CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215358Orig1s008

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 119257
Request Receipt Date	03/14/2024
Product	Asciminib
Indication	Treatment of adult patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP)
Drug Class/Mechanism of Action	BCR-ABL1 tyrosine kinase inhibitor
Sponsor	Novartis
ODE/Division	OOD / DHM1
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	May 13, 2024

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

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

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

   The applicant is seeking indication for the treatment of adult patients with:
   - Newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Deny Breakthrough Therapy Designation ☐

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

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

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

- *Information regarding the disease and intended population for the proposed indication.*
- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

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

Chronic myeloid leukemia (CML) is a myeloproliferative disease characterized by the presence of the Philadelphia chromosome (Ph) which results from a reciprocal translocation between chromosomes 9 and 22 and leads to the formation of BCR-ABL1 fusion gene. CML has 3 phases which are chronic (CP-CML), accelerated (AP-CML) and blastic phase (BP-CML). Most patients are diagnosed in chronic phase, and when untreated, the disease has a course such that it progresses from chronic to accelerated and then to blastic phase which on average takes 3 to 5 years (Shah et al. 2023).

ABL1 is a ubiquitously expressed, tightly regulated kinase. Unlike other tyrosine kinase inhibitors which bind to the ATP site of BCR-ABL protein, asciminib binds to the ABL1 myristoyl pocket which normally functions as a negative control for kinase activity. In CML, the function of the myristoyl pocket is lost and the enzyme is constitutively activated. Consequently, asciminib recovers the original autoregulatory mechanism leading to the inactive conformation, and it inhibits downstream signaling pathways (Breccia et al. 2021).

In clinical practice, the standard of care for the treatment of newly diagnosed CP-CML is the first-generation tyrosine kinase inhibitor (TKI) imatinib or one of the second-generation BCR-ABL TKIs (nilotinib, dasatinib, bosutinib) (Shah et al. 2023). Real-world analysis from a large commercial claims database in the US showed that about half of newly diagnosed CP-CML patients use imatinib as first-line treatment and the other half are treated with second generation TKIs (Kota et al. 2023).

Asciminib was approved on 29 October 2021 for the treatment of adult patients with Ph+ CML in CP previously treated with 2 or more TKIs (accelerated approval) and Ph+ CML in CP harboring the T315I mutation (regular approval). The first indication was converted to regular approval on 12 October 2022.

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

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

The preliminary clinical data is based on the ongoing, phase 3, open-label study CABL001J12301 (ASC4FIRST, referred to as study J12301) which is a randomized study of oral asciminib 80 mg once daily versus one of the investigator-selected TKIs (IS-TKIs) (imatinib, nilotinib, dasatinib, or bosutinib) at their approved dosages.

Study J12301 has two primary efficacy endpoints. One of them is major molecular response (MMR) at 48 weeks with asciminib vs. IS-TKIs. The second primary endpoint is MMR at 48 weeks with asciminib vs. imatinib (both within the stratum of patients with imatinib as their pre-randomization selected TKI).

There are also two key secondary efficacy endpoints. One of them is MMR at 96 weeks with asciminib vs. IS-TKIs. The second is MMR at 96 weeks with asciminib vs. imatinib (both within the stratum of patients with imatinib as their pre-randomization selected TKI).

MMR is a BCR-ABL ratio $\leq 0.1\%$ on the International Scale and is considered a key surrogate endpoint which indicates successful CML treatment.

MMR at 48 weeks is an established surrogate efficacy endpoint used for accelerated approval in newly diagnosed CP-CML. MMR at 96 weeks is also a well-established endpoint in CP-CML.

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

- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*

- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*

- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

Endpoints used by the agency for approval in newly diagnosed CP-CML were progression-free survival (PFS), and CCyR (complete cytogenetic response, no Ph-positive metaphases). In recent years, MMR has been used as the primary endpoint in newly diagnosed CP-CML patients. For accelerated approval in patients with newly diagnosed CP-CML, the Agency has accepted MMR with at least 12 months of follow up. Regular approval in patients with newly diagnosed CP-CML has been granted based on MMR with at least 5 years of follow up.

MMR indicates successful treatment of CML and is associated with longer overall survival (OS) and progression-free survival (PFS). MMR at 48 weeks is an acceptable primary endpoint that is highly likely to predict clinical benefit and is acceptable for regulatory decisions.

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

Other biomarkers are not yet established for this condition.

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

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

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

TKI approvals in CP-CML

	Front-line	
	Trial	Topline results
Imatinib (Gleevec®)	Imatinib vs. IFN+ARA-C	PFS (84-mo data): 81.2% (95%CI: 78, 85) vs. 60.6% (95%CI: 56, 65) (p<0.0001) CCyR (84-mo data): 74.7% (95%CI: 70.8, 78.3) vs. 6.5% (95%CI: 4.6, 8.9) (p<0.001)
Dasatinib (Sprycel®)	Dasatinib vs. Imatinib	CCyR (within 12 mo): 76.8% (95%CI: 71.2, 81.8) vs. 66.2% (95%CI: 60.1, 71.9) (p=0.007) MMR (at 12 mo): 52.1% (95%CI: 45.9, 58.3) vs. 33.8% (95% CI: 28.1, 39.9) (p<0.0001) MMR (at 60 mo): 76.4% ((95%CI: 70.8, 81.5) vs. 64.2% (95%CI: 58.1, 70.1) (p<0.0001)
Nilotinib (Tasigna®)	Nilotinib vs. Imatinib	CCyR (by 12 months): 80% (95%CI: 75.0, 84.6) vs. 65% (95%CI: 59.2, 70.6)

		MMR (at 12 mo): 44% (95%CI: 38.4, 50.3) vs. 22% (95%CI: 17.6, 27.6) MMR (at 24 mo): 62% (95%CI: 55.8, 67.4) vs. 38% (95%CI:31.8, 43.4)
Bosutinib (Bosulif®)	Bosutinib vs. Imatinib	CCyR (by 12 mo): 77% (95%CI: 72, 83) vs. 66% (95%CI: 60, 72) (p=0.0075) MMR (at 12 mo): 47% (95%CI: 41, 53) vs. 37% (95%CI: 31, 43) (p=0.0200) MMR (by 18 mo) 61% (95%CI: 55, 67) vs. 53 (95%CI: 46, 59) (p=0.0606)

Source: USPIs for imatinib, dasatinib, nilotinib, and bosutinib.

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

There are no other drugs that have been granted BTD for the same or similar indications.

11. Information related to the preliminary clinical evidence:

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

The BTDR is based on results from their phase 3 J12301 trial.

Results of the phase 3 J12301 trial

Trial design	
Design	Ongoing, phase 3, open-label, 1:1 randomized study
Eligible population	Newly diagnosed Philadelphia-positive (Ph+) CML in chronic phase (CP)
Treatment schedule	Arm 1: • Asciminib (oral) 80 mg QD Arm 2: Investigator-selected TKI • Imatinib (oral) 400 mg QD • Nilotinib (oral) 300 mg BID • Dasatinib (oral) 100 mg QD • Bosutinib (oral) 400 mg QD Continuous treatment
Planned sample size	405 patients randomized 1:1 to Asciminib vs. IS-TKI • Asciminib arm (201 patients) • IS-TKI arm (204 patients total: imatinib, 102 patients; nilotinib, 49 patients; dasatinib, 42 patients; and bosutinib, 11 patients)

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

Primary efficacy endpoint	Two primary efficacy endpoints: • MMR at 48 weeks with asciminib vs. IS-TKI • MMR at 48 weeks with asciminib vs. imatinib (both within the stratum of patients with imatinib as their pre-randomization selected TKI)			
Selected secondary endpoints	Two main secondary efficacy endpoints: • MMR at 96 weeks with asciminib vs. IS-TKI • MMR at 96 weeks with asciminib vs. imatinib (both within the stratum of patients with imatinib as their pre-randomization selected TKI)			
Results				
	Overall Asciminib N=201	Overall IS-TKI N=204	Imatinib Stratum Asciminib N=101	Imatinib Stratum Imatinib N=101
MMR (BCR/ABL ≤ 0.1%) at 48 weeks	67.7%	49.0%	69.3%	40.2%
Difference	18.9%[a]		29.6%[b]	
MR4 (BCR/ABL ≤ 0.01%) by 24 weeks	23.4%	9.8%	23.8%	4.9%
MR4 (BCR/ABL ≤ 0.01%) by 48 weeks	40.8%	22.1%	45.5%	15.7%
MR4.5 (BCR/ABL ≤ 0.0032%) by 24 weeks	14.4%	5.4%	14.9%	2.9%
MR4.5 (BCR/ABL ≤ 0.0032%) by 48 weeks	19.9%	11.8%	21.8%	5.9%

[a] (95%CI: 9.6, 28.2); [b] (95%CI: 16.9, 42.2)

The median time to first MMR was 24.3 weeks in the asciminib arm vs. 36.4 weeks in the IS-TKI arm. Within the imatinib stratum, the median time to first MMR was 24.1 weeks in the asciminib arm vs. 48.6 weeks in the imatinib arm.

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

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*
- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*
- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

When we consider all grade AEs and grade ≥3 AEs, SAEs, AEs leading to discontinuation, dose adjustment or interruption, asciminib appears to be more favorable compared to IS-TKIs, imatinib, and second generation (2G)-TKIs. There were no deaths in the study.

The most frequent all grade AEs ≥ 14% were COVID-19, diarrhea, cytopenias, rash and constitutional symptoms; and they were less frequent with asciminib compared to IS-TKIs. Among the most frequent grade 3-4 AEs ≥ 4%, thrombocytopenia, decreased platelet count, and hypertension were more frequent with asciminib than with IS-TKIs. Other grade 3-4 AEs were less frequent with asciminib.

All grades adverse events of special interest (AESI) of myelosuppression (including thrombocytopenia, neutropenia), gastrointestinal toxicity, hypersensitivity, hepatotoxicity, acute pancreatitis, ischemic heart and CNS conditions, edema and fluid retention, QTc prolongation were less frequent in the asciminib arm compared to the IS-TKI arm. Arterial-occlusive events were similar in both arms.

Grade ≥ 3 AESI, except thrombocytopenia, ischemic heart and CNS conditions, QTc prolongation were less frequent with asciminib. Acute pancreatitis and arterial-occlusive events were similar. Overall, AESI were less frequent in patients treated with asciminib.

Given that both primary endpoints of the study were achieved and asciminib was more favorable in its safety profile than IS-TKIs, it is reasonable to grant breakthrough designation for asciminib for the treatment of adult patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP).

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

☒ GRANT:

Provide brief summary of rationale for granting. If the division is proposing a revised indication for the designation please include it here, along with the rationale for the revision:

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

Newly diagnosed Ph+ CP-CML is a life-threatening disease if left untreated. Treatment options include imatinib, nilotinib, dasatinib, or bosutinib. Generally, patients with low risk scores, elderly patients, or patients with multiple comorbidities are treated with the first generation TKI imatinib which is less potent than 2G-TKIs. This may lead to disease progression and emergence of resistant mutations. Patients who are younger and have high-risk scores are recommended to be treated with 2G-TKIs which are more potent but can lead to more adverse events than imatinib. Asciminib has achieved significantly better MMR rates at 48 weeks when compared to IS-TKIs and also when compared to imatinib within the imatinib stratum of patients. In addition, all grade and grades 3-4 AEs, SAEs, AEs leading to discontinuation, dose adjustment / interruption, most frequent grade 3-4 AEs (except thrombocytopenia, decreased platelet count and hypertension), and all grades AESI (except arterial occlusive events) were less frequent with asciminib vs. IS-TKIs.

☐ DENY:

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

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

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

The sponsor is planning to submit a supplemental New Drug Application based on results of study J12301 at the end of April 2024.

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

14. List references, if any:

Breccia M, Colafigli G, Scalzulli E, Martelli M. Asciminib: an investigational agent for the treatment of chronic myeloid leukemia. Expert Opin Investig Drugs. 2021 Aug;30(8):803-811.

Kota VK, Wei D, Yang D, et al. Treatment Patterns and Modifications of Tyrosine Kinase Inhibitors (TKI) Therapy in Early Lines in Patients with Chronic Myeloid Leukemia in Chronic Phase: Real World Analysis from a Large Commercial Claims Database in the United States. 65th American Society of Hematology Congress Annual Meeting & Exposition. San Diego-CA, December 9-12, 2023.

Shah NP, Bhatia R, Altman K, et al. NCCN Clinical Practice Guidelines in Oncology, Chronic Myeloid Leukemia. Version 2.2024. December 5, 2023.

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

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

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: Gulsum Pamuk, MD {See appended electronic signature page}
Team Leader Signature: Lori Ehrlich, MD, PhD {See appended electronic signature page}
Division Director Signature: Angelo De Claro, MD {See appended electronic signature page}

Revised 2-26-2024 /M. Raggio

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

GULSUM E PAMUK
05/06/2024 07:05:38 PM

LORI A EHRLICH
05/07/2024 08:44:48 AM

ROMEO A DE CLARO
05/07/2024 11:57:24 AM

IND 119257

MEETING PRELIMINARY COMMENTS

Novartis Pharmaceuticals Corporation
Attention: Tina Lertharakul, PharmD
Senior Global Program Regulatory Manager
One Health Plaza
East Hanover, NJ 07936

Dear Tina Lertharakul:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Scemblix (asciminib).

We also refer to your January 10, 2024, correspondence requesting a meeting to discuss and obtain Agency feedback on the planned supplemental NDA submission to update the indication as follows: Scemblix is indicated for the treatment of adult patients with newly diagnosed or previously treated Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP).

Our preliminary responses to your meeting questions are enclosed.

You should provide me with an electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting. In accordance with FDA policy, you should not make audio or visual recordings of the discussion at this meeting. Consistent with 21 CFR 10.65(e), the official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Rachel McMullen, MPH, MHA
Senior Regulatory Project Manager
Hematologic Malignancies I
Division of Regulatory Operations for Oncologic Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-sNDA

Meeting Date and Time: March 4, 2024; 9:00AM-10:00AM (ET)
Meeting Location: Teleconference

Application Number: IND 119257
Product Name: Asciminib
Indication: For the treatment of newly diagnosed or previously treated patients with chronic myeloid leukemia in chronic phase (CML-CP)

Applicant Name: Novartis Pharmaceuticals Corporation
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for March 4, 2024; 9:00AM-10:00AM (ET) between Novartis Pharmaceuticals Corporation and the Division of Hematologic Malignancies I (DHMI). We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Novartis requested this pre-sNDA meeting to obtain feedback from the Agency on their planned supplemental New Drug Application (sNDA) submission to broaden the treatment indication for Scemblix. The proposed updated indication is for the treatment of adult patients with newly diagnosed or previously treated Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP).

The registrational study will be CABL001J12301 (ASC4FIRST, J12301), which is an ongoing Phase III, multi-center, open label, randomized study, to investigate the safety and efficacy of asciminib (80 mg q.d.) versus Investigator-selected TKI (IS-TKI: imatinib, nilotinib, dasatinib, or bosutinib) in patients with newly diagnosed Ph+ CML-CP.

The Applicant will also provide interim data on patients treated with asciminib in the second line from a supplemental study, CABL001AUS08 (ASC2ESCALATE, AUS08) which is a Phase II single arm study of asciminib single agent in first- or second-line CML-CP.

Novartis also had a preliminary breakthrough designation meeting with the Agency on February 21, 2024.

2.0 SPONSOR QUESTIONS & FDA PRELIMINARY RESPONSES

***Question 1:* Study J12301 primary analysis results**
The primary analysis results from Study J12301 are considered to be adequate to support the sNDA submission in the intended indication.

Does the Agency agree?

FDA Response to Question 1:
Yes, we agree that the primary analysis results from Study J12301 appear reasonable to support the sNDA submission. However, whether they are sufficient for review will be determined at filing. The granted indication will be determined after review of the sNDA submission.

***Question 2*: Interim analysis results of Study AUS08 to be included in the submission**

Does the Agency agree with the proposed plan for inclusion of clinical data from Study AUS08 as part of the sNDA?

FDA Response to Question 2:
Yes, we agree with your proposed plan for inclusion of clinical data from Study AUS08 as part of your planned sNDA.

***Question 3*: Priority Review**

Does the Agency agree that the sNDA application could qualify for Priority Review?

FDA Response to Question 3:
Determination of priority review will be made at the time of NDA submission. If breakthrough therapy designation is granted for the treatment of newly-diagnosed CML in chronic phase, then we anticipate that the sNDA application would qualify for priority review.

***Question 4*: Real Time Oncology Review**

Does the Agency agree with Novartis's proposal that the sNDA be reviewed under the Real Time Oncology Review (RTOR) program and with the proposed content and timing of batches?

FDA Response to Question 4:
Yes, the Agency agrees to review the planned sNDA under the RTOR (real-time oncology review) program. We generally agree with the content and timing of the batches. Please clarify when the datasets for Study J12301 will be submitted. To aid in the Agency review, we recommend that datasets are submitted with batch 1.

Question 5: Project Orbis

Does the Agency agree with Novartis's proposal that the sNDA be reviewed under Project Orbis?

FDA Response to Question 5:
Yes, the Agency agrees to with the proposal to review the sNDA under Project Orbis.

Question 6: ODAC

Is FDA considering an Oncologic Drugs Advisory Committee (ODAC) meeting will be necessary to discuss the proposed indication expansion for Scemblix in the context of the FDA public comments suggesting "more advisory committees"?

FDA Response to Question 6:
Whether an ODAC will be needed will be decided during the review of the sNDA.

Question 7: Financial disclosure

Does the Agency agree with the proposal for submission of financial disclosure information for the registrational Phase III study J12301 only?

FDA Response to Question 7:
Yes, we agree with your proposed financial disclosure plan.

Question 8: User fee waiver

Scemblix® has been granted orphan drug designation for "treatment of chronic myelogenous leukemia" (#16-5564). Therefore, the sNDA should qualify for a user fee waiver. Does the Agency agree?

FDA Response to Question 8:
Supplemental NDA submissions do not have an associated user fee; therefore, a waiver of the user fee would not be applicable to this submission.

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for

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

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

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

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

For the latest version of the molecular target list, please refer to FDA.gov.[1]

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

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating, "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

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

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

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

reproductive potential.

- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[5]

ONCOLOGY PILOT PROJECTS

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

- RTOR[6]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- Assessment Aid[7]

[5] https://www.fda.gov/media/85061/download
[6] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[7] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

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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/

RACHEL S MCMULLEN
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