CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215358Orig1s000
215358Orig2s000

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	119257 / SDN#223
Request Receipt Date	12/08/2020
Product	Asciminib
Indication	Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs).
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)	February 5, 2021

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:
   - 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.

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.*

[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

- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

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 myristate pocket and mimics myristolated Gly-2 residue and stabilizes inactive conformation of the enzyme. Therefore, it does not have the off-target kinase-mediated effects seen with other ATP-competitive tyrosine kinase inhibitors (TKI) and has potent activity against point mutations, like T315I mutation, which confer resistance to ATP-competitive TKIs.

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 (Deininger et al. 2020).

In clinical practice, about half of CP-CML patients use imatinib, a first-generation BCR-ABL TKI, as first-line treatment, and the other half of patients are treated with second-generation BCR-ABL TKIs (nilotinib, dasatinib, bosutinib). If patients have failed two second-generation TKIs, the third-generation TKI ponatinib might be used, but it has cardiovascular and arteriovascular side effects (hypertension, peripheral arterial occlusive disease, ischemic heart disease, cerebrovascular accident, venous thromboembolism, and platelet dysfunction). If patients are not candidates for TKI therapy, omacetaxine mepesuccinate which is a protein synthesis inhibitor that reduces BCR-ABL1 levels might be considered (Jabbour et al. 2015). The final option is allogeneic stem cell transplantation, but it is available for patients with a donor, good performance status and normal organ functions.

As CP-CML patients develop disease resistance or intolerance to TKIs, especially if they had failure with 2 or more TKIs, treatment options become very limited. Mutations of BCR-ABL1 kinase might develop in 21% to 33% of patients. If patients have intolerance to a certain TKI, cross-tolerance and carry over toxicity might be encountered with other agents.

The most common cause of resistance in CML is BCR-ABL1 mutations. In patients who are using imatinib or second-generation TKIs first-line, resistance is associated with mutations in 10% to 68% of patients, and 14% to 33% of patients using nilotinib or dasatinib as second line treatment develop BCR-ABL1 mutations. T315I mutation is the most frequent mutation (14%) in CML patients who are resistant to TKIs. Patients with this mutation are resistant to imatinib, nilotinib, dasatinib, and bosutinib. Ponatinib is the only approved agent for patients with T315I mutation, but it has serious side effects. The presence of this mutation confers shorter OS and PFS. Other options might be allogeneic stem cell transplantation, supportive care or other therapies not targeting this mutation. However, these carry many adverse events and poor treatment outcomes.

The investigational product, asciminib, is being used in CML or Philadelphia-chromosome positive ALL (Ph+ ALL) patients (including those with T315I mutation) and has also been investigated in healthy volunteers. The FIH trial was the phase 1 study CABL001X2101, and the phase 3 study was CABL001A2301.

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 phase 3 randomized study of oral asciminib versus bosutinib in CP-CML patients treated with ≥ 2 TKIs (CABL001A2301, ASCEMBL, referred as study A2301) and is complemented by data from their FIH trial, study CABL001X2101 (referred as study X2101)

The primary efficacy endpoint of study A2301 is major molecular response (MMR) at 24 weeks while on study treatment without meeting any treatment failure criteria prior to 24 weeks.

Major molecular response is a BCR-ABL ratio ≤ 0.1% on the International Scale and is considered a key surrogate endpoint which indicates successful CML treatment.

The secondary efficacy endpoint is major molecular response (MMR) at 96 weeks while on study treatment without meeting any treatment failure criteria prior to 96 weeks. This is also a well-established surrogate and the MMR at 96 weeks is expected to be higher than the MMR at 24 weeks.

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 CP-CML were MCyR (major cytogenetic response, 0-35% Ph-positive metaphases), CCyR (complete cytogenetic response, no Ph-positive metaphases), and duration of response (DOR). In recent years, MMR and MR4.5 (BCR-ABL1 ≤ 0.032%) have been used as primary endpoints in CP-CML patients. For accelerated approval in patients with resistant/intolerant CP-CML, the Agency has accepted MCyR or MMR with at least 6 months follow up. Regular approval has been granted based on MCyR or MMR with at least 2 years of follow up.

MMR indicates successful treatment of CML and is associated with longer OS and PFS. MMR at 24 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		Relapsed or Intolerant	
	Trial	Topline results	Trial	Topline results
Imatinib	Imatinib vs. IFN+ARA-C	PFS (84-mo data): 81.2% vs. 60.6% (p<0.0001) CCyR (84-mo data): 74.7% vs. 6.5% (p<0.001)	IFN-failure CP-CML (Single arm)	MCyR: 60% (95% CI: 55.3-63.8) CCyR (unconfirmed): 39% (47%)
Dasatinib	Dasatinib vs. Imatinib	CCyR (within 12 mo): 76.8% vs. 66.2% (p=0.007) MMR (60 mo): 76.4% vs. 64.2% (p<0.0001)	Imatinib-resistant or -intolerant CP-CML (Single arm)	CCyR (min 24 mo): 50% (95% CI: 42-58) MMR (7 years): 44%
Nilotinib	Nilotinib vs. Imatinib	CCyR (by 24 months): 87% (95%CI: 82.4, 90.6) vs. 77% (95%CI: 71.7, 81.8) MMR (at 24 mo): 62% (95%CI: 55.8, 67.4) vs. 38% (95%CI:31.8, 43.4)	Imatinib-resistant or -intolerant CP-CML (Single arm)	MCyR (min 24 mo): 51% (95% CI: 46-57) CCyR (min 24 mo): 37% (95% CI: 32-42)
Bosutinib	Bosutinib vs. Imatinib	CCyR (by month 12): 77.2% vs. 66.4% (p=0.0075) MMR (at month 12): 47.2% vs. 36.9% (p=0.02)	Imatinib-resistant or -intolerant CP-CML (Single arm)	MCyR (by week 24): 40.1% (95% CI: 34.1, 46.3)
Ponatinib	NA	NA	CP-CML resistant or resistant/intolerant to at least 2 prior TKIs (Single arm) CP-CML with T315I (single arm)	MCyR (by 12 mo): 49% (95%CI: 38, 60) BCR-ABL1 ≤1% (at 12 mo): 42% (95%CI: 32, 53) MCyR (by 12 mo): 50% (95%CI: 29, 71) BCR-ABL1 ≤1% (at 12 mo): 42% (95%CI: 22, 3)

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

Studies on 2G TKIs in third or further lines of therapy in patients with CML in chronic phase

TKI	Cumulative CCyR (%)	Cumulative MMR (%)	Median duration of follow-up in months (range)
Dasatinib 3L n=16 Nilotinib 3L n=9	31 11	13 33	13 (0.5-41) (all pts including 21 with AP/BP-CML
Nilotinib 3L n=39	24 (based on 37 pts)	NA	12 (all pts including 21 with AP-CML
Dasatinib or Nilotinib 3L n=26	34.6	19.2	21.5 (6-46.5)
Dasatinib 3L n=5 Nilotinib 3L n=13	13 (based on 15 pts)	24 (based on 17 pts)	52 (7-75)
Nilotinib 3L/4L n=3/3	24 (3L+)	NA	8.6 (0.7-53.8)

Dasatinib 3L n=6 Bosutinib 3L n=12 Inv. Agent 3L/4L n=5/1			
Bosutinib 3L n=5 Dasatinib 3L n=33 Nilotinib 3L n=18	21	NA	21 (1-67)
Dasatinib 3L n=6 Nilotinib 3L n=15	Only best response reported: Dasatinib: 1 CCyR and 2 MMR Nilotinib: 8 MMR		12 (1-42)

Source: Sponsor's BTDR application.

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 A2301 trial and was complemented by data from the phase 1 trial X2101.

Results of the phase 3 trial A2301

Trial design			
Design	Phase 3, active-controlled, open-label randomized, asciminib vs. bosutinib		
Eligible population	CP-CML patients treated with at least 2 prior ATP-binding site TKIs who failed or were intolerant to their most recent TKI		
Treatment schedule	Asciminib (oral): 40 mg BID Bosutinib (oral): 500 mg QD Continuous treatment		
Planned sample size	233 patients, randomized 2:1		
Primary efficacy endpoint	MMR at 24 weeks		
Selected secondary endpoints	MMR at 96 weeks (MR2 at 24 weeks, MR4 at 24 weeks, MR4.5 at 24 weeks, MMR rates as 3rd, 4th, or ≥5th lines of therapy, MMR in patients with prior TKI failure or intolerance, MMR in patients with or without MCyR, CCyR at 24 weeks		
Results			
	Asciminib N=157	Bosutinib N=76	Risk difference (95% CI)
MMR (BCR/ABL ≤ 0.1%) rate at 24 weeks	25.5%	13.2%	0.70 (2.11-22.53)
MR2 (BCR/ABL ≤ 1%) rate at 24 weeks	44.4%	22.6%	

[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.

MR4 (BCR/ABL ≤ 0.01%) rate at 24 weeks	10.8%	5.2%	
MR4.5 (BCR/ABL ≤ 0.0032%) rate at 24 weeks	8.9%	1.3%	
MMR rate as 3rd line therapy	29.3%	20.0%	9.3 (-8.1, 26.6)
MMR rate as 4th line therapy	25%	13.8%	11.2 (-6.7, 29.1)
MMR rate as ≥5th line therapy	16.1%	0%	16.1 (3.2, 29.1)
MMR rate in patients with prior TKI failure	21.1%	5.6%	0.26 (5.3-25.7)
MMR rate in patients with prior TKI intolerance	7/16 = 44%	1/12 = 8%	0.18 (-20.8-25.0)
MMR rate in patients with MCyR	45.7%	18.2%	0.39 (5.9-49.1)
MMR rate in patients without MCyR	17.1%	11.1%	0.64 (-4.9-16.9)
CCyR rate at week 24	40.8%	24.2%	p-value: 0.019

Results of the phase 1 trial X2101

Trial design	
Design	Phase 1, FIH dose escalation, asciminib alone vs. asciminib in combination with either nilotinib, imatinib, or dasatinib
Eligible population	CP, AP, BP-CML and Ph+ ALL patients treated with at least 2 prior ATP-binding site TKIs who failed or were intolerant to their most recent TKI CP and AP CML patients who exhibited relapsed disease associated with the presence of the T315I mutation after at least one TKI This protocol included CP-CML and AP-CML patients treated with single agent asciminib at different dose levels and CP-CML patients harboring the T315I mutation treated at 200 mg BID dose (Arm 1 which is included in the BTDR)
Treatment schedule	Asciminib (oral): 10 mg, 20 mg, 40 mg, 80 mg, 150 mg, 160 mg, or 200 mg BID or 80 mg, 120 mg, or 200 mg QD (Arm 1) Asciminib (oral): 200 mg BID in CP-CML patients with T315I mutation (Arm 1) Repeat every 28 days
Planned sample size	200 patients in arm 1 (185 with CP-CML, 48 with T315I mutation)
Primary efficacy endpoint	MMR at 24 weeks
Selected secondary endpoints	MMR at 48, 72 and 96 weeks

Results in T315I positive CP-CML patients			
	Ponatinib-pretreated CP-CML patients with T315I mutation N=26 n (%)	Ponatinib-naïve CP-CML patients with T315I mutation N=19 n (%)	All CP-CML patients with T315I mutation N=45 n (%)
Overall MMR	9 (34.6)	13 (68.4)	22 (48.9)

MMR rate at 24 weeks Confidence Interval	8 (30.8) (16.3-48.7)	11 (57.9) (36.8-77.0)	19 (42.2) (27.7-57.8)
MMR rate at 48 weeks	11 (36.7)	6 (40.0)	20 (44.4)

The median time to first MMR was 20.9 weeks (2-192 weeks) and the median (maximum) duration of treatment exposure was 124.6 (302) weeks. The majority of patients who achieved MMR (20/22) maintained this response level or achieved deeper response and the median time to first MMR was 12.2 weeks (min-max: 4-84 weeks).

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.*

Cumulative response on asciminib and in studies of authorized TKIs for patients with CP-CML resistant to intolerant of prior TKIs

	Study X2101 3L+	Study A2301 3L+		2L Dasatinib	2L Nilotinib	3L+ Bosutinib	3L+ Ponatinib
	Asciminib	Asciminib	Bosutinib				
Primary analysis publications							
Median duration of treatment (months)	42.2	10	6.7	8	8	8.3	12.8
Cumulative CCyR (%)	-	43.7	30.7	41	31	24	40
Cumulative MMR (%)	58.1	34.4	18.4	-	-	15	27
Latest publications							
Median duration of treatment (months)	42.2	10	6.7	37	18.4	8.6	32.1
Cumulative CCyR (%)	-	43.7	30.7	-	44	32	49
Cumulative MMR (%)	58.1	34.4	18.4	46	28	-	35

Source: Sponsor's BTDR submission.

Regarding safety in the randomized phase 3 trial, asciminib appeared to have less gastrointestinal toxicity (diarrhea, nausea, vomiting), hepatotoxicity, and rash when compared to bosutinib; however, there was more frequent thrombocytopenia with asciminib (events related to hemorrhage were similar in both arms). Safety profile of asciminib in CP-CML patients with T315I mutation in study X2101was similar to that of patients in study A2301. Asciminib had lower rates of arterial occlusive events when compared to ponatinib (4.2% vs. 20%).

Given the lack of established therapy for the above-mentioned two indications, the efficacy of asciminib and its relatively benign safety profile, it is reasonable to grant breakthrough designation 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 in Ph+ CML in CP harboring the T315I mutation.

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

☒ GRANT:

Provide brief summary of rationale for granting:

CP-CML previously treated with 2 or more TKIs and CP-CML with T315I mutation are life-threatening diseases if left untreated. Treatment options for CP-CML previously treated with 2 or more TKIs is very limited and patients have cross resistance to other TKIs. Ponatinib is the only available treatment for CP-CML patients with T315I mutation; however, it causes increased risk of vascular events. Asciminib has achieved significantly better MMR rates at 24 weeks when compared to bosutinib in CP-CML previously treated with 2 or more TKIs and it was found effective in CP-CML patients with T315I mutation who were ponatinib-naïve and ponatinib-pretreated. The safety profile was at least similar to other TKIs and AEs were manageable.

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

☐ DENY:

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 New Drug Application based on results of study A2301 which will be supported by data from study X2101. Their data cut-off date for study A2301 was 25 May 2020 for the BTDR. For the NDA, they are planning to send data with a cut-off date of January 2021 for both studies.

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

14. List references, if any:

1. Deininger MW, Shah NP, Altman JK, et al. NCCN Clinical Practice Guidelines in Oncology, Chronic Myeloid Leukemia. Version 2.2021. August 28, 2020.
2. Jabbour E., Kantarjian H, Cortes J. Use of Second- and Third-Generation Tyrosine Kinase Inhibitors in the Treatment of Chronic Myeloid Leukemia: An Evolving Treatment Paradigm. Clinical Lymphoma, Myeloma & Leukemia 2015; 15(6):323-334.

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

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

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}

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

Revised 10/13/20/M. Raggio

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

/s/

GULSUM E PAMUK
02/01/2021 06:32:13 PM

LORI A EHRLICH
02/02/2021 09:12:51 AM

ROMEO A DE CLARO
02/02/2021 10:12:26 AM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	119257 / SDN#232
Request Receipt Date	01/29/2021
Product	Asciminib
Indication	Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP) harboring the T315I mutation.
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)	March 30, 2021

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:
   - 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.

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.*

[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

- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

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 myristate pocket and mimics myristolated Gly-2 residue and stabilizes inactive conformation of the enzyme. Therefore, it does not have the off-target kinase-mediated effects seen with other ATP-competitive tyrosine kinase inhibitors (TKI) and has potent activity against point mutations, like T315I mutation, which confer resistance to ATP-competitive TKIs.

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 (Deininger et al. 2020).

In clinical practice, about half of CP-CML patients use imatinib, a first-generation BCR-ABL TKI, as first-line treatment, and the other half of patients are treated with second-generation BCR-ABL TKIs (nilotinib, dasatinib, bosutinib). If patients have failed two second-generation TKIs, the third-generation TKI ponatinib might be used, but it has cardiovascular and arteriovascular side effects (hypertension, peripheral arterial occlusive disease, ischemic heart disease, cerebrovascular accident, venous thromboembolism, and platelet dysfunction). If patients are not candidates for TKI therapy, omacetaxine mepesuccinate which is a protein synthesis inhibitor that reduces BCR-ABL1 levels might be considered (Jabbour et al. 2015). The final option is allogeneic stem cell transplantation, but it is available for patients with a donor, good performance status and normal organ functions.

As CP-CML patients develop disease resistance or intolerance to TKIs, especially if they had failure with 2 or more TKIs, treatment options become very limited. Mutations of BCR-ABL1 kinase might develop in 21% to 33% of patients. If patients have intolerance to a certain TKI, cross-tolerance and carry over toxicity might be encountered with other agents.

The most common cause of resistance in CML is BCR-ABL1 mutations. In patients who are using imatinib or second-generation TKIs first-line, resistance is associated with mutations in 10% to 68% of patients, and 14% to 33% of patients using nilotinib or dasatinib as second line treatment develop BCR-ABL1 mutations. T315I mutation is the most frequent mutation (14%) in CML patients who are resistant to TKIs. Patients with this mutation are resistant to imatinib, nilotinib, dasatinib, and bosutinib. Ponatinib is the only approved agent for patients with T315I mutation, but it has serious side effects. The presence of this mutation confers shorter OS and PFS. Other options might be allogeneic stem cell transplantation, supportive care or other therapies not targeting this mutation. However, these carry many adverse events and poor treatment outcomes.

The investigational product, asciminib, is being used in CML or Philadelphia-chromosome positive ALL (Ph+ ALL) patients (including those with T315I mutation) and has also been investigated in healthy volunteers. The FIH trial was the phase 1 study CABL001X2101, and the phase 3 study was CABL001A2301.

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 phase 3 randomized study of oral asciminib versus bosutinib in CP-CML patients treated with ≥ 2 TKIs (CABL001A2301, ASCEMBL, referred as study A2301) and is complemented by data from their FIH trial, study CABL001X2101 (referred as study X2101)

The primary efficacy endpoint of study A2301 is major molecular response (MMR) at 24 weeks while on study treatment without meeting any treatment failure criteria prior to 24 weeks.

Major molecular response is a BCR-ABL ratio ≤ 0.1% on the International Scale and is considered a key surrogate endpoint which indicates successful CML treatment.

The secondary efficacy endpoint is major molecular response (MMR) at 96 weeks while on study treatment without meeting any treatment failure criteria prior to 96 weeks. This is also a well-established surrogate and the MMR at 96 weeks is expected to be higher than the MMR at 24 weeks.

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 CP-CML were MCyR (major cytogenetic response, 0-35% Ph-positive metaphases), CCyR (complete cytogenetic response, no Ph-positive metaphases), and duration of response (DOR). In recent years, MMR and MR4.5 (BCR-ABL1 ≤ 0.032%) have been used as primary endpoints in CP-CML patients. For accelerated approval in patients with resistant/intolerant CP-CML, the Agency has accepted MCyR or MMR with at least 6 months follow up. Regular approval has been granted based on MCyR or MMR with at least 2 years of follow up.

MMR indicates successful treatment of CML and is associated with longer OS and PFS. MMR at 24 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	Relapsed or Intolerant

	Trial	Topline results	Trial	Topline results
Imatinib	Imatinib vs. IFN+ARA-C	PFS (84-mo data): 81.2% vs. 60.6% (p<0.0001) CCyR (84-mo data): 74.7% vs. 6.5% (p<0.001)	IFN-failure CP-CML (Single arm)	MCyR: 60% (95% CI: 55.3-63.8) CCyR (unconfirmed): 39% (47%)
Dasatinib	Dasatinib vs. Imatinib	CCyR (within 12 mo): 76.8% vs. 66.2% (p=0.007) MMR (60 mo): 76.4% vs. 64.2% (p<0.0001)	Imatinib-resistant or -intolerant CP-CML (Single arm)	CCyR (min 24 mo): 50% (95% CI: 42-58) MMR (7 years): 44%
Nilotinib	Nilotinib vs. Imatinib	CCyR (by 24 months): 87% (95%CI: 82.4, 90.6) vs. 77% (95%CI: 71.7, 81.8) MMR (at 24 mo): 62% (95%CI: 55.8, 67.4) vs. 38% (95%CI:31.8, 43.4)	Imatinib-resistant or -intolerant CP-CML (Single arm)	MCyR (min 24 mo): 51% (95% CI: 46-57) CCyR (min 24 mo): 37% (95% CI: 32-42)
Bosutinib	Bosutinib vs. Imatinib	CCyR (by month 12): 77.2% vs. 66.4% (p=0.0075) MMR (at month 12): 47.2% vs. 36.9% (p=0.02)	Imatinib-resistant or -intolerant CP-CML (Single arm)	MCyR (by week 24): 40.1% (95% CI: 34.1, 46.3)
Ponatinib	NA	NA	CP-CML resistant or resistant/intolerant to at least 2 prior TKIs (Single arm) CP-CML with T315I (single arm)	MCyR (by 12 mo): 49% (95%CI: 38, 60) BCR-ABL1 ≤1% (at 12 mo): 42% (95%CI: 32, 53) MCyR (by 12 mo): 50% (95%CI: 29, 71) BCR-ABL1 ≤1% (at 12 mo): 42% (95%CI: 22, 3)

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

Studies on 2G TKIs in third or further lines of therapy in patients with CML in chronic phase

TKI	Cumulative CCyR (%)	Cumulative MMR (%)	Median duration of follow-up in months (range)
Dasatinib 3L n=16 Nilotinib 3L n=9	31 11	13 33	13 (0.5-41) (all pts including 21 with AP/BP-CML
Nilotinib 3L n=39	24 (based on 37 pts)	NA	12 (all pts including 21 with AP-CML
Dasatinib or Nilotinib 3L n=26	34.6	19.2	21.5 (6-46.5)
Dasatinib 3L n=5 Nilotinib 3L n=13	13 (based on 15 pts)	24 (based on 17 pts)	52 (7-75)
Nilotinib 3L/4L n=3/3 Dasatinib 3L n=6 Bosutinib 3L n=12 Inv. Agent 3L/4L n=5/1	24 (3L+)	NA	8.6 (0.7-53.8)

Bosutinib 3L n=5 Dasatinib 3L n=33 Nilotinib 3L n=18	21	NA	21 (1-67)
Dasatinib 3L n=6 Nilotinib 3L n=15	Only best response reported: Dasatinib: 1 CCyR and 2 MMR Nilotinib: 8 MMR		12 (1-42)

Source: Sponsor's BTDR application.

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 A2301 trial and was complemented by data from the phase 1 trial X2101.

Results of the phase 3 trial A2301

Trial design			
Design	Phase 3, active-controlled, open-label randomized, asciminib vs. bosutinib		
Eligible population	CP-CML patients treated with at least 2 prior ATP-binding site TKIs who failed or were intolerant to their most recent TKI		
Treatment schedule	Asciminib (oral): 40 mg BID Bosutinib (oral): 500 mg QD Continuous treatment		
Planned sample size	233 patients, randomized 2:1		
Primary efficacy endpoint	MMR at 24 weeks		
Selected secondary endpoints	MMR at 96 weeks (MR2 at 24 weeks, MR4 at 24 weeks, MR4.5 at 24 weeks, MMR rates as 3rd, 4th, or ≥5th lines of therapy, MMR in patients with prior TKI failure or intolerance, MMR in patients with or without MCyR, CCyR at 24 weeks		
Results			
	Asciminib N=157	Bosutinib N=76	Risk difference (95% CI)
MMR (BCR/ABL ≤ 0.1%) rate at 24 weeks	25.5%	13.2%	0.70 (2.11-22.53)
MR2 (BCR/ABL ≤ 1%) rate at 24 weeks	44.4%	22.6%	
MR4 (BCR/ABL ≤ 0.01%) rate at 24 weeks	10.8%	5.2%	
MR4.5 (BCR/ABL ≤ 0.0032%) rate at 24 weeks	8.9%	1.3%	

[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.

MMR rate as 3rd line therapy	29.3%	20.0%	9.3 (-8.1, 26.6)
MMR rate as 4th line therapy	25%	13.8%	11.2 (-6.7, 29.1)
MMR rate as ≥5th line therapy	16.1%	0%	16.1 (3.2, 29.1)
MMR rate in patients with prior TKI failure	21.1%	5.6%	0.26 (5.3-25.7)
MMR rate in patients with prior TKI intolerance	7/16 = 44%	1/12 = 8%	0.18 (-20.8-25.0)
MMR rate in patients with MCyR	45.7%	18.2%	0.39 (5.9-49.1)
MMR rate in patients without MCyR	17.1%	11.1%	0.64 (-4.9-16.9)
CCyR rate at week 24	40.8%	24.2%	p-value: 0.019

Results of the phase 1 trial X2101

Trial design	
Design	Phase 1, FIH dose escalation, asciminib alone vs. asciminib in combination with either nilotinib, imatinib, or dasatinib
Eligible population	CP, AP, BP-CML and Ph+ ALL patients treated with at least 2 prior ATP-binding site TKIs who failed or were intolerant to their most recent TKI CP and AP CML patients who exhibited relapsed disease associated with the presence of the T315I mutation after at least one TKI This protocol included CP-CML and AP-CML patients treated with single agent asciminib at different dose levels and CP-CML patients harboring the T315I mutation treated at 200 mg BID dose (Arm 1 which is included in the BTDR)
Treatment schedule	Asciminib (oral): 10 mg, 20 mg, 40 mg, 80 mg, 150 mg, 160 mg, or 200 mg BID or 80 mg, 120 mg, or 200 mg QD (Arm 1) Asciminib (oral): 200 mg BID in CP-CML patients with T315I mutation (Arm 1) Repeat every 28 days
Planned sample size	200 patients in arm 1 (185 with CP-CML, 48 with T315I mutation)
Primary efficacy endpoint	MMR at 24 weeks
Selected secondary endpoints	MMR at 48, 72 and 96 weeks

Results in T315I positive CP-CML patients			
	Ponatinib-pretreated CP-CML patients with T315I mutation N=26 n (%)	Ponatinib-naïve CP-CML patients with T315I mutation N=19 n (%)	All CP-CML patients with T315I mutation N=45 n (%)
Overall MMR	9 (34.6)	13 (68.4)	22 (48.9)
MMR rate at 24 weeks Confidence Interval	8 (30.8) (16.3-48.7)	11 (57.9) (36.8-77.0)	19 (42.2) (27.7-57.8)
MMR rate at 48 weeks	11 (36.7)	6 (40.0)	20 (44.4)

The median time to first MMR was 20.9 weeks (2-192 weeks) and the median (maximum) duration of treatment exposure was 124.6 (302) weeks. The majority of patients who achieved MMR (20/22) maintained this response level or achieved deeper response and the median time to first MMR was 12.2 weeks (min-max: 4-84 weeks).

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.*

Cumulative response on asciminib and in studies of authorized TKIs for patients with CP-CML resistant to intolerant of prior TKIs

	Study X2101 3L+	Study A2301 3L+		2L Dasatinib	2L Nilotinib	3L+ Bosutinib	3L+ Ponatinib
	Asciminib	Asciminib	Bosutinib				
Primary analysis publications							
Median duration of treatment (months)	42.2	10	6.7	8	8	8.3	12.8
Cumulative CCyR (%)	-	43.7	30.7	41	31	24	40
Cumulative MMR (%)	58.1	34.4	18.4	-	-	15	27
Latest publications							
Median duration of treatment (months)	42.2	10	6.7	37	18.4	8.6	32.1
Cumulative CCyR (%)	-	43.7	30.7	-	44	32	49
Cumulative MMR (%)	58.1	34.4	18.4	46	28	-	35

Source: Sponsor's BTDR submission.

Regarding safety in the randomized phase 3 trial, asciminib appeared to have less gastrointestinal toxicity (diarrhea, nausea, vomiting), hepatotoxicity, and rash when compared to bosutinib; however, there was more frequent thrombocytopenia with asciminib (events related to hemorrhage were similar in both arms). Safety profile of asciminib in CP-CML patients with T315I mutation in study X2101was similar to that of patients in study A2301. Asciminib had lower rates of arterial occlusive events when compared to ponatinib (4.2% vs. 20%).

Given the lack of established therapy for the above-mentioned two indications, the efficacy of asciminib and its relatively benign safety profile, it is reasonable to grant breakthrough designation 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 in Ph+ CML in CP harboring the T315I mutation.

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

☒ GRANT:

Provide brief summary of rationale for granting:

CP-CML previously treated with 2 or more TKIs and CP-CML with T315I mutation are life-threatening diseases if left untreated. Treatment options for CP-CML previously treated with 2 or more TKIs is very limited and patients have cross resistance to other TKIs. Ponatinib is the only available treatment for CP-CML patients with T315I mutation; however, it causes increased risk of vascular events. Asciminib has achieved significantly better MMR rates at 24 weeks when compared to bosutinib in CP-CML previously treated with 2 or more TKIs and it was found effective in CP-CML patients with T315I mutation who were ponatinib-naïve and ponatinib-pretreated. The safety profile was at least similar to other TKIs and AEs were manageable.

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

☐ DENY:

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 New Drug Application based on results of study A2301 which will be supported by data from study X2101. Their data cut-off date for study A2301 was 25 May 2020 for the BTDR. For the NDA, they are planning to send data with a cut-off date of January 2021 for both studies.

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

14. List references, if any:

1. Deininger MW, Shah NP, Altman JK, et al. NCCN Clinical Practice Guidelines in Oncology, Chronic Myeloid Leukemia. Version 2.2021. August 28, 2020.
2. Jabbour E., Kantarjian H, Cortes J. Use of Second- and Third-Generation Tyrosine Kinase Inhibitors in the Treatment of Chronic Myeloid Leukemia: An Evolving Treatment Paradigm. Clinical Lymphoma, Myeloma & Leukemia 2015; 15(6):323-334.

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

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

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

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

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
02/01/2021 06:35:07 PM

LORI A EHRLICH
02/02/2021 09:13:31 AM

ROMEO A DE CLARO
02/02/2021 10:13:23 AM

IND 119257

MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Alexandra Hendzel, PharmD, MPA
Sr. Global Program Regulatory Manager; Regulatory Affairs, Oncology
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Hendzel:

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

We also refer to the meeting between representatives of your firm and the FDA on November 10, 2020. The purpose of the meeting was to discuss the overall strategy for your proposed marketing application.

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

If you have any questions, call Rachel McMullen, Senior Regulatory Project Manager at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Lori Ehrlich, MD, PhD
Acting Clinical Team Lead
Division of Hematologic Malignancies 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:
- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date:	November 10, 2020
Meeting Time:	11:00AM-12:00PM (ET)
Meeting Location:	Teleconference
Application Number:	IND 119257
Product Name:	Asciminib
Indication:	Asciminib is indicated 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.
Sponsor Name:	Novartis Pharmaceuticals Corporation
Regulatory Pathway:	505(b)(1) of the Food, Drug, and Cosmetics Act
Meeting Chair:	Lori Ehrlich, MD, PhD
Meeting Recorder:	Rachel McMullen, MPH, MHA

FDA ATTENDEES

Office of Oncologic Diseases (OOD)/Division of Hematologic Malignancies 1 (DHM1)

Angelo de Claro, MD, Director
Lori Ehrlich, MD, PhD, Clinical Team Lead
Gulsum Pamuk, MD, Clinical Reviewer
Rachel McMullen, MPH, MHA, Senior Regulatory Project Manager

Office of Oncologic Diseases (OOD)/Immediate Office(IO)

Shanthi Marur, MBBS, MD, Associate Director for Safety (Acting)
Felicia Diggs, RN, OOD Safety Regulatory Project Manager

Office of Oncologic Diseases (OOD)/Division of Hematology, Oncology, Toxicology (DHOT)

Brenda Gehrke, PhD, Pharmacology Toxicology Team Lead
Natalie Simpson, PhD, Pharmacology Toxicology Reviewer

Office of Biostatistics

Jonathon Vallejo, PhD, Statistical Team Lead
Haiyan Chen, PhD, Statistical Reviewer

Office of Clinical Pharmacology
Ruby Leong, PharmD, Clinical Pharmacology Team Lead
Lauren Price, PharmD, Clinical Pharmacology Reviewer
Lian Ma, PhD, Pharmacometrics Team Lead
Robyn Konicki, PharmD, Pharmacometrics Reviewer

Office of Pharmaceutical Quality
Sherita McLamore, PhD, CMC Team Lead

Office of Surveillance and Epidemiology
Hina Mehta, PharmD, Team Lead
Neil Vora, PharmD, MBA, PMP, Safety Regulatory Project Manager

SPONSOR ATTENDEES
Novartis Pharmaceuticals Corporation
Annarita Gabriele, Global Program Head
Paola Aimone, Global Program Clinical Head
Betty Molloy, Global Program Biostatistics Head
Ildiko Zsolnai-Nagy, Sr. Global Program Safety Lead
Matthias Hoch, Sr. Clinical Pharmacology Scientist
Danielle Roman , Preclinical Sciences, Director
Farkad Ezzet, Pharmacometrics, Director
Alejandra Martin-Alos, Regulatory CMC, Associate Director
Vera Berchten , Regulatory Affairs, Global Therapeutic Area Lead
Sara Lorie , Regulatory Affairs, Global Program Regulatory Director
Alexandra Hendzel, Regulatory Affairs, Sr. Global Program Regulatory Manager

1.0 BACKGROUND

Novartis Pharmaceuticals is developing asciminib (ABL001) for the proposed treatment of chronic myelogenous leukemia (CML) (b) (4) The Sponsor has Orphan Designation for the above indication. Fast Track designation was granted on August 24, 2020. A marketing application is planned for Q1 of 2021.

The purpose of this Pre-NDA meeting is to obtain feedback from the Agency on the overall strategy for the Sponsor's planned NDA in support of the following proposed indication:
Asciminib is indicated 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.

The proposed NDA will be based on the pivotal registration study, CABL001A2301, also referred to as ASCEMBL. Study CABL001A2301 is an ongoing multi-center, open-label, randomized study of oral asciminib versus bosutinib in patients with chronic myelogenous leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors. Results from the first-in- human study, CABL001X2101, will support the inclusion of CML patients in chronic phase harboring the T315I mutation.

FDA sent preliminary comments to Novartis on November 4, 2020.

2.0 DISCUSSION

Preamble: Based on the topline data provided in the meeting package, FDA recommends the following programs to expedite the submission and review of the planned NDA submission. At the meeting, please provide your plans to participate in the following programs.

1. Breakthrough Therapy Designation. The preliminary clinical evidence may demonstrate an improvement over available therapy, and you may consider submitting a request for Breakthrough Therapy Designation (BTD), which would aid with FDA's scheduling of clinical site and manufacturing facility inspections, in addition to the enhanced communication under the BTD program.

2. Project Orbis. FDA would recommend consideration of asciminib, provided that the Sponsor can provide a global submission plan to available Project Orbis countries, which would include Australia, Brazil, Canada, Singapore, Switzerland, and the United Kingdom. The global submission plan should include the proposed submission timeline and the respective contact information for the Sponsor for each country. In general, FDA recommends submission of the marketing applications within 1 month of the final component of the NDA submission to the US.

3. Assessment Aid. We recommend submission of the multi-disciplinary Assessment Aid document to Module 1.11.4 Multiple module information amendment to facilitate the review of your application. This is also a required component under Project Orbis. If you are participating in Project Orbis, we will also request you to submit a separate Product Quality Assessment Aid document to facilitate the product quality review of your application.

4. Real-Time Oncology Review (RTOR). FDA would be amenable to review this application under RTOR. You will need to provide a submission plan. RTOR is only applicable for the FDA submission.

Please see relevant additional information below:

Guidance for Industry: Expedited Programs for Serious Conditions-Drugs and Biologics: https://www.fda.gov/media/86377/download

RTOR: https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program

Assessment Aid: https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

DISCUSSION: The Agency notes the Sponsor's intention to submit a Breakthrough Therapy Designation (BTD) request and confirmed that a preliminary BTDR advice submission is not necessary as we have already reviewed the topline data.

Regarding inspections during the pandemic, we refer the Sponsor to the FDA published guidances. Relevant information on the impact to inspections is available via the following link: https://www.fda.gov/drugs/coronavirus-covid-19-drugs/manufacturing-supply-chain-and-drug-inspections-covid-19.

The Sponsor and FDA discussed the Sponsor's plan for submission to the (b) (4) vs. Project Orbis.

The Agency acknowledges the Sponsor's plan to submit a multi-disciplinary Assessment Aid, but not a Product Quality Assessment Aid. If the Sponsor choses to participate in Project Orbis, a Product Quality Assessment Aid would also be necessary.

The Sponsor indicated that they will participate in the Real Time Oncology Review (RTOR) program which will be detailed in a later submission with 4 proposed submission waves with justification provided for additional waves, if needed.

Clinical and Clinical Pharmacology

Question 1: main clinical data supporting the NDA

The results from the registration study A2301, "A phase 3, multi-center, open-label, randomized study of oral ABL001 versus bosutinib in patients with Chronic Myelogenous Leukemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors" (ASCEMBL), complemented by data from the first–in-human study, X2101, are proposed as being adequate to assess the benefit/risk profile of asciminib for the intended indication:

TRADENAME (asciminib) is indicated 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.*

Does the Agency agree?

FDA Response: Yes. Your proposed clinical data appears reasonable for NDA submission, but whether the package is sufficient for review will be determined at filing.

DISCUSSION: There was no discussion.

Question 2: studies included in the NDA
Does the Agency agree with the proposed clinical package to be included in the NDA?

FDA Response: Yes. The agency agrees with the clinical package to be included in the NDA.

DISCUSSION: There was no discussion.

Question 3: clinical pharmacology package
Novartis believes that the proposed content of the Clinical Pharmacology package is adequate to support the filing of the NDA. Does the Agency agree?

FDA Response: In general, the proposed Clinical Pharmacology package appears reasonable. We have the following comments:

a) Provide justification for the selected dosing regimen of 200 mg BID in patients with T315I mutation including comparison of predicted and observed asciminib exposures to relevant effective concentrations (e.g., EC50, EC90, EC99).
b) Present the incidence of treatment emergent dose reductions and interruptions separately for the 200 mg BID regimen.
c) Evaluate additional safety endpoints in your planned exposure-safety analysis including Grade ≥3 TEAEs and TEAEs leading to dose adjustment and interruption.
d) Based on the pooled dataset from study A2301 and study X2101, provide a safety summary by individual dosing regimen instead of combining dosing groups.
e) Whether the planned assessment of the effects of UGT genotype on the PK of asciminib is adequate to characterize potential UGT-related interactions will be a review issue.
f) Whether the justification for not conducting clinical drug interaction studies for transporters (including BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, and MATE2-K) is adequate will be a review issue. Provide assessments based on the Guidance for Industry entitled “In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions”, available at: https://www.fda.gov/media/134582/download.
g) Asciminib inhibits multiple renal transporters in vitro. Include an assessment of changes in serum creatinine in subjects treated with asciminib.
h) Refer to the Additional Clinical Pharmacology Comments in the Type C Meeting Minutes dated July 29, 2020 for additional advice in preparing the Clinical Pharmacology sections of the NDA submission.

DISCUSSION: The Sponsor will provide the Agency's recommended analyses in bullet points a, b, c, d, and g in the planned marketing application. The Sponsor acknowledges the Agency's comments in bullet points e, f, and h.

The Sponsor's proposals as outlined in the response to preliminary meeting comments appear reasonable.

Question 4: Potential 80 mg QD dosing regimen based on exposure-response modeling

Given the favorable benefit/risk profile demonstrated with 40 mg BID in study A2301, exposure-response modeling was conducted using data from study X2101 to evaluate a more patient-centric dosing regimen of 80 mg QD. Does the Agency consider the proposed modeling and simulation approach and the available data from studies X2101 and A2301 sufficient to support a recommended dose of 80 mg QD?

FDA Response: The final determination of acceptability of the 80 mg QD dose will be made at the time of NDA review, and will be based on totality of evidence including adequacy of the model, and available clinical and non-clinical data.

The proposed modeling and simulation plans appear reasonable. Given the potential differences in treatment sensitivity between T315I positive and T315I negative patients, we recommend that you evaluate T315I mutation status as one of the covariates on EC50 in your updated PK/PD analysis. EC90 and EC99 estimates for the T315I negative patients should also be provided.

DISCUSSION: The Sponsor clarified their selection of the recommended dose of 80 mg QD. The Agency recommends proposing both the 40 mg BID and 80 mg QD dosing regimens and providing supporting data and justification in the marketing application.

The Agency clarified that the rationale for requesting EC50, EC90, and EC99 estimates for the T315I negative patients was to seek additional justification for the proposed 80 mg QD regimen especially for the predicted lower Ctrough compared to 40 mg BID regimen. The Sponsor discussed the model limitations related to lack of placebo data or doses with very low exposure to achieve an accurate estimate of EC50 and proposed alternative approaches. The Agency agreed with the proposed approach to support filing, but noted that the limitations due to lack of data at low exposure would contribute to the uncertainties of model prediction and will be a review issue when assessing the adequacy of this approach to support the 80 mg QD regimen.

Statistical Considerations

Question 5: statistical methodology and analysis plan

Does the Agency agree that the statistical methodology and the planned analyses from the Phase III registration study, A2301, and the FIH study, X2101, are adequate to support the NDA submission?

FDA Response: Yes. Your proposed statistical methodology and analysis plan appears reasonable for NDA submission.

DISCUSSION: There was no discussion.

NDA Content and Format

Question 6: safety and efficacy update
A Safety Update will be submitted within 90 days after the date of the NDA, in the event Priority Review is granted. In addition to the Safety Update, Novartis plans to submit an Efficacy Update. Does the Agency agree with the content and amount of additional safety and efficacy data for the proposed Safety and Efficacy Updates?

FDA Response: We agree with the proposed content of the safety update including updated efficacy information.

DISCUSSION: The Agency agrees with the Sponsor's proposal for safety and efficacy updates using a January 2021 data cutoff.

Regulatory

Question 7: Priority Review
Novartis believes that the results of studies A2301 and X2101 are clinically compelling to provide treatment for a population with an unmet medical need. Novartis is planning to submit a Priority Review request at the time of NDA submission. Does the Agency agree that the NDA application could qualify for Priority Review?

FDA Response: Determination of Priority Review will be made at the time of NDA submission.

DISCUSSION: There was no discussion.

Question 8: Rolling Review
Novartis plans to Request for Submission of Portions of a NDA application. Does the Agency agree that the proposed submission waves for Rolling Review of the NDA application would be acceptable?

FDA Response: Yes. Your proposed submission waves for Rolling Review appear acceptable. However, you will need to submit a formal request for Rolling Review and provide a proposed schedule for submission of portions of an application to your IND file as soon as possible.

A request for submission of portions of an application should be sent as an amendment to the IND along with a completed Form FDA 1571. The amendment should be clearly identified as a **REQUEST FOR SUBMISSION OF PORTIONS OF AN APPLICATION** in bold, uppercase letters. Pending review, the Agency will respond to your request by letter. For further information regarding Fast Track Drug Development Programs and Rolling Review, please refer to the guidance for industry *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*, available at https://www.fda.gov/media/86377/download

Please note that the RTOR program would allow for greater flexibility in submission of the eCTD modules as partial module submissions would be considered under RTOR. For RTOR, we suggest a maximum of 4 submission waves which may include the rolling review components that you proposed.

DISCUSSION: The Agency acknowledges the Sponsor's plan to participate in the RTOR program and not utilize rolling review.

Question 9: User fee waiver
Novartis believes the NDA qualifies for a user fee waiver based on the orphan drug designation received. Does the Agency agree?

FDA Response: Yes. Based on the orphan drug designation for asciminib for treatment of chronic myelogenous leukemia on February 27, 2017, the NDA qualifies for a user fee waiver.

DISCUSSION: There was no discussion.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. **The Agency and the Sponsor reached agreement on the definition of a complete application.**

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

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan. **The need for a REMS will be determined during review of the marketing application.**

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

- **The Sponsor does not have any plans to pursue a separate CMC pre-NDA meeting.**

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 draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

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

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

[1] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

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 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.

---

[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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

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

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

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

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

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

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA,**

ANDA, BLA, Master File (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[5]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[6]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

MANUFACTURING FACILITIES

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

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

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

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

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

Corresponding names and titles of onsite contact:

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

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[7] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[8]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

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

[7] https://www.fda.gov/media/84223/download
[8] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

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*.[9]

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

- Assessment Aid[11]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

A copy of the Sponsor's presentation is attached for reference.

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

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

---

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/

LORI A EHRLICH
11/13/2020 03:10:25 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND119257

MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Omer Munir, RPh
Senior Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Mr. Munir:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ABL001.

We also refer to the meeting between representatives of your firm and the FDA on October 20, 2016. The purpose of the meeting was to discuss plans to conduct a Phase 3 pivotal registration study for the proposed indication: "*Treatment of patients with Philadelphia positive chronic myeloid leukemia in chronic phase (Ph+ CML-CP) previously treated with at least 2 tyrosine kinase inhibitors*." The sponsor is seeking the Agency's advice and agreement on the proposed non-clinical, clinical, and safety package in support of a New Drug Application.

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

If you have any questions, call Rachel McMullen, Regulatory Project Manager at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Lead
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2/Pre-Phase 3

Meeting Date and Time: October 20, 2016; 2:00-3:00PM (EST)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Application Number: IND 119257
Product Name: ABL001
Indication: Chronic Myelogenous Leukemia (CML) (b) (4)

Sponsor/Applicant Name: Novartis Pharmaceuticals Corporation

Meeting Chair: R. Angelo de Claro, MD
Meeting Recorder: Rachel McMullen, MPH, MHA

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Ann Farrell, MD, Director
R. Angelo De Claro, MD, Clinical Team Leader
Tanya Wroblewski, MD, Clinical Reviewer
Rachel McMullen, MPH, MHA, Regulatory Project Manager

Division of Hematology Oncology Toxicology Staff
Christopher Sheth, PhD, Supervisory Pharmacologist/Toxicologist
Brenda Gehrke, PhD, Pharmacologist/Toxicologist

Office of Biostatistics/Division of Biometrics V
Yuan Li Shen, PhD, Team Leader
Jingjing Ye, PhD, Statistical Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Stacy Shord, PharmD, Team Leader
Chen Yuhong, MD, PhD, Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality/Office of New Drug Products
Sherita McLamore-Hines, Acting Team Leader

SPONSOR ATTENDEES

Novartis

Renaud Capdeville, Global Program Head
Aby Buchbinder, Global Clinical Program Head
Pascal Edrich, Program Statistician
Manu Sondhi, Brand Safety Leader
Raluca Kreft, Global Program Regulatory Director
Sanjeev Thohan, Pre-clinical Safety
Julia Zack
Hans Menssen, Clinical Pharmacology
Global Clinical Leader
Shanthi Ganeshan, Drug Regulatory Affairs, North America Head
Omer Munir, Drug Regulatory Affairs, Oncology Development
Karen Habucky, US Clinical Strategy Head, Hematology Franchise

1.0 BACKGROUND

ABL001 is an orally bioavailable specific BCR-ABL1 inhibitor which inhibits ABL tyrosine kinase activity by binding to a particular allosteric site on the kinase domain that is utilized by a myristate group to auto-regulate the native ABL1 kinase. ABL001 is distinct from other TKI inhibitors which act in an ATP-competitive fashion and usually do inhibit other tyrosine kinases. The proposed indication for use is treatment of patients with Philadelphia positive chronic myeloid leukemia in chronic phase (Ph+ CML-CP) previously treated with at least 2 tyrosine kinase inhibitors (TKIs).

Currently, ABL001 does not have any market authorizations from any Health Authority worldwide. The following studies: CABL001X2101, CABL001A2102, and CABL001A2103 are being conducted under IND 119257 which was submitted to the Agency on December 17, 2013 and is the only IND for ABL001.

The sponsor proposes to conduct a randomized, open-label, active-controlled multi-center study, for the proposed indication: *treatment of patients with Philadelphia positive (Ph+) chronic myeloid leukemia in chronic phase (Ph+ CML-CP) previously treated with at least 2 tyrosine kinase inhibitors (TKIs).* The purpose of pivotal study CABL001A2301 is to compare the efficacy of ABL001 with that of bosutinib in the treatment of patients with Ph+ CML-CP having failed a minimum of two prior ATP-binding site TKIs with BCR-ABL ratios ≥1% IS at screening. The sponsor is seeking the Agency's advice and agreement on the proposed non-clinical, clinical, and safety package to support a New Drug Application.

FDA sent Preliminary Comments to Novartis on October 18, 2016.

2. DISCUSSION

NON-CLINICAL

Question 1: Acceptability of non-clinical package to support registration

Does the Agency agree that the proposed non-clinical safety package is adequate to support the filing of a New Drug Application of ABL001 in the proposed indication?

FDA Response: No. An assay assessing the effects of ABL001 on chromosomal aberrations is needed to complete the genotoxicity assessment. To complete the nonclinical package, a chromosomal aberrations assay should be submitted to the NDA along with the other completed and planned nonclinical studies listed. The adequacy of the studies to support the filing of the NDA submission and marketing will be determined during the review of the NDA.

Additionally, assessment of carcinogenicity and pre- and post-natal development are required to support marketing of ABL001 for the proposed indication of treatment of patients with Philadelphia positive chronic myeloid leukemia in chronic phase previously treated with at least 2 tyrosine kinase inhibitors. The potential for ABL001 to induce carcinogenicity should be studied in two species. We recommend that you submit each of the protocols for the carcinogenicity studies as Special Protocol Assessments along with the toxicology studies needed to support the doses of the proposed carcinogenicity studies to the IND. The carcinogenicity and pre- and post-natal studies may be conducted as post-marketing requirements; however, the studies should be ongoing at the time of the NDA submission. The final study reports can be submitted post-approval.

***Discussion:* This question was not discussed during the meeting.**

Post-meeting Addendum:

The Agency has the following clarifying comments regarding Question 1.

1. ***In the preliminary meeting comments, the FDA response stated that a chromosomal aberrations assay is needed to complete the genotoxicity assessment; however, in the slides for the meeting, Novartis proposed to conduct an in vitro human lymphocyte micronucleus test. The Agency reiterates that to complete the genotoxicity assessment, a chromosomal aberrations assay should be conducted. Conduct an in vitro chromosomal assay or submit a rational for conducting the in vitro human lymphocyte micronucleus test instead of the in vitro chromosomal aberrations assay.***
2. ***Regarding the need for carcinogenicity studies: The need for carcinogenicity studies was discussed internally with the team, and it was determined that the studies would be required based on the proposed patient population. A step wise approach with the 2 year rat study being conducted first is acceptable. If the rat study is clearly positive, then a mouse carcinogenicity study would not be required. The carcinogenicity studies can be completed post-approval.***
3. ***Regarding the need for a pre- and post-natal development study: All completed and ongoing embryo-fetal development studies being conducted with ABL001 need to be submitted and reviewed before a final determination on whether a study is needed. Based on our current thinking, if the studies demonstrate that ABL001 is clearly teratogenic, then a pre- and post-natal development study will not be needed.***

PHARMACOKINETICS AND CLINICAL

Question 2: Dose and Dosing Schedule
Does the Agency agree with the rationale and proposal to evaluate the 40mg dose BID of ABL001 in the pivotal study to support filing of the NDA?

FDA Response: In general, a dose of 40 mg BID for the proposed trial CABL001A2301 appears reasonable based on the available nonclinical, pharmacokinetic and safety data; however, the Agency recommends that you consider a lower starting dose of 20 mg BID, based on the available activity and safety data from the first-in-human trial. The Agency notes that long term adherence is an important consideration for patients with chronic phase CML. An intra-patient dose escalation approach may be acceptable to a dose of 40mg BID that is based upon standard time point assessments for response for chronic phase CML.

Discussion: There was no discussion.

Question 3: Study Design
Novartis believes that the pivotal study design (CABL001A2301) is adequate to establish the benefit/risk of ABL001and will support a New Drug Application filing for the proposed indication. Does the Agency agree?

FDA Response: No, a filing decision is not made until after the submission of the Application and preliminary review by FDA.

We have the following comments regarding your study design:

1. Your proposed primary endpoint of major molecular response(MMR) at 24 weeks may be acceptable as an endpoint reasonably likely to predict clinical benefit. To verify the clinical benefit of ABL001 we recommend that you evaluate MMR at 2 years as the first key secondary endpoint (tested with a two sided alpha of 0.05 after the primary endpoint MMR at week 24 is tested significant at a two sided alpha of 0.05) in your proposed clinical trial.

   Discussion: There was no discussion.

2. Your trial design may potentially enroll patients who have not achieved a molecular response but who may have a partial cytogenetic response or complete cytogenetic response (CCyR). Any imbalances in the population between treatment arms may confound the interpretability of key secondary endpoints.

   Discussion: There was no discussion.

3. The additional secondary endpoints that categorize the cytogenetic response will be important during the review process. Ultimately, the magnitude and durability of all responses will be important review issues.

   Discussion: There was no discussion.

4. (b) (4)

Discussion: The Agency provided clarification on (b) (4)

This may result in problems with evaluation of the two year results of the trial for efficacy and safety which may require the conduct of another trial. The proposed primary endpoint of MMR at 24 weeks would be an acceptable endpoint for accelerated approval.

5. To reduce potential bias in the trial, we recommend conducting the trial as a randomized, double-blinded trial.

Discussion: The Agency would be open to consider an open label trial design, provided that the sponsor includes measures in the protocol to mitigate the risk of bias between arms.

6. Because some of the patients may start in a response status (e.g., PCyR or CCyR) at baseline, imbalance in terms of response between two arms at baseline may lead to bias. We recommend that you include response status at baseline as a stratification factor. To incorporate this stratification factor, you may reduce the number of your current stratification factors as they are likely correlated.

Discussion: There was no discussion.

7. Your imputation rules are problematic. You indicated that (b) (4) There is a scheduled efficacy assessment at week 16, (b) (4) Please provide a rationale (b) (4) You may want to consider a plan when week 16 is available to be used in the imputation. We also note that missing data could undermine the reliability and confidence of the results. Sensitivity analyses with an appropriate method of imputation under the null hypothesis should be performed to account for the limitation of the data and to examine the potential impact of missing data.

Discussion: There was no discussion.

Question 4: Patient population
Does the Agency agree that the proposed patient population in the pivotal study is well defined and adequate to support the filing of a New Drug Application for ABL001 in the proposed indication?

FDA Response: No, a filing decision is not made until after the submission of the Application and preliminary review by FDA.

However, your proposed patient population is well-defined and includes patients who will have BCR-ABL IS >1% and who may or may not be in complete or partial cytogenetic remission. We note that imbalances between arms may occur which will confound the interpretability of the secondary endpoint of complete cytogenetic remission.

We note that there were patients enrolled on Study CABL001X2101 that had BCR-ABL > 0.01-0.1% IS at time of screening. Provide further clarification and description for this population enrolled in your first-in-human trial.

Additionally, modify the eligibility criteria as follows:
- Exclude patients with baseline hepatic impairment defined by Child-Pugh criteria.
- Exclude patients with baseline creatinine clearance < 50 mL/min.
- Exclude patients taking moderate CYP3A4 inhibitors and inducers.
- Permit patients to take short acting antacids with bosutinib and ABL100 using staggered administration times.

Discussion:

The sponsor proposed that the Child-Pugh criteria will not be used to exclude patients in the protocol since these criteria only apply to patients with cirrhosis. No discussion occurred during the meeting; however, the sponsor should be aware the recommendation was made based on Bosulif's labeling.

Question 5: Choice of Comparator
Does the Agency agree with bosutinib as the proposed comparator in the pivotal study?

FDA Response: Yes, your proposed comparator appears acceptable. We express concerns with (b) (4)

Discussion: No discussion occurred at the meeting; however the proposed comparator arm of bosutinib is acceptable.

Post Meeting Addendum:
The Agency had a discussion regarding (b) (4) ***and we refer to the discussion captured under question 3, point 4:***

(b) (4)
This may result in problems

with evaluation of the two year results of the trial for efficacy and safety which may require the conduct of another trial.

Question 6: Primary and Secondary Endpoints
Does the Agency agree with the proposed primary and secondary endpoints for the pivotal study?

FDA Response: No, while your proposed primary endpoint of MMR at 24 weeks is acceptable as an endpoint likely to predict clinical benefit, we do not agree with the proposed key secondary endpoints (b) (4)

We recommend that MMR at 2 years as the first key secondary endpoint.

The evaluation of MMR will need to be based on a validated test.

Discussion: The Agency noted (b) (4) ***Regarding the time to MMR endpoint, the Agency recommends descriptive presentation of the results based on the responder population.***

BIOMETRICS, DATA MANAGEMENT AND STATISTICAL

Question 7: Statistical methodology for the primary endpoint
Does the Agency agree with the sample size and proposed analysis for the primary endpoint in the pivotal study?

FDA Response: The sample size appears to be acceptable given the assumptions used in the calculation for the primary endpoint. However, you should ensure that the trial is adequately powered for evaluation of MMR at 2 years as the first key secondary endpoint.

Refer also to response to Question 8.

Discussion: There was no discussion.

Question 8: Statistical methodology for the key secondary endpoints
Does the Agency agree that the proposed analyses and alpha adjustment methods planned for key secondary endpoints in the pivotal study are well defined and adequate?

FDA Response: You will need to submit a revised analysis plan based on the recommendations provided in response to Questions 3 and 6.

In general, the gatekeeping procedure for the secondary endpoint for controlling overall alpha appears to be acceptable. If additional key secondary endpoints are included in the analyses, please provide a revised gatekeeping procedure to control the overall alpha.

However, if the analysis of time to MMR is based on the responder population and not the ITT population, time to MMR cannot be used for labeling claim(s) based on statistical comparisons of time to MMR between two treatment arms.

In addition, you indicated that you will use Kaplan-Meier approach in time to MMR analysis. Please note the difference between Kaplan-Meier plot and your time to MMR plot. Kaplan-Meier approach starts with 100% at time 0, however, in time to MMR, the curves would start from 0% at time 0.

***Discussion:* There was no discussion.**

SAFETY

Question 9: Overall safety data base at time of submission
Novartis considers that the expected safety data base is adequate to support the filing of a New Drug Application in the proposed indication, which constitutes an unmet medical need in a rare subset of CML patients. Does the Agency agree?

FDA Response: No, the adequacy of the safety data base to support a filing of a NDA will be determined at the time of the filing review. In addition, we do not agree (b) (4) See also response to question 3.

We note that the ubiquitous expression of ABL tyrosine kinase appears to have diverse biological effects and there are literature reports of conditional knock-out ABL1 mice models exhibiting impairments in vascular development to including cardiac and lung defects (Chislock et al 2013). In addition, we note safety adverse events reports of pulmonary edema, cardiac failure, and interstitial lung disease in patients treated with ABL001.

Given the potential concern for cardiac and pulmonary adverse events, we recommend that you include baseline and scheduled safety assessments for cardiac and pulmonary function by echocardiogram and pulmonary function tests with DLCO, respectively.

In addition, we note that the safety database of patients with CP-CML who will be treated at proposed dose of 40mg BID of ABL001 consists of approximately 174 patients. The long term safety follow-up of at least 2 years for the population you are seeking an indication as well as the long-term follow-up of all patients in your safety database for ABL001 will be important considerations in the overall benefit-risk analyses.

***Discussion:* The Agency and the sponsor discussed the Agency's recommendations for additional cardiac and pulmonary safety assessments.**

CLINICAL PHARMACOLOGY PACKAGE

Question 10: Planned Clinical Pharmacology Studies
Novartis considers that the planned clinical pharmacology studies are sufficient to support filing for the proposed indication. Does the Agency agree?

FDA Response: The Agency agrees with the proposal to complete the following studies: drug interaction with multiple substrates and acid-reducing agents, mass balance, hepatic impairment, severe renal impairment, population pharmacokinetic analyses, exposure-responses analyses for safety, efficacy and pharmacodynamic biomarkers, and food effect with final market image based on available data. In addition, the Agency recommends that Novartis conduct the following studies in support of the original NDA submission.

1. A 'thorough QT' study to evaluate ABL001 for its QT prolongation potential. Submit a QT evaluation plan to the IND for FDA review and comment. Refer to the FDA Guidance for Industry entitled "E14 Clinical Evaluation of QT/QTc Interval Prolongation" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf.

2. An assessment of nonclinical and clinical information to determine whether a clinical pharmacokinetic study is needed to determine an appropriate dose of ABL001 with a BCRP inhibitor, as the in vitro data shows that ABL001 is a substrate of BCRP transporter.

Additionally, provide a tabular summary of the ABL100 drug product used in each clinical trial and the available pharmacokinetic data for each drug product in the fasted or fed state in the original NDA submission.

Discussion: ***There was no discussion.***

Additional Clinical Pharmacology Comment:
Regarding to the proposed phase 3 trial CABL001A2301, revise the protocol to avoid BCRP inhibitors based on the in vitro data that indicates that ABL001 is a BCRP substrate.

Discussion: ***The Sponsor proposed not to avoid the BCRP inhibitors during the study CABL001A2301. However, the sponsor proposed to avoid the inhibitors of P-gp during the study CABL001A2301, because this may result in a clinically relevant drug interaction. The Agency stated that the Sponsor's proposal appears acceptable.***

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (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, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies 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 PSP 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 PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17,

2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at
http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission

types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA to sponsors/applicants when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), sponsors/applicants must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

No action items were identified.

6.0 ATTACHMENTS AND HANDOUTS

A copy of the sponsor's response and presentation is attached for reference.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALBERT B DEISSEROTH
10/24/2016