminib free base, and per the proposed labeling, (depending on the presence/absence of a specific gene mutation) the recommended dosages of asciminib tablets are 80 mg once daily, and 40 mg or 200 mg twice daily. Note also that the labeling recommends that the tablets be taken on an *empty stomach* because concomitant administration with a low-fat meal and a high-fat meal was observed to reduce bioavailability by 30% and 62%, respectively.

The solubility is generally higher for asciminib HCl salt (b) (4) (b) (4) in various pH media except in pH 1.0 (0.1N HCl) buffer medium at 37 °C (refer to Tables 2-1 and 2-2 in the IR Response of SN-15). (b) (4)

Drug Substance Permeability – Information **NOT** Sufficient to Classify as Highly Permeable:
An absolute BA study was not conducted. In the human Mass Balance Study CABL001A2102, 9 days following administration of a single 80 mg oral dose of [^{14}C] ABL001 (as oral powder) in healthy subjects, 91% radioactivity was recovered; approximately 22% was associated with the feces (as metabolites) and 11% with the urine (as metabolites and unchanged drug). The Applicant reported that in the feces, 57% of the radioactivity was associated with the unchanged drug, and based on PBPK modeling, estimated ~31% of the total clearance to be due to biliary and intestinal secretion by BCRP transporter.

(b) (4)

(b) (4) however, the bioavailability/absorption predictions of the PBPK models were not considered by this Reviewer as supportive of the high permeability claim because (***i***) per the FDA Pharmacometrics Reviewer, the PBPK (SIMCYP®) model (b) (4) is not adequate because (b) (4)

In vitro Caco-2 cell line permeability data was not submitted.

Reviewer Note: The SUPAC-IR Guidance has stricter documentation requirements for any level of formulation change affecting BCS-IV (low solubility, low permeability) drug substances. Since there were no formulation composition changes to the proposed commercial final market image (FMI) asciminib hydrochloride film-coated tablets that were used in pivotal clinical/primary registration stability/process validation studies, at this pre-approval stage, it is not necessary to finalize the permeability and thus, BCS-II or BCS-IV classification of asciminib hydrochloride drug substance.

Drug Product Dissolution – Not Rapid Across the Entire Physiologic pH Range
The dissolution of the proposed drug product is (b) (4) For the dissolution profile data of the pivotal clinical trial/primary registration stability and the process evaluation lots, refer to the tables and figures in Dissolution Comparability Report/DCR.

Additional FDA comment:
The solubility of asciminib hydrochloride (drug substance) and the dissolution of asciminib tablets (drug product) are both pH dependent, (b) (4) In SN-30, the Applicant provided *in vitro* dissolution profile data of asciminib HCl film-coated tablets (b) (4) . Such *in vitro* dissolution findings for the drug product could explain (at least in part) the findings of PK Study A1101, which did not find a clinically significant drug-drug interaction (DDI) between asciminib tablets (single 40 mg dose) and rabeprazole (a proton-pump inhibitor/PPI; 20 mg daily for 4 days); refer to the Clinical Pharmacology review of the DDI study for details.

b. DISSOLUTION TEST

USP Apparatus	Paddle Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion
II (paddle)	60 rpm	900 mL	37 ± 0.5 ºC	Citrate buffer pH 3.0	Q= (b) (4)% in 20 min

Biopharmaceutics Figure 1: Dissolution Profiles as a function of:

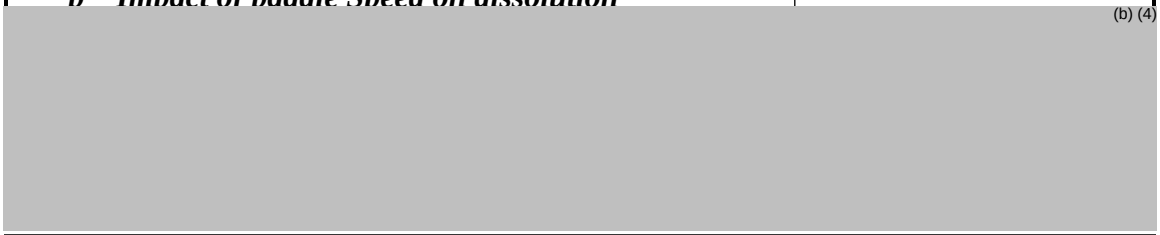
a. Impact of medium pH on dissolution

(b) (4)

FDA Comment:
It is noted that the comparative *in vitro* dissolution profiles in Figure 1a above were generated (b) (4) Additionally, a similar trend was observed using a paddle speed of 60 rpm based on the dissolution profile data in various pH media of the pivotal clinical trial/primary registration and the process validation lots of asciminib tablets as provided in PDR-Dissolution Comparability Report.

b Impact of paddle Speed on dissolution

(b) (4)



(b) (4)

FDA Comment:
The Applicant's decision to choose a paddle speed of 60 rpm (b) (4) Refer also to the section below for the Reviewer's evaluation of the proposed dissolution method (regarding justification for chosen dissolution method parameters).

c. Impact of other parameters on dissolution (add as appropriate)

(b) (4)

FDA Comment:
Refer to the section below for the Reviewer's evaluation of the proposed dissolution method (analytical method validation).

d. Justification for selection of the acceptance criteria (or criterion)

Fig: 20 mg FCT dissolution profile at pH 3.0, 60 rpm – registration stability batch	Applicant's comments: Dissolution profile of registration stability batches in the proposed dissolution method is provided.

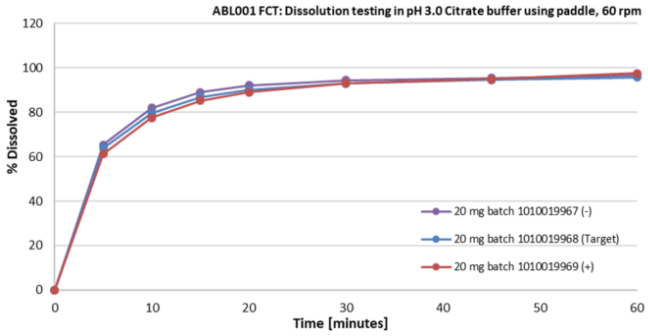
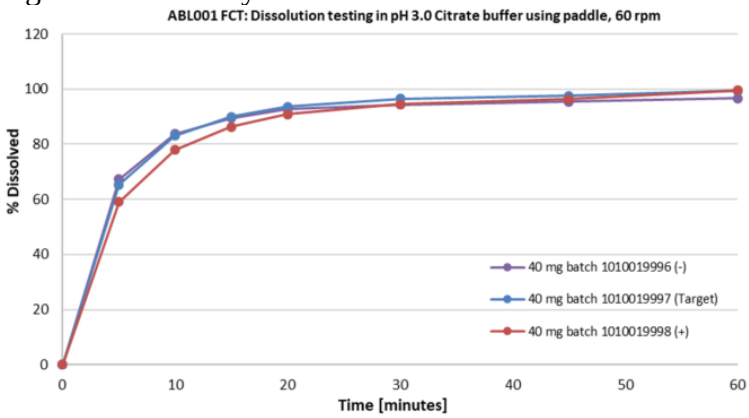


Fig: 40 mg FCT dissolution profile at pH 3.0, 60 rpm – registration stability batch



Comparative dissolution profile of registration stability batches and commercial scale (Process evaluation batches) is provided in dissolution comparability report General report-ARD000115 from section 3.2.P.2.3.

FDA Comment:
The Applicant indicated that the registration stability lots were also used in the Phase 3 pivotal clinical trial and in multi-media dissolution comparison (vs. the process evaluation lots). Refer to the section below for the Reviewer's evaluation of the proposed dissolution acceptance criteria.

	Applicant to fill:	FDA assessment:
The dissolution method is discriminating for:		
i) Particle size distribution (PSD) Link[1]: Development Report-MDR50101	Not discrimitating Page#: 43-47	Agree
ii) Polymorph/solid state form Link[1]: Development Report-MDR50101 3.2.P.2.2	Discriminating Page#: 53-60 Page#: 16	Not applicable *(Not evaluated)*
iii) Formulation variations Link[1]: Development Report-MDR50101	Not discrimitating Page#: 49	Agree
iv) Manufacturing process variations Link[1]: Development Report-MDR50101	Discriminating Page#: 50-52	Not agree
v) Other (specify): Link[1]: Chemical form	Not applicable Page#:	*Discriminating*

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

FDA Comments

DISSOLUTION METHOD – Adequate

Justification for Chosen Method Parameters

Per the Applicant, USP Apparatus II (paddle) is widely accepted as standard apparatus for dissolution testing of immediate release tablets, and the medium volume of 900 mL is recognized as the standard medium volume for BCS classification studies. The dissolution medium (pH 3.0 citrate buffer) and the paddle speed of 60 rpm were selected to achieve complete dissolution over a reasonable time frame, without sacrificing ability to discriminate changes/differences in quality attributes critical to biovailability. Additionally, a paddle speed of 60 rpm (b) (4) , that was observed with the original QC dissolution method (b) (4)

Discriminating Power/Stability-Indicating Potential

The Applicant investigated the impact on dissolution of the quality attributes of the input drug substance and the formulation and process variables that could potentially impact the bioavailability of asciminib hydrochloride tablets (refer to Table 2-3 of the IR Response in SN-15), with the exception of another potential CQA, i.e., API polymorphic form/modification.

Unlike the original proposed QC dissolution (b) (4) method, the final proposed QC dissolution (pH 3.0) method is able to discriminate tablet batches with vs. without changes in API chemical form in the drug product during accelerated storage, as shown in Figures 3-1 and 3-2 of PDR-Formulation Development.

That the proposed dissolution method has stability-indicating potential was based on the Applicant's observation of significant dissolution slow down under stressed/accelerated temperature & humidity (but not under long-term) storage conditions for both the (b) (4) packaged and the HDPE bottle packaged 20 mg and 40 mg tablets. Refer to Figures 5-24 to 5-28 of the DMDR for the effect of storage temperature, as well as Tables 9-89 vs 9-110 and Tables 9-95 vs 9-113 for the effect of storage time on (b) (4) and bottle- packaged tablets (and the figures in Appendix 1_Q2 of the IR Response in SN-15). Such temperature and time-dependent change was attributed (at least in part) to the (b) (4) ; refer to Table 5-6. Based on the comparative dissolution profile on stability data, the Applicant's decision to market the tablets in HDPE bottles (b) (4) is reasonable from a Biopharmaceutics perspective.

Additionally, the proposed dissolution method is able to show the anticipated rank-order relationship between dissolution rate and other critical quality attributes

including drug substance particle size distribution and tablet hardness, as shown in Figure 5-13 & 5-14/Table 5-4 of the DMDR).

Judging from the similar dissolution profiles of the API PSD "variants" with similar tablet hardness levels in these two figures, and based on this Reviewer's exploratory linear extrapolation analysis of dissolution data from the pivotal clinical trial lots, the proposed asciminib hydrochloride X_{90} upper tolerance limit (NMT (b) (4) µm) and X_{10} lower tolerance limit (NLT (b) (4) µm), as measured by Laser Diffraction (Cuvette), appear reasonable.

(b) (4)

From a Biopharmaceutics' standpoint, because the drug substance particle size is considered as a critical bioavailability attribute, the particle size distribution should be appropriately controlled. However, the final decision (b) (4) *is deferred to the Drug Substance Reviewer as well as the Process Reviewer since the Applicant reported that drug substance PSD* (b) (4)

Furthermore, when comparing across tablet strengths that were manufactured using the same API batch, and (in Figures 5-17 to 5-18 of the DMDR), the anticipated effect of tablet hardness/compression force levels is reflected on the relative dissolution rates of the film-coated tablet lots. The dissolution profiles of the tablet hardness variants in these figures appear to support the proposed mean target tablet core hardness levels (b) (4)

(b) (4)N for 20 mg, and (b) (4)N for 40 mg); *however, the acceptability of the target hardness ranges, as well as the Applicant's proposal* (b) (4) *will be evaluated by the Process Reviewer.*

(b) (4)

Analytical Method Validation
HPLC (with UV detection at 313 nm) is used to quantify drug in the dissolution samples. Supplementary analytical method validation using the final paddle speed of 60 rpm included intermediate precision, and robustness with respect to the dissolution method investigated via a DoE matrix study design. Per the Applicant, the dissolution results were robust with respect to paddle speed (60 (b) (4)rpm), dissolution medium temperature (37 (b) (4)°C), dissolution medium volume (900 (b) (4)mL) and the pH of the dissolution medium (3.0 (b) (4), sample filtration type (different filters; single vs. multiple use), sampling procedure (manual vs. automatic), and presence/absence of (b) (4). Per the Drug Product Reviewer, the analytical method validation for dissolution is adequate.

Sink Conditions
Given that the drug substance solubility in pH 3.0 citrate buffer at 37 °C is 0.1729 mg/mL, sink conditions is anticipated to be achieved and maintained in 900 mL of the proposed dissolution medium during dissolution testing of the 20 mg and 40 mg tablets.

DISSOLUTION ACCEPTANCE CRITERION – Adequate

The proposed dissolution acceptance criterion (Q = (b) (4)% at 20 min) for batch release and stability testing was based on the data of registration batches of the 20 mg and 40 mg tablets; see Figure 1d above, as well as the available data for clinical, process transfer and process evaluation lots. A single-point specification was selected by the Applicant because the proposed drug product is intended for immediate drug release. Additionally, (b) (4), the Applicant chose 20 minutes as the dissolution specification time point for Q = (b) (4)%.

Based mainly on the dissolution profile data of the pivotal clinical trial lots generated during time of use in the pivotal clinical trials (b) (4), this Reviewer finds the proposed dissolution acceptance criterion (Q = (b) (4)% at 20 min) acceptable. Note that in SN-15, the Applicant indicated that the FMI tablets were 3 to 44 months old at

the time of use in Clinical Study X2101 and 13 to 45 months old at the time of use in Clinical Study A2301. (b) (4) the dissolution specification time point from the proposed 20 minutes (b) (4) is not considered reasonable/feasible based on the dissolution profile data of the pivotal clinical/primary registration-stability lots in Applicant Figure 8d above.

This Reviewer does not object to the proposal to apply USP Acceptance Table 1, i.e. up to "level"/stage 2 (n=12) for batch release testing and up to "level"/stage 3 (n=24) for shelf-life testing. Note: This Reviewer assumes that "level" is a typographical error.

A single dissolution specification time point appears justified for the following reasons: ***1***) ascminib hydrochloride tablets is an immediate release drug product, ***2***) almost complete dissolution is already achieved within (b) (4) minutes of testing the 20 mg and 40 mg tablets using the proposed QC dissolution method (which as discussed above is deemed adequate for finished product QC). For example, some pivotal clinical study A2301 lots such as 20 mg Lot 1010019968/HDPE bottle exhibited (b) (4) % at 20 min) at 12 months of long-term storage using the proposed dissolution method. Similarly, at batch release, 40 mg Pivotal Clinical A2301 Lot 101009997 and Process Evaluation Lot 1010029995 both exhibited (b) (4) % dissolution at 20 min. ***3***) Although asciminib drug substance is poorly soluble per BCS criteria, the Applicant indicates that at therapeutic doses, asciminib does not have a clinically relevant effect on the QT interval. The CDER-QT-IRT Team concluded that asciminib does not cause a large mean increase in the QTc interval at the maximum recommended clinical dose of 200 mg BID. ***4***) Additionally, given the wide range of recommended dosage (40 mg b.i.d. to 200 mg b.i.d.) the Applicant believes (and the Clinical Pharmacology Reviewer, Dr. Yibo Wang) generally agrees, at this time) that asciminib has a wide therapeutic index.

Dissolution on Stability

Note that up to Month 12 of long-term primary/registration stability testing, the dissolution data were generated using the original method (b) (4) and the dissolution acceptance criterion was Q (b) (4) In the February 2020 CMC meeting with FDA, (b) (4) were proposed. However, to adopt the FDA recommendation, in the NDA submission (b) (4)

Based on the dissolution profile data of the registration/stability lots under accelerated storage conditions, this Reviewer agrees with the Applicant that the original (b) (4) dissolution method appears to have lower discriminating power (b) (4) and/or lower stability-indicating potential than the final proposed commercial dissolution (pH 3.0) method. To be conservative, the Applicant indicated that both original and current/proposed commercial dissolution methods will be used from Month 18 and onwards of registration/stability testing, i.e., to support

future NDA supplements proposing to extend the approved product's expiration dating period (b) (4).

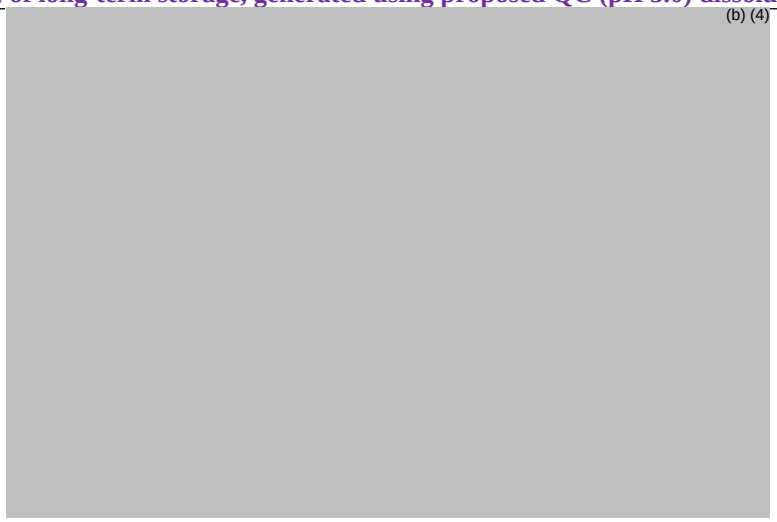
Per the Applicant, the pilot-scale registration/stability lots (three each per strength) manufactured by Novartis, Basel (using the proposed commercial formulation/process/equipment/packaging configuration) met the dissolution acceptance criteria during 24 months of long-term storage (25°C/60% RH), i.e., dissolution at (b) (4) during the first 12 months, and dissolution at 20 min using the proposed commercial pH 3.0 method starting at Month 18. Based on this Reviewer's exploratory 'dissolution methods bridging' analysis using the dissolution profile data available for six clinical/primary registration lots sampled at the Months 18 and 24 long-term stability time points (and because the dissolution profiles generated by the original and proposed commercial dissolution methods converge at the 20 minute time point), it is possible that no significant dissolution (at 20 min) on stability changes/trends occurred during the Month 0 to Month 24 long-term storage of these tablet lots (refer to Reviewer Figures A & B below). Furthermore, the additional dissolution data for the available (and retrospectively analyzed) pivotal clinical trial stability batches up to 48 months and for the initial time point for the process evaluation lots (using the proposed pH 3.0 dissolution method; COMM3.xpt) provide support to the observation that there were no apparent dissolution on stability trends (refer to Reviewer Figure C below).

Reviewer Figures A & B

(b) (4)

Reviewer Figure C
Dissolution on Profiles of Pivotal Clinical Lots (at Months 0 and 48) and Process Evaluation Lots (at Month 0) of long-term storage, generated using proposed QC (pH 3.0) dissolution method

(b) (4)



In SN-27, the Applicant confirmed that both Pivotal Clinical and Process Evaluation lots were packaged in HDPE Bottles during stability testing.
The FMI tablets were 3 to 44 months old at the time of use in the two pivotal clinical trials (X2101 and A2301). The proposed drug product expiration dating period is 24 months when stored at USP Controlled Room Temperature.

As mentioned above, the Applicant observed a significant dissolution slow-down during 6 months of accelerated (40°C/75% RH) storage of the registration/stability lots of the asciminib hydrochloride tablets packaged in (b) (4) and 60-count HDPE bottles, using the pH 3.0 dissolution method. Based on the data in Figures 5-26 and 5-27 of the DMDR, the Applicant's proposed dissolution acceptance criterion (Q = (b) (4)% at 20 min) would be sufficient to reject the bottle-packaged lots that exhibited dissolution slow down (b) (4) after 6 months of accelerated temperature/humidity storage. Per Tables 1-1 and 1-2 of 3.2.P.5.6 Justification of Specifications, this Reviewer considers that it is more reasonable to estimate that dissolution failure will be imminent for tablet lots containing (b) (4) , as estimated from the stability data of three registration/pivotal clinical lots based on Stage 2/n=12 dissolution failure) which is more conservative compared to the Applicant's estimated limit of detection of (b) (4) (b) (4) (based on data from Stage 1/n=6 dissolution failure). Overall, the proposed QC dissolution method's sensitivity (b) (4) in the drug product is considered acceptable (b) (4)

(b) (4)

(b) (4) (4) Based on the provided dissolution profile data (expressed as % of labeled amount of asciminib) and the summary stability data in Section 7f above, the Final-Market-Image (FMI) tablets in the proposed commercial packaging appear to exhibit stable Assay data during 24 months of long-term storage (refer to Reviewer Figures A and B above). Based on the available dissolution profile on stability data, there are no apparent trends for the 60-count (commercial) and 14-count (physician pack) tablet bottle packaging configurations as shown in Reviewer Figures A and B above. (5) It is acknowledged that XRPD studies conducted by the Applicant demonstrated that (b) (4) formation did not occur in the registration stability lots at least up to Month 24 of long-term storage (as well as the "up to 48 months for the clinical tablets in HDPE bottles). Per the IR Response in SN-27, it is also acknowledged that XRPD testing did not detect (b) (4) in the beyond the end-of-shelf-life clinical stability samples, and 24-month registration stability samples. *The acceptability of the Applicant's proposal* (b) (4) *will be assessed by the Drug Product Reviewer.*

Note that at the current time only dissolution at batch release data are available for the first commitment stability drug product lots and the process evaluation lots that were produced by the proposed commercial drug product manufacturer using the API from the proposed commercial drug substance. However, per SN-27, the Applicant expects the proposed commercial drug product to have comparable or even better stability behavior than the clinical and registration stability lots because of the process optimizations that were introduced (b) (4) Additionally, the proposed labeling will recommend to store the product at temperatures not exceeding 25°C, and in the original package in order to protect from moisture.

The acceptability of the proposed expiration dating period (24 months) of the commercial pack tablets (60-count HDPE bottle (b) (4) *and the physician pack tablets (14-count HDPE bottle* (b) (4) *when stored in the*

original packaging configuration under USP Controlled Room Temperature conditions will be decided by the Drug Product Reviewer.

Note that in SN-15, the Applicant provided dissolution at 20 min data and XRPD data to demonstrate that the film coated tablets packaged in HDPE bottles and exposed to shipping storage conditions at 25°C/60% RH, 30°C/75% RH and 40°C/75% RH for up to 1 month will continue to conform to the dissolution specifications, and contain undetectable levels of (b) (4). *The adequacy of the stability data to support shipping conditions for the packaged drug product is deferred to the Drug Product Reviewer.*

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

The commercial formulation has been used in pivotal clinical studies CABL001A2301 and CABL001X2101.

Pivotal clinical batches and drug product registration stability batches were manufactured at pilot scale at Novartis Pharma AG, Basel, Switzerland. The manufacturing process was then transferred to Novartis Pharma Stein AG in Stein, Switzerland which is the proposed commercial manufacturing site. The manufacturing process has been the same in terms of unit operations and their sequence throughout development with a few minor changes implemented as a consequence of process improvements. (b) (4)

summarized briefly in section (b) and in detail in 3.2.P.2.3.

A comparative dissolution study was used to compare registration stability batches (used in pivotal clinical study CABL001A2301) and other batches used in clinical studies (incl., CABL001X2101) from Novartis Pharma AG, Basel, Switzerland with commercial process evaluation batches manufactured at the commercial manufacturing site Novartis Pharma AG Stein, Switzerland. The dissolution profiles were demonstrated to be similar, and the results are provided in a dissolution comparability report provided in 3.2.P.2.3.

Two relative bioavailability studies were performed to bridge between formulations, and these are described in Table below and in detail in section CTD 2.7.1 Summary of biopharmaceutics studies, Section 2.

Table 8-1 Relative bioavailability studies

Study	Reference material	Comparative material	Result
CABL001A2101	Capsules with (b) (4)	Test FCT formulations with (b) (4) and asciminib hydrochloride salt	Comparable rate and extent of absorption achieved between capsules with (b) (4) and FCT with asciminib hydrochloride salt

Study	Reference material	Comparative material	Result
CABL001A2104	Capsules with (b) (4)	Final FCT formulation with asciminib hydrochloride salt	No dose adjustments needed for the switch from capsule formulation to the final FCT formulation

Link: 3.2.P.2.3 Page#: 5 to 8

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

The four formulations/drug products used in clinical studies used to support registration of asciminib tablets are shown in the excerpted Applicant table below. The overall approach used to evaluate and/or establish the bridge among these four formulations/products (A, B, C, D) to the final to-be-marketed drug product (E) are shown in Reviewer Figure D.

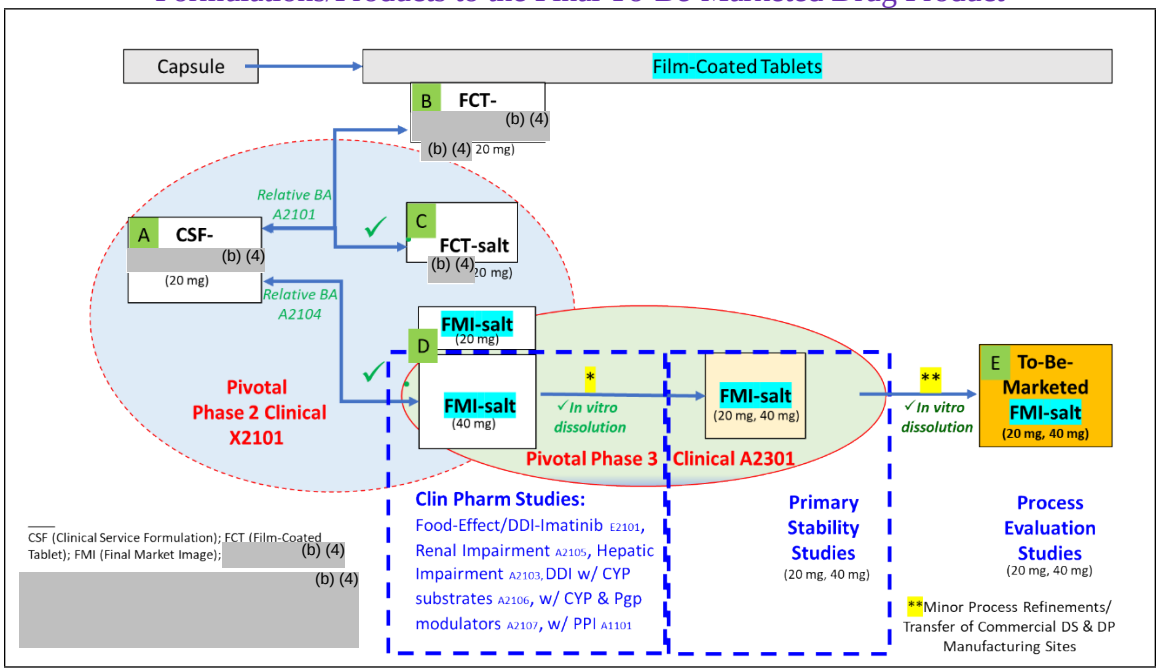
Table 1-2 Drug product formulations used in clinical studies supportive of asciminib development

Drug formulation	Clinical studies [a, b]
CSF Capsule formulation (b) (4)	A2101, A2104, X2101
FCT variant made from (b) (4)	A2101
First FCT variant made from asciminib hydrochloride salt form	A2101, X2101
FMI FCT formulation made from asciminib hydrochloride salt form	X2101, E2101, A2103, A2104, A2105, A2106, A2107, A2301, A1101
Powder in bottle made from asciminib hydrochloride salt form	A2102

[a] Study A2101 was a relative bioavailability study conducted to compare CSF capsule versus asciminib hydrochloride salt form and asciminib free form tablet variants
[b] Study A2104 was a relative bioavailability study conducted to compare CSF capsule versus FMI (asciminib hydrochloride salt form) tablet variant.
CSF: clinical service form; FCT: film-coated tablets; FMI: final market image
Refer [Module 3.2.P.2.CTFO] for further details.

Reviewer Figure D

Overall Approach for Bridging Pivotal Clinical Trial/Primary Stability Study Formulations/Products to the Final To-Be-Marketed Drug Product



As shown in Reviewer Figure D above, both 20 mg and 40 mg strengths of the proposed commercial final market image (FMI) asciminib HCl film coated tablet formulation (Formulation "D") were evaluated in the pivotal Phase 2 clinical trial (Study X2101/dose expansion), the pivotal Phase 3 clinical trial (Study A2301), as well as the primary registration/stability studies. (b) (4) without a change in drug product formula. In SN-15, data were provided to demonstrate that these minor differences (b) (4) did not impact *in vitro* dissolution of the FMI tablets (using the proposed QC dissolution method); see additional discussion below regarding changes in drug substance manufacturing process and site during development.

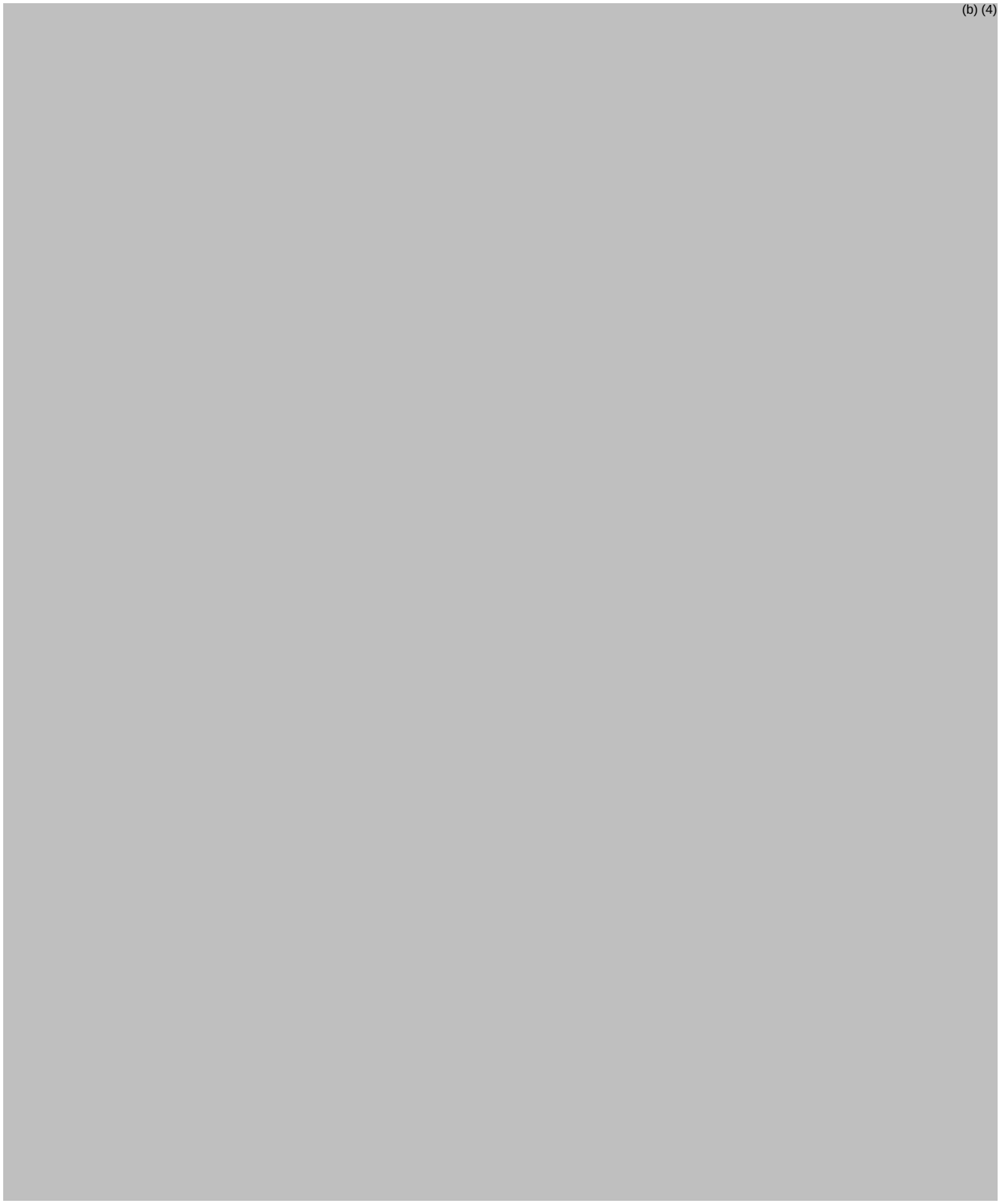
Formulation Bridging from "A" to "D", and "A" to "C":

Per the Clinical Pharmacology Reviewer (Dr. Yibo Wang), Relative BA Study A2101 and Study A2104 provide the *in vivo* PK bridge that adequately links the first FCT (b) (4) and the FMI FCT (salt form) 40 mg, respectively, to the clinical service formulation (CSF) (b) (4) capsule. The 40 mg FMI FCT was also evaluated in Study E2101 (food-effect & DDI with imatinib), as well as A2103 (PK in hepatic impairment), A2105 (PK in renal impairment), A2106 (DDI with CYP substrates), A2107 (DDI with CYP & Pgp modulators), A1101 (DDI with PPI).

Product "D" to Product "E":

1. Changes in the FMI Tablet Manufacturing Site with Process Adaptations, and Change in Drug Substance Manufacturing Process & Site: Novartis Basel + Basel (clinical & registration stability lots) → Novartis Stein + Pratteln (process evaluation lot & proposed commercial)

(b) (4)



(b) (4)

d. BIOWAIVER REQUEST

The Applicant's Position:

The NDA does not contain a biowaiver request.

A biowaiver is not needed for asciminib film-coated tablets because the composition of the proposed commercial tablet formulation is the same as the one used for pivotal clinical supplies. The dosage strengths 20 mg and 40 mg are dose proportional. A comparative multimedia dissolution study was performed with f2 analysis to confirm that the commercial process evaluation are similar to pivotal clinical batches including registration stability batches. Dissolution profile equivalence was met (b) (4) . In pH 4.5 and pH 6.8 media, similarity factor (f2) values were between 50 and 100, thus confirming similarity.

Link: General report- ARD000115 Page#: 7of section 3.2.P.2.3

The FDA's Assessment: *Adequate*

Both 20 mg and 40 mg strengths of the FMI film-coated tablets were evaluated in the pivotal Phase 2 and Phase 3 clinical studies. The pivotal Phase 3 clinical study evaluated a dosage of 40 mg BID with a dosage reduction option to 20 mg BID. Thus, a biowaiver request for a strength(s) of the FMI tablet not evaluated in clinical trials does not apply.

(b) (4)

(b) (4)

e. DATA TO SUPPORT IVIVC AND/OR PBBM MODELING, IF APPLICABLE.

Link: Module 5 Clinical study reports Tabular listing of all clinical studies, Section 1.3. (b) (4) Page#: 10

The FDA's Assessment: ***PBPK model not considered for decision making***

(b) (4)

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LABELING

USPI

Highlights: ***Adequate***

(b) (4)

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

(b) (4)

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

(b) (4)

(b) (4)

Section 11 Description: ***Adequate***

(b) (4)

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.

Section 16 How Supplied/Storage and Handling: ***Adequate***
(Add notes as necessary)

(b) (4)

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

(b) (4)

Carton/Container Label ***Adequate***

20 mg tablet:

(b) (4)

40 mg tablet:

(b) (4)

Carton (40 mg): 5 bottles

Final Risk Assessments

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	Medium	Controlled via specs	Low	The assay shows little change on stability. No trends observed.
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	High	Controlled via Specs at stability	Low	The assay shows little change on stability. No trends observed at the proposed storage condition.
Content Uniformity	• Formulation • Container closure • Raw material • Process Parameters • Scale/equipment • Site	Low	Controlled via specs	Low	Conforms to USP <905> No trends observed.
Moisture content	• Formulation • Container closure • Process parameters • Scale/equipment • Site	High	Controlled via specs	Low	Change in container closure system should be evaluated carefully. Adequate instructions in USPI.
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low	Controlled via specs	Low	Microbial test performed for release of commercial batches and during stability. Testing method adhere to USP <61>/<62> and acceptance criteria adhere to USP <1111>.
Dissolution – BCS Class II & IV	• Formulation • Container Closure • Raw materials • Process parameters • Scale/equipment • Site	Medium		Low	

Recommendation

Drug Substance: Approval

Primary Reviewer: Rajan Pragani Date: September 10, 2021
Secondary Reviewer: Paresma Patel Date: September 10, 2021

Drug Product: Approval

Primary Reviewer: Rajiv Agarwal Date: September 30, 2021
Secondary Reviewer: Anamitro Banerjee Date: September 30, 2021

Process and Facility: Approval

Primary Reviewer: Yifan Wang Date: October 4, 2021
Secondary Reviewer: Bogdan Kurtyka Date: October 4, 2021

Biopharmaceutics: Approval

Primary Reviewer: Gerlie Gieser Date: September 29, 2021
Secondary Reviewer Om Anand Date: September 29, 2021

Application Technical Lead: Approval

Sherita D. McLamore Date: October 6, 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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