CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215358Orig1s000
215358Orig2s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 10/15/2021

To: Rachel McMullen, Senior Regulatory Project Manager, DHM1

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Deputy Division Director, OPDP

Subject: OPDP Labeling Comments for SCEMBLIX (asciminib) tablets, for oral use

NDA: 215358

In response to DHM1's consult request dated June 28, 2021, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for SCEMBLIX (asciminib) tablets, for oral use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling emailed to OPDP on October 6, 2021, and updated based on the labeling accessed from SharePoint on October 15, 2021 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover.

Carton and Container Labeling:

OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on date, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Rachael Conklin at rachael.conklin@fda.hhs.gov.

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/s/

RACHAEL E CONKLIN
10/15/2021 09:41:55 AM

Consult Memorandum

Date:	10/26/2021
To:	Rachel McMullen, RPM and clinical reviewer by CDER/OND/ORO/DROOD
From:	Brittany Aguila, Ph.D., Scientific Reviewer, CDRH/OIR/DMGP/MGB
Through:	Zivana Tezak, Ph.D., Branch Chief (Acting), CDRH/OPEQ/OIDRH/DMGP/MGB, and Reena Philip, Ph.D., Director, CDRH/OPEQ/OIDRH/DMGP
ICC Number:	ICC2100855 (ICCR#00792871)
Subject:	NDA215358 [Study CABL001X2101; A Phase I Study of Oral ABL001 in Patients with CML or Ph+ALL]
Drug Name:	Asciminib (ABL001)
Drug Sponsor	Novartis
Biomarker(s):	BCR-ABL, T315I mutation
Device Name:	E13a2-e14a2 mutation analysis, p210 BCR-ABL mutation test, (b) (4) Sanger sequencing test
Device Sponsor:	Unknown
Related Submissions:	

I. BACKGROUND and PURPOSE

Novartis was requested to provide information regarding the T315I testing (local and central) conducted in the CABL001X2101 trial on September 29, 2021. Novartis responded to this request on October 12, 2021 providing answers to the minimum performance questions asked. This consult was received on October 13, 2021 from CDER requesting CDRH input on labeling recommendations regarding the minimal performance characteristics for T315I testing.

II. PROPOSED INDICATION

The p210 BCR-ABL mutation test by Sanger Sequencing was performed to enable the identification of the T315I mutation in patients with CML at study entry by the Novartis designated central laboratory, (b) (4)

III. CDRH RESPONSE TO [SPONSOR/CDER] QUESTIONS

CDER requested CDRH to provide labeling recommendations (if any) regarding minimal performance characteristics for T315I testing conducted by the sponsor; include 1-2 sentences on the performance characteristics of the T315I test to be placed in section 14 of the drug labeling.

IV. RECOMMENDATIONS TO CDER

CDRH labeling recommendation (Clinical studies in Section 14) regarding minimal performance characteristics for T315I testing conducted by the sponsor:

A qualitative p210 BCR-ABL mutation test utilizing Sanger Sequencing was performed to enable identification of the T315I mutation in CML patients using approximately 100ng of cDNA collected from patients' peripheral blood. This test utilized an assay cutoff of approximately 20% mutant (MAF) in a background of 80% wild-type, and displayed 100% concordance compared to validated reference test including 100% sample level positive percent agreement (PPA) and 100% sample level negative percent agreement (NPA). Limit of blank analysis on 20 healthy donors showed no amplification, and limit of

detection was determined to be 20% mutation in a background of wild-type BCR-ABL RNA. Sequencing results were manually reviewed by trained technologists.

V. CDRH ADDITIONAL COMMENTS TO CDER

Although we have written a paragraph for asciminib labeling, our understanding is that since the paradigm is still in its preliminary stages, we will not add this paragraph to the drug labeling. However, we do suggest that the highlighted sentence above to added to section 14 (clinical trial description) of the drug labeling in order to mention the assay that was used.

This consult review is limited to the information provided in the USPI and minimum performance characteristics provided by the sponsor. If there are any questions regarding this review, please contact Brittany Aguila by email at Brittany.Aguila@fda.hhs.gov.

Brittany E. Aguila -S

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/s/

RACHEL S MCMULLEN
10/28/2021 11:25:14 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 13, 2021
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 215358
Product Name and Strength:	Scemblix (asciminib) tablets, 20 mg and 40 mg
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation
OSE RCM #:	2021-663-2
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on October 12, 2021 for Scemblix. We reviewed the revised container labels and carton labeling for Scemblix (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Iverson, N. Label and Labeling Review for Scemblix (NDA 215358). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 OCT 05. RCM No.: 2021-663-1.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	October 13, 2021
To:	Rachel McMullen, MPH, MHA Senior Regulatory Project Manager **Division of Hematologic Malignancies 1 (DHM1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rachael Conklin, MS, RN Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	SCEMBLIX (asciminib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 215358
Applicant:	Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On June 24, 2021, Novartis Pharmaceuticals Corporation submitted for the Agency's review the final submission for a Real-Time Oncology Review (RTOR) for an original New Drug Application (NDA) 215358 for SCEMBLIX (asciminib) tablets. The proposed indication for SCEMBLIX (asciminib) tablets is 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.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematologic Malignancies 1 (DHM1) on June 28, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for SCEMBLIX (asciminib) tablets.

2 MATERIAL REVIEWED

- Draft SCEMBLIX (asciminib) tablets PPI received on May 25, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 6, 2021.
- Draft SCEMBLIX (asciminib) tablets Prescribing Information (PI) received on May 25, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 6, 2021.
- Approved ICLUSIG (ponatinib) NDA 203469, comparator labeling dated December 18, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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RACHAEL E CONKLIN
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BARBARA A FULLER
10/13/2021 01:04:16 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 5, 2021
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 215358
Product Name and Strength:	Scemblix (asciminib) tablets, 20 mg and 40 mg
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation
OSE RCM #:	2021-663-1
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on September 27, 2021 for Scemblix. We reviewed the revised container labels and carton labeling for Scemblix (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective. We note (b) (4) is included in the (b) (4) the container labels and carton labeling. In addition, we note the storage statement, "Store Scemblix in the original container to protect from moisture" is inconsistent with the Prescribing Information.

3 RECOMMENDATIONS FOR NOVARTIS PHARMACEUTICALS CORPORATION

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels and Carton labeling)

[a] Iverson, N. Label and Labeling Review for Scemblix (NDA 215358). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 SEP 01. RCM No.: 2021-663.

1. We recommend removing (b) (4) and not necessary on the container labels and carton labeling.
2. We recommend retaining the statement, “Dispense and store Scemblix in the original container to protect from moisture.” to be consistent with the Prescribing Information.

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CLINICAL INSPECTION SUMMARY

Date	September 1, 2021
From	Anthony Orencia M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Gulsum Pamuk, M.D., Medical Officer Lori Ehrlich, M.D., Ph.D., Team Leader R. Angelo de Claro, M.D., Division Director Rachel McMullen, M.P.H., M.H.A., Regulatory Project Manager Division of Hematologic Malignancy 1 (DHM1) Office of Oncology Drugs
NDA	NDA 215358
Applicant	Novartis Pharmaceuticals Corporation
Drug	Scemblix™ (asciminib)
NME	Yes
Division Classification	Tyrosine kinase inhibitor
Proposed Indication	Treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in the chronic phase and Ph+ CML in the chronic phase harboring the T315I mutation.
Review Type	Priority
Consultation Request Date	June 9, 2021
Summary Goal Date	September 30, 2021
Action Goal Date	October 29, 2021
PDUFA Date	February 24, 2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from two studies were submitted to the Agency in support of a New Drug Application (NDA 215358) for asciminib (Scemblix™), proposed for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in the chronic phase, previously treated with two or more tyrosine kinase inhibitors (TKIs), and Ph+ CML in the chronic phase harboring the T315I mutation. The Sponsor (Novartis Pharmaceuticals Corporation) was inspected to support the review of NDA 215358 Study CABL001X2101 and Study CABL001A2301.

Based on the results of the inspection, the sponsor conduct and oversight are adequate, and the data generated from Studies CABL001X2101 and CABL001A2301 appear to be acceptable in support of this NDA for the proposed indication.

II. BACKGROUND

Asciminib (ABL001) inhibits ABL tyrosine kinase activity by binding to a particular allosteric site on the kinase domain, identified on ABL1, ABL2 and BCR-ABL ABL001 potently and selectively inhibits the proliferation of cell lines that express BCR-ABL. The Sponsor submits this NDA, proposed for treatment of patients with Ph+ CML.

The specific indications proposed for treatment of adult patients with (1) Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in the chronic phase, previously treated with two or more tyrosine kinase inhibitors, and (2) Ph+ CML in the chronic phase harboring the T315I mutation.

For this NDA under the PDUFA program review, Studies CABL001X2101 and CABL001A2301 were part of the FDA submission for which a sponsor site inspection was sought.

Study CABL001X2101

CABL001X2101 was a Phase I, multicenter, open-label study of oral asciminib (ABL001) in patients with chronic myelogenous leukemia or Philadelphia chromosome-positive acute lymphoblastic leukemia. The five arms were: (1) asciminib as a single agent in patients with CML-chronic phase (CP)-accelerated phase (AP), (2) asciminib in combination with nilotinib in patients with CML-CP/-AP, (3) asciminib in combination with imatinib in patients with CML-CP/-AP, (4) asciminib in combination with dasatinib in patients with CML-CP/-AP, and (5) asciminib as a single agent in patients with CML-blast phase with Ph+ acute lymphoblastic leukemia.

The primary endpoint was the maximum tolerated doses and recommended doses for expansion for asciminib as a single agent, and asciminib in combination with nilotinib, imatinib, and dasatinib. Secondary endpoint was major molecular response by 24 weeks in patients with T315I to support the Ph+ CML in CP harboring the T315I mutation indication.

Study CABL001X2101 was conducted in Australia, France, Germany, Italy, Japan, Singapore, South Korea, Spain, The Netherlands, and United States. The study started on April 24, 2014. The data cut-off date was April 2, 2020. For this ongoing study, there were 317 patients enrolled as of the cut-off date.

Study CABL001A2301

Study CABL001A2301was a multi-center, open-label randomized study of oral ABL001 versus bosutinib in patients with Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP), previously treated with two or more tyrosine kinase inhibitors.

The primary objective of the study was to show superiority of the activity of asciminib (ABL001) compared to bosutinib in patients with CML-CP who had received at least two prior tyrosine kinase inhibitors.

The primary efficacy endpoint was the major molecular response (MMR) rate at 24 weeks. A patient will be counted as having achieved response at 24 weeks based on the BCRABL/ABL ratio ≤0.1% at 24 weeks. The primary analysis (cut-off date) was defined as the date when all randomized patients have been on treatment for 24 weeks or discontinued early.

This study was conducted in 87 centers in 25 countries. There were 233 patients (157 study subjects randomized to treatment with asciminib, and 76 study subjects to treatment with bosutinib) who enrolled and analyzed. The first subject's first clinic visit date was October 26, 2017. The cut-off date was May 25, 2020. The study is ongoing.

III. RESULTS

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936

The inspection was conducted from June 29 to July 9, 2021.

The sponsor onsite inspection evaluated Novartis Pharmaceuticals Corporation's responsibilities for oversight of Study CABL001X2101 and Study CABL001A2301.

FDA evaluated, in part, the following records at the sponsor site: organizational charts, transfer of regulatory obligations, Form FDA 1572 (statement of the investigator), financial disclosure forms, training records, electronic data capture (EDC) audit trails, clinical operations, vendor oversight, standard operating procedures, monitoring plans, monitoring visit reports, monitoring follow-up letters, independent data monitoring meeting minutes, reporting of study subject adverse events, and investigational product accountability records.

For Study CABL001X2101, sponsor records for Sites 1001, 2001, and 3001 were assessed. For Study CABL001A2301, documents and records related to Sites 3600, 3602, and 4603 were evaluated. No discrepancies were noted.

In general, the Sponsor appeared to have maintained adequate study oversight of the two clinical studies. An FDA Form 483, Inspectional Observations, was not issued at the close of the inspection.

{See appended electronic signature page}
Anthony Orencia, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 1, 2021
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 215358
Product Name, Dosage Form, and Strength:	Scemblix (asciminib) tablets, 20 mg and 40 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation
FDA Received Date:	March 31, 2021, May 25, 2021, and July 20, 2021
OSE RCM #:	2021-663
DMEPA 2 Safety Evaluator:	Nicole Iverson, PharmD, BCPS
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As part of the approval process for Scemblix (asciminib) tablets, 20 mg and 40 mg, this review the evaluates proposed Scemblix Prescribing Information (PI), patient information, container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Novartis Pharmaceuticals Corporation submitted a 505(b)(1) application to obtain marketing approval of Scemblix tablets. Scemblix is proposed 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 Ph+ CML in CP harboring the T315I mutation.

We performed a risk assessment of the proposed container labels, carton labeling, PI and patient information for Scemblix tablets to determine whether there are significant concerns in terms of safety related to preventable medication errors. The proposed patient information is acceptable from a medication error perspective. We identified areas of the proposed container

labels, carton labeling, and PI that could be revised to improve clarity and readability of important information. For the Division, we note that the PI lacks clarity in the dosage instructions, administration instructions, and how supplied information. We also note the use of symbols. For the Applicant, we note a graphic in front of the proprietary name, lack of clarity in the net quantity statement, administration and storage instructions. In addition, we note inadequate font color differentiation between the strength statement and proprietary name. These factors may confuse the user and inadvertently lead to medication errors. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

The proposed patient information is acceptable from a medication error perspective. We identified areas in the proposed container label, carton labeling, PI and patient information, that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for Novartis Pharmaceuticals Corporation to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 1 (DHM 1)

A. Highlights of Prescribing Information

1. Dosage and Administration Section

a. The Dosage and Administration Section lacks clarity which may lead to dosing errors. Therefore, we recommend the following revisions.

i. Revise the Recommended Dosage in Ph+ CML in CP from, (b) (4) to "80 mg orally once daily or 40 mg orally twice daily." for clarity and to include the route of administration.

ii. Revise the Recommended Dosage to include the route of administration in Ph+ CML in CP Harboring the T315I mutation from (b) (4) to "200 mg orally twice daily."

iii. Revise the statement, (b) (4) to "Avoid food for at least 2 hours before and 1 hour after taking SCEMBLIX."

iv. SCEMBLIX should not be broken, crushed, or chewed. To prevent administration errors, consider including the statement, "Swallow tablets whole. Do not (b) (4) crush, or chew the tablets."

b. Adverse Reactions

i. Consider replacing the symbols ">" with their intended meaning to prevent misinterpretation and confusion.

B. Full Prescribing Information

1. Consider replacing the symbols "≥" and "<" with their intended meanings to prevent misinterpretation and confusion.

2. Dosage and Administration Section

a. We recommend revising the statements, [redacted] to "The recommended dose of SCEMBLIX is 80 mg taken orally once daily at approximately the same time each day or as 40 mg taken orally twice daily at approximately 12-hour intervals."

b. We recommend revising the title of Section 2.5 [redacted] to "*Administration*" to be consistent with current labeling practices.

c. We recommend revising the statements, [redacted] to [redacted] Advise patients to swallow SCEMBLIX whole. Do not break, crush, or chew the tablets. "

3. How Supplied/Storage and Handling Section

a. We note the carton labeling states, "Dispense and store Scemblix in the original [redacted] to protect moisture."; however the PI indicates, [redacted] Therefore, we recommend revising the statement, [redacted] in order to protect from moisture." to "Dispense and store in the original [redacted] to be consistent with the carton labeling.

b. The How Supplied information lacks clarity as the description of the tablets [redacted]. We recommend revising as follows:

Scemblix tablets are available as:

Table 8: SCEMBLIX Package Configurations and NDC Numbers

Package Configuration	Tablet Strength	NDC Number
Bottle of 60 (b) (4) tablets	20 mg	NDC 0078-1091-20
Bottle of 60 (b) (4) tablets	40 mg	NDC 0078-1098-20
Carton containing 5 bottles. Each bottle contains 60 (b) (4) tablets.	40 mg	NDC 0078-1098-30

- SCEMBLIX (asciminib) 20 mg film-coated tablets are supplied as pale yellow, unscored, round, biconvex, with beveled edges, film-coated tablet containing 20 mg of asciminib (equivalent to 21.62 mg of asciminib HCl). Each tablet is debossed with "20" on one side and "Novartis logo" on the other side.
- SCEMBLIX (asciminib) 40 mg film-coated tablets are supplied as violet white, unscored, round, biconvex, with beveled edges, film-coated tablet containing 40 mg of asciminib (equivalent to 43.24 mg of asciminib HCl). Each tablet is debossed with "40" on one side and "Novartis logo" on the other side.

4.2 RECOMMENDATIONS FOR NOVARTIS PHARMACEUTICALS CORPORATION

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. The placement of the graphic in front of the first letter "S" in the proprietary name is prominent. Placement of the graphic in front of the first letter in the proprietary name competes with readability of the proprietary name, which may lead to misinterpretation of the proprietary name as "OSCEMBLIX". We recommend moving or decreasing the prominence of the graphic in front of the proprietary name as it may lead to misinterpretation of the proprietary name.
2. (b) (4) Lack of adequate differentiation may contribute to product selection errors. Color differentiation is most effective when the color used has no association with a particular feature and there is no pattern in the application of the color scheme. Revise the font color of the 20 mg strength

such that the strength and the proprietary name appear in their own unique colors.

B. Container Labels

1. We recommend adding the statements, “Swallow tablets whole. Do not (b) (4) crush, or chew the tablets.” on the principal display panel of the container labels to mitigate the risk of product administration errors.
2. The font size of the net quantity statement competes in prominence with the established name and dosage form. We recommend decreasing the font size and revising the net quantity statement from, (b) (4) to “60 Tablets”.
3. The carton labeling states “Dispense and store Scemblix in the original (b) (4) to protect moisture.” however this statement is missing from the container labels. To ensure this important information is not missed we recommend including the statement “Dispense and store Scemblix in original container to protect from moisture.” on the side panel of the container labels.

C. Carton Labeling

1. Add the statements, “Swallow tablets whole. Do not (b) (4), crush, or chew the tablets.” on the principal display panel of the carton labeling. We recommend this revision to mitigate the risk of product administration errors.
2. We recommend revising the net quantity statement from, (b) (4) to “5 x 60 Tablets”.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Scemblix received on July 20, 2021 from Novartis Pharmaceuticals Corporation.

Table 2. Relevant Product Information for Scemblix	
Initial Approval Date	N/A
Active Ingredient	asciminib
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.
Route of Administration	Oral
Dosage Form	tablets
Strength	20 mg and 40 mg
Dose and Frequency	• Recommended Dosage in Ph+ CML in CP: 80 mg total daily dose (either 80 mg once daily or 40 mg twice daily). • Recommended Dosage in Ph+ CML in CP Harboring the T315I mutation: 200 mg twice daily.
How Supplied	• 20 mg film-coated tablets: Each bottle contains 60 film-coated tablets. • 40 mg film-coated tablets: Each bottle contains 60 film-coated tablets. • 40 mg film-coated tablets: Each (b) (4) contains 5 bottles. Each bottle contains 60 film-coated tablets
Storage	Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Store in the original (b) (4) in order to protect from moisture.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 28, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, Scemblix. Our search identified did not identify and previous labeling reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Scemblix labels and labeling submitted by Novartis Pharmaceuticals Corporation.

- Container labels received on March 31, 2021
- Carton labeling received on March 31, 2021
- Professional Sample Labels received on March 31, 2021
- Prescribing Information and Patient Information (Image not shown) received on July 20, 2021 available from \\CDSESUB1\evsprod\nda215358\0005\m1\us\proposed-clean.pdf

G.2 Label and Labeling Images

Container labels

2 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/

NICOLE F IVERSON
09/01/2021 09:08:36 AM

HINA S MEHTA
09/03/2021 02:25:58 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 215358
Submission Number	0005
Submission Date	6/24/2021
Date Consult Received	6/28/2021
Drug Name	Asciminib
Indication	for the treatment of adult patients with 1) Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors; 2) Ph+ CML in CP harboring the T315I mutation.
Therapeutic Dose	• Ph+ CML in CP: 80 mg total daily dose (either 80 mg once daily [QD] or 40 mg twice daily [BID]) • Ph+ CML in CP Harboring the T315I mutation: 200 mg BID • Avoid food for at least 2 hours before and 1 hour after taking asciminib tablet
Clinical Division	DHM1
Protocol Review	Link

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 6/28/2021 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review under IND 119257 dated 08/02/2019 in DARRTS;
- Proposed label (Submission 0003);
- CABL001X2101 protocol and clinical study report (Submission 0002);
- QT assessment report (Submission 0003);
- QT assessment report submission checklist (Submission 0003);
- Highlights of clinical pharmacology and cardiac safety (Submission 0003).

1 SUMMARY

No large QTc prolongation effect (i.e., >20 msec) of asciminib was observed in this QTc assessment. Because the study does not include a placebo control or a high exposure margin to waive the need of a separate positive control, we are reluctant to conclude a lack of a QT prolongation effect.

The effect of asciminib was evaluated in the first-in-human, open-label study CABL001X2101 in patients. The highest dose that was evaluated was 280 mg BID,

which covers the maximum therapeutic exposure. Data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that asciminib is associated with large mean increases in the QTc interval (refer to section 0) – see Table 1: Point Estimates and the 90% CIs (FDA Analysis) for overall results. Findings of this analysis are further supported by the available nonclinical data (section 3.1.2) and by-time analysis (section 4.3). Categorical analysis showed few QTcF >500 ms in 3/241 (1.2%) patients (1 of these patients also had increase in QTcF >60 mg from baseline after receiving asciminib 80 mg QD).

Table 1: Point Estimates and the 90% CIs (FDA Analysis)

Treatment	Concentration (ng/mL)	ΔQTcF	90% CI
Asciminib 40 mg BID	796	3.5	(2.5 to 4.6)
Asciminib 200-280 mg BID	5329	6.6	(4.7 to 8.5)

Based on sponsor's summary of clinical pharmacology data, none of the intrinsic or extrinsic factors studied (i.e., age, sex, race, organ impairment, clarithromycin [CYP3A4 inhibitor], quinidine [P-gp inhibitor], or food) increases Cmax by more than 30%.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label provided under Submission 0003 (link). Our changes are highlighted (addition, ~~deletion~~) as a suggestion only and we defer final labeling decisions to the Division.

The clinical ECG and AE data from study CABL001X2101 do not suggest large mean increases in the QTc interval at the highest proposed therapeutic dose (i.e., 200 mg BID). (b) (4)

12.2 Pharmacodynamics

Cardiac Electrophysiology

Asciminib does not cause a large mean increase in QTc interval (i.e., >20 msec) at the maximum recommended clinical dose (200 mg BID). Based on available clinical data, QTc interval prolongation cannot be excluded.

(b) (4)

Reviewer's comment: *Our suggestions are in accordance with the recommendations in the draft Guidance for Industry on QT Information in Labeling for Oncology Drug and Biological Products.*

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

The CSS-IRT reviewed the QT assessment proposal previously under IND 119257 (08/02/2019 in DARRTS). The proposal is based on pooled data from Arms 1 and 5 in the first-in-human, open-label study CABL001X2101 (study X2101) in the patient population. The primary analysis is concentration-QTc analysis on QTcF to exclude a large mean increases on the QTc interval (i.e. >20 msec). The maximum proposed therapeutic dose increased from 40 mg BID in the previous review to 200 mg BID in the current submission.

The sponsor also provided data from study CABL001A2301 (study A2301) to support the safety assessment (QT/QTc effect) of asciminib. Study A2301 is the pivotal Phase 3 study comparing asciminib 40 mg BID (n=156) to bosutinib (n=76) using a randomized, open-label design.

The reviewer's analyses focus on study AX2101 only because this study provided sufficient sample size and wider exposure.

Highlight of clinical pharmacology:

Geometric mean (CV%) Cmax and AUC_{tau} at the 200 mg BID dose is reported to be 5642 ng/mL (40%) and 29925 ng.hr/mL (41%). The average accumulation ratio ranged from 1.7-2.3 for the BID dosing. No major metabolite was identified. Tmax occurred around 2-3 hours postdose and the terminal half-life was reported to be 7-15 hours. Biliary secretion via BCRP and CYP3A4 contributed to 31% and 36% of total clearance. Excretion occurred mostly through the fecal route (79%). Age, sex, race, organ impairment, clarithromycin (CYP3A4 inhibitor), or quinidine (P-gp inhibitor) increases Cmax by <30%. Food decreases drug exposure.

3.1.2 Nonclinical Safety Pharmacology Assessments

The IC50 for asciminib in the hERG patch clamp assay was 11.4 μM. This translates into a clinical safety margin >200-fold, > 100-fold, and > 30-fold when compared to free Cmax exposure in patients at therapeutic dose of 40 mg b.i.d., 80 mg q.d., and 200 mg b.i.d., respectively. Moderate cardiovascular effects (increased heart rate, decreased

systolic pressure, decreased mean arterial pressure, and decreased arterial pulse pressure) were observed in in vivo cardiac safety studies in dogs at 600 mg/kg (free Cmax of 6.3 μM). No QTc prolongation was observed in dogs. The estimated asciminib exposure estimated in dogs at 600 mg/kg correspond to free Cmax at steady-state 100-, 60-, and 18-fold higher than that achieved in patients at the dose of 40 mg b.i.d., 80 mg q.d., and 200 mg b.i.d., respectively.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for asciminib was based on exposure-response analysis. Please see section 3.2.3 for additional details.

Reviewer's comment: *Sponsor provided tabulated summary statistics at each time points for each treatment arms. Reviewers' assessments are based on grouped treatment arms. Please see section 4.3 for more details.*

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

The sponsor did not conduct QT bias assessment.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis HR (<45 or >100 beats/min), PR (>220 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline). There were 3 (1.2%) patients had observed QTc above >500 msec and 2 of them also had corresponding change from baseline below 60.

Reviewer's comment: *These results are generally consistent with results from reviewers' assessments. Reviewer's analysis identified 1 patient with both observed QTc >500 msec and change from baseline above 60 msec. Please see section 4.4 for more details.*

3.2.3 Exposure-Response Analysis

The PK/ECG analysis set included all CML and Ph+ ALL patients (N=239) in single agent treatment cohorts from Study X2101 who provided baseline ECG (QT or PR or QRS or HR) data and at least one corresponding post-dose time-matched plasma asciminib concentration and ECG (QT or PR or QRS or HR) record. A linear mixed effects model was used to characterize the change from baseline QTcF vs. time matched plasma asciminib concentrations with baseline QTcF as covariate and patient as random effect using the PK/ECG analysis set.

Overall, there was no apparent hysteresis for QTcF change which supports the use of a concentration-effect model with matched concentration and ECG assessments. The regression line shows a slightly positive slope suggesting a small concentration-dependent increase in ΔQTcF in the relevant range of concentrations. Based on the PK-QTcF model, the estimated mean ΔQTcF at the geometric mean Cmax (832 ng/mL observed on Cycle 1 Day 15 for patients in Arm 1 and Arm 5 pooled) of the therapeutic

dose of 40 mg b.i.d. was 3.35 ms (upper bound of the 90% CI: 4.43 ms), at geometric mean Cmax of 1511 ng/mL with 80 mg q.d. was 3.64 ms (upper bound of the 90% CI: 4.68 ms), and at geometric mean Cmax of 5589 ng/mL with 200 mg b.i.d. was 5.37 ms (upper bound of the 90% CI: 6.77 ms).

Reviewer's comment: *Reviewer's primary analysis used data from Cycle 1 only. The predicted QTc increase is numerically higher than the sponsor's results, but the overall conclusions are the same.*

3.2.4 Safety Analysis Related to Torsade/ QTc prolongation

Study A2301

Across asciminib dose cohorts, 13/243 (5.3%) patients were identified with AEs using the broad search criteria of SMQ 'Torsade de Pointes/QT prolongation' in addition to the preferred term "Seizure". Of note, no events were reported at the highest dose evaluated (280 mg b.i.d.) (Table 5-12).

Below is the summary of the reported events:

- 8/243 (3.3%) patients had events of syncope (including 1 patient in 40 mg b.i.d., 2 patients in 80 mg q.d., and 3 patients in 200 mg b.i.d. cohorts). Grade 3 syncope was reported in 4/243 (1.6%) patients and no grade 4 event was reported. Events in the other 4 patients were grade 1 or 2. Syncope was reported as an SAE (grade 3) in two patients. None of the eight events were considered related to the study drug by the Investigator. None of these events required dose adjustment/interruption, or led to treatment discontinuation. None of the patients had ECGs at the same time or day as the syncopal event. All syncope events including SAEs were reported to be resolved. It should be noted that 2 of the 8 events (including one of the SAEs) occurred after treatment with asciminib was discontinued, described in the narratives (Appendix 1), with no strong evidence to attribute the events to QTc prolongation.
- 2/243 (0.8%) patients with CML-BP or Ph+ ALL were reported with ECG QT prolonged (both in 160 mg b.i.d. cohort). Among the two patients, one with grade 3 event reported 2 days after stopping treatment with asciminib and was not considered to be treatment related. In the other patient, a grade 1 treatment-related event was reported. However, no ECG data was provided to support the event. In the reported ECGs, QTcF was not reported to be >500 ms or >60 ms from baseline. Concurrent conditions and concomitant medications may provide a plausible explanation of the event as described in Appendix 1.
- 1/243 (0.4%) severely ill patient in the 160 mg b.i.d. cohort suffered two episodes of seizure (grade 1) during septic shock approximately 3 weeks after discontinuing the asciminib therapy. The events were not considered treatment-related.
- 1/243 (0.4%) patient in the 80 mg q.d. cohort had cardiac arrest which was a serious event with fatal outcome reported approximately 44 months after starting the study treatment. Concurrent conditions, at the time of the events, included hypertension, myocardial ischemia, and acute kidney injury therefore the fatal

cardiac arrest was not considered to be related to QT prolongation, noting that no relevant changes in QTcF were observed during the long treatment duration as described in Appendix 1.

- 1/243 (0.4%) patient in the 200 mg b.i.d. cohort had ventricular tachycardia (grade 3) which was reported approximately 4 weeks after stopping treatment with asciminib as a serious event. The SAE was reported following allogeneic stem cell transplantation and was attributed to insufficient termination of an implantable defibrillator. No relevant changes in QTcF were observed during the treatment duration as described in Appendix 1.

In Study X2101, new QTcF >500 ms was noted in 3/241 (1.2%) patients (2 of these also had increase in QTcF >60 mg from baseline), however, none of these abnormalities were associated with cardiac-related symptoms. In Study A2301, new QTcF >500 ms with increase in QTcF >60 ms from baseline was noted in 1 (0.6%) patient which was reported as treatment related grade 3 ECG QT prolongation. This event was managed with treatment interruption and dose reduction and no subsequent episodes of QTcF>500 ms were observed.

Reviewer's comment: *Overall, the AE data do not suggest a proarrhythmic risk due delayed cardiac repolarization. There were, however, a few subjects with treatment related prolonged QTc interval.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable as no large increases or decreases in heart rate (i.e., |mean| <10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

1012 out of 13822 digital ECGs were digitized for study CABL001X2101, while 112 out of 243 subjects had some digitized ones. Paper ECGs were also submitted for those digitized ones, but automatic measurements were not available. Overall, ECG acquisition and interpretation in this study appear acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer evaluated the ΔQTcF effect using descriptive statistics.

4.3.1 QTc

Figure 1 displays the time profile of ΔQTcF for different treatment groups. The maximum ΔQTcF values by treatment are shown in Table 2.

Figure 1: Mean and 90% CI of ΔQTcF Time-course (unadjusted CIs).

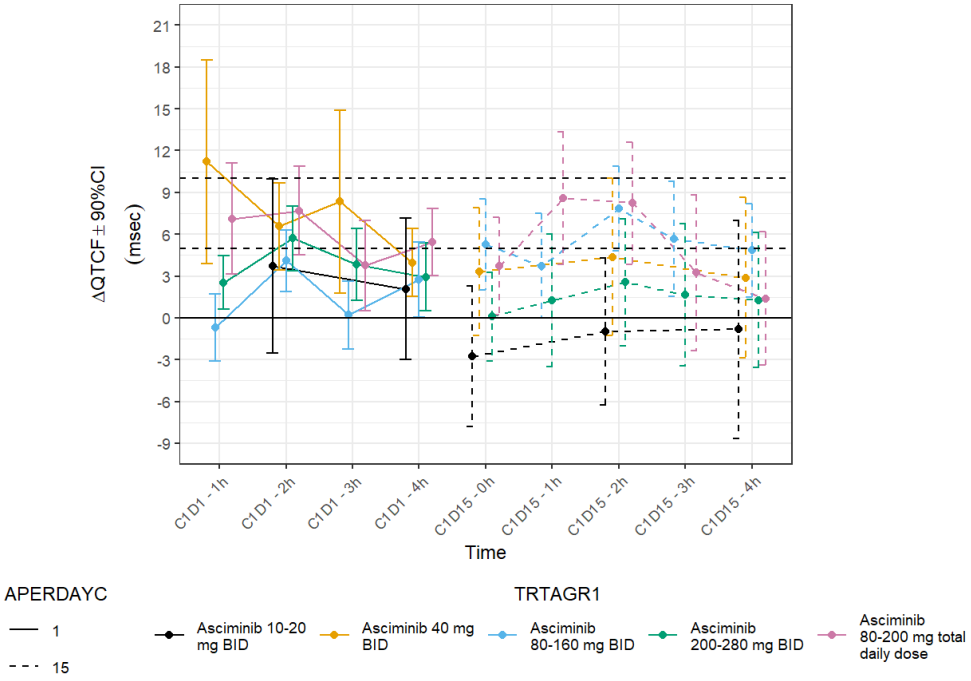


Table 2: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔQTcF

TRTAGR1	Analysis Nominal Period Day (C)	N	Time (Hours)	ΔQTCF (msec)	90.0% CI (msec)
Asciminib 10-20 mg BID	1	14	2.0	3.7	(-2.5 to 10.0)
Asciminib 10-20 mg BID	15	6	4.0	-0.8	(-8.6 to 7.0)
Ascimin b 40 mg BID	1	5	1.0	11.2	(3.9 to 18.5)
Ascimin b 40 mg BID	15	16	2.0	4.4	(-1.3 to 10.0)
Ascimin b 80-160 mg BID	1	58	2.0	4.1	(1.9 to 6.3)
Ascimin b 80-160 mg BID	15	55	2.0	7.8	(4.8 to 10.9)
Asciminib 200-280 mg BID	1	69	2.0	5.7	(3.4 to 8.0)
Asciminib 200-280 mg BID	15	31	2.0	2.5	(-2.0 to 7.1)
Ascimin b 80-200 mg total daily dose	1	24	1.0	7.1	(3.1 to 11.1)
Ascimin b 80-200 mg total daily dose	15	24	1.0	8.6	(3.8 to 13.3)

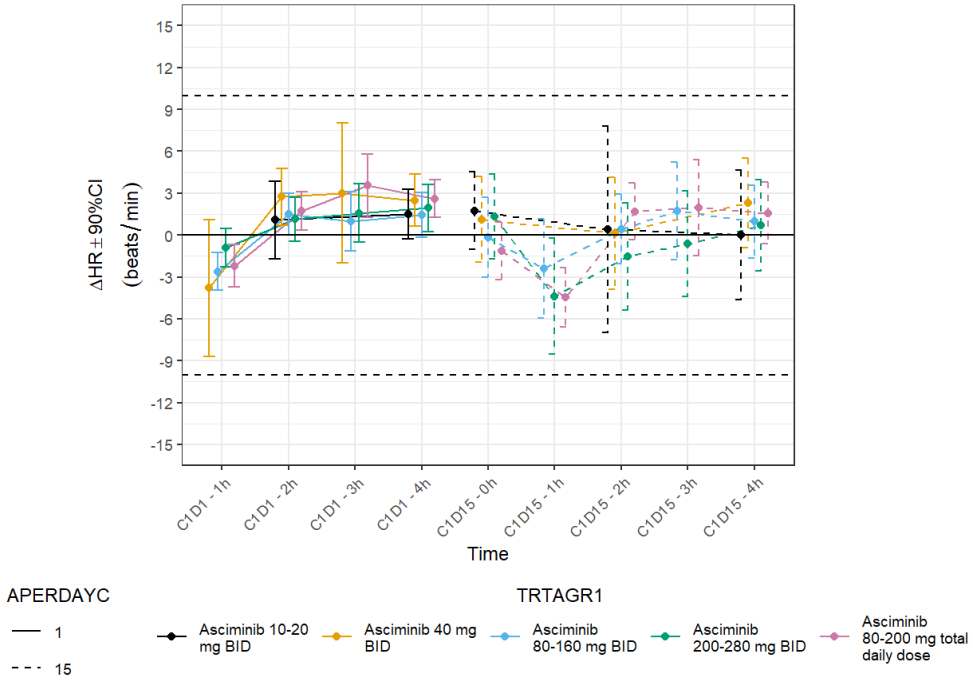
4.3.1.1 Assay Sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔHR for different treatment groups.

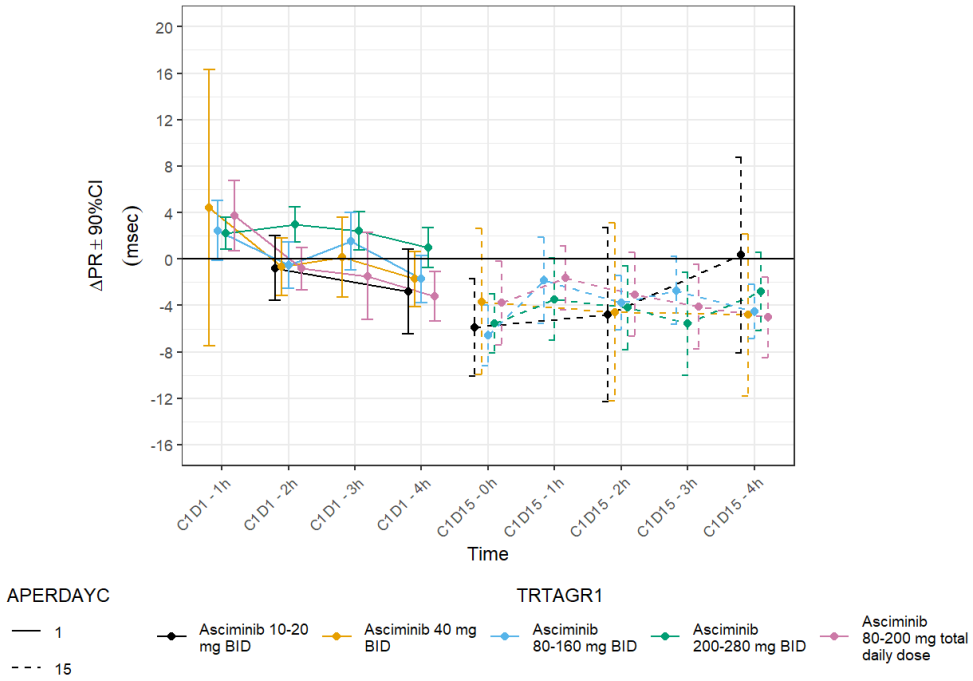
Figure 2: Mean and 90% CI of ΔHR Time-course



4.3.3 PR

Figure 3 displays the time profile of ΔPR for different treatment groups.

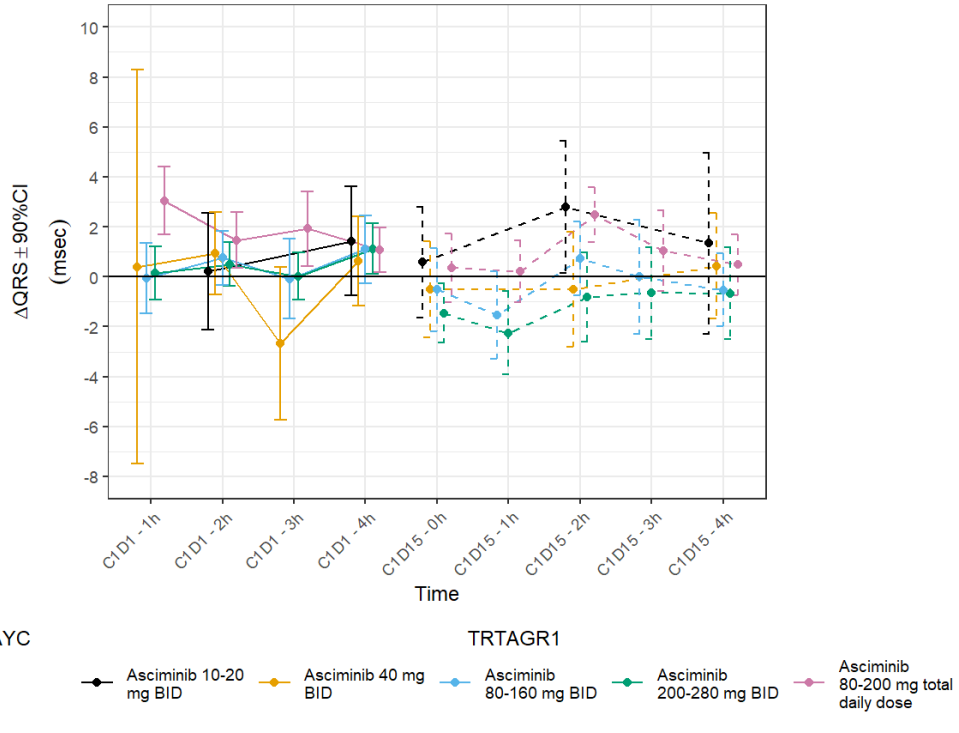
Figure 3: Mean and 90% CI of ΔPR Time-course



4.3.4 QRS

Figure 4 displays the time profile of ΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔQRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population from Study CABL001X2101, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

Table 3 lists the number of subjects, as well as the number of observations with QTcF values of ≤450 msec, >450 and ≤480 msec, >480 and ≤500 msec, and >500 msec with or without a change from baseline >60 msec. There was one subject having observed QTcF above 500 msec with increase over baseline above 60 msec after receiving asciminib 200 mg BID.

Table 3: Categorical Analysis for QTcF (maximum)

TRTAGR1	Value <=450 msec / Total		450 msec < Value <=480 msec		480 msec < Value <=500 msec		Value >500 msec & Δ <=60 msec		Value >500 msec & Δ >60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Asciminib 10-20 mg BID	12 / 15 (80.0%)	172 / 187 (92.0%)	3 (20.0%)	15 (8.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Asciminib 40 mg BID	30 / 38 (78.9%)	427 / 468 (91.2%)	7 (18.4%)	40 (8.5%)	1 (2.6%)	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Asciminib 80-160 mg BID	52 / 63 (82.5%)	754 / 790 (95.4%)	11 (17.5%)	36 (4.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Asciminib 200-280 mg BID	58 / 73 (79.5%)	898 / 991 (90.6%)	13 (17.8%)	82 (8.3%)	0 (0%)	8 (0.8%)	1 (1.4%)	2 (0.2%)	1 (1.4%)	1 (0.1%)

TRTAGR1	Value <=450 msec / Total		450 msec < Value <=480 msec		480 msec < Value <=500 msec		Value >500 msec & Δ <=60 msec		Value >500 msec & Δ >60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Asciminib 80-200 mg total daily dose	39 / 52 (75.0%)	628 / 713 (88.1%)	9 (17.3%)	65 (9.1%)	3 (5.8%)	19 (2.7%)	1 (1.9%)	1 (0.1%)	0* (0%)	0 (0%)

** One subject received ABL001 80 mg QD was included sponsors outlier count as QTcF > 500 msec and change from baseline above 60 msec. The subject had one of triplicates having change from baseline above 60 msec. The averaged change from baseline at that time point is below 60 msec and therefore the subject is count as QTcF > 500 msec and change from baseline ≤ 60 msec in this report.*

Table 4 lists the categorical analysis results for ΔQTcF (<30 msec, >30 and <60, and >60 msec). There were two subjects having observed ΔQTcF above 60 msec after receiving asciminib 200 mg BID.

Table 4: Categorical Analysis for ΔQTcF (maximum)

TRTAGR1	Total (N)		Value <=30 msec		30 msec < Value <= 60 msec		Value >60 msec	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Asciminib 10-20 mg BID	15	187	13 (86.7%)	185 (98.9%)	2 (13.3%)	2 (1.1%)	0 (0%)	0 (0%)
Asciminib 40 mg BID	38	468	33 (86.8%)	463 (98.9%)	5 (13.2%)	5 (1.1%)	0 (0%)	0 (0%)
Asciminib 80-160 mg BID	63	790	53 (84.1%)	771 (97.6%)	10 (15.9%)	19 (2.4%)	0 (0%)	0 (0%)
Asciminib 200-280 mg BID	73	991	61 (83.6%)	970 (97.9%)	10 (13.7%)	19 (1.9%)	2 (2.7%)	2 (0.2%)
Asciminib 80-200 mg total daily dose	52	713	43 (82.7%)	691 (96.9%)	9 (17.3%)	22 (3.1%)	0 (0%)	0 (0%)

4.4.2 HR

Table 5 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min).

Table 5: Categorical Analysis for HR (maximum)

TRTAGR1	Total (N)		Value <=100 beats/min		Value >100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Asciminib 10-20 mg BID	15	187	15 (100.0%)	187 (100.0%)	0 (0%)	0 (0%)
Asciminib 40 mg BID	38	468	36 (94.7%)	463 (98.9%)	2 (5.3%)	5 (1.1%)
Asciminib 80-160 mg BID	63	790	55 (87.3%)	767 (97.1%)	8 (12.7%)	23 (2.9%)
Asciminib 200-280 mg BID	73	991	66 (90.4%)	964 (97.3%)	7 (9.6%)	27 (2.7%)
Asciminib 80-200 mg total daily dose	52	713	50 (96.2%)	711 (99.7%)	2 (3.8%)	2 (0.3%)

4.4.3 PR

Table 6 lists the categorical analysis results for PR (<200 msec, >200 and ≤220 msec, and >220 msec; with and without 25% increase over baseline). There was one subject having observed PR above 220 msec with increase over baseline above 25% after receiving asciminib 40 mg BID.

Table 6: Categorical Analysis for PR

TRTAGR1	Total (N)		Value <=220 msec		Value >220 msec & Δ<25%		Value >220 msec & Δ>=25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Asciminib 10-20 mg BID	15	187	13 (86.7%)	177 (94.7%)	2 (13.3%)	10 (5.3%)	0 (0%)	0 (0%)
Asciminib 40 mg BID	38	467	35 (92.1%)	442 (94.6%)	2 (5.3%)	24 (5.1%)	1 (2.6%)	1 (0.2%)
Asciminib 80-160 mg BID	62	775	56 (90.3%)	752 (97.0%)	6 (9.7%)	23 (3.0%)	0 (0%)	0 (0%)
Asciminib 200-280 mg BID	72	963	67 (93.1%)	920 (95.5%)	5 (6.9%)	43 (4.5%)	0 (0%)	0 (0%)
Asciminib 80-200 mg total daily dose	51	698	47 (92.2%)	677 (97.0%)	4 (7.8%)	21 (3.0%)	0 (0%)	0 (0%)

4.4.4 QRS

Table 7 lists the categorical analysis results for QRS (≤120 msec, and >120 msec; with and without 25% increase over baseline). There was one subject having observed QRS above 120 msec with increase over baseline above 25% after receiving asciminib 160 mg BID.

Table 7: Categorical Analysis for QRS

TRTAGR1	Total (N)		Value <=120 msec		Value >120 msec & Δ<25%		Value >120 msec & Δ>=25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Asciminib 10-20 mg BID	15	187	14 (93.3%)	175 (93.6%)	1 (6.7%)	12 (6.4%)	0 (0%)	0 (0%)
Asciminib 40 mg BID	38	468	36 (94.7%)	465 (99.4%)	2 (5.3%)	3 (0.6%)	0 (0%)	0 (0%)
Asciminib 80-160 mg BID	63	790	58 (92.1%)	738 (93.4%)	4 (6.3%)	51 (6.5%)	1 (1.6%)	1 (0.1%)
Asciminib 200-280 mg BID	73	991	68 (93.2%)	942 (95.1%)	5 (6.8%)	49 (4.9%)	0 (0%)	0 (0%)
Asciminib 80-200 mg total daily dose	52	713	47 (90.4%)	645 (90.5%)	5 (9.6%)	68 (9.5%)	0 (0%)	0 (0%)

4.5 EXPOSURE-RESPONSE ANALYSIS

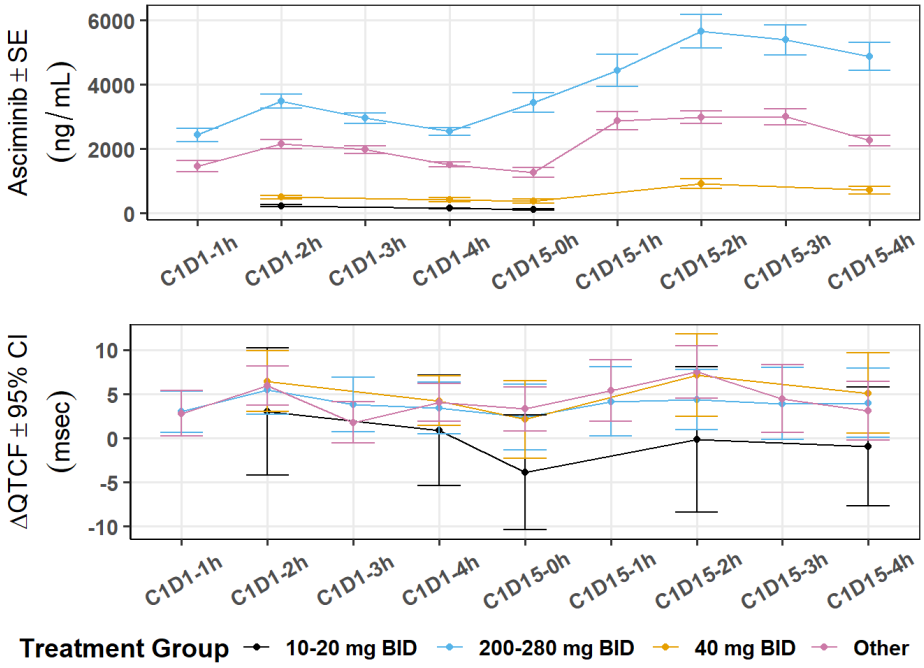
Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK in the first cycle. The 200-280 mg BID dose group included 67 patients on 200 mg BID treatment and 5 patients on 280 mg BID treatment.

4.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model need to be evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) absence of delay between plasma concentration and ΔQTcF; and 3) absence of a nonlinear relationship.

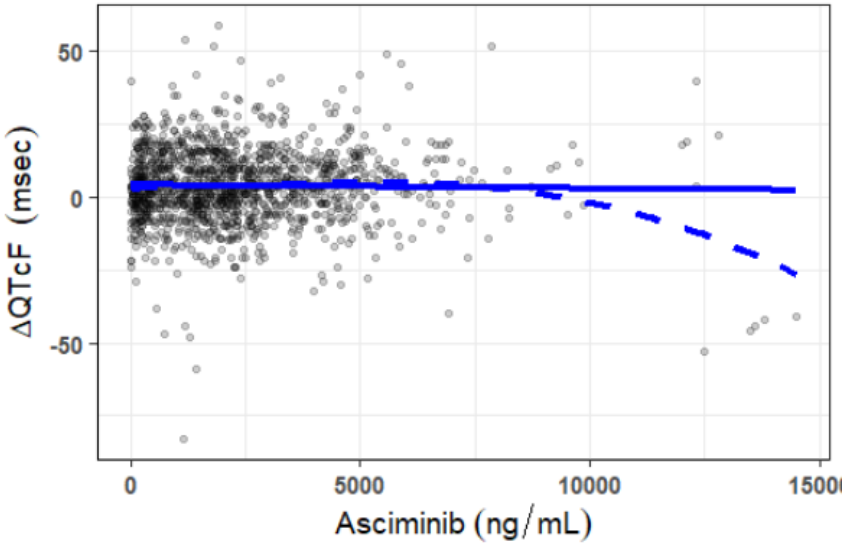
Figure 2 shows the time-course of ΔHR, with an absence of significant ΔHR changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and ΔQTcF, with no appearance of significant hysteresis. The time-course of ΔQTcF profiles highly overlap between the three higher dose groups. Figure 6 shows the relationship between drug concentration and ΔQTcF, and supports the use of a linear model.

Figure 5: Time-course of Drug Concentration (top) and QTcF (bottom)[1]



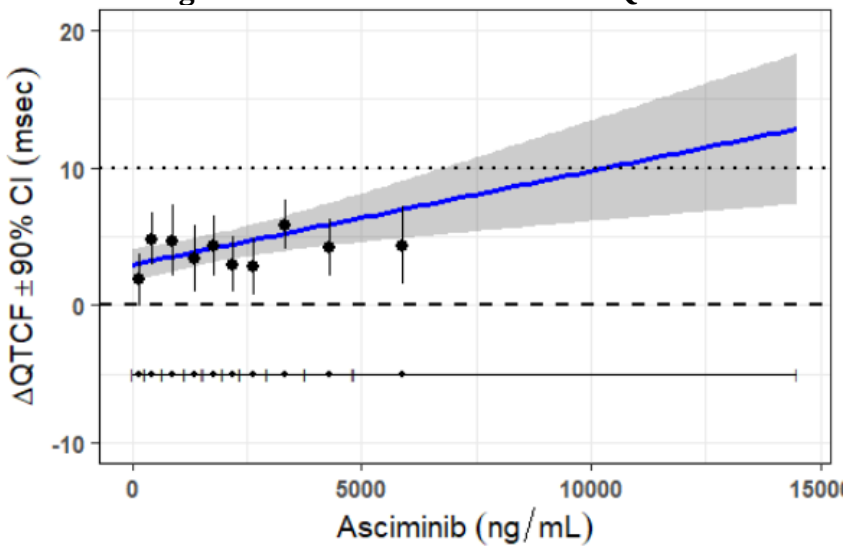
[1] ΔQTcF shown were obtained via descriptive statistics. Only timepoints with a sample size graeter than 10 are shown in this figure.

Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 1. The model suggested a positive but shallow concentration-QTc slope.

Figure 7: Goodness-of-fit Plot for QTcF



We obtained similar results in supportive analyses when digitized ECGs were excluded from the analysis or when all time-match PK/ECG data were included.

4.5.1.1 Assay Sensitivity

Not applicable.

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/

DEVI KOZELI on behalf of NAN ZHENG
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