CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

212608Orig1s006

Trade Name:	AYVAKIT
Generic or Proper Name:	avapritinib
Sponsor:	Blueprint Medicines Corporation
Approval Date:	June 16, 2021
Indication:	Ayvakit is a kinase inhibitor indicated for: Gastrointestinal Stromal Tumor (GIST) • the treatment of adults with unresectable or metastatic GIST harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations. Advanced Systemic Mastocytosis (AdvSM) • the treatment of adult patients with AdvSM. AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL). • Limitations of Use: Ayvakit is not recommended for the treatment of patients with AdvSM with platelet counts of less than 50 X 10^9/L.

CENTER FOR DRUG EVALUATION AND RESEARCH

212608Orig1s006

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212608Orig1s006

APPROVAL LETTER

NDA 212608/S-006

SUPPLEMENT APPROVAL

Blueprint Medicines Corporation
Attention: Gemma Mandell, BSc
Senior Director, Regulatory Affairs
45 Sidney Street
Cambridge, MA 02139

Dear Ms. Mandell:

Please refer to your supplemental new drug application (sNDA) dated and received December 16, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ayvakit (avapritinib) film-coated tablets.

This Prior Approval supplemental new drug application provides for the following:

1. New indication for the treatment of adult patients with advanced systemic mastocytosis (AdvSM), including patients with aggressive systemic mastocytosis (ASM) and systemic mastocytosis with an associated hematological neoplasm (SM-AHN).

2. Two additional tablet strengths (25 mg and 50 mg), and manufacturing site, (b) (4)

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on December 16, 2020, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 212608/S-006**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Ayvakit (avapritinib) was approved on January 9, 2020, we have become aware of safety signals of intracranial hemorrhage and cognitive adverse reactions associated with avapritinib, which need to be further evaluated in ongoing clinical trials, such as the trial BLU-285-2202. We consider this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to fully assess the signal of serious risks of intracranial hemorrhage and cognitive adverse reactions.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only clinical trials (rather than a nonclinical or observational study) will be sufficient to fully assess a signal of serious risks of intracranial hemorrhage and cognitive adverse reactions.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

4101-1 Conduct a pooled analysis of data from completed and on-going avapritinib trials, including Studies BLU-285-1101, BLU-285-2101, BLU-285-2202, and BLU-285-1303, to further characterize avapritinib-associated intracranial hemorrhage in patients with gastrointestinal stromal tumor and advanced systemic mastocytosis. Include patient narratives with the onset and resolution date for each event, results of investigations (laboratory, imaging, other), avapritinib dose history and action taken, concomitant medications, patient comorbidities and outcome for intracranial hemorrhage events. Submit datasets, and patient narratives for intracranial hemorrhage events in the final report.

The timetable you submitted on June 8, 2021, states that you will conduct this study according to the following schedule:

Trial Completion:	06/2021
Final Report Submission:	12/2021

4101-2 Conduct a pooled analysis of data from completed and on-going avapritinib trials, including Studies BLU-285-1101, BLU-285-2101, BLU-285-2202, and BLU-285-1303, to further characterize avapritinib-associated cognitive adverse reactions (including memory impairment, cognitive disorder, confusional state, amnesia, somnolence, speech disorder, delirium, hallucination, mood altered, agitation, personality change, dementia, mental status changes, psychotic disorder, disorientation, mental impairment, and encephalopathy) in patients with gastrointestinal stromal tumor and advanced systemic mastocytosis. Include patient narratives with the onset and resolution date for each event, results of investigations (laboratory, imaging, other), avapritinib dose history and action taken, concomitant medications, patient comorbidities and outcome of each event. Submit datasets, and patient narratives for serious cognitive adverse events in the final report.

The timetable you submitted on June 8, 2021, states that you will conduct this study according to the following schedule:

Trial Completion:	06/2021
Final Report Submission:	12/2021

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 124159, with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

4101-3 Complete Study BLU-285-2202, "An open-label, single-arm, Phase 2 study to evaluate efficacy and safety of avapritinib (BLU-285), a selective KIT mutation-targeted tyrosine kinase inhibitor, in patients with advanced systemic mastocytosis". Include an updated summary of safety, efficacy analyses, and datasets at the time of final clinical study report submission.

The timetable you submitted on June 8, 2021, states that you will conduct this study according to the following schedule:

Trial Completion:	01/2026
Final Report Submission:	12/2026

Submit clinical protocols to your IND 124159 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Brittany Garr-Colón, MPH, Regulatory Project Manager, at (301) 796-6153 or via email at Brittany.Garr-Colon@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Deputy Director
Division of Nonmalignant Hematology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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

/s/

ALBERT B DEISSEROTH
06/16/2021 02:16:40 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212608Orig1s006

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AYVAKIT safely and effectively. See full prescribing information for AYVAKIT.

AYVAKIT™ (avapritinib) tablets, for oral use
Initial U.S. Approval: 2020

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	6/2021
Dosage and Administration (2)	6/2021
Warnings and Precautions (5)	6/2021

----------INDICATIONS AND USAGE----------

AYVAKIT is a kinase inhibitor indicated for:

Gastrointestinal Stromal Tumor (GIST)

- the treatment of adults with unresectable or metastatic GIST harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations. (1.1, 2.1)

Advanced Systemic Mastocytosis (AdvSM)

- the treatment of adult patients with AdvSM. AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL). (1.2)
- Limitations of Use: AYVAKIT is not recommended for the treatment of patients with AdvSM with platelet counts of less than 50 X 10^9/L (1.2)

----------DOSAGE AND ADMINISTRATION----------

- GIST: Select patients for treatment with AYVAKIT based on the presence of a PDGFRA exon 18 mutation. (2.1)
- GIST: The recommended dosage is 300 mg orally once daily. (2.2)
- AdvSM: The recommended dosage is 200 mg orally once daily. (2 3)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 25 mg, 50 mg, 100 mg, 200 mg and 300 mg. (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Intracranial Hemorrhage: Permanently discontinue for any occurrence of any grade. (2.5, 5.1)
- Cognitive Effects: A broad spectrum of cognitive adverse reactions can occur in patients receiving AYVAKIT. Depending on the severity, continue AYVAKIT at same dose, withhold and then resume at same or reduced dose upon improvement, or permanently discontinue. (2.5, 5.2)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females and males of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.3, 8.1, 8.3)

----------ADVERSE REACTIONS----------

The most common adverse reactions (incidence ≥ 20%) are:

- GIST: edema, nausea, fatigue/asthenia, cognitive impairment, vomiting, decreased appetite, diarrhea, hair color changes, increased lacrimation, abdominal pain, constipation, rash, and dizziness. (6.1)
- AdvSM: edema, diarrhea, nausea, and fatigue/asthenia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Blueprint Medicines Corporation at 1-888-258-7768 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Strong and Moderate CYP3A Inhibitors: Avoid coadministration of AYVAKIT with strong and moderate CYP3A inhibitors. If coadministration of AYVAKIT with a moderate inhibitor cannot be avoided, reduce dose of AYVAKIT. (2.6, 7.1)
- Strong and Moderate CYP3A Inducers: Avoid coadministration of AYVAKIT with strong and moderate CYP3A inducers. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 6/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 PDGFRA Exon 18 Mutation-Positive Unresectable or Metastatic Gastrointestinal Stromal Tumor (GIST)

AYVAKIT™ is indicated for the treatment of adults with unresectable or metastatic GIST harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations *[see Dosage and Administration (2.1)]*.

1.2 Advanced Systemic Mastocytosis (AdvSM)

AYVAKIT is indicated for the treatment of adult patients with advanced systemic mastocytosis (AdvSM). AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).

Limitations of Use:

AYVAKIT is not recommended for the treatment of patients with AdvSM with platelet counts of less than 50 X 10^9/L *[see Warnings and Precautions (5.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection for GIST Harboring PDGFRA Exon 18 Mutations

Select patients for treatment with AYVAKIT based on the presence of a PDGFRA exon 18 mutation *[see Clinical Studies (14.1)]*. An FDA-approved test for the detection of exon 18 mutations is not currently available.

2.2 Recommended Dosage for GIST Harboring PDGFRA Exon 18 Mutations

The recommended dosage of AYVAKIT is 300 mg orally once daily in patients with GIST. Continue treatment until disease progression or unacceptable toxicity.

2.3 Recommended Dosage for Advanced Systemic Mastocytosis

The recommended dosage of AYVAKIT is 200 mg orally once daily in patients with AdvSM. Continue treatment until disease progression or unacceptable toxicity.

Modify dosage for adverse reactions as outlined in Table 2 *[see Dosage and Administration (2.5)]*.

2.4 Recommended Administration

Administer AYVAKIT orally on an empty stomach, at least 1 hour before or 2 hours after a meal *[see Clinical Pharmacology (12.3)]*.

Do not make up for a missed dose within 8 hours of the next scheduled dose.

Do not repeat dose if vomiting occurs after AYVAKIT but continue with the next scheduled dose.

2.5 Dosage Modifications for Adverse Reactions

The recommended dose reductions and dosage modifications for adverse reactions are provided in Tables 1 and 2.

Table 1. Recommended Dose Reductions for AYVAKIT for Adverse Reactions

Dose Reduction	GIST (starting dose 300 mg)*	AdvSM (starting dose 200 mg)**
First	200 mg once daily	100 mg once daily
Second	100 mg once daily	50 mg once daily
Third	-	25 mg once daily

* Permanently discontinue AYVAKIT in patients with GIST who are unable to tolerate a dose of 100 mg once daily.
** Permanently discontinue AYVAKIT in patients with AdvSM who are unable to tolerate a dose of 25 mg once daily.

Table 2. Recommended Dosage Modifications for AYVAKIT for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modification
Patients with GIST or AdvSM		
Intracranial Hemorrhage *[see Warnings and Precautions (5.1)]*	Any grade	Permanently discontinue AYVAKIT.
Cognitive Effects *[see Warnings and Precautions (5.2)]*	Grade 1	Continue AYVAKIT at same dose or reduced dose or withhold until improvement to baseline or resolution. Resume at same dose or reduced dose.
	Grade 2 or Grade 3	Withhold AYVAKIT until improvement to baseline, Grade 1, or resolution. Resume at same dose or reduced dose.
	Grade 4	Permanently discontinue AYVAKIT.
Other *[see Adverse Reactions (6.1)]*	Grade 3 or Grade 4	Withhold AYVAKIT until improvement to less than or equal to Grade 2. Resume at same dose or reduced dose, as clinically appropriate.
Patients with AdvSM		
Thrombocytopenia *[see Warnings and Precautions (5.1)]*	$<50 \times 10^9$/L	Interrupt AYVAKIT until platelet count is $\geq 50 \times 10^9$/L, then resume at reduced dose (per Table 1). If platelet counts do not recover above 50×10^9/L, consider platelet support.

*Severity as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0

2.6 Concomitant Use of Strong or Moderate CYP3A Inhibitors

Avoid concomitant use of AYVAKIT with strong or moderate CYP3A inhibitors. If concomitant use with a moderate CYP3A inhibitor cannot be avoided, the starting dosage of AYVAKIT is as follows *[see Drug Interactions (7.1)]*:

- GIST: 100 mg orally once daily
- AdvSM: 50 mg orally once daily

3 DOSAGE FORMS AND STRENGTHS

Tablets:

- 25 mg, round, white film-coated tablet with debossed text. One side reads “BLU” and the other side reads “25”.
- 50 mg, round, white film-coated tablet with debossed text. One side reads “BLU” and the other side reads “50”.
- 100 mg, round, white film-coated, printed with blue ink “BLU” on one side and “100” on the other side.
- 200 mg, capsule shaped, white film-coated, printed with blue ink “BLU” on one side and “200” on the other side.
- 300 mg, capsule shaped, white film-coated, printed with blue ink “BLU” on one side and “300” on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Intracranial Hemorrhage

Serious intracranial hemorrhage may occur with AYVAKIT treatment; fatal events occurred in less than 1% of patients. Overall, intracranial hemorrhage (e.g., subdural hematoma, intracranial hemorrhage, and cerebral hemorrhage) occurred in 2.9% of the 749 patients who received AYVAKIT.

Monitor patients closely for the risk of intracranial hemorrhage including those with thrombocytopenia, vascular aneurysm or a history of intracranial hemorrhage or cerebrovascular accident within the prior year.

Permanently discontinue AYVAKIT if intracranial hemorrhage of any grade occurs *[see Dosage and Administration (2.5)]*.

Gastrointestinal Stromal Tumors

Intracranial hemorrhage occurred in 3 of 267 patients (1.1%). Two (0.7%) of the events were Grade ≥ 3 and resulted in discontinuation of study drug. Events of intracranial hemorrhage occurred in a range from 1.7 months to 19.3 months after initiating AYVAKIT.

Advanced Systemic Mastocytosis

In patients with AdvSM who received AYVAKIT at 200 mg daily, intracranial hemorrhage occurred in 2 of 75 patients (2.7%) who had platelet counts ≥ 50 X 10^9/L prior to initiation of therapy and in 3 of 80 patients (3.8%) regardless of platelet counts.

In patients with AdvSM, a platelet count must be performed prior to initiating therapy; AYVAKIT is not recommended in patients with AdvSM with platelet counts < 50 X 10^9/L. Following treatment initiation, platelet counts must be performed every 2 weeks for the first 8 weeks regardless of baseline platelet count. After 8 weeks of treatment, monitor platelet counts every 2 weeks (or more frequently as clinically indicated) if values are less than 75 X 10^9/L, every 4 weeks if values are between 75 and 100 X 10^9/L, and as clinically indicated if values are greater than 100 X 10^9/L.

Manage platelet counts of < 50 X 10^9/L by treatment interruption or dose-reduction of AYVAKIT. Platelet support may be necessary *[see Dosage and Administration (2.5)]*. Dose-interruptions and dose-

reductions for thrombocytopenia occurred in 20% and 22% of AYVAKIT-treated patients, respectively. Thrombocytopenia was generally reversible by reducing or interrupting AYVAKIT.

5.2 Cognitive Effects

Cognitive adverse reactions can occur in patients receiving AYVAKIT. These cognitive adverse reactions occurred in 39% of the 749 patients who received AYVAKIT. These adverse reactions were managed with dose interruption and/or reduction. Overall, 12.4% led to dose interruptions, 8.5% led to dose reductions and 2.5% led to permanent discontinuation of AYVAKIT treatment.

Depending on the severity, withhold AYVAKIT and then resume at the same dose or at a reduced dose upon improvement, or permanently discontinue AYVAKIT *[see Dosage and Administration (2.5)]*.

Gastrointestinal Stromal Tumors

Cognitive adverse reactions occurred in 41% of 601 patients with GIST who received AYVAKIT; 5% were Grade $\geq$ 3. Memory impairment occurred in 21% of patients; <1% of these events were Grade 3. Cognitive disorder occurred in 12% of patients; 1.2% of these events were Grade 3. Confusional state occurred in 6% of patients; <1% of these events were Grade 3. Amnesia occurred in 3% of patients; <1% of these events were Grade 3. Somnolence and speech disorder occurred in 2% of patients; none of these events were Grade 3. Other events occurred in less than 2% of patients.

The median time to onset of the first cognitive adverse reaction was 8.4 weeks (range: 1 day to 4 years). Among patients who experienced a cognitive effect of Grade 2 or worse (impacting activities of daily living), the median time to improvement to Grade 1 or complete resolution was 7.9 weeks. Overall, 2.7% of all patients who received AYVAKIT required permanent discontinuation for a cognitive adverse reaction, 13.5% required a dosage interruption, and 8.5% required dose reduction.

Systemic Mastocytosis

Cognitive adverse reactions occurred in 28% of 148 patients with systemic mastocytosis who received AYVAKIT; 3% were Grade $\geq$ 3. Memory impairment occurred in 16% of patients; all events were Grade 1 or 2. Cognitive disorder occurred in 10% of patients; <1% of these events were Grade 3. Confusional state occurred in 6% of patients; <1% of these events were Grade 3. Other events occurred in less than 2% of patients.

The median time to onset of the first cognitive adverse reaction was 13.3 weeks (range: 1 day to 1.8 years). Among patients who experienced a cognitive effect of Grade 2 or worse (impacting activities of daily living), the median time to improvement to Grade 1 or complete resolution was 8.1 weeks. Overall, 2% of all patients who received AYVAKIT required permanent discontinuation for a cognitive adverse reaction, 8.1% required a dosage interruption, and 8.8% required dose reduction.

5.3 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, AYVAKIT can cause fetal harm when administered to pregnant women. Oral administration of avapritinib during the period of organogenesis was teratogenic and embryotoxic in rats at exposures approximately 6.3 and 2.7 times the human exposure based on area under the curve (AUC) at the 200 mg and 300 mg dose, respectively. Advise pregnant women of the potential risk to a fetus. Advise females and males of reproductive potential to use effective contraception during treatment with AYVAKIT and for 6 weeks after the final dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Intracranial hemorrhage *[see Warnings and Precautions (5.1)]*
- Cognitive effects *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the WARNINGS AND PRECAUTIONS reflect exposure to AYVAKIT at 30 mg to 600 mg orally once daily in 749 patients enrolled in one of four clinicals trials conducted in patients with advanced malignancies and systemic mastocytosis, including NAVIGATOR, EXPLORER and PATHFINDER *[see Clinical Studies (14.1, 14.2)]*. These patients included 601 patients with GIST and 148 patients with systemic mastocytosis. Among the 749 patients receiving AYVAKIT, 46% were exposed for 6 months or longer and 23% were exposed for greater than 1 year.

Gastrointestinal Stromal Tumors

Unresectable or Metastatic GIST

The safety of AYVAKIT in patients with unresectable or metastatic GIST was evaluated in NAVIGATOR *[see Clinical Studies (14.1)]*. The trial excluded patients with history of cerebrovascular accident or transient ischemic attacks, known risk of intracranial bleeding, and metastases to the brain. Patients received AYVAKIT 300 mg or 400 mg orally once daily (n = 204). Among patients receiving AYVAKIT, 56% were exposed for 6 months or longer and 44% were exposed for greater than one year.

The median age of patients who received AYVAKIT was 62 years (range: 29 to 90 years), 60% were <65 years, 62% were male, and 69% were White. Patients had received a median of 3 prior kinase inhibitors (range: 0 to 7).

Serious adverse reactions occurred in 52% of patients receiving AYVAKIT. Serious adverse reactions occurring in ≥1% of patients who received AYVAKIT were anemia (9%), abdominal pain (3%), pleural effusion (3%), sepsis (3%), gastrointestinal hemorrhage (2%), vomiting (2%), acute kidney injury (2%), pneumonia (1%), and tumor hemorrhage (1%). Fatal adverse reactions occurred in 3.4% of patients. Fatal adverse reactions that occurred in more than one patient were sepsis and tumor hemorrhage (1% each).

Permanent discontinuation due to adverse reactions occurred in 16% of patients who received AYVAKIT. Adverse reactions requiring permanent discontinuation in more than one patient were fatigue, abdominal pain, vomiting, sepsis, anemia, acute kidney injury, and encephalopathy.

Dosage interruptions due to an adverse reaction occurred in 57% of patients who received AYVAKIT. Adverse reactions requiring dosage interruption in >2% of patients who received AYVAKIT were anemia, fatigue, nausea, vomiting, hyperbilirubinemia, memory impairment, diarrhea, cognitive disorder, and abdominal pain.

Dose reduction due to an adverse reaction occurred in 49% of patients who received AYVAKIT. Median time to dose reduction was 9 weeks. Adverse reactions requiring dosage reduction in more than 2% of patients who received AYVAKIT were fatigue, anemia, hyperbilirubinemia, memory impairment, nausea, and periorbital edema.

The most common adverse reactions (≥ 20%) were edema, nausea, fatigue/asthenia, cognitive impairment, vomiting, decreased appetite, diarrhea, hair color changes, increased lacrimation, abdominal

pain, constipation, rash, and dizziness. Table 3 summarizes the adverse reactions observed in NAVIGATOR.

Table 3. Adverse Reactions (≥ 10%) in Patients with GIST Receiving AYVAKIT in NAVIGATOR

Adverse Reactions	AYVAKIT N=204	
	All Grades %	Grade ≥ 3 %
General		
Edema[a]	72	2
Fatigue/asthenia	61	9
Pyrexia	14	0.5
Gastrointestinal		
Nausea	64	2.5
Vomiting	38	2
Diarrhea	37	4.9
Abdominal pain[b]	31	6
Constipation	23	1.5
Dyspepsia	16	0
Nervous System		
Cognitive impairment[c]	48	4.9
Dizziness	22	0.5
Headache	17	0.5
Sleep disorders[d]	16	0
Taste effects[e]	15	0
Mood disorders[f]	13	1
Metabolism and nutrition		
Decreased appetite	38	2.9
Eye		
Increased lacrimation	33	0
Skin and subcutaneous tissue		
Rash[g]	23	2.1
Hair color changes	21	0.5
Alopecia	13	-
Respiratory, thoracic and mediastinal		
Dyspnea	17	2.5
Pleural effusion	12	2
Investigations		
Weight decreased	13	1

*Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and 5.0

[a] Edema includes face swelling, conjunctival edema, eye edema, eyelid edema, orbital edema, periorbital edema, face edema, mouth edema, pharyngeal edema, peripheral edema, edema, generalized edema, localized edema, peripheral swelling, testicular edema.

[b] Abdominal pain includes abdominal pain, upper abdominal pain, abdominal discomfort, lower abdominal pain, abdominal tenderness, and epigastric discomfort.

[c] Cognitive impairment includes memory impairment, cognitive disorder, confusional state, disturbance in attention, amnesia, mental impairment, mental status changes, encephalopathy, dementia, abnormal thinking, mental disorder, and retrograde amnesia.
[d] Sleep disorders includes insomnia, somnolence, and sleep disorder.
[e] Taste effects include dysgeusia and ageusia.
[f] Mood disorders includes agitation, anxiety, depression, depressed mood, dysphoria, irritability, mood altered, nervousness, personality change, and suicidal ideation.
[g] Rash includes rash, rash maculo-papular, rash erythematous, rash macular, rash generalized, and rash papular.

Clinically relevant adverse reactions occurring in <10% of patients were:

Vascular: hypertension (8%)

Endocrine: thyroid disorders (hyperthyroid, hypothyroid) (3%)

Skin and subcutaneous: palmar-plantar erythrodysesthesia (1%)

Table 4 summarizes the laboratory abnormalities observed in NAVIGATOR.

Table 4. Select Laboratory Abnormalities (≥ 10%) Worsening from Baseline in Patients with GIST Receiving AYVAKIT in NAVIGATOR

Laboratory Abnormality	AYVAKIT[a] N=204	
	All Grades (%)	Grade ≥ 3 (%)
Hematology		
Decreased hemoglobin	81	28
Decreased leukocytes	62	5
Decreased neutrophils	43	6
Decreased platelets	27	0.5
Increased INR	24	0.6
Increased activated partial thromboplastin time	13	0
Chemistry		
Increased bilirubin	69	9
Increased aspartate aminotransferase	51	1.5
Decreased phosphate	49	13
Decreases potassium	34	6
Decreased albumin	31	2
Decreased magnesium	29	1
Increased creatinine	29	0
Decreased sodium	28	7
Increased alanine aminotransferase	19	0.5
Increased alkaline phosphatase	14	1

[a] The denominator used to calculate the rate varied from 154 to 201 based on the number of patients with a baseline value and at least one post-treatment value.

Advanced Systemic Mastocytosis

The safety of AYVAKIT in patients with AdvSM was evaluated in EXPLORER and PATHFINDER *[see Clinical Studies (14.2)]*. Patients received a starting dose of AYVAKIT ranging from 30 mg to 400 mg orally once daily (n = 131), including 80 patients who received the recommended starting dose of 200 mg once daily. Among patients receiving AYVAKIT, 70% were treated for 6 months or longer and 37% were exposed for greater than one year.

The median age of patients who received AYVAKIT was 68 years (range: 31 to 88 years), 38% were <65 years, 57% were male, and 88% were White.

Serious adverse reactions occurred in 34% of patients receiving the recommended starting dose of 200 mg once daily and in 50% of patients receiving AYVAKIT at all doses. Serious adverse reactions occurring in ≥1% of patients who received AYVAKIT were anemia (5%), subdural hematoma (4%), pleural effusion, ascites and pneumonia (3% each), acute kidney injury, gastrointestinal hemorrhage, intracranial hemorrhage, encephalopathy, gastric hemorrhage, large intestine perforation, pyrexia, and vomiting (2% each). Fatal adverse reactions occurred in 2.5% of patients receiving the recommended starting dose of 200 mg once daily and in 5.3% of patients receiving AYVAKIT at all doses. No specific adverse reaction leading to death was reported in more than one patient.

Permanent discontinuation due to adverse reactions occurred in 10% of patients receiving the recommended starting dose of 200 mg once daily and in 15% of patients who received AYVAKIT at all doses. Of patients receiving 200 mg once daily, subdural hematoma was the only adverse reaction requiring permanent discontinuation in more than one patient.

Dosage interruptions due to an adverse reaction occurred in 60% of patients receiving the recommended starting dose of 200 mg once daily and in 67% of patients who received AYVAKIT at all doses. Adverse reactions requiring dosage interruption in >2% of patients who received AYVAKIT at 200 mg once daily were thrombocytopenia, neutropenia, neutrophil count decreased, platelet count decreased, anemia, white blood cell decreased, cognitive disorder, blood alkaline phosphatase increased, and edema peripheral.

Dose reduction due to an adverse reaction occurred in 68% of patients receiving the recommended starting dose of 200 mg once daily and 70% of patients who received AYVAKIT at all doses. Median time to dose reduction was 1.7 months. Adverse reactions requiring dosage reduction in more than 2% of patients who received AYVAKIT at 200 mg once daily were thrombocytopenia, neutropenia, edema peripheral, neutrophil count decreased, platelet count decreased, periorbital edema, cognitive disorder, anemia, fatigue, arthralgia, blood alkaline phosphatase increased, and white blood cell count decreased.

The most common adverse reactions (≥ 20%) at all doses were edema, diarrhea, nausea, and fatigue/asthenia. Table 5 summarizes the adverse reactions observed in EXPLORER and PATHFINDER.

Table 5. Adverse Reactions (≥ 10%) in Patients with AdvSM Receiving AYVAKIT in EXPLORER and PATHFINDER

Adverse Reactions	AYVAKIT (200 mg once daily) N=80	
	All Grades %	Grade ≥ 3 %
General		
Edema[a]	79	5
Fatigue/asthenia	23	4
Gastrointestinal		
Diarrhea	28	1
Nausea	24	1
Vomiting	18	3
Abdominal pain[b]	14	1
Constipation	11	0
Nervous system		
Headache	15	0
Cognitive effects[c]	14	1
Taste effects[d]	13	0
Dizziness	13	0
Musculoskeletal and connective tissue		
Arthralgia	10	1
Respiratory, thoracic and mediastinal		
Epistaxis	11	0

*Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and 5.0
[a] Edema includes face swelling, eyelid edema, orbital edema, periorbital edema, face edema, peripheral edema, edema, generalized edema, and peripheral swelling.
[b] Abdominal pain includes abdominal pain, upper abdominal pain, and abdominal discomfort.
[c] Cognitive effects include memory impairment, cognitive disorder, confusional state, delirium, and disorientation.
[d] Taste effects include dysgeusia.

Clinically relevant adverse reactions occurring in <10% of patients were:

Cardiac: cardiac failure (2.5%), and cardiac failure congestive (1.3%)

Gastrointestinal: ascites (5%), gastrointestinal hemorrhage (1.3%), and large intestine perforation (1.3%)

Hepatobiliary: cholelithiasis (1.3%)

Infections and infestations: upper respiratory tract infection (6%), urinary tract infection (6%), and herpes zoster (2.5%)

Vascular: flushing (3.8%), hypertension (3.8%), hypotension (3.8%), and hot flush (2.5%)

Nervous: insomnia (6%)

Musculoskeletal and connective tissue: pain in extremity (6%)

Respiratory, thoracic and mediastinal: dyspnea (9%), and cough (2.5%)

Skin and subcutaneous tissue: rash[a] (8%), alopecia (9%), pruritus (8%), and hair color changes (6%)

Metabolism and nutrition: decreased appetite (8%)

Eye: lacrimation increased (9%)

Laboratory abnormality: decreased phosphate (9%)

[a]Grouped terms

Rash includes rash and rash maculo-papular

Table 6 summarizes the laboratory abnormalities observed in EXPLORER and PATHFINDER.

Table 6. Select Laboratory Abnormalities (≥ 10%) Worsening from Baseline in Patients with AdvSM Receiving AYVAKIT in EXPLORER and PATHFINDER

Laboratory Abnormality	AYVAKIT (200 mg once daily) N=80	
	All Grades (%)	Grade ≥ 3 (%)
Hematology		
Decreased platelets	64	21
Decreased hemoglobin	55	23
Decreased neutrophils	54	25
Decreased lymphocytes	34	11
Increased activated partial thromboplastin time	14	1
Increased lymphocytes	10	0
Chemistry		
Decreased calcium	50	3
Increased bilirubin	41	3
Increased aspartate aminotransferase	38	1
Decreased potassium	26	4
Increased alkaline phosphatase	24	5
Increased creatinine	20	0
Increased alanine aminotransferase	18	1
Decreased sodium	18	1
Decreased albumin	15	1
Decreased magnesium	14	1
Increased potassium	11	0

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on AYVAKIT

Strong and Moderate CYP3A Inhibitors

Coadministration of AYVAKIT with a strong or moderate CYP3A inhibitor increases avapritinib plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may increase the incidence and severity of adverse reactions of AYVAKIT. Avoid coadministration of AYVAKIT with strong or moderate CYP3A inhibitors. If coadministration of AYVAKIT with a moderate CYP3A inhibitor cannot be avoided, reduce the dose of AYVAKIT *[see Dosage and Administration (2.6)]*.

Strong and Moderate CYP3A Inducers

Coadministration of AYVAKIT with a strong or moderate CYP3A inducer decreases avapritinib plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may decrease efficacy of AYVAKIT. Avoid coadministration of AYVAKIT with strong or moderate CYP3A inducers.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, AYVAKIT can cause fetal harm when administered to a pregnant woman. There are no available data on AYVAKIT use in pregnant women. Oral administration of avapritinib to pregnant animals during the period of organogenesis was teratogenic and embryotoxic in rats at exposure levels approximately 6.3 and 2.7 times the human exposure based on AUC at the 200 mg and 300 mg dose, respectively *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In a reproductive toxicity study, administration of avapritinib to rats during the period of organogenesis resulted in decreased fetal body weights, post-implantation loss, and increases in visceral (hydrocephaly, septal defect, and stenosis of the pulmonary trunk) and skeletal (sternum) malformations at doses greater than or equal to 10 mg/kg/day (approximately 6.3 and 2.7 times the human exposure based on AUC at the 200 mg and 300 mg dose, respectively).

8.2 Lactation

Risk Summary

There are no data on the presence of avapritinib or its metabolites in human milk or the effects of avapritinib on the breastfed child or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with AYVAKIT and for 2 weeks following the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating AYVAKIT *[see Use in Specific Populations (8.1)]*.

Contraception

AYVAKIT can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Females

Advise females of reproductive potential to use effective contraception during treatment with AYVAKIT and for 6 weeks after the final dose.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with AYVAKIT and for 6 weeks after the final dose.

Infertility

Females

Based on findings from animal studies, AYVAKIT may adversely affect early embryogenesis in humans *[see Use in Specific Populations (8.1) and Nonclinical Toxicology (13.1)]*. In repeat dose toxicology studies of 6 months in rats, cystic degeneration of corpora lutea was not reversible within a two-month recovery period. Vaginal mucification was observed but not present at the end of recovery period. In a fertility study, females presented an increase in pre-implantation loss and in early resorptions with an overall decrease in viable embryos.

Males

Based on findings from animal studies, AYVAKIT may impair spermatogenesis *[see Nonclinical Toxicology (13.1)]*. There were no direct effects on fertility in rats. In repeat dose toxicology studies of 9 months in dogs, hypospermatogenesis was observed and it was not reversible within a two-month recovery period. In a fertility study in rats, a reduction in sperm production and testicular weight were observed. The reversibility of the effects on sperm production and testicular weight is unknown.

8.4 Pediatric Use

The safety and effectiveness of AYVAKIT in pediatric patients have not been established.

8.5 Geriatric Use

Of the 204 patients with unresectable or metastatic GIST who received AYVAKIT in NAVIGATOR, 40% were 65 years or older, while 6% were 75 years and older. Of the 131 patients with AdvSM who received AYVAKIT in EXPLORER and in PATHFINDER, 62% were 65 years or older, while 21% were 75 years and older. No overall differences in safety or efficacy were observed between these patients and younger adult patients.

8.6 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment [creatinine clearance (CLcr) 30 to 89 mL/min estimated by Cockcroft-Gault]. The recommended dose of AYVAKIT has not been established for patients with severe renal impairment (CLcr 15 to 29 mL/min) or end-stage renal disease (CLcr <15 mL/min) *[see Clinical Pharmacology (12.3)]*.

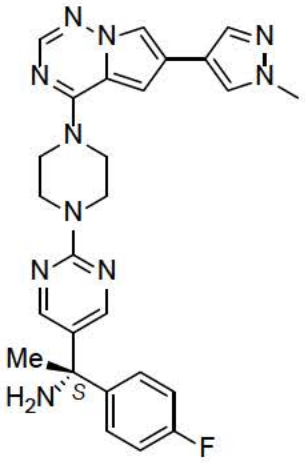
8.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild [total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or total bilirubin > 1 to 1.5 times ULN and any AST] or moderate [total bilirubin >1.5 to 3 times ULN and any AST] hepatic impairment. The recommended dose

of AYVAKIT has not been established for patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

Avapritinib is a kinase inhibitor with the chemical name (*S*)-1-(4-fluorophenyl)-1-(2-(4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)piperazin-yl)pyrimidin-5-yl)ethan-1-amine. The molecular formula is $C_{26}H_{27}FN_{10}$, and the molecular weight is 498.57 g/mol. Avapritinib has the following chemical structure:



The solubility of avapritinib in 0.1N HCl (pH 1.0) and buffer solutions at pH 2.5, 4.0, and 7.0 (at 25°C) is 3.6 mg/mL, 0.14 mg/mL, 0.07 mg/mL and <0.001 mg/mL respectively, indicating a decrease in solubility with increasing pH.

AYVAKIT (avapritinib) film-coated tablets for oral use are supplied with five strengths that contain 25 mg, 50 mg, 100 mg, 200 mg or 300 mg of avapritinib. The tablets also contain inactive ingredients: copovidone, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablet coating consists of polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. The blue printing ink, used only for avapritinib 100 mg, 200 mg and 300 mg strength tablets, contains ammonium hydroxide, black iron oxide, esterified shellac, FD&C blue 1, isopropyl alcohol, n-butyl alcohol, propylene glycol, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Avapritinib is a tyrosine kinase inhibitor that targets KIT D816V, PDGFRA and PDGFRA D842 mutants as well as multiple KIT exon 11, 11/17 and 17 mutants with half maximal inhibitory concentrations (IC_{50s}) less than 25 nM in biochemical assays. Certain mutations in PDGFRA and KIT can result in the autophosphorylation and constitutive activation of these receptors which can contribute to tumor and mast cell proliferation. Other potential targets for avapritinib include wild type KIT, PDGFRB, and CSFR1.

In cellular assays, avapritinib inhibited the autophosphorylation of KIT D816V with an IC_{50} of 4 nM, approximately 48-fold lower concentration than wild-type KIT. In cellular assays, avapritinib inhibited the proliferation in KIT mutant cell lines, including a murine mastocytoma cell line and a human mast cell leukemia cell line. Avapritinib also showed growth inhibitory activity in a xenograft model of murine mastocytoma with KIT exon 17 mutation.

Avapritinib inhibited the autophosphorylation of PDGFRA D842V, a mutation associated with resistance to approved kinase inhibitors, with an IC_{50} of 30 nM. Avapritinib also had anti-tumor activity in mice implanted with an imatinib-resistant patient-derived xenograft model of human GIST with activating KIT exon 11/17 mutations.

12.2 Pharmacodynamics

Exposure-Response Relationships

Based on the data from four clinicals trials conducted in patients with advanced malignancies and systemic mastocytosis, including NAVIGATOR, EXPLORER, and PATHFINDER, higher exposure was associated with increased risk of Grade ≥ 3 related adverse effects, any Grade pooled cognitive adverse effects, Grade ≥ 2 pooled cognitive adverse effects, and Grade ≥ 2 pooled edema adverse effects over the dose range of 30 mg to 400 mg (0.1 to 1.33 times the recommended dose for GIST and 0.15 to 2 times the recommended dose for AdvSM) once daily.

Based on exposure and efficacy data from EXPLORER and PATHFINDER (n=84), higher avapritinib exposure was associated with faster time to response over the dose range of 30 mg to 400 mg (0.15 to 2 times the recommended dose for AdvSM) once daily.

Cardiac Electrophysiology

The effect of AYVAKIT on the QTc interval was evaluated in an open-label, single-arm study in 27 patients administered dose of 300 mg or 400 mg (1.33 times the recommended 300 mg dose) once daily. No large mean increase in QTc (i.e.> 20 ms) was detected at the mean steady state maximum concentration (C_{max}) of 899 ng/mL.

12.3 Pharmacokinetics

Avapritinib C_{max} and AUC increased proportionally over the dose range of 30 mg to 400 mg once daily in patients with GIST (0.1 to 1.33 times the recommended 300 mg dose). Avapritinib C_{max} and AUC increased proportionally over the dose range of 200 mg to 400 mg once daily in patients with systemic mastocytosis (1 to 2 times the recommended 200 mg dose). Steady state concentration of avapritinib was reached by day 15 following daily dosing. Steady state pharmacokinetic parameters per recommended dosing regimen are described in Table 7.

Table 7. Steady State Pharmacokinetic Parameters of AYVAKIT Following Different Dosing Regimen

Dosing Regimen	**200 mg once daily (Systemic Mastocytosis)**	**300 mg once daily (GIST)**
Geometric Mean (CV%) steady state C_{max} (ng/mL)	377 (62%, n=18)	813 (52%, n=110)
Geometric Mean (CV%) steady state AUC_{0-24h} (h•ng/mL)	6600 (54%, n=16)	15400 (48%, n=110)
Mean accumulation ratio	6.41 (n=9)	3.82 (n=34)

Absorption

The median time to peak concentration (T_{max}) ranged from 2 to 4 hours following single doses of avapritinib 30 mg to 400 mg in patients with GIST and single doses of avapritinib 30 mg to 300 mg in patients with systemic mastocytosis.

Effect of Food

The C_{max} of avapritinib was increased by 59% and the $AUC_{0\text{-}INF}$ was increased by 29% when AYVAKIT was taken with a high-calorie, high-fat meal (approximately 909 calories, 58 grams carbohydrate, 56 grams fat and 43 grams protein) compared to those in the fasted state.

Distribution

The mean apparent volume of distribution of avapritinib is 1200 L (43%) at 300 mg for patients with GIST, and 1900 L (43%) at 200 mg in patients with systemic mastocytosis. In vitro protein binding of avapritinib is 98.8% and is independent of concentration. The blood-to-plasma ratio is 0.95.

Elimination

The mean plasma elimination half-life of avapritinib was 32 hours to 57 hours following single doses of avapritinib 30 mg to 400 mg (0.1 to 1.33 times the recommended 300 mg dose) in patients with GIST, and 20 hours to 39 hours following single doses of avapritinib 30 mg to 400 mg (0.15 to 2 times the recommended 200 mg dose) in patients with systemic mastocytosis. The steady state mean apparent oral clearance of avapritinib is 21.8 L/h (12%) at 300 mg for patients with GIST, and 40.3 L/h (86%) at 200 mg in patients with systemic mastocytosis.

Metabolism

Avapritinib is primarily metabolized by CYP3A4, CYP3A5 and to a lesser extent by CYP2C9 in vitro. Following a single oral dose of approximately 310 mg of radiolabeled avapritinib to healthy subjects, unchanged avapritinib (49%) and its metabolites M690 (hydroxy glucuronide; 35%) and M499 (oxidative deamination; 14%) were the major circulating compounds. The formation of the glucuronide M690 is catalyzed mainly by UGT1A3. Following oral administration of AYVAKIT 300 mg once daily in patients, the steady state AUC of M499 is approximately 80% of the AUC of avapritinib. M499 is not likely to contribute to efficacy at the recommended dose of avapritinib.

Excretion

Following a single oral dose of approximately 310 mg of radiolabeled avapritinib to healthy subjects, 70% of the radioactive dose was recovered in feces (11% unchanged) and 18% in urine (0.23% unchanged).

Specific Populations

No clinically significant differences in the pharmacokinetics of avapritinib were observed based on age (18 to 90 years), sex, race (White, Black, or Asian), body weight (39.5 to 156.3 kg), mild to moderate (CLcr 30 to 89 mL/min estimated by Cockcroft-Gault) renal impairment, or mild (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1 to 1.5 times ULN and any AST) to moderate (total bilirubin > 1.5 to 3 times ULN and any AST) hepatic impairment. The effect of severe renal impairment (CLcr 15 to 29 mL/min), end-stage renal disease (CLcr < 15 mL/min), or severe hepatic impairment (total bilirubin > 3 times ULN and any AST) on the pharmacokinetics of avapritinib is unknown.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Effect of Strong and Moderate CYP3A Inhibitors on Avapritinib: Coadministration of AYVAKIT 300 mg once daily with itraconazole 200 mg once daily (a strong CYP3A inhibitor) is predicted to increase avapritinib AUC by 600% at steady state.

Coadministration of AYVAKIT 300 mg once daily with fluconazole 200 mg once daily (a moderate CYP3A inhibitor) is predicted to increase avapritinib AUC by 210% at steady state *[see Drug Interactions (7.1)]*.

Effect of Strong and Moderate CYP3A Inducers on Avapritinib: Coadministration of AYVAKIT 400 mg as a single dose with rifampin 600 mg once daily (a strong CYP3A inducer) decreased avapritinib C_{max} by 74% and $AUC_{0\text{-}INF}$ by 92%.

Coadministration of AYVAKIT 300 mg once daily with efavirenz 600 mg once daily (a moderate CYP3A inducer) is predicted to decrease avapritinib C_{max} by 55% and AUC by 62% at steady state *[see Drug Interactions (7.1)]*.

Effect of Acid-Reducing Agents on Avapritinib: No clinically significant differences in the pharmacokinetics of avapritinib were identified when coadministered with gastric acid reducing agents in patients with GIST and AdvSM.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: In vitro studies indicate that avapritinib is a time-dependent inhibitor as well as an inducer of CYP3A at clinically relevant concentrations.

Avapritinib is an inhibitor of CYP2C9 at clinically relevant concentrations. Avapritinib is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C19, or CYP2D6 at clinically relevant concentrations.

Avapritinib is not an inducer of CYP1A2 or CYP2B6. Avapritinib is a substrate of CYP3A.

M499 is an inhibitor of CYP3A, CYP2C8, or CYP2C9 at clinically relevant concentrations. M499 is not an inhibitor of CYP1A2, CYP2B6, CYP2C19, or CYP2D6 at clinically relevant concentrations.

Transporter Systems: Avapritinib is an inhibitor of P-glycoprotein (P-gp), intestinal BCRP, MATE1, MATE2-K, and BSEP, but not an inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, OCT1, or OCT2. Avapritinib is not a substrate of P-gp or BCRP, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K and BSEP. The effect of M499 on transporter systems is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with avapritinib have not been conducted. Avapritinib was not mutagenic in vitro in the bacterial reverse mutation assay (Ames test). Avapritinib was positive in the in vitro chromosome aberration test in human peripheral blood lymphocytes but negative in the in vivo rat bone marrow micronucleus test, and overall non-genotoxic.

Avapritinib may impair spermatogenesis and adversely affect early embryogenesis. Reduction in sperm production and testicular weight were observed in male rats and hypospermatogenesis in dogs administered avapritinib at exposure of 1 to 5 times and 1 time the 200 mg human dose, respectively. There were no direct effects on fertility in rats of either sex. Avapritinib partitioned into seminal fluids up to 0.5 times the concentration found in human plasma at 200 mg. In female rats there was an increase in pre-implantation loss at the dose of 20 mg/kg/day (12.6 times the human exposure at 200 mg) and in early

resorptions at doses ≥ 10 mg/kg (6.3 times the human exposure at 200 mg) with an overall decrease in viable embryos at doses ≥ 10 mg/kg. Cystic degeneration of corpora lutea and vaginal mucification was also observed in female rats administered avapritinib for up to 6 months at doses greater than or equal to 3 mg/kg day (approximately 3.0 times the human exposure based on AUC at the 200 mg dose).

13.2 Animal Toxicology and/or Pharmacology

In repeat dose toxicology studies, administration of avapritinib to rats and dogs for up to 3 months resulted in tremors at doses greater than or equal to 30 mg/kg/day (approximately 1.5 times the human exposure based on AUC at the 300 mg dose). Hemorrhage in the brain and spinal cord and choroid plexus edema in the brain occurred in dogs at doses greater than or equal to 7.5 mg/kg/day (approximately 0.4 times the human exposure based on AUC at the 300 mg dose), but were not observed in a 9-month study at 5 mg/kg/day.

An in vitro phototoxicity study in 3T3 mouse fibroblasts and an in vivo phototoxicity study in pigmented rats demonstrated that avapritinib has a slight potential for phototoxicity.

14 CLINICAL STUDIES

14.1 Gastrointestinal Stromal Tumors

The efficacy of AYVAKIT was demonstrated in NAVIGATOR (NCT02508532), a multi-center, single-arm, open-label clinical trial. Eligible patients were required to have a confirmed diagnosis of GIST and an ECOG performance status (PS) of 0 to 2. Patients received AYVAKIT 300 mg or 400 mg (1.33 times the recommended dose) orally once daily until disease progression or unacceptable toxicity. The trial initially enrolled patients at a starting dose of 400 mg, which was later reduced to the recommended dose of 300 mg due to toxicity. As there was no apparent difference in overall response rate (ORR) between patients who received 300 mg daily compared to those who received 400 mg daily, these patients were pooled for the efficacy evaluation. The major efficacy outcome measure was ORR based on disease assessment by independent radiological review using modified RECIST v1.1 criteria, in which lymph nodes and bone lesions were not target lesions and progressively growing new tumor nodules within a pre-existing tumor mass was progression. An additional efficacy outcome measure was duration of response (DOR).

Patients with GIST Harboring a PDGFRA Exon 18 Mutation

Patients with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation were identified by local or central assessment using a PCR- or NGS-based assay. The assessment of efficacy was based on a total of 43 patients, including 38 patients with PDGFRA D842V mutations. The median duration of follow up for patients with PDGFRA exon 18 mutations was 10.6 months (range: 0.3 to 24.9 months).

The study population characteristics were median age of 64 years (range: 29 to 90 years), 67% were male, 67% were White, 93% had an ECOG PS of 0-1, 98% had metastatic disease, 53% had largest target lesion >5 cm, and 86% had prior surgical resection. The median number of prior kinase inhibitors was 1 (range: 0 to 5).

Efficacy results in patients with GIST harboring PDGFRA exon 18 mutations including the subgroup of patients with PDGFRA D842V mutations enrolled in NAVIGATOR are summarized in Table 8.

Table 8. Efficacy Results for Patients with GIST Harboring PDGFRA Exon 18 Mutations in NAVIGATOR

Efficacy Parameter	**PDGFRA exon 18[1] N = 43**	**PDGFRA D842V N = 38**
Overall Response Rate (95% CI)	84% (69%, 93%)	89% (75%, 97%)
Complete Response, n (%)	3 (7%)	3 (8%)
Partial Response, n (%)	33 (77%)	31 (82%)
Duration of Response	n=36	n=34
Median in months (range)	NR (1.9+, 20.3+)	NR (1.9+, 20.3+)
Patients with DOR ≥ 6-months, n (%)*	22 (61%)	20 (59%)

Abbreviations: CI=confidence interval; NR=not reached; NE=not estimable
+ Denotes ongoing response
[1] Exon 18 mutations other than D842V included in this population are: deletion of D842_H845 (n=3); D842Y (n=1); and deletion of D842_H845 with insertion of V (n=1).
* 11 patients with an ongoing response were followed < 6 months from onset of response.

14.2 Advanced Systemic Mastocytosis

The efficacy of AYVAKIT was demonstrated in EXPLORER (NCT02561988) and PATHFINDER (NCT03580655), two multi-center, single-arm, open-label clinical trials. Response-evaluable patients include those with a confirmed diagnosis of AdvSM per World Health Organization (WHO) and deemed evaluable by modified international working group-myeloproliferative neoplasms research and treatment-European competence network on mastocytosis (IWG-MRT-ECNM) criteria at baseline as adjudicated by an independent central committee, who received at least 1 dose of AYVAKIT, had at least 2 post-baseline bone marrow assessments, and had been on study for at least 24 weeks, or had an end of study visit. All enrolled patients had an ECOG performance status (PS) of 0 to 3 and 91% had a platelet count of ≥ 50 X 10^9/L prior to initiation of therapy.

Patients enrolled in EXPLORER received a starting dose of AYVAKIT ranging from 30 mg to 400 mg (0.15 – 2 times the recommended dose) orally once daily. In PATHFINDER, patients were enrolled at a starting dose of 200 mg orally once daily. The efficacy of AYVAKIT in the treatment of AdvSM was based on overall response rate (ORR) in 53 patients with AdvSM dosed at up to 200 mg daily per modified IWG-MRT-ECNM criteria as adjudicated by the central committee. Additional efficacy outcome measures were duration of response (DOR), time to response, and changes in individual measures of mast cell burden.

The median duration of follow up for these patients was 11.6 months (95% confidence interval: 9.9, 16.3).

The study population characteristics were median age of 67 years (range: 37 to 85 years), 58% were male, 98% were White, 68% had an ECOG PS of 0-1, 32% had an ECOG PS of 2-3, 40% had ongoing corticosteroid therapy use for AdvSM at baseline, 66% had prior antineoplastic therapy, 47% had received prior midostaurin, and 94% had a D816V mutation. The median bone marrow mast cell infiltrate was 50%, the median serum tryptase level was 255.8 ng/mL, and the median KIT D816V mutant allele fraction was 12.2%.

Efficacy results in patients with AdvSM enrolled in EXPLORER and PATHFINDER are summarized in Table 9.

Table 9. Efficacy Results for Patients with AdvSM in EXPLORER and PATHFINDER

	All evaluable patients	**ASM**	**SM-AHN**	**MCL**
Overall Response Rate[1], % per modified IWG-MRT-ECNM (95% CI[2])	**N=53** 57 (42, 70)	**N=2** 100 (16, 100)	**N=40** 58 (41, 73)	**N=11** 45 (17, 77)
Complete Remission with full or partial hematologic recovery, %	28	50	33	9
Partial Remission, %	28	50	25	36
Clinical Improvement, %	15	0	20	0
Stable Disease, %	19	0	13	45

Abbreviations: CI=confidence interval; CR=complete remission; CRh=complete remission with partial recovery of peripheral blood counts; PR=partial remission

[1] Overall Response Rate (ORR) per modified IWG-MRT-ECNM is defined as patients who achieved a CR, CRh or PR (CR + CRh + PR)

[2] Clopper–Pearson confidence interval

For all evaluable patients, the median duration of response was 38.3 months (95% confidence interval: 19, not estimable) and the median time to response was 2.1 months.

In the subgroup of patients with MCL, the efficacy of AYVAKIT was based on complete remission (CR).

16 HOW SUPPLIED/STORAGE AND HANDLING

AYVAKIT (avapritinib) tablets are supplied as follows:

- 25 mg, round, white film-coated tablet with debossed text. One side reads “BLU” and the other side reads “25”; available in bottles of 30 tablets (NDC 72064-125-30).
- 50 mg, round, white film-coated tablet with debossed text. One side reads “BLU” and the other side reads “50”; available in bottles of 30 tablets (NDC 72064-150-30).
- 100 mg, round, white film-coated tablet, printed with blue ink “BLU” on one side and “100” on the other side; available in bottles of 30 tablets (NDC 72064-110-30).
- 200 mg, capsule shaped, white film-coated tablet, printed with blue ink “BLU” on one side and “200” on the other side; available in bottles of 30 tablets (NDC 72064-120-30).
- 300 mg, capsule shaped, white film-coated tablet, printed with blue ink “BLU” on one side and “300” on the other side; available in bottles of 30 tablets (NDC 72064-130-30).

Store at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Intracranial Hemorrhage

Advise patients to contact their healthcare provider immediately if experiencing neurological signs and symptoms that may be associated with intracranial hemorrhage (i.e., severe headache, vomiting, drowsiness, dizziness, confusion, slurred speech, or paralysis) *[see Warnings and Precautions (5.1)]*.

Inform patients with AdvSM of the need to monitor platelet counts before and during treatment *[see Warnings and Precautions (5.1)]*.

Cognitive Effects

Advise patients and caretakers to notify their healthcare provider if they experience new or worsening cognitive symptoms. Advise patients not to drive or operate hazardous machinery if they are experiencing cognitive adverse reactions *[see Warnings and Precautions (5.2)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception during treatment with AYVAKIT and for 6 weeks after the final dose *[see Use in Specific Populations (8.3)]*.

Advise males with female partners of reproductive potential to use effective contraception during treatment with AYVAKIT and for 6 weeks after the final dose *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*.

Lactation

Advise women not to breastfeed during treatment with AYVAKIT and for 2 weeks following the final dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise females of reproductive potential that AYVAKIT may impair fertility *[see Use in Specific Populations (8.3)]*. Advise males of reproductive potential that AYVAKIT may decrease sperm production *[see Use in Specific Populations (8.3)]*.

Drug Interactions

Advise patients and caregivers to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products *[see Drug Interactions (7.1)]*.

Administration

Advise patients to take AYVAKIT on an empty stomach, at least 1 hour before or at least 2 hours after a meal *[see Dosage and Administration (2.4)]*.

Manufactured for:

Blueprint Medicines Corporation, Cambridge, MA 02139, USA

PATIENT INFORMATION
AYVAKIT™ (aye' vah kit)
(avapritinib)
tablets, for oral use

What is AYVAKIT?

AYVAKIT is a prescription medicine used to treat adults with:

- a certain type of stomach, bowel, or esophagus cancer called gastrointestinal stromal tumor (GIST) that cannot be treated with surgery or that has spread to other parts of the body (metastatic), and that is caused by certain abnormal platelet-derived growth factor receptor alpha (PDGFRA) genes. Your healthcare provider will perform a test to make sure that you have this abnormal PDGFRA gene and that AYVAKIT is right for you.
- advanced systemic mastocytosis (AdvSM), including aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).

  AYVAKIT is not recommended for the treatment of AdvSM in people with low platelet counts (less than 50 X 10^9/L).

It is not known if AYVAKIT is safe and effective in children.

Before taking AYVAKIT, tell your healthcare provider about all of your medical conditions, including if you:

- have low platelet counts
- bulging or weakening of a blood vessel wall (aneurysm) or history of bleeding in your brain
- history of stroke within the last year
- are pregnant or plan to become pregnant. AYVAKIT can cause harm to your unborn baby.
  Females who are able to become pregnant:
  - Your healthcare provider should do a pregnancy test before you start treatment with AYVAKIT.
  - You should use effective birth control (contraception) during treatment with AYVAKIT and for 6 weeks after the final dose of AYVAKIT. Talk to your healthcare provider about birth control methods that may be right for you.
  - Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with AYVAKIT.

  Males with female partners who are able to become pregnant should use effective birth control (contraception) during treatment and for 6 weeks after the final dose of AYVAKIT.
- are breastfeeding or plan to breastfeed. It is not known if AYVAKIT passes into your breast milk. Do not breastfeed during treatment with AYVAKIT and for at least 2 weeks after the final dose of AYVAKIT. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. AYVAKIT may affect the way other medicines work, and certain other medicines may affect how AYVAKIT works. Talk to your healthcare provider prior to starting a new medicine.

How should I take AYVAKIT?

- Take AYVAKIT exactly as your healthcare provider tells you to take it.
- Do not change your dose or stop taking AYVAKIT unless your healthcare provider tells you to.
- Take AYVAKIT 1 time each day.
- Take AYVAKIT tablet(s) on an empty stomach at least 1 hour before or at least 2 hours after a meal.
- If you miss a dose of AYVAKIT, take it as soon as you remember unless your next scheduled dose is due within 8 hours. Take the next dose at your regular time.
- If you vomit after taking a dose of AYVAKIT, do not take an extra dose. Take your next dose at your next scheduled time.

What should I avoid while taking AYVAKIT?

- **Do not** drive or operate heavy machinery if you have confusion or trouble thinking during treatment with AYVAKIT.

What are the possible side effects of AYVAKIT?
AYVAKIT may cause serious side effects, including:

- **Bleeding in your brain.** Serious bleeding in the brain may happen during treatment with AYVAKIT and may lead to death. Stop taking AYVAKIT and tell your healthcare provider right away if you develop any symptoms such as severe headache, vomiting, drowsiness, dizziness, confusion, or severe weakness on one or more side of your body.

  If you have AdvSM, your healthcare provider will check your platelet counts before and during treatment with AYVAKIT.
- **Cognitive effects.** Cognitive side effects are common with AYVAKIT and can be severe. Tell your healthcare provider if you develop any new or worsening cognitive symptoms including:
  - forgetfulness
  - confusion
  - getting lost
  - trouble thinking
  - drowsiness
  - trouble staying awake (somnolence)
  - word finding problems
  - seeing objects or hearing things that are not there (hallucinations)
  - change in mood or behavior

The most common side effects of AYVAKIT in people with GIST include:

- fluid retention or swelling
- nausea
- tiredness
- muscle weakness
- vomiting
- decreased appetite
- diarrhea
- increased eye tearing
- stomach area (abdominal) pain
- constipation
- rash
- dizziness
- hair color changes
- changes in certain blood tests

The most common side effects of AYVAKIT in people with AdvSM include:

- fluid retention or swelling
- diarrhea
- nausea
- tiredness
- changes in certain blood tests

Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with AYVAKIT if you develop certain side effects.

AYVAKIT may cause fertility problems in females and may decrease sperm production in males, which may affect your ability to have a child. Talk to your healthcare provider if this is a concern for you.

These are not all of the possible side effects of AYVAKIT.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AYVAKIT?

- Store AYVAKIT tablets at room temperature between 68°F to 77°F (20°C to 25°C).

Keep AYVAKIT and all medicines out of the reach of children.

General information about the safe and effective use of AYVAKIT.

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information leaflet. Do not take AYVAKIT for a condition for which it was not prescribed. Do not give AYVAKIT to other people, even if they have the same condition that you have. It may harm them. You can ask your healthcare provider or pharmacist for more information about AYVAKIT that is written for health professionals.

What are the ingredients in AYVAKIT?

Active ingredient: avapritinib

Inactive ingredients: copovidone, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose.
Film coat: polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.
Blue printing ink (100 mg, 200 mg and 300 mg tablets only): ammonium hydroxide, black iron oxide, esterified shellac, FD&C blue 1, isopropyl alcohol, n-butyl alcohol, propylene glycol, and titanium dioxide.

Manufactured for: Blueprint Medicines Corporation, Cambridge, MA 02139, USA

For more information, go to www.AYVAKIT.com or call 1-888-258-7768.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: June/2021

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212608Orig1s006

SUMMARY REVIEW

M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: June 16, 2021

From: Albert Deisseroth
Deputy Division Director
Division of Nonmalignant Hematology (DNH) OCHEN OND CDER

Subject: Summary Review for Avapritinib (Ayvakit®)
NDA 212608 Supplement 006

The regulatory recommendation of the Deputy Director of DNH for NDA 212608 S-006 is for regular approval. The Summary Review of NDA 212608 S-006 from the Deputy Director of the DNH has been incorporated into the Cross Discipline Team Leader (CDTL) Review of NDA 212608 Supplement 006 uploaded on June 16, 2021.

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

/s/

ALBERT B DEISSEROTH
06/16/2021 12:02:22 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212608Orig1s006

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross Discipline Team Leader Review

Application Type	Efficacy Supplement
Application Number	212608 Supplement 006
Priority or Standard	Priority
Submit Date(s)	December 16, 2020
Received Date(s)	December 16, 2020
PDUFA Goal Date	June 16, 2021
Division/Office	Division of Nonmalignant Hematology (DNH)/Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)
Reviewer Name(s)	Andrew Dmytrijuk, M.D. (NDA 212608 S006 Efficacy Reviewer) Qin Ryan, M.D./Ph.D. (NDA 212608 S006 Safety Reviewer) and Albert Deisseroth, M.D./Ph.D. (Clinical Team Leader and CDTL)
Review Completion Date	June 14, 2021
Established/Proper Name	Avapritinib
(Proposed) Trade Name	Ayvakit®
Applicant	Blueprint Medicines Corporation
Dosage Form(s)	Tablet
Applicant Proposed Dosing Regimen(s)	200 mg Administered Orally Once Daily
Applicant Proposed Indication(s)/Population(s)	Ayvakit® is indicated for the treatment of adult patients with advanced systemic mastocytosis (AdvSM) (b) (4)
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s)	The recommended indication is avapritinib for the treatment of adult patients with AdvSM. AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).

Teams	Reviewers
Primary Clinical and Safety Review	Andrew Dmytrijuk, MD and Qin Ryan, MD, PhD
Pharmacology/Toxicology	Bo Yeon Lee, PhD, Pedro Del Valle, PhD, and Todd Bourcier, PhD
Labeling	Virginia Kwitkowski
CMC	Sarah C. Zimmermann, PhD and Ramesh Raghavachari PhD
Biometrics (Efficacy) Review	Xiaoyu Cai, PhD, Yeh-Fong Chen, PhD, and Thomas Gwise, PhD
Clinical Pharmacology	Robyn Konicki PharmD and Lian Ma, PhD
Regulatory Program Manager	Brittany Garr-Colon

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Avapritinib (Ayvakit®) is an orally administered inhibitor of the KIT exon 17 D816V Mutation. The proposed indication for avapritinib is for the treatment of adult patients with advanced systemic mastocytosis (AdvSM). AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematologic neoplasm (SM-AHN) and mast cell leukemia (MCL). The proposed dose of avapritinib for the treatment of patients with AdvSM is 200 mg administered orally once daily until unacceptable toxicity or disease progression.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The pooled efficacy analysis from Studies BLU-285-2101 and BLU-285-2202 based on the response evaluable patient group shows that 2/2 patients with ASM achieved a response during the treatment period (ORR 100%; 95% CI=16%, 100%). There were 17/32 patients in the response evaluable group with SM-AHN who achieved a response during the treatment period (ORR of 53%; 95% CI=34%, 71%). The median duration of response was not reached at the time of data cut-off. Patients with AdvSM (ASM or SM-AHN) are considered to have a durable response to therapy. Also, the median time to response was 4.6 months among patients with ASM and the median time to response was 2 months among patients with SM-AHN.

1.3. Benefit-Risk Assessment

The most common AEs reported in ≥ 20% of patients with AdvSM include edema, diarrhea, nausea, fatigue/asthenia, vomiting, cognitive effects, and abdominal pain. Important clinical AEs associated with avapritinib therapy include intracranial bleeding and cognitive adverse effects. In patients with AdvSM who received avapritinib at 200 mg daily, intracranial hemorrhage occurred in 2 of 75 patients (3%) who had platelet counts ≥ 50,000/µL prior to initiation of therapy and in 3 of 80 patients (4%) regardless of platelet counts prior to initiation of therapy. Cognitive adverse reactions occurred in 28% of 148 patients of which 3% were Grade > 3. Avapritinib offers patients with AdvSM a treatment option other than midostaurin. The Applicant has attempted to reduce the risk of intracranial bleeding or cognitive impairment by recommending frequent clinical monitoring of patients and avapritinib dosing adjustments.

Benefit-Risk Integrated Assessment

All subtypes of SM are rare and as a group the incidence of SM is estimated to be 5-10 patients per million people. KIT D816V mutations mediate ligand independence in AdvSM. Chronic inflammatory mediator release is associated with cachexia, chronic gastrointestinal symptoms, diffuse musculoskeletal pains, tissue remodeling, fibrosis, and end organ damage. Therefore, ASM, SM-AHN and MCL, i.e., advanced systemic mastocytosis (AdvSM), are serious and potentially fatal conditions. Few treatment options are currently available for patients with AdvSM, i.e., imatinib and midostaurin. Treatment with imatinib requires prior determination of the D816V c-Kit mutation status. For patients with ASM associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFRα, a starting dose of 100 mg/day is recommended for patients' treatment with imatinib which limits the types of patients that may be imatinib therapy candidates. The pooled efficacy analysis from Studies BLU-285-2101 and BLU-285-2202, which are based on patients in the response evaluable patient group, shows that 2/2 patients with ASM achieved a response during the treatment period (ORR 100%; 95% CI=16%, 100%). There were 17/32 patients in the response evaluable group with SM-AHN who achieved response during the treatment period (ORR of 53%; 95% CI=34%, 71%). The median duration of response was not reached at the time of data cut-off. Therefore, patients with AdvSM (ASM or SM-AHN) were considered to have a durable response to therapy. Also, the median time to response was 4.6 months among patients with ASM and the median time to response was 2 months among patients with SM-AHN. The most common AEs reported in ≥ 20% patients with AdvSM include edema, diarrhea, nausea, fatigue/asthenia, vomiting, cognitive effects, and abdominal pain. Important clinical AEs associated with avapritinib therapy include intracranial bleeding and cognitive adverse effects. In patients with AdvSM who received avapritinib at 200 mg daily, intracranial hemorrhage occurred in 2 of 75 patients (3%) who had platelet counts ≥ 50,000/µL prior to initiation of therapy and in 3 of 80 patients (4%) regardless of platelet counts. Cognitive adverse reactions occurred in 28% of 148 patients of which 3% were Grade > 3. Avapritinib offers patients with AdvSM another treatment option. The risk of intracranial or cognitive impairment is mitigated by recommendation for frequent patient clinical monitoring and avapritinib dosing adjustments.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• All subtypes of SM are rare and as a group the incidence of SM is estimated to be 5-10 patients per million people. • KIT D816V mutations mediate ligand independence in AdvSM. • Chronic inflammatory mediator release is associated with cachexia,	• ASM, SM-AHN and MCL, i.e., advanced systemic mastocytosis (AdvSM), are serious and potentially fatal conditions.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	chronic gastrointestinal symptoms, diffuse musculoskeletal pains, tissue remodeling, fibrosis, and end organ damage	
Current Treatment Options	• Imatinib is a kinase inhibitor indicated for the treatment of adult patients with ASM without the D816V c-Kit mutation or with c-Kit mutational status unknown. • Midostaurin is a kinase inhibitor indicated for the treatment of adult patients with ASM, SM-AHN, MCL.	• Currently only two treatment options are approved for treatment of patients with AdvSM, i.e., imatinib and midostaurin.
Benefit	• The pooled efficacy analysis from Studies BLU-285-2101 and BLU-285-2202, which are based on patients in the response evaluable patient group, shows that 2/2 patients with ASM achieved a response during the treatment period (ORR 100%; 95% CI=16%, 100%). There were 17/32 patients in the response evaluable group with SM-AHN who achieved a response during the treatment period (ORR of 53%; 95% CI=34%, 71%). The median duration of response was not reached at the time of data cut-off.	• Patients with AdvSM (ASM or SM-AHN) had a response to therapy. • The median time to response was 4.6 months among patients with ASM and the median time to response was 2 months among patients with SM-AHN.
Risk and Risk Management	• The most common AEs reported in ≥ 20% patients with AdvSM include edema, diarrhea, nausea, fatigue/asthenia, vomiting, cognitive effects, and abdominal pain. • Important clinical AEs associated with avapritinib therapy include intracranial bleeding and cognitive adverse effects. • In patients with AdvSM who received avapritinib at 200 mg daily, intracranial hemorrhage occurred in 2 of 75 patients (3%) who had platelet counts ≥ 50,000/µL prior to initiation of therapy and in 3 of 80 patients (4%) regardless of platelet counts. • Cognitive adverse reactions occurred in 28% of 148 patients of which	• Avapritinib offers patients with AdvSM another treatment option. • AdvSM is a serious and potentially fatal disease. • The risk of intracranial bleeding or cognitive impairment is mitigated by recommendation for frequent patient clinical monitoring and avapritinib dosing adjustments.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	3% were Grade > 3.	

The recommendations of all the review disciplines as to whether their reviews support an approval, are summarized in Table 1 below.

Table 1: Recommendations of All the Review Disciplines

CMC	Approval
Non-clinical	Approval
Clinical Pharm	Approval
Biostatics (Efficacy)	Approval
Clinical (Safety)	Approval

CDTL table

Regulatory Recommendation: Approval of avapritinib for treatment of adults with ASM and SM-AHN

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

X	The patient experience data that was submitted as part of the application includes:	Section where discussed, if applicable
	X Clinical outcome assessment (COA) data, including the Total Symptom Score assessed by the AdvSM-SAF TSS tool, Patient's Global Impression of Symptom Severity (PGIS) score and EORTC QLQ-C30 global health status score.	Section 5.3.5.2
	X Patient reported outcome (PRO): AdvSM-SAF TSS tool, Patient's Global Impression of Symptom Severity (PGIS) score and EORTC QLQ-C30 global health status score	Section 5.3.5.2. These endpoints were considered exploratory. Dr. Xiaoyu Cai (Statistical Reviewer in the Division of Biometrics IX) states in the review of the avapritinib application for the AdvSM indication under NDA 212608 supporting document 80, a letter date December 16, 2020 (received December 16, 2020) that efficacy claims cannot be made in the PRO outcomes assessed in studies 2101 and 2202 because the studies did not have a control arm for meaningful comparison. Any PRO results are only exploratory. I agree with Dr. Cai's review and recommendation.
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	Not applicable
	□ Patient-focused drug development or other stakeholder meeting summary reports	Not applicable
	□ Observational survey studies designed to capture patient experience data	Not applicable

	□ Natural history studies	Not applicable
	□ Patient preference studies (e.g., submitted studies or scientific publications)	Not applicable
	□ Other: (Please specify)	Not applicable
□	Patient experience data that were not submitted in the application, but were considered in this review: *Reviewer comment: Not applicable*	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Systemic mastocytosis (SM) is comprised of five clinical subtypes, i.e., indolent systemic mastocytosis (ISM), smoldering systemic mastocytosis (SSM), aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematologic neoplasm (SM-AHN) and mast cell leukemia (MCL). ISM and SSM usually have median survival measured in decades while ASM, SM-AHN and MCL have a shorter median survival measured in months to years. As such, the term "advanced systemic mastocytosis" (AdvSM) is used to collectively refer to ASM, SM-AHN, and MCL. All subtypes of SM are rare and as a group the incidence of SM is estimated to be 5-10 patients per million people (Horny, 2008).

KIT D816V mutations mediate ligand independence in AdvSM (Verstovsek, 2013). KIT 816V mutation leads to constitutive phosphorylation and activation of KIT tyrosine kinase and subsequent transformation of mast cells into malignant clones (Longley, 1999). Avapritinib is an orally administered small molecule inhibitor of KIT D816V. Avapritinib is being developed under IND 124159 for the treatment of SM. Avapritinib is also being developed under IND 125379 for the treatment of patients with gastrointestinal stromal tumors (GIST).

SM is characterized by the presence of fixed accumulations of mast cells in the skin which may present as urticaria pigmentosa (UP) and other types of urticaria and skin problems. ASM, SM-AHN and MCL, i.e., advanced systemic mastocytosis (AdvSM), are serious and potentially fatal conditions. Inflammatory mediator release by mast cells can cause episodes of vasodilation,

hypotension, flushing, pruritus, syncope, abdominal pain, nausea, vomiting, diarrhea, fatigue, and headache. Chronic inflammatory mediator release is associated with cachexia, chronic gastrointestinal symptoms, diffuse musculoskeletal pains, tissue remodeling, fibrosis, and end organ damage (Lichtman, 2003).

2.2. Analysis of Current Treatment Options

The reviewer's Table 2 below shows the current approved FDA treatments for AdvSM.

Table 2: FDA Approved Treatments

Product Name	NDA Number	Approval Date	Relevant Indication	Route and Frequency of Administration	Important Safety and Tolerability Issues	Reviewer Comment
Imatinib (Gleevec®)	21588	April 18, 2003	Gleevec® is a kinase inhibitor indicated for the treatment of adult patients with ASM without the D816V c-Kit mutation or with c-Kit mutational status unknown.	400 mg administered orally once daily	Generally, edema, fluid retention, cytopenias and hepatotoxicity have been reported with imatinib therapy. Cardiogenic shock/left ventricular dysfunction has been associated with the initiation of imatinib in patients with conditions associated with high eosinophil and ASM.	The imatinib product label approved August 10, 2020 under NDA 21588 states that prior determination of the D816V c-Kit mutation status is recommended. For patients with ASM associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFRα, a starting dose of 100 mg/day is recommended.
Midostaurin (Rydapt®)	207997	April 28, 2017	Rydapt® is a kinase inhibitor indicated for the treatment of adult patients with ASM, SM-AHN, MCL.	100 mg administered orally twice daily	Generally, interstitial lung disease or pneumonitis have been reported with midostaurin therapy. The most common adverse reactions (≥ 20%) were	The midostaurin product label approved April 20, 2021 under NDA 207997 states that monitoring for cytopenias, gastrointestinal and other non-hematological toxicities be

					nausea, vomiting, diarrhea, edema, musculoskeletal pain, abdominal pain, fatigue, upper respiratory tract infection, constipation, pyrexia, headache, and dyspnea in patients with ASM, SM-AHN and MCL undergoing midostaurin therapy.	performed at least weekly for the first four weeks, then every other week for 8 weeks then monthly thereafter.

Reviewer's table

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Avapritinib (Ayvakit®) was approved for marketing on January 9, 2020 under NDA 212608. Currently avapritinib is indicated for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations. The recommended dosage of avapritinib is 300 mg orally once daily on an empty stomach, at least 1 hour before and 2 hours after a meal for the treatment of GIST. The avapritinib product label approved January 9, 2020 under NDA 212608 states that intracranial hemorrhage and central nervous system effects (including cognitive impairment, dizziness, sleep disorders, mood disorders, speech disorders, and hallucinations) have been reported in patients treated with avapritinib. The product label also states that the most common adverse reactions (incidence ≥ 20%) are edema, nausea, fatigue/asthenia, cognitive impairment, vomiting, decreased appetite, diarrhea, hair color changes, increased lacrimation, abdominal pain, constipation, rash, and dizziness. Dose reductions to 200 mg administered orally once daily and 100 mg administered orally once daily are recommended for patients with these adverse reactions.

3.2. Summary of Pre-submission Regulatory Activity

The reviewer's Table 3 below summarizes the current avapritinib pre-submission regulatory activity.

Table 3: Avapritinib Pre-submission Regulatory Activity

Date(s)	Action(s)
January 6, 2016 and January 21, 2016	Avapritinib granted Orphan Drug Designation for GIST and SM indications
January 9, 2020	Approved for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations
October 12, 2018	Avapritinib granted Breakthrough Therapy Designation (BTD) for AdvSM (IND 124159)
December 16, 2020	Submission of NDA 212608 Supplement 006 for the treatment of ASM and SM-AHN and NDA 212608 Supplement 007 for the treatment of MCL. This DNH review focuses on NDA 212608 Supplement 006.
December 23, 2020	Avapritinib granted BTD for treatment of moderate to severe indolent systemic mastocytosis (ISM)
February 5, 2021	Applicant orientation meeting for NDA 212608 Supplements 006 and 007.

Reviewer's table

3.3. Foreign Regulatory Actions and Marketing History

On March 3, 2021, the Applicant reported on the website (https://www.biospace.com/article/releases/blueprint-medicines-announces-ema-validation-of-type-ii-variation-marketing-authorization-application-for-ayvakyt-avapritinib-for-the-treatment-of-advanced-systemic-mastocytosis/; last accessed May 20, 2021) that the European Medicines Agency (EMA) has validated the company's Type II variation marketing authorization application for avapritinib for the treatment of advanced systemic mastocytosis (SM). Validation of the application confirms that the submission is sufficiently complete to begin the formal review process. The European Commission has granted orphan medicinal product designation to avapritinib for the treatment of mastocytosis. On September 25, 2020 the sponsor reported on the website (https://ir.blueprintmedicines.com/news-releases/news-release-details/blueprint-medicines-announces-european-commission-approval; last accessed May 20, 2021) that the European Commission (EC) granted conditional marketing authorization to avapritinib as a monotherapy for the treatment of adult patients with unresectable or metastatic GIST harboring the PDGFRA D842V mutation.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

An OSI review was completed by Dr. Anthony Orencia in the Division of Clinical Compliance Evaluation (DCCE) final signature date May 21, 2021. In his review Dr. Orencia states that a single clinical investigator site (Daniel DeAngelo, M.D.) and the Applicant (Blueprint Medicines Corporation) were inspected to support the review of NDA 212608 Supplement 006. Dr. Orencia states that based on the results of these inspections, Studies BLU-285-2101 and BLU285-2202 appear to have been conducted adequately, and the data generated from Dr. DeAngelo and the Applicant appear to be acceptable in support of this NDA for the proposed indication.

4.2. Product Quality

Dr. Sarah C. Zimmermann, who is the FDA CMC reviewer, states in her review of NDA 212608 supplement 006 (final signature date May 27, 2021) that avapritinib immediate release tablets, available in 100 mg, 200 mg, and 300 mg strengths, are indicated for the treatment of gastrointestinal stromal tumors (GIST). Dr. Zimmerman's review of NDA 212608 supplement 006 contains the following summary of the key CMC information for the application.

- All tablet strengths are manufactured (b) (4) 100 mg, 200 mg, or 300 mg tablets which are film coated and printed before packaging into HDPE bottles with 0.5 g desiccant and an induction sealed (b) (4). The drug substance, avapritinib, is currently manufactured at (b) (4) (FEI: (b) (4)), and (b) (4) (FEI: (b) (4), approved S-003). The drug product (100 mg, 200 mg, 300 mg tablets) is currently manufactured at (b) (4) (FEI: (b) (4)). The 100 mg, 200 mg, and 300 mg tablets are manufactured using a (b) (4) process and utilizing a (b) (4) for all dosage strengths. The manufacturing process comprises (b) (4) .
- In the initial original submission, NDA 212608-ORIG-1, 18-month shelf-life was granted for 100 mg and 200 mg strengths and 12-month shelf-life was granted for 300 mg due to the (b) (4) dissolution trend. (b) (4)

- This supplemental application (i.e., NDA 212608 supplement 006) proposes the following change(s) for avapritinib. (The same CMC information and review by Dr. Zimmerman apply to NDA 212608 supplement 007 which is being reviewed by DNH1).
    - New indication as a treatment for adult patients with advanced systemic mastocytosis (AdvSM) (b) (4) AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).
    - Additional tablet strengths (25 mg and 50 mg).
    - Addition of (b) (4). (FEI: (b) (4)) as a new manufacturing and analytical testing facility of the proposed 25 mg and 50 mg tablets.
- Dr Zimmerman's review of NDA 212608 supplement 006 also states the following.
    - The proposed 25 mg and 50 mg strengths are manufactured dose proportional to the currently marketed 100 mg, 200 mg, and 300 mg strength tablets. The manufacturing process proposed at (b) (4) is the same as that for the current 100 mg, 200 mg, 300 mg tablets manufactured at (b) (4), with the exception of the imprinting (the 25 mg and 50 mg tablets will be debossed) and the removal of a (b) (4) The equipment is similar with the exception of (b) (4) used, however, manufacturing parameters at (b) (4) were optimized based on the manufacturing equipment used. The firm is using the same excipients and film coating as used in the current tablets with the exception of the (b) (4) blue printing ink because the proposed 25 mg and 50 mg tablets are debossed. In-process controls (b) (4) The same primary packaging site as is currently used with the 100 mg, 200 mg, and 300 mg tablets, (b) (4), will be used for commercial packaging of the proposed 25 mg and 50 mg tablets.
    - Specifications of the proposed 25 mg and 50 mg tablets are identical with the specifications for the current 100 mg, 200 mg, and 300 mg tablets with the exception of the appearance and identification. The identity of the 25 mg and 50 mg is confirmed by comparing the HPLC/UV instead of the current FTIR and HPLC retention time. The combined use of HPLC/UV diode array for an identification is in agreement with ICH Q6A. Elemental impurities assessment was provided, and based on vendor statements, the amount of elemental impurities in the drug product is not greater than (b) (4)% PDE and no additional controls for elemental impurities need to be provided. Method transfer reports and method validation reports were provided, and the methods are suitable for their intended use.
    - Batch analyses of six batches (clinical and registration) of 25 mg tablets, and three batches of both 50 mg and 100 mg tablets do not show any quality concerns and are within specified limits. The 100 mg tablets were manufactured

at (b) (4) for clinical studies but will not be manufactured at (b) (4) for commercial use. Temperature cycling studies, photostability studies, and forced degradation studies do not show any quality concerns compared to the current 100 mg, 200 mg, and 300 mg tablets. Long-term and accelerated stability studies were performed on 25 mg and 100 mg tablets manufactured at the proposed (b) (4), with the 50 mg tablets bracketed. Up to 12 months long term, and 6 months accelerated for both the 25 mg and 100 mg tablets do not show any quality concerns or significant trending. The firm is proposing a 24 month expiration date, which is acceptable based on the 12 month long-term stability data provided.

- The firm is proposing the commercial packaging is the same as the current tablets, except with 2 g of desiccant instead of 0.5 g of desiccant. The increased desiccant seems to have mitigated quality concerns discussed in previous supplements and the original NDA submission with (b) (4) and dissolution.
- A post-approval stability commitment was provided to continue the ongoing long-term stability studies on the three registration lots of 25 mg and 100 mg tablets will be conducted through 48 months. Additionally, the first three commercial-scale batches of 25mg and 50 mg tablets will be placed on stability and one lot per year of each 25 mg and 50 mg tablets, if manufactured that production year, will be placed on long term stability.
- The proposed labeling has been amended to include the 25 mg and 50 mg tablets. The proposed labeling is acceptable from a CMC standpoint.

As noted above, Dr. Zimmermann did not find any information that would preclude approval of NDA 212608 S-006. Therefore, she is recommending approval of supplement S-006 of NDA 212608.

A Biopharmaceutics Review was completed by Dr. Linyi Wei in the Division of Biopharmaceutics final signature date May 24, 2021. Dr. Wei's review states that from a Biopharmaceutic perspective, NDA-212608 Supplement 006 and Supplement 007 for avapritinib tablets, 25 and 50 mg, are adequate and the review recommends approval.

4.3. Nonclinical Pharmacology/Toxicology of Avapritinib

A Pharmacology/Toxicology Review was completed by Dr. Bo Lee, final signature date May 28, 2021. The review states: "Based on the results of minimal to mild severity of avapritinib effects and the reversibility of the findings on spleen, bone marrow, testis, ovary, and vagina, avapritinib was tolerated at the 5 mg/kg/day, and the Applicant proposed a no-observed-adverse effect level (NOAEL) as 5 mg/kg/day. The review states that the proposed NOAEL of 5 mg/kg/day in dogs via oral administration for 39 weeks is acceptable and the corresponding AUC was 7930 and 7250 ng*h/mL in males and females, respectively.

In the Non-clinical Review of NDA 212608 S-006, Dr. Bo Yeon Lee stated: "To support the proposed label expansion for avapritinib to the treatment of adult patients with the following two subtypes of advanced systemic mastocytosis (AdvSM): 1. aggressive systemic mastocytosis (ASM), and 2. systemic mastocytosis with an associated hematological neoplasm (SM-AHN), the Applicant conducted additional PK/ADME studies and repeat-dose toxicology studies in rats for 26 weeks and in dogs for 39 weeks."

"The results from the additional PK/ADME studies showed that CYP3A4 and CYP3A5 are involved in the metabolism of avapritinib (BLU-285), and that avapritinib is metabolized to its hydroxylamine M514 first and subsequently M514 was metabolized to the glucuronide conjugate M690 by UGT1A3 and CYP3A4. Avapritinib doesn't appear to be a substrate for human OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp or BSEP under the study conditions.

GLP-compliant repeat-dose toxicology studies were conducted in rats for 26 weeks and in dogs for 39 weeks with 8-week recovery period. Rats were administered orally with avapritinib at 1, 3, or 10 mg/kg/day for 26 weeks.

The results from these experiments showed: Target organs of toxicity identified included the adrenal gland, bone marrow, prostate gland, thymus, ovaries, and vagina with corresponding histopathological findings of cortical hyperplasia, necrosis and thrombus in the adrenal gland, decreased cellularity in the bone marrow, mixed cell inflammation and hemorrhage in the prostate gland, decreased lymphoid cellularity and hemorrhage in the thymus, corpus luteum cystic degeneration and hemorrhage in the ovaries, and increased epithelial mucification of the vagina.

The thrombus in the adrenal gland, corpus luteum cystic degeneration and hemorrhage in the ovaries, and hemorrhage in the thymus persisted at the end of the 2-month recovery period. Based on the finding's lack of reversibility and severity of findings at the HD, the NOAEL was determined at the MD of 3 mg/kg/day. The safety margins of human exposure were: 1.5X for males, and 3X for females.

Dogs were treated orally with avapritinib at 0.5, 1.5, or 5 mg/kg for 39 weeks. Target organs of toxicity identified included bone marrow, lymph nodes, spleen, testis, and thymus with corresponding microscopic findings of decreased cellularity in the bone marrow in high dose (HD) males and ≥ medium dose (MD) females, decreased cellularity (HD) and erythrocytosis (≥ low dose (LD) in lymph nodes (axillary and mandibular), increased extramedullary hematopoiesis and pigmented macrophages in the spleen, hypoplasia and hypospermatogenesis in testis of MD and HD males, and decreased cellularity in the thymus. Avapritinib-related histopathological findings generally recovered except for findings of pigmented macrophages in the spleen although noted with less frequency and severity, and hypoplasia and hypospermatogenesis in MD and HD males that were still present at the end of

the recovery period. Avapritinib was tolerated up to HD and the NOAEL was determined at 5 mg/kg/day in dogs for 39-week treatment. Safety margins of human exposure: 1.2X male, 1.1X female."

Conclusion and Summary of Review of Non-clinical Data: Drs. Bo Yeon Lee and Pedro Del Valle stated following their review of the above listed non-clinical studies: "Based on the results of minimal to mild severity of avapritinib effects and the reversibility of the findings on spleen, bone marrow, testis, ovary, and vagina, avapritinib was tolerated at the 5 mg/kg/day, and the Sponsor proposed no-observed-adverse effect level (NOAEL) as 5 mg/kg/day. The reviewer finds that the proposed NOAEL of 5 mg/kg/day in dogs via oral administration for 39 weeks is acceptable and the corresponding AUC was 7930 and 7250 ng*h/mL in males and females, respectively."

The conclusion reached by Drs. Bo Yeon Lee and Pedro Del Valle, on the basis of the above work and on the basis of their analysis of the results of these experiments, was to grant the approval of avapritinib for the treatment in adults with AdvSM.

4.4. Clinical Pharmacology

A Clinical Pharmacology review was completed by Dr. Robyn Konicki (final signature date May 28, 2021). The review states that "The Office of Clinical Pharmacology has reviewed the information contained in NDA 212608 Supplement 006 and Supplement 007 and the application is approvable from a clinical pharmacology perspective. Also, the review states that the recommended dosage is 200 orally once daily in patients with AdvSM and that no dose adjustment is needed in specific populations within patients with AdvSM.

(The section below was derived verbatim from the review of Dr. Robyn Koniki and Dr. Lian Ma). The focus of the review of the Clinical Pharmacology group was whether the dosing regimen for avapritinib is appropriate (safe and effective). Avapritinib is targeted to the D816V mutation which is located in exons 11, 11/17, and 17 of the Kit protein kinase. The primary source of the data showing the appropriateness of the dose was the two studies: BLU-285-2101 and BLU-285-2202. The recommended dosage is 200 mg orally once daily in patients with AdvSM. The Cmax and the AUC are increased proportionally over the dose range of 200-400 mg when given once daily orally. The steady state concentration is reached by day 15 of daily dosing. The two competing issues in the determination of the dose is to avoid exceeding the safety threshold (above which the risk of intracranial hemorrhage appears to be increased) and to avoid too little of avapritinib such that the efficacy is decreased. The clinical pharmacology review team (Drs. Robyn Koniki and Lian Ma) made the following conclusions after the review of the data. Based on efficacy, pharmacokinetics (PK) and safety data in Study BL-285-2101, the starting dose was 200 mg administered orally (po) once daily (qd). The recommended phase 2 dose (RP2D) in patients with AdvSM was originally identified as 300 mg qd in Study BLU-285-2101.

Drs. Koniki and Ma then stated that after identification of the 300 mg qd dose in study BLU-285-2101 concerns arose about the increased risk of intracranial hemorrhage at 300 mg po qd, and the finding that the mean concentration at steady state was above that predicted for the IC990 for inhibition of the D816V mutation in c-Kit in a patient-derived xenograft model (189 mg/mL) for doses 200 mg over the entire dosing interval.

The exposure-response (E-R) analysis for safety did not show a clear relationship between avapritinib exposure and intracranial bleeding AEs (all grades). Higher exposure was associated with an increase in the risk of grade 3 or greater TEAEs (intracranial hemorrhage) any cognitive AEs, or grade >2 pooled cognitive AEs.

The SM-AHN and MCL subtypes were associated with higher risk for grade 3 or higher TEAEs compared to other SM subtypes and GIST. Lower platelet counts were associated with an increased risk of intracranial bleeding AEs. Subjects with a baseline platelet count of <50 x 10E9/L (n=11 subjects with SM) had a significantly higher risk of intracranial bleeding compared to subjects with a baseline platelet ≥50 x 10^9/L (n=514). For details, please see the Clinical Pharmacology review of Drs. Robyn Koniki and Lian Ma.

Conclusions of the Clinical Pharmacology Review Team: The dosing regimen of 200 mg po qd with a platelet count of ≥50 X 10^9/L is supported by the overall favorable benefit/risk profile for the general risk patient population with AdvSM. Approval of 200 mg po qd of avapritinib was recommended for approval for AdvSM.

4.5. Devices and Companion Diagnostic Issues

Not applicable.

4.6. Consumer Study Reviews

Not applicable.

Reviewer comment for Section 4: The Clinical Reviewers agree with the reviews and recommendations for NDA 212608 supplement 006 by Drs. Orencia, Wei, Lee, and Konicki final signature dates May 21, 2021; May 24, 2021; May 28, 2021 and May 28, 2021, respectively.

5. Sources of Clinical Data and Review Strategy

5.1.Table of Clinical Studies

The Applicant's table below summarizes the key studies supporting NDA 212608 Supplement 006.

Table 4: Table of Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
Efficacy, Safety, PK	BLU-285-2101	5.3.5.2	Safety, dose finding, PK/PD, and QOL	Phase 1, multicenter, single-arm, open-label	Avapritinib; Part 1: 3+3 dose-escalation design using cohorts of 3 patients from 30 to 400 mg QD Part 2: 200 mg QD (previously 300 mg in Cohort 1) Oral, fasted	Part 1: 32 Part 2: 54	Male or female patients who are ≥18 years-old with AdvSM and other relapsed or refractory myeloid malignancies	Enrollment Complete, Ongoing; Clinical Study Report DLP = 27 May 2020
Efficacy, Safety, PK	BLU-285-2202	5.3.5.2	Efficacy, safety and QOL	Phase 2, multicenter, single-arm, open-label	Avapritinib; 200 mg QD Oral, fasted	62 as of DLP ~103 planned	Male or female patients who are ≥18 years-old with AdvSM	Ongoing; Clinical Study Report DLP = 23 June 2020

AdvSM = advanced systemic mastocytosis; DLP = data lock point; GIST = gastrointestinal stromal tumor; ISS = integrated summary of safety; PD = pharmacodynamics; PK = pharmacokinetics; PDGFRA = platelet derived growth factor receptor alpha; PO = oral dosing; QD = once daily; QOL = quality of life; RP2D = recommended Phase 2 dose
Sponsor's table module 5.2.

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5.2. Review Strategy

The Applicant submitted the clinical data supporting the indication under NDA 212608 Supplement 006 and Supplement 007 on December 16, 2020 (received December 16, 2016), respectively. This clinical review by the Division of Nonmalignant Hematology (DNH) focuses on NDA 212608 Supplement 006 in which the Applicant submitted data supporting the non-malignant portion of the proposed new indication for avapritinib, i.e., ASM and SM-AHN. Review of the clinical data supporting the malignant portion of the indication (NDA 212608 Supplement 007) will be conducted by the Division of Malignant Hematology 1 (DHM1) separately.

This review focuses on pooled safety and efficacy data from the two clinical studies BLU-285-2101 (EXPLORER) and BLU-285-2202 (PATHFINDER) that are summarized in the Applicant's table in Section 5.1 titled, "Table of Clinical Studies" in this review above. The key design elements of the two studies are also summarized in Section 6 Review of Relevant Individual Studies Used to Support Efficacy in this review below. This review also only focuses on data from enrolled patients with ASM and SM-AHN. (b) (4) The MCL portion of the proposed indication is reviewed separately by DMH1.

6. Review of Relevant Individual Studies Used to Support Efficacy

This section summarizes the key study design elements of Studies BLU-285-2101 (EXPLORER) and BLU-285-2202 (PATHFINDER).

6.1 BLU-285-2101 (EXPLORER)

Overview and Objective

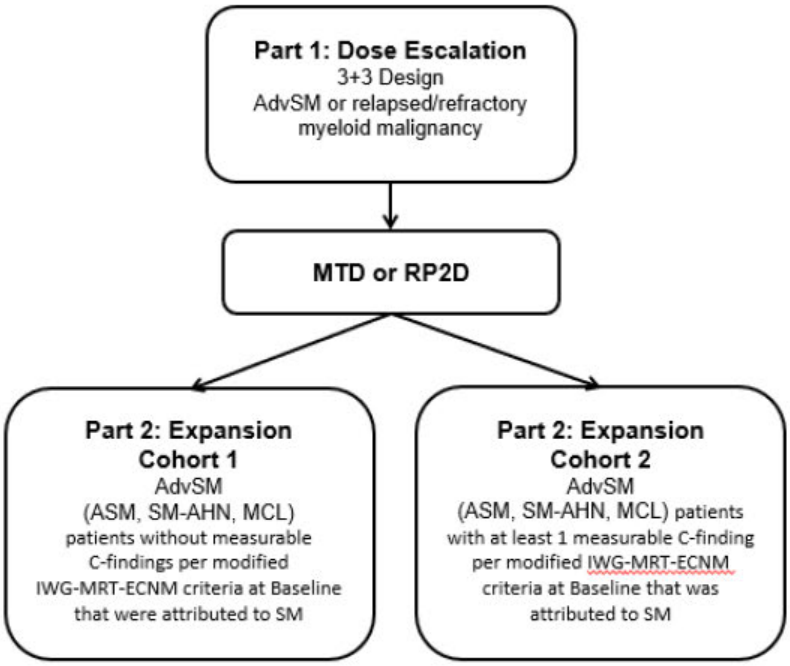
Study BLU-285-2101 is titled, "A Phase 1 Study of BLU-285 in Patients with Advanced Systemic Mastocytosis (AdvSM) and Relapsed or Refractory Myeloid Malignancies." The study was initiated March 10, 2016 and is ongoing (estimated completion date November 2021 but the study has been fully enrolled as of May 27, 2020). The study was conducted in the United States and European Union. The primary objective of the study is to identify the maximum tolerated dose (MTD) and RP2D of avapritinib for the treatment of patients with AdvSM. Secondary objectives of the study are to assess preliminary evidence of avapritinib antineoplastic activity; evaluate of the pharmacokinetics (PK) of avapritinib; evaluate changes in serum tryptase concentration during treatment with avapritinib; evaluate changes in KIT D816V mutant allele fraction (MAF) during treatment with and evaluate changes in patient-reported outcomes

(PROs) and quality of life (QoL).

Trial Design

This is a Phase 1, open-label, dose-escalation study. The study consists of 2 parts, a dose-escalation part (Part 1) and an expansion part (Part 2). The Applicant proposes to enroll a total of 80 patients. Part 1 of the study is a "3+3" design in which up to 25 patients have been enrolled. Evaluation, measurement, and assessment of disease responses was based on modified International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) & European Competence Network on Mastocytosis (ECNM) consensus response criteria (Gotlib, 2013). Response to therapy was adjudicated by the Response Adjudication Committee (RAC). The starting dose of avapritinib was 30 mg administered orally once daily in 28-day cycles. Doses levels evaluated were 30 mg, 60 mg, 100 mg, 130 mg, 200 mg, 300 mg, and 400 mg. Therapy was to continue until unacceptable toxicity or disease progression. Adverse events were characterized and graded according to Nation Cancer Institute – Common Terminology for Adverse Events (NCI-CTCAE) v. 4.03 criteria. The MTD was defined as the highest dose level at which ≤1 patient experienced dose limiting toxicities (DLTs) in Cycle 1 during Part 1 of the study. At least 6 patients must have been treated at this dose to determine that it was the MTD. In the 400 mg dose cohort 1 DLT of grade 4 vomiting was reported. The MTD was not reached. Based on safety, PK, pharmacodynamic, and antitumor activity, the RP2D was considered to be 300 mg once daily and the starting dose for initiation of Part 2 of the study. However, due to at least 50% of patients in the 300 mg dose cohort reporting cytopenias, and efficacy appeared to be maintained the avapritinib 200 mg was considered the RP2D. Part 2 of the study was an expansion design in which up to 55 patients were to be enrolled. The Applicant's figure below shows the study schema. The safety population included all patients who received ≥ 1 dose of avapritinib.

Figure 1: Study Schema BLU-285-2101



Abbreviations: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; MCL = mast cell leukemia; MTD = maximum tolerated dose; N = overall number of patients to be enrolled; RP2D = recommended Phase 2 dose; SM = systemic mastocytosis; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm.
Note: Patients in Part 2, Cohort 1 were initially treated with an avapritinib starting dose of 300 mg QD. Patients in Part 2, Cohort 2, which was established in Protocol Amendment 6, received an avapritinib starting dose of 200 mg QD.
Sponsor's figure Completed Study Report (CSR) BLU-285-2101 page 6

The key inclusion criteria are as follows.

- Patient age ≥ 18 years.
- Diagnoses based on World Health Organization (WHO) diagnostic criteria of ASM; SM-AHN or MCL.
- At least 1 C-finding attributable to SM.
- Histologically- or cytologically- confirmed myeloid malignancy that is relapsed or refractory to standard treatments or KIT D816V mutation.
- Eastern Cooperative Oncology Group (ECOG) performance status 0-3.
- For part 2 of the study:
    - ANC < 1,000/µL or hemoglobin (Hgb) < 10 g/dL or platelet count < 75,000/µL.
    - Symptomatic ascites or pleural effusion requiring medical intervention such as:
    - Use of diuretics (Grade 2) *or* ≥ 2 therapeutic paracenteses or thoracenteses (Grade 3) at least 28 days apart over the 12 weeks before study entry and 1 of the procedures is performed during the 6 weeks before study start (C1D1).
    - ≥ Grade 2 abnormalities in direct bilirubin (> 1.5 × upper limit of normal [ULN]), aspartate aminotransferase (AST; > 3.0 × ULN), alanine aminotransferase (ALT; > 3.0 × ULN), or alkaline phosphatase (> 2.5 × ULN) with 1 of the following present: ascites

or clinically relevant portal hypertension or liver mast cell (MC) infiltration that is biopsy-proven or no other identified cause of abnormal liver function.
- ≥ Grade 2 hypoalbuminemia (< 3.0 g/dL).
- A spleen that is palpable ≥ 5 cm below the left costal margin.
- Transfusion-dependent anemia defined as: transfusion of ≥ 6 units packed red blood cells (PRBCs) in the 12 weeks before start of treatment (C1D1) and most recent transfusion occurring during the preceding 4 weeks and transfusion administered for hemoglobin ≤ 8.5 g/dL and reason for transfusion is not bleeding, hemolysis, or therapy-related.

The key exclusion criteria of the study are as follows.

- Patient has any of the following within 14 days prior to the first dose of study drug:
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN); > 5 × ULN if associated with clinically suspected liver infiltration by mastocytosis or another disease for which the patient enrolled into the study.
  - Serum total bilirubin (TBili) > 1.5 × ULN; > 3 × ULN if associated with liver infiltration by the disease being treated or in the presence of Gilbert's Disease.
  - Estimated (Cockcroft-Gault formula) or measured creatinine clearance < 40 mL/min.
  - Platelet count < 50,000/µL; absolute neutrophil count (ANC) < 500/µL.
  - Eosinophilia and known positivity for the FIP1L1-PGDFRA fusion.
- Diagnosis of AML, MDS that is very high- or high-risk as defined by the IPSS-R, or a Philadelphia chromosome positive malignancy.
- Stable corticosteroid dose for ≥ 7 days.
- Antineoplastic therapy < 14 days prior to bone marrow assessment at screening.
- Surgical procedure within 14 days of the first dose of study drug.
- History of another primary malignancy that has been diagnosed or required therapy within 1 year prior to the first dose of study drug.
- QT interval corrected using Fridericia's formula (QTcF) > 480 millisec; history of prolonged QT syndrome or Torsades de pointes.
- History of a seizure disorder or history of a cerebrovascular accident or transient ischemic attacks within 1 year prior to the first dose of study drug or known risk of intracranial bleeding, such as a brain aneurysm or history of subdural or subarachnoid bleeding.
- Primary brain malignancy or metastases to the brain.
- New York Heart Association congestive heart failure Grade III or IV.
- Known diagnosis of human immunodeficiency virus infection or active viral hepatitis.

DLT's were defined as follows.

- Dose limiting toxicity is defined as any treatment-emergent adverse event (AE) of Grade ≥ 3 occurring during C1 and not clearly attributable to a cause other than avapritinib, with the following exceptions.
    - Thrombocytopenia with platelet count on C1D1 of Grade 0-2.
    - Grade 3 and associated with bleeding, or if the platelet count is <10,000/µL of for any duration.
    - Platelet count on C1D1 of Grade 3 or worse (i.e., < 50,000/µL).
    - Neutropenia with neutrophil count on C1D1 of Grade 0-2.
    - Neutrophil count on C1D1 of Grade 3 or worse (< 1000/µL).
    - Anemia Grade 4.
    - Nausea Grade 3 and persists > 3 days despite therapy.
    - Vomiting Grade 4, or Grade 3 and persists > 3 days despite therapy.
    - Diarrhea Grade 4, or Grade 3 and persists > 3 days despite therapy.
    - Alkaline phosphatase (AlkP) Grade 4; total bilirubin (TBili) Grade 2 if associated with alanine aminotransferase (ALT) ≥ Grade 2.
    - Infection Grade 4 or if it is Grade 3 and persists > 7 days.
    - Fever in the absence of neutropenia Grade 4 despite antipyretic therapy.
    - Abnormalities of serum calcium, magnesium, and phosphate Grade 4, or Grade 3 and the patient is clinically symptomatic, requires hospitalization, or if the specific abnormality is not able to be corrected to Grade ≤ 2 within 3 days.
    - Tumor lysis syndrome (TLS) Grade 4.
    - Rash Grade 4, or if it is Grade 3 and persists > 7 days.
    - Fatigue is not considered a DLT as it is a prominent symptom of the disease.

The Applicant's table below shows the study schedule.

Table 5: Study Schedule BLU-285-2101

Study Activities[a]														
Cycle	Screening	C1						C2		C3-C12	≥C14	EOT[b]	Safety F/U	PFS/OS F/U[c]
Study Day	-56 to -8	Baseline		D2	D8	D15	D22	D1	D15	D1	D1 of every even numbered cycle	14 days post last dose	30 days post last dose[d]	Every 6 months after Safety F/U
		-7 to -1	D1											
Window (Days)					±1	±2	±2	±3[e]	±3	±7[e]	±7[e]	±7	±7	±14
Informed consent	X													
Inclusion/Exclusion criteria	X													
Demographics	X													
Medical history[f]	X													
Physical examination[g]	X		X[k]		X	X	X	X	X	X	X	X		X[c]
Vital signs[h]	X		X[k]		X	X	X	X	X	X	X	X		
Serum Pregnancy (β-hCG) test[i]	X							X		X	X			
ECOG PS	X		X[k]		X	X	X	X	X	X	X	X		
12-lead ECG	X		See Appendix 2 (Part 1) or Appendix 3 (Part 2, Cohorts 1 and 2)											

Study Activities[a]														
Cycle	Screening	C1						C2		C3-C12	≥C14	EOT[b]	Safety F/U	PFS/OS F/U[c]
Study Day	-56 to -8	Baseline: -7 to -1	Baseline: D1	D2	D8	D15	D22	D1	D15	D1	D1 of every even numbered cycle	14 days post last dose	30 days post last dose[d]	Every 6 months after Safety F/U
Window (Days)					±1	±2	±2	±3[e]	±3	±7[e]	±7[e]	±7	±7	±14
Complete blood count[g]	X	X[j]	X[k]		X	X	X	X	X	X	X (q28d)	X		
Coagulation[l]	X		X[k]		X	X	X	X	X	X		X		
Serum chemistry[m]	X		X[k]		X	X	X	X	X	X	X	X		
Urinalysis	X		X[k]									X		
Avapritinib administration[n]			X											
PK Blood Samples[n,o]			See Appendix 2 (Part 1) or Appendix 3 (Part 2, Cohorts 1 and 2)											
Blood Sample for KIT D816V mutant allele burden			X			X		X		X[p]	X[p]	X		
Blood sample for Exploratory Biomarkers			X					X		X		X		
Blood sample for serum tryptase			X			X		X		X[p]	X[p]	X		
BM biopsy and aspiration and peripheral blood smear collection	X[q]									X[r]	X[r]	X[p]		X

Study Activities[a]														
Cycle	Screening	C1						C2		C3-C12	≥C14	EOT[b]	Safety F/U	PFS/OS F/U[c]
Study Day	-56 to -8	Baseline: -7 to -1	Baseline: D1	D2	D8	D15	D22	D1	D15	D1	D1 of every even numbered cycle	14 days post last dose	30 days post last dose[d]	Every 6 months after Safety F/U
Window (Days)					±1	±2	±2	±3[e]	±3	±7[e]	±7[e]	±7	±7	±14
Response per modified IWG-MRT-ECNM criteria at time point[g]										X[f]	X[f]	X[b]		
PI attribution assessment of C-findings per modified IWG-MRT-ECNM criteria	X		X	X				X		X	X	X		
Imaging of liver and spleen[i]	X									X[f]	X[f]	X[b]		X
Imaging of brain	X							X		X[n]				
AdvSM-SAF[v]		X	X											
EORTC QLQ-C30[w] and PGIS[w]			X[w]					X[w]		X[w]				
AE Monitoring[x]		X												
SAE Monitoring[y]	X													
Concomitant medications[y]	X													

Abbreviations: AdvSM = Advanced Systemic Mastocytosis; AdvSM-SAF = AdvSM Symptom Assessment Form; AE = adverse event; β-hCG = beta human chorionic gonadotropin; BM = bone marrow; C = cycle; CM = cutaneous mastocytosis; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30 = European Organization for Research

and Treatment of Cancer Core Quality of Life Questionnaire; EOT = end-of-treatment; F/U = follow up; Hgb = hemoglobin; IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; KIT = V-Kit Hardy-Zuckerman 4 Feline Sarcoma Viral Oncogene Homolog; MRI = magnetic resonance imaging; PFS = progression-free survival; PGIS = patient's global impression of symptom severity; PK = pharmacokinetic(s); q28d = every 28 days; QD = once daily; SAE = serious adverse event.

Note: Every effort should be made to keep the schedule of assessments on time for each patient.

a On days when study drug is to be administered in the clinic, all tests or procedures must be completed pre-dose at each study visit unless otherwise indicated. Additional safety tests may be performed whenever clinically indicated, at the Investigator's discretion. Whenever a test result is questionable, it should be repeated immediately.

b The EOT visit must occur no more than 21 days after last dose of study drug. An interval of > 56 days without dosing is not permitted without Medical Monitor approval. If an alternate cytoreductive treatment is to be started within 14 days after the last study drug dose, the EOT visit should be conducted prior to the first dose of alternate therapy. End-of-treatment assessments (including hematology, chemistry, serum tryptase, KIT D816V mutant allele burden, measurement of liver and spleen by palpation, imaging of liver and spleen, and BM biopsy and aspirate) will be performed if they have not been performed within the preceding 6 months or the preceding 4 months if the patient discontinues before Cycle 11.

c After completing the Safety Follow-up visit, patients without documented progressive disease and/or initiation of other cytoreductive therapy are to be followed for response assessments (including limited physical examination for liver and spleen measurement by palpation only, liver and spleen imaging, and BM biopsy and aspirate) every 6 months (±14 days) until the documentation of progressive disease and/or initiation of another antineoplastic therapy. All patients, regardless of disease status, will be contacted by telephone every 3 months to assess survival until death or closure of the study by the Sponsor.

d The 30-day Safety Follow-up visit may be performed by telephone.

e After C1D1, the first day of a cycle may be delayed up to 56 days to allow for resolution of toxicities. Any delay longer than 56 days must be discussed with the medical monitor. In general, any patient requiring a delay > 56 days should have the EOT visit performed and then followed every 6 months until progressive disease is documented, or alternative antineoplastic therapy initiated.

f A complete medical history will be obtained at the Screening visit, including a history of AdvSM and/or other malignancies and hematologic disorders, prior treatments, response to each treatment (if available), and concurrent illnesses.

g A complete physical examination including weight, evaluation of the skin (including CM), head and neck, lymph nodes, heart, lungs, chest, abdomen (including measurement by palpation of liver and spleen), pelvis (if indicated based on symptoms), musculoskeletal system and neurologic system (including a basic assessment of mental status) will be performed at the Screening visit. Subsequent physical examinations will include signs of CM and AdvSM (or relapsed or refractory myeloid malignancy), measurement of liver and spleen by palpation, changes from previous physical examinations, weight and AEs.

h Vital signs include temperature, pulse, and systolic/diastolic blood pressure.

i To be performed for women of child-bearing potential. A serum pregnancy test will be obtained within 7 days prior to the first dose of study drug. Subsequent pregnancy tests (serum or urine) will be performed on D1 of even numbered cycle (eg, C4, C6).

j Hematology parameters to be measured include Hgb, white blood cell with differential count, platelet count, RBC count, MCV, MCH and MCHC. Patients with any degree of thrombocytopenia must repeat a CBC with differential approximately 28 days before C1D1 and again within 7 days before dosing. A CBC with differential must be obtained approximately every 28 days (±7 days).

k For Part 1, Baseline safety assessments may be obtained within 7 days before the first study drug dose. Should Screening assessments occur within 7 days of the first study drug dose, they do not need to be repeated. For Part 2: Screening assessments must be done during screening (D-56 through

D-8). The patient must be eligible before they start the PRO (AdvSM-SAF) on D-7. Baseline assessments may be obtained within 7 days before C1D-7, when the patient begins the AdvSM-SAF assessment. If Baseline assessments are collected during this time, they will not need to be re-done at C1D1.

l Coagulation studies include international normalized ratio, activated partial thromboplastin time, and fibrinogen. If they are within the normal range through C3D1 than they can be discontinued and obtained only as clinically indicated.

m The comprehensive serum chemistry panel includes sodium, potassium, blood urea nitrogen or urea, bicarbonate (venous), creatinine, calcium, chloride, magnesium, phosphorus, albumin, aspartate aminotransaminase, alanine aminotransaminase, alkaline phosphatase, and total and direct bilirubin. Any alkaline phosphatase ≥ Grade 3 should be fractionated to determine if it is of bone or liver origin.

n Avapritinib will be administered QD in the morning at least 2 hours after and 1 hour before eating. On study visit days when PK samples are collected, patients will take their dose of avapritinib under observation at the study clinic after the pre-dose (trough) PK sample has been obtained.

o PK sampling will be performed as specified in Appendix 2 (Part 1) or Appendix 3 (Part 2, Cohorts 1 and 2). Additionally, investigators may obtain blood samples for PK analysis at the time(s) that significant drug-related AEs occur.

p Blood samples for tryptase and KIT mutant allele burden will be obtained on C1D1, C1D15, C2D1, C3D1, C5D1, C7D1, C11D1, C18D1 and every 6 cycles thereafter, including post EOT in those patients discontinued from treatment for reasons other than progressive disease or initiation of other cytoreductive therapy. Samples should also be obtained at the time of disease progression.

q Bone marrow biopsy and aspiration. For further details refer to (Section 7.4).

r Bone marrow biopsy and aspiration, a peripheral blood smear, and imaging of the liver and spleen will be performed on C3D1, C5D1 (imaging only), C7D1, C11D1, C18D1, and every 6 cycles thereafter. For further details refer to Section 7.4. Response per modified IWG-MRT-ECNM criteria should be assessed on the same schedule as BM sampling ie. C3D1, C7D1, C11D1, C18D1 and every 6 cycles thereafter.

s Patients with a response of CR, CRh or PR will have their response confirmed 12 weeks after documentation of first response. This confirmation will include bone marrow biopsy and aspirate, measurement of liver and spleen by palpation and imaging, serum tryptase and hematology and chemistry laboratories. Additional study visit and procedures may be necessary if this 12 week confirmation does not coincide with a scheduled study visit.

t MRI is the primary measure of liver and spleen volume; CT may be used for patients not eligible for MRI (eg, metal clips in body; claustrophobia). See (Section 7.5) for further details. For Part 2, scans should be performed according to procedures outlined in the vendor provided Study Manual and scans will be sent for Central Review.

u MRI or CT of the brain to be performed at C2D1, C3D1, and C4D1.

v Only during Part 2, patients will complete the AdvSM-SAF daily from C1D7 through and including C12D28.

w Only during Part 2, EORTC QLQ-C30 and PGIS will be administered on D1 of each cycle for C1 through C12.

x AEs are to be collected from the start of study drug administration through the Safety Follow-up visit.

y SAEs and concomitant medications are to be collected from the date of the informed consent signature through the Safety Follow-up visit.

Sponsor's table protocol Blu-285-2101 pages 102-106

Study Endpoints

The primary efficacy endpoints were the MTD and RP2D. Secondary endpoints included PK evaluation; change in serum tryptase level; change in KIT D816V mutant allele fraction; evaluation of overall response rate (ORR) and duration of response; by modified IWG-MRT-ECNM criteria; and change in patient reported outcomes as assessed by the AdvSM-SAF, PGIS, and EORTC QLQ-C30 tools (Part 2 only). However, due to the single arm design of the study no conclusion regarding change in PRO or QoL components could be made.

Compliance with Good Clinical Practices

A signed written informed consent form is required for enrollment into the study. The study is conducted according to International Conference on Harmonization (ICH) and Good Clinical Practice Guidelines. An Independent Ethics Committee (IEC) and Institutional Review Board

(IRB) will review and monitor the study.

Patient Disposition

This study enrolled a total of 86 patients in the Safety Population. The primary reasons for treatment discontinuation were disease progression and adverse events. Patient disposition in the response evaluable group, which excluded 33 patients who are not response evaluable by modified (i.e., mIWG-MRT-ECNM) criteria, was similar to the Safety Population based on all enrolled patients. The reviewer's Table 6 below shows the patient disposition in study BLU-285-2101.

Table 6: Disposition (BLU-285-2101)

Disposition Reason	Response Evaluable N=53 n, (%)
Discontinued from treatment	28 (53%)
Continuing on treatment	25 (47%)
Discontinued from study	22 (42%)
Disease progression	14 (26%)
AML	6 (11%)
Adverse event(s) Related	8 (15%) 4 (8%)
Withdrew consent	2 (4%)
Investigator's decision	3 (6%)
Administrative/other	1 (2%)
Adverse event(s) Death Withdrew consent Initiation of another neoplastic therapy Investigator's decision	1 (2%) 15 (28%) 3 (6%) 2 (4%) 1 (2%)

Reviewer's table with assistance from Dr. Cai.

6.2 BLU-285-2202 (PATHFINDER)

Overview and Objective

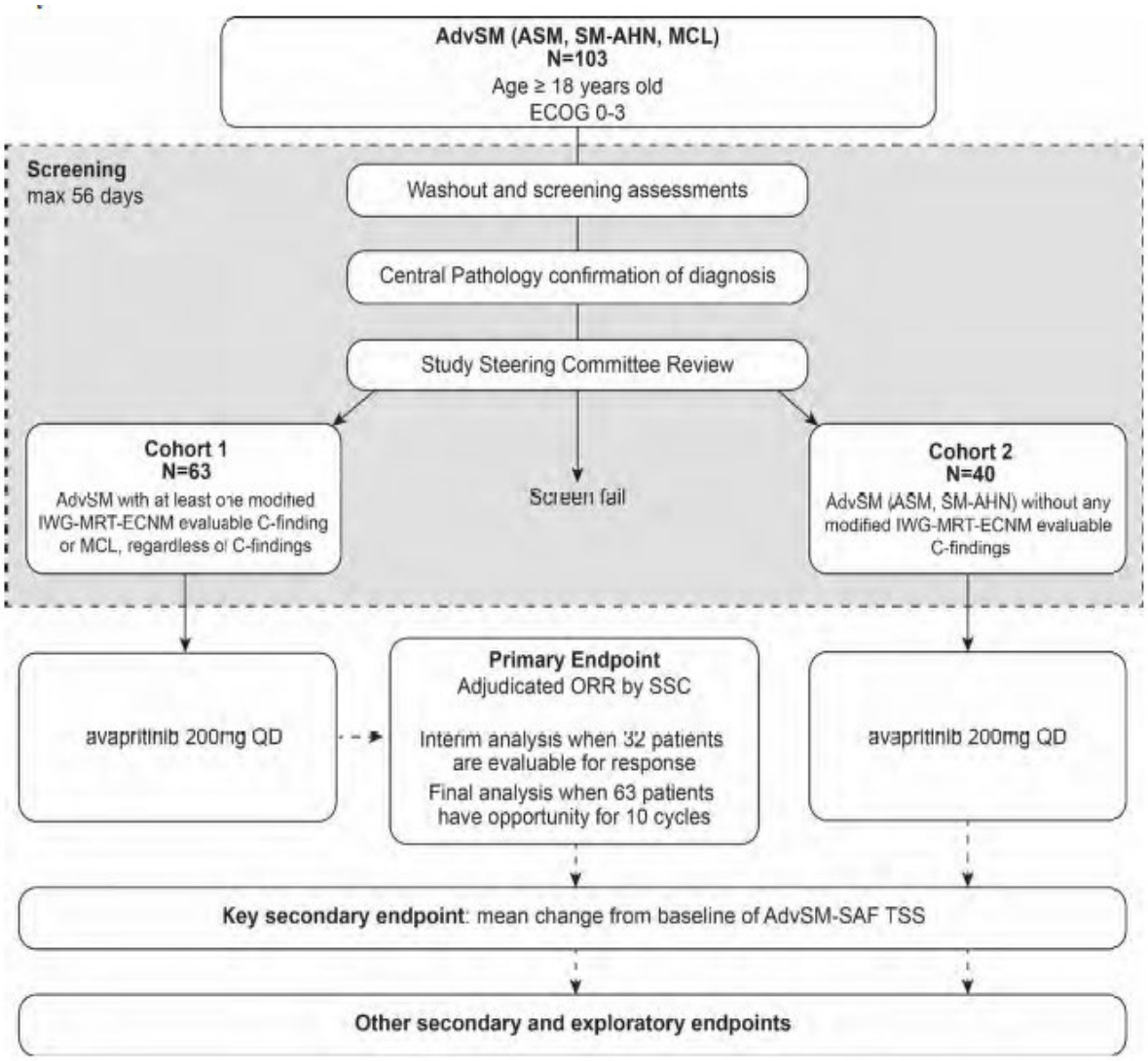
Study BLU-285-2202 is titled, "An Open-label, Single Arm, Phase 2 Study to Evaluate Efficacy and Safety of Avapritinib (BLU-285), A Selective KIT Mutation-Targeted Tyrosine Kinase Inhibitor, in Patients with Advanced Systemic Mastocytosis." The study was initiated November

21, 2018 and the data cutoff date was June 23, 2020. The Applicant states that the study is ongoing and the planned completion date is May 2022. The study was conducted in the United States and European Union. The primary objective of the study was to determine adjudicated ORR based on mIWG-MRT-ECNM consensus response criteria in patients with AdvSM. The key secondary objective was to assess mean change from baseline in AdvSM-SAF TSS. However, due to the single arm design of the study no conclusion can be made regarding the PRO TSS. Additional secondary endpoints included duration of response, change in bone marrow mast cell burden, change in KIT D816V mutant allele burden, and change in serum tryptase level.

Trial Design

This study is an open-label, single-arm, Phase 2 study in patients with AdvSM. The study enrolled two cohorts of patients, i.e., cohort 1 consisting of patients with AdvSM with ≥ 1 mIWG-MRT-ECNM criteria for evaluable disease (severe and quantifiable organ damage; an evaluable C-finding or have MCL; or cohort 2 consisting of patients with AdvSM patients who were not considered eligible for an adjudicated response and were confirmed centrally to have ASM or SM-AHN, but were lacking an evaluable C-finding. Approximately 103 patients total were planned to be enrolled. The starting avapritinib dose was 200 mg administered orally once daily in 28-day cycles until unacceptable toxicity or disease progression. The starting dose was reduced to 100 mg once daily for patients with platelet counts from 25,000/μL to 50,000/μL at baseline, resulting in the enrollment of one patient who met this criterion. Due to the potential increased risk of bleeding in patients with platelet counts <50,000/μL, these patients were excluded from enrollment entirely with subsequent protocol amendments. This review focuses on the evaluation of safety and efficacy primarily among patients who were treated with an avapritinib starting dose of 200 mg. The avapritinib 200 mg starting dose is the Applicant's proposed recommended starting dose for avapritinib for patients with AdvSM. The safety population included all patients who received ≥ 1 dose of avapritinib. AEs were characterized and graded according to NCI-CTCAE v. 5.0 criteria. There are only minor differences between NCI-CTCAE v. 4.03 and v5.0 criteria consisting primarily in the baseline status (normal/abnormal) of clinical laboratories that were used in deriving toxicity (Zhong, 2020) The Applicant's figure below shows the study schema

Figure 2: Study Schema BLU-285-2202



Abbreviations: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; ECOG = Eastern Cooperative Oncology Group; IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; MCL = mast cell leukemia; ORR = overall response rate; PR = partial remission; QD = once daily; SAF = Symptom Assessment Form; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm; SSC = Study Steering Committee; TSS = total symptom score.

Sponsor's figure Completed Study Report (CSR) BLU-285-2202 page 5

The key inclusion criteria are as follows.

- Patient age ≥ 18 years.
- Diagnoses based on World Health Organization (WHO) diagnostic criteria of ASM; SM-AHN or MCL.
- At least 1 C-finding attributable to SM for cohort 1.

- Histologically confirmed disease by bone marrow biopsy performed within 56 days of C1D1.
- Eastern Cooperative Oncology Group (ECOG) performance status 0-3.
- Serum tryptase ≥ 20 ng/mL.

The key exclusion criteria of the study are as follows.

- No prior avapritinib therapy.
- Patient has received any cytoreductive therapy (including midostaurin and other TKIs, hydroxyurea, azacitidine) or an investigational agent less than 14 days, and for cladribine, interferon alpha, pegylated interferon and any antibody therapy (e.g., brentuximab vedotin) less than 28 days before obtaining screening bone marrow biopsy.
- Patient received any hematopoietic growth factor within 14 days of screening.
- Surgical procedure within 14 days of the first dose of study drug.
- Candidate for allogeneic hematopoietic stem cell transplantation for treatment of SM.
- Patient has eosinophilia and known positivity for the FIP1L1-PGDFRA fusion unless the patient has demonstrated relapse or PD on prior imatinib therapy.
- Patient has history of another primary malignancy that has been diagnosed or required therapy within 3 years before the first dose of study drug.
- Serum aspartate amino transferase (AST) or ALT > 3.0 × ULN. There is no restriction if due to suspected liver infiltration by mast cells (MCs).
- Serum TBili > 1.5 × ULN. There is no restriction if due to suspected liver infiltration by MCs or Gilbert's disease.
- Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 or creatinine> 1.5 × ULN.
- Platelet count < 50,000/μL.
- QTcF > 480 msec.
- History of a seizure disorder.
- History of a cerebrovascular accident or transient ischemic attacks within 1 year before the first dose of study drug.

The study schedule is shown below.

Table 7: Study Schedule (BLU-285-2202)

Study Activities			Study Treatment							EOT[a]	Safety F/U	F/U for PD[g]	F/U for OS[b]
						Every 2 months C3 to C11		Every 3 months after C11[c]					
Time Period/Cycle	Screening		C1		C2	C3, C7, C11 (S&E)	C5, C9 (S)	C14, C20, etc. (S)	C17, C23, etc. (S&E)				
Study Day	-56 to -8	-7 to -1	Baseline D1	D15	D1	D1	D1	D1	D1	14 days post last dose	30 days post last dose	Every 6 months	Every 3 months
Window (Days)		+3		±2	±3	±7	±7	+14	+14	±7	±7	±14	±14
Informed consent[d]	X												
Inclusion/exclusion criteria	X												
Demographics	X												
Medical history[e]	X												
RBC and platelet transfusion data collection[f]	X	X										X[g]	
Paracenteses and thoracenteses and diuretics[h]	X	X										X[g]	
Height	X												

D-8). The patient must be eligible before they start the PRO (AdvSM-SAF) on D-7. Baseline assessments may be obtained within 7 days before C1D-7, when the patient begins the AdvSM-SAF assessment. If Baseline assessments are collected during this time, they will not need to be re-done at C1D1.

l Coagulation studies include international normalized ratio, activated partial thromboplastin time, and fibrinogen. If they are within the normal range through C3D1 than they can be discontinued and obtained only as clinically indicated.

m The comprehensive serum chemistry panel includes sodium, potassium, blood urea nitrogen or urea, bicarbonate (venous), creatinine, calcium, chloride, magnesium, phosphorus, albumin, aspartate aminotransaminase, alanine aminotransaminase, alkaline phosphatase, and total and direct bilirubin. Any alkaline phosphatase ≥ Grade 3 should be fractionated to determine if it is of bone or liver origin.

n Avapritinib will be administered QD in the morning at least 2 hours after and 1 hour before eating. On study visit days when PK samples are collected, patients will take their dose of avapritinib under observation at the study clinic after the pre-dose (trough) PK sample has been obtained.

o PK sampling will be performed as specified in Appendix 2 (Part 1) or Appendix 3 (Part 2, Cohorts 1 and 2). Additionally, investigators may obtain blood samples for PK analysis at the time(s) that significant drug-related AEs occur.

p Blood samples for tryptase and KIT mutant allele burden will be obtained on C1D1, C1D15, C2D1, C3D1, C5D1, C7D1, C11D1, C18D1 and every 6 cycles thereafter, including post EOT in those patients discontinued from treatment for reasons other than progressive disease or initiation of other cytoreductive therapy. Samples should also be obtained at the time of disease progression.

q Bone marrow biopsy and aspiration. For further details refer to (Section 7.4).

r Bone marrow biopsy and aspiration, a peripheral blood smear, and imaging of the liver and spleen will be performed on C3D1, C5D1 (imaging only), C7D1, C11D1, C18D1, and every 6 cycles thereafter. For further details refer to Section 7.4. Response per modified IWG-MRT-ECNM criteria should be assessed on the same schedule as BM sampling ie. C3D1, C7D1, C11D1, C18D1 and every 6 cycles thereafter.

s Patients with a response of CR, CRh or PR will have their response confirmed 12 weeks after documentation of first response. This confirmation will include bone marrow biopsy and aspirate, measurement of liver and spleen by palpation and imaging, serum tryptase and hematology and chemistry laboratories. Additional study visit and procedures may be necessary if this 12 week confirmation does not coincide with a scheduled study visit.

t MRI is the primary measure of liver and spleen volume; CT may be used for patients not eligible for MRI (eg, metal clips in body; claustrophobia). See (Section 7.5) for further details. For Part 2, scans should be performed according to procedures outlined in the vendor provided Study Manual and scans will be sent for Central Review.

u MRI or CT of the brain to be performed at C2D1, C3D1, and C4D1.

v Only during Part 2, patients will complete the AdvSM-SAF daily from C1D7 through and including C12D28.

w Only during Part 2, EORTC QLQ-C30 and PGIS will be administered on D1 of each cycle for C1 through C12.

x AEs are to be collected from the start of study drug administration through the Safety Follow-up visit.

y SAEs and concomitant medications are to be collected from the date of the informed consent signature through the Safety Follow-up visit.

Sponsor's table protocol Blu-285-2101 pages 102-106

Study Endpoints

The primary efficacy endpoint was overall response rate (ORR) and duration of response; by modified IWG-MRT-ECNM criteria change in serum tryptase level. The key secondary endpoint was patient reported outcomes as assessed by the AdvSM-SAF. Other secondary endpoints included change in KIT D816V mutant allele fraction; change in serum tryptase level and change in bone marrow mast cell burden.

Compliance with Good Clinical Practices

A signed written informed consent form is required for enrollment into the study. The study is conducted according to International Conference on Harmonization (ICH) and Good Clinical Practice Guidelines. An Independent Ethics Committee (IEC) and Institutional Review Board (IRB) will review and monitor the study.

Patient Disposition

This study enrolled a total of 62 patients in the Safety Population. The primary reasons for treatment discontinuation were disease progression and adverse events. Patient disposition in the Response-evaluable Population, which excluded 30 patients who are not response-evaluable by mIWG-MRT-ECNM criteria, was similar to the Safety Population of all enrolled patients. The reviewer's Table 8 below shows the patient disposition in study BLU-285-2202.

Table 8: Disposition (BLU-285-2202)

Disposition Reason	Response Evaluable N=32 n, (%)
Discontinued from treatment	8 (25%)
Continuing on treatment	24 (75%)
Discontinued from study	7 (22%)
Disease progression	2 (6%)
AML	1 (3%)
Adverse event(s) Related	5 (16%) 2 (6%)
Withdrew consent	1 (3%)
Investigator's decision	1 (3%)
Administrative/other	1 (3%)
Adverse event(s) Death Withdrew consent	4 (13%) 4 (13%) 1 (3%)

Reviewer's table with assistance from Dr. Cai.

Reviewer comment for Section 6 Review of Relevant Individual Studies Used to Support Efficacy: AdvSM consists of rare disease subtypes, i.e., ASM, SM-AHN and MCL. The Studies BLU-285-2101 and BLU-285-2202 are adequately designed to evaluate response rates based on mIWG-MRT-ECNM criteria. Responses were adjudicated in both studies by a Central Adjudication Committee (CAC). Also, these criteria were used to evaluate the efficacy of midostaurin which is indicated for the treatment of patients with AdvSM. This review focuses on evaluation of safety and efficacy among patients with ASM and SM-AHN who were primarily treated with the recommended dose of avapritinib, i.e., 200 mg administered orally once daily.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The efficacy of avapritinib was demonstrated in Study BLU-285-2101 and Study BLU-285-2202, which were two multi-center, single-arm, open-label studies. In Study BLU-285-2101, the median age was 65 years (range: 34 to 83 years). The baseline characteristics of patients in the response evaluable group were similar to the safety population based on all enrolled patients. The demographics of the patients enrolled is summarized in the reviewer's Table 9 below.

Table 9: Summary Key Demographics (BLU-285-2101)

Criterion	Response Evaluable (N=53) n, (%)
Age (years) <65 / ≥65 median, (range)	26 / 27 (49% / 51%) 65 (34, 83)
Female	23 (43%)
White	47 (89%)
KIT D816V Mutation Positive	51 (96%)
Prior Antineoplastic Therapy	32 (60%)
Prior Midostaurin	17 (32%)
ECOG ≥ 2	17 (32%)

Reviewer's table consisting of input from Dr. Ryan, Dr. Dmytrijuk, and Dr. Cai

In Study BLU-285-2202 the median age was 69 years (range: 31 to 88 years).
The baseline characteristics of patients in the response evaluable group were similar to the Safety Population of all enrolled patients. The demographics of the patients enrolled is summarized in the reviewer's Table 10 below.

Table 10: Summary Key Demographics (BLU-285-2202)

Criterion	Response Evaluable (N=53) n, (%)
Age (years) <65 / ≥65 median, (range)	12/ 20 (38% / 63%) 68 (37, 85)
Female	14 (44%)
White	32 (100%)
KIT D816V Mutation Positive	30 (94%)
Prior Antineoplastic Therapy	23 (72%)
Prior Midostaurin	17 (53%)
ECOG ≥ 2	11 (66%)

Reviewer's table consisting of input from Dr. Ryan, Dr. Dmytrijuk, and Dr. Cai

Overall the demographics of patients in the two studies BLU-285-2101 and BLU-285-2202 were similar with the exception that patients in Study BLU-285-2202 had a higher proportion of patients with ECOG performance status ≥ 2 (66%) compared to the proportion of patients in Study BLU-285-2101 (32%). It is not likely that this imbalance had an impact on the primary efficacy endpoint because of the objective nature of mIWG-MRT-ECNM criteria which were adjudicated but could have an impact on survival/durability of response.

7.1.1. Primary Endpoints

The reviewer's Table 11 below show the results of the pooled efficacy analysis for the response evaluable group from Studies BLU-285-2101 and BLU-285-2202. There were 2/2 patients in the response evaluable group with ASM who achieved complete response (CR), complete hematologic response (CRh) or partial response (PR) during the treatment period (ORR 100%; 95% CI=16%, 100%). The median time to response was 4.6 months. The median duration of response was not reached at the time of data cut-off. There were 17/32 patients in the response evaluable group with SM-AHN who achieved CR, CRh or PR during the treatment period (ORR of 53%; 95% CI=34%, 71%). The median time to response was 2 months. The median duration of response was not reached at the time of data cut-off.

Table 11: Pooled Efficacy Analysis (BLU-285-2101 and BLU-285-2202)

	200 mg Dose		≤ 200mg Doses		All Doses	
	ASM	SM-AHN	ASM	SM-AHN	ASM	SM-AHN
Best Response by mIWG-MRT-ECNM Criteria						
Response-evaluable patients, N	N=2	N=32	N=2	N=40	N=5	N=63
CR, n (%)	0	0	0	2 (5%)	0	5 (7.94%)
CRh, n (%)	1 (50%)	7 (21.88%)	1 (50%)	11 (27.5%)	3 (60%)	14 (22.22%)
PR, n (%)	1 (50%)	10 (31.25%)	1 (50%)	10 (25%)	2 (40%)	21 (33.33%)
CI, n (%)	0	7 (21.88%)	0	8 (20%)	0	9 (14.29%)
SD, n (%)	0	4 (12.5%)	0	5 (12.5%)	0	10 (15.87%)
PD, n (%)	0	0	0	0	0	0
NE, n (%)	0	4 (12.5%)	0	4 (10%)	0	4 (6.35%)
ORR=CR+CRh+PR, n (%)	2 (100%)	17 (53.12%)	2 (100%)	23 (57.5%)	5 (100%)	40 (63.49%)
95% confidence interval for ORR (using the nominal one-sided alpha=0.025)	(15.81%, 100%)	(34.74%, 70.91%)	(15.81%, 100%)	(40.89%, 72.96%)	(47.82%, 100%)	(50.4%, 75.27%)
98.75% confidence interval for ORR (using the protocol specified interim analysis one-sided alpha=0.00625)	(7.91%, 100%)	(30.48%, 74.88%)	(7.91%, 100%)	(36.84%, 76.4%)	(36.24%, 100%)	(47.02%, 77.98%)
99.48% confidence interval for ORR (using the O'Brien-Fleming interim one-sided alpha=0.0026)	(5.1%, 100%)	(28.22%, 76.95%)	(5.1%, 100%)	(34.66%, 78.25%)	(30.41%, 100%)	(45.16%, 79.41%)
Wald test p-value (null ORR=17%)	NA[1]	<.0001	NA[1]	<.0001	NA[1]	<.0001
Wald test p-value (null ORR=25%)	NA[1]	0.0007	NA[1]	<.0001	NA[1]	<.0001
Time to response[2] (month)						
Median	4.6	1.9	4.6	1.9	3.7	2
Min – Max	3.71-5.55	1.71-26.74	3.71-5.55	1.71-26.74	1.87-5.55	1.71-26.74
Duration of Response[3] (month)						
Events, n	0	1	0	4	0	9
Censored, n	2	16	2	19	5	31
Median	NR	NR	NR	38.3	NR	38.3
Min – Max	5.03[4]-6.47[4]	3.71[4]-15.67[4]	5.03[4]-6.47[4]	3.75[4]-41.1[4]	5.03[4]-25.53[4]	2.99-41.1[4]
95% approximate confidence interval for median	(NE, NE)	(NE, NE)	(NE, NE)	(19.35,NE)	(NE, NE)	(19.35, NE)
95% exact confidence interval for median	(NE, NE)	(NE, NE)	(NE, NE)	(19.35,NE)	(NE, NE)	(19.35, NE)

Wald test is not applicable when the estimated ORR=0 or 1. 2. Time to response was defined as the time from the start of treatment to the time a CR/CRh/PR was first met. Patients without confirmed CR/CRh/PR were excluded from analysis. 3. Duration of response is defined as the time in months from first documented response to the date of first documented disease progression, loss of response, or death due to any cause, whichever occurs first. Patients without confirmed response are excluded from this analysis. Patients who are still in response at the time of data cutoff were censored at their last valid assessment. 4. Censored observation.
Reviewer's table adapted from Dr. Cai.

7.1.2. Secondary and Other Endpoints

Change in patient reported outcomes as assessed by the AdvSM-SAF, PGIS, and EORTC QLQ-C30 tools was a primary or secondary efficacy analysis in the studies. However, due to the single

arm design of the study, no conclusion regarding change in PRO or QoL components could be made.

Dr. Xiaoyu Cai notes that the Safety Population was used for key secondary analyses, all safety analyses, patient-reported outcome analyses, and the efficacy analyses that were not based on mIWG-MRT-ECNM response criteria. The Response-evaluable Population was used for the primary efficacy analysis and for all secondary efficacy analyses related to response.

The primary endpoint for efficacy is the overall response rate (ORR), which is defined as the sum of the proportions of patients with a confirmed best response of complete remission (CR), CR with partial recovery of counts (CRh), or partial response (PR), as defined by the modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis (mIWG-MRT-ECNM) criteria, confirmed 12 weeks after initial response.

Dr. Xiaoyu Cai stated in her biostatistics efficacy review: "Success for the primary endpoint was met if the lower bound of the 99.48% confidence intervals (CI) was greater than the pre-defined ORR value of 17% for the SM-AHN population." Dr. Cai continued: "There were too few response-evaluable patients in the ASM population, therefore no meaningful statistical inference can be concluded. Note that the reason why the 99.48% CI should be considered is because the studies were terminated earlier and thus the type I error rate should be adjusted via some valid group sequential testing procedure such as O'Brien-Fleming alpha spending method."

All subtypes of SM are rare and as a group the incidence of SM is estimated to be 5-10 patients per million people. KIT D816V mutations mediate ligand independence in AdvSM. Chronic inflammatory mediator release is associated with cachexia, chronic gastrointestinal symptoms, diffuse musculoskeletal pains, tissue remodeling, fibrosis and end organ damage. Therefore, ASM, SM-AHN and MCL, i.e., advanced systemic mastocytosis (AdvSM), are serious and potentially fatal conditions. Few treatment options are currently available for patients with AdvSM, i.e., imatinib and midostaurin.

Treatment with imatinib requires prior determination of the D816V c-Kit mutation status. For patients with ASM associated with eosinophilia, a clonal hematological disease related to the fusion kinase FIP1L1-PDGFRα, a starting dose of 100 mg/day is recommended for patients' treatment with imatinib which limits the types of patients who may be imatinib therapy candidates. The pooled efficacy analysis from Studies BLU-285-2101 and BLU-285-2202 based on patients the response evaluable patient group shows that 2/2 patients with ASM who achieved response during the treatment period (ORR 100%; 95% CI=16%, 100%). There were 17/32 patients in the response evaluable group with SM-AHN who achieved response during the treatment period (ORR of 53%; 95% CI=34%, 71%). The median duration of response was

not reached at the time of data cut-off. Therefore, patients with AdvSM (ASM or SM-AHN) had a response to therapy. Also, the median time to response was 4.6 months among patients with AdvSM and the median time to response was 2 months among patients with SM-AHN.

Dr. Xiaoyu Cai reported the following conclusions in her statistics review of efficacy:

1. (b) (4)

2. The 2 patients with ASM are not sufficient to support by themselves an indication. However, Dr. Cai stated: "Whether the ASM indication can be approved is deferred to the clinical reviewer's scientific judgement."

3. Dr. Cai concluded: "The Applicant's data support the efficacy of avapritinib in the treatment of adult patients with SM-AHN."

8. Review of Safety

8.1. Safety Review Approach

The safety review was focused on the patients with AdvSM in Studies BLU-285-2202 and BLU-285-2101 (Primary Safety Populations). Pooled safety population included patients with AdvSM (Studies BLU-285-2101 and BLU-285-2202) and unresectable or metastatic GIST (BLU-285-1101 and BLU-285-1303) who received avapritinib at any dose (Pooled Safety Population). The reviewer also sub-grouped both primary and pooled safety population by the starting dose to facilitate comparative safety analysis, as shown in Table 12.

Table 12: Safety Subpopulation List

Safety Population	Trial Source	Dose Group (mg)	Diagnosis Included (n)
AdvSM200 N = 81	BLU-285-2202, BLU-285-2101	200	ASM (10) SM-AHM (55), MCL (16)
Primary Safety N = 148	BLU-285-2202, BLU-285-2101	30, 60, 100, 200, 300, 400	SSM (2) ISM (14), SM-AHM (91), ASM (17), MCL(22), Non SM (1)
Pooled safety population N = 749	BLU-285-2202, BLU-285-2101, BLU-285-1101 BLU-285-1303	30, 60, 100, 200, 300, 400 for SM; 30, 60, 135, 200, 300, 400, 600 for GIST	SM & AdvSM (148), GIST (601)

Source: The FDA's table.

The pooled SP contains 749 patients, 148 were from AdvSM trials, which includes MCL, and 601 patients were from GIST trials. Pooled SP dosing groups by the assigned starting dose including 30, 60, 100, 130, 135, 200, 300, 400, and 600 mg. The pooled SP was used for assessing overall safety profile and the difference of avapritinib toxicity between AdvSM and GIST.

In the primary safety population, grouped by starting dose, 81 patients were in AdvSM 200 mg group, and 50 in the AdvSM 300 mg group. The safety population subgroups, especially AdvSM 200 mg and 300 mg groups, provided pertinent information to evaluate dose-toxicity relationships in patients with AdvSM. Available safety data from all patients with systemic mastocytosis, as well as advanced GIST were used to support the analysis of safety in a larger patient population, as shown in Table 12 above.

It's noteworthy that at the time of this NDA supplement submission, all four trials included to support the safety are still ongoing, as shown in Table 13 below. The two GIST trials 1101 and 1303 were reviewed previously for the original NDA.

Table 13: Avapritinib Trials Included in the Safety Datasets

	Study Number			
	BLU-285-2101	BLU-285-2202	BLU-285-1101[a]	BLU-285-1303[a]
Status	Ongoing	Ongoing	Ongoing	Ongoing
Phase	1	2	1	3
Study Design and Objectives	Multicenter, open-label, dose escalation with expansion Primary: MTD, RP2D, safety and tolerability Secondary: PK, pharmacodynamics, QoL, clinical activity	Multicenter, open-label, single-arm Primary: ORR Secondary: Safety and tolerability, clinical activity, QoL, PK	Multicenter, open-label, dose escalation with expansion at the MTD or RP2D Primary: dose escalation - MTD, RP2D, safety and tolerability; expansion - ORR, safety and tolerability Secondary: PK, clinical activity	Multicenter, open-label, randomized with comparator (regorafenib) and crossover option Primary: progression-free survival Secondary: PK, QoL, safety and tolerability, clinical activity
Study Population	Patients with AdvSM and other relapsed or refractory myeloid malignancies. Patients in Cohort 1 did not meet mIWG-MRT-ECNM criteria. Patients in Cohort 2 did meet mIWG-MRT-ECNM criteria.	Patients with AdvSM including aggressive systemic mastocytosis, systemic mastocytosis with an associated hematologic neoplasm, and mast cell leukemia. Patients in Cohort 1 met mIWG-MRT-ECNM criteria. Patients in Cohort 2 did not meet mIWG-MRT-ECNM criteria.	Dose escalation: patients with unresectable GIST (PD after imatinib + 1 other TKI or disease with PDGFRA D842 mutation) or advanced solid tumor other than GIST relapsed or refractory to treatment Expansion: patients with unresectable GIST who had PD after imatinib + 1 other TKI and did not have PDGFRA D842 mutation; patients with unresectable GIST who had PDGFRA D842 mutation; or patients with unresectable GIST who had PD and/or were intolerant to imatinib and did not have PDGFRA D842 mutation	Patients with metastatic and/or unresectable GIST with PD, inadequate clinical benefit, or intolerance to imatinib and 1 or 2 other TKIs
Study Drug Dose(s) and Regimen(s)	Dose escalation: avapritinib PO at 30, 60, 100, 130, 200, 300, 400 mg QD on Days 1 to 28 of each 28-day cycle	Avapritinib: 200 mg PO QD on Days 1 to 28 of each 28-day cycle	Dose escalation: avapritinib PO at 30, 60, 90, 135, 200, 300, 400, 600 mg QD on Days 1 to 28 of each 28-day cycle Expansion: avapritinib PO at 300 mg (RP2D) or 400 mg (MTD) QD	Avapritinib: 300 mg PO QD on Days 1 to 28 of each 28-day cycle; may escalate to 400 mg QD after 2 consecutive cycles

	Study Number			
	BLU-285-2101	BLU-285-2202	BLU-285-1101[a]	BLU-285-1303[a]
	Expansion: avapritinib PO at 300 mg and 200 mg[b] (Cohort 1) or 200 mg (Cohort 2) QD			Regorafenib: 160 mg PO QD on Days 1 to 21 of each 28-day cycle
Treatment Duration	Until toxicity, noncompliance, withdrawal of consent, physician decision, PD, death, or closure of study by Sponsor	Until toxicity, noncompliance, pregnancy, withdrawal of consent, physician decision, PD, death, or closure of study by Sponsor	Until toxicity, noncompliance, withdrawal of consent, physician decision, PD, death, or closure of study by Sponsor	Until toxicity, noncompliance, pregnancy, withdrawal of consent, physician decision, PD, death, or closure of study by Sponsor
Number of Countries (Sites) with Centers Enrolling Patients	2 (11)	8 (18)	9 (18)	18 (94)
Number of Patients	Planned: 80 (dose escalation up to 25; expansion up to 55) Dosed: 86 (32 dose escalation; 54 expansion) Discontinued treatment: 41 Continuing treatment: 45	Planned: 103 Dosed: 62 Discontinued treatment: 10 Continuing treatment: 52	Planned: 235 (dose escalation up to 50; expansion up to 185) Dosed: 250 (46 dose escalation; 204 expansion) Discontinued treatment: 207 Continuing treatment: 43	Planned: 460 (230 avapritinib; 230 regorafenib) Dosed: 473 (239 with avapritinib, 234 with regorafenib)
Demographics	46 M/40 F 34-83 years (median 64 years) White: 87.2%; Asian: 2.3%; Black: 1.2%; Other/Unknown: 9.3%	34 M/28 F 31-88 years (median 68.5 years) White: 87.1%; Asian: 1.6%; Black: 0%; Other/Unknown: 11.3%	154 M/96 F 25-90 years (median 61.0 years) White: 72.4%; Asian: 8.8%; Black: 4.8%; Other/Unknown: 12.8%	316 M/157 F 31-91 years (median 61.0 years) White: 59.0%; Asian: 27.1%; Black: 3.0%; Other/Unknown: 10.6%
Analysis Cutoff Date for Integrated Safety Analyses: 27 May 2020 for BLU-285-1101, BLU-285-1303, and BLU-285-2101; 23 June 2020 for BLU-285-2202.				
Analysis Cutoff Date for Late-breaking Safety Information: 18 September 2020				

Abbreviations: AdvSM = advanced systemic mastocytosis; CSR = clinical study report; F = female; GIST = gastrointestinal stromal tumor; M = male; mIWG-MRT-ECNM = modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on
Source: NDA 212608-S6, 2.7.4, 1.1, table 1.

The Applicant proposed a regimen of 200 mg once daily with a dose reduction schema for patients with AdvSM, including ASM, SM-AHM, and MCL. Study BLU-285-2101 initially determined avapritinib 300 mg once daily to be the maximum tolerate dose for AdvSM and therefore, the dose expansion portion of the trial initially enrolled patients at a starting dose of 300 mg. Due to a high rate of central nervous system adverse events (predominantly cognitive effects), the starting dose was reduced to 200 mg. The 200 mg starting dose was recommended and implemented for the phase 2 study, Study BLU-285-2202.

The Primary Safety Population in this review includes all patients with AdvSM enrolled in Studies BLU-285-2202 and BLU-285-2101. The safety evaluation includes both 200 and 300 mg dose groups, as well as other doses. All safety analyses were conducted on the datasets provided by the Applicant for Studies BLU-285-2101 and BLU-285-2202, which used a data cut-off date of 5/27/2020 and 6/23/2020, respectively. The data cut-off date for the two GIST Studies (BLU-285-1101 and BLU-285-1303) was also 5/27/2020. However, the 120-day safety

update data cut-off are the same for all four trials (12/18/2020). In addition, late-breaking safety data from 12/18/2020 through 2/12/2021 are also submitted.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The FDA's exposure analysis is shown in Table 14 below, which is consistent with the applicant's analysis. A total of 749 patients were exposed to avapritinib at any given dose, ranging from 30 mg to 600 mg once daily as the staring dose, in the pooled safety population. Primary Safety Population included 148 patients from AdvSM trials. Among them, 131 patients had AdvSM, 81 and 50 patients with AdvSM received 200 mg and 300 mg daily dose of avapritinib, respectively.

Table 14: Avapritinib Exposure in AdvSM and Pooled Safety Populations

Exposure Parameters	AdvSM			Ava (AdvSM +GIST)
	200 mg N=81	≥ 300 mg N=50	All N=148	All N=749
Overall Treatment Duration[a] (weeks)				
Mean (StdDev)	35.29 (28.496)	85.32 (48.072)	64.45 (56.094)	40.16 (45.042)
Median	30.29	89.64	41.29	24.00
Min, Max	0.9, 179.3	14.1, 168.9	0.9, 220.0	0.1, 239.4
Interval Exposure				
≤ 4 weeks	3 (3.7)	0	4 (2.7)	53 (7.1)
> 4 to ≤ 8 weeks	5 (6.2)	0	6 (4.1)	116 (15.5)
> 8 to ≤ 12 weeks	2 (2.5)	0	2 (1.4)	61 (8.1)
> 12 to ≤ 16 weeks	10 (12.3)	1 (2.0)	11 (7.4)	56 (7.5)
> 16 to ≤ 20 weeks	8 (9.9)	2 (4.0)	10 (6.8)	49 (6.5)
> 20 to ≤ 24 weeks	5 (6.2)	4 (8.0)	9 (6.1)	40 (5.3)
> 24 to ≤ 28 weeks	5 (6.2)	0	6 (4.1)	43 (5.7)
> 28 to ≤ 32 weeks	8 (9.9)	1 (2.0)	9 (6.1)	39 (5.2)
> 32 to ≤ 36 weeks	7 (8.6)	4 (8.0)	11 (7.4)	39 (5.2)
> 36 to ≤ 40 weeks	4 (4.9)	1 (2.0)	5 (3.4)	20 (2.7)
> 40 to ≤ 44 weeks	5 (6.2)	3 (6.0)	8 (5.4)	24 (3.2)
> 44 to ≤ 48 weeks	3 (3.7)	1 (2.0)	4 (2.7)	20 (2.7)
> 48 to ≤ 52 weeks	2 (2.5)	0	2 (1.4)	14 (1.9)
> 52 to ≤ 56 weeks	1 (1.2)	1 (2.0)	3 (2.0)	9 (1.2)
> 56 weeks	13 (16.0)	32 (64.0)	58 (39.2)	166 (22.2)
Exposure Intensity[b] (administered mg/planned mg /day)[c]				
Mean (± StdDev)	0.68 (0.262)	0.56 (0.196)	0.71 (0.389)	0.94 (0.567)
Median	0.62	0.54	0.63	0.89
Min, Max	0.2, 1.4	0.3, 1.1	0.2, 2.9	0.2, 7.8
Exposure Intensity[b] (%)[d]				

< 75%	51 (63.0)	43 (86.0)	95 (64.2)	295 (39.4)
≥ 75% to < 90%	6 (7.4)	4 (8.0)	14 (9.5)	90 (12.0)
≥ 90% to < 120%	23 (28.4)	3 (6.0)	31 (20.9)	251 (33.5)
≥ 120% to < 150%	1 (1.2)	0	3 (2.0)	35 (4.7)
≥ 150%	0	0	5 (3.4)	78 (10.4)

AdvSM = advanced systemic mastocytosis; Ava = avapritinib; GIST = gastrointestinal stromal tumor; Max = maximum; Min = minimum; StdDev = standard deviation.

a. Duration of treatment (weeks) = (treatment end date - treatment start date + 1)/7.
b. Exposure intensity was defined as the ratio of dose intensity/planned dose intensity by the applicant.
c. Exposed intensity was calculated as the cumulative dose divided by the treatment duration. Planned dose intensity was based on the initially assigned daily dose.
d. Percentages are based on the number of patients in the Safety Population in each column.

Source: FDA's analysis by using NDA 212608 S6 dataset submitted 12/16/2020.

In the Primary Safety Population (Studies BLU-285-2101 and BLU-285-2202), the median duration of exposure to avapritinib was 41.3 weeks for all AdvSM patients treated at all doses of avapritinib. The median duration of exposure to avapritinib was 30.3 weeks and 89.6 weeks for the 200 mg and ≥300 mg dose groups, respectively. The maximum exposure time was 179 and 169 weeks for the 200 mg and the ≥300 mg dose groups, respectively.

In addition, 88.5% (131/148) of the patients in the Primary Safety Population received avapritinib the proposed daily dose of 200 mg or higher sometime during the AdvSM trials. In the 200 mg AdvSM group, the median treatment duration was 30 weeks with a median exposure of 62% of planned exposure. Patients with AdvSM who received 75% or higher of the planned dose intensity were 37% in 200 mg group and 14% in 300 mg group.

In the Pooled Safety Population pool (n=749), the median duration of exposure to avapritinib was 24 weeks (mean 40 weeks), with a maximum exposure time of 239 weeks. A total of 45 patients in SM trials were exposed to avapritinib for more than 12 months.

Besides treatment drug exposure, many patients also received concomitant medications. The concomitant medications included diuretics, analgesics/antipyretics, antiemetics, corticosteroids, H_2 blockers, and proton pump inhibitors.

8.2.2. Relevant characteristics of the safety population:

Two AdvSM Studies, BLU-285-2101 and BLU-285-2202, enrolled patients with SM at various stages, including ASM (n=17) , SM-AHN (n – 91), MCL (n = 23), ISM (n = 14) and SSM (n = 2). One patient did not have a SM diagnosis, as shown in Table 15 below.

Table 15: Individuals Exposed to Avapritinib by Trial and Diagnosis

Clinical Trial Groups Exposed to avapritinib (n)[1]	ASM	SM-AHN	MCL	AdvSM Total	ISM	SSM	Non SM
BLU-285-2101	8	48	13	69	14	2	1
BLU-285-2202	9	43	10	62	0	-	
SM Total	17	91	23	131	14	2	1
Clinical Trial	Total Subjects Exposed to avapritinib (any dose level)						
BLU-285-2101 and BLU-285-2202 (SM and MCL)	148						
BLU-285-1303 and BLU-285-1011 (GIST)[2]	601						
SM + GIST Total	749						

1. The SM subtype is summarized based on the applicant's reports.
2. Randomized trial Blu-285-1013 had 239 subjects exposed to avapritinib.
3. Reviewed in original NDA for GIST indication.

Source: The FDA generated table based on the applicant provided reports.

The number of patients from Trials BLU-285-2201 and BLU-285-2202 treated at each avapritinib starting dose group are shown in the Table 16 below.

Table 16: Patients with AdvSM Treated in Each Avapritinib Dosing Group

Dose exposed (mg)	Total	2101	2202
30	3	3	0
60	4	4	0
100	4	3	1
130	3	3	0
200	82	21	61
300	43	43	0
400	7	7	0

Source: FDA's analysis using NDA 212608 S6 dataset submitted 12/16/2020

The number of patients with adjudicated diagnosis of SM subtypes by the applicant re-adjudicated committee (RAC) treated in assigned avapritinib groups are shown in Table 17 below.

Table 17: Avapritinib Exposure in SM Subtypes

SM stage	2101		2202		Combined	
Datasets	All	200 mg	All	200 mg	All	200 mg
ASM	8	1	9	9	17	10
SM-AHN	48	13	43	42	91	55
SSM	2	0	0	0	2	0
ISM	14	1	0	0	14	1
Non-SM	0	0	0	0	1	0
SM Total	*72*	*15*	*52*	*51*	*124*	*66*
MCL	13	6	10	10	23	16
AdvSM	*56*	*14*	*52*	*51*	*108*	*65*
AdvSM + MCL	*69*	*20*	*62*	*61*	*131*	*81*

Source: FDA's analysis by code SMGR2 (RAC adjudicated diagnosis) using NDA 212608 S6 dataset submitted 12/16/2020.

Reviewer Comments: The two Adv-SM trials, BLU-285-2101 and BLU-285-2202, enrolled a mixed population. In addition to patients with Adv-SM (ASM, SM-AHM, and MCL), the trials also included patients with SSM, ISM, and non-SM. The mixed patient population and various dosing group/exposure are challenges for safety and efficacy review.

8.2.3. Adequacy of the safety database:

The size of the safety database is adequate to reasonably estimate adverse reactions that may be observed in patients with AdvSM exposed to avapritinib; and the duration of treatment is adequate to allow assessment of adverse reactions over time. There are no randomized data regarding the safety of avapritinib in comparison to either a standard of care agent or placebo in patients with AdvSM, which would be helpful in understanding the contribution of the underlying disease to adverse reactions.

The demographics of the patients included in the safety pool (see Table 18 below) are representative of typical patients with AdvSM that participate in clinical trials. The median age of AdvSM population is older than that of the pooled population. Male/female ratio is fairly balanced.

White is the dominate race in AdvSM, 87%, with 3 % Hispanic, 2% Asian and <1% black. 100% patients are from Europe and North America. Of patients enrolled in AdvSM trials, about 30% patients had ECOG performance status 2 or 3 and about 40% had prior midostaurin use. Less than 10% of patients had platelet counts less than 50 x 10^9/L at baseline.

In addition, gene analyses were conducted in patients enrolled in the AdvSM trials. About 95% patients in AdvSM trials were tested positive for D816V or Y mutations.

Table 18: Safety Population Demographics

	AdvSM			Ava (AdvSM +GIST)
	200 mg N=81	≥ 300 mg N=50	All N=148	All N=749
Age (years)[a]				
Mean (StdDev)	66.8 (11.66)	62.8 (11.03)	64.6 (11.86)	61.1 (11.31)
Median	68.0	66.0	67.0	62.0
Min, Max	31, 88	34, 83	31, 88	25, 91
Age Group (years), n (%)[a]				
< 65	30 (37.0)	23 (46.0)	64 (43.2)	436 (58.2)
≥ 65	51 (63.0)	27 (54.0)	84 (56.8)	313 (41.8)
Sex, n (%)				
Female	35 (43.2)	23 (46.0)	68 (45.9)	273 (36.4)
Male	46 (56.8)	27 (54.0)	80 (54.1)	476 (63.6)
Race, n (%)				
American Indian or Alaska Native	0	0	0	2 (< 1)
Asian	1 (1.2)	2 (4.0)	3 (2.0)	124 (16.6)
Black or African American	0	1 (2.0)	1 (< 1)	24 (3.2)
Native Hawaiian or Other Pacific Islander	0	0	0	3 (< 1)
White	72 (88.9)	43 (86.0)	129 (87.2)	513 (68.5)
Other	6 (7.4)	0	7 (4.7)	26 (3.5)
Unknown	2 (2.5)	4 (8.0)	8 (5.4)	57 (7.6)
Ethnicity, n (%)				
Hispanic or Latino	3 (3.7)	1 (2.0)	5 (3.4)	22 (2.9)
Not Hispanic or Latino	72 (88.9)	46 (92.0)	134 (90.5)	648 (86.5)
Unknown	1 (1.2)	3 (6.0)	4 (2.7)	35 (4.7)
Not reported	5 (6.2)	0	5 (3.4)	44 (5.9)
Region, n (%)				
Asia	0	0	0	111 (14.8)
Europe	36 (44.4)	8 (16.0)	49 (33.1)	316 (42.2)
North America	45 (55.6)	42 (84.0)	99 (66.9)	322 (43.0)
Height (cm)				
n	76	45	137	699
Mean (+/- StdDev)	170.16 (9.422)	168.83 (9.566)	170.03 (9.556)	170.71 (9.657)
Weight (kg)				
n	81	50	148	748
Mean (+/-StdDev)	73.50 (15.231)	74.20 (17.605)	74.23 (16.484)	74.88 (18.636)

	AdvSM			Ava (AdvSM +GIST)
	200 mg N=81	≥ 300 mg N=50	All N=148	All N=749
BMI (kg/m^2)				
n	76	45	137	699
Mean (StdDev)	25.45 (5.018)	25.26 (4.590)	25.46 (4.904)	25.56 (5.542)
ECOG Performance Status, n (%)				
0	15 (18.5)	13 (26.0)	31 (20.9)	304 (40.6)
1	41 (50.6)	23 (46.0)	76 (51.4)	388 (51.8)
2	18 (22.2)	9 (18.0)	29 (19.6)	45 (6.0)
3	7 (8.6)	5 (10.0)	12 (8.1)	12 (1.6)
Prior Midostaurin Use, n (%)				
Yes	42 (51.9)	13 (26.0)	59 (39.9)	-
No	39 (48.1)	37 (74.0)	89 (60.1)	-
Nadir Platelet Count in Screening, n (%)				
< 50,000/µL	5 (6.2)	7 (14.0)	14 (9.5)	-
≥ 50,000/µL	76 (93.8)	43 (86.0)	134 (90.5)	-

AdvSM = advanced systemic mastocytosis; Ava = avapritinib; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; GIST = gastrointestinal stromal tumor; Max = maximum; Min = minimum; StdDev = standard deviation; TKI = tyrosine kinase inhibitor.

a. Age was calculated as [(year of consent) - (year of birth)] - [(month of consent) ≤ (month of birth)] + [(month of consent) = (month of birth) and (day of consent) ≥ (day of birth)].

Note: Prior TKIs received were for GIST population only and was not included.

Source: FDA's analysis using NDA 212608 S6 dataset submitted 12/16/2020.

Reviewer comments: Due to the protocol design differences between the two AdvSM trials, less patients with baseline platelet counts of < 50,000/µL enrolled in the 200 mg group (6%) compared to the 300 mg group (14%).

Table 19 below shows the study groups defined by starting daily dose and used to conduct and describe the safety analyses.

Table 19: Avapritinib Dose Groups

Treatment Group Title	Treatment Group Definition
AdvSM All	Patients from Studies BLU-285-2101 and BLU-285-2202 who received avapritinib at any starting dose
AdvSM 200 mg	Patients from Studies BLU-285-2101 and BLU-285-2202 who received a 200 mg starting dose of avapritinib
AdvSM ≥ 300 mg	Patients from Study BLU-285-2101 who received a starting dose of avapritinib ≥ 300 mg
GIST All	Patients from Studies BLU-285-1101 and BLU-285-1303 who received avapritinib at any starting dose
GIST 300 mg	Patients from Studies BLU-285-1101 and BLU-285-1303 who received a 300 mg starting dose of avapritinib, and patients from Study BLU-285-1303 who received a 300 mg starting dose of avapritinib after crossing over from regorafenib treatment
1303 Ava	Patients from Study BLU-285-1303 who received avapritinib after initial randomization
1303 Rego	Patients from Study BLU-285-1303 who received regorafenib after initial randomization
Ava (AdvSM+GIST) All	Patients who received avapritinib at any starting dose

Source: NDA212608-S6, 2.7.4, 1.1.3.2 Table2.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The safety data reviewed:

- S6 submission dated 12/16/020 (SDN80)
- Response to IR dated 2/26/2021 (SDN87)
- Safety updates dated 4/15/2021 (SDN 97)

The quality of the safety data submitted was adequate for primary review. The applicant provided analysis datasets for subjects on Trials BLU-285-2101, BLU-285-2202, BLU-285-1101 and BLU-285-1303, as well as data subsets for patients with AdvSM. In addition, the applicant provided narratives for subjects on all clinical trials who:

- Died within 30 days of last dose of study drug
- Discontinued from study drug due to an adverse event
- Experienced a treatment-related serious adverse event
- Experienced an adverse event of special interest
    - Cognitive Effects

- Intracranial hemorrhage

The data of patients with AdvSM on avapritinib dose level 200 mg and 300 mg, as well as patients with AdvSM who had severe or fatal AEs on other dose levels were traced back to the primary source (individual case report forms) and cross referenced to narrative, if available. No discrepancies were identified.

8.3.2. Categorization of Adverse Events

Adverse events were defined according to ICH E2A guidelines. Adverse events were reported and graded by the investigator using the NCI-CTCAE. CTCAE Version 4.03 were used for trials BLU-285-2101 and BLU-285-2101, CTCAE version 5.0 were used for trials BLU-285-1303 and BLU-285-2202. The data were collected and coded by the Applicant using MedDRA version 18.1.

Terms that referred directly to relapse, persistence of disease or progression of systemic mastocytosis or GIST were excluded from the FDA's analyses. Treatment-emergent adverse events (TEAE) excluded events that started before the start of the study drug or that started more than 30-days after the last dose of avapritinib. TEAEs were summarized by maximum grade per patient. The FDA compared the verbatim adverse event term with the coded MedDRA preferred term for all adverse events reported on trials BLU-285-2101, BLU-285-2202, BLU-285-1101, and BLU-285-1303, and did not identify any irregularities. The FDA grouped some related preferred terms for safety analyses. SMQ analysis was also performed and no additional safety signals were identified beyond those discussed below.

8.3.3. Routine Clinical Tests

Clinical laboratory evaluations for safety were performed at a local laboratory. Clinical laboratory evaluations were conducted at the time points outlined in study protocols. Safety laboratory tests evaluated by the Investigator included hematology, coagulation, serum chemistry, urinalysis, and serum or urine pregnancy test. In addition, all clinically significant laboratory abnormalities noted on testing were followed by repeat testing and further investigated according to the judgment of the Investigator.

8.4. Safety Results

As mentioned previously, the Studies BLU-285-2201 and BLU-285-2202 were single arm trials and not randomized trials with a comparator, the safety results are mainly hypothesis generating. Furthermore, both trials are conducted under varying conditions, adverse reaction rates observed in these trials may not reflect the rates observed in practice.

The overall adverse event frequencies are summarized in Table 20 below. All patients experienced AEs in the AdvSM trials; 33% and 72% of patients experienced serious AEs in the 200 mg and the 300 mg groups, respectively. In comparison, 50% of patients in the GIST 300 mg group experienced serious AEs. Overall, 49% of patients in any dosing group of the AdvSM trials and 51% of patients in the pooled safety population experienced SAEs.

Grade 3/4 AEs were 72% and 94% in AdvSM 200 mg and 300 mg groups, respectively, compared to 75% in GIST 300 mg group (not shown here), and 77% in the pooled safety population. AEs leading to dose discontinuation and interruption were similar between AdvSM population and pooled safety population (AdvSM+ GIST trials). There were 11% more AEs leading to dose reduction in AdvSM 300 mg group than that of GIST 300 mg group, 82% vs. 71%.

The most frequent AEs leading to avapritinib treatment termination in patients with AdvSM were AML, ascites, cognitive disorder, and intracranial bleeding. The AML and Ascites were disease related. The Cognitive and intracranial bleeding events will be discussed later.

In addition, the most frequent AEs leading to avapritinib treatment interruption in patients with AdvSM were thrombocytopenia, anemia, neutropenia, cognitive disorder, and pleural effusion.

Finally, the most frequent AEs leading to avapritinib dose reduction in patient with AdvSM were thrombocytopenia, anemia, neutropenia, cognitive disorder, and peripheral edema.

AEs leading to death are shown in Table 21 and will be discussed in the next section.

Table 20: Overall AE Summary

Patients with AE	AdvSM			Ava (AdvSM +GIST)
	200 mg N=81 n (%)	≥ 300 mg N=50 n (%)	All N=148 n (%)	All N=749 n (%)
Any AE	81 (100.0)	50 (100.0)	148 (100.0)	739 (98.7)
SAE	27 (33.3)	36 (72.0)	73 (49.3)	384 (51.3)
Grade ≥ 3 AE	58 (71.6)	47 (94.0)	120 (81.1)	576 (76.9)
AE leading to Ava discontinuation	9 (11.1)	13 (26.0)	26 (17.6)	127 (17.0)
AE leading to Ava dose interruption	49 (60.5)	41 (82.0)	101 (68.2)	527 (70.4)
AE leading to Ava dose reduction	55 (67.9)	46 (92.0)	105 (70.9)	423 (56.5)
Intracranial bleeding	3 (3.7)	8 (16.0)	11 (7.4)	22 (2.9)
Serious intracranial bleeding	3 (3.7)	5 (10.0)	8 (5.4)	17 (2.3)
Intracranial bleeding leading to Ava discontinuation	2 (2.5)	2 (4.0)	4 (2.7)	11 (1.5)
Cognitive AE	12 (14.8)	26 (52.0)	42 (28.4)	291 (38.9)
Serious cognitive AE	0	4 (8.0)	4 (2.7)	27 (3.6)
Cognitive AE leading to Ava discontinuation	0	2 (4.0)	3 (2.0)	19 (2.5)
AE leading to death (last dose ≤ 30 days)	3 (3.7)	5 (10.0)	9 (6.1)	63 (8.4)

Abbreviations: AdvSM = advanced systemic mastocytosis; AE = adverse event; AESI = adverse event of special interest; Ava = avapritinib; GIST = gastrointestinal stromal tumor; SAE = serious adverse event.
The AE number was counted worst grade per preferred term per patients. The AE rate (%) are based on the number of patients in the Safety Population in each column. The preferred terms are sorted by order of frequency using the AdvSM All column.
GIST patients who received a starting dose of 600 mg were included in the Ava (AdvSM+GIST) columns.
Source: Analysis based on the applicant provided dataset, analysis, and program files

Reviewer Comments: Overall, the safety profile for patients with AdvSM treated with avapritinib 300 mg daily dosing is substantially inferior compared to the 200 mg daily dosing group. Therefore, avapritinib 300 mg daily or dose escalation to 300 mg daily should not be used for AdvSM outside of clinical trial setting.

8.4.1. Deaths

In the pooled safety population, 95 (12.7%) patients treated with avapritinib died due to AEs during or after the study, as shown in Table 21 below. About third of AEs leading to death were disease progression (29 patients, 3.1%).

Table 21: Deaths in Pooled Safety Population

Trials	Deaths (n)
BLU-285-1101	39
BLU-285-1303	44
BLU-285-2101	6
BLU-285-2202	4
Total	95

Source: The reviewer's analysis using NDA212608-S6 dataset.

Of these patients, 63 (8.4%) patients died due to AEs during the active treatment phase and within 30 days after the date of the last dose of avapritinib. For 23 patients (3.1%), AEs leading to death were disease progression.

Summarized by MedDRA SOC and PT, AEs leading to death for all patients in the Safety Population are also tabulated in Table 22 below.

Table 22: AEs Leading to Death in Primary and Pooled Safety Population

	AdvSM			Ava (AdvSM +GIST)
Preferred Term	200 mg N=81 n (%)	≥ 300 mg N=50 n (%)	All N=148 n (%)	All N=749 n (%)
Patients with any adverse event leading to death	3 (3.7)	5 (10.0)	9 (6.1)	63 (8.4)
Acute myeloid leukemia	0	0	1 (< 1)	1 (< 1)
Cardiac arrest	0	1 (2.0)	1 (< 1)	1 (< 1)
Disease progression	1 (1.2)	0	1 (< 1)	23 (3.1)
Gastric hemorrhage	0	1 (2.0)	1 (< 1)	1 (< 1)
Hemorrhage intracranial	0	1 (2.0)	1 (< 1)	1 (< 1)
Necrotizing fasciitis	1 (1.2)	0	1 (< 1)	1 (< 1)
Septic shock	0	1 (2.0)	1 (< 1)	1 (< 1)
Shock hemorrhagic	1 (1.2)	0	1 (< 1)	1 (< 1)
Staphylococcal sepsis	0	1 (2.0)	1 (< 1)	1 (< 1)
Abdominal pain	0	0	0	1 (< 1)
Ascites	0	0	0	1 (< 1)
Cardiac failure	0	0	0	2 (< 1)

Preferred Term	AdvSM			Ava (AdvSM +GIST)
	200 mg N=81 n (%)	≥ 300 mg N=50 n (%)	All N=148 n (%)	All N=749 n (%)
Coma	0	0	0	1 (< 1)
Gastrointestinal hemorrhage	0	0	0	1 (< 1)
General physical health	0	0	0	7 (< 1)
Hepatic failure	0	0	0	1 (< 1)
Hyperbilirubinemia	0	0	0	1 (< 1)
Intestinal perforation	0	0	0	1 (< 1)
Intra-abdominal hemorrhage	0	0	0	1 (< 1)
Malignant neoplasm progression	0	0	0	1 (< 1)
Metastatic neoplasm	0	0	0	1 (< 1)
Multi-organ failure	0	0	0	2 (< 1)
Neoplasm progression	0	0	0	1 (< 1)
Pulmonary edema	0	0	0	1 (< 1)
Respiratory distress	0	0	0	1 (< 1)
Respiratory failure	0	0	0	1 (< 1)
Schizophrenia	0	0	0	1 (< 1)
Sepsis	0	0	0	3 (< 1)
Small intestinal obstruction	0	0	0	1 (< 1)
Tumor hemorrhage	0	0	0	2 (< 1)

Source: The reviewer's analysis

Table 23 below shows FDA's causality assessment on the relationship between deaths and avapritinib exposure based on cross-evaluation of the applicant's narratives, amendments, datasets and CRFs.

In Studies Blu-285-2101 and BLU-285-2202, there was a total of 10 fatalities. Among them, 9 patients had AdvSM, 5 patients assigned at 300 mg daily dose, 3 at 200 mg daily dose and 1 at 30 mg daily dose (BLU-285-2101-[redacted] (b) (6)). It is apparent that more fatal AEs occurred in the 300 mg group than in the 200 mg group. As shown in Table 23 below, 8 of the deaths (7 AdvSM and 1 MCL) associated with treatment emerged AEs which occurred during the active treatment phase or within 30 days of the last dose of avapritinib at 200 mg or higher dose level.

At 200 mg daily dose of avapritinib, the AEs leading to death were disease progression /hemorrhagic shock (BLU-285-2202-(b) (6)), necrotizing fasciitis (BLU-285-2202-(b) (6)), sepsis (BLU-285-2202-(b) (6)) and shock hemorrhagic each.

Of note, fatal hemorrhagic shock (BLU-285-2202-(b) (6)) occurred in a patient with CML after avapritinib dose escalated to 300 mg daily per protocol design. In addition, there is also one AML/post-transplant fatality due to sepsis which occurred 4 months after avapritinib was terminated due to disease progression.

At 300 mg daily dose of avapritinib, the AEs leading to death were cardiac arrest (BLU-285-2101-(b) (6)), gastric hemorrhage (BLU-285-2101-(b) (6)), hemorrhage intracranial (BLU-285-2101-(b) (6)), septic shock (BLU-285-2101-(b) (6)) and Staphylococcal sepsis (BLU-285-2101-(b) (6)) each.

As shown in Table 23 below, 8 of 9 patients with AdvSM who had a fatal event were older than 65 years, except one patient was 37 year old. The categorical causes of death were 3 infection/sepsis, 3 disease progression, 3 bleeding diathesis, and 1 cardiac arrest. All fatal cases are likely related to underlying diseases. To summarize Table 23, the reviewer assessment of these cases is based on the CRF and the Applicant's narratives of fatal cases, suggested most of the deaths were confounded for causality assessment due to underlying AdvSM, as well as disease or supportive care related complications (thrombocytopenia, infection, or platelet transfusion associated sepsis). Furthermore, the data is noncomparative and the sample size is too small to be definitive. Therefore, the causal association of avapritinib is still uncertain given the evidence that the applicant has abandoned 300 mg dose and restrict treatment for AdvSM to 200 mg dose level.

Reviewer Comments: Overall, the safety profile for patients with AdvSM treated with avapritinib 300 mg daily dosing is substantially inferior compared to the 200 mg daily dosing group. Therefore, avapritinib 300 mg daily or dose escalation to 300 mg daily should not be used for AdvSM outside of clinical trial setting.

The causal assessment of avapritinib to death is confounded and subject to multiple interpretations due to coexisting factors, small sample size, and lacking comparators. The confluence of the disease and avapritinib dose in these cases created difficulty to determine the role of each in these fatal cases, especially in hemorrhagic deaths.

Table 23: FDA Assessment in Death Associated AEs

N	ID/Diagnosis	Avapritinib dose/ duration	Description	Relation to Avapritinib
	Trial BLU-285-21-1			
1	BLU-285-2101-(b) (6) / ASM	30 mg QD / 193 days	A 82-year-old, white male patient died of AML. He was diagnosed with ASM and enrolled in the United Kingdom. He received avapritinib 30 mg QD for 193 days. His disease was progressing and was diagnosed with AML. The cause of death was AML and reported unrelated.	Unrelated
2	BLU-285-2101-(b) (6) / SM-AHN	300 mg QD / 274 days	A 76-year-old, male patient died of platelet transfusion related sepsis. He was diagnosed with SM-AHN and enrolled in the United Kingdom. On day 49, the patient developed pleural effusion (Grade 1). An echocardiogram showed good left ventricular function, mild 1+ aortic insufficiency, clinically significant mitral regurgitation, and right pleural effusion. The patient's avapritinib dose was decreased to 200 mg on treatment day 226 for decreased appetite. Two thoracenteses were performed as treatment for the pleural effusion, a liter of fluid was drained on Day 156 and 2 litter drained on day 236. The pleural effusion culture was negative for acid-fast bacilli. Prednisone 20 mg PO were then given for 14 days and the effusion resolved. His avapritinib was interrupted and restarted at 100 mg on day 274 for ongoing plural effusion. On 288 days on avapritinib he developed thrombocytopenia (grade 3), received platelet transfusion and avapritinib was stopped. On day 302, 6 days after last dose of avapritinib, the patient was hospitalized for staphylococcal sepsis (grade 4 and 5). Blood cultures grew S. aureus. Left knee joint aspirate grew S. aureus and E. coli. At time of event, WBC of 1.5 x 10^9/L (normal (nl) range 4-11), neutrophils of 1.1 x 10^9/L (nl range 2-7.5). No autopsy performed. The thrombocytopenia and sepsis were reported unrelated. The pleural effusion was reported probably related.	Confounded
3	BLU-285-2101-(b) (6) SM-AHN	300 mg QD /651 days	A 72-year-old, male patient died of cardiac arrest. He was diagnosed with SM-AHNMD and enrolled in the United Kingdom. Avapritinib was reduced to 200 mg QD on day 15 due to ocular hyperemia. On day 37, avapritinib was reduced to 100 mg QD due to anemia. This dose was continued to day 651 when he has cardiac arrest and die. His past medical history is significant for myelodysplastic syndrome, dyspnea exertional, fatigue, edema peripheral, pyrexia, type 2 diabetes mellitus, vitamin B complex deficiency, chromaturia, anemia, thrombocytopenia, jaundice, intervertebral disc protrusion, pain in extremity, paranesthesia, blood alkaline phosphatase increased, and optic ischemic neuropathy. Patient collapsed in hospital lobby and was found to have O_2 sat of 78%. He had been unwell for a few days with shortness of breath. When put on transport bed, he went into cardiac arrest. No clots or bleeds were found. No cause of death revealed during autopsy. It was also note that the patient developed grade 2 delirium with memory impairment on day 588 and resolved on day 591 without medical interventions or diagnostic procedures.	Confounded
4	BLU-285-2101-(b) (6) /ASM	300 mg QD/259 days	A 68-year-old, male patient died of gastric hemorrhage. He was diagnosed with aggressive systemic mastocytosis (ASM) and enrolled in the United Kingdom. Relevant medical history of duodenal ulcer perforation (b) (6), anemia, and ongoing upper GI hemorrhage. On day 23, the patient developed anemia (grade 3). On day 30, his dose was	Confounded

			decreased to 200 mg for anemia. One day 192, his avapritinib dose further reduced to 100 mg QD for recurrent anemia. On day 230, avapritinib was interrupted due to an event of gastric antral vascular ectasia. The patient was hospitalized for gastric hemorrhage (Grade 4) secondary to gastric antral vascular ectasia and non-cirrhotic portal hypertensive gastropathy, followed by liver abscess (Grade 3), and acute kidney injury (Grade 2). The patient was treated with IV piperacillin and tazobactam. On day 253, 23 days after being held off, avapritinib was restarted at the reduced dose of 100 mg QD. On day 259, avapritinib was discontinued due to general deterioration (not considered by the investigator to be an SAE). while hospitalized, the patient was treated successfully for sepsis and liver abscess; however, the patient continued to deteriorate and had ongoing gastric hemorrhage. The patient died 16 days after the last dose of study drug due to gastric hemorrhage (Grade 5).	
5	BLU-285-2101-(b) (6) / SM-AHN	300 mg QD 135 days	A 73 years old female died of E coli sepsis. Her SM-AHN had progressed after treatment with obinutuzumab, chlorambucil, imatinib, and midostaurin prior to enrolling the trial 2101. At the time of enrollment, her ongoing clinical issues included cerebral small vessel ischemic disease, drug hypersensitivity, sinus congestion, hyperlipidemia, vitreous floaters, osteopenia, spinal column stenosis, aortic arteriosclerosis, lumbosacral radiculopathy, scoliosis, dizziness, dyspnea exertional, fatigue, chronic eosinophilic leukemia, leukocytosis, anemia, thrombocytopenia, depression, insomnia, sputum discolored, stomatitis, decreased appetite, ascites, and musculoskeletal pain. She was started avapritinib at 300 mg QD, which was reduced to 200 mg QD on day 85 and terminated on day 135 due to disease progression. Day 146, 11 days after her last dose of avapritinib, she developed sepsis shock with blood culture positive for E coli. Laboratory test results showed white blood cell count $206.7\times10^3/\mu L$ and peripheral blood blasts 15%. On day 147, 12 days after the last dose of avapritinib, the patient died of septic shock.	Confounded
6	BLU-285-2101-(b) (6) /ASM	300 mg QD/ 567 days	A 69-year-old, male patient died of intracranial hemorrhage secondary to possible head trauma. He was diagnosed with ASM and enrolled in the United States. On day 57, avapritinib dose was reduced to 200 mg QD due to pancytopenia. His significant past medical history diarrhea, back pain, dizziness, weight increased, abdominal distension, ascites, anemia, thrombocytopenia, coeliac disease, fatigue, rash, Sjogren's syndrome, splenomegaly, hyperkaliemia, dyspnea, chronic kidney disease, neuropathy peripheral, insomnia, chronic obstructive pulmonary disease, dysphagia, visual impairment, abdominal pain, hyporeflexia, and hydrocele. On day 565, the patient was to have intracranial bleeding (Grade 4) while being evaluated in ED for weakness secondary to a fall 3 weeks ago. On day 566, the patient underwent anterior right parietal and posterior left frontal evacuation of subdural hematomas without complications. Overnight, the patient complained frontal headache and weakness, spike fever and presented with neurological deficits. On day 567, a follow-up CT scan showed slight interval increase in the right frontoparietal hemorrhage with intraventricular extension to the right greater than left lateral ventricles. The same day, the patient died due to the event of hemorrhage intracranial (Grade 5). His last dose of avapritinib was given on day 567.	Confounded
	Trial BLU-285-2202			
1	BLU-285-2202-(b) (6) / SM-	200 mg QD/7 days	A 73-year-old male patient, died from sepsis secondary to necrotizing fasciitis. He was diagnosed with SM-AHN (10 months before study) and treated with midostaurin prior to enrolling in trial 2202 in the USA. At the time of	Confounded

	AHN		enrollment, location of SM-AHN involvement included bone marrow, liver, and gastrointestinal tract. The patient's significant past medical history included immune thrombocytopenic purpura (8 months prior to enrollment), staphylococcal bacteremia secondary to limb abscess, and sepsis (7 months before enrollment). Ongoing conditions at the time of study initiation included abdominal distension, anemia, anxiety, ascites, atrial fibrillation, atrial flutter, blood alkaline phosphatase increased, bundle branch block right, decreased appetite, drug hypersensitivity, electrocardiogram qt prolonged, hemorrhoids, heart rate increased, hypertension, insomnia, mastoid effusion, , nausea, night sweats, pruritus generalized, pyrexia, sinus tachycardia, splenomegaly, and weight decreased. The patient's baseline lab result included hemoglobin 112 g/L (LLN 135), hematocrit ratio 0.343 (LLN 0.400), RBCs 3.61 × 1012/L (LLN 4.40), RBC distribution width 17.6% (ULN 14.5), platelets 78 × 10^9/L (LLN 150), WBCs 11.7 × 10^9/L (ULN 11.0), lymphocytes 0.77 × 10^9/L (LLN 1.00), eosinophils 4.48 × 10^9/L (ULN 0.60), sodium 131 mmol/L (LLN 135), potassium 3.2 mmol/L (LLN 3.5), albumin 31 g/L (LLN 35), ALP 360 U/L (ULN 130), GGT 186 U/L (ULN 40), prothrombin time 15.3 sec (ULN 14.7), aPTT 37.3 sec (ULN 35.7), and INR ratio 1.3 (ULN 1.2). On study day 7, the patient hospitalized for necrotizing fasciitis (grade 4) after presented to the emergency department for spiked fever of 103.5 F and mild peri-rectal pain. Avapritinib was held. He was managed for sepsis due to rectal and scrotal infection with gas forming organisms. He was taken to the OR for management of sepsis due peri-rectal abscess debridement. Post operation, he was transfer to ICU, intubated, and on intubation and vasopressors. He also received 2 units of packed RBCs. His blood cultures were positive for moderate growth of *Streptococcus anginosus*. Anaerobic culture was positive for heavy growth of *Prevotella* species, and moderate growth of *Escherichia coli*. Regardless IV clindamycin, gentamicin, vancomycin and topical zosyn, the patient continued to have fever of 103 F and received second debridement. He then developed severe septic shock, acute respiratory failure on the ventilator, and acute kidney injury. On day the patient died from necrotizing fasciitis. An autopsy was not performed. The cause of death was sepsis identified as *E. coli* infection.	
2	BLU-285-2202-(b) (6) / SM-AHN	200 mg QD / 112 days	A 69 year-old male patient die of hemorrhagic shock secondary to multiple paracentesis of massive ascites. The patient was diagnosed with SM and treated with cladribine × 2 and midostaurin, 4 months prior to enrolling in the trial in Germany a central diagnosis of SM-AHN. At the time of enrollment, location of SM-AHN involvement included the bone marrow, the liver, and the lymph nodes. The patient's resolved medical history included a transient ischemic attack. Ongoing conditions at the time of study initiation included anemia, Adv associated ascites with frequent paracentesis, blood albumin decreased, hepatitis, hyperuricemia, leukopenia, benign prostatic hyperplasia, bundle branch block left, cardiac disorder, inguinal hernia, iron deficiency anemia, and renal cyst. The patient's relevant out of range laboratory results at screening included: APTT 37.3 sec (normal range: 25.1-35), PT-INR 1.87 (normal range: 0.85-1.15). The patient initiated avapritinib at 200 mg and was reduced to 100 mg on Day 35, due to an AE of decreased white blood cells. On day 54, the patient develop anemia (grade 3) after removal of 6L of ascites via paracentesis the day before. The patient collapsed due to anemia and was hospitalized for observation. He was transfused 2 units of packed red blood cells, and on the same day, blood results showed hemoglobin 52 g/L (reference range 137-175 g/L) and platelet 27 × 10^9/L (normal range 150-400). The patient received parenteral nutrition since hospitalization. Subsequently, the patient received another unit of	Confounded

			packed red blood cells (PRBCs) and 1 unit of platelet on day 55. On the same day, avapritinib was interrupted due to thrombocytopenia (Grade 4). Day 57, his platelet count was 13 × 10^9/L (normal range 150-400), hemoglobin was 72 mg/L, and albumin was 25 g/L (normal range 35-52). Day 63, the patient again underwent paracentesis because of mastocytosis-associated ascites. On day 64, the patient experienced shock (Grade 4) due to intra-abdominal hemorrhage. His blood test results showed hemoglobin 71 g/L (reference range: 137 - 175 g/L) and platelet count 39 × 10^9/L (reference range: 150 - 400). On (b) (6), blood results showed hemoglobin 80 g/L and platelet count 34 × 10^9/L (reference range: 150 - 400). He received transfusions on days 65, 68, 71, 78, and 79. Avapritinib was resumed at 50 mg QD due to ongoing thrombocytopenia Grade 4 on day 72. On day 78, 8L of ascites was drained via paracentesis and the subject collapsed in the evening with unmeasurable blood pressure. The patient was transferred to ICU with mechanical ventilation, pressers, and transfusion with 16 units of PRBS, 8 units FFP, and 2 units of platelet concentrates. An emergency laparotomy was performed for intraabdominal bleeding from the inferior epigastric artery detected by CT. Day 78, avapritinib was interrupted due to systemic inflammatory response syndrome (grade 2), which was resolved on Day 86. Day 87, avapritinib was resumed at 100 mg QD Day 113, avapritinib was discontinued due to hemorrhagic shock, of which the patient died on Day 114.	
3	BLU-285-2202-(b) (6) * / SM-AHN	200 mg QD / 40 days	A 63-year-old white male patient died of sepsis due to disease progression with resolved treatment related hemorrhagic diathesis at the time of death. The patient was diagnosed with SM and progress to SM-AHN after Midostaurin and Cladribine prior to his enrollment in Germany. At the time of enrollment, location of SM-AHN involvement included bone marrow. The patient's past medical history included breast abscess, cholecystitis, cholelithiasis, coronary artery disease, peritonitis bacterial, and platelet count decreased. Ongoing conditions at the time of avapritinib initiation included anemia, ascites, benign prostatic hyperplasia, benign prostatic hyperplasia, diverticulum intestinal, electrocardiogram PR prolongation, electrocardiogram QRS complex prolonged, factor VII deficiency, factor X deficiency, hydronephrosis, hypertension, edema peripheral, esophagitis, and sleep apnea syndrome. Before starting avapritinib at 200 mg QD, the patient's relevant laboratory test results included the following: Hemoglobin 114.402 g/L (135.349-175.632), Platelets 76 x 10^9/L (140-360), Leukocytes 3.3 x 10^9/L (3.5-9.8), Neutrophils 1.21 x 10^9/L (1.6-7.1), Lymphocytes 0.24 x 10^9/L (1-2.9), Monocytes 1.48 x 10^9/L (0.2-0.6), Eosinophils 0.18 x 10^9/L (0-0.5), Sodium 134.7 mmol/L (135-145), Creatinine 29 µmol/L (59-104), Calcium 1.98 mmol/L (2.19-2.54), Albumin 23 g/L (35-52), Alkaline Phosphatase 196.406 x U/L (40.12-128.742), Prothrombin Time 16.7 sec (10.3-16.6), Activated Partial Thromboplastin Time 38.6 sec (25-37), PT INR 1.7 (0.85-1.15). On day 29, avapritinib was reduced to 100 mg QD due to a hemorrhagic diathesis (grade 2) and prolonged hospitalization. A subcutaneous hematoma at the thoracoabdominal junction were formed. The patient was treated with factor XIII replacement due to a 64% XIII (reference range more than 70) and platelet count of 78 x10^9/L, 58 x10^9/L, and 89 x10^9/L (reference range 140-360), with reported nose bleeding, intramuscular bleeding, hyposphagma, and intra-articular bleeding. Coagulation tests were reported as not applicable. On day 30, the patient anemia and thrombocytopenia worsened while in the hospital, with hemoglobin 4.80 µmol/L (reference range: 8.4-10.0) and platelet count of 52 x10^9/L and 56 x10^9/L (reference range: 140-360). Avapritinib was interrupted on the same	Confounded

			day. The patient received replacement of Factors XIII, II, IX, VII, X, and protein C. Day 33, avapritinib resumed at 100 mg QD Days 34 and 35, the patient's platelet count was 3 x 10^9/L. Day 38, the patient developed intra-abdominal hematoma (Grade 2), which was treated with factor replacement and antibiotics. Day 39, the hemorrhagic diathesis was considered resolved and was assessed as related to avapritinib. The platelet count on this day was 79 x10^9/L (reference range 140-360). Day 40, the patient was terminated from the study treatment, i.e., avapritinib due to hemorrhagic diathesis, intra-abdominal hematoma, and dyspnea. Four and half months after the last dose, the patient develop enterococcal sepsis (Grade 4, vancomycin-resistant enterococci, VRE) after high dose chemotherapy and stem cell transplantation for AML and died of multiorgan failure with progressive lactic acidosis in VRE sepsis a week later.	
4	BLU-285-2202-(b) (6) / MCL	200 mg QD / 138 days	A 37 year old male died of hemorrhagic shock. The patient with MCL progressed after Imatinib. The patient started avapritinib at 200 mg QD with mild anemia. His anemia worsened to grade 3 at day 65. However, his avapritinib was escalated to 300 mg QD on day 84 per protocol. Day 145, the patient was hospitalized for worsening thrombocytopenia and spleen rupture. The patient died of post splenectomy hemorrhagic shock on day 147. The investigator assessed cause of death was due to disease progression and unrelated to avapritinib.	Unrelated

* Death occurred beyond 30 days of last dose avapritinib.
Source: Analysis based on the applicant provided dataset, narratives, and CRFs.

8.4.2. Serious Adverse Events

As shown in Table 24 below, 49% of patients with Adv-SM experienced SAEs. The most frequent SAEs were anemia (4.7%), pleural effusion and subdural hematoma (3.4% each), and acute myeloid leukemia, ascites, and pneumonia (2.7% each). In the 200 mg group, the most common SAEs were anemia and subdural hematoma (3 patients, 3.7% each).

Table 24: Serious Adverse Events

Preferred Term	AdvSM			Ava (AdvSM +GIST)
	200 mg N=81 n (%)	≥ 300 mg N=50 n (%)	All N=148 n (%)	All N=749 n (%)
Patients with any serious adverse event	27 (33.3)	36 (72.0)	73 (49.3)	384 (51.3)
Anemia	3 (3.7)	4 (8.0)	7 (4.7)	68 (9.1)
Pleural effusion	1 (1.2)	4 (8.0)	5 (3.4)	18 (2.4)
Subdural hematoma	3 (3.7)	2 (4.0)	5 (3.4)	8 (1.1)
Acute myeloid leukemia	1 (1.2)	0	4 (2.7)	4 (< 1)
Ascites	1 (1.2)	3 (6.0)	4 (2.7)	13 (1.7)
Pneumonia	0	4 (8.0)	4 (2.7)	12 (1.6)
Acute kidney injury	1 (1.2)	2 (4.0)	3 (2.0)	12 (1.6)
Gastric hemorrhage	0	2 (4.0)	3 (2.0)	12 (1.6)
Gastrointestinal hemorrhage	1 (1.2)	2 (4.0)	3 (2.0)	18 (2.4)
Hemorrhage intracranial	0	3 (6.0)	3 (2.0)	7 (< 1)
Pyrexia	0	3 (6.0)	3 (2.0)	10 (1.3)
Vomiting	0	1 (2.0)	3 (2.0)	18 (2.4)
Cholecystitis	0	2 (4.0)	2 (1.4)	3 (< 1)
Diverticulitis	1 (1.2)	1 (2.0)	2 (1.4)	2 (< 1)
Encephalopathy	0	2 (4.0)	2 (1.4)	6 (< 1)
Large intestine perforation	1 (1.2)	0	2 (1.4)	2 (< 1)

Abbreviations: AdvSM = advanced systemic mastocytosis; Ava = avapritinib; GIST = gastrointestinal stromal tumor.
Source: Analysis based on the applicant provided dataset, analysis, and program files

Overall, the incidence of anemia (38%), thrombocytopenia (28%), fatigue (12%), hypophosphatemia (6%), gastric hemorrhage (6%) and plural effusion (4%) were higher in the

300 mg group than in 200 mg group, as shown in Table 24 above. This safety profile is difference from that was observed n GIST trials, which is likely related to the underlying AdvSM.

As shown in Table 25 below, there were more ≥ grade 3 AEs reported in the AdvSM trials than in the Pooled safety population (AdvSM+ GIST trials). The most common Grade ≥3 AE was anemia (24.3%), followed by thrombocytopenia (20.9%) and neutropenia (14.2%).

Table 25: Grade 3 and 4 AEs Reported in Avapritinib Trials

Preferred Term	**AdvSM**			**Ava (AdvSM +GIST)**
	200 mg N=81 n (%)	**≥ 300 mg N=50 n (%)**	**All N=148 n (%)**	**All N=749 n (%)**
Patients with ≥ 3 grade adverse event	58 (71.6)	47 (94.0)	120 (81.1)	576 (76.9)
Anemia	16 (19.8)	19 (38.0)	36 (24.3)	227 (30.3)
Thrombocytopenia	12 (14.8)	14 (28.0)	31 (20.9)	32 (4.3)
Neutropenia	12 (14.8)	6 (12.0)	21 (14.2)	36 (4.8)
Fatigue	3 (3.7)	6 (12.0)	10 (6.8)	48 (6.4)
Platelet count decreased	7 (8.6)	1 (2.0)	9 (6.1)	15 (2.0)
Blood alkaline phosphatase increased	3 (3.7)	2 (4.0)	8 (5.4)	9 (1.2)
Neutrophil count decreased	6 (7.4)	2 (4.0)	8 (5.4)	50 (6.7)
White blood cell count decreased	4 (4.9)	1 (2.0)	7 (4.7)	25 (3.3)
Back pain	2 (2.5)	2 (4.0)	5 (3.4)	8 (1.1)
Hypophosphatemia	1 (1.2)	3 (6.0)	5 (3.4)	27 (3.6)
Pneumonia	0	5 (10.0)	5 (3.4)	13 (1.7)
Vomiting	2 (2.5)	1 (2.0)	5 (3.4)	20 (2.7)
Acute myeloid leukemia	1 (1.2)	0	4 (2.7)	4 (< 1)
Gastric hemorrhage	0	3 (6.0)	4 (2.7)	11 (1.5)
Nausea	1 (1.2)	2 (4.0)	4 (2.7)	22 (2.9)
Periorbital edema	2 (2.5)	1 (2.0)	4 (2.7)	9 (1.2)
Pleural effusion	2 (2.5)	2 (4.0)	4 (2.7)	17 (2.3)

Abbreviations: AdvSM = advanced systemic mastocytosis; Ava = avapritinib; GIST = gastrointestinal stromal tumor.
The AE incidence was calculated by worst grade reported per preferred term per patients. The AE rates (%) are based on the number of patients in the Safety Population in each column. The preferred terms are sorted by order of frequency using the AdvSM All column.
GIST patients who received a starting dose of 600 mg were included in the Ava (AdvSM+GIST) columns.
Source: Analysis based on the applicant provided dataset, analysis, and program files.

Overall, Grade 3 or greater thrombocytopenia and platelet count decrease were substantially increased in Adv trials, 20 % and 6% respectively, compared to the reported value of 4% in pooled safety population (less than 1% for both AEs in GIST trials, data not shown). Interestingly, the rate at which events of platelet count decrease (laboratory adverse event) were reported was 4 fold higher in the 200 mg group than in the 300 mg group, whereas thrombocytopenia events reported in 200 mg group were only half of thrombocytopenia reported in the 300 mg. The logical explanation of this phenomenon is due to the safety report practice: the events of grade 3 platelet count decrease without other clinical complication reported as platelet decrease; and events of platelet count decrease with clinical complications reported as thrombocytopenia. This difference suggested that more events of grade 3 platelet count decrease with clinical complication occurred in the 300 mg group than the in the 200 mg group. More events of grade 3 platelet decrease without clinical complications observed in the 200 mg group.

Grade 3/4 Neutropenia was also substantially increased in AdvSM trials. No obvious difference in neutrophil and white blood cell counts were identified comparing to what was reported in the GIST trials. However, neutrophil count decrease was reported 2-fold higher in the 200 mg group than 300 mg group.

Reviewer Comments: Based on the exploration of the events difference between thrombocytopenia and platelet decrease in the 200 mg and 300 mg groups was likely due to the grade 3 thrombocytopenia with or without clinical complication. The thrombocytopenia was reported at a greater rate than platelet count decrease suggests higher frequency of grade 3 platelet decrease associated complications observed in the 300 mg avapritinib group. This is another reason for eliminating the 300 mg dose in AdvSM population.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

As shown in Table 26 below, in patients with any AE leading to avapritinib discontinuation in AdvSM trials, there were 11% in the 200 mg group, and 26% in the 300 mg group. Among the 26% of discontinuations in the 300 mg avapritinib group, concerning AEs leading to discontinuation were ascites (4%), intracranial hemorrhage (4%), cognitive disorder (2%), and subdural hematoma (2%).

The overall discontinuation rates were similar among the AdvSM population (17.6%), the All SP (16.8%) population and the GIST populations alone (17%, not shown in Table 26). The leading reason cited for treatment termination was AML (2.7%), followed by 1.4% each of ascites, cognitive disorder, intracranial hemorrhage, subdural hematoma, and thrombocytopenia. Beside disease progression (AML and ascites), other reasons for avapritinib discontinuation are related to avapritinib (cognitive disorder) or related to both disease and avapritinib (hemorrhage and thrombocytopenia).

Table 26: Treatment Discontinuation due to AEs (>1%)

Preferred Term	AdvSM			Ava (AdvSM +GIST)
	200 mg N=81 n (%)	≥ 300 mg N=50 n (%)	All N=148 n (%)	All N=749 n (%)
Patients with adverse event leading to treatment discontinuation	9 (11.1)	13 (26.0)	26 (17.6)	127 (17.0)
Acute myeloid leukemia	1 (1.2)	0	4 (2.7)	4 (< 1)
Ascites	0	2 (4.0)	2 (1.4)	4 (< 1)
Cognitive disorder	0	1 (2.0)	2 (1.4)	3 (< 1)
Hemorrhage intracranial	0	2 (4.0)	2 (1.4)	4 (< 1)
Subdural hematoma	2 (2.5)	0	2 (1.4)	4 (< 1)
Thrombocytopenia	1 (1.2)	1 (2.0)	2 (1.4)	2 (< 1)

Abbreviations: AdvSM = advanced systemic mastocytosis; Ava = avapritinib; GIST = gastrointestinal stromal tumor.
The AE number was counted worst grade per preferred term per patients. The AE rate (%) are based on the number of patients in the Safety Population in each column. The preferred terms are sorted by order of frequency using the AdvSM All column.
GIST patients who received a starting dose of 600 mg were included in the Ava (AdvSM+GIST) columns.
Source: Analysis based on the applicant provided dataset, analysis, and program files

As shown in Table 27 below, 68% of patients in the AdvSM trials experienced an AE that led to avapritinib dose interruption, which is similar to the results observed the pooled population (70%). AEs leading to dose interruption were reported more in 300 mg group (82%) than the 200 mg group (60%). The most frequent AEs leading to dose interruptions were thrombocytopenia (12%), anemia (8%), neutropenia (7%), cognitive disorder (3%), and pleural effusion (3%). The reasons for dose interruption are related to either disease (pleural effusion) or avapritinib (cognitive disorder) or both (anemia, neutropenia, and thrombocytopenia). A 22% great dose interruption rate in the 300 mg group support the elimination of using 300 mg dose in patients with AdvSM.

Table 27: Treatment Emergent AEs (>2%) Leading to Dose Interruption

	AdvSM			Ava (AdvSM +GIST)
Preferred Term	**200 mg N=81 n (%)**	**≥ 300 mg N=50 n (%)**	**All N=148 n (%)**	**All N=749 n (%)**
Patients with adverse event leading to dose interruption	49 (60.5)	41 (82.0)	101 (68.2)	527 (70.4)
Thrombocytopenia	10 (12.3)	7 (14.0)	17 (11.5)	19 (2.5)
Anemia	4 (4.9)	8 (16.0)	12 (8.1)	114 (15.2)
Neutropenia	8 (9.9)	2 (4.0)	11 (7.4)	26 (3.5)
Neutrophil count decreased	6 (7.4)	1 (2.0)	7 (4.7)	43 (5.7)
Platelet count decreased	6 (7.4)	0	7 (4.7)	12 (1.6)
Cognitive disorder	2 (2.5)	2 (4.0)	5 (3.4)	38 (5.1)
Pleural effusion	1 (1.2)	4 (8.0)	5 (3.4)	21 (2.8)
Blood alkaline phosphatase	2 (2.5)	1 (2.0)	4 (2.7)	5 (< 1)
Confusion state	1 (1.2)	2 (4.0)	4 (2.7)	10 (1.3)
Fatigue	1 (1.2)	1 (2.0)	4 (2.7)	50 (6.7)
Gastroenteritis	0	3 (6.0)	4 (2.7)	11 (1.5)
Vomiting	0	2 (4.0)	4 (2.7)	33 (4.4)
White blood cell count decreased	3 (3.7)	0	4 (2.7)	20 (2.7)
Blood bilirubin increased	0	3 (6.0)	3 (2.0)	49 (6.5)
Influenza like illness	1 (1.2)	1 (2.0)	3 (2.0)	12 (1.6)
Memory impairment	0	2 (4.0)	3 (2.0)	37 (4.9)

Abbreviations: AdvSM = advanced systemic mastocytosis; Ava = avapritinib; GIST = gastrointestinal stromal tumor. The AE number was counted worst grade per preferred term per patients. The AE rate (%) are based on the number of patients in the Safety Population in each column. The preferred terms are sorted by order of frequency using the AdvSM All column.
GIST patients who received a starting dose of 600 mg were included in the Ava (AdvSM+GIST) columns.
Source: Analysis based on the applicant provided dataset, analysis, and program files

As shown in Table 28 below, 71% patients in AdvSM trials experience an AE that led to avapritinib dose reduction, which is more than those observed the pooled safety population (56%). AEs caused dose reduction were reported more in the 300 mg group (92%) and less in the 200 mg group (68%). The most frequent AEs caused dose reductions were thrombocytopenia (12%), periorbital edema (10%), anemia (9%), neutropenia (7%), cognitive disorder (5%), peripheral edema (5%), memory impairment (4%), fatigue (3%), and pleural effusion (3%). Majority reasons for dose reduction are related to avapritinib. A 24% increase of

dose reduction supports eliminating 300 mg dose in patients with AdvSM.

Table 28: Treatment Emergent AEs (>2%) Leading to Dose Reduction

	AdvSM			Ava (AdvSM +GIST)
Preferred Term	**200 mg N=81 n (%)**	**≥ 300 mg N=50 n (%)**	**All N=148 n (%)**	**All N=749 n (%)**
Patients with any adverse event leading to dose reduction	55 (67.9)	46 (92.0)	105 (70.9)	423 (56.5)
Thrombocytopenia	12 (14.8)	6 (12.0)	18 (12.2)	18 (2.4)
Periorbital edema	5 (6.2)	9 (18.0)	15 (10.1)	31 (4.1)
Anemia	3 (3.7)	10 (20.0)	13 (8.8)	74 (9.9)
Neutropenia	6 (7.4)	4 (8.0)	11 (7.4)	21 (2.8)
Cognitive disorder	4 (4.9)	3 (6.0)	8 (5.4)	28 (3.7)
Edema peripheral	6 (7.4)	2 (4.0)	8 (5.4)	17 (2.3)
Memory impairment	1 (1.2)	4 (8.0)	6 (4.1)	28 (3.7)
Neutrophil count decreased	6 (7.4)	0	6 (4.1)	36 (4.8)
Platelet count decreased	6 (7.4)	0	6 (4.1)	11 (1.5)
Fatigue	2 (2.5)	3 (6.0)	5 (3.4)	47 (6.3)
Pleural effusion	1 (1.2)	3 (6.0)	4 (2.7)	15 (2.0)
Blood bilirubin increased	0	3 (6.0)	3 (2.0)	32 (4.3)
Diarrhea	1 (1.2)	2 (4.0)	3 (2.0)	9 (1.2)
Nausea	0	3 (6.0)	3 (2.0)	19 (2.5)
Subdural hematoma	1 (1.2)	2 (4.0)	3 (2.0)	4 (< 1)

Abbreviations: AdvSM = advanced systemic mastocytosis; Ava = avapritinib; GIST = gastrointestinal stromal tumor. The AE number was counted worst grade per preferred term per patients. The AE rates (%) are based on the number of patients in the Safety Population in each column. The preferred terms are sorted by order of frequency using the AdvSM All column.
GIST patients who received a starting dose of 600 mg were included in the Ava (AdvSM+GIST) columns.
Source: Analysis based on the applicant provided dataset, analysis, and program files

Reviewer Comments: Based on these results, treatment discontinuation, appropriated dose interruption and dose reduction for AdvSM indication should be implemented in the event of clinically significant AEs. No 300 mg dose or dose escalation to 300 mg is recommended in the AdvSM disease setting.

8.4.4. Significant Adverse Events

Adverse events of special interested (AESI) defined for the avapritinib clinical development included: intracranial hemorrhage and cognitive effects. An analysis of these toxicities in ongoing trials BLU-285-2101, BLU-285-22-2, BLU-285-1101, and BLUE-285-1103 were provided by the Applicant.

8.4.4.1 Intracranial bleeding

Intracranial bleeding (see Table 29 below) was initially identified in preclinical animal studies and reported in previously reviewed GIST clinical trials. The intracranial bleeding event group includes three PTs: Hemorrhage intracranial, Cerebral hemorrhage, and Subdural hematoma.

In the pooled safety population (GIST, N = 601 and AdvSM, N = 148), the overall incidence of intracranial bleeding was 2.9% (see Table 29 below). The incidence of intracranial bleeding was higher in patients with AdvSM (7.4%) than in patients with GIST, resulting in a lower incidence of intracranial bleeding in the pooled SP (1.9%). Intracranial bleeding events were reported predominantly in the AdvSM 300 mg group, 16%, compare to 3.7% in AdvSM 200 mg group, as shown in Table 29. It is also noted that in patients with AdvSM who received avapritinib, serious intracranial bleeding was reported in 10% of patients in the 300 mg group and 3.7% of patients in the 200 mg group. Permanent discontinuation of avapritinib due to intracranial bleeding was 4% in the 300 mg group and 2.5% in the 200 mg group. These results suggested that both underlying disease and avapritinib may be contribute to the intracranial bleeding. The confluence of the disease and avapritinib in these cases created difficulty to determine the role of each in intracranial hemorrhage. Given the small sample size and single arm design of the AdvSM trials, the issue cannot be further addressed based on the available data.

Table 29: Intracranial Bleeding Events

Category	AdvSM			Ava (AdvSM +GIST)
Preferred Term	200 mg N=81 n (%)	≥ 300 mg N=50 n (%)	All N=148 n (%)	All N=749 n (%)
Intracranial bleeding	3 (3.7)	8 (16.0)	11 (7.4)	22 (2.9)
Subdural hematoma	3 (3.7)	3 (6.0)	6 (4.1)	10 (1.3)
Hemorrhage intracranial	0	5 (10.0)	5 (3.4)	10 (1.3)
Cerebral hemorrhage	0	0	0	3 (< 1)
Grade ≥ 3 intracranial bleeding	1 (1.2)	2 (4.0)	3 (2.0)	10 (1.3)
Hemorrhage intracranial	0	2 (4.0)	2 (1.4)	5 (< 1)
Subdural hematoma	1 (1.2)	0	1 (< 1)	3 (< 1)
Cerebral hemorrhage	0	0	0	3 (< 1)
Serious intracranial bleeding	3 (3.7)	5 (10.0)	8 (5.4)	17 (2.3)
Subdural hematoma	3 (3.7)	2 (4.0)	5 (3.4)	8 (1.1)
Hemorrhage intracranial	0	3 (6.0)	3 (2.0)	7 (< 1)
Cerebral hemorrhage	0	0	0	3 (< 1)
Intracranial bleeding leading to permanent discontinuation	2 (2.5)	2 (4.0)	4 (2.7)	11 (1.5)
Hemorrhage intracranial	0	2 (4.0)	2 (1.4)	4 (< 1)
Subdural hematoma	2 (2.5)	0	2 (1.4)	4 (< 1)
Cerebral hemorrhage	0	0	0	3 (< 1)

Abbreviations: AdvSM = advanced systemic mastocytosis; Ava = avapritinib; GIST = gastrointestinal stromal tumor. The AE number was counted worst grade per preferred term per patients. The AE rate (%) are based on the number of patients in the Safety Population in each column. The preferred terms are sorted by order of frequency using the AdvSM All column.
GIST patients who received a starting dose of 600 mg were included in the Ava (AdvSM+GIST) columns.
Source: Analysis based on the applicant provided dataset, analysis, and program files

Based on the experience of BLU-285-2101 trial, the Study BLU-285-2202 required enrolled patients to have at baseline, an MRI or CT scan of the brain, no clinically significant neurological events, and platelet counts > 50,000/μL. Patients with abnormalities indicative of a risk for hemorrhage, or prior, recent, or current hemorrhage, were excluded from the study. This enrollment eligibility criterion probably reduced the risk of intracranial bleeding in Study BLU-285-2202.

Severe thrombocytopenia prior to or at the time of the event was identified as a risk factor for intracranial bleeding in AdvSM patients. Prior to or at the time of the intracranial bleeding

events, 9 of the 11 patients had severe thrombocytopenia with platelet counts below 50 x 10^9/L, and 2 patients had mild thrombocytopenia (platelet counts between below the lower limit of normal and 75 x 10^9/L) at the time of the event. Of these 2 patients with mild thrombocytopenia at the time of the event, 1 patient had a history of coagulopathy and brain imaging at the time of the event showing possible hemorrhagic metastases or cavernous malformation with hemorrhage, and the other patient developed a subdural hematoma as a result of hitting her head during a fall down the stairs. Three of the 11 patients who reported intracranial bleeding events had severe thrombocytopenia at baseline, while 2 patients had moderate thrombocytopenia (platelet counts between 50 and <75x 10^9/L), 5 patients had mild thrombocytopenia, and 1 patient had a normal platelet count at baseline.

Reviewer Comments: Intracranial bleeding is assessed as an AESI and important risk associated with avapritinib treatment, regardless confounding factors identified, and was observed to occur at a higher incidence in patients with AdvSM compared to the GIST population. Severe thrombocytopenia known to be associated with the underlying AdvSM disease was identified as the primary risk factor for intracranial bleeding, with avapritinib doses of ≥ 300 mg QD considered as contributing to the risk of intracranial bleeding. Risk minimization measures have been implemented with starting dose of 200 mg daily and withhold dosing when platelet below 50 x 10^9/L, which appear to be effective in reducing the incidence of intracranial bleeding. A PMR will be issued to further characterize the risk of intracranial hemorrhage associated with avapritinib.

8.4.4.2.1 Cognitive Effects

Among the 148 AdvSM patients, 42 (28.4%) experienced cognitive effects (see Table 30 below). The most commonly reported event was memory impairment (15.5%), followed by cognitive disorder (10.1%), confusional state (6.1%), and encephalopathy (2.0%). The less frequent events included amnesia, delirium, disorientation, and somnolence (1.4% each), and dementia, hallucination, and mental status changes (< 1% each).

The median time to onset of the first cognitive adverse reaction was 13.3 weeks (range 1 day to 1.8 years). In terms of severity, 26 patients (17.6%) reported Grade 1 events, 12 patients (8.1%) reported Grade 2 events, and 4 patients (2.7%) reported Grade 3 events; no Grade 4 or Grade 5 events were reported. Three patients (2.0%) reported cognitive effects that led to permanent discontinuation of avapritinib (see Table 30 below).

There were 4 patients reporting 7 serious cognitive effects. One patient reported 3 events (2 reports of encephalopathy and 1 report of mental status changes) that were Grade 3 in severity, resolved, and were assessed as not related to avapritinib; 1 patient reported 2 events of encephalopathy that were Grade 3 in severity, resolved with sequelae, and were assessed as related to avapritinib; and 1 patient each reported events of dementia and confusional state

that were both Grade 2 in severity, ongoing, and assessed as not related to avapritinib. Four serious events resulted in temporary interruption of study drug, and 3 events resulted in no change in study drug dosing or the patient was not receiving study drug at the time of the event.

Patients with a medical history of cognitive effects and patients ≥ 65 years old were more likely to experience Grade ≥ 2 cognitive effects. The majority of patients with cognitive effects continued treatment with avapritinib, with 2.5% of patients overall (2.0% of AdvSM patients and 2.7% of GIST patients) experiencing cognitive effects leading to permanent discontinuation of study treatment. No AdvSM patients treated at 200 mg QD experienced cognitive effects leading to permanent discontinuation of study treatment.

No AdvSM patients treated at 200 mg QD experienced cognitive effects leading to permanent discontinuation of study treatment. This observation implies that the cognitive effects are considered tolerable and acceptable in the context of the severity of the disease.

Table 30: Cognitive Effects Adverse Events by the Applicant's Criteria

Category **Preferred Term**	**AdvSM**			**Ava (AdvSM +GIST)**
	200 mg N=81 n (%)	**≥ 300 mg N=50 n (%)**	**All N=148 n (%)**	**All N=749 n (%)**
Cognitive effects	12 (14.8)	26 (52.0)	42 (28.4)	291 (38.9)
Memory impairment	5 (6.2)	15 (30.0)	23 (15.5)	148 (19.8)
Cognitive disorder	4 (4.9)	8 (16.0)	15 (10.1)	90 (12.0)
Confusional state	3 (3.7)	5 (10.0)	9 (6.1)	43 (5.7)
Encephalopathy	0	3 (6.0)	3 (2.0)	10 (1.3)
Amnesia	0	2 (4.0)	2 (1.4)	20 (2.7)
Delirium	1 (1.2)	1 (2.0)	2 (1.4)	10 (1.3)
Disorientation	1 (1.2)	0	2 (1.4)	4 (< 1)
Somnolence	0	2 (4.0)	2 (1.4)	16 (2.1)
Dementia	0	1 (2.0)	1 (< 1)	3 (< 1)
Hallucination	0	1 (2.0)	1 (< 1)	6 (< 1)
Mental status changes	0	1 (2.0)	1 (< 1)	3 (< 1)
Agitation	0	0	0	4 (< 1)

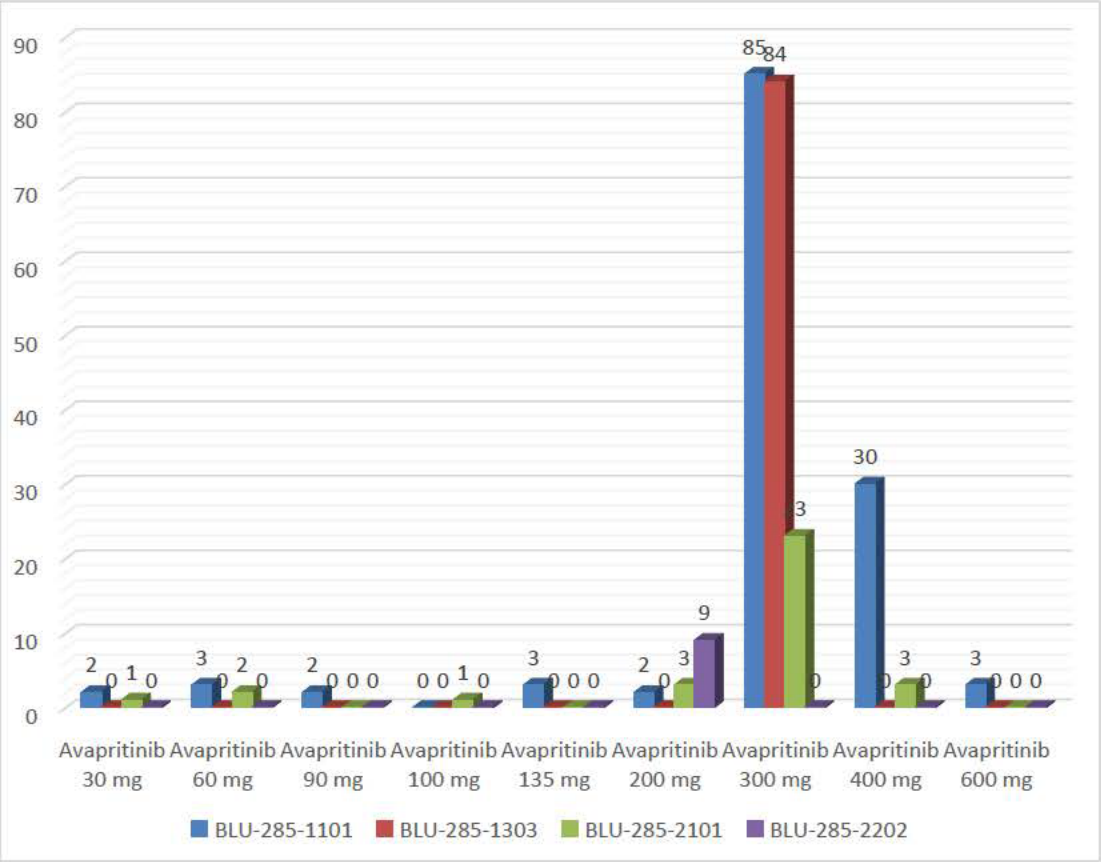
Mental impairment	0	0	0	7 (< 1)
Mood altered	0	0	0	6 (< 1)
Personality change	0	0	0	4 (< 1)
Psychotic disorder	0	0	0	3 (< 1)
Confusional state	0	1 (2.0)	1 (< 1)	6 (< 1)
Dementia	0	1 (2.0)	1 (< 1)	2 (< 1)
Mental status changes	0	1 (2.0)	1 (< 1)	2 (< 1)
Agitation	0	0	0	1 (< 1)
Cognitive disorder	0	0	0	6 (< 1)
Delirium	0	0	0	3 (< 1)
Mood altered	0	0	0	1 (< 1)
Personality change	0	0	0	1 (< 1)
Psychotic disorder	0	0	0	2 (< 1)
Somnolence	0	0	0	1 (< 1)
Cognitive effects leading to permanent discontinuation of Ava	0	2 (4.0)	3 (2.0)	19 (2.5)
Cognitive disorder	0	1 (2.0)	2 (1.4)	3 (< 1)
Dementia	0	1 (2.0)	1 (< 1)	1 (< 1)
Encephalopathy	0	1 (2.0)	1 (< 1)	4 (< 1)
Amnesia	0	0	0	2 (< 1)
Confusional state	0	0	0	3 (< 1)
Delirium	0	0	0	2 (< 1)
Memory impairment	0	0	0	3 (< 1)
Mental status changes	0	0	0	1 (< 1)
Psychotic disorder	0	0	0	2 (< 1)

Abbreviations: AdvSM = advanced systemic mastocytosis; AESI = adverse event of special interest; Ava = avapritinib; GIST = gastrointestinal stromal tumor. Notes: Percentages are based on the number of patients in the Safety Population in each column.
Source: Analysis based on the applicant provided dataset, analysis, and program files

In this submission, the Applicant provided an evaluation of cognitive adverse effects associated with avapritinib including: Memory impairment, Cognitive disorder, Confusional state, Amnesia, Somnolence, Speech disorder, Delirium, Hallucination, Mood altered, Agitation, Personality change, Dementia, Mental status changes, Psychotic disorder, Disorientation, Mental impairment, and Encephalopathy.

The graphical analysis using the applicant's recognized Cognitive events are shown in the following figures. Figure 3 below depicts the number of patients who experienced at least one Cognitive event at various dose level from the pooled safety population.

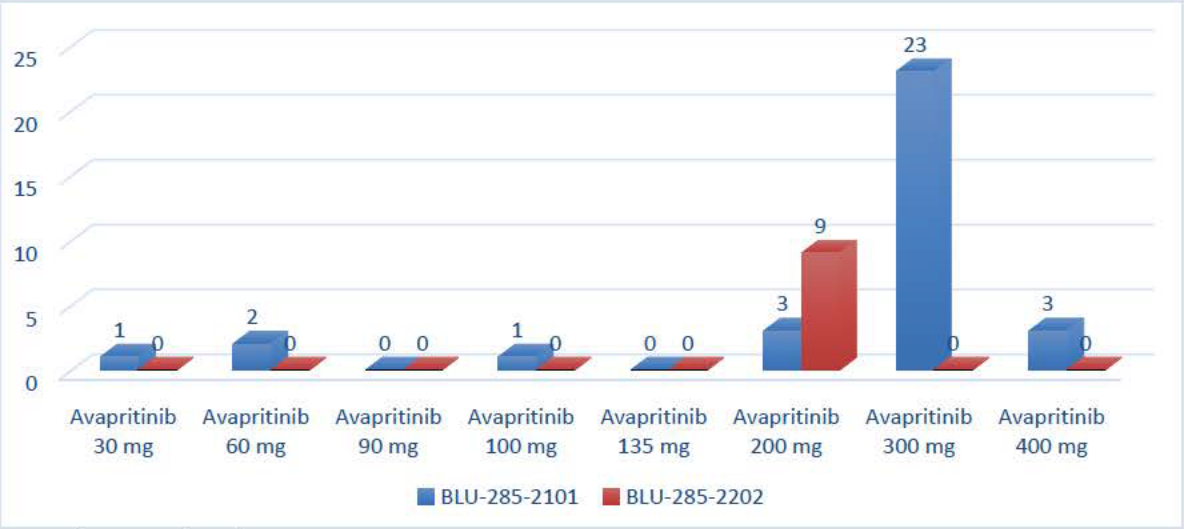
Figure 3: Analysis of the Applicant Defined Cognitive Events in the Pooled Safety Population



Source: The reviewer's analysis.

Figure 4 below is a closer look at the number of patients in the primary safety population who experienced Cognitive event at various dose level.

Figure 4: Analysis of the Applicant Defined Cognitive Events in the Primary Safety Population



Source: The reviewer's analysis.

The figures suggest the number of patients with cognitive event are substantially lower in the AdvSM 200 mg group than in the 300 mg AdvSM group. In addition, more cognitive events reported in patients with GIST than those with AdvSM.

To more comprehensively assess the full range of cognitive adverse effect associated with avapritinib in addition to the cognitive effects identified by the applicant, the clinical reviewer evaluated the broader set of preferred terms in Table 31 below.

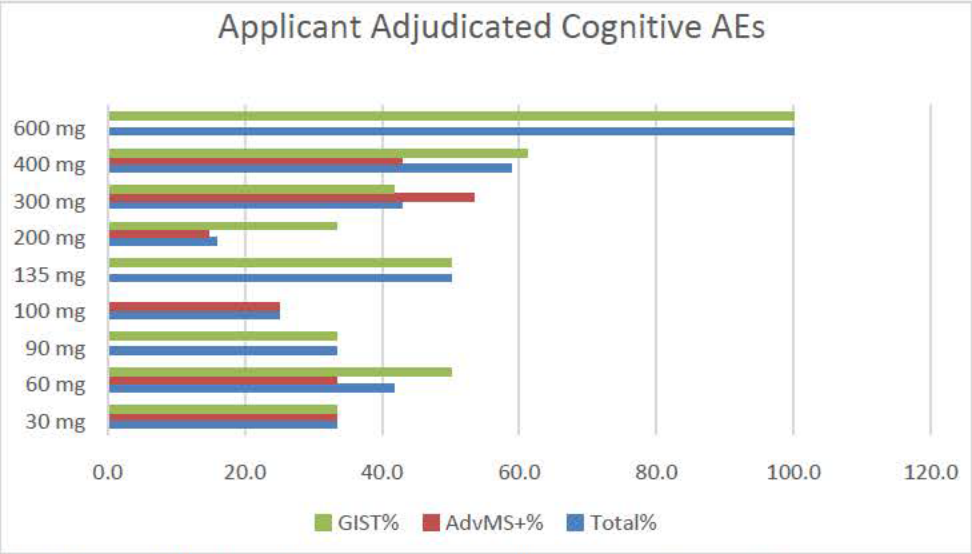
Table 31: The Reviewer's Broad Search Terms

Group Term	Preferred Term
Cognitive Impairment	Memory impairment Amnesia Cognitive disorder Confusional state Disturbance in attention Dementia Mental impairment Encephalopathy Mental disorder Mental status changes Abnormal thinking Retrograde amnesia
Dizziness	Dizziness
Sleep disorders	Sleep disorder Insomnia Somnolence
Speech disorders	Speech disorder Aphasia Dysarthria Slow Speech
Hallucinations	Auditory hallucination Visual hallucination Hallucination
Mood disorders	Agitation Anxiety Depression Depressed mood Dysphoria Irritability Mood altered Nervousness Personality Changes Suicidal ideation

Source: The reviewer defined terms

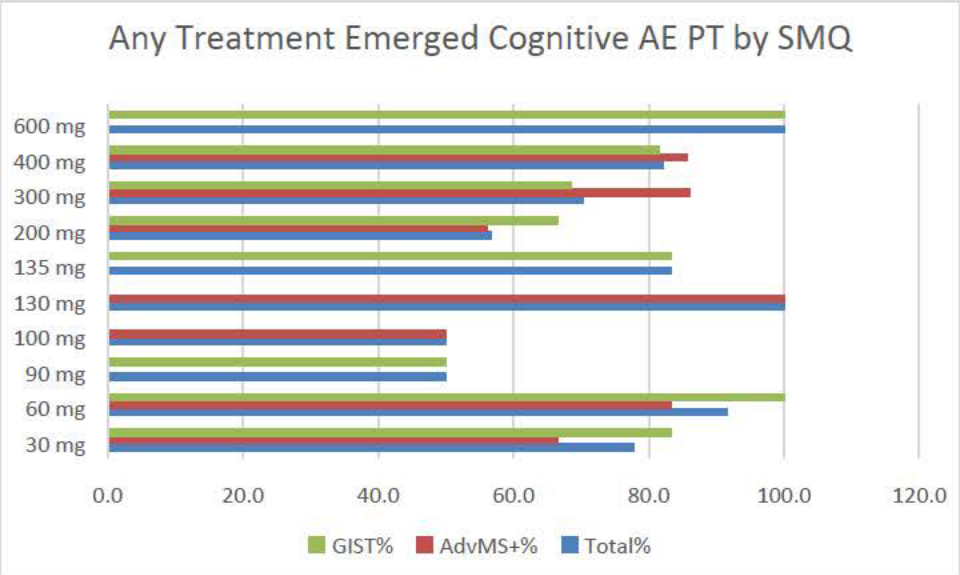
The next two figures (Figures 5-6) summarize a comparative analysis between the terms defined by the applicant and the reviewer. The figures graphically compared incidence of cognitive effect of avapritinib by disease, AdvSM, GIST and pool SP, as well as by dosing groups. The analysis using the applicant's algorithm is depicted in Figure 5 and the analysis using the reviewer's broad terms search is depicted in Figure 6.

Figure 5: Subjects' Experience Cognitive AEs by Dose Level and Disease by the Applicant's Definition



Abbreviations: AdvSM = advanced systemic mastocytosis; GIST = gastrointestinal stromal tumor.
Source: The reviewer's analysis using the applicant's algorithm

Figure 6: Subjects' Experience Cognitive AEs by Dose Level and Disease by MedDRA SMQ



Abbreviations: AdvSM = advanced systemic mastocytosis; GIST = gastrointestinal stromal tumor.
Source: Analysis using the reviewer's broader terms

Per the applicant's terms, cognitive events occurred in 15% of patients in the 200 mg group and 52% of patients in the 300 mg group. Using the reviewer's broader term, the frequency of cognitive events in the AdvSM population increased across all dose groups. The difference

between cognitive events in the 200 mg and 300 mg groups in patients with AdvSM became smaller. Also, the difference between the incidence of cognitive event between AdvSM and GIST populations became smaller.

Reviewer Comments: The patterns of cognitive event incidences change as the search group terms changed. Given the small sample size and single arm design of the AdvSM trials, the issue cannot be further addressed based on the available data. While the clinical trials reported in this supplemental NDA (sNDA) are still ongoing, continued monitoring and follow up on cognitive effect of avapritinib is critical to further define and characterize. A PMR will be issued to further characterize this safety issue.

8.4.5. Treatment Emergent Adverse Events

At the time of data cut off, 100% patients in the primary safety population experienced at least one AE, and 99% of the pooled population experienced AEs.

Table 32 below shows common AEs reported in ≥ 10% of patients with AdvSM treated at 200 mg, 300 mg in the primary safety population (any AdvSM dose groups), as well as in the pooled safety population. The listing of AEs when ordered by frequency in the primary safety population is as follows: periorbital edema (54.7%), followed by anemia and peripheral edema (43.9% each), thrombocytopenia (37.2%), diarrhea (35.8%), nausea (33.1%), fatigue (29.7%), and vomiting (28.4%). The neutropenia was 15.5% in AdvSM.

Table 32: Treatment Emergent Adverse Events (>10%)

	AdvSM			Ava (AdvSM +GIST)
Preferred Term	200 mg N=81 n (%)	≥ 300 mg N=50 n (%)	All N=148 n (%)	All N=749 n (%)
Patients with any adverse event	81 (100.0)	50 (100.0)	148 (100.0)	739 (98.7)
Periorbital edema	32 (39.5)	40 (80.0)	81 (54.7)	289 (38.6)
Anemia	26 (32.1)	32 (64.0)	65 (43.9)	377 (50.3)
Edema peripheral	39 (48.1)	22 (44.0)	65 (43.9)	230 (30.7)
Thrombocytopenia	28 (34.6)	21 (42.0)	55 (37.2)	73 (9.7)
Diarrhea	23 (28.4)	20 (40.0)	53 (35.8)	257 (34.3)
Nausea	20 (24.7)	22 (44.0)	49 (33.1)	356 (47.5)
Fatigue	15 (18.5)	22 (44.0)	44 (29.7)	328 (43.8)
Vomiting	15 (18.5)	22 (44.0)	42 (28.4)	230 (30.7)

Arthralgia	9 (11.1)	16 (32.0)	29 (19.6)	55 (7.3)
Hair color changes	6 (7.4)	16 (32.0)	27 (18.2)	129 (17.2)
Abdominal pain	10 (12.3)	11 (22.0)	26 (17.6)	158 (21.1)
Constipation	9 (11.1)	13 (26.0)	25 (16.9)	123 (16.4)
Dizziness	11 (13.6)	10 (20.0)	24 (16.2)	124 (16.6)
Dysgeusia	11 (13.6)	11 (22.0)	24 (16.2)	105 (14.0)
Headache	12 (14.8)	6 (12.0)	24 (16.2)	109 (14.6)
Memory impairment	5 (6.2)	15 (30.0)	23 (15.5)	148 (19.8)
Neutropenia	13 (16.0)	6 (12.0)	23 (15.5)	61 (8.1)
Decreased appetite	7 (8.6)	12 (24.0)	22 (14.9)	193 (25.8)
Hypokalemia	6 (7.4)	11 (22.0)	20 (13.5)	114 (15.2)
Pruritus	6 (7.4)	10 (20.0)	20 (13.5)	57 (7.6)
Dyspnea	7 (8.6)	8 (16.0)	19 (12.8)	100 (13.4)
Epistaxis	9 (11.1)	9 (18.0)	19 (12.8)	30 (4.0)
Upper respiratory tract infection	6 (7.4)	6 (12.0)	18 (12.2)	54 (7.2)
Face edema	9 (11.1)	6 (12.0)	17 (11.5)	180 (24.0)
Pain in extremity	6 (7.4)	10 (20.0)	17 (11.5)	46 (6.1)
Urinary tract infection	6 (7.4)	10 (20.0)	17 (11.5)	53 (7.1)
Alopecia	7 (8.6)	7 (14.0)	16 (10.8)	87 (11.6)
Blood bilirubin increased	7 (8.6)	9 (18.0)	16 (10.8)	171 (22.8)
Insomnia	5 (6.2)	8 (16.0)	16 (10.8)	83 (11.1)
Blood alkaline phosphatase	7 (8.6)	5 (10.0)	15 (10.1)	27 (3.6)
Cognitive disorder	4 (4.9)	8 (16.0)	15 (10.1)	90 (12.0)
Cough	2 (2.5)	10 (20.0)	15 (10.1)	77 (10.3)
Hypophosphatemia	5 (6.2)	7 (14.0)	15 (10.1)	85 (11.3)
Lacrimation increased	7 (8.6)	6 (12.0)	15 (10.1)	160 (21.4)

Abbreviations: AdvSM = advanced systemic mastocytosis; Ava = avapritinib; GIST = gastrointestinal stromal tumor.
If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term.
Source: The reviewer analysis using the applicant provided ISS ADAE datasets

As shown in Table 32 above, the most common AEs reported in ≥ 20% of AdvSM patients of the 200 mg group were: edema peripheral (48.1%), followed by periorbital edema (39.5%), thrombocytopenia (34.6%), anemia (32.1%), diarrhea (28.4%), and nausea (24.7%). Neutropenia was 16%. This pattern is different from what was observed in the pooled safety population which predominately populated by patients with GIST.

Reviewer Comments: The overall safety profile of common AEs > 20% of avapritinib 200 mg daily for AdvSM are different from those observed in the GIST and Pooled populations, and therefore is likely associated at least in part with the underlying disease. The results shown in Table 32 also indicated that all grade AE rates in 300 mg group are substantially greater in all but few AE terms compare to those in the 200 mg group, supporting eliminating the use of 300 mg dose in AdvSM population.

8.4.6. Laboratory Findings

According to the applicant, clinical laboratory evaluations for safety were performed at a local laboratory. Clinical laboratory evaluations were conducted at the time points described in the protocol review section. Safety laboratory tests evaluated by the Investigator included hematology, coagulation, serum chemistry, urinalysis, and serum or urine pregnancy test. In addition, study sites could perform locally a platelet aggregation assay for patients with platelet count > 150,000/µL.

Table 33 below shows the proportion of patients with shifts in selected hematology parameters from grade ≤ 2 at baseline to grade ≥ 3 at worst value on study. About 20% -30% of patient with AdvSM had at least one CTCAE grade drop in Hb, Platelet, or neutrophils.

Table 33: Proportion of Patients with Shifts in Hematology Parameters from Grade ≤ 2 at Baseline to ≥ 3 at Worst Value on Study

	AdvSM			Ava (AdvSM +GIST)
Parameter	200 mg N=81 n (%)	≥ 300 mg N=50 n (%)	All N=148 n (%)	All N=749 n (%)
Hemoglobin decreased	18/81 (22.2)	24/50 (48.0)	44/148 (29.7)	201/749 (26.8)
Platelets decreased	16/81 (19.8)	13/50 (26.0)	35/148 (23.6)	40/749 (5.3)
Neutrophils decreased	18/81 (22.2)	11/50 (22.0)	34/148 (23.0)	91/749 (12.1)
Lymphocytes decreased	9/81 (11.1)	12/50 (24.0)	25/148 (16.9)	139/749 (18.6)
Leukocytes decreased	8/81 (9.9)	9/50 (18.0)	21/148 (14.2)	64/749 (8.5)

Source: The applicant's analysis verified by the reviewer.

Reviewer Comments: Cytopenias, especially thrombocytopenia and neutropenia are substantially more common in AdvSM than pooled population (GIST dominated) and are likely due to both avapritinib and their underlying disease. The greater rates of anemia, thrombocytopenia and lymphopenia were seen in the 300 mg group comparing to those in the 200 mg group. The rate of neutropenia showed no difference between the 200 mg and 300 mg

dosing groups. The overall hematology laboratory results supporting eliminate the 300 mg dose to use in AdvSM.

A small number of Patients with Shifts in Selected Chemistry Parameters from Grade 2 and under at Baseline to Grade ≥ 3 and over at Worst Value on Study are shown in Table 34 below.

Table 34: Proportion of Patients with Shifts in Selected Chemistry Parameters from Grade ≤ 2 to Grade ≥ 3 at Worst Value on Study

	AdvSM			Ava (AdvSM +GIST)
Parameter	200 mg N=81 n (%)	≥ 300 mg N=50 n (%)	All N=148 n (%)	All N=749 n (%)
ALP increased	4/81 (4.9)	3/50 (6.0)	11/148 (7.4)	16/749 (2.1)
Phosphate decreased	1/81 (1.2)	6/50 (12.0)	9/148 (6.1)	48/749 (6.4)
Bilirubin increased	2/81 (2.5)	4/50 (8.0)	8/148 (5.4)	57/749 (7.6)
Potassium decreased	3/81 (3.7)	3/50 (6.0)	6/148 (4.1)	44/749 (5.9)
AST increased	1/81 (1.2)	2/50 (4.0)	3/148 (2.0)	13/749 (1.7)
ALT increased	1/81 (1.2)	1/50 (2.0)	2/148 (1.4)	9/749 (1.2)

Source: The applicant's analysis verified by the reviewer.

Reviewer Comments: The percentage of abnormal chemistries was found to be similar between AdvSM and pooled populations (GIST dominated) , except for ALP, which is likely related to disease progression.

8.4.7. Vital Signs

Vital signs measurements included temperature, systolic/diastolic blood pressure, pulse, and weight performed at the time points described in the protocol review section. In the AdvSM 200 mg group, body temperature and heart rate showed some fluctuations during study treatment, but these changes were generally small and not clinically meaningful.

Mean weight at baseline was 74.229 kg. Thereafter, mean weight generally increased at most time points and the highest mean value (where n was ≥ 10) was 81.011 kg at Week 132. Mean systolic blood pressure at baseline was 125.6 mmHg. Mean values thereafter (where n was ≥ 10) were between 120 and 140 mmHg.

Mean diastolic blood pressure at baseline was 70.6 mmHg. The highest mean value (where n was ≥ 10) was 72.8 mmHg at Week 124; mean values thereafter showed some fluctuations but were all < 80 mmHg. The All grade AEs related to vital sign measurement reported were < 10%

and grade 3 or greater AEs were < 2%.

Reviewer Comments: No safety concerns regarding vital sign results.

8.4.8. Electrocardiograms (ECGs)

Twelve-lead ECGs were obtained for all patients at the time points described in the protocol review section.

8.4.9. QT

The QT study was evaluated during the original NDA review. The effect of avapritinib was evaluated in a subset of 27 patients in Study BLU-285- 1101. The highest dose that was evaluated was 400 mg daily. The data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that avapritinib is associated with large mean increases in the QTc interval. The findings of this analysis are further supported by the available nonclinical data, central tendency analysis and categorical analysis.

Previously approved label described QT events occurred in 1.5% of patients with GIST in the clinical trials. As summarized in Table 35 below, AE search using the PTs from the SMQ Torsade de pointes/QT Prolongation revealed 33 patients (4.4%, 9 with AdvSM and 24 with GIST) who experienced 36 events within the SMQ for QT prolongation. The events included electrocardiogram QT prolonged, syncope, ventricular arrhythmia, cardiac arrest, loss of consciousness, and ventricular tachycardia. Serious events were reported in 4 patients (2 with AdvSM and 2 with GIST), which included syncope, cardiac arrest, and ventricular tachycardia.

Table 35: QT Prolongation SMQ Adverse Events by PT

Preferred Term	AdvSM			Ava (AdvSM +GIST)
	200 mg N=81 n (%)	≥ 300 mg N=50 n (%)	All N=148 n (%)	All N=749 n (%)
Patients with treatment-emergent torsade de pointes/QT prolongation SMQ adverse event	2 (2.5)	4 (8.0)	9 (6.1)	33 (4.4)
Electrocardiogram QT prolonged	1 (1.2)	2 (4.0)	5 (3.4)	20 (2.7)
Syncope	1 (1.2)	1 (2.0)	3 (2.0)	8 (1.1)
Cardiac arrest	0	1 (2.0)	1 (< 1)	1 (< 1)
Loss of consciousness	0	0	0	1 (< 1)
Ventricular arrhythmia	0	0	0	3 (< 1)
Ventricular tachycardia	0	0	0	1 (< 1)

Abbreviations: AdvSM = advanced systemic mastocytosis; Ava = avapritinib; GIST = gastrointestinal stromal tumor; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standardized MedDRA query.
Preferred terms are sorted in decreasing order of frequency using the AdvSM All column.
If a patient experienced more than 1 event within a given SMQ category or preferred term, that patient was counted only once for that category or term.
Source: The applicant's analysis verified by the reviewer.

As described in Table 35 above:

- Electrocardiogram QT prolonged: 21 events in 20 patients (5 patients with AdvSM of which 1 patient received a starting dose of 200 mg QD and 15 patients with GIST)
- Syncope: 8 events in 8 patients (3 patients with AdvSM of which 1 patient received a starting dose of 200 mg QD and 5 patients with GIST)
- Ventricular arrhythmia: 4 events in 3 patients (all 3 patients with GIST)
- Cardiac arrest: 1 event in 1 patient with AdvSM
- Loss of consciousness: 1 event in 1 patient with GIST
- Ventricular tachycardia: 1 event in 1 patient with GIST

The 4 SAEs (2 patients with AdvSM and 2 patients with GIST) were all assessed as not related to avapritinib and are described below:

- Patient BLU-285-2101-(b) (6) had Grade 3 syncope that resolved and was not related to avapritinib
- Patient BLU-285-2101-(b) (6) had Grade 5 cardiac arrest that was fatal and was not related to avapritinib
- Patient BLU-285-1101-(b) (6) had Grade 3 syncope that resolved and was not related to avapritinib

The QT prolongation events in 200 mg group were 1.2% QT prolongation and 1.2% syncope, both assess unrelated to avapritinib by the applicant.

Reviewer comments: The incidence of QT SMQ events in AdvSM 200 mg group is similar to those labeled for GIST.

8.4.10. Immunogenicity

See approved label.

8.4.11. 120-day Safety updates

The avapritinib 120-day safety update was submitted on April 15, 2021. This submission included a safety summary and a data listing of AEs observed in Adv and GIST trials. The safety summary also included a postmarketing summary. No dataset was submitted with 120-day safety updates.

At the 120-day safety update data cut-off (December 18, 2020), three of the four trials, AdvSM trials 2101 and 2202 , as well as GIST trial 1101 were still ongoing. The GIST trial 1303 was completed. For this safety report, safety data were available for a total of 798 patients in the overall safety population who received treatment with avapritinib. The primary population of AdvSM patients treated with avapritinib was 188 at all doses and 121 treated at 200 mg, as shown in Table 36 below.

Table 36: Safety Population at 120-Day Safety Update

Population		SCS (Data Cutoff Dates of 27 May 2020 and 23 Jun 2020 a)	120-Day Safety Update (Data Cutoff Date of 18 Dec 2020)
AdvSM	200 mg QD	81	121
	≥ 300 mg QD	50	50
	All	148	188
GIST	300 mg QD	516	525
	All	601	610
All (AdvSM+GIST)	All	749	798

Abbreviations: AdvSM = advanced systemic mastocytosis; Ava = avapritinib; GIST = gastrointestinal stromal tumor; QD = once daily; SCS = Summary of Clinical Safety.
a 27 May 2020 for BLU-285-1101, BLU-285-1303, and BLU-285-2101; 23 June 2020 for BLU-285-2202.
Source: sNDA Module 2.7.4, table 5, table 18.3.1.2

In 200 mg dosing group, 121 AdvSM patients received ≥ 1 dose of avapritinib at a starting dose of 200 mg QD. As of the data cutoff date, 93 (76.9%) of patients in 200 mg group continued to receive avapritinib. Sixty-two patients (51.2%) had previously received midostaurin treatment. Median treatment duration was 32.00, ranged 0.3 to 188.1 weeks for AdvSM patients treated at 200 mg QD, with 29.8% having been exposed to avapritinib for > 56 weeks.

A total of 28 of the 121 patients (23.1%) had discontinued treatment. The primary reason for discontinuation of treatment was AE (16 patients, 13.2%), followed by disease progression (5 patients, 4.1%) and withdrawal of consent (4 patients, 3.3%).

As of the data cutoff date, 23 patients (19.0%) had discontinued from the study. The primary reason for study discontinuation was death (11.6%), followed by withdrawal of consent (3.3%) and administrative/other (2.5%).

Discontinuation from treatment was lower for AdvSM patients treated at 200 mg QD (23.1%) compared with AdvSM patients treated at ≥ 300 mg QD (58.0%). Discontinuation from the study was also lower for AdvSM patients treated at 200 mg QD (19.0%) compared with AdvSM patients treated at ≥ 300 mg QD (36.0%).

At the data cut-off, 67.8% of AdvSM patients treated at 200 mg QD who had ≥ 1 dose reduction due to an AE, lower than that of AdvSM patients treated at ≥ 300 mg QD (92.0%). In addition, 57.9% of AdvSM patients treated at 200 mg QD with ≥ 1 dose interruption due to an AE, lower than that of AdvSM patients treated at ≥ 300 mg QD (82%).

As shown in Table 37 below, 117 (96.7%) patients in the 200 mg group experienced AEs. Through the update period, no clinically relevant increase (< 1%) in treatment emergent AEs, SAEs, ≥ Grade 3 AEs were observed. An increase incidence (<2%) was noted for deaths due to AEs, AE leading to discontinuation from avapritinib, and cognitive effects events compared with the sNDA reports. The incidence of SAEs, Grade ≥ 3 AEs, AEs leading to discontinuation of treatment, AEs leading to dose interruption, AEs leading to dose reduction, and events of intracranial bleeding and cognitive effects was lower for AdvSM patients treated at 200 mg group compared with patients treated at ≥ 300 mg group. These results also suggest that 300 mg dose should not be used for AdvSM indication as of the safety concern.

Table 37: Adverse Event 120-day Safety Updates

	AdvSM			Ava (AdvSM+GIST)
Patients with any:	200 mg N=121 n (%)	≥ 300 mg N=50 n (%)	All N=188 n (%)	All N=798 n (%)
AE	117 (96.7)	50 (100.0)	184 (97.9)	787 (98.6)
% Change from previous cut-off	-3.3	0	-2.1	-0.01
SAE	39 (32.2)	37 (74.0)	87 (46.3)	418 (52.4)
% Change from previous cut-off	-1.1	+2	-3	-1.1
Grade ≥ 3 AE	84 (69.4)	47 (94.0)	146 (77.7)	617 (77.3)
% Change from previous cut-off	-1.2	0	-2.4	+0.7
AE leading to Ava discontinuation	15 (12.4)	13 (26.0)	32 (17.0)	143 (17.9)
% Change from previous cut-off	+1.3	0	-0.6	-0.9
AE leading to dose interruption	70 (57.9)	41 (82.0)	123 (65.4)	570 (71.4)
% Change from previous cut-off	-2.6	0	-2.8	+1.4
AE leading to dose reduction	82 (67.8)	46 (92.0)	132 (70.2)	464 (58.1)
% Change from previous cut-off	-0.1	0	-0.7	+1.6
AESI of intracranial bleeding	3 (2.5)	8 (16.0)	11 (5.9)	23 (2.9)
% Change from previous cut-off	-1.2	0	-1.5	0
Serious AESI of intracranial bleeding	3 (2.5)	6 (12.0)	9 (4.8)	18 (2.3)
% Change from previous cut-off	-1.2	+2	0.6	0

AESI of intracranial bleeding leading to Ava discontinuation	2 (1.7)	3 (6.0)	5 (2.7)	12 (1.5)
% Change from previous cut-off	-0.8	+2	0	0
AESI of cognitive effects	20 (16.5)	26 (52.0)	52 (27.7)	314 (39.3)
% Change from previous cut-off	+1.7	0	-0.7	-0.6
Serious AESI of cognitive effects	0	4 (8.0)	4 (2.1)	28 (3.5)
% Change from previous cut-off	0	0	-0.6	-0.1
AESI of cognitive effects leading to Ava discontinuation	1 (< 1)	2 (4.0)	4 (2.1)	23 (2.9)
% Change from previous cut-off	0	0	-0.1	+0.4
AE leading to death	6 (5.0)	5 (10.0)	12 (6.4)	74 (9.3)
% Change from previous cut-off	+1.3	0	+0.3	+0.9

Abbreviations: AdvSM = advanced systemic mastocytosis; AE = adverse event; AESI = adverse event of special interest; Ava = avapritinib; GIST = gastrointestinal stromal tumor; SAE = serious adverse event.

Notes: Percentages are based on the number of patients in the Safety Population in each column.

Source: 120-day safety update table 18.3.3.1.1. and the reviewer's assessment.

As for the common adverse events, no notable differences in the profile of the most common AEs (> 10%) were reported at the safety update compared to what was reported in the sNDA. Overall, the most common AEs in ≥ 20% of AdvSM patients treated at 200 mg group at the safety update were consistent with what was reported in the sNDA. In addition, no notable differences in the severity of AEs at the update were Found. Total deaths at the 120-day safety update are shown in Table 38 below. Three additional deaths have been reported since the database cutoff dates for the original submission through the late-breaking data cutoff date (see Table 39 below). The applicant assessed that none of these deaths were considered to be related to avapritinib treatment.

Table 38: The Applicant's Summary of Death

Patient ID	Starting Dose (mg)	Cycle Day of Death	Days from First Dose	Days from Previous Dose	Reason for Death [a]	Treatment Related[b]
Indication: AdvSM						
BLU-285-2101-(b) (6)	30	C7D29	197	4	AE: Acute myeloid	No
BLU-285-2101-(b) (6)	300	C11D40	320	18	AE: Staphylococcal sepsis	No
BLU-285-2101-(b) (6)	300	C24D7	651	0	AE: Cardiac arrest	No
BLU-285-2101-(b) (6)	300	C10D23	275	16	AE: Gastric hemorrhage	No
BLU-285-2101-(b) (6)	300	C5D35	147	12	AE: Septic shock	No
BLU-285-2101-(b) (6)	300	C21D7	567	0	AE: Hemorrhage	Yes
BLU-285-2202-(b) (6) *	200	C1D26	26	2	AE: Intra-abdominal	No
BLU-285-2202-(b) (6)	200	C1D8	8	2	AE: Necrotizing fasciitis	No
BLU-285-2202-(b) (6) *	200	C3D21	77	2	AE: Acute kidney injury	No
BLU-285-2202-(b) (6)	200	C4D30	114	2	AE: Shock hemorrhagic	No
BLU-285-2202-(b) (6)	200	C5D35	147	9	AE: Disease progression	No
BLU-285-2202-(b) (6) *	200	C2D15	43	1	AE: Gastritis erosive	No

Abbreviations: AdvSM = advanced systemic mastocytosis; AE = adverse event; CxDx = Cycle x Day x; GIST = gastrointestinal stromal tumor; ID = identification; MedDRA = Medical Dictionary for Regulatory Activities; sNDA = supplemental New Drug Application.

a Coded using MedDRA version 18.1.

b The applicant's assessment.

* Indicates new event since the sNDA submission

Source: 120-day safety update table 99.3.1.1.

Table 39: Death Cases that Occurred Between Clinical Cut-Off and Safety Update Cut-Off

Patient ID	Preferred Term(s)	Relationship to Study Drug*
BLU-285-2202-(b) (6)	Subarachnoid hemorrhage	Not related
BLU-285-2202-(b) (6)	Intra-abdominal hemorrhage	Not related
BLU-285-2202-(b) (6)	Enterococcal sepsis	Not related

Abbreviation: ID = identification.
*The applicant's assessment
Source: Data on file, Blueprint Pharmacovigilance Department.

A brief narrative for patients who experienced fatal AEs considered not related to study drug is provided here:

- Patient BLU-285-2101-(b) (6), a 67-year-old male patient, experienced a Grade 5 SAE of ischemic stroke in the context of decreased hemoglobin and platelet counts. The patient received red blood cell and platelet transfusions but died 4 days later. The SAE was considered not related to avapritinib.

- Patient BLU-285-2202-(b) (6), a 78-year-old female patient, experienced a Grade 5 SAE of infection. The patient received antibiotics for recurrent fever and C-reactive protein elevation but died 12 days later. The SAE was considered not related to avapritinib.

- Patient BLU-285-2202-(b) (6), a 59-year-old male patient, experienced a Grade 5 SAE of bipolar disorder (pending clarification on the cause of death). The patient had been hospitalized after deterioration of previous episodes of bipolar disorder. The patient was transferred from the psychiatry unit to an internal medicine ward due to aspiration pneumonia. The patient died 7 days later. The cause of death was aspiration pneumonia that was a complication of bipolar disorder. The SAE was considered not related to avapritinib.

Reviewer Comments: The overall safety profile at the 120-day safety cut-off appears to be consistent with that of sNDA clinical cut-off. No new safety information was identified that would negatively impact the established benefit-risk profile of avapritinib for treatment of adult patients with AdvSM treated at 200 mg group.

8.5. Analysis of Submission-Specific Safety Issues

All adverse events are discussed in section 8.4.

8.6. Safety Analyses by Demographic Subgroups

Among the 81 AdvSM patients treated at 200 mg QD, 30 patients (37.0%) were < 65 years and 51 patients (63.0%) were ≥ 65 years. The incidence of AEs overall was the same (100%) for both subgroups.

The overall incidence of Grade ≥ 3 AEs was similar between the younger (76.7%) and older (68.6%) patients. The overall incidence of SAEs was also similar (30.0% and 35.3%, respectively).

Differences between the subgroups for the most commonly reported AEs are summarized in Table 40 below.

Table 40: Difference in Most AE Incidence of **≥** 10% Between Age Groups in **≥** 20% of Patients with AdvSM Treated in the 200 mg Group

Preferred Term	**< 65 Years N=30 n (%)**	**≥ 65 Years N=51 n (%)**	**Total N=81 n (%)**
Periorbital edema	15 (50.0)	17 (33.3)	32 (39.5)
Thrombocytopenia	7 (23.3)	21 (41.2)	28 (34.6)
Nausea	4 (13.3)	16 (31.4)	20 (24.7)

Abbreviations: AdvSM = advanced systemic mastocytosis; QD = once daily.
Source: The applicant's analysis verified by the reviewer.

Reviewer Comments: The incidence of preorbital edema and decreased appetite but not nausea were reported substantially higher in patients with GIST and younger than 65 years. The higher incidence of thrombocytopenia in patient with AdvSM older than 65 may be associated with age factor. However, there were no age difference in frequency of intracranial hemorrhage in subpopulation analysis. Also, there were no age difference in cognitive adverse effects identified.

8.7. Specific Safety Studies/Clinical Trials

Besides four ongoing clinical trials discussed in this review, no specific safety studies or clinical trials were submitted.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Based on the original NDA review (DARRTS 2/20/2020 approval), the applicant did not conduct studies investigating the carcinogenic potential of avapritinib as such studies are not needed to support a marketing application for patients with advanced cancer. Avapritinib was not mutagenic in a bacterial reverse mutation (Ames) assay. Avapritinib was clastogenic in the in vitro chromosome aberration test in human peripheral blood lymphocytes at concentrations ≥ 5 µg/mL (22-hour incubation); these aberrations appeared structural rather than numerical. Avapritinib was, however, not clastogenic in the in vivo rat bone marrow micronucleus test at doses up to 150 mg/kg). Based on the weight of evidence, avapritinib was not considered genotoxic.

8.8.2. Human Reproduction and Pregnancy

See previously approved label.

8.8.3. Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of avapritinib in pediatric patients has not been investigated by the applicant.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The applicant did not provide any reported cases of overdose of avapritinib in the GIST population. Avapritinib does not appear to have abuse potential.

8.9. Safety in the Postmarket Setting

Avapritinib was approved in the US on 09 January 2020 by FDA for the treatment of adults with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations. The approved pharmaceutical strengths of avapritinib are 100 mg, 200 mg, and 300 mg tablets. Post-marketing data are available from the time of first launch globally in the US on 09 January 2020 through 30 September 2020. As of 30 September 2020, an estimated (b) (4) patients have received at least 1 dose of avapritinib for an estimated (b) (4) patient-years exposure. Since marketing authorization, reported events are consistent with the known safety profile of avapritinib; no new risks have been identified in the post-marketing setting.

Safety data from compassionate use of avapritinib were also provided. The applicant reported (b) (4) patients received avapritinib as compassionate use. Of these (b) (4) patients, 157 events were reported, including 70 of grade 3, 7 of grade 4 and 30 deaths. The type of frequent adverse events reported under compassionate use. The most frequently reported AEs were cognitive events, intracranial bleeding, anemia, disease progression and neurological abnormalities. The indicated disease of patients on compassionate avapritinib was not provided.

8.10. Integrated Assessment of Safety

The Primary Safety population consist 148 patients with SM (AdvSM, SSM, ISM and non-SM), with focus on 131 patients with AdvSM (ASM, SM-AHM, and MCL) including 81 patients in the 200 mg avapritinib and 50 patients in the 300 mg avapritinib from trials BLU-285-2101 and BLU-285-2202. The Pooled Safety Population consisted of 749 patients with either systemic mastocytosis (n = 148) and unresectable or metastatic GIST (n=601) who received avapritinib at any dose in Trials BLU-285-2101, Trial BLU-285-2202, Trial BLU-285-1101, or Trial BLU-285-1303. In the Primary Safety Population (n=131), the median duration of exposure to avapritinib was 41 weeks (mean 56 weeks), with a maximum exposure time of 220 weeks. In the Pooled Safety Population, the median duration of exposure to avapritinib was 24 weeks (mean 45 weeks), with a maximum exposure time of 239 weeks.

In the AdvSM Safety Population, 8.4 % (8/131) of patients died due to an AE within 30 days of receiving avapritinib. At 200 mg daily dose of avapritinib, the AEs leading to death were disease progression /hemorrhagic shock (BLU-285-2202-(b) (6)), necrotizing fasciitis (BLU-285-2202-(b) (6)), sepsis (BLU-285-2202-(b) (6)) and shock hemorrhagic each. Of note, the fatal hemorrhagic shock event (BLU-285-2202-(b) (6)) occurred in a patient with CML and avapritinib dose escalation to 300 mg daily. Due to underlying disease and comorbidities, avapritinib may not be the cause of death in these patients.

All (100%) of patients in the Primary Safety Population experienced at least one adverse event, of these 81% were Grade 3-4. This rate was higher than in pooled safety population which included predominantly patients with GIST (n = 601 of 749). In AdvSM 200 mg group, the most frequent Grade 3 AEs are Anemia (19.8%), Neutropenia and thrombocytopenia (14.8% each), with the addition of Platelet count decreased (8.6%), and neutrophil count decreased (7.4%).

The most common (>20%) adverse events in patients in the Primary Safety Population were periorbital edema, anemia, peripheral edema, thrombocytopenia, diarrhea, nausea, fatigue, and vomiting.

The most frequent SAEs were anemia (4.7%), pleural effusion and subdural hematoma (3.4% each), and acute myeloid leukemia, ascites, and pneumonia (2.7% each). In the 200 mg group, the most common SAEs were anemia and subdural hematoma (3 patients, 3.7% each). In patients with any AE lead to avapritinib discontinuation in AdvSM trials, there were 11% in the 200 mg group, and 26% in the 300 mg group. The top reason for treatment termination was AML (2.7%), followed by 1.4% each of ascites, cognitive disorder, intracranial hemorrhage, subdural hematoma, and thrombocytopenia. Approximately 68% patients in AdvSM trials experience an AE that led to avapritinib dose interruption, which is similar to those observed the pooled population (70%). The most frequent AEs caused dose interruptions were thrombocytopenia (12%), anemia (8%), neutropenia (7%), cognitive disorder (3%), and pleural effusion (3%).

Approximately 71% patients in AdvSM trials experience an AE that led to avapritinib dose interruption, which is greater than those observed the pooled safety population (56%). The most frequent AEs leading to dose interruptions were thrombocytopenia (12%), periorbital edema (10%), anemia (9%), neutropenia (7%), cognitive disorder (5%), peripheral edema (5%), memory impairment (4%), fatigue (3%), and pleural effusion (3%).

The AESI defined for the avapritinib clinical development program were Intracranial bleeding and Cognitive effects. Each one of these events are being investigated clinically investigation under an established post marketing commitment.

In pooled safety population of this supplement (GIST, N = 601 and AdvSM, N = 148), the overall incidence of intracranial bleeding was 2.9%. The incidence of intracranial bleeding was higher in patients with AdvSM (7.4%) than in patients of pooled SP (1.9%). Intracranial bleeding events were reported predominantly in the AdvSM 300 mg group, 16%, compare to 3.7% in AdvSM 200 mg group. It is also noted that in patients with AdvSM received avapritinib, serious intracranial bleeding was reported 10% in the 300 mg group and 3.7% in the 200 mg group. Permanent discontinuation of avapritinib due to intracranial bleeding was 4% in the 300 mg group and 2.5% in the 200 mg group. Incidence of grade 3 or greater intracranial bleeding was 1.4% and 4% in 200 mg and 300 mg groups, respectively. A subgroup of patients with AdvSM and platelet count > 50 x 10^9/L, and receiving avapritinib 200 mg, the incidence of intracranial bleeding was 2.6%.

In the primary safety population, 42 (28.4%) experienced cognitive effects. The most commonly reported event was memory impairment (15.5%), followed by cognitive disorder (10.1%), confusional state (6.1%), and encephalopathy (2.0%). The less frequent events included amnesia, delirium, disorientation, and somnolence (1.4% each), and dementia, hallucination, and mental status changes (< 1% each).

In terms of severity, 26 patients (17.6%) reported Grade 1 events, 12 patients (8.1%) reported Grade 2 events, and 4 patients (2.7%) reported Grade 3 events; no Grade 4 or Grade 5 events were reported. Three patients (2.0%) reported cognitive effects that led to permanent discontinuation of avapritinib. No AdvSM patients treated at 200 mg daily experienced cognitive effects leading to permanent discontinuation of study treatment. Patients with a medical history of cognitive effects and patients ≥ 65 years old were more likely to experience Grade ≥ 2 cognitive effects.

The safety profile of avapritinib is still evolving as the clinical trials are ongoing. Although the data from AdvSM clinical trials contained mixed population and various dosing groups, the safety data reviewed is adequate to support the safety of the proposed indication by this sNDA.

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee Meeting or other external consultation are recommended for this application.

10. Labeling Recommendations

The reviewers' Table 41 below summarizes the key clinical labeling changes based on recommendations from various FDA review disciplines of NDA 212608 supplement 006. Final wording of the label will depend on agreement with reviewers in the DMH1 and the Applicant.

Table 41: Summary of Significant Labeling Changes

High Level changes and Not Direct Quotations from Review Disciplines		
Section	Applicant Proposed Labeling	FDA Proposed Labeling
Highlights		
Indication	Ayvakit is indicated for the treatment of adult patients with AdvSM (b) (4). AdvSM includes patients with ASM, SM-AHN, and MCL.	FDA proposed wording is as follows (b) (4) i.e., Ayvakit is indicated for the treatment of adult patients with AdvSM. AdvSM includes patients with ASM, SM-AHN, and MCL.
Full Prescribing Information		
1. Indication	The same indication for Ayvakit is proposed by the sponsor in the Indication Section of the product label.	See FDA Proposed Labeling Comment for the Highlights Section above.
(b) (4)	The applicant proposed to (b) (4)	FDA proposed wording to move (b) (4) to Section (b) (4) Dosage Modifications for Adverse

	(b) (4)	(b) (4)
5.1 Intracranial Hemorrhage	The applicant proposes that overall, intracranial hemorrhage (e.g., subdural hematoma, intracranial hemorrhage, and cerebral hemorrhage) occurred in 2.9% of the 749 patients who received Ayvakit.	FDA proposed the following wording to be, "Serious intracranial hemorrhage may occur with AYVAKIT treatment; fatal events occurred in less than 1% of patients. Overall, intracranial hemorrhage (e.g., subdural hematoma, intracranial hemorrhage, and cerebral hemorrhage) occurred in 2.9% of the 749 patients who received Ayvakit." Also, FDA proposed that the following wording should be added, i.e., "Dose-interruptions and dose-reductions for thrombocytopenia occurred in 20% and 22% of Ayvakit-treated patients, respectively. Thrombocytopenia was generally reversible by reducing or interrupting Ayvakit."
6.1 Clinical Trials Experience under the section titled, "Advanced Systemic Mastocytosis"	The applicant did not propose wording (b) (4). The sponsor proposed, "Patients received a starting dose of Ayvakit ranging from 30 mg to 400 mg orally once daily (n = (b) (4)), including (b) (4) patients who received the recommended starting dose of 200 mg once daily.	FDA recommends the following updated wording, "Patients received a starting dose of Ayvakit ranging from 30 mg to 400 mg orally once daily (n = 131), including 80 patients who received the recommended starting dose of 200 mg once daily. Among patients receiving Ayvakit, 70% were treated for 6 months or longer and 37% were exposed for greater

		than one year."
6.1 Clinical Trials Experience under the section titled, "Advanced Systemic Mastocytosis." "	The sponsor proposed to include a table of adverse reactions reported in ≥ 10% of patients with AdvSM (b) (4) . Also, the sponsor proposed a similar table describing the proportion of patients with select laboratory abnormalities reported in ≥ 10% patients with AdvSM (b) (4) .	FDA proposed (b) (4) adverse reactions reported in ≥ 10% of patients who were treated with the recommended starting dose of 200mg administered orally once daily (b) (4) FDA proposed a similar recommendation for the table describing the proportion of patients with select laboratory abnormalities reported in ≥ 10% patients with AdvSM, (b) (4)
8.5 Geriatric Use	The sponsor proposed the description that of the (b) (4) patients who received Ayvakit in the Blu-285-2101 and in the BLU-285-2202 studies, (b) (4) % were 65 years or older, while (b) (4) % were 75 years and older.	FDA recommended that the sponsor update the wording (b) (4) of the 131 patients with AdvSM who received Ayvakit in the Blu-285-2101 and in the BLU-285-2202 studies, 62% were 65 years or older, while 21% were 75 years and older.
14 Clinical Studies	The sponsor proposed (b) (4)	FDA recommended deletion of the applicant's proposed (b) (4)

	(b) (4)		

Reviewer's table

11. Risk Evaluation and Mitigation Strategies (REMS)

No Risk Evaluation and Mitigation Strategy is recommended for this avapritinib efficacy supplement application for the treatment of patients with AdvSM.

12. Postmarketing Requirements and Commitments

The clinical reviewers recommend the following Postmarketing Commitments (PMR/PMC) be issued for avapritinib for the treatment of patients with AdvSM:

PMRs:

1. Conduct a pooled analysis of data from completed and on-going avapritinib trials, including Studies BLU-285-1101, BLU-285-2101, BLU-285-2202, and BLU-285-1303, to further characterize avapritinib-associated intracranial hemorrhage in patients with gastrointestinal stromal tumor and advanced systemic mastocytosis. Include patient narratives with the onset and resolution date for each event, results of investigations (laboratory, imaging, other), avapritinib dose history and action taken, concomitant medications, patient comorbidities and outcome for intracranial hemorrhage events. Submit datasets, and patient narratives for intracranial hemorrhage events in the final report.

2. Conduct a pooled analysis of data from completed and on-going avapritinib trials, including Studies BLU-285-1101, BLU-285-2101, BLU-285-2202, and BLU-285-1303, to further characterize avapritinib-associated cognitive adverse reactions (including memory impairment, cognitive disorder, confusional state, amnesia, somnolence, speech disorder, delirium, hallucination, mood altered, agitation, personality change, dementia, mental status changes, psychotic disorder, disorientation, mental impairment, and encephalopathy) in patients with gastrointestinal stromal tumor and advanced systemic mastocytosis. Include patient narratives with the onset and resolution date for each event, results of investigations (laboratory, imaging, other), avapritinib dose history and action taken, concomitant medications, patient comorbidities and outcome of each event. Submit datasets, and patient narratives for serious cognitive adverse events in the final report.

PMC:

1. Complete Study BLU-285-2202, "An open-label, single-arm, Phase 2 study to evaluate efficacy and safety of avapritinib (BLU-285), a selective KIT mutation-targeted tyrosine kinase inhibitor, in patients with advanced systemic mastocytosis". Include an updated summary of safety, efficacy analyses, and datasets at the time of final clinical study report submission

13. References

Horny, H.P., et al.: Mastocytosis. Dtsch. Arztbl. Int. 2008; 105(40): 686-692.

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Longley, J., et al.: Activating and dominant inactivating c-KIT catalytic domain mutations in distinct clinical forms of human mastocytosis. Proc. Natl. Acad. Sci. 1999; 96(4):1609-1614.

Lichtman, M. A. et al.: Williams Manual of Hematology 6th ed. 2003.

Gotlib, J., et al.: International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) & European Competence Network on Mastocytosis (ECNM) consensus response criteria in advanced systemic mastocytosis. Blood. 2013; 121(13):2393-2401.

Zhong, X.: Get to the Bottom of Lab Toxicity Grading: Challenges and Implementation of CTCAE Version 5. The Clin. Data Sci. Conf. Paper DH16.

14. Financial Disclosure

Covered Clinical Study (Name and/or Number): BLU-285-2101 and BLU-285-2202

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: There were 10 study sites that enrolled patients in study BLU-285-2101 = 10 and there were 18 study sites that enrolled patients in study BLU-285-2202.		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study(ies): 0 Sponsor of covered study(ies): 0 *Reviewer comment: The sponsor reported three investigators, i.e., (b) (4), Study Site # (b) (4), (b) (4) Study Site # (b) (4) and (b) (4) (no study site number listed); received significant other payments ≥ $25,000 and served on the Response Assessment Committee (RAC), respectively. The sponsor states the following steps were taken to mitigate any bias in (b) (4) role as RAC members:* • *The RAC and SSC are responsible for adjudicating patient disease response on these studies. To minimize any potential for bias as per the RAC Charters there are four other voting committee members on the BLU-285-2101 RAC and five other voting members on the BLU-285-2202 study.* • *In the BLU-285-2202 study, per the Charter, (b) (4) refrained from reviewing his own patients and the review was delegated to a different RAC member.* • *In both BLU-285-2101 and BLU-285-2202 the primary analysis of overall response rate was based on RAC central evaluation of response and not local Investigator*		

evaluations of response.

- *Algorithmic calculations of patient responses, using the IWG-MRT-ECNM criteria were performed to support the adjudicated response rate.*
- *One hundred percent source data verification of the investigator-assessed response criteria was required.*

From a clinical perspective, the sponsor's investigator strategies to mitigate bias for the three investigators who had significant other financial payments appears to be acceptable and would minimize investigator bias in studies BLU-285-2101 and BLU-285-2202. (b) (4) *The overall impact of potential bias from the three listed investigators appears to be minimal.*

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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/

ANDREW DMYTRIJUK
06/16/2021 11:31:15 AM

QIN C RYAN
06/16/2021 12:00:57 PM

ALBERT B DEISSEROTH
06/16/2021 12:14:15 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212608Orig1s006

MEDICAL REVIEW(S)

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

FROM:	Margaret Thompson, MD; Medical Officer, DO3/OOD
THROUGH:	Steven Lemery, MD; Division Director, DO3/OOD
TO:	File
SUBJECT:	Changes made to GIST portion of label
PRODUCT:	Ayvakit ® (avapritinib)
DATE:	4/21/2021

BACKGROUND

- On 1/9/2020, FDA approved Ayvakit (Avapritinib) for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor alpha (PDGFR) exon 18 mutation, including PDGFRA D842V mutation.

- On 12/16/2020, Blueprint Medicines Corp submitted efficacy supplements 6 (b) (4) and 7 (mast cell leukemia) for Ayvakit.

- On 1/25/2021, DO3 received a consult from DNH requesting review of the changes made to the GIST portion of Warnings and Precautions of the USPI, which were included in Supplements 6 and 7.

SUMMARY OF PROPOSED LABELING CHANGES

Section 5.1 Intracranial Hemorrhage:
The Applicant removed reference to the pooled safety population (N=335), leaving data from the GIST Safety population (N=267).

DO3 expanded the information to state that there were 3 cases of GIST, 2 of which were Grade 3, both which lead to discontinuation. DO3 deleted the statement that 0.9% of patients receiving AYVAKIT required permanent discontinuation and 1.2% required dosage interruption followed by dose reduction as this statement applies to N=334 pooled safety population rather than the GIST Safety population. These changes were based on the safety analysis reported in the Unireview for the original GIST application.

Section 5.2 Cognitive Effects

The Applicant changed the header from Central Nervous System. The analysis population for GIST changed to 601 patients who received Avapritinib for a diagnosis of GIST. In addition, the preferred terms (PT) included in the grouped term Cognitive Effects was narrowed and now includes cognitive disorders, confusional state, amnesia, and somnolence. PTs removed from the group term include dizziness, sleep disorders, mood disorders, speech disorders, and hallucinations. DO3 accepted the change to the definition of the grouped term Cognitive Effects as the frequencies for the PTs removed from the grouped term are included in Table (b) (4) in Section 6 and the events for these PTs were rarely Grade ≥ 3.

Additional Comments:

- DO3 recommended (b) (4)

RECOMMENDATIONS

DO3 conveyed its recommendations to the primary teams reviewing supplements 6 and 7 prior to and during the labeling meetings. DO3 agrees with the final agreed upon label.

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/

MARGARET C THOMPSON
05/11/2021 02:20:49 PM

STEVEN J LEMERY
05/13/2021 10:54:48 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212608Orig1s006

CHEMISTRY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. NDA Supplement Number: NDA 212608 / S-006
NDA 212608 / S-007

sNDA Recommendation:
☒ **Approval**
☐ **Complete Response**

sNDA managed by:
☐ **OPQ**
☒ **OND**

2. Submission(s) Being Reviewed:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement [a]	SE	12/16/2020	12/16/2020	12/22/2020	06/16/2021	05/14/2021
IR Response[b] SD87		02/26/2021	02/26/2021			
IR Response[c] SD90		03/08/2021	03/08/2021			
IR Response[d] SD93		03/18/2021	03/18/2021			
IR Response[c] SD94		04/02/2021	04/02/2021			
IR Response[d] SD95		04/06/2021	04/06/2021			
120 Day Safety Update SD97		04/15/2021	04/15/2021			
Labeling IR SD98		04/29/2021	04/29/2021			
IR Response[e] SD99		04/30/2021	04/30/2021			
Labeling IR SD100		05/04/2021	05/04/2021			
Inspector Findings SD101		05/04/2021	05/04/2021			
IR Response[f]		05/17/2021	05/17/2021			05/24/2021
IR Response[d]		05/19/2021	05/19/2021			
IR Response[g]		05/21/2021	05/21/2021			

[a] Administratively split into S006 and S007
[b] Clinical and Stats issued an IR to the firm on February 10, 2021.
[c] Pharmacometrics issued an IR to the firm on February 23, 2021, and March 19, 2021, respectively.
[d] Clinical issued an IR to the firm on March 10, 2021, and March 31, 2021, and May 14, 2021, respectively.
[e] Stats issued an IR to the firm on April 21, 2021.
[f] CMC issued an IR to the firm on May 14, 2021.
[g] Labeling negotiations.

3. Provides For:

This supplemental application proposes the following change(s) for Ayvakit (avapritinib):

1. New indication as a treatment for adult patients with advanced systemic mastocytosis (AdvSM) (b) (4) AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).
2. Additional tablet strengths (25 mg and 50 mg)
3. Addition of (b) (4) (FEI: (b) (4)) as a new manufacturing and analytical testing facility of the proposed 25 mg and 50 mg tablets.

For administrative purposes, the Agency has administratively split the supplement, designated as follows:

- NDA 212608/S-006 - Patients with Aggressive Systemic Mastocytosis (ASM), and Systemic Mastocytosis with an Associated Hematological Neoplasm (SMAHN).
- NDA 212608/S-007 - Mast Cell Leukemia (MCL).

4. **Review #**: 01a

5. **Clinical Review Division**: DO3; NDA 212608/S-006 will be reviewed by the Division of Non-Malignant Hematology (DNH) and NDA 212608/S-007 will be reviewed by the Division of Hematologic Malignancies I (DHMI).

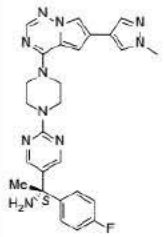
6. **Name and Address of Applicant**:
Blueprint Medicines Corporation
45 Sidney Street
Cambridge, MA, USA 02139

Contact: Gemma Mandell
Phone: (b) (6)
Email: gmandell@blueprintmedicines.com

7. **Drug Product**:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product	Orphan Designation
AYVAKIT (avapritinib)	Tablets	100 mg, 200 mg, 300 mg	Oral	Rx	Yes	15-5065

8. **Chemical Name and Structure of Drug Substance**:

	USAN: Avapritinib Chemical name: (S)-1-(4-fluorophenyl)-1-(2-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)piperazin-1-yl)pyrimidin-5-yl)ethan-1-amine Molecular formula: $C_{26}H_{27}FN_{10}$ MW: 498.57 g/mol

9. **Indication**:
AYVAKIT is indicated for the treatment of adults with unresectable or metastatic gastrointestinal Stromal Tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations.

10. **Supporting/Relating Documents**:
- Biopharm Assessment available on Panorama 05/24/2021 (Reviewer: Kevin Wei).
- Facilities Overall Inspection Management Form available on Panorama 02/08/2021 for S006 (Reviewer: Yong Wu), and 02/23/2021 for S007 (Reviewer: Shu-Wei Yang).

11. Consults:

Consults	Recommendation	Date	Reviewer
OPF/Facility (S-006)	APPROVE	02/08/2021	Yong Wu
OPF/Facility (S-007)	APPROVE	02/23/2021	Shu-Wei Yang
Biopharm	ADEQUATE[1]	05/24/2021	Kevin Wei
Clinical	ADEQUATE	05/20/2021	Peter Demaria
Stats	Pending		Xiaoyu Cai
Clin Pharm	Pending		Sudharshan Hariharan
Pharmacometrics	Pending		Robyn Konicki
Non-clinical	Pending		Bo Yeon Lee
Labeling	Pending		Virginia Kwitkowski
OSI/Clinical Inspection	ADEQUATE	05/21/2021	Anthony Orencia
OPDP	Comments sent to firm	04/15/2021	Emily Dvorsky
DMPP	PPI Acceptable with recommended changes	04/13/2021	Susan Redwood
DMEPA	USPI can be improved, comments sent to firm. PPI, container labels, and carton labels are acceptable.	03/25/2021	Stephanie DeGraw

[1]Biowaver request for the proposed 25 mg and 50 mg strengths was granted per 21 CFR 320.22(d)(2)

12. Executive Summary:

AYVAKIT (avapritinib) immediate release tablets, available in 100 mg, 200 mg, and 300 mg strengths, are indicated in the treatment of Gastrointestinal Stromal Tumor (GIST). All tablet strengths are manufactured (b) (4) 100 mg, 200 mg, or 300 mg tablets which are film coated and printed before packaging into HDPE bottles with 0.5 g desiccant and an induction sealed (b) (4). The drug substance, avapritinib, is currently manufactured at (b) (4) (FEI: (b) (4)), and (b) (4) (FEI: (b) (4), approved S-003). The drug product (100 mg, 200 mg, 300 mg tablets) is currently manufactured at (b) (4) (FEI: (b) (4)). The 100 mg, 200 mg, and 300 mg tablets are manufactured using a (b) (4) process and utilizing a (b) (4) for all dosage strengths. The manufacturing process comprises (b) (4) .

In the initial original submission, **NDA 212608-ORIG-1**, 18-month shelf-life was granted for 100 mg and 200 mg strengths and 12-month shelf-life was granted for 300 mg due to the (b) (4) dissolution trend. (b) (4)

This supplemental application (S-006 and S-007) proposes the following change(s) for Ayvakit (avapritinib):

1. New indication as a treatment for adult patients with advanced systemic mastocytosis (AdvSM) (b) (4) AdvSM includes patients with aggressive systemic mastocytosis

(ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).

2. Additional tablet strengths (25 mg and 50 mg)

3. Addition of (b) (4) (FEI: (b) (4)) as a new manufacturing and analytical testing facility of the proposed 25 mg and 50 mg tablets.

For administrative purposes, the Agency has administratively split the supplement, designated as follows, S-006 - Patients with Aggressive Systemic Mastocytosis (ASM), and Systemic Mastocytosis with an Associated Hematological Neoplasm (SMAHN); and S-007 - Mast Cell Leukemia (MCL).

The proposed 25 mg and 50 mg strengths are manufactured dose proportional to the currently marketed 100 mg, 200 mg, and 300 mg strength tablets. The manufacturing process proposed at (b) (4) is the same as that for the current 100 mg, 200 mg, 300 mg tablets manufactured at (b) (4), with the exception of the imprinting (the 25 mg and 50 mg tablets will be debossed) and the removal of (b) (4) The equipment is similar with the exception of (b) (4) used, however, manufacturing parameters at (b) (4) were optimized based on the manufacturing equipment used. The firm is using the same excipients and film coating as used in the current tablets with the exception of the (b) (4) blue printing ink because the proposed 25 mg and 50 mg tablets are debossed. In-process controls (b) (4) The same primary packaging site as is currently used with the 100 mg, 200 mg, and 300 mg tablets, (b) (4), will be used for commercial packaging of the proposed 25 mg and 50 mg tablets.

Specifications of the proposed 25 mg and 50 mg tablets are identical with the specifications for the current 100 mg, 200 mg, and 300 mg tablets with the exception of the appearance and identification. The identity of the 25 mg and 50 mg is confirmed by comparing the HPLC/UV instead of the current FTIR and HPLC retention time. The combined use of HPLC/UV diode array for an identification is in agreement with ICH Q6A. Elemental impurities assessment was provided, and based on vendor statements, the amount of elemental impurities in the drug product is not greater than (b) (4)% PDE and no additional controls for elemental impurities need to be provided. Method transfer reports and method validation reports were provided, and the methods are suitable for their intended use.

Batch analyses of six batches (clinical and registration) of 25 mg tablets, and three batches of both 50 mg and 100 mg tablets do not show any quality concerns and are within specified limits. The 100 mg tablets were manufactured at (b) (4) for clinical studies, but will not be manufactured at (b) (4) for commercial use. Temperature cycling studies, photostability studies, and forced degradation studies do not show any quality concerns compared to the current 100 mg, 200 mg, and 300 mg tablets. Long-term and accelerated stability studies were performed on 25 mg and 100 mg tablets manufactured at the proposed (b) (4), with the 50 mg tablets bracketed. Up to 12 months long term, and 6 months accelerated for both the 25 mg and 100 mg tablets do not show any quality concerns or significant trending. The firm is

proposing a 24 month expiration date, which is acceptable based on the 12 month long-term stability data provided.

The firm is proposing the commercial packaging is the same as the current tablets, except with 2 g of desiccant instead of 0.5 g of desiccant. The increased desiccant seems to have mitigated quality concerns discussed in previous supplements and the original NDA submission with (b) (4) and dissolution.

A post-approval stability commitment was provided to continue the ongoing long-term stability studies on the three registration lots of 25 mg and 100 mg tablets will be conducted through 48 months. Additionally, the first three commercial-scale batches of 25mg and 50 mg tablets will be placed on stability and one lot per year of each 25 mg and 50 mg tablets, if manufactured that production year, will be placed on long term stability.

The proposed labeling has been amended to include the 25 mg and 50 mg tablets. The proposed labeling is acceptable from a CMC standpoint.

Biopharm has found the dissolution data acceptable and granted a biowaiver for the proposed 25 mg and 50 mg strengths was granted per 21 CFR 320.22(d)(2) (05/24/2021, Reviewer: Kevin Wei).

Facilities recommends the proposed (b) (4) site for approval (S006: 02/08/2021, Reviewer: Yong Wu; S007: 02/23/2021, Reviewer: Shu-Wei Yang).

The changes proposed in S006 and S007 are acceptable from a CMC standpoint.

13. Conclusions & Recommendations:

This supplement is recommended for approval.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer:
Sarah C. Zimmermann, Ph.D., CMC reviewer, Branch 1, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

16. Secondary Reviewer:
Ramesh Raghavachari, Ph.D., Branch Chief, Branch 1, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ

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Ramesh Raghavachari

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Sarah Zimmermann

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/s/

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212608Orig1s006

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA 212608/S-006
Supporting document/s:	80
Applicant's letter date:	Dec 16, 2020
CDER stamp date:	Dec 16, 2020
Product:	Ayvakit (avapritinib)
Indication:	Advanced Systemic Mastocytosis (AdvSM)
Applicant:	Blueprint Medicines Corporation
Review Division:	DPT CHEN on behalf of the Division of Non-Malignant Hematology
Reviewer:	Bo Yeon Lee, Ph.D.
Supervisor/Team Leader:	Pedro Del Valle, Ph.D., FATS
Division Director:	Todd Bourcier, Ph.D. DPT CHEN Ann Farrell, MD DNH
Project Manager:	Brittany Garr-Colon, MPH

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 212608 are owned by Blueprint Medicines Corporation or are data for which Blueprint Medicines Corporation has obtained a written right of reference. Any information or data necessary for approval of NDA 212608 that Blueprint Medicines Corporation does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 212608.

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1 Executive Summary

1.1 Introduction

Blueprint medicine has developed avapritinib, currently marketed as AYVAKIT™ (NDA 212608 approved on January 9, 2020), a highly potent and selective small molecule inhibitor designed to inhibit the conformation of KIT and platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation.

In the U.S., AYVAKIT™ (avapritinib) is indicated for the treatment of adults with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations, and in the E.U., AYVAKYT® (avapritinib) is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic GIST harboring the PDGFRA D842V mutation.

Development of avapritinib for the systemic mastocytosis was conducted under IND 124159 receiving Breakthrough Therapy Designation for the treatment of AdvSM and Orphan Drug Designation (ODD #15-5065) for the treatment of mastocytosis.

On December 16, 2021, the Sponsor submitted a supplemental new drug application, NDA 212608-006 for the advanced systemic mastocytosis (ADVSM). To support the proposed label expansion, the Sponsor has conducted additional PK/ADME studies and repeat-dose toxicology studies in rats for 26 weeks and in dogs for 39 weeks.

1.2 Brief Discussion of Nonclinical Findings

Results from the additional PK/ADME studies showed that CYP3A4 and CYP3A5 are involved in the metabolism of avapritinib (BLU-285), and avapritinib is metabolized to its hydroxylamine M514 first and subsequently M514 was metabolized to the glucuronide conjugate M690 by UGT1A3 and CYP3A4. Avapritinib doesn't appear to be a substrate for human OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp or BSEP under the study conditions.

GLP-compliant repeat-dose toxicology studies were conducted in rats for 26 weeks and in dogs for 39 weeks with 8-week recovery period.

Rats were administered orally with avapritinib at 1, 3, or 10 mg/kg/day for 26 weeks. Target organs of toxicity identified included the adrenal gland, bone marrow, prostate gland, thymus, ovaries, and vagina with corresponding histopathological findings of cortical hyperplasia, necrosis and thrombus in the adrenal gland, decreased cellularity in the bone marrow, mixed cell inflammation and hemorrhage in the prostate gland, decreased lymphoid cellularity and hemorrhage in the thymus, corpus luteum cystic degeneration and hemorrhage in the ovaries, and increased epithelial mucification of the vagina. The thrombus in the adrenal gland, corpus luteum cystic degeneration and hemorrhage in the ovaries, and hemorrhage in the thymus persisted at the end of the 2-month recovery period. Based on the finding's lack of reversibility and severity of

findings at the HD, the NOAEL was determined at the MD of 3 mg/kg/day. Safety margins of human exposure: 1.5X males, 3X female.

Dogs were treated orally with avapritinib at 0.5, 1.5, or 5 mg/kg for 39 weeks. Target organs of toxicity identified included bone marrow, lymph nodes, spleen, testis, and thymus with corresponding microscopic findings of decreased cellularity in the bone marrow in HD males and ≥ MD females, decreased cellularity (HD) and erythrocytosis (≥ LD) in lymph nodes (axillary and mandibular), increased extramedullary hematopoiesis and pigmented macrophages in the spleen, hypoplasia and hypospermatogenesis in testis of MD and HD males, and decreased cellularity in the thymus. Avapritinib-related histopathological findings generally recovered except for findings of pigmented macrophages in the spleen although noted with less frequency and severity, and hypoplasia and hypospermatogenesis in MD and HD males that were still present at the end of the recovery period. Avapritinib was tolerated up to HD and the NOAEL was determined at 5 mg/kg/day in dogs for 39-week treatment. Safety margins of human exposure: 1.2X male, 1.1X female.

Table 1 Safety Margin for Human Exposure Based on the Animal Exposure from Toxicology Studies.

Toxicity	Species	NOAEL (mg/kg) M/F	AUC (ng•h/mL) M/F	Safety Margin Based on AUC*
26-W	Rat	3	9710/19900	1.5/3
39-W	Dog	5	7930/7250	1.2/1.1

*AUC in human: 6600 ng.hr/ml at 200 mg/day.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Study Title: Identification of the UDP-Glucuronosyltransferase Enzymes Involved in the Metabolism of BLU-285 Hydroxylamine and Confirmation of the Identity of the Glucuronide Observed in Human Plasma (Study number BLU-R0104)
Non-GLP compliant

BLU-285 (avapritinib) was assessed to confirm the identity the glucuronide of BlU-285 hydroxylamine observed in human plasma and identify UDP-glucuronosyltransferase (UGT) enzymes involved in its formation.

BLU-285 incubated with NADPH-fortified human liver microsomes (HLM) and recombinant CYP3A4 (rCYP3A4) resulted in formation of its hydroxylamine metabolite M514, and this metabolite was also detected in incubations with human hepatocytes.

Incubation of M514 with HLM with a co-factor, Uridine-5'-diphosphoglucuronic acid (UDPGA) led to formation of a glucuronide conjugate M690 metabolite, which was also observed in human hepatocytes.

The metabolite M690 was formed mainly by rUGT1A3, and rUGT1A4 and 2B7 as well when M514 (10 µM) was incubated with a panel of rUGTs.

Table 2. Formation of BLU-285 Hydroxylamine Glucuronide Following Incubation of BLU-285 Hydroxylamine (10 µM) with rUGT Enzymes and HLM

(Excerpted from submission)

Sample	Peak Area Ratio
HLM	0.321
UGT1A1	ND
UGT1A3	0.0817
UGT1A4	0.0084
UGT1A6	ND
UGT1A9	ND
UGT2B7	0.0108
UGT2B15	ND

ND: Not determined as there was no parent depletion

Based on the results, BLU-285 is metabolized to its hydroxylamine M514 first and subsequently M514 was metabolized to the glucuronide conjugate M690 by UGT1A3 and CYP3A4.

Study Title: Assessment of BLU-285 as a substrate of human OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp and BSEP mediated transport. (Study Number OPT-2019-223)

BLU-285 (avapritinib) was assessed to determine if it is a substrate of human OAT1, OAT3, OCT1, OCT2, OAP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp and BSEP mediated transport.

BLU-285 was evaluated at 1, 10, 50 µM as well as 10 µM in the presence of prototypical reference inhibitor of each transporter.

At all concentrations of BLU-285, the difference in uptake was < 2-fold between transporter-transfected cells and control cells observed in human OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, and MATE2-K. The difference in update between vesicles supplied with ATP compared to vesicles supplied with AMP for BSEP-expressing vesicles was less than 2-fold and the net flux ratios were below 2 for both BCRP and P-gp.

Based on the analysis, BLU-285 doesn't appear to be a substrate for human OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp or BSEP under the study conditions.

Study Title: Assessment of the Metabolism of BLU-285 (X720776) by Human Cytochrome P450 (CYP) 3A4 AND 3A5 (Study Number R2001070)
Non-GLP compliant

BLU-285 (1 and 10 µM) was incubated with cDNA-expressed human CYP3A4 and 3A5 enzymes, pooled human liver microsome (HLM), or single donor HLM of various CYP3A5 genotypes to determine if human cytochrome P450 3A5 metabolizes BLU-285,

Metabolism of BLU-285 was observed in incubation with cDNA-expressed CYP3A4 with 30% and 66% parent remaining or with cDNA expressed CYP3A5 with 55% and 76% parent remaining (1 and 10 µM of BLU-285, respectively). Negative controls (without NADPH or microsomal protein, or with vector control) did not deplete parent or formed M499 metabolite.

Table 3. BLU-285 Metabolism by cDNA-expressed CYP3A4 and 3A5 (100 pmol/mL)

	BLU-285 concentration (µM)			Average % Remaining
Isoform	BLU-285	0 min	45 min	
CYP3A4 (+NAPDH)	1	0.61	0.19	30
	10	8.9	5.9	66
CYP3A4 (-NADPH)	1	0.56	0.65	117
	10	9.3	9.5	102

	BLU-285 concentration (μM)			Average % Remaining
Isoform	BLU-285	0 min	45 min	
CYP3A5 (+NAPDH)	1	0.56	0.30	55
	10	9.9	7.5	76
CYP3A5 (-NAPDH)	1	0.67	0.74	111
	10	9.0	9.2	103
Vector control[1]	1	0.81	0.79	99
	10	11	13	119
No protein[2]	1	0.42	0.51	123
	10	4.7	4.2	95

1 Vector control supersomes not expressing any CYP protein
2 Incubations containing buffer, NADPH, and BLU-285 only

Metabolite of BLU-285, M499 was formed in incubations with CYP3A4 & 3A5, and all HLM in the presence of NADPH, representing <10% of initial BLU-285.

Incubation of BLU-285 with pooled HLM or single donor HLM of various CYP3A5 genotypes (CYP3A5*1*1, *1*3, *3*3) for 45 min did not result in parent depletion or M499 formation.

Taken together, the results suggest that CYP3A4 and CYP3A5 are able to catalyze the metabolism of BLU-285 in vitro as assessed by parent depletion and M499 metabolite formation.

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: BLU-285: A 26-Week (Once Daily) Oral (Gavage) Toxicity Study in Sprague Dawley Rats with an 8-Week Recovery Period

Study no.: 00124815
Study report location: eCTD 4.2.3.2
Conducting laboratory and location: (b) (4) (b) (4)
Date of study initiation: July 23, 2018
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and purity: BLU-285, 0285/02, 98.6

Key Study Findings

- Red staining of fur mostly in HD rats was still present at the end of recovery.
- Avapritinib-related dose-dependent decrease in RBC mass and WBCs were observed at the end of dosing but similar values compared to control were observed at the end of recovery.
- Avapritinib-related organ weight changes, macroscopic and microscopic findings were observed in adrenal gland, bone marrow, spleen, thymus, and reproductive organs (ovary, vagina, uterus, testis, epididymis, and prostate gland)
- Target organs of toxicity included all organs with weight changes, macroscopic and microscopic findings listed above.

Methods

Doses:	0 (control), 1 (Low Dose: LD), 3 (Mid Dose: MD), 10 (High Dose: HD) mg/kg/day
Frequency of dosing:	Once daily
Route of administration:	Oral
Dose volume:	10 mL/kg
Formulation/Vehicle:	0.5 % carboxymethylcellulose (CMC; medium viscosity)-Na (w/v): 1 % Tween 80 (v/v) in deionized water (pH 2–3)
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	Dosing= 20/sex/group Recovery= 5/sex/group
Age:	7 weeks/ sexually mature
Weight:	159-283g at the initiation of dosing
Satellite groups:	TK= 4/sex/control, 10/sex/ LD, MD, HD groups
Unique study design:	Standard design
Deviation from study protocol:	Several with no impact on quality or integrity of the data

Observations and Results

Mortality

Mortality and physical signs were observed twice daily.
No avapritinib-related mortality occurred during the dosing and recovery period.

Clinical Signs

Rats were observed for the clinical signs on predose and Dosing day 1 and weekly during the dosing and recovery period.

Red staining of fur was observed in avapritinib-treated animals, mostly in HD. Thin cover of fur, partly missing pinna, and skin scab were also observed in the avapritinib treated groups. Partial reversibility of red staining of fur was noted after the recovery phase (Day 239/240).

Table 4. Clinical Sings in Rats with Avapritinib Treatment for 6 Months

After dosing (Day 183)		Male (n=15/groups)				Female (n=15/groups)			
Sign	Location of a Finding	Control	LD	MD	HD	Control	LD	MD	HD
Fur, Staining, Red	Mouth				2/1				
	Muzzle		2/1	3/2	5/3				
	Periorbital, Left				1/1				10/1
	Periorbital, Right				10/2				
	Ventral Cervical							12/2	
Fur, Thin Cover	Cranium		9/1	53/4			10/1	7/2	18/2
Pinna Partly Missing,	Left							23/1	10/1
	Right			27/1					
Skin, Scab	Cranium		8/1	24/3			12/3	5/2	10/1

Number of times recorded / Number of animals affected
LD=1 mg/kg/day, MD= 3 mg/kg/day, HD= 10 mg/kg/day

Body Weight Gain

Body weights were recorded weekly during the dosing and recovery period.
HD males started showing increased body weight gain on Day 22 which corresponds to the increased food consumption. Dose-related increase in body weight gains in all avapritinib-treated groups (12.3 ↑ in HD) were noted on dosing Day 182.

Feed Consumption

Food consumption was measured weekly during the dosing and recovery period.
HD males presented higher food consumption up to ~10% compared to controls from Dosing Week 1 (Day 1-8) to Week 15 (Day 99-106) which corresponds to the body weight increase observed in HD males.

Ophthalmoscopy

Ophthalmic examinations were conducted on Pre-Dosing Day 10 and Dosing Day 181
No avapritinib-related effects were observed.

Hematology

Blood samples for hematology and serum chemistry were collected from the jugular vein or retro orbital sinus from animals fasted prior to blood collection.

Dosing Phase (Day 183/184):
Avapritinib-treated animals presented avapritinib-related dose-dependent **decrease in RBC mass** [RBC, reticulocytes, mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) (in males and females), hematocrit and hemoglobin (in females only)] **and WBCs** [monocyte and neutrophil (in males and females), basophils, eosinophil, and lymphocyte (in males only)]. The decreased RBC and WBCs after

avapritinib treatment is with corresponding histological findings in spleen, thymus, bone, and bone marrow. Increased platelet counts were observed in LD-HD females, see Table 5.

Recovery Phase (Day 239/240):
The decrease in red cell mass reversed to baseline in avapritinib-treated animals after the recovery period. The Sponsor stated that inconsistent changes in WBCs after the recovery period were not considered to be the effect of avapritinib, but rather biologic variation since the changes lacked dose-relation and corresponding clinical or histopathological findings.

Table 5. Changes (%) in Hematology Parameters in Rats with Avapritinib Treatment for 6 Months with 8-week recovery period

After Dosing (Day 183/184)	Male (N=15 / group)				Female (N=15 / group)			
Parameter	Control[a]	LD	MD	HD	Control[a]	LD	MD	HD
Basophils (10^9/L)	0.02	-8	-36	-20	0.01	-40	0	-10
Eosinophils (10^9/L)	0.17	-13	-19	-39**	0.11	3	-19	-3
MCH (pg)	17	3	10**	37**	19	1	5**	20**
MCV (fL)	53	3	8**	36**	56	2	6**	23**
Erythrocytes (10^9/L)	9	-1	**-10****	**-31****	8	-5	**-13****	**-27****
Hematocrit (%)	47	2	-3	-7**	47	-3	-8**	-11**
Hemoglobin (g/dL)	15	2	-1	-6*	16	-4	-9**	-13**
Large Unstained Cells (10^9/L)	0.06	21	0	13	0.03	9	60	65
Leukocytes (10^9/L)	9	12	-10	-28	6	7	0	-5
Lymphocytes (10^9/L)	6	7	-8	-19	4	0	2	-1
Monocytes (10^9/L)	0.3	-5	-24	**-56****	0.2	26	5	-13
Neutrophils (10^9/L)	2	31	-12	-49	1	28	-7	-21
Platelets (10^9/L)	1220	-1	-6	-4	920	15	**22****	**37****
Reticulocytes (10^9/L)	281	-17	**-34****	**-42****	187	-7	**-17***	**-21****
After Recovery	Male (N=5 / group)				Female (N=5 / group)			
Parameters	Control[a]	LD	MD	HD	Control[a]	LD	MD	HD
Basophils (10^9/L)	0.01	-14	-43	229	0.004	50	-50	50
Eosinophils (10^9/L)	0.2	34	-14	3	0.2	-29	-56	-17
Large Unstained Cells (10^9/L)	0.1	8	-38	19	0.02	33	42	33
Leukocytes (10^9/L)	10.2	-15	-23	3	5.1	27	18	21
Lymphocytes (10^9/L)	7.9	-17	-35	-1	3.5	33	28	35
Monocytes (10^9/L)	0.3	-11	-17	20	0.2	4	-2	7
Neutrophils (10^9/L)	1.8	-12	29	15	1.2	21	5	-11
Platelets (10^9/L)	1036.2	-1	-5	-12	809	-2	16	10

* = p<0.05 and ** = p<0.01 when compared to the control group using Dunnett's test.

a Values in this column represent the actual control group mean for each respective parameter.
MCH= mean corpuscular hemoglobin, MCV= mean corpuscular volume,
LD=1 mg/kg/day, MD= 3 mg/kg/day, HD= 10 mg/kg/day

Coagulation:

Blood samples for coagulation parameters were collected from the inferior vena cava at the end of dosing Day 183/184

Prothrombin time was increased with dose dependency in avapritinib-treated animals at the end of dosing, but the change was reversed after the recovery phase.

Table 6. Changes (%) of Coagulation Parameter in Rats with Avapritinib Treatment for 6 Months

Parameter	Males			Females		
	LD	MD	HD	LD	MD	HD
Prothrombin time (sec)						
Dosing Day 183 (n=15)	2.7	**6.0****	**10.9****	2.8	3.4	**6.8****
Recovery Day 239 (n=5)	3.0	6.0	0	0	1.8	-0.6

** = p<0.01 when compared to the control group using Dunnett's test.
LD=1 mg/kg/day, MD= 3mg/kg/day, HD= 10mg/kg/day

Clinical Chemistry

HD males and females presented increased urea nitrogen, creatinine, alanine aminotransferase (ALT), and aspartate aminotransferase (AST; males only), and decreased sorbitol dehydrogenase and triglyceride levels at the end of dosing (Day 183/184) and these findings reversed to base line except sorbitol dehydrogenase in HD female after the recovery period (Day 239/240). Total bilirubin level was increased dose-dependently in avapritinib-treated animals with reversibility after the recovery period. There were no corresponding histopathological findings in liver.

Table 7. Changes (%) of Serum Chemistry Parameters in Rats treated with Avapritinib for 6 Months with 8-week Recovery Period

Dosing period (Day 183)	Male (n=15 / group)			Female (n=15 / group)		
Parameter	LD	MD	HD	LD	MD	HD
Total bilirubin (mg/dL)	-14.3	**57.1****	**271.4****	50.0	**87.5****	**162.5****
Urea nitrogen (mg/dL)	100.8	12.7	**11.1**	5.4	5.4	**20.3****
Creatinine (mg/dL)	131.7	9.8	**19.5**	14.3	16.3	**26.5****
Alanine aminotransferase (U/L)	-32.9	-1.3	**26.6**	-22.7	15.2	**24.2**
Aspartate aminotransferase (U/L)	-6.8	72.7	**52.3**	-17.0	12.4	6.5
Sorbitol dehydrogenase (mg/dL)	-58.6	-24.1	**-79.3**	-37.5	-34.4	**-59.4**
Triglyceride (mg/dL)	1.9	-19.4	**-52.8 ****	-12.4	-36.1	**-47.4 ***
Recovery period (Day 230)	**Male (n=5 / group)**			**Female (n=5 / group)**		
Parameter	LD	MD	HD	LD	MD	HD
Sorbitol dehydrogenase (mg/dL)	50.0	650.0	350.0	-3.8	-42.3	**-69.2**

* = p<0.05 and ** = p<0.01 when compared to the control group using Dunnett's test.
LD=1 mg/kg/day, MD= 3 mg/kg/day, HD= 10 mg/kg/day

Urinalysis

Urine was collected overnight using metabolism cages.

HD males and females presented lower mean urine specific gravity with corresponding higher mean total urine volumes and urine pH of MD and HD animals were higher compared to controls at the end of dosing (Day 183). These findings reversed to baseline after the recovery period (Day 239).

Table 8. Urinalysis findings in Rats treated with Avapritinib for 6 Months

Dosing period (Day 183)	Males (N=15 / group)				Females (N=15 / group)			
Parameter	Control[a]	LD	MD	HD	Control[a]	LD	MD	HD
Specific Gravity	1.039	1.028	1.028	**1.026**	1.035	1.028	1.028	**1.023****
pH	7.8	8.0	**8.5****	**8.4***	6.4	6.9	**7.0***	**7.3****
Total Volume (mL)	7.7	9.4	12.8	**13.6**	3.8	5.9	6.1	**6.1**

* = p<0.05 and ** = p<0.01 when compared to the control group using Dunnett's test.
LD=1 mg/kg/day, MD= 3 mg/kg/day, HD= 10 mg/kg/day

Gross Pathology

Macroscopic findings in adrenal gland (enlargement, mottled discoloration, dark red focus, and cyst), ovary (dark red discoloration, enlargement, and cyst) and thymus (small) and prostate gland (green and white focus) were noted in HD animals with corresponding histopathologic findings and organ weights at the end of dosing (Day 183).
One HD female presented enlargement and mottled discoloration of adrenal gland after the recovery phase (Day 239).

Organ Weights

The organs were weighed at necropsy and paired organs were weighed together.

Avapritinib-related organ weight changes were noted in adrenal gland, pituitary gland, liver, spleen, thymus, and reproductive organs (epididymis, prostate gland, testis, ovary/oviduct, and uterus) in males and females. These findings correspond to macro/microscopic findings after avapritinib treatment.

Dosing Phase (Day 183)
Higher adrenal gland was noted in HD males and females. In males, lower weights of liver, thymus, epididymis, and testes at HD and lower spleen weights in MD and HD were observed. In females, lower pituitary gland and uterus weights and higher ovary/oviduct weights were observed at HD, see Table 9.

Recovery Phase (Day 239)
Lower spleen weights (MD and HD) and prostate gland and testes weights (HD) were noted in males. Females of all doses presented higher organ weights of adrenal gland, spleen and uterus, and higher ovary weights were noted in HD.

Reviewer's comment: Avapritinib-related lower weights of spleen and thymus were observed in MD and HD males which corresponded with decreased RBC and WBC and correlated with increased hematopoiesis in spleen. Lower liver weight was observed in

HD males without corresponding histopathological changes observed in liver. Changes in testes weight was partially reversible after recovery period.

Table 9. Changes of Organ Weight (%; Organ to Body Weight Ratio) in Rats treated with Avapritinib for 6 Months with 8-week recovery period

Dosing period (Day 183)	Male (N=15 / group)				Female (N=15 / group)			
Organ/Tissue	Control[a]	LD	MD	HD	Control[a]	LD	MD	HD
Adrenal gland	0.01	1	4	**28**	0.02	4	**15**	**50**
Epididymis	0.22	-4	-8	**-13**				
Liver	2.72	-2	-9	**-13**	2.95	-4	-5	-5
Ovary/Oviduct					0.03	6	-5	**124**
Pituitary gland	0.002	-6	-8	-8	0.01	-9	-5	**-18**
Prostate gland	0.57	11	3	**-9**				
Spleen	0.15	-4	-16	**-22**	0.17	4	-6	-8
Testis	0.56	2	-6	**-14**				
Thymus	0.02	0	-1	**-26**	0.04	-13	-8	-3
Uterus					0.22	17	1	**-21**
Recovery period (Day 239)	Male (N=5 / group)				Female (N=5 / group)			
Organ/Tissue	Control	LD	MD	HD	Control	LD	MD	HD
Adrenal gland	0.01	19	3	6	0.02	**31**	**45**	**82**
Prostate gland	0.53	-1	4	**-19**				
Ovary/Oviduct					0.03	-21	0	**14**
Spleen	0.14	-2	-12	**-10**	0.13	**21**	**31**	**25**
Testis	0.57	-7	-3	-9				
Uterus					0.19	**29**	**25**	**18**

* = p<0.05 and ** = p<0.01 when compared to the control group using Dunnett's test.

[a] Values in this column represent the actual control group mean for each respective parameter.
LD=1 mg/kg/day, MD= 3 mg/kg/day, HD= 10 mg/kg/day

Histopathology

Adequate Battery: Yes
Peer Review: Yes
Histological Findings:

Dosing Phase (Day 183)
Avapritinib-related histopathological findings were noted in adrenal gland (cortical hyperplasia, LD and MD), bone (femur thickness ↑, HD), bone marrow (sternum, cellularity ↓, HD), lymph node (erythrocytosis, MD), spleen (pigmented macrophages ↑, HD), thymus (cyst, hemorrhage, cellularity ↓, LD-HD), and prostate gland (hemorrhage, inflammation, LD and HD) in males. Females presented similar histological findings in the same organs, adrenal gland, bone marrow, ovary, spleen, thymus, vagina (increase mucification LD-HD) and ovary (corpus luteum degeneration with cysts & hemorrhage) mostly in HD, see Table 10.

Recovery Phase (Day 239)
One HD female presented thrombus in adrenal gland and the histological findings in ovary were not fully reversed in 1-3 females. In thymus of males and females, hemorrhage (LD-HD males, HD females) and inflammation (HD females) were noted.

Reviewer's comment: Avapritinib appears to target similar organs in both sexes and the histopathological findings correspond to the organ weight changes and macroscopic findings. Findings in the spleen, thymus, bone, bone marrow, and lymph node seem to correspond to the hematological parameter changes of decreased RBC and WBC mass which were reversible partially after the recovery. The findings in ovary were also partially reversible.

Table 10. Histopathological Findings after Avapritinib treatment for 6 Months in Rats

Dosing period (Day 183)			Male (n=15 / group)				Female (n=15 / group)			
Organ/ Tissue	Findings Severity*		Control	LD	MD	HD	Control	LD	MD	HD
Adrenal gland	Angiectasis	1						1		2
		2								1
		3							1	
	Cystic; Degeneration	1						1		3
		2	1				1			1
		3								1
	Cortical; Hyperplasia	1		2	3					6
		2			2					1
	Mononuclear cell infiltration	1								2
	Necrosis	4								1
	Thrombus	4								1
	Cortical vacuolation	1						1		
Bone	Femur; increased thickness	1				3				
Bone marrow	Sternum; Decreased cellularity	1			3	10			4	7
		2				5				1
Lymph node; (erythrocytosis)	Axillary	1			3		2			1
	Mandibular	1			1		2			2
		2	1							
		3			1					
	Mediastinal							1		
	Mesenteric	1			1					
Ovary	Corpus luteum; Degeneration, Hemorrhagic & Cystic	1							1	1
		2								6
		3								5
		4								3
	Pigmented, Macrophage	1							4	
		2							2	11
		3								4
Prostate gland	Hemorrhage	4		1						
	Inflammation, Mixed cell	1	1							
		2				5				

Dosing period (Day 183)			Male (n=15 / group)				Female (n=15 / group)			
Organ/ Tissue	Findings	Severity*	Control	LD	MD	HD	Control	LD	MD	HD
		3		1	1	1				
	Infiltration, mixed cell	1	1	1	5	4				
		2				1				
Spleen	Increased pigmented macrophages	1				3				14
Thymus	Cyst					1				
	Lymphoid; Decreased cellularity	1	4	2	2	7	3	2	1	2
		3		1						
	Ectopia	3							1	
	Hemorrhage	1	1	3	5	5	1	4	1	2
		2	1	2	1					
Vagina	Increased mucification	1					1	2	2	2
		2					1			5
		3					1		1	5
Recovery period (Day 239)			Male (n=5 / group)				Female (n=5 / group)			
Organ/ Tissue	Findings	Severity*	Control	LD	MD	HD	Control	LD	MD	HD
Adrenal Gland	Thrombus	4								1
Bone Marrow	Sternum; Decreased cellularity				1					
Ovary	Corpus Luteum; Degeneration, Hemorrhagic & Cystic	2								1
		3								1
	Pigmented, Macrophage	1							4	1
		2							1	3
		3								1
Thymus	Hemorrhage	1		2	1	3				1
	Inflammation, Mixed cell									1

* Severity grade1=minimal, 2=mild, 3=moderate, 4=marked, 5-severe
LD=1 mg/kg/day, MD= 3mg/kg/day, HD= 10mg/kg/day

Toxicokinetics

Blood samples were collected from the jugular vein from animals fasted overnight on Day 1 and 182 of the dosing phase.

Systemic exposure to avapritinib increased with increasing dose levels as defined by C_{max} and AUC. The increases in AUC_{0-t} were approximately dose proportional in males and females but it was 1.3-fold greater than dose proportional between the MD and HD in males at the end of dosing (Day 182). The increases in C_{max} was greater than dose proportional in both sexes except the MD and HD males showing less than dose proportionality by 0.5-fold. The gender difference was evident in exposure of avapritinib with ~ 2-fold higher C_{max} and AUC_{0-t} in females compared to males at the end of dosing.

2-3-fold increase of AUC between Dosing Day 1 and 182 indicates the accumulation of avapritinib with repeated dosing. The T_{max} ranged from 2 to 8hr after the dosing of avapritinib.

Table 11. Mean Toxicokinetic Parameters in Rat Plasma after dosing Avapritinib on Day 1 and Day 182

		$AUC_{(0-t)}$ (ng•hr/mL)		C_{max} (ng/mL)		T_{max} (hr)	
	mg/kg/day	Day 1	Day 182	Day 1	Day 182	Day 1	Day 182
Males	1	1380	2740	99.7	169	4	2
	3	4910	9710	329	622	8	4
	10	17,000	40,500	1460	3380	2	4
Females	1	2150	5970	126	322	8	8
	3	6940	19,900	477	1260	8	2
	10	27,500	62,500	1690	3560	4	4

*Reviewer's conclusion: Avapritinib-related effects were observed in the hematopoiesis related organs such as spleen, thymus, bone, and bone marrow with decreased RBC and WBC mass mostly in HD animals with severity and higher frequency. Also, the adrenal gland and reproductive organs (testis, ovary, and prostate gland) were affected in males and females. Based on the severity and the reversibility of the findings at HD, the sponsor's proposed no-observed-adverse-effect level (NOAEL) of 3 mg/kg/day for both sexes in rats via oral administration for 26 weeks that correspond to an AUC of 9710 and 19900 ng*h/mL, in males and females, respectively. The reviewer finds that the NOAEL defined at 3 mg/kg/day is appropriate.*

6.3 Repeat-Dose Toxicity

Study title: BLU-285: A 39-Week (Once Daily) Oral (Gavage) Toxicity Study in Beagle Dogs with an 8-Week Recovery Period

Study no.:	00124816
Study report location:	eCTD 4.2.3.2
Conducting laboratory and location:	(b) (4) (b) (4)
Date of study initiation:	July 23, 2018
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and purity:	BLU-285, 0285/02, 98.6

Key Study Findings

- Signs of anemia with pale gum/skin and dull fur were observed in MD and HD at the end of recovery and corresponded with observed avapritinib-related dose-dependent decrease of RBC mass and WBCs.

- Increased extramedullary hematopoiesis and pigmented macrophages were observed in spleen and the weight of spleen was lower in ≥ MD animals compared to control. Microscopic findings in spleen were partially recovered.
- Decreased cellularity in bone marrow sternum of HD males and ≥ MD females and in thymus of MD males and LD and HD females were noted which were no longer present after recovery.
- Decreased cellularity (HD) and erythrocytosis (≥ LD) in lymph nodes (axillary and mandibular) were observed in avapritinib treated animals.
- Microscopic findings of hypospermatogenesis and hypoplasia were still observed at the end of recovery.

Methods

Doses:	0 (control), 0.5 (Low Dose: LD), 1.5 (Mid Dose: MD), 5 (High Dose: HD) mg/kg/day
Frequency of dosing:	Once daily
Route of administration:	Oral
Dose volume:	5 mL
Formulation/Vehicle:	0.5% carboxymethylcellulose (CMC; medium viscosity)-Na (w/v): 1 % Tween 80 (v/v) in deionized water (pH 2-3)
Species/Strain:	Dog/Beagle
Number/Sex/Group:	Dosing= 4/sex/group Recovery= 2/sex/group
Age:	5-7 months/ sexually mature
Weight:	159-283g at the initiation of dosing
Satellite groups:	None
Unique study design:	Standard design
Deviation from study protocol:	Several with no impact on quality or integrity of the data

Observations and Results

Mortality

Mortality and physical signs were observed twice daily.

No avapritinib-related mortality occurred during the dosing and recovery period.

One LD female was euthanized on Day 70 due to poor clinical condition with significant body weight loss and lower food consumption with signs consistent with renal failure. Macro findings of moderate fibrosis and histopathologic findings of mild mixed cell inflammation, mild urothelial degeneration and hyperplasia, moderate tubule dilatation, and moderate mineralization were noted in right kidney of the animal. The findings were considered to be incidental but not avapritinib-related since observation was in one LD animal and there were no other animals presenting similar findings in kidney.

Clinical Signs

Dogs were observed pre/post-dosing for clinical signs on predose and dosing Day 1 and weekly during the dosing and recovery period.

All MD and HD dogs presented pale gum/skin and dull fur from dosing Week 6 throughout dosing period and redness in the eyeballs was observed in MD (3/6) and HD (2/6) males and 33% HD females on Day 190.

The signs of anemia with pale gum/skin and dull fur in MD and HD remained after the recovery period which corresponded with irreversible hematological findings of decreased RBC mass with avapritinib treatment.

Body Weights

Body weights were recorded predose and weekly during the dosing and recovery period.

Avapritinib-treated males presented higher body weight gains compared to controls from Dosing Week 4 (Days 22-29) and remained higher throughout the dosing period. The mean body weights were 6.8%, 9.3%, and 10.1% higher in LD, MD, and HD males and higher body weight gain corresponds to the higher food consumption in males.

Feed Consumption

Food consumption was quantitatively measured on pre-dosing day and weekly during the dosing and recovery period.

The overall food consumption was 16% higher in HD males throughout the dosing period, and this corresponds to the higher body weight gain at the end of dosing (day 273). MD female also presented 12% higher overall food consumption throughout the dosing period without corresponding higher body weight gains.

Ophthalmoscopy

Ophthalmic examinations were conducted on pre-Dosing Day 11 and Dosing Day 270

No avapritinib-related effects were observed.

ECG

Electrocardiograms (ECGs) and heart rates were recorded on pre-Dosing Day 7 and Dosing Day 268.

No avapritinib-related effects were observed in heart rate, RR interval, PR interval, QRS duration, QT interval, or QTc interval.

Hematology

Blood samples were collected from a jugular vein for hematology and clinical chemistry.

Dosing Phase (Day 274):
Avapritinib-related dose-dependent decrease of RBC, reticulocytes, hematocrit and hemoglobin were observed in both sexes at MD and HD. Decrease of WBC (basophils, eosinophil, monocytes, and lymphocyte (females only)) were observed. Increased platelet counts were observed in HD males and LD-HD females.

Recovery Phase (Day 331):
The decrease of RBC and WBC is not reversed after the recovery period in both males and females of avapritinib-treated animals after the recovery period. The inconsistent and fluctuating changes in WBCs were without statistical significance after the recovery period which doesn't seem to be the effect of avapritinib.

Reviewer's comment: Decreased RBC and WBCs after avapritinib treatment is with corresponding histological findings in spleen, thymus, bone, and bone marrow.

Table 12. Changes (%) in Hematology Parameters in Dogs with Avapritinib treatment for 9 Months with 8-week Recovery Phase

Dosing period (Day 274)	Male (N=6 / group)				Female (N=6 / group)			
Parameter	Control[a]	LD	MD	HD	Control[a]	LD[b]	MD	HD
Basophils (10^9/L)	0.1	-31	-27	-38	0.1	-23	-4	-54
Eosinophils (10^9/L)	0.2	-35	-8	-65	0.3	-31	11	-77
Erythrocytes (10^12/L)	6.9	-7	**-16**	**-31**	6.8	-8	**-12**	**-32**
Hematocrit (%)	45.4	-4	**-12**	**-26**	47.2	-7	**-13**	**-31**
Hemoglobin (g/dL)	14.8	-4	**-12**	**-27**	15.3	-5	**-13**	**-32**
Leukocytes (10^9/L)	8.5	-15	-18	-25	8.5	-20	-12	-38
Lymphocytes (10^9/L)	1.8	-3	0	6	1.9	-14	-6	-25
Monocytes (10^9/L)	0.6	-10	-9	-12	0.6	-28	-18	-43
Neutrophils (10^9/L)	5.8	**-19**	**-25**	**-34**	5.7	-20	-15	-40
Platelets (10^9/L)	272.3	9	7	**53**	233.0	**45**	**61**	**83**
Reticulocytes (10^9/L)	76.6	**-61**	**-69**	**-70**	26.2	25	26	-4
Recovery period (Day330)	Male (N=2 / group)				Female (N=2 / group)			
Parameter	Control[a]	LD	MD	HD	Control[a]	LD	MD	HD
Basophils (10^9/L)	0.1	-30	-10	-20	0.1	56	56	33
Eosinophils (10^9/L)	0.2	47	-37	19	0.6	-65	-64	-32
Large Unstained Cells (10^9/L)	0.03	-60	0	-80	0.03	0	-17	50
Leukocytes (10^9/L)	9.1	-6	1	-27	10.5	-27	-12	-4
Lymphocytes (10^9/L)	2.5	6	26	-7	2.4	3	9	18
Monocytes (10^9/L)	0.3	36	11	-6	0.6	-31	-43	-30
Neutrophils (10^9/L)	5.9	-15	-9	-39	6.8	-34	-12	-6
Platelets (10^9/L)	294.5	0	-5	-12	296.0	8	8	32
Reticulocytes (10^9/L)	61.1	-29	-42	-48	44.9	-59	-46	-32

[a] Values in this column represent the actual control group mean for each respective parameter.
[b] N=5 due to one LD female early termination for clinical condition.
LD= 0.5 mg/kg/day, MD= 1.5 mg/kg/day, HD= 5mg/kg/day

Coagulation

The coagulation parameters of activated partial thromboplastin time and prothrombin time did not show any evidence of avapritinib effects.

Clinical Chemistry

HD males and females presented decreased albumin, total protein, and globulin. Avapritinib-related changes of liver enzymes (AST ↑, ALP ↓), glucose ↑, cholesterol ↓ were also noted in HD males and females at the end of dosing period (Day 274). The changes were reversible and without correlated histopathological findings.

Table 13. Changes (%) of Clinical Chemistry Parameters in Dogs treated with Avapritinib for 9 Months

Dosing period (Day 274)	Male (N=6 / group)				Female (N=6 / group)			
Parameter	Control[a]	LD	MD	HD	Control[a]	LD[b]	MD	HD
Alanine Aminotransferase (U/L)	47	-11	-10	-27	34	14	4	-7
Albumin (g/dL)	3.2	2	-1	-10	3.2	-2	-4	-17
Alkaline Phosphatase (U/L)	110	-51	-54	-66	50	-7	-22	-19
Aspartate Aminotransferase (U/L)	37	-4	9	21	33	-7	6	47
Bilirubin (mg/dL)	0.06	46	42	4	0.06	-20	40	24
Cholesterol (mg/dL)	144	-15	-18	-22	148	4	-10	-30
Creatinine (mg/dL)	0.7	0	6	-19	0.64	-7	-9	-21
Globulin(g/dL)	2.2	6	-5	-6	2	10	-1	-14
Glucose (mg/dL)	80	11	6	15	82	14	3	19
Protein(g/dL)	5.3	4	-2	-8	5.2	3	-3	-16
Sorbitol Dehydrogenase (U/L)	4	-19	0	0	5	-26	-21	32
Triglycerides (mg/dL)	33	5	-23	-13	35	7	-8	-29
Urea Nitrogen (mg/dL)	19.3	-3	-15	-21	19.7	-20	-26	-10
Recovery period (Day 330)	Male (N=2 / group)				Female (N=2 / group)			
Parameter	Control[a]	LD	MD	HD	Control[a]	LD	MD	HD
Alanine Aminotransferase (U/L)	31	74	-7	7	25	32	4	-18
Alkaline Phosphatase (U/L)	46	33	26	20	45	42	-9	-17
Aspartate Aminotransferase (U/L)	32	63	-11	36	24	62	26	9
Bilirubin (mg/dL)	0.01	300	-50	200	0.01	-100	400	-50
Cholesterol (mg/dL)	140	3	17	-2	145	3	10	23
Creatinine (mg/dL)	0.63	2	6	5	0.7	-21	-6	-14
Phosphate (mg/dL)	4.4	-2	-8	8	3.9	-1	0	21
Sorbitol Dehydrogenase (U/L)	3	200	33	17	4	0	0	13
Triglycerides (mg/dL)	27	87	62	45	41	14	-19	-7
Urea Nitrogen (mg/dL)	17.2	24	17	14	20.5	-12	-6	-19

[a] Values in this column represent the actual control group mean for each respective parameter.
[b] N=5 due to one LD female early termination for clinical condition.
LD= 0.5 mg/kg/day, MD= 1.5 mg/kg/day, HD= 5 mg/kg/day

Urinalysis

Urine was collected over night using cage pans.
The urinary volume and the specific gravity values were highly variable between animals within each group without dose-dependency. There was no evidence of avapritinib-related effects observed.

Gross Pathology

No avapritinib-related changes were observed.

Organ Weights

Male dogs presented increase in prostate gland weights (23% ↑ LD, 45% ↑ HD) and decrease in epididymis (11%↓ HD) without dose-dependency and no correlated histopathological findings observed in prostates. Avapritinib-treated males and females presented lower weights of spleen which was reversible, and this finding was correlated to the histopathological findings of hematopoiesis observed in spleen.

Table 14. Changes of Organ Weight (%; Organ to Body Weight Ratio) in Dogs treated with Avapritinib for 9 Months

Day 274/275	Male (N=4 / group)				Female (N=4 / group)			
Organ/Tissue (g)	Control [a]	LD	MD	HD	Control [a]	LD [b]	MD	HD
Epididymis	0.03	-1.7	-3	**-11**				
Prostate gland	0.08	23	5	**45**				
Liver	2.77	-15	-24	**-11**	2.95	7	6	11
Ovary/Oviduct					0.01	33	38	**51**
Spleen	1.62	-13	-21	**-33**	1.75	-24	-26	-21
Testis	0.13	0.17	-14	**-7**				
Thymus	0.03	21	9	**10**	0.03	85	43	21

[a] Values in this column represent the actual control group mean for each respective parameter,
[b] N=3 due to one LD female early termination for clinical condition.
LD= 0.5 mg/kg/day, MD= 1.5 mg/kg/day, HD= 5 mg/kg/day

Histopathology

Adequate Battery: Yes
Peer Review: Yes

Histological Findings:

<u>Dosing Phase (Day 274)</u>
Avapritinib-related findings included:

- Decreased cellularity of bone marrow sternum was noted in HD males and ≥ MD females.
- Mild decreased cellularity in thymus was also noted in MD male and LD and HD females.

- Decreased cellularity (HD) and erythrocytosis (≥ LD) in lymph nodes (axillary and mandibular) were observed
- Minimal to mild increased extramedullary hematopoiesis and pigmented macrophage in spleen.
- Males presented hypospermatogenesis in LD and HD and hypoplasia in MD.

Recovery Phase (Day 330)
Pigmented macrophage in spleen of MD and HD males and females were noted with less frequency and severity. Hypospermatogenesis was still present in MD and HD, and hypospermatogenesis in MD male was unilateral.

Reviewer's note: The findings in spleen and bone marrow are consistent with hematological findings of RBC and WBC mass decrease. The sponsor states that the findings of hypospermatogenesis is not avapritinib-related considering that it was unilateral finding.

Table 15. Histopathological Findings after Avapritinib Treatment for 9 Months in Dogs with 8-week recovery period

Dosing period (Day 274)			Male (N=4 /group)				Female (N=4 / group)			
Organ/ Tissue	Finding	Severity	Control	LD	MD	HD	Control	LD[b]	MD	HD
ADRENAL GLAND	Vacuolation	2					1			
BONE MARROW, STERNUM	Decreased Cellularity	1		1	3	1			4	7
		2				2			2	2
LYMPH NODE; Axillary	Decreased Cellularity	1				1				
	Erythrocytosis	1				1				1
		2		1				1	1	1
		3				1				
LYMPH NODE; Mandibular	Decreased Cellularity	2				1				
	Erythrocytosis	1		1				2		
OVARY	Cyst	1								1
	Mineralization	1						1		1
SPLEEN	Increased Extramedullary Hematopoiesis	1		1	3	4	1	2	2	3
		2								1
	Pigmented Macrophage	1		1	3	4	1	3	2	1
		2								3
TESTIS	Hypoplasia	1	1		2					
	Hypospermatogenesis	1		1		3				
THYMUS	Decreased Cellularity	1	2	2	1	1				
		2			1			1		1
VAGINA	Edema	2							1	

Recovery period (Day 330)			Male (N=2 / group)				Female (N=2 / group)			
Organ/Tissue	Finding	Severity	Control	LD	MD	HD	Control	LD	MD	HD
ADRENAL GLAND	Vacuolation	2		1						
	Angiectasis	1				1				
	Hypertrophy	1			1					
OVARY	Cyst						1			1
	Mineralization							1		
SPLEEN	Decreased Cellularity	2						1		
	Increased Extramedullary Hematopoiesis	1					1			
	Increased Pigmented Macrophage	1			1	2			1	2
Testis	Hypoplasia	1		1						
	Hypospermatogenesis	1			1	2				

* Severity grade 1=minimal, 2=mild, 3=moderate, 4=marked, 5-severe, [b] N= 3 due to one LD female early termination for clinical condition.
LD= 0.5 mg/kg/day, MD= 1.5 mg/kg/day, HD= 5 mg/kg/day

Toxicokinetics

Blood was collected via jugular vein at 0.5, 1, 2, 4, 8, 24 hours post-dose.

Systemic exposure to avapritinib increased with increasing dose levels as defined by C_{max} and AUC. Increases in C_{max} and AUC_{0-t} were generally dose proportional and the gender difference was not evident in exposure of avapritinib based on C_{max} and AUC_{0-t} on Day 273. Minimal accumulation (< 2-fold) of avapritinib was observed at the end of dosing (Day 273) and T_{max} ranged from 1.5 - 3 hrs.

Table 16. Toxicokinetic Parameters after Administration of Avapritinib in Dogs for 9 months

	Dosage (mg/kg/day)	AUC(0-t) (ng•h/mL)		Cmax (ng/mL)		Tmax (h)	
		Day 1	Day 273	Day 1	Day 273	Day 1	Day 273
Male	0.5	355	736	24.2	47.7	2	1.5
	1.5	1170	2220	80.9	144	3	2
	5	4570	7930	342	504	2	2
Female	0.5	346	675	24.3	44.7	2	2
	1.5	1030	2140	77.3	148	2	2
	5	4580	7250	338	472	2	2

Reviewer's conclusion:
*Based on the results of minimal to mild severity of avapritinib effects and the reversibility of the findings on spleen, bone marrow, testis, ovary, and vagina, avapritinib was tolerated at the 5 mg/kg/day, and the Sponsor proposed no-observed-adverse effect level (NOAEL) as 5 mg/kg/day. The reviewer finds that the proposed NOAEL of 5mg/kg/day in dogs via oral administration for 39 weeks is acceptable and the corresponding AUC was 7930 and 7250 ng*h/mL in males and females, respectively.*

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/

BO Y LEE
05/28/2021 05:17:41 PM

PEDRO L DELVALLE
05/28/2021 05:24:21 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212608Orig1s006

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 212608
Supplement #:	006
Drug Name:	AYVAKIT (avapritinib)
Indication(s):	Treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN) (b) (4)
Applicant:	Blueprint Medicines Corporation
Date(s):	Submission date: December 16, 2020
	PDUFA date: June 16, 2021
	Review completion date: May 28, 2021
Review Priority:	Priority
Biometrics Division:	Division of Biometrics IX
Statistical Reviewer:	Xiaoyu Cai, Ph.D.
Concurring Reviewers:	Yeh-Fong Chen, Ph.D., Team Leader
	Thomas Gwise, Ph.D., DB IX Division Director
Medical Division:	Division of Nonmalignant Hematology
Clinical Team:	Andrew Dmytrijuk, M.D., clinical reviewer
	Qin Ryan, M.D., safety reviewer
Project Manager:	Brittany Garr-Colón

Keywords: single-arm open label trial design; overall response rate (ORR); interim analysis; response-evaluable population, safety population

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1 EXECUTIVE SUMMARY

The applicant submitted AYVAKIT (avapritinib) supplemental New Drug Application (sNDA), including two single arm trials (Phase I BLU-285-2101, and Phase II BLU-285-2202) to seek an indication expansion for avapritinib in the treatment of adult patients with advanced systemic mastocytosis (AdvSM) (b) (4) AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).

This sNDA was administratively split to be reviewed by the two medical divisions based on subtypes of diseases. The Division of Nonmalignant Hematology reviewed the (b) (4) ASM, SM-AHN, and the Division of Hematologic Malignancies 1 reviewed the MCL. (b) (4) this review mainly focused on evaluating the efficacy of avapritinib for patients with ASM or SM-AHN even though patients' baseline disease status were analyzed based on the entire patient population of the studies.

For both Studies BLU-285-2101 and BLU-285-2202, the primary efficacy endpoint is overall response rates (ORR), defined as the proportion of patients with a confirmed best response of complete remission (CR), complete remission with partial recovery of peripheral blood counts (CRh) or partial remission (PR) by modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis (mIWG-MRT-ECNM) criteria, confirmed 12 weeks after initial response. Given that both studies enrolled AdvSM patients and required patients to be mIWG-MRT-ECNM evaluable for the ORR primary endpoint, the pooled analysis for the two studies was determined acceptable by the review team. The lower bound of the 99.48% confidence intervals (CI) was greater than the pre-defined benchmarks ORR value of 17% for SM-AHN population. There were too few response-evaluable patients in the ASM population, therefore no meaningful statistical inference can be concluded. Note that the reason why the 99.48% CIs should be considered is because the studies were terminated earlier and thus the type I error rate should be adjusted via some valid group sequential testing procedure such as O'Brien-Fleming alpha spending method. A brief summary of the efficacy results from the pooled two studies for patients with the starting dose no more than the target dose level 200 mg once daily are displayed in the following Table 1.

Table 1: Brief Summary of Study 2101 and study 2202 Pooled Treatment Response Result per mIWG-MRT-ECNM Criteria (Response-evaluable Population)

Disease Subtype	Dose	Enrolled Patients, n	Response-evaluable Patients , n	Responders by mIWG-MRT-ECNM Criteria, n	ORR, %	95% CI for ORR	99.48% CI for ORR
ASM	≤ 200mg	11	2	2	100%	(15.81%, 100%)	(5.1%, 100%)
SM-AHN		63	40	23	57.5%	(40.89%, 72.96%)	(34.66%, 78.25%)

ASM=aggressive systemic mastocytosis ; CI=confidence interval; ORR=overall response rate; mIWG-MRT-ECNM= modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; SM-AHN=systemic mastocytosis with an associated hematological neoplasm
Source: FDA analysis

The statistical reviewer confirmed the applicant's efficacy results. The major issues identified were the study patient populations and doses for the final efficacy claim. After communicating with the Agency via information requests, the applicant had successfully addressed those issues.

Based on the efficacy results from the pooled two studies BLU-285-2101 and BLU-285-2202 for patients with the starting dose no more than the target dose level 200 mg once daily, the statistical review team has the following recommendations:

- (b) (4)
- The sample size for response-evaluable patients with ASM is too small to make meaningful statistical inference. Whether the ASM indication can be approved is deferred to the clinical reviewer's scientific judgment.
- The applicant's data support the efficacy of avapritinib in the treatment of adult patients with SM-AHN.

2 INTRODUCTION

2.1 Overview

Product and Proposed Indication Expansion

AYVAKIT (avapritinib) is a kinase inhibitor, proposed for the following indication expansion: the treatment of adult patients with advanced systemic mastocytosis (AdvSM) (b) (4) AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).

This review will focus on evaluations for the proposed indication expansion in ASM and SM-AHN disease subtypes because of the following reasons.

- *administrative split of the avapritinib marketing application between the Division of Nonmalignant Hematology (which is reviewing the* (b) (4) *ASM, SM-AHN portion of the application) and Division of Hematologic Malignancies 1 (which is reviewing the MCL portion of the application)*
- (b) (4)

Disease Overview

Systemic mastocytosis (SM) is a rare clonal mast cell neoplasm, primarily driven by mast cells carrying the KIT D816V mutation that results in constitutive, ligand-independent activation of the receptor tyrosine kinase. Patients with AdvSM and SSM suffer from a wide variety of severe and unpredictable symptoms and reduced quality of life. Patients with AdvSM (comprising 5 to 10% of patients with SM) have adverse clinicopathological features and poor overall survival, even with available therapies. Table 2 summarizes systemic mastocytosis subclassification based on WHO criteria.

Table 2: Systemic Mastocytosis Subclassification Based on WHO Criteria

Variant		Diagnostic criteria
Non-advanced SM	Indolent SM (ISM)	No C-findings; < 2 B-findings
	Smoldering SM (SSM)	No C-findings; ≥ 2 B-findings
Advanced SM (AdvSM)	SM with an associated hematological neoplasm (SM-AHN)	Meets diagnostic criteria for AHN
	Aggressive SM (ASM)	≥ 1 C-finding Does not meet criteria for MCL
	Mast cell leukemia (MCL)	≥ 20% mast cells in bone marrow smear

Patients with AdvSM have limited treatment options and patients with SSM have no approved treatment options. In AdvSM, current recommended therapies include midostaurin (approved in US and EU), cladribine, interferon (both used off label) and imatinib (approved in the USA for only a very small subset of ASM patients without the D816V KIT mutation or with unknown KIT mutational status).

Clinical Studies

Because of the small number of the response-evaluable patients in study BLU-285-2101 (denote '2101' afterwards) and study BLU-285-2202 (denote '2202' afterwards), the primary assessments for efficacy of avapritinib will be evaluated based the pooled data of the two studies. Given that both studies enrolled AdvSM patients and required patients to be mIWG-MRT-ECNM evaluable for the ORR primary endpoint, the pooled analysis for the two studies was determined acceptable by the review team. Individual studies' analysis results for the primary endpoint ORR, analyses on selected secondary endpoints (i.e. time to response, duration of response, overall survival, patient-reported outcomes) and subgroup analyses of ORR by baseline factors are also provided in Sections 3.2.4. The following Table 3 summaries the two major clinical studies conducted for assessing efficacy of avapritinib.

Table 3: Overview of Avapritinib Clinical Studies

Study	Design	Avapritinib Starting Dose	Primary Efficacy Endpoint	Safety Population Sample size	Response-evaluable Population Sample size
BLU-285-2101 (phase I)	Multi-center, single-arm, open-label study	30 mg to 400 mg orally once daily	SSC adjudicated ORR by mIWG-MRT-ECNM criteria, confirmed 12 weeks after initial response	86	53
BLU-285-2202 (phase II)	Multi-center, single-arm, open-label study	200 mg orally once daily	SSC adjudicated ORR by mIWG-MRT-ECNM criteria, confirmed 12 weeks after initial response	62	32

mIWG-MRT-ECNM= modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; ORR = overall response rate; SSC=Study Steering Committee

Analysis Population

Populations in Table 3 were defined by the following criteria:

- Safety Population: All patients who received ≥ 1 dose of avapritinib;
- Response-evaluable Population: All patients who received ≥ 1 dose of avapritinib, were deemed evaluable per mIWG-MRT-ECNM criteria at baseline as assessed by SSC review, and had 1 of the following conditions:
  - ≥ 2 complete postbaseline bone marrow assessments, and had been on study for ≥ 6 cycles (6 x 28 days);
  - had an end of study visit.

Note that the Safety Population was used for key secondary analyses, all safety analyses, patient-reported outcome analyses, and the efficacy analyses that were not based on mIWG-MRT-ECNM response criteria. The Response-evaluable Population was used for the primary efficacy analysis and for all secondary efficacy analyses related to response.

2.2 Data Sources

Materials reviewed for this application: protocols, statistical analysis plans, study reports, and submitted datasets for studies 2101 and 2202.

Reviewed data were provided electronically with SDTM and ADaM data formats. Datasets are located at:
\\CDSESUB1\evsprod\NDA212608\0058\m5\datasets\blu-285-2101-advsm (for study 2101)
and
\\CDSESUB1\evsprod\NDA212608\0058\m5\datasets\blu-285-2202-advsm (for study 2202)

During the review cycle, the medical and statistical review team requested the applicant to submit separate safety and efficacy data sets (SDTM and ADaM) for studies 2101 and 2202 that excludes patients with MCL. Response to this request was provided on February 26, 2021.

Datasets excluding patients with MCL are located at

\\CDSESUB1\evsprod\NDA212608\0065\m5\datasets\blu-285-2101-advsm (for study 2101)

and

\\CDSESUB1\evsprod\NDA212608\0065\m5\datasets\blu-285-2202-advsm (for study 2202)

The statistical review team requested the applicant to submit additional efficacy analysis results for "200 mg dose" and "≤ 200 mg doses" populations for studies 2101 and 2202. Response to this request was provided on May 19, 2021.

Additional efficacy analysis results for "200 mg dose" and "≤ 200 mg doses" populations for studies 2101 and 2202 are located at
\\CDSESUB1\evsprod\NDA212608\0082\m1\us

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data from studies 2101 and 2202 were provided electronically with SDTM and ADaM data formats. Data quality was determined to be acceptable.

3.2 Evaluation of Efficacy

The primary evaluation for treatment efficacy of avapritinib were based on the pooled data from studies 2101 and 2202 for different dose groups (i.e. "200 mg dose", "≤ 200 mg doses" and "all doses"). In addition to the pooled studies, efficacy findings from individual studies 2101 and 2202 are also presented for demonstrating the consistency of findings from the pooled analysis.

3.2.1 Study Design and Endpoints

Study 2101 was a phase 1, multicenter, single-arm, open-label study designed to evaluate the safety, tolerability, PK, pharmacodynamics, and antineoplastic activity (efficacy) of avapritinib, administered orally, in adult patients with AdvSM and relapsed or refractory myeloid malignancies. The original

primary objective was to establish the maximum tolerated dose and recommended Phase 2 dose. This 2-part study included an initial dose escalation (Part 1, completed) to evaluate safety and tolerability of increasing doses of avapritinib in patients with a local diagnosis of AdvSM or other relapsed or refractory myeloid malignancies, and an expansion (Part 2, still ongoing) to further evaluate safety, PK, pharmacodynamics, and efficacy, as per mIWG-MRT-ECNM response criteria, of avapritinib in AdvSM. Part 2 enrolled patients with a WHO diagnosis of AdvSM. A central pathological review was implemented to confirm diagnosis for all patients and to assess response for patients in Part 1 and 2. Patients enrolled in study 2101 received a starting dose of avapritinib ranging from 30 mg to 400 mg (0.15 – 2 times the recommended dose) orally once daily. At the time of data cut-off (May 27, 2020), enrollment was completed, 86 patients were enrolled to this study, 53 of those patients were considered evaluable for treatment response according to the mIWG-MRT-ECNM response criteria.

Study 2202 was a phase 2, multicenter, single-arm, open-label study designed to evaluate the efficacy and safety of avapritinib in patients with a WHO diagnosis of AdvSM. Patients with a centrally confirmed WHO diagnosis of AdvSM were enrolled into 1 of 2 cohorts:

- Cohort 1: AdvSM patients with ≥ 1 mIWG-MRT-ECNM criteria for evaluable disease (have an evaluable C-finding or have MCL) as determined by the Study Steering Committee
- Cohort 2: AdvSM patients who were not considered eligible for an adjudicated mIWG-MRT-ECNM response as determined by the Study Steering Committee

Patients in Cohort 1 support the primary objective of determining Study Steering Committee adjudicated overall response rate (ORR) by mIWG-MRT-ECNM criteria. Both cohorts are included in the analyses of secondary and exploratory efficacy objectives. As per protocol, an interim analysis was performed when 32 patients enrolled in Cohort 1 were considered evaluable for response. In accordance with the protocol, if positive, this interim analysis would be considered final. Patients enrolled in study 2202 received a starting dose of 200 mg orally once daily. At the time of data cut-off (June 23, 2020), enrollment was still ongoing, but the interim analysis was completed. There were 62 patients enrolled to study 2202 and 32 of those patients were considered evaluable for treatment response according to the mIWG-MRT-ECNM response criteria.

For both studies 2101 and 2202, the primary efficacy endpoint was overall response rate (ORR), defined as the proportion of patients with a confirmed best response of complete remission (CR), complete remission with partial recovery of peripheral blood counts (CRh) or partial remission (PR) by modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis (mIWG-MRT-ECNM) criteria, confirmed 12 weeks after initial response. Secondary efficacy endpoints included time to response, duration of response, overall survival, etc. In addition, patient-reported outcomes were assessed as secondary endpoints in both studies using the AdvSM-SAF, PGIS, and EORTC QLQ-C30 instruments. However, the results of the overall survival and patient-reported outcomes cannot be interpreted due to lack of a pre-planned comparator in these single arm open label studies.

3.2.2 Statistical Methodologies

Protocol Defined Analyses

The protocol-defined primary analysis population for study 2101 consisted of 53 patients with AdvSM, (3 ASM, 37 SM-AHN and 13 MCL) who were evaluable at baseline by mIWG-MRT-ECNM

criteria.

The protocol-defined primary analysis population for study 2202 consisted of 32 patients with AdvSM, (2 ASM, 26 SM-AHN and 4 MCL) who were evaluable at baseline by mIWG-MRT-ECNM criteria.

ORR (CR+CRh+PR) was estimated using frequency, percentage, and two-sided 95% confidence interval based on the exact binomial distribution (Clopper-Pearson). Statistical test on binomial proportion against a null of 17% was performed using one sided α=0.025. Note that this 17% threshold was pre-defined in the study protocol and agreed by the Agency for each of the individual study. Wald test p-value was presented. The null hypothesis would be rejected if the p-value is less than 0.025. Time-to-event endpoints (such as time to response, duration of response, overall survival, etc.) were estimated using Kaplan-Meier methodology. Patient-reported quality of life outcomes were assessed by the Advanced Systemic Mastocytosis-Symptom Assessment Form (AdvSM-SAF), Patient's Global Impression of Symptom Severity (PGIS), and European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) instruments.

For study 2101, the planed sample size for Part 1 and Part 2 was decided by safety considerations, there were no formal hypotheses for sample size determination. It was expected that approximately 25 patients who met the criteria for the Dose-Determining population would be enrolled in Part 1. For Part 2, approximately 45 patients were planned for enrollment in Cohort 1 at a starting dose of 300 mg once daily; subsequently, approximately 10 patients were planned to be enrolled in Cohort 2 at starting dose of 200 mg once daily.

For study 2202, the sample size of approximately 63 patients in Cohort 1 was estimated based on the intention to provide 93.5% power at the 1-sided significance level of 0.025 for testing the assumption of a null hypothesis CR+CRh+PR+CI of 28% vs the alternative hypothesis CR+CRh+PR+CI of 50%. Enrollment of the SM-AHN subgroup was capped at 70% of 63 patients (i.e. maximum of 45 patients) to ensure the study population reflects the general AdvSM patient population. As per protocol, an interim analysis was performed when 32 patients enrolled in Cohort 1 were determined evaluable for response. In accordance with the protocol, if positive, this interim analysis would be considered the final.

Supportive Analyses

In addition to the analyses using results from the pooled two studies 2101 and 2202, supportive analyses on the primary endpoint ORR and selected secondary endpoints for each of the individual study were also conducted and included in this report.

The applicant provided analyses on the efficacy endpoints using the pooled data from patients under different doses (i.e. 30 mg to 400 mg once daily). Supportive analyses on the primary endpoint, i.e., ORR and selected secondary endpoints are also included in this review for the target dose (i.e. 200 mg once daily) and no more than the target dose (i.e. $\leq$200 mg once daily) populations.

The applicant's analyses on the primary efficacy endpoint, i.e., ORR used the response evaluable population by mIWG-MRT-ECNM criteria. Supportive analyses result using all the enrolled patient population (i.e. Safety Population) are also included in this statistical review. The response of the non-evaluable patients via mIWG-MRT-ECNM criteria are imputed by the following three ways

- Impute all non-evaluable patients as non-responder
- Only impute non-evaluable patients due to no evaluable baseline C-finding as non-responder
- Only impute non-evaluable patients due to limited follow-up as non-responder

Reviewer Comments:

- *The primary assessment for efficacy of avapritinib was based on the pooled data of studies 2101 and 2202 for dose groups "200 mg dose", "≤ 200 mg doses" and "all doses". After evaluation, the pooling of studies was determined acceptable for AdvSM patients because both studies required patients to be mIWG-MRT-ECNM evaluable for the efficacy evaluation for ORR.*
- *The applicant's pre-specified 17% for ORR was determined by the point estimate for the ORR from a previously approved drug RYDAPT® (midostaurin) for the same indication which was calculated based on mIWG-MRT-ECNM criteria. The review team was concerned that this 17% may not be sufficient to address the variability of the midostaurin data.*
- *The applicant used nominal significant value alpha=0.025 to draw conclusion for efficacy of avapritinib. Since the treatment response data submitted for study 2202 were based on an interim analysis result at 50% information time, the applicant's approach is not appropriate. If according to the protocol proposed sequential testing procedure, the alpha for 50% information time is 0.00625, the 98.75% CI should be used instead of 95% CI for assessing the efficacy of avapritinib. Furthermore, if according to the commonly used O'Brien-Fleming sequential testing procedure, the alpha for 50% information time is 0.0026, the 99.48% CI should be used instead of 95% CI for assessing the efficacy of avapritinib.*
- *The applicant pooled data from patients with different dose levels (i.e. 30 mg to 400 mg once daily) for the final analyses of the efficacy endpoints without any justifications. Concerning the safety of higher doses than 200 mg (refer to clinical review), the review team decided to exclude data from patients with dose levels higher than the recommended dose (i.e. 200mg once daily) for the final efficacy claim.*
- *Among 148 total enrolled patients from studies 2101 and 2202, only 85 of them are evaluable by the mIWG-MRT-ECNM criteria. It was not clear whether it is appropriate to exclude 63 patients from the efficacy analyses, and the applicant did not consider any imputation for the non-evaluable patients in their analyses.*
- *Due to the single-arm and open label design of both studies 2101 and 2202, which can result in biased results, overall survival and patient-reported outcomes cannot be used for any efficacy claims.*

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Study 2101 enrolled a total of 86 patients in the Safety Population. At the time of data cut-off (May 27, 2020), enrollment was completed, and treatment was ongoing with 45 patients (52.3%). The primary reasons for treatment discontinuation were disease progression and adverse events. Patient disposition in the Response Evaluable Population, which excluded 33 patients who are not response-evaluable by mIWG-MRT-ECNM criteria, was similar to the Safety Population based on all enrolled patients.

Table 4: Study 2101 Patient Disposition

Disposition Category	All Doses of Avapritinib, n (%)	
	Response-evaluable Population N=53	Safety Population N=86
Discontinued from treatment	28 (52.8%)	41 (47.7%)
Continuing on treatment	25 (47.2%)	45 (52.3%)
Discontinued from study	22 (41.5%)	28 (32.6%)
Reasons for discontinuation of treatment		
Disease progression	14 (26.4%)	14 (16.3%)
AML	6 (11.3%)	6 (7.0%)
Adverse event(s)	8 (15.1%)	15 (17.4%)
Related	4 (7.5%)	9 (10.5%)
Withdrew consent	2 (3.8%)	6 (7%)
Investigator's decision	3 (5.7%)	4 (4.7%)
Administrative/other	1 (1.9%)	2 (2.3%)
Reasons for discontinuation of study		
Adverse event(s)	1 (1.9%)	2 (2.3%)
Death	15 (28.3%)	16 (18.6%)
Withdrew consent	3 (5.7%)	7 (8.1%)
Initiation of another neoplastic therapy	2 (3.8%)	2 (2.3%)
Investigator's decision	1 (1.9%)	1 (1.2%)

AML = acute myeloid leukemia

Source: Study BLU-285-2101 CSR

Table 5 gives a summary on demographics and other baseline characteristics for patients in study 2101. The median age was 64 years (range: 34 to 83 years). Approximately 82.6% of the patients were enrolled in the US. The baseline characteristics of patients in the Response-evaluable Population were similar to the Safety Population based on all enrolled patients.

Table 5: Study 2101 Demographics and Other Baseline Factors

Factor	Response-evaluable Population N= 53	Safety Population N=86
Age (years)		
<65 / ≥65, n (%)	26 / 27 (49.1% / 50.9%)	44 / 42 (51.2% / 48.8%)
mean (SD), median, min-max	63.9 (11.2), 65, 34-83	62.6 (12.1), 64, 34-83
Sex		
Female / Male, n (%)	23 / 30 (43.4% / 56.6%)	40 / 46 (46.5% / 53.5%)
Race		
White / Other / Unknown, n (%)	47 / 3 / 3 (88.7%/ 5.7% / 5.7%)	75 / 4 / 7 (87.2% / 4.7% / 8.1%)
Region		
US / Other, n (%)	43/10 (81.1%/18.9%)	71 / 15 (82.6% / 17.4%)
KIT D816V mutation		
Positive / Negative , n (%)	51 / 2 (96.2% / 3.8%)	78 / 8 (90.7% / 9.3%)
Prior Antineoplastic Therapy		
Yes / No, n (%)	32 / 21 (60.4% / 39.6%)	51 / 35 (59.3% / 40.7%)
Prior Midostaurin		
Yes / No, n (%)	17 / 36 (32.1% / 67.9%)	25 / 61 (29.1% / 70.9%)
Baseline S/A/R Genotype		
Positive / Negative, n (%)	27 / 26 (50.9% / 49.1%)	39 / 47 (45.3% / 54.7%)
ECOG performance status		
0-1 / ≥2, n (%)	36 / 17 (67.9% / 32.1%)	64 / 22 (74.4% / 25.6%)

ECOG: Eastern Cooperative Oncology Group; S/A/R = SRSF1/ASXL1/RUNX1; SD: standard deviation,

Source: FDA analysis

Study 2202 enrolled a total of 62 patients in the Safety Population. At the time of data cut-off (June 23, 2020), enrollment was ongoing, but the interim analyses was completed, and treatment was ongoing in 52 patients (83.9%). The primary reasons for treatment discontinuation were disease progression and adverse events. Patient disposition in the Response-evaluable Population, which excluded 30 patients who are not response-evaluable by mIWG-MRT-ECNM criteria, was similar to the Safety Population of all enrolled patients.

Table 6: Study 2202 Patient Disposition

Disposition Category	All Doses of Avapritinib, n (%)	
	Response-evaluable Population N=32	Safety Population N=62
Discontinued from treatment	8 (25%)	10 (16.1%)
Continuing on treatment	24 (75%)	52 (83.9%)
Discontinued from study	7 (21.9%)	8 (12.9%)
Reasons for discontinuation of treatment		
Disease progression	2 (6.3%)	3 (4.8%)
AML	1 (3.1%)	1 (1.6%)
Adverse event(s)	5 (15.6%)	6 (9.7%)
Related	2 (6.3%)	3 (4.8%)
Death	0	0
Withdrew consent	1 (3.1%)	1 (1.6%)
Reasons for discontinuation from study		
Death	4 (12.5%)	4 (6.5%)
Disease progression	0	0
Adverse event(s)	4 (12.5%)	4 (6.5%)
Other	0	0
Lost to follow-up	0	0
Withdrew consent	1 (3.1%)	1 (1.6%)
Sponsor decision	1 (3.1%)	1 (1.6%)
Other	1 (3.1%)	2 (3.2%)

AML = acute myeloid leukemia
Source: Study BLU-285-2202 CSR

Table 7 gives a summary on demographics and other baseline characteristics for patients in study 2202. The median age was 68.5 years (range: 31 to 88 years). Approximately 43.5% of the patients were enrolled in the US. The baseline characteristics of patients in the Response-evaluable Population were similar to the Safety Population of all enrolled patients.

Table 7: Study 2202 Demographics and Other Baseline Factors

Factor	Response-evaluable Population N= 32	Safety Population N=62
Age (years)		
<65 / ≥65, n (%)	12 / 20 (37.5% / 62.5%)	20 / 42 (32.3% / 67.7%)
mean (SD), median, min-max	66.2 (10.48), 68.0, 37-85	67.5 (11.02), 68.5, 31-88
Sex		
Female / Male, n (%)	14 / 18 (43.8% / 56.3%)	28 / 34 (45.2% / 54.8%)
Race		
White / Other / Unknown, n (%)	32 / 0 / 0 (100% / 0 / 0)	54 / 7 / 1 (87.1% / 11.3% / 1.6%)
Region		
US / Other, n (%)	17 / 15 (53.1% / 46.9%)	27 / 35 (43.5% / 56.5%)
KIT D816V mutation		
Positive / Negative, n (%)	30 / 2 (93.8% / 6.3%)	59 / 3 (95.2% / 4.8%)
Prior Antineoplastic Therapy		
Yes / No, n (%)	23 / 9 (71.9% / 28.1%)	42 / 20 (67.7% / 32.3%)

Prior Midostaurin		
Yes / No, n (%)	17 / 15 (53.1% / 46.9%)	34 / 28 (54.8% / 45.2%)
Baseline S/A/R Genotype		
Positive / Negative, n (%)	17 / 15 (53.1% / 46.9%)	26 / 36 (41.9% / 58.1%)
ECOG performance status		
0-1 / ≥2, n (%)	21 / 11 (65.6% / 34.4%)	43 / 19 (69.4% / 30.6%)

ECOG: Eastern Cooperative Oncology Group; S/A/R = SRSF1/ASXL1/RUNX1; SD: standard deviation
Source: FDA analysis

3.2.4 Efficacy Results

3.2.4.1 Treatment Response

This review focused on evaluations for the proposed indication expansion in ASM and SM-AHN disease subtypes due to the administrative split of the avapritinib marketing application between the Division of Nonmalignant Hematology (which is reviewing the (b) (4) ASM, SM-AHN portion of the application) and Division of Hematologic Malignancies 1 (which is reviewing the MCL portion of the application), (b) (4)

The primary analysis of ORR (Table 8) was conducted based on the pooled Response-evaluable Population, which included 5 patients with ASM and 63 patients with SM-AHN from studies 2101 and 2202.

For patients with the starting dose of the target dose level 200 mg once daily, we found the following results:

- 2 out of 2 response-evaluable patients with ASM achieved a confirmed response (CR, CRh or PR) during the treatment for an ORR of 100% (95% CI: [15.81%, 100%]), including 1 patient achieved a CRh and 1 patient achieved a PR as the best response. The median time to response was 4.6 months. The median duration of response was not reached at the time of data cut-off.
- 17 out of 32 response-evaluable patients with SM-AHN achieved a confirmed response (CR, CRh or PR) during the treatment for an ORR of 53.12% (95% CI: [34.74%, 70.91%]), including 7 patients achieved a CRh and 10 patients achieved a PR as the best response. The median time to response was 1.9 months. The median duration of response was not reached at the time of data cut-off.

For patients with the starting dose no more than the target dose level 200 mg once daily, we found the following results:

- 2 out of 2 response-evaluable patients with ASM achieved a confirmed response (CR, CRh or PR) during the treatment for an ORR of 100% (95% CI: [15.81%, 100%]), including 1 patient achieved a CRh and 1 patient achieved a PR as the best response. The median time to response was 4.6 months. The median duration of response was not reached at the time of data cut-off.
- 23 out of 40 response-evaluable patients with SM-AHN achieved a confirmed response (CR, CRh or PR) during the treatment for an ORR of 57.5% (95% CI: [40.89%, 72.96%]), including 2 patients achieved a CR , 11 patients achieved a CRh and 10 patients achieved a PR as the best response. The median time to response was 1.9 months. The median duration of response was 38.3 months.

For patients with any starting dose ranging from 30 to 400 mg once daily, we found the following results:

- 5 out of 5 response-evaluable patients with ASM achieved a confirmed response (CR, CRh or PR) during the treatment for an ORR of 100% (95% CI: [47.82%, 100%]), including 3 patients achieved a CRh and 2 patients achieved a PR as the best response. The median time to response was 3.7 months. The median duration of response was not reached at the time of data cut-off.
- 40 out of 63 response-evaluable patients with SM-AHN achieved a confirmed response (CR, CRh or PR) during the treatment for an ORR of 63.49% (95% CI: [50.4%, 75.27%]), including 5 patients achieved a CR , 14 patients achieved a CRh and 21 patients achieved a PR as the best response. The median time to response was 2 months. The median duration of response was 38.3 months.

Table 8: Study 2101 and study 2202 Pooled Treatment Response Result per mIWG-MRT-ECNM Criteria (Response-evaluable Population)

	200 mg Dose		≤ 200mg Doses		All Doses	
	ASM	**SM-AHN**	**ASM**	**SM-AHN**	**ASM**	**SM-AHN**
Best Response by mIWG-MRT-ECNM Criteria						
Response-evaluable patients, N	N=2	N=32	N=2	N=40	N=5	N=63
CR, n (%)	0	0	0	2 (5%)	0	5 (7.94%)
CRh, n (%)	1 (50%)	7 (21.88%)	1 (50%)	11 (27.5%)	3 (60%)	14 (22.22%)
PR, n (%)	1 (50%)	10 (31.25%)	1 (50%)	10 (25%)	2 (40%)	21 (33.33%)
CI, n (%)	0	7 (21.88%)	0	8 (20%)	0	9 (14.29%)
SD, n (%)	0	4 (12.5%)	0	5 (12.5%)	0	10 (15.87%)
PD, n (%)	0	0	0	0	0	0
NE, n (%)	0	4 (12.5%)	0	4 (10%)	0	4 (6.35%)
ORR=CR+CRh+PR, n (%)	2 (100%)	17 (53.12%)	2 (100%)	23 (57.5%)	5 (100%)	40 (63.49%)
95% confidence interval for ORR (using the nominal one-sided alpha=0.025)	(15.81%, 100%)	(34.74%, 70.91%)	(15.81%, 100%)	(40.89%, 72.96%)	(47.82%, 100%)	(50.4%, 75.27%)
98.75% confidence interval for ORR (using the protocol specified interim analysis one-sided alpha=0.00625)	(7.91%, 100%)	(30.48%, 74.88%)	(7.91%, 100%)	(36.84%, 76.4%)	(36.24%, 100%)	(47.02%, 77.98%)
99.48% confidence interval for ORR (using the O'Brien-Fleming interim one-sided alpha=0.0026)	(5.1%, 100%)	(28.22%, 76.95%)	(5.1%, 100%)	(34.66%, 78.25%)	(30.41%, 100%)	(45.16%, 79.41%)
Wald test p-value (null ORR=17%)	NA[1]	<.0001	NA[1]	<.0001	NA[1]	<.0001
Wald test p-value (null ORR=25%)	NA[1]	0.0007	NA[1]	<.0001	NA[1]	<.0001
Time to response[2] (month)						
Median	4.6	1.9	4.6	1.9	3.7	2
Min – Max	3.71-5.55	1.71-26.74	3.71-5.55	1.71-26.74	1.87-5.55	1.71-26.74
Duration of Response[3] (month)						
Events, n	0	1	0	4	0	9
Censored, n	2	16	2	19	5	31
Median	NR	NR	NR	38.3	NR	38.3
Min – Max	5.03[4]-6.47[4]	3.71[4]-15.67[4]	5.03[4]-6.47[4]	3.75[4]-41.1[4]	5.03[4]-25.53[4]	2.99-41.1[4]
95% approximate confidence interval for median	(NE, NE)	(NE, NE)	(NE, NE)	(19.35,NE)	(NE, NE)	(19.35, NE)
95% exact confidence interval for median	(NE, NE)	(NE, NE)	(NE, NE)	(19.35,NE)	(NE, NE)	(19.35, NE)

1. Wald test is not applicable when the estimated ORR=0 or 1
2. Time to response was defined as the time from the start of treatment to the time a CR/CRh/PR was first met. Patients without confirmed CR/CRh/PR were excluded from analysis.
3. Duration of response is defined as the time in months from first documented response to the date of first

documented disease progression, loss of response, or death due to any cause, whichever occurs first. Patients without confirmed response are excluded from this analysis. Patients who are still in response at time of data cutoff were censored at their last valid assessment.

4. Censored observation

ASM=aggressive systemic mastocytosis ; CI=clinical improvement; CR=complete remission; CRh=complete remission with partial recovery of peripheral blood counts; ORR=overall response rate; mIWG-MRT-ECNM= modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; NA=not applicable; NE=not evaluable; NR=not reached; PD=progressive disease; PR=partial remission; SD=stable disease; SM-AHN=systemic mastocytosis with an associated hematological neoplasm

Source: FDA analysis

Separated analyses of ORR was also conducted in the Response-evaluable Population of 3 patients with ASM and 37 patients with SM-AHN from study 2101 (Table 9) as well as 2 patients with ASM and 26 patients with SM-AHN from study 2202 (Table 10).

Table 9: Study 2101 Treatment Response Result per mIWG-MRT-ECNM Criteria (Response-evaluable Population)

	200 mg Dose		**≤ 200mg Doses**		**All Doses**	
	ASM	**SM-AHN**	**ASM**	**SM-AHN**	**ASM**	**SM-AHN**
Best Response by mIWG-MRT-ECNM Criteria						
Response-evaluable patients, N	N=0	N=7	N=0	N=14	N=3	N=37
CR, n (%)	NA	0	NA	2 (14.29%)	0	5 (13.51%)
CRh, n (%)		2 (28.57%)		6 (42.86%)	2 (66.67%)	9 (24.32%)
PR, n (%)		2 (28.57%)		2 (14.29%)	1 (33.33%)	13 (35.14%)
CI, n (%)		0		0	0	1 (2.7%)
SD, n (%)		2 (28.57%)		3 (21.43%)	0	8 (21.62%)
PD, n (%)		0		0	0	0
NE, n (%)		1 (14.29%)		1 (7.14%)	0	1 (2.7%)
ORR=CR+CRh+PR, n (%)		4 (57.14%)		10 (71.43%)	3 (100%)	27 (72.97%)
95% confidence interval for ORR (using the nominal one-sided alpha=0.025)		(18.41%, 90.1%)		(41.90%, 91.61%)	(29.24%, 100%)	(55.88%, 86.21%)
Wald test p-value (null ORR=17%)		0.0159		<.0001	NA[1]	<.0001
Wald test p-value (null ORR=25%)		0.0429		<.0001	NA[1]	<.0001
Time to response[2] (month)						
Median	NA	1.9	NA	4.6	1.9	2.4
Min – Max		1.84-26.74		1.84-26.74	1.87-5.55	1.77-26.74
Duration of Response[3] (month)						
Events, n	NA	1	NA	4	0	9
Censored, n		3		6	3	18
Median		NR		38.3	NR	38.3
Min – Max		6.47[4]-13.6[4]		6.47[4]-41.1[4]	23.03[4]-25.53[4]	2.99-41.1[4]
95% approximate confidence interval for median		(11.2, NE)		(14.82, NE)	(NE, NE)	(19.35, NE)
95% exact confidence interval for median		(11.2, NE)		(14.82, NE)	(NE, NE)	(19.35, NE)

1. Wald test is not applicable when the estimated ORR=0 or 1
2. Time to response was defined as the time from the start of treatment to the time a CR/CRh/PR was first met. Patients without confirmed CR/CRh/PR were excluded from analysis.
3. Duration of response is defined as the time in months from first documented response to the date of first documented disease progression, loss of response, or death due to any cause, whichever occurs first. Patients without confirmed response are excluded from this analysis. Patients who are still in response at time of data cutoff were censored at their last valid assessment.
4. Censored observation

ASM=aggressive systemic mastocytosis ; CI=clinical improvement; CR=complete remission; CRh=complete remission with partial recovery of peripheral blood counts; ORR=overall response rate; mIWG-MRT-ECNM= modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European

Competence Network on Mastocytosis; NA=not applicable; NE=not evaluable; NR=not reached; PD=progressive disease; PR=partial remission; SD=stable disease; SM-AHN=systemic mastocytosis with an associated hematological neoplasm
Source: FDA analysis

Table 10: Study 2202 Treatment Response Result per mIWG-MRT-ECNM Criteria (Response-evaluable Population)

	200 mg Dose		≤ 200mg Doses		All Doses	
	ASM	**SM-AHN**	**ASM**	**SM-AHN**	**ASM**	**SM-AHN**
Best Response by mIWG-MRT-ECNM Criteria						
Response-evaluable patients, N	N=2	N=25	N=2	N=26	N=2	N=26
CR, n (%)	0	0	0	0	0	0
CRh, n (%)	1 (50%)	5 (20%)	1 (50%)	5 (19.23%)	1 (50%)	5 (19.23%)
PR, n (%)	1 (50%)	8 (32%)	1 (50%)	8 (30.77%)	1 (50%)	8 (30.77%)
CI, n (%)	0	7 (28%)	0	8 (30.77%)	0	8 (30.77%)
SD, n (%)	0	2 (8%)	0	2 (7.69%)	0	2 (7.69%)
PD, n (%)	0	0	0	0	0	0
NE, n (%)	0	3 (12%)	0	3 (11.54%)	0	3 (11.54%)
ORR=CR+CRh+PR, n (%)	2 (100%)	13 (52%)	2 (100%)	13 (50%)	2 (100%)	13 (50%)
95% confidence interval for ORR (using the nominal one-sided alpha=0.025)	(15.81%, 100%)	(31.31%, 72.2%)	(15.81%, 100%)	(29.93%, 70.07%)	(15.81%, 100%)	(29.93%, 70.07%)
98.75% confidence interval for ORR (using the protocol specified interim analysis one-sided alpha=0.00625)	(7.91%, 100%)	(26.71%, 76.56%)	(7.91%, 100%)	(25.5%, 74.5%)	(7.91%, 100%)	(25.5%, 74.5%)
99.48% confidence interval for ORR (O'Brien-Fleming interim one-sided alpha=0.0026)	(5.1%, 100%)	(24.33%, 78.8%)	(5.1%, 100%)	(23.21%, 76.79%)	(5.1%, 100%)	(23.21%, 76.79%)
Wald test p-value (null ORR=17%)	NA[1]	0.0002	NA[1]	0.0004	NA[1]	0.0004
Wald test p-value (null ORR=25%)	NA[1]	0.0034	NA[1]	0.0054	NA[1]	0.0054
Time to response[2] (month)						
Median	4.6	1.9	4.6	1.9	4.6	1.9
Min – Max	3.71-5.55	1.71-9.3	3.71-5.55	1.71-9.3	3.71-5.55	1.71-9.3
Duration of Response[3] (month)						
Events, n	0	0	0	0	0	0
Censored, n	2	13	2	13	2	13
Median	NR	NR	NR	NR	NR	NR
Min – Max	5.03[4]-6.47[4]	3.75[4]-15.67[4]	5.03[4]-6.47[4]	3.75[4]-15.67[4]	5.03[4]-6.47[4]	3.75[4]-15.67[4]
95% approximate confidence interval for median	(NE, NE)	(NE, NE)	(NE, NE)	(NE, NE)	(NE, NE)	(NE, NE)
95% exact confidence interval for median	(NE, NE)	(NE, NE)	(NE, NE)	(NE, NE)	(NE, NE)	(NE, NE)

1. Wald test is not applicable when the estimated ORR=0 or 1
2. Time to response was defined as the time from the start of treatment to the time a CR/CRh/PR was first met. Patients without confirmed CR/CRh/PR were excluded from analysis.
3. Duration of response is defined as the time in months from first documented response to the date of first documented disease progression, loss of response, or death due to any cause, whichever occurs first. Patients without confirmed response are excluded from this analysis. Patients who are still in response at time of data cutoff were censored at their last valid assessment.
4. Censored observation

ASM=aggressive systemic mastocytosis ; CI=clinical improvement; CR=complete remission; CRh=complete remission with partial recovery of peripheral blood counts; ORR=overall response rate; mIWG-MRT-ECNM= modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; NA=not applicable; NE=not evaluable; NR=not reached; PD=progressive disease; PR=partial remission; SD=stable disease; SM-AHN=systemic mastocytosis with an associated hematological neoplasm
Source: FDA analysis

Supportive analyses based on all enrolled patients (i.e. Safety Population) are provided in Table 11 for the pooled two studies 2101 and 2202. The response of the non-evaluable patients by mIWG-MRT-ECNM criteria are imputed by the following three ways

- Impute all non-evaluable patients as non-responder
- Only impute non-evaluable patients due to no evaluable baseline C-finding as non-responder
- Only impute non-evaluable patients due to limited follow-up as non-responder

Table 11: Study 2101 and study 2202 Pooled Treatment Response Result (Safety Population)

	200 mg Dose		≤ 200mg Doses		All Doses	
	ASM	**SM-AHN**	**ASM**	**SM-AHN**	**ASM**	**SM-AHN**
Safety population patients, N	N=9	N=55	N=11	N=63	N=17	N=91
Response-evaluable patients per mIWG-MRT-ECNM Criteria, n	2	32	2	40	5	63
Impute all non-evaluable patients as non-responder						
Evaluated patients[1] , n	9	55	11	63	17	91
ORR=CR+CRh+PR, n (%)	2 (22.22%)	17 (30.91%)	2 (18.18%)	23 (36.51%)	5 (29.41%)	40 (43.96%)
95% confidence interval for ORR	(2.81%, 60.01%)	(19.14%, 44.81%)	(2.28%, 51.78%)	(24.73%, 49.6%)	(10.31%, 55.96%)	(33.56%, 54.75%)
Only impute non-evaluable patients due to no evaluable baseline C-finding as non-responder						
Evaluated patients[1] , n	5	42	6	50	12	78
ORR=CR+CRh+PR, n (%)	2 (40%)	17 (40.48%)	2 (33.33%)	23 (46%)	5 (41.67%)	40 (51.28%)
95% confidence interval for ORR	(5.27%, 85.34%)	(25.63%, 56.72%)	(4.33%, 77.72%)	(31.81%, 60.68%)	(15.17%, 72.33%)	(39.69%, 62.77%)
Only impute non-evaluable patients due to limited follow-up as non-responder						
Evaluated patients[1] , n	6	45	7	53	10	76
ORR=CR+CRh+PR, n (%)	2 (33.33%)	17 (37.78%)	2 (28.57%)	23 (43.4%)	5 (50%)	40 (52.63%)
95% confidence interval for ORR	(4.33%, 77.72%)	(23.77%, 53.46%)	(3.67%, 70.96%)	(29.84%, 57.72%)	(18.71%, 81.29%)	(40.84%, 64.21%)

1. number of evaluated patients after the imputation

ASM=aggressive systemic mastocytosis; CR=complete remission; CRh=complete remission with partial recovery of peripheral blood counts; ORR=overall response rate; PR=partial remission; SM-AHN=systemic mastocytosis with an associated hematological neoplasm

Source: FDA analysis

Reviewer Comments:

- *According to the recommendation of the clinical review team, the approval of avapritinib should be based on the ORR of the pooled two studies 2101 and 2202 with the starting dose no more than the target dose level 200 mg once daily.*
- *Patients with SM-AHN achieved an ORR ≥ 50% for all considered dose groups (i.e. "200 mg Dose", "≤ 200mg Doses" and "All Doses") for the pooled two studies 2101 and 2202 as well as for each of the individual study. The 95% confidence interval for ORR passes the 17% cut-off points (i.e. the lower limit of the 95% confidence interval for ORR is greater than 17%), and the p-value of the Wald test against a null ORR of 17% is greater than a significate value of 0.025 for all cases.*
- *Patients with ASM achieved an ORR=100% for all considered dose groups (i.e. "200 mg Dose", "≤ 200mg Doses" and "All Doses") for the pooled two studies 2101 and 2202 as well as for each of the individual study, except for study 2101 when the treatment dose is "200 mg"*

or "≤ 200mg", which has no patients belong to these categories. The lower limit of the 95% confidence intervals for ORR are lower than the 17% cut-off points for most cases, and the Wald-test is not applicable when ORR=0 or 100%. However, due to the extremely small sample size for the response-evaluable ASM population, these confidence intervals and statistical testing results are not adequately powered. Therefore, results are not meaningful for making any statistical inferences. Whether the ASM indication can be approved is deferred to the clinical reviewer's scientific judgment.

- *The applicant selected 17% decision threshold for ORR, which was determined by the point estimate for the ORR of a previous approved drug for the same indication RYDAPT® (midostaurin) calculated based on mIWG-MRT-ECNM criteria, which may not be sufficient to address the variability of the midostaurin data. The testing results (i.e. confidence interval and p-value) for comparing the avapritinib ORR to a null value of 25% (i.e. the upper limit of the 95% confidence interval for midostaurin ORR) are also provided in Table 8-10.*
  1) *ASM results will not be statistically interpreted due to its small sample size.*
  2) *For the pooled two studies 2101 and 2202, the lower limit of the 95% confidence intervals are greater than 25% and the Wald test results are still highly significant (i.e. p-value<0.001) for SM-AHN population in all cases.*
  3) *For the separated studies 2101 and 2202, the lower limit of the 95% confidence intervals are greater than 25% and the Wald test results are still significant (i.e. p-value<0.025) for SM-AHN population in all cases, except for study 2101 with 200 mg dose level which has a 18.41% lower limit for the 95% confidence interval and a 0.0429 p-value for the Wald test result. Since there are only 7 SM-AHN patients in study 2101 with 200 mg dose level, the confidence interval and statistical testing results are not adequately powered to provide meaningful inferences.*
- *Since the efficacy data submitted for study 2202 are from an interim analysis result at 50% information time, it is not appropriate to compare the testing results (i.e. confidence interval and p-value) calculated based on data from study 2202 with the nominal significant value alpha=0.025. The testing results using the applicant's proposed interim analysis significant value of alpha=0.00625 and the commonly used O'Brian-Fleming interim analysis significant value alpha=0.0026 are also shown in Table 8-10 for the pooled studies 2101 and 2202 as well as the individual study 2202.*
  1) *ASM results cannot be statistically interpreted due to its small sample size.*
  2) *For the pooled studies 2101 and 2202, the lower limits of the 98.75% and 99.48% confidence intervals are greater than 17% and 25%, and the Wald test results are still significant (i.e. p-value<0.00625 and <0.0026) for null ORR values of 17% and 25% for all cases in SM-AHN population.*
  3) *For the individual study 2202, the lower limits of the 98.75% and 99.48% confidence intervals are greater than 17%, and the Wald test results are still significant (i.e. p-value<0.00625 and <0.0026) for a null ORR value of 17% for all cases in SM-AHN population, but failed for a null ORR value of 25% for some cases. The results should be interpreted with caution since the study is not powered for a null ORR of 25%.*
- *The number of responders is small (i.e. <30) for most of cases, therefore, the normal approximation used for calculating the 95% confidence interval for the Kaplan-Meier estimate for median duration of response may not be valid. The exact 95% confidence interval based on bootstrapping methodology are also provided in Table 8-10. The results are consistent with*

the approximate confidence intervals.

- *Treatment response was evaluated for Safety Population in the pooled two studies 2101 and 2202. ASM results are not be statistically interpreted due to its small sample size and thus make it very sensitive to the considered imputations. For SM-AHN population, the lower limit of the 95% confidence intervals for ORR are all greater than 17% for all the following three ways of imputation in Table 11, and all considered dose groups (i.e. "200 mg Dose", "≤ 200mg Doses" and "All Doses").*
  1) *Impute all non-evaluable patients as non-responder*
  2) *Only impute non-evaluable patients due to no evaluable baseline C-finding as non-responder*
  3) *Only impute non-evaluable patients due to limited follow-up as non-responder*

3.2.4.2 Treatment Response by Baseline Characteristics

Table 12 displays the results on ORR by key baseline characteristics subgroups for all AdvSM populations (i.e. ASM, SM-AHN and MCL) from the pooled two studies 2101 and 2202 for different dose groups *(i.e. "200 mg Dose", "≤ 200mg Doses" and "All Doses")*.

Table 12 : Pooled Studies 2101 and 2202 Overall Response Rate by Baseline Factors

Factor	Subgroup	Dosage Groups		
		200 mg r / n, (%) [95% CI]	**≤ 200 mg r / n, (%) [95% CI]**	**All doses r / n, (%) [95% CI]**
Age	< 65 years	10/20,(50%)[27.2%,72.8%]	14/25,(56%)[34.9%,75.6%]	24/38,(63.2%)[46%,78.2%]
	≥ 65 years	13/24,(54.2%)[32.8%,74.4%]	16/28,(57.1%)[37.2%,75.5%]	29/47,(61.7%)[46.4%,75.5%]
Gender	Female	10/18,(55.6%)[30.8%,78.5%]	13/22,(59.1%)[36.4%,79.3%]	24/37,(64.9%)[47.5%,79.8%]
	Male	13/26,(50%)[29.9%,70.1%]	17/31,(54.8%)[36.0%,72.7%]	29/48,(60.4%)[45.3%,74.2%]
Region	US	16/28,(57.1%)[37.2%,75.5%]	21/33,(63.6%)[45.1%,79.6%]	40/60,(66.7%)[53.3%,78.3%]
	Other	7/16,(43.8%)[19.8%,70.1%]	9/20,(45%)[23.1%,68.5%]	13/25,(52%)[31.3%,72.2%]
Race	White	23/44,(52.3%)[36.7%,67.5%]	29/52,(55.8%)[41.3%,69.5%]	48/79,(60.8%)[49.1%,71.6%]
	Other or Unknown	-	1/1,(100%)[2.5%,100%]	5/6,(83.3%)[35.9%,99.6%]
KIT D816V mutation	Positive	21/41,(51.2%)[35.1%,67.1%]	28/50,(56%)[41.3%,70%]	51/81,(63%)[51.5%,73.4%]
	Negative	2/3,(66.7%)[9.4%,99.2%]	2/3,(66.7%)[9.4%,99.2%]	2/4,(50%)[6.8%,93.2%]
Prior Antineoplastic Therapy	Yes	14/31,(45.2%)[27.3%,64.0%]	17/35,(48.6%)[31.4%,66%]	30/55,(54.5%)[40.6%,68%]
	No	9/13,(69.2%)[38.6%,90.9%]	13/18,(72.2%)[46.5%,90.3%]	23/30,(76.7%)[57.7%,90.1%]
Prior Midostaurin	Yes	10/23,(43.5%)[23.2%,65.5%]	11/25,(44%)[24.4%,65.1%]	17/34,(50%)[32.4%,67.6%]
	No	13/21,(61.9%)[38.4%,81.9%]	19/28,(67.9%)[47.6%,84.1%]	36/51,(70.6%)[56.2%,82.5%]
Baseline S/A/R Genotype	Positive	10/22,(45.5%)[24.4%,67.8%]	13/26,(50%)[29.9%,70.1%]	25/44,(56.8%)[41%,71.7%]
	Negative	13/22,(59.1%)[36.4%,79.3%]	17/27,(63%)[42.4%,80.6%]	28/41,(68.3%)[51.9%,81.9%]
ECOG performance	0-1	14/29,(48.3%)[29.4%,67.5%]	20/36,(55.6%)[38.1%,72.1%]	35/57,(61.4%)[47.6%,74%]
	>=2	9/15,(60%)[32.3%,83.7%]	10/17,(58.8%)[32.9%,81.6%]	18/28,(64.3%)[44.1%,81.4%]

r / n: number of responders/number of eligible patients according to the respective response criteria;
ECOG: Eastern Cooperative Oncology Group; CI: confidence interval.
Source: FDA analysis

3.2.4.3 Overall Survival

Table 13 presents the overall survival result from patients in the pooled studies 2101 and 2202 based on Safety Population as well as individual studies.

For patients with the starting dose of the target dose level 200 mg once daily, we found the following:

- in study 2101, the median overall survival for patients with ASM was not reached at the time of data cut-off; the median overall survival for patients with SM-AHN was 13 months (95% CI: [7.98, NE]).
- in study 2202, the median overall survival for patients with either ASM or SM-AHN was not reached at the time of data cut-off.
- in the pooled two studies 2101 and 2202, the median overall survival for patients with either ASM or SM-AHN was not reached at the time of data cut-off.

For patients with the starting dose no more than the target dose level 200 mg once daily, we found the following:

- in study 2101, the median overall survival for patients with ASM was not reached at the time of data cut-off; the median overall survival for patients with SM-AHN was 46.9 months (95% CI: [13.01, NE]).
- in study 2202, the median overall survival for patients with either ASM or SM-AHN was not reached at the time of data cut-off.
- in the pooled two studies 2101 and 2202, the median overall survival for patients with ASM was not reached at the time of data cut-off; the median overall survival for patients with SM-AHN was 46.9 months (95% CI: [24.48, NE]).

For patients with any starting dose ranging from 30 to 400 mg once daily, we found the following:

- in study 2101, the median overall survival for patients with ASM was not reached at the time of data cut-off; the median overall survival for patients with SM-AHN was 46.9 months (95% CI: [24.48, NE]).
- in study 2202, the median overall survival for patients with either ASM or SM-AHN was not reached at the time of data cut-off.
- in the pooled two studies 2101 and 2202, the median overall survival for patients with ASM was not reached at the time of data cut-off; the median overall survival for patients with SM-AHN was 46.9 months (95% CI: [24.48, NE]).

Table 13: Overall Survival[1] (Safety Population)

	200 mg Dose		≤ 200mg Doses		All Doses	
	ASM	**SM-AHN**	**ASM**	**SM-AHN**	**ASM**	**SM-AHN**
Study 2101						
Number of enrolled patients, N	1	13	2	20	8	48
Events, n	0	4	0	7	0	15
Censored, n	1	9	2	13	8	33
Median[2]	NR	13	NR	46.9	NR	46.9
Min – Max	7.46[3]-7.46[3]	2.33[3]-41.23[3]	7.46[3]-48.56[3]	2.33[3]-50.6[3]	7.46[3]-48.56[3]	2.33[3]-50.6[3]
95% approximate confidence interval for median	(NE, NE)	(7.98,NE)	(NE, NE)	(13.01,NE)	(NE, NE)	(24.48, NE)
Study 2202						
Number of enrolled patients, N	8	42	9	43	9	43
Events, n	0	4	0	4	0	4
Censored, n	8	38	9	39	9	39
Median[2]	NR	NR	NR	NR	NR	NR
Min – Max	0.39[3]-12.71[3]	0.23[3]-18.17[3]	0.39[3]-12.71[3]	0.23[3]-18.17[3]	0.39[3]-12.71[3]	0.23[3]-18.17[3]
95% approximate confidence interval for median	(NE, NE)	(NE, NE)	(NE, NE)	(NE, NE)	(NE, NE)	(NE, NE)
Study 2101+2202						
Number of enrolled patients, N	9	55	11	63	17	91
Events, n	0	8	0	11	0	19
Censored, n	9	47	11	52	17	72
Median[2]	NR	NR	NR	46.9	NR	46.9
Min – Max	0.39[3]-12.71[3]	0.23[3]-41.23[3]	0.39[3]-48.56[3]	0.23[3]-50.6[3]	0.39[3]-48.56[3]	0.23[3]-50.6[3]
95% approximate confidence interval for median	(NE, NE)	(NE, NE)	(NE, NE)	(24.48,NE)	(NE, NE)	(24.48, NE)

1. Overall survival is defined as the time in months from the start of treatment to the date of death. Patients who die before or on the data cutoff date were considered to have had an overall survival event. All patients who did not have a death record prior to or on the cutoff date were censored at the last date known alive.
2. Estimated by Kaplan-Meier method
3. Censored observation

ASM=aggressive systemic mastocytosis ; NE=not evaluable; NR=not reached; SM-AHN=systemic mastocytosis with an associated hematological neoplasm
Source: FDA analysis

Reviewer Comments:

- *Because Studies 2101 and 2202 have single-arm, the overall survival results presented in this section cannot be interpretable for an efficacy claim. The overall survival results presented in this section are only to be considered as exploratory purpose.*
- *The duration of study 2202 is much shorter than that of study 2101, the pooled overall survival results appeared driven by data from study 2101.*

3.2.4.4 Patient-Reported Outcomes (PRO)

The applicant's PRO study results are briefly summarized below for studies 2101 and 2202, respectively for exploratory purpose.

Study 2101

Patients on avapritinib showed improvements in both symptoms and quality of life assessed by the PRO questionnaires. The AdvSM-SAF total symptom score decreased from baseline, indicating an improvement of SM symptoms from the patient's perspective. By Cycle 11 Day 1, there was a significant decrease from baseline of 10.89 points (one sample t-test p-value = 0.0020 for a null hypothesis of ≥ 0 in mean change of total symptom score). The PGIS score decreased over time

among all patients, suggesting an improvement in patient-assessed disease symptoms. The EORTC QLC-C30 global health status score increased over time, also suggesting an improvement in the quality of life.

The mean global health status score increased (improved) over time. At baseline, the mean (StdDev) global health status score for 43 AdvSM patients was 43.8 (25.53). On Cycle 12 Day 1, mean (StdDev) global health status score was 62.96 (24.63; n=18), an increase from baseline of 23.44 (25.68).

Study 2202

Patients on avapritinib showed improvements in both symptoms and quality of life assessed by the PRO questionnaires. The AdvSM-SAF total symptom score decreased from baseline, suggesting an improvement of SM symptoms from the patient's perspective. By Cycle 11 Day 1, there was a significant decrease from baseline of 9.76 points (one sample t-test p-value < 0.001 for a null hypothesis of ≥ 0 in mean change of total symptom score). The PGIS score decreased over time among all patients, suggesting an improvement in patient-assessed disease symptoms. The EORTC QLQ-C30 global health status score generally increased over time, suggesting an improvement in the quality of life.

The mean global health status score increased (improved) over time. At baseline, the mean (StdDev) global health status score for 54 AdvSM patients was 37.81 (24.158). On Cycle 7 Day 1, mean (StdDev) global health status score was 61.11 (17.663; n=24), an increase from baseline of 28.13 (33.587).

Reviewer Comment:

- *Efficacy claims cannot be made in the PRO outcomes assessed in studies 2101 and 2202 because the studies did not have a control arm for meaningful comparison. The PRO results presented in this section are only for exploratory purpose.*

3.3 Evaluation of Safety

To support the proposed indication expansion of avapritinib as a treatment of adult patients with AdvSM (b) (4), the evaluation of safety is mainly based on pooled Safety Population consisting of 148 patients from studies 2101 and 2202. 81 of the patients in the Safety Population were treated with the target starting dose of 200 mg once daily. There was no pre-specified hypothesis testing for safety.

According to the applicant's submitted Clinical Overview, overall, duration of treatment was imbalanced between the AdvSM groups, being considerably shorter in the targeted AdvSM 200 mg group (mean 35.29 weeks) than in the AdvSM All group (mean 64.45 weeks). All treated AdvSM patients from all doses experienced adverse events and 141 (95.3%) experienced adverse events related to avapritinib. A total of 92 patients (62.2%) experienced Grade ≥ 3 related adverse events, 73 (49.3%) experienced serious adverse events, and 28 (18.9%) experienced related serious adverse events. AdvSM patients treated at 200 mg once daily experienced fewer adverse events related to treatment 76 (93.8%) in comparison to patients treated at all dose levels. At the 200 mg once daily dose, a total of 44 patients (54.3%) experienced Grade ≥ 3 related adverse events, 27 (33.3%)

experienced serious adverse events, and 9 (11.1%) experienced related serious adverse events. The highest incidences of treatment-related adverse events were periorbital oedema (54.7%), anaemia (43.9%), and oedema peripheral (43.9%). There were 9 (6.1%) patients with an adverse event leading to death.

Please refer to the safety review from Dr. Qin Ryan for detailed safety evaluation and clinical interpretation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Please refer to Table 11 for the ORR results by age, gender, region and race in the pooled studies 2101 and 2202.

4.2 Other Special/Subgroup Populations

Please refer to Table 11 for the ORR results by other baseline factors in the pooled studies 2101 and 2202, including: KIT D816V mutation, prior antineoplastic therapy, prior midostaurin, baseline S/A/R genotype and ECOG performance status.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The proposed indication expansion for avapritinib in AdvSM (b) (4) is mainly supported by the pooled data from single-arm studies 2101 and 2202.

This review focused on evaluations for the proposed indication in ASM and SM-AHN disease subtypes because the administrative split of the avapritinib marketing application between the Division of Nonmalignant Hematology (which is reviewing the (b) (4) ASM, SM-AHN portion of the application) and Division of Hematologic Malignancies 1 (which is reviewing the MCL portion of the application). (b) (4)

The primary treatment efficacy in patients with ASM and SM-AHN was evaluated in the pooled two studies 2101 and 2202 based on overall response rate (ORR), defined as the proportion of patients with a confirmed best response of complete remission (CR), complete remission with partial recovery of peripheral blood counts (CRh) or partial remission (PR) by modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis (mIWG-MRT-ECNM) criteria, confirmed 12 weeks after initial response.

For patients with the starting dose of the target dose level 200 mg once daily, we found the following results:

- 2 out of 2 response-evaluable patients with ASM achieved a confirmed response (CR, CRh or PR) during the treatment for an ORR of 100% (95% CI: [15.81%, 100%]), including 1 patient

achieved a CRh and 1 patient achieved a PR as the best response. The median time to response was 4.6 months. The median duration of response was not reached at the time of data cut-off.

- 17 out of 32 response-evaluable patients with SM-AHN achieved a confirmed response (CR, CRh or PR) during the treatment for an ORR of 53.12% (95% CI: [34.74%, 70.91%]), including 7 patients achieved a CRh and 10 patients achieved a PR as the best response. The median time to response was 1.9 months. The median duration of response was not reached at the time of data cut-off.

For patients with the starting dose no more than the target dose level 200 mg once daily, we found the following results:

- 2 out of 2 response-evaluable patients with ASM achieved a confirmed response (CR, CRh or PR) during the treatment for an ORR of 100% (95% CI: [15.81%, 100%]), including 1 patient achieved a CRh and 1 patient achieved a PR as the best response. The median time to response was 4.6 months. The median duration of response was not reached at the time of data cut-off.
- 23 out of 40 response-evaluable patients with SM-AHN achieved a confirmed response (CR, CRh or PR) during the treatment for an ORR of 57.5% (95% CI: [40.89%, 72.96%]), including 2 patients achieved a CR , 11 patients achieved a CRh and 10 patients achieved a PR as the best response. The median time to response was 1.9 months. The median duration of response was 38.3 months.

For patients with any starting dose ranging from 30 to 400 mg once daily, we found the following results:

- 5 out of 5 response-evaluable patients with ASM achieved a confirmed response (CR, CRh or PR) during the treatment for an ORR of 100% (95% CI: [47.82%, 100%]), including 3 patients achieved a CRh and 2 patients achieved a PR as the best response. The median time to response was 3.7 months. The median duration of response was not reached at the time of data cut-off.
- 40 out of 63 response-evaluable patients with SM-AHN achieved a confirmed response (CR, CRh or PR) during the treatment for an ORR of 63.49% (95% CI: [50.4%, 75.27%]), including 5 patients achieved a CR , 14 patients achieved a CRh and 21 patients achieved a PR as the best response. The median time to response was 2 months. The median duration of response was 38.3 months.

Separated analyses of ORR was also conducted in the Response-Evaluable Population for patients with ASM and SM-AHN from individual studies 2101 and 2202. In addition, supportive analyses based on all enrolled patients (i.e. Safety Population) are provided for the pooled two studies 2101 and 2202.

Overall survival was assessed for patients with ASM and SM-AHN in the pooled two studies 2101 and 2202 as well as individual studies. Patient-reported outcomes were also assessed for all enrolled patients in each of the individual study 2101 and 2202. However, the overall survival and patient-reported outcomes were not interpretable for making efficacy claims due to a concern of potential bias from these open-label and single arm studies.

The major statistical issues identified during the review were related to the study populations and also the doses for the final approval because of safety concern of the doses higher than 200 mg. After communicating with the applicant, those issues had been successfully resolved.

5.2 Conclusions and Recommendations

Based on the efficacy results from the pooled two studies 2101 and 2202 for patients with the starting dose no more than the target dose level 200 mg once daily, the statistical review team has the following recommendations:

- (b) (4)
- The sample size for response-evaluable patients with ASM is too small to make meaningful statistical inference. Whether the ASM indication can be approved is deferred to the clinical reviewer's scientific judgment.
- The applicant's data support the efficacy of avapritinib in the treatment of adult patients with SM-AHN.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212608Orig1s006

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA number	212608
Submission type	Efficacy Supplement, S-006
Submission date	12/16/2020
Sponsor	Blueprint Medicines Corporation
Brand name	AVYAKIT
Generic name	Avapritinib
Dosage form	Tablets
Dosage strengths	200 mg orally once-daily
Proposed Indication	Treatment of adult patients with advanced systemic mastocytosis (AdvSM) (b) (4)
OCP Reviewer	Sudharshan Hariharan, Ph.D

EXECUTIVE SUMMARY

This memo provides summary review of the in vitro studies submitted as a part of the efficacy supplement, S-006, pertaining to metabolism and transporter characterization of avapritinib. A separate clinical pharmacology/pharmacometrics review addressing the proposed dosing recommendation for treatment of adult patients with advanced systemic mastocytosis (AdvSM) (b) (4) is filed by Drs. Konicki and Ma (DARRTS: 5/28/2021) .

Studies reviewed

- 2001071: Assessment of the metabolism of BLU-285 by human CYP3A4 and 3A5
- BLU-R0104: Identification of UGT enzymes involved in the metabolism of BLU-285 hydroxylamine and confirmation of the identity of the glucuronide observed in human plasma
- OPT-2019-223: Assessment of BLU-285 as a substrate of human OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp and BSEP

Summary of evaluation

Study 2001071

The purpose of this study is to determine if human cytochrome P450 (CYP) 3A5 metabolizes BLU-285[1]. The test systems used were pooled human liver microsomes (HLM), single donor HLM of various CYP3A5 genotypes (CYP3A5*1*1, *1*3, *3*3) and cDNA-expressed enzymes. Incubations with BLU-285 in the presence of 100 pmol/mL cDNA-expressed CYP3A4 and CYP3A5 for 45 min resulted in the metabolism of BLU-285 with 30% and 66% parent remaining and 55% and 76% parent remaining at 1 and 10 μM BLU-285, respectively. The incubations with 1 and 10 μM BLU-285 in the presence of 1 mg/mL pooled HLM or single donor HLM of various CYP3A5 genotypes (CYP3A5*1*1, *1*3, *3*3) for 45 min did not result in significant turnover of BLU-285 with ≥83% of parent remaining for all conditions tested. Formation of the M499 metabolite of BLU-285 was observed with all HLM preparations in presence of NADPH and represented <10% of the initial BLU-285 concentration. In summary, these results suggest that CYP3A5 is involved in the metabolism of avapritinib, albeit its contribution could be minimal.

Study BLU-R0104

The purpose of this study was to confirm the identity of the glucuronide of BLU-285 hydroxylamine observed in human plasma and identify the UGT enzymes involved in its formation. Incubations of BLU-285 with NADPH-

[1] BLU-285 = avapritinib

fortified HLM, recombinant CYP3A4 or human hepatocytes (HHep) led to the formation of its hydroxylamine metabolite M514. The identity of this metabolite was confirmed by comparison with an authentic standard of BLU-285 hydroxylamine, M514. Further incubation of 10 μM M514 in a panel of recombinant UGTs lead to the formation of metabolite M690 when incubated with rUGT1A3, 1A4 and 2B7. Based on the LC/MS/MS peak area ratio, the main enzyme involved in the glucuronidation of M514 appears to be UGT1A3.

Study OPT-2019-223
The purpose of the study is to determine whether BLU-285 is a substrate of human OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp and BSEP mediated transport. BLU-285 was tested at 1, 10, and 50 μM as well as at 10 μM in the presence of prototypical reference inhibitor of each transporter. BLU-285 assays were performed in the presence of 0.1% BSA to minimize the effects of nonspecific binding.

At all three concentrations of BLU-285 tested, less than a 2-fold difference in uptake between transporter-transfected cells and control cells was observed for human OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, and MATE2-K. Less than a 2-fold difference in uptake was observed between vesicles supplied with ATP compared to vesicles supplied with AMP for BSEP-expressing vesicles. The net flux ratios were below 2 for both BCRP and P-gp. All probe substrates showed sufficient transport and all reference inhibitors showed sufficient inhibition to meet the acceptance criteria set by the performing laboratory. These results suggest that BLU-285 is not a sensitive substrate to any of the tested transporters.

Conclusion
In summary, avapritinib is found to be metabolized to its hydroxylamine M514 first and subsequently M514 is metabolized either to the glucuronide conjugate M690 or to the oxidative deaminated product M499. The formation of these metabolites is found to be mediated by UGT1A3 and CYP3A4 (major)/CYP3A5 (minor), respectively.

In addition, avapritinib does not appear to be a sensitive substrate of OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp or BSEP.

Recommendation
The proposed labeling changes to section 12.3 to identify additional enzymes involved in the metabolism of avapritinib i.e., CYP3A5 and UGT1A3, is acceptable. Addition of language stating the lack of substrate affinity of avapritinib towards P-gp, BCRP, OAT1/3, OCT1/2, OATP1B1/3, MATE1/2-K and BSEP is acceptable.

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Office of Clinical Pharmacology Review

Application Type	Efficacy Supplement
Application Number(s)	NDA 212608 /S-006, S-007
Priority or Standard	Priority
Submit Date(s)	16 December 2020
Received Date(s)	16 December 2020
PDUFA Goal Date	16 June 2021
Established/Proper Name	Avapritinib
(Proposed) Trade Name	Ayvakit
Applicant	Blueprint Medicines Corporation
Dosage form	Tablets
Applicant proposed Dosing Regimen	200 mg orally once daily
Applicant Proposed Indication(s)/Population(s)	The treatment of adult patients with advanced systemic mastocytosis (AdvSM) (b) (4)
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s) (if applicable)	The treatment of adult patients with AdvSM. AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).
Recommended Dosing Regimen	200 mg orally once daily
Clinical Pharmacology/ Pharmacometrics Reviewer	Robyn Konicki, PharmD
Pharmacometrics Team Leader	Lian Ma, Ph.D.

Table of Contents

1. Executive Summary

The Clinical Pharmacology Section of the sNDA is supported by PK characterization, population PK (PopPK) analysis and exposure-response (E-R) analyses. The key review question focuses on the appropriateness of the proposed dosing regimen.

The Office of Clinical Pharmacology has reviewed the information contained in NDA 212608 /S-006, S-007. This NDA is approvable from a clinical pharmacology perspective. The review issues with specific recommendations and comments are summarized below:

Review Issues	**Recommendations and Comments**
Evidence of effectiveness	The primary evidence of effectiveness was demonstrated Studies BLU-285-2101 and BLU 285 2202, two multi-center, single-arm, open-label clinical trials.
General Dosing instructions	The recommended dosage is 200 mg orally once daily in patients with AdvSM. Continue treatment until disease progression or unacceptable toxicity. Administer orally on an empty stomach, at least 1 hour before or 2 hours after a meal.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose adjustment is needed in specific populations within patients with AdvSM.
Labeling	Generally acceptable. The review team has specific content and formatting change recommendations.

There is no additional Post-Marketing Requirement (PMR) or Post-Marketing Commitment (PMC) from a clinical pharmacology perspective.

2. Summary of Clinical Pharmacology Assessment

2.1 Pharmacology and Clinical Pharmacokinetics

Avapritinib is a tyrosine kinase inhibitor that targets KIT D816V, PDGFRA and PDGFRA D842 mutants as well as multiple KIT exon 11, 11/17 and 17 mutants.

Avapritinib C_{max} and AUC increased proportionally over the dose range of 200 mg to 400 mg once daily in patients with SM. Steady state concentration of avapritinib was reached by day 15 following daily dosing.

For additional information on general pharmacology and PK characteristics of Avapritinib, refer to the multi-disciplinary review for the original NDA 212608 submission (DARRTS ID: 4543562).

2.2 General Dosing and Therapeutic Individualization

General Dosing
The recommended dosage is 200 mg orally once daily in patients with AdvSM. Continue treatment until disease progression or unacceptable toxicity. In case of severe toxicity in patients with AdvSM, stepwise dose reductions to 100 mg, 50 mg, and 25 mg QD are recommended.

Administer orally on an empty stomach, at least 1 hour before or 2 hours after a meal.

Therapeutic Individualization

No therapeutic individualization is recommended in patients with AdvSM.

Outstanding Issues

There are no outstanding clinical pharmacology issues.

3. Comprehensive Clinical Pharmacology Review

3.1 General Pharmacology and Pharmacokinetic Characteristics

Only new data related to the current submission are summarized below. For additional information on general pharmacology and PK characteristics of Avapritinib, refer to the multi-disciplinary review for the original NDA 212608 submission (DARRTS ID: 4543562).

Avapritinib C_{max} and AUC increased proportionally over the dose range of 200 mg to 400 mg once daily in patients with SM. Steady state concentration of avapritinib was reached by day 15 following daily dosing. Steady state pharmacokinetic parameters per recommended dosing regimen for AdvSM are described in **Table 1**.

Table 1. Steady State Pharmacokinetic Parameters of Avapritinib

Dosing Regimen	**200 mg once daily (AdvSM)**
Geometric Mean (CV%) steady state C_{max} (ng/mL)	377 (62%, n=18)
Geometric Mean (CV%) steady state $AUC_{0\text{-}24h}$ (h•ng/mL)	6600 (54%, n=16)
Mean accumulation ratio	6.41

CV = coefficient of variation

Absorption

The median time to peak concentration (T_{max}) ranged from 2 to 4 hours following single doses of avapritinib 30 mg to 300 mg in patients with SM.

Distribution

The mean (CV%) apparent volume of distribution of avapritinib was 1900 L (43%) at 200 mg in patients with SM.

Elimination

The mean plasma elimination half-life of avapritinib was 20 hours to 39 hours following single doses of avapritinib 30 mg to 400 mg in patients with SM. The steady state mean (CV%) apparent oral clearance of avapritinib was 40.3 L/h (86%) at 200 mg once daily in patients with SM.

3.2 Clinical Pharmacology Questions

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimen of 200 mg QD is effective and shows to have a manageable safety profile in patients with AdvSM, including patients with MCL. It is also supported by the exposure-response findings of efficacy and safety from Studies BLU-285-2101 and BLU-285-2202.

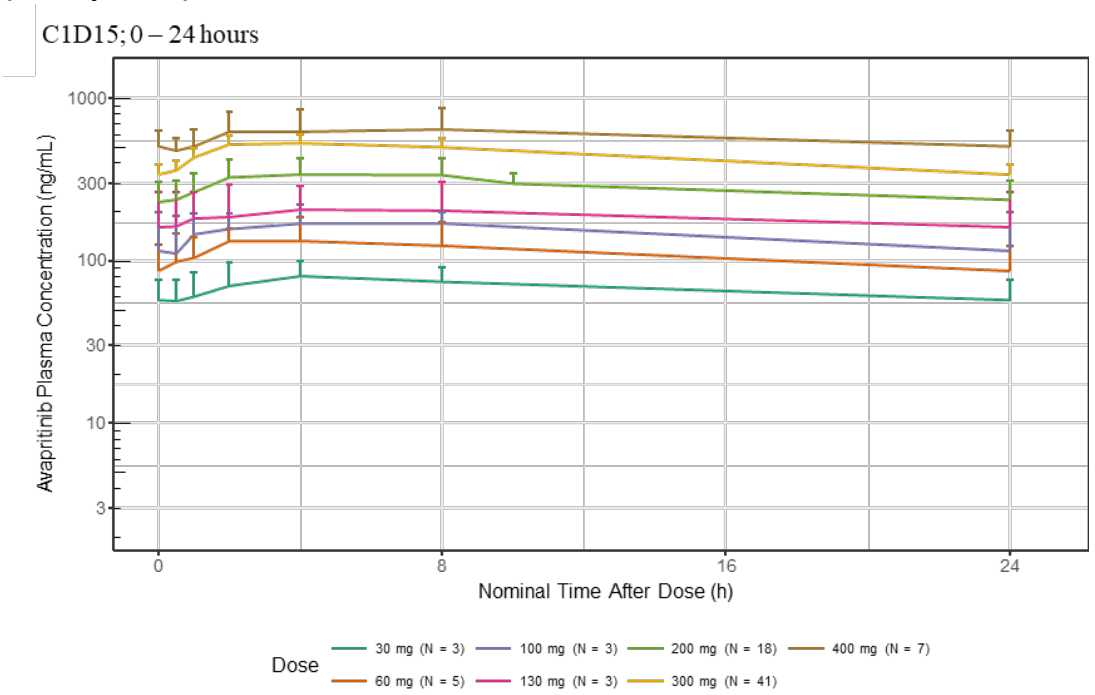
Dose Selection Rationale

200 mg QD was determined to be the starting dose for Study BLU-285-2202 based on efficacy, PK, and safety data in Study BLU-285-2101.

In patients with AdvSM, the RP2D was initially identified in Study BLU-285-2101 as 300 mg QD. After further evaluation of efficacy, PK, and long-term safety data for avapritinib, 200 mg QD was determined to be a more appropriate starting dose for Part 2 (expansion) of Study BLU-285-2101 and as the starting dose for Study BLU-285-2202.

In addition, mean concentration at steady state was above predicted IC90 for inhibition of KIT D816V in patient-derived xenograft model (189 ng/mL) for doses ≥ 200 mg QD over the entire dosing interval (**Figure 1**).

Figure 1. Mean (+SD) Plasma Concentration-Time Profiles of Avapritinib on C1D15 (Steady-State)



BLQ data (< 2 ng/mL) are excluded. Lines are coloured by dose level. For C1D15 the predose concentration (C1D14) was used as the nominal 24 h concentration. Y-axis is on a log scale. N = number of subjects in each dose cohort.
BLQ = below limit of quantification; C1D15 = cycle 1 day 15; SD = standard deviation.
Source: Figure 4 from Applicant's NCA PK Report for Study BLU-285-2101

Exposure-Response Relationships

Based on exposure and efficacy data from Studies BLU-285-2101 and BLU-285-2202 (n=84), higher avapritinib exposure was significantly associated with faster time to response (TTR) over the dose range of 30 mg to 400 mg once daily in subjects with AdvSM. TTR was shorter with higher exposure in the AdvSM subtypes of both ASM (n = 5) and MCL (n = 8), but these relationships were not statistically significant. This may be due to the relatively small sample sizes. In subjects with SM-AHN (n = 40), there was a significant relationship between shorter TTR and higher exposure. Refer to Section 4.2.2.1 for detailed information.

Based on the data from four clinicals trials conducted in patients with advanced malignancies and SM, including Studies BLU-285-2101 and BLU-285-2202, higher exposure was associated with increased risk of grade ≥3 treatment-emergent adverse events (TEAEs), any grade pooled cognitive AEs, grade ≥2 pooled cognitive AEs, and grade ≥2 pooled edema AEs over the dose range of 30 mg to 400 mg once daily. Subjects with SM had shorter time to event (TTE) for grade ≥3 TEAEs compared to subjects with GIST. The SM-AHN and MCL subtypes were associated with higher risk and shorter TTE for grade ≥3 TEAEs compared to other SM subtypes and GIST. There were also trends where subjects with SM-AHN had a slower onset of any grade

pooled cognitive AEs and subjects with SM-AHN or MCL had a slower onset of grade ≥2 pooled cognitive AEs compared to subjects with GIST. See Section 4.2.1.1 for detailed information.

The E-R analysis for safety did not show a clear relationship between avapritinib exposure and the risk of intracranial bleeding AEs (all grades). However, lower platelet counts (both at baseline and during treatment) were identified to be associated with an increased risk of intracranial bleeding AEs. Subjects with a baseline platelet count of < 50 x 10^9/L (n = 11 subjects with SM, n = 0 subjects with GIST) had a significantly higher risk of intracranial bleeding compared to subjects with baseline platelet count of ≥50 x 10^9/L (n=514). See Section 4.2.1.4 for detailed information.

In summary, the proposed dosing regimen of 200 mg QD with a platelet count of ≥50 x 10^9/L is supported by the overall favorable benefit/risk profile for the general patient population with AdvSM.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. A dose adjustment for subpopulations based on intrinsic factors is not necessary.

No clinically significant differences in the PK of avapritinib were observed based on age (18 to 90 years), sex, race (White, Black, or Asian), body weight (39.5 to 156.3 kg), mild to moderate renal impairment (CrCl 30 to 89 mL/min estimated by Cockcroft-Gault), or mild (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1 to 1.5 times ULN and any AST) to moderate (total bilirubin > 1.5 to 3 times ULN and any AST) hepatic impairment. The effect of severe renal impairment (CrCl 15 to 29 mL/min), end-stage renal disease (CrCl < 15 mL/min), or severe hepatic impairment (total bilirubin > 3 times ULN and any AST) on the PK of avapritinib is unknown.

4. Appendix (Pharmacometric Review)

4.1 Population PK Analysis

The applicant's population pharmacokinetics (popPK) analysis is acceptable. The goodness-of-fit plots and the visual predictive checks indicate that the final avapritinib popPK model is adequate in characterizing the pharmacokinetic (PK) profile of avapritinib in adults with advanced systemic mastocytosis (AdvSM), which includes the SM subtypes of aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasms (SM-AHN), and mast cell leukemia (MCL). The applicant's analyses were verified by the reviewer, with no significant discordance identified.

4.1.1 Introduction

The primary objectives of applicant's analysis were to:

- Evaluate and update the previously developed population PK model for avapritinib in healthy volunteers and patients with gastrointestinal stromal tumors (GIST) to describe the plasma concentration-time data from clinical studies BLU-285-2101 and BLU-285-2202 in patients with AdvSM.
- Quantify population PK parameters, including typical parameter values and random inter-individual variability (IIV) and residual variability.
- Identify and quantify covariate effects which describe variability in the PK of avapritinib.

4.1.2 Applicant's Population PK Analysis

Data

The final avapritinib NONMEM data file for analysis contained 8314 PK observations from 487 subjects. The study design, study population, and timing of blood samples varied among the 6 clinical studies that contributed data to the population PK analysis. Brief descriptions of these 6 studies are presented in **Table 2**. Summary statistics of the baseline demographic covariates in the analysis dataset are presented in **Table 3**.

Table 2. Summary of Clinical Studies Included in Population PK Analysis

STUDY	Subjects	Description	Subject Status	Dose(s)
BLU-285-0101	30	Single-dose crossover study to evaluate the relative bioavailability (tablet vs capsule)	Healthy volunteers	200 mg
BLU-285-0102	30	Single-dose crossover study to evaluate the effect of food on PK (only fasting subjects were included in population PK analysis)	Healthy volunteers	200 mg
BLU-285-0105	62	Single-dose crossover, bioequivalence study (1 x 400 mg tablet versus 4 x 100 mg tablets)	Healthy volunteers	400 mg

STUDY	Subjects	Description	Subject Status	Dose(s)
BLU-285-1101	221	Phase 1 open-label, first-in-human study	GIST and other relapsed or refractory solid tumors	Dose-Escalation: 30 to 600 mg once daily; Dose-Expansion: 400 or 300 mg once daily
BLU-285-2101	86	Phase 1 open-label, first-in-human study	Systemic mastocytosis and relapsed or refractory myeloid malignancies	Dose-Escalation: 30 to 400 mg once daily; Dose-Expansion: 300 or 200 mg once daily
BLU-285-2202	58	Phase 2 open-label, single arm study to evaluate efficacy and safety	Systemic mastocytosis	200 mg once daily

Source: Reviewer Analysis of Applicant's Datasets

Table 3. Summary of Baseline Characteristics in the Population PK Dataset

Covariate	Statistic	Healthy volunteers	GIST	SM	Overall
	n	122	221	144	487
Systemic Mastocytosis Subtype					
Aggressive Systemic Mastocytosis	n (%)	N/A	N/A	17 (11.8%)	17 (3.5%)
Indolent Systemic Mastocytosis	n (%)	N/A	N/A	14 (9.7%)	14 (2.9%)
Mast Cell Leukemia	n (%)	N/A	N/A	23 (16.0%)	23 (4.7%)
Smoldering Systemic Mastocytosis	n (%)	N/A	N/A	2 (1.4%)	2 (0.4%)
Systemic Mastocytosis with Associated Hematological Malignancy	n (%)	N/A	N/A	87 (60.4%)	87 (17.9%)
Not SM	n (%)	N/A	N/A	1 (0.7%)	1 (0.2%)
Dose					
30 mg once daily	n (%)	0 (0 %)	6 (2.7 %)	3 (2.1 %)	9 (1.8 %)
60 mg once daily	n (%)	0 (0 %)	6 (2.7 %)	6 (4.2 %)	12 (2.5 %)
90 mg once daily	n (%)	0 (0 %)	6 (2.7 %)	0 (0 %)	6 (1.2 %)
100 mg once daily	n (%)	0 (0 %)	0 (0 %)	5 (3.5 %)	5 (1 %)
130 mg once daily	n (%)	0 (0 %)	0 (0 %)	3 (2.1 %)	3 (0.6 %)
135 mg once daily	n (%)	0 (0 %)	6 (2.7 %)	0 (0 %)	6 (1.2 %)
200 mg once daily	n (%)	60 (49.2 %)	6 (2.7 %)	77 (53.5 %)	143 (29.4 %)
300 mg once daily	n (%)	0 (0 %)	141 (63.8 %)	43 (29.9 %)	184 (37.8 %)
400 mg once daily	n (%)	62 (50.8 %)	50 (22.6 %)	7 (4.9 %)	119 (24.4 %)
Formulation					
Subjects with PK data for tablet formulation	n (%)	15 (12.3 %)	123 (55.7 %)	34 (23.6 %)	172 (35.3 %)
Subjects with PK data for capsule formulation	n (%)	107 (87.7 %)	101 (45.7 %)	110 (76.4 %)	318 (65.3 %)
Sex					
Male	n (%)	108 (88.5 %)	138 (62.4 %)	77 (53.5 %)	323 (66.3 %)
Female	n (%)	14 (11.5 %)	83 (37.6 %)	67 (46.5 %)	164 (33.7 %)
Race					
White	n (%)	95 (77.9 %)	160 (72.4 %)	126 (87.5 %)	381 (78.2 %)
Black or African-American	n (%)	16 (13.1 %)	9 (4.1 %)	1 (0.7 %)	26 (5.3 %)

Covariate	Statistic	Healthy volunteers	GIST	SM	Overall
Asian	n (%)	2 (1.6 %)	20 (9 %)	3 (2.1 %)	25 (5.1 %)
Other	n (%)	9 (7.4 %)	32 (14.5 %)	14 (9.7 %)	55 (11.3 %)
Age (years)	Mean (SD)	38.6 (8.6)	59.7 (10.9)	64.6 (11.8)	55.9 (14.7)
	Median	38	62	67	57
	Min - Max	18 - 55	29 - 90	31 - 88	18 - 90
Actual Body Weight (kg)	Mean (SD)	80.4 (11.8)	77.1 (21.3)	74.2 (16.4)	77.1 (18)
	Median	78.7	75	71	75.9
	Min - Max	52.3 - 107.5	39.5 - 156.3	42.5 - 115.8	39.5 - 156.3
Lean Body Weight (kg)	Mean (SD)	58 (8.4)	53.7 (13.1)	51.5 (11.8)	54.1 (11.9)
	Median	58.9	55.9	51.9	55.6
	Min - Max	39.1 - 76.3	28 - 85.5	29.6 - 76.7	28 - 85.5
BSA (m^2)	Mean (SD)	1.9 (0.2)	1.9 (0.3)	1.8 (0.2)	1.9 (0.2)
	Median	1.9	1.9	1.8	1.9
	Min - Max	1.5 - 2.4	1.3 - 2.6	1.3 - 2.4	1.3 - 2.6
Albumin (g/L)	Mean (SD)	45.2 (2.4)	37.6 (5.6)	38.5 (6.3)	39.8 (6.1)
	Median	45	38	40	41
	Min - Max	40 - 51	19 - 49.5	12.7 - 50	12.7 - 51
Alkaline phosphatase (IU/L)	Mean (SD)	77.3 (21.8)	119.8 (95)	249.1 (253.4)	147.4 (166.5)
	Median	73	87	152	91
	Min - Max	43 - 128	32 - 608	27 - 1747	27 - 1747
Alanine aminotransferase (IU/L)	Mean (SD)	25.3 (10.9)	26.4 (20.2)	22.4 (19.8)	24.9 (18.2)
	Median	23	21	16	21
	Min - Max	Jul-56	4 - 215	3 - 185	3 - 215
Aspartate transaminase (IU/L)	Mean (SD)	22.7 (6.4)	30.8 (16.7)	17.7 (10.4)	24.9 (14.2)
	Median	22	27	15	22
	Min - Max	Nov-53	8 - 135	May-61	5 - 135
Bilirubin (µmol/L)	Mean (SD)	9.9 (4.1)	10.8 (6.1)	12.7 (8.2)	11.1 (6.5)
	Median	8.6	9.9	10.3	9.9
	Min - Max	3.4 - 23.9	1.7 - 35.9	1.7 - 52	1.7 - 52
Creatinine Clearance (mL/min)	Mean (SD)	126.6 (23.9)	97.4 (40.1)	91.9 (36.6)	103.1 (38.1)
	Median	124	89.8	85.9	99.7
	Min - Max	77.7 - 212.2	27.6 - 328.7	34.2 - 214.9	27.6 - 328.7
Estimated glomerular filtration rate (mL/min/1.73m^2)	Mean (SD)	97.3 (15.4)	86.6 (26.8)	87.7 (30.6)	89.6 (26)
	Median	93.7	83.1	86	88.2
	Min - Max	63.6 - 138.8	33.2 - 194.4	41.9 - 273.1	33.2 - 273.1
Renal Function Category (eGFR)					
Normal	n (%)	80 (65.6 %)	82 (37.1 %)	61 (42.4 %)	223 (45.8 %)
Mild Dysfunction	n (%)	42 (34.4 %)	110 (49.8 %)	62 (43.1 %)	214 (43.9 %)
Moderate Dysfunction	n (%)	0 (0 %)	29 (13.1 %)	21 (14.6 %)	50 (10.3 %)
Severe Dysfunction	n (%)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
End-Stage Renal Disease	n (%)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
Hepatic Function Category					
Normal	n (%)	121 (99.2 %)	163 (73.8 %)	118 (81.9 %)	402 (82.5 %)
Mild Dysfunction	n (%)	1 (0.8 %)	52 (23.5 %)	19 (13.2 %)	72 (14.8 %)
Moderate Dysfunction	n (%)	0 (0 %)	6 (2.7 %)	7 (4.9 %)	13 (2.7 %)
Severe Dysfunction	n (%)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
Liver Transplant	n (%)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
PPI Use					

Covariate	Statistic	Healthy volunteers	GIST	SM	Overall
No PPI use ≥14 days prior to any PK samples	n (%)	122 (100 %)	133 (60.2 %)	82 (56.9 %)	337 (69.2 %)
PPI use between 5-14 days prior to ≥1 PK sample	n (%)	0 (0 %)	11 (5 %)	3 (2.1 %)	14 (2.9 %)
PPI use for ≥5 days prior to ≥1 PK sample	n (%)	0 (0 %)	77 (34.8 %)	59 (41 %)	136 (27.9 %)
H2RA Use					
H2RA use for ≥5 days prior to ≥1 PK sample	n (%)	0 (0 %)	23 (10.4 %)	93 (64.6 %)	116 (23.8 %)
Use of CYP3A4 Inducers					
CYP3A4 inducer use for ≥5 days prior to ≥1 PK sample	n (%)	0 (0 %)	24 (10.9 %)	56 (38.9 %)	80 (16.4 %)
Use of CYP3A4 Inhibitors					
CYP3A4 inhibitor use for ≥5 days prior to ≥1 PK sample	n (%)	0 (0 %)	26 (11.8 %)	15 (10.4 %)	41 (8.4 %)

eGFR = estimated glomerular filtration rate; GIST = Gastrointestinal Stromal Tumor; H2RA = H2 receptor antagonist; N/A = not applicable; PK = pharmacokinetic; PPI = proton pump inhibitor; SM = systemic mastocytosis.
Source: Reviewer Analysis of Applicant's Datasets

Base Model

The base model was developed from a previous popPK covariate model for healthy volunteers and patients with GIST. The base model retained the same structure as the previous covariate model, which was a two-compartment PK model with first-order elimination and additional absorption transit compartments (4 transit compartments for tablet absorption and 5 transit compartments for capsule absorption). Covariate effects from the previous model (lean body weight effect on apparent central volume of distribution [V/F], effect of tablet versus capsule formulation on rate of transit absorption [KTR], decreased relative bioavailability [F1] for GIST patients, and decreased F1 for patients with proton pump inhibitor [PPI] use) were also retained in the base model. PPI use was defined as five or more consecutive days of use before PK sampling.

The base model included additional covariate effects related to the SM subject status. Patients with SM (versus GIST or healthy volunteers) had a proportional shift effect on CL/F as well as a time-dependent decrease in CL/F modeled with an Emax function. Subjects with SM also had a covariate effect on KTR. The F1 was estimated for subjects with SM and for subjects with GIST separately.

Inter-individual variability (IIV) in the base model was applied to the parameters of CL/F, V/F, KTR with a correlation between BSV on CL/F and V/F. Between-occasion variability was applied to F1 and KTR for the occasions of Cycle 1 Day 1 post-dose PK sampling, Cycle 1 Day 15 post-dose PK sampling, and PK sampling at any other time point. Three separate residual unexplained variability terms were estimated for Study BLU-285-0101 + BLU-285-0102 (healthy volunteers), Study BLU-285-0105 (healthy volunteers), Study BLU-285-2101 + BLU-285-2202 (patients with SM), and Study BLU-285-1101 (patients with GIST).

Covariate Analysis

The lean body weight effect on V/F and the PPI comedication effect on F1 were not reevaluated in the covariate analysis, and their values were fixed to the base model final estimates. Covariates that were assessed for inclusion in the final population PK model are listed in **Table 4**.

Table 4. Covariates Assessed in the Population Pharmacokinetic Analysis

Covariate	Code	Value	Parameters
Age at baseline (yr)	AGE	Continuous	CL/F, Vc/F
Total body weight at baseline (kg)	WT	Continuous	CL/F, Vc/F
[a]Lean body weight at baseline (kg)	LBW	Continuous	CL/F, Vc/F
[b]Creatinine clearance at baseline (mL/min)	CRCL	Continuous	CL/F
[c]Estimated glomerular filtration rate at baseline (mL/min/1.73 m^2)	EGFR	Continuous	CL/F
Alanine aminotransferase at baseline (U/L)	ALT	Continuous	CL/F
Aspartate aminotransferase at baseline (U/L)	AST	Continuous	CL/F
Bilirubin at baseline (µmol/L)	BILI	Continuous	CL/F
Albumin at baseline (g/L)	ALB	Continuous	CL/F
Sex	SEX	Categorical	CL/F, Vc/F
Race	RACE	Categorical	CL/F, Vc/F
Concomitant CYP3A4 inhibitor	CYPINB	Categorical	CL/F, F
Concomitant CYP3A4 inducer	CYPIND	Categorical	CL/F, F
Concomitant PPI	PPI	Categorical	CL/F, KTR, F
Concomitant H2RA	H2RA	Categorical	CL/F, KTR, F
Formulation (capsule, tablet)	FORM	Categorical	CL/F, KTR, F
Disease Subpopulation (HV / GIST / SM)	DSSTAT	Categorical	CL/F, Vc/F, KTR, F

CL/F = apparent clearance; F = bioavailability; GIST = gastrointestinal stromal tumor; H2RA = H2 receptor antagonist; HV = healthy volunteer; KTR = absorption rate constant; PPI = proton pump inhibitor; SM = systemic mastocytosis; Vc/F = apparent central volume of distribution.
Source: Table 12 from Applicant's Population PK Report

Final Model

The Applicant's parameter estimates for the final model are listed in **Table 5**.

Table 5. Applicant Parameter Estimates for the Final Population PK Model

Parameter Name	Estimated Value (%RSE)
Apparent Clearance (CL/F, L/h)	15.9 (2.8)
Maximum Time-dependent Decrease of CL/F for SM Patients (Fold)	0.381 (10.2)
Time at Half Maximum Decrease of CL/F for SM Patients (h)	211 (26.8)
Covariate Effect of SM on CL/F (Fold)	1.34 (5.4)
Covariate Effect of Black Race on CL/F (Fold)	1.25 (5.7)
Covariate Effect of Asian Race on CL/F (Fold)	0.835 (20.9)
Covariate Effect of Female Sex on CL/F (Fold)	0.924 (5.7)
Apparent Central Volume of Distribution (Vc/F, L)	987 (2.4)

Covariate Effect of LBW on Vc/F	0.37 FIX*
Apparent Peripheral Volume of Distribution (Vp/F, L)	233 (8.1)
Apparent Inter-compartmental Clearance (Q/F, L/h)	13.7 (17.9)
Rate of Transit Absorption for Tablets (KTRT, 1/h)	3.31 (1.4)
Rate of Transit Absorption for Capsules (KTRC, 1/h)	3.79 (2.3)
Covariate Effect of SM on KTR (Fold)	1.23 (3.2)
Covariate Effect of PPI Use on KTR (Fold)	0.85 (3.4)
Relative Bioavailability for SM Patients (Fold)	0.656 (5.1)
Relative Bioavailability for GIST Patients (Fold)	0.818 (3.3)
Covariate Effect of PPI Comedication on F (Fold)	0.769 FIX*
Between Subject Variability for CL/F (%)	42.1 (4.4)
Between Subject Variability for Vc/F (%)	47.8 (5.0)
Correlation between CL/F-Vc/F	0.606 (6.9)
Between Subject Variability for Rate of Transit Absorption (%)	26.8 (12.3)
Between-occasion Variability for Bioavailability (%)	25.1 (4.4)
Between-occasion Variability for Rate of Transit Absorption (%)	30.7 (6.3)
Residual Unexplained Variability for Study BLU-285-0101/BLU-285-0102 (Proportional) (%)	17.1 (6.5)
Residual Unexplained Variability for Study BLU-285-0105 (Proportional) (%)	18.4 (4.6)
Residual Unexplained Variability for Study BLU-285-2101/BLU-285-2202 (Proportional) (%)	23.1 (4.2)
Residual Unexplained Variability for Study BLU-285-1101 (Proportional) (%)	26.2 (4.0)

GIST = gastrointestinal stromal tumor; h = hours; KTR = transit rate constant; LBW = lean body weight; PPI = proton pump inhibitor; SM = systemic mastocytosis.
Source: Table 13 from Applicant's Population PK Report

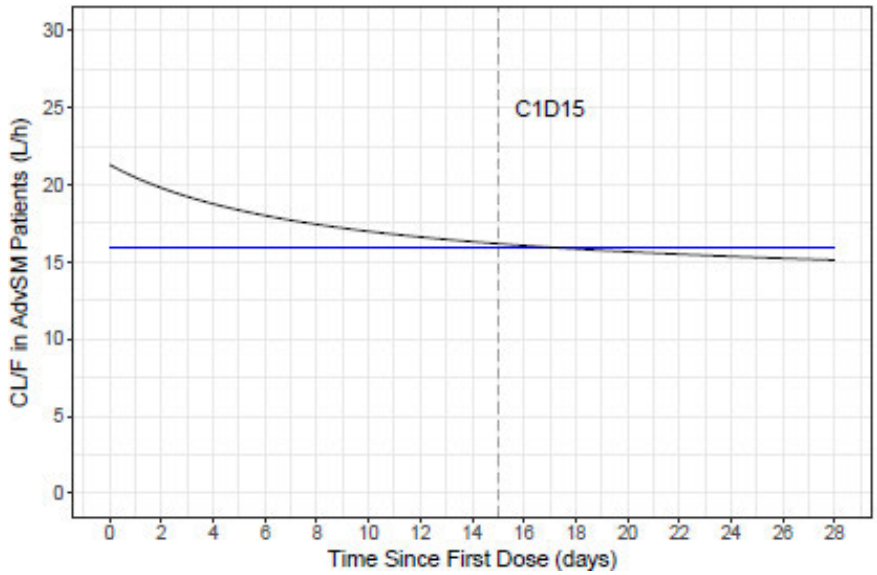
The final model retained the same structure as the base model. The final model contained all of the parameters included in the base model as well as a small number of new fixed-effect parameters. The lean body weight effect on V/F and PPI comedication effect on F1 were included in the final model with values fixed to the base model final estimates. The parameters effects estimated by both the base model and final model included an SM proportional shift effect on CL/F, SM time-dependent effect on CL/F using an Emax model , SM effect on KTR, SM effect on F1, and GIST effect on F1. The final model also estimated parameter effects of race on CL/F (where Black subjects had increased CL/F and Asian subjects had decreased CL/F), female sex on CL/F, and PPI use on KTR.

The typical value of CL/F over the first cycle is shown in **Figure 2** for each subject status (SM, GIST, or healthy volunteer). The time-dependent effect on CL/F resulted in a typical value of CL/F on Cycle 1 Day 1 (C1D1) that was 34% higher in subjects with SM compared to subjects with GIST and healthy volunteers. Steady-state was achieved by Cycle 1 Day 15 (C1D15), and the typical value of CL/F at steady-state was similar for all subjects regardless of subject status. The CL/F decreased over time by a maximum of 38.1% in subjects with SM.

The time-dependent decrease in CL/F was similar to the apparent biphasic elimination for subjects with SM demonstrated in the noncompartmental analysis (NCA) of Study BLU-285-2101. The NCA found that geometric mean CL/F was higher on C1D1 compared to C1D15 at all dose levels.[1] In subjects with SM who received 300 mg QD, the geometric mean

CL/F was 74.8% higher on C1D1 (46.5 L/h, n=15) compared to C1D15 (26.6 L/h, n=40). In subjects with SM who received 200 mg QD, the geometric mean CL/F was 12.5% higher on C1D1 (33.4 L/h, n=12) compared to C1D15 (29.7 L/h, n=7). Small and uneven sample sizes made it difficult to determine the exact comparison between C1D1 and C1D15 in the Study BLU-285-2101 NCA.

Figure 2. Representation of the Model Predicted Apparent Clearance in Patients with SM Versus Healthy Volunteers or Patients with GIST

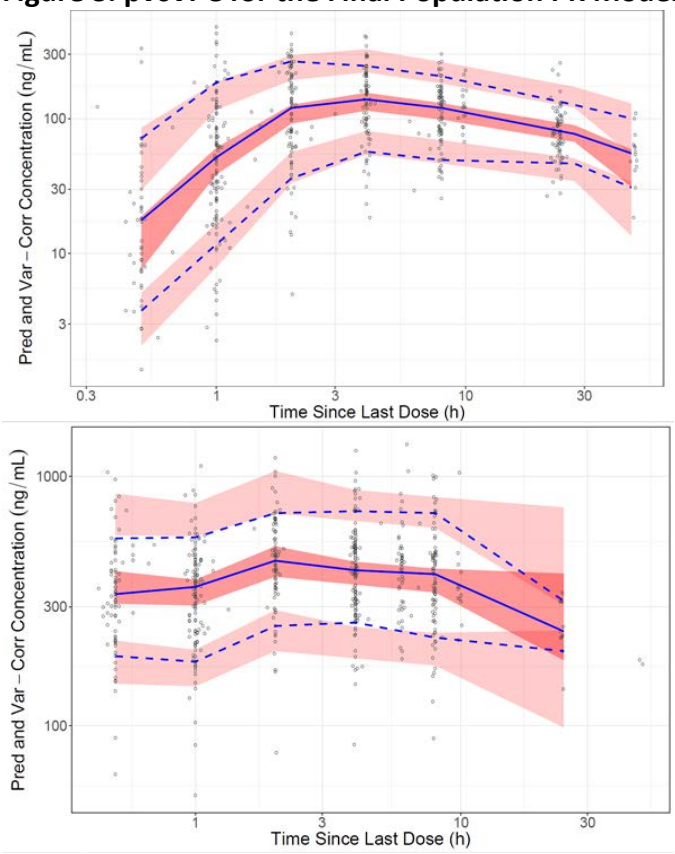


Black line represents the typical CL/F of patients with SM as estimated from the final model, and the blue line represents the typical CL/F of healthy volunteers or patients with GIST (15.9 L/h). Dashed vertical line denotes time at Cycle 1, Day 15.
AdvSM = advanced systemic mastocytosis; C1D15 = Cycle 1 Day 15; CL/F = apparent clearance;
GIST = gastrointestinal stromal tumor; SM = systemic mastocytosis.
Source: Figure 28 from Applicant's Population PK Report

The final model estimated the same between-subject variability (BSV) parameters, between-occasion variability parameters, and residual unexplained variability parameters as the base model. BSV was applied to the parameters of CL/F, V/F, KTR with a correlation between BSV on CL/F and V/F. Between-occasion variability was applied to F1 and KTR for the occasions of Cycle 1 Day 1 post-dose PK sampling, Cycle 1 Day 15 post-dose PK sampling, and PK sampling at any other time point. Four separate residual unexplained variability terms were estimated for Study BLU-285-0101 + BLU-285-0102 (healthy volunteers), Study BLU-285-0105 (healthy volunteers), Study BLU-285-2101 + BLU-285-2202 (patients with SM), and Study BLU-285-1101 (patients with GIST).

The prediction-and-variability-corrected Visual Predictive Check (pvcVPC) plots for subjects with SM indicate acceptable prediction of avapritinib PK, as shown in **Figure 3** for Cycle 1 Day 1 (top) and for Cycle 1 Day 15 (bottom).

Figure 3. pvcVPC for the Final Population PK Model (Patients with SM)



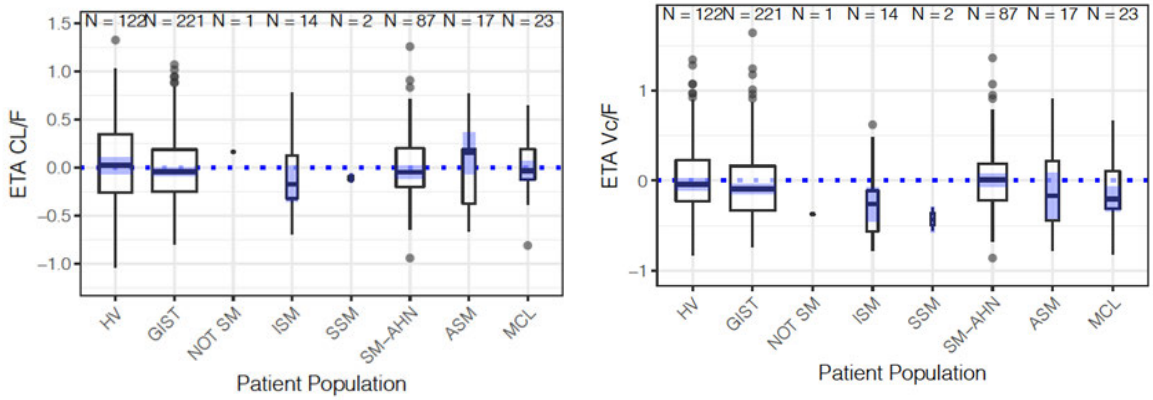
Top: Cycle 1 Day 1; Bottom: Cycle 1 Day 15 (steady-state). Open circles = individual observed, dashed blue lines = observed 10th & 90th percentiles of the observed data, solid blue line = observed median concentration, shaded red area = 95% prediction interval around the model predicted 10th, 50th, & 90th percentile. Log-log scale is used.

pvcVPC = prediction-and-variability-corrected visual predictive check; SM = systemic mastocytosis.

Source: Figure 46 and Figure 47 from Applicant's Population PK Report

The Applicant investigated potential differences in avapritinib PK according to SM disease subtype and found no clinically significant trends. Neither the IIV on apparent clearance nor the IIV on apparent central volume of distribution differed significantly by SM subtype, as shown in **Figure 4.**

Figure 4. Box plot of Final Model Inter-Individual Variability on Apparent Clearance and on Apparent Central Volume of Distribution by Systemic Mastocytosis Disease Subtype



ASM = aggressive systemic mastocytosis; CL/F = apparent clearance; GIST = gastrointestinal stromal tumor; HV = healthy volunteer; ISM = indolent systemic mastocytosis; MCL = mast cell leukemia; SM = systemic mastocytosis; SM-AHN = systemic mastocytosis with associated hematological neoplasm; SSM = smoldering systemic mastocytosis; Vc/F = apparent volume of distribution.
Source: Figure 2 and Figure 4 from Applicant's Response to FDA 23 February 2021 Information Request

Reviewer Comments

There was no discordance between the Applicant's final model results and the Reviewer's final model results. The Reviewer's parameter estimates for the final model are listed in ***Table 6****.*

Two fixed-effects parameters, covariate effect of Asian race on CL/F and covariate effect of female sex on CL/F, had 95% confidence intervals (CI) that contained the null hypothesis of 1.0 in both the Applicant's and Reviewer's final model results. In the Reviewer's results, the effect of Asian race on CL/F had a 95% CI of 0.492 - 1.178 and the effect of female sex on CL/F had a 95% CI of 0.821 - 1.027. The 95% CI for the effect of Asian race may be as wide as it is due to the small sample size (25 Asian subjects out of 487 total subjects in the popPK dataset). Because the 95% CIs contain the null hypothesis, female sex and Asian race may not significantly affect avapritinib PK.

The goodness of fit (GOF) plots for the final model are in ***Figure 5****. Stratified goodness of fit plots are displayed by subject status (healthy volunteer, GIST, or SM) in* ***Figure 6*** *and indicate acceptable fit with no significant differences in fit for any group.*

Overall, based on the GOF plots, the final population PK model appears adequate in characterizing the PK profile of avapritinib in healthy adult volunteers, adult subjects with GIST, and adult subjects with SM.

Table 6. Independent Review Final Parameter Estimates for the Final Population PK Model

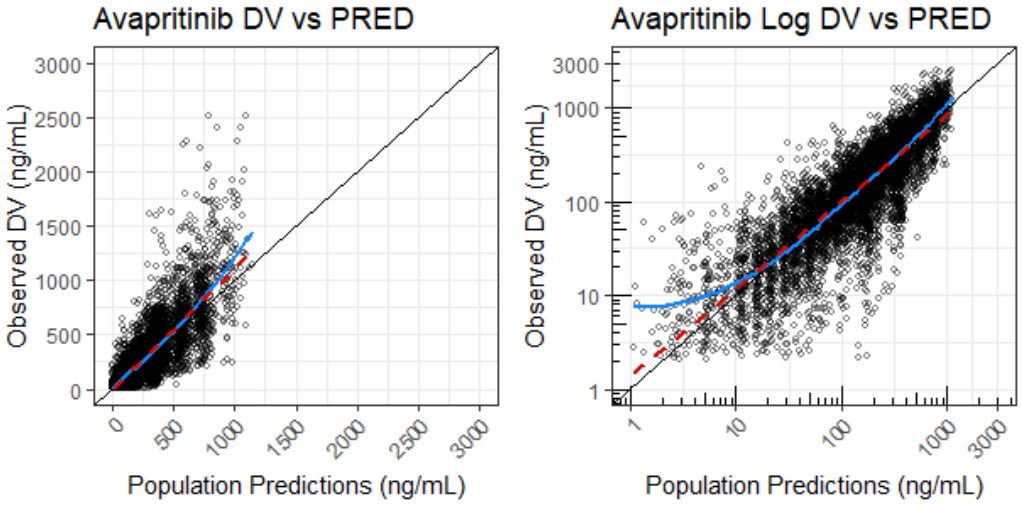
Fixed-Effects Parameters					
Parameter Name	**Description (units)**	**Estimate**	**SE**	**RSE (%)**	**Confidence Interval (95%)**
tvKTRT	Typical value of transit absorption constant for tablets (1/h)	3.31	0.0469	1.417	3.218 - 3.402
tvKTRC	Typical value of transit absorption constant for	3.79	0.0888	2.343	3.616 - 3.964

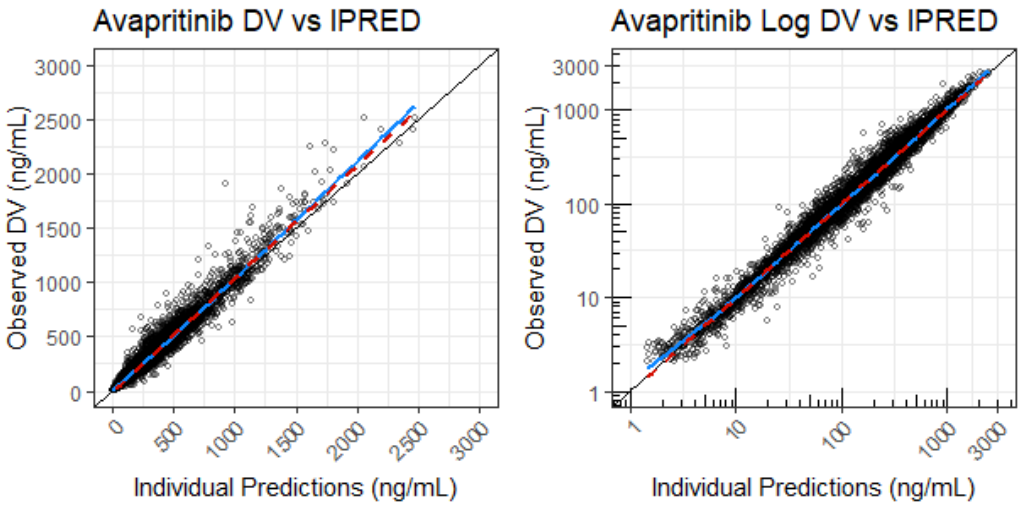
	capsules (1/h)				
tvCL	Typical value of clearance (L/h)	15.9	0.433	2.723	15.05 - 16.75
tvV	Typical value of central volume of distribution (L)	988	22.4	2.267	944.1 - 1032
SM_F	Effect of SM subject status on relative bioavailability	0.656	0.0337	5.137	0.5899 - 0.7221
tvV2	Typical value of peripheral volume of distribution (L)	233	19.2	8.24	195.4 - 270.6
tvQ	Typical value of peripheral clearance (L/h)	13.7	2.55	18.61	8.702 - 18.7
LBWT_V	Effect of lean body weight on central volume of distribution (FIXED)	0.37 (FIXED)	-	-	-
PPI_F	Effect of PPI comedication on relative bioavailability (FIXED)	0.769 (FIXED)	-	-	-
IMAX	Maximum time-dependent decrease of apparent clearance for subjects with SM	0.381	0.0391	10.26	0.3044 - 0.4576
IT50	Time of half-maximum decrease of apparent clearance for subjects with SM (h)	211	56.7	26.87	99.87 - 322.1
SM_KTR	Effect of SM subject status on transit rate constant	1.23	0.0394	3.203	1.153 - 1.307
SM_CL	Effect of SM subject status on clearance	1.34	0.0746	5.567	1.194 - 1.486
GIST_F	Effect of GIST subject status on relative bioavailability	0.818	0.0266	3.252	0.7659 - 0.8701
PPI_KTR	Effect of PPI use on transit rate constant	0.85	0.0287	3.376	0.7937 - 0.9063
RACEBC	Effect of Black or African-American race on apparent clearance	1.25	0.0712	5.696	1.11 - 1.39
RACEAC	Effect of Asian race on apparent clearance	0.835	0.175	20.96	0.492 - 1.178
SEX_CL	Effect of female sex on clearance	0.924	0.0523	5.66	0.8215 - 1.027
Inter-Individual and Between-Occasion Variability Parameters					
Parameter Name	**Description**	**Estimate (CV%)**	**SE**	**RSE (%)**	**Shrinkage (%)**
IIV_CL	IIV on clearance	0.177 (42.07%)	0.0155	8.757	11.78
Corr(IIV_CL - IIV_V)	Correlation between IIV on clearance and IIV on central volume of distribution	0.122 (0.6073%)	0.0167	13.69	-
IIV_V	IIV on central volume of distribution	0.228 (47.75%)	0.0229	10.04	13.94
IIV_KTR	IIV on transit rate constant	0.072 (26.83%)	0.0176	24.44	33.48
BOV_F	BOV on relative bioavailability for Cycle 1 Day 1 postdose	0.0629 (25.08%)	0.00592	9.412	37.00
BOV_F_2	BOV on relative bioavailability for Cycle 1 Day 15 postdose	0.0629 (25.08%)	0.00592	9.412	52.23
BOV_F_3	BOV on relative bioavailability for time points other than Cycle 1 Day 1 postdose or Cycle 1 Day 15 postdose	0.0629 (25.08%)	0.00592	9.412	55.21
BOV_KTR	BOV on transit rate constant for Cycle 1 Day 1 postdose	0.0942 (30.69%)	0.0147	15.61	24.99
BOV_KTR_2	BOV on transit rate constant for Cycle 1 Day 15 postdose	0.0942 (30.69%)	0.0147	15.61	59.36
BOV_KTR_3	BOV on transit rate constant for time points	0.0942	0.0147	15.61	79.22

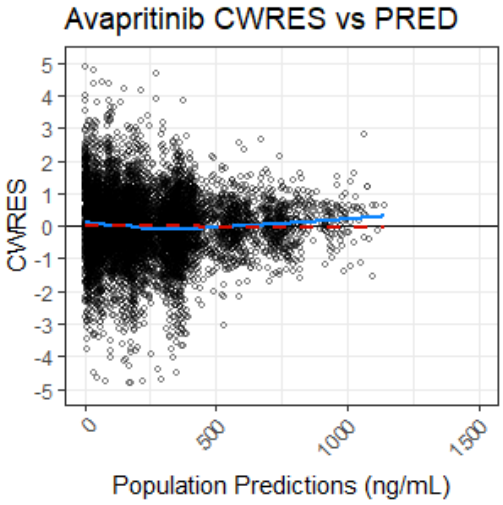
	other than Cycle 1 Day 1 postdose or Cycle Day 15 postdose	(30.69%)			
Intra-Individual Variability Parameters					
Parameter Name	**Description**	**Estimate (CV%)**	**SE**	**RSE (%)**	**Shrinkage (%)**
Sigma(1)	Residual unexplained variability on Study BLU-285-0101/BLU-285-0102 (Proportional)	0.0292 (17.09%)	0.00377	12.91	8.28
Sigma(2)	Residual unexplained variability on Study BLU-285-0105 (Proportional)	0.0339 (18.41%)	0.00311	9.174	5.47
Sigma(3)	Residual unexplained variability on Study BLU-285-2101/BLU-285-2202 (Proportional)	0.0533 (23.09%)	0.00449	8.424	14.85
Sigma(4)	Residual unexplained variability on Study BLU-285-1101 (Proportional)	0.0685 (26.17%)	0.00551	8.044	15.99

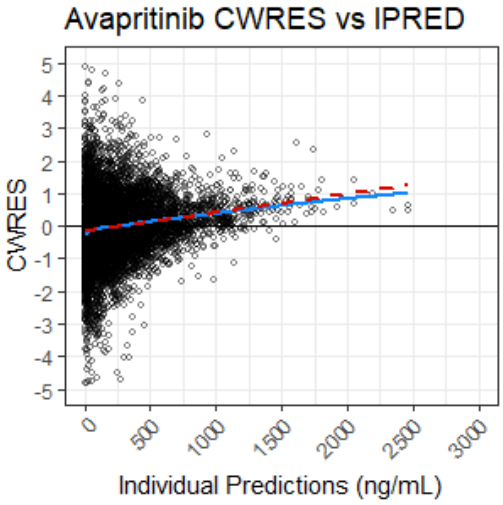
OBJV = -12082.747; Condition = 28.362.
BOV = between-occasion variability; CV = coefficient of variation; GIST = gastrointestinal stromal tumor; h = hours; IIV = interindividual variability; PPI = proton pump inhibitor; RSE = relative standard error; SE = standard error; SM = systemic mastocytosis.
Source: Reviewer Analysis

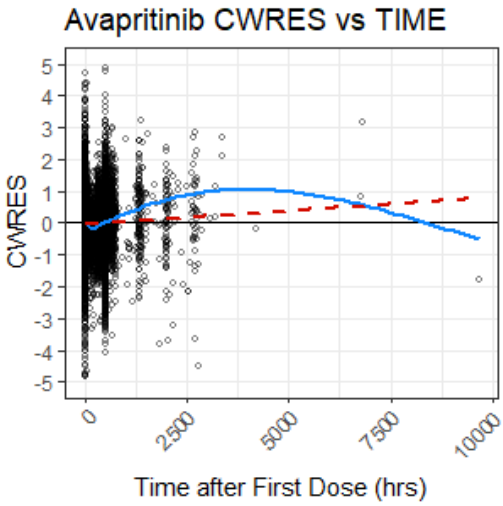
Figure 5. Goodness of Fit Plots for Final Model





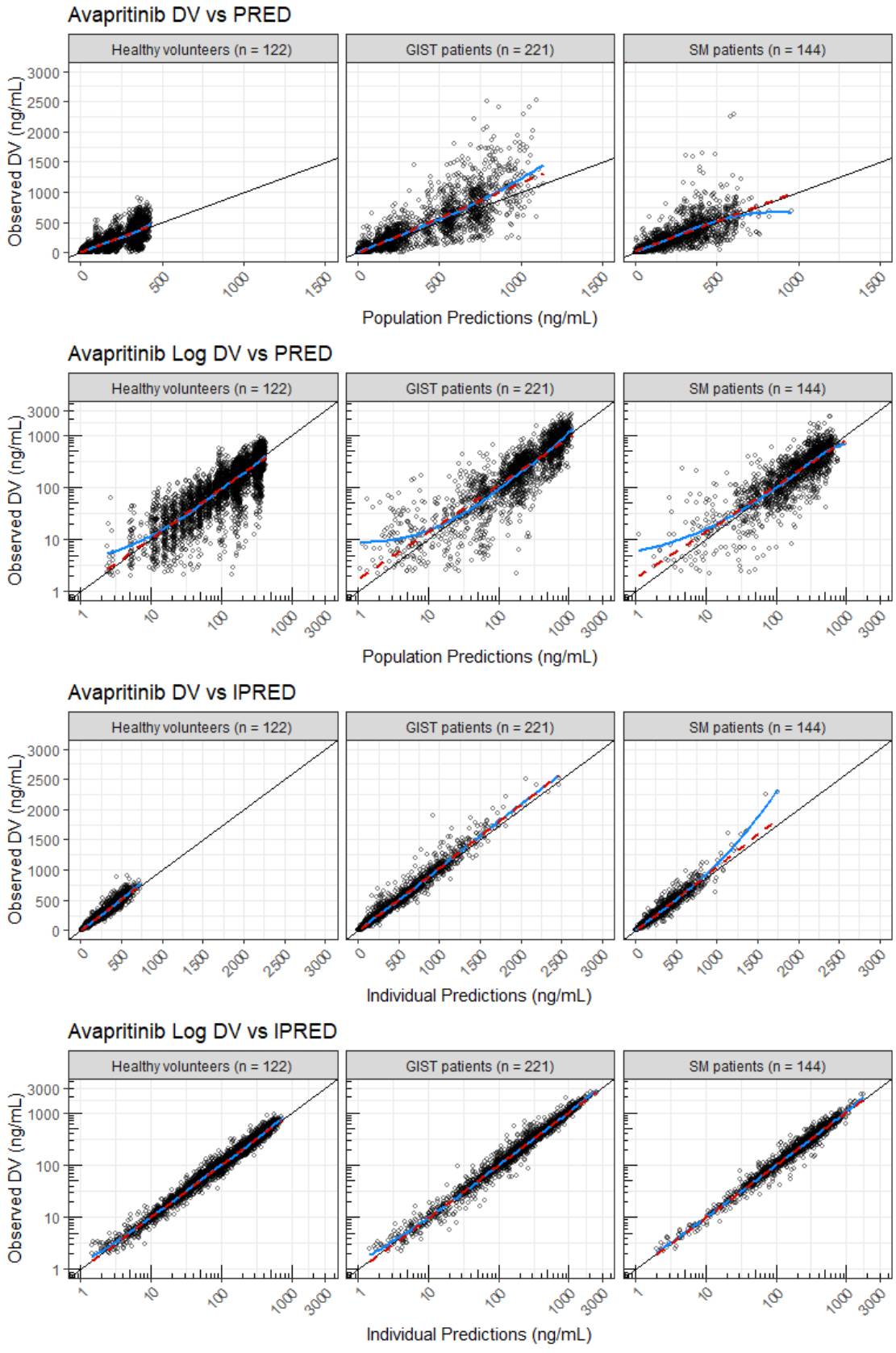


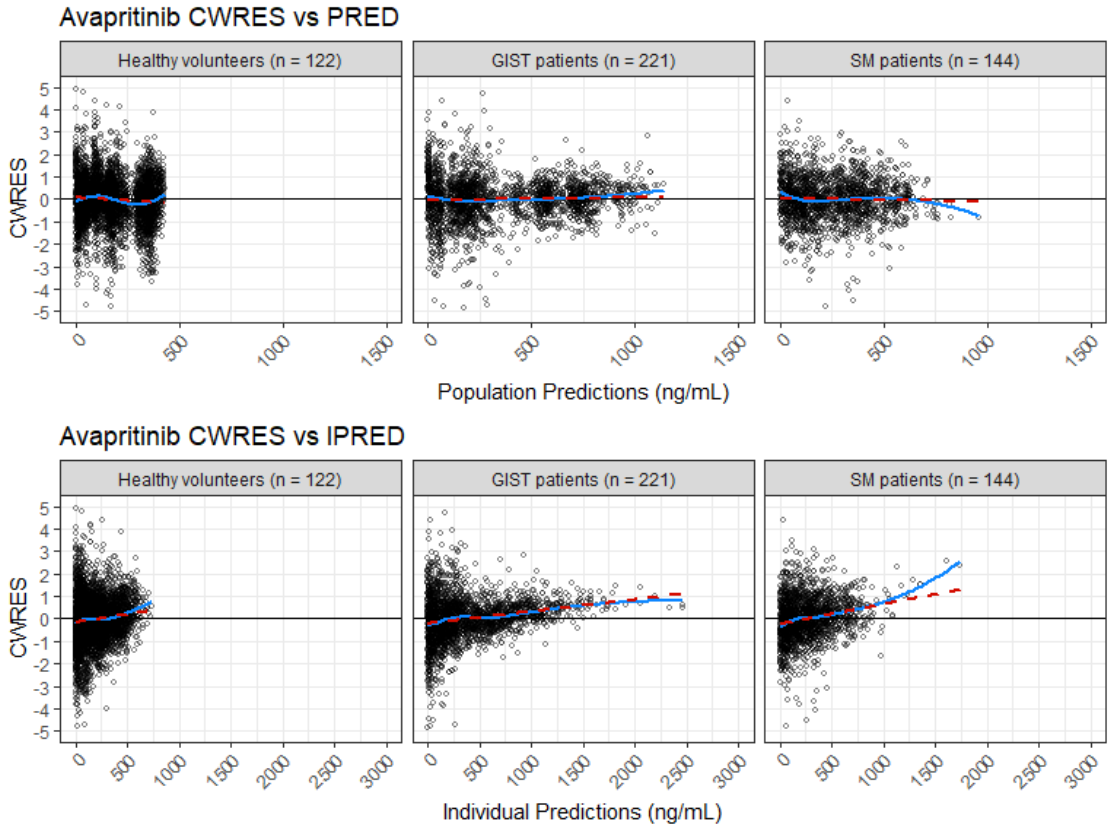




Loess in solid blue; Linear regression in dashed red. Avapritinib LLOQ=2 ng/mL.
CWRES=conditional weighted residuals; DV = observed concentration; hrs = hours; IPRED=individual prediction of concentration; LLOQ = lower limit of quantification; PRED=population prediction of concentration.
Source: Reviewer Analysis

Figure 6. Goodness of fit Plots for the Final Model According to Subject Status



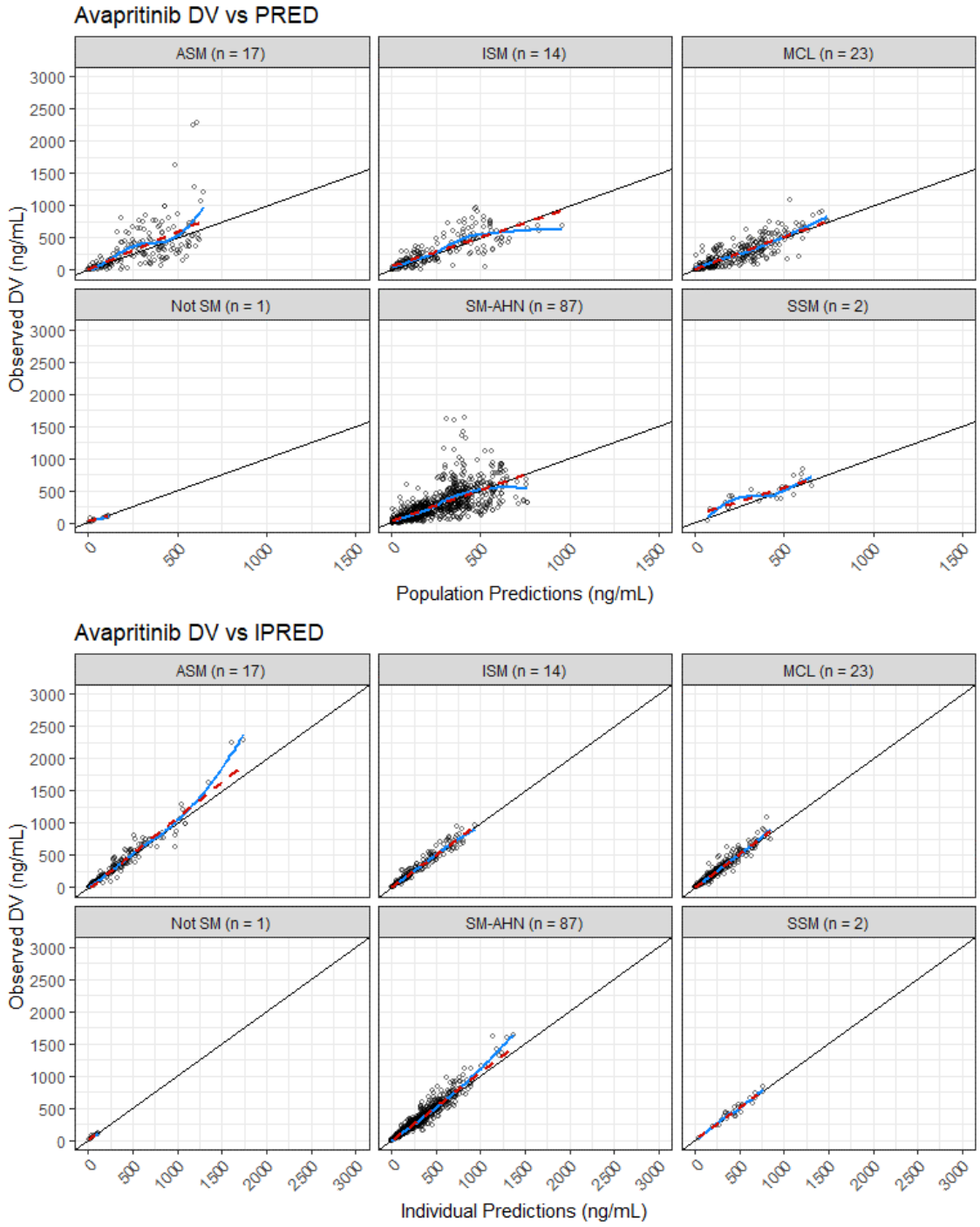


Loess in solid blue; Linear regression in dashed red. Avapritinib LLOQ=2 ng/mL.
CWRES=conditional weighted residuals; DV = observed concentration; hrs = hours; GIST = gastrointestinal stromal tumor; IPRED=individual prediction of concentration; LLOQ = lower limit of quantification; PRED=population prediction of concentration; SM = systemic mastocytosis.
Source: Reviewer Analysis

Goodness of fit with the final model was also analyzed according to SM subtype within the subgroup of patients from Study BLU-285-2101 and Study BLU-285-2201 in the population PK dataset. Key GOF plots for this subgroup according to SM subtype are presented in **Figure 7.** *Key GOF plots for the subgroup of patients with AdvSM (including subjects with ASM, MCL, and SM-AHN) and non-advanced SM are presented in* **Figure 8**.

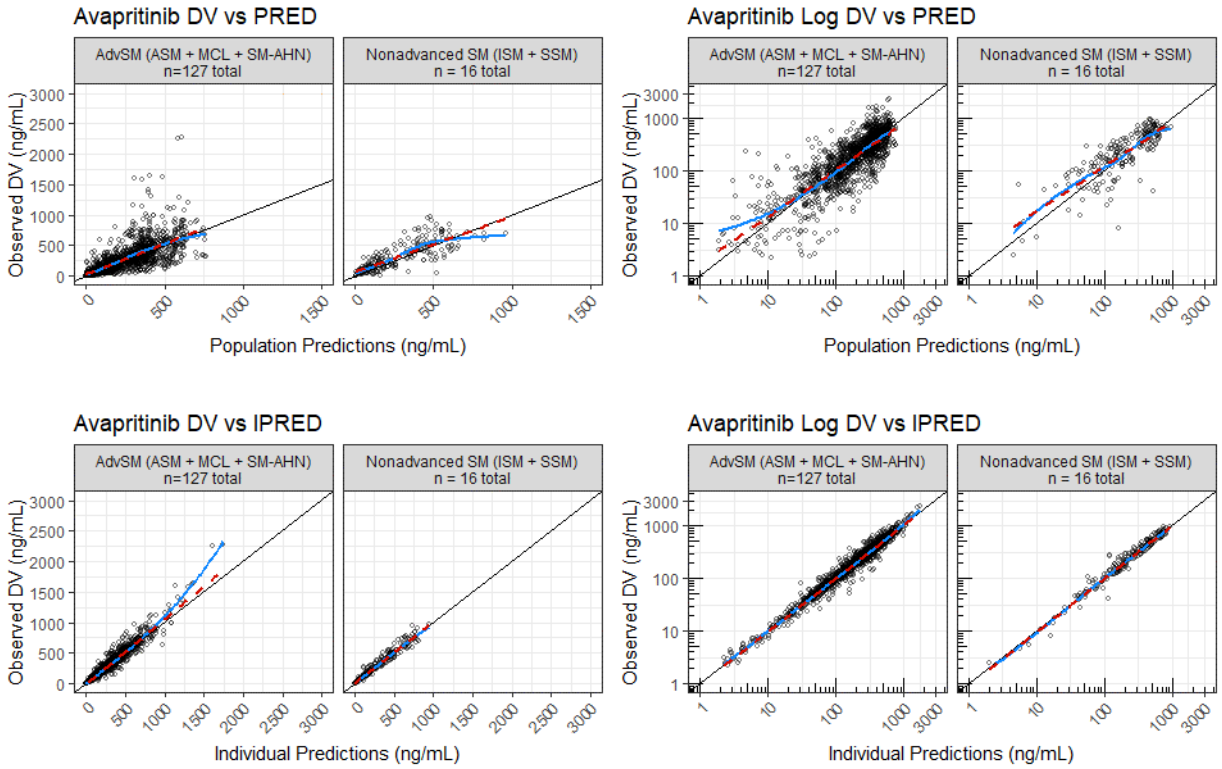
The sample sizes of patients with ASM (n=17), ISM (n=14), and MCL (n=23) were much smaller than the sample size of patients with SM-AHN (n=87). There were also not enough data in subjects with SSM (n=2) to evaluate the GOF in this subgroup. There was a slight tendency to under-predict higher observed concentrations (>1000 ng/mL) with ASM and SM-AHN. Although there were many more subjects with AdvSM (n=127) compared to nonadvanced SM (n=16), the GOF did not differ significantly between subjects with AdvSM and those with nonadvanced SM. Overall, according to the GOF plots, the final population PK model appears adequate in characterizing the PK profile of avapritinib in subjects with AdvSM, including each the three subtypes of AdvSM (ASM, MCL, and SM-AHN).

Figure 7. Key Goodness of Fit Plots in Subjects with Systemic Mastocytosis for the Final Model According to Disease Subtype



Loess in solid blue; Linear regression in dashed red. Avapritinib LLOQ=2 ng/mL.
ASM = aggressive systemic mastocytosis; DV = observed concentration; IPRED=individual prediction of concentration; ISM = indolent systemic mastocytosis; MCL = mast cell leukemia; PRED=population prediction of concentration; SM = systemic mastocytosis; SM-AHN = systemic mastocytosis with associated hematological neoplasm; SSM = smoldering systemic mastocytosis.
Source: Reviewer Analysis

Figure 8. Key Goodness of Fit Plots in Subjects with Advanced and Non-advanced Systemic Mastocytosis for the Final Model



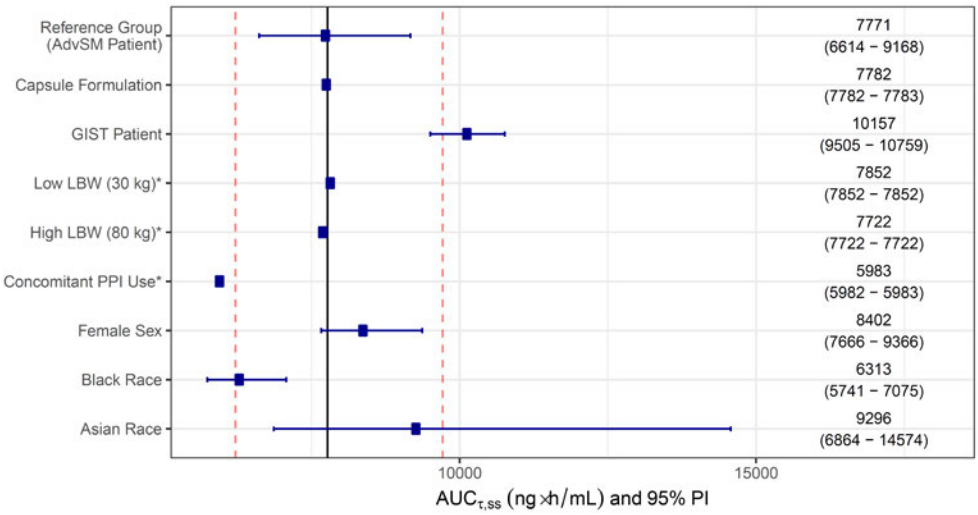
Loess in solid blue; Linear regression in dashed red. Avapritinib LLOQ=2 ng/mL.
AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; DV = observed concentration; IPRED=individual prediction of concentration; ISM = indolent systemic mastocytosis; MCL = mast cell leukemia; PRED=population prediction of concentration; SM-AHN = systemic mastocytosis with associated hematological neoplasm; SSM = smoldering systemic mastocytosis.
Source: Reviewer Analysis

4.1.3 Simulation of Avapritinib Exposure by Covariates

The Applicant used the final population PK model to simulate avapritinib concentration at steady-state in order to predict differences in exposure according to various covariates. Key covariate effects and their impact on individual predicted steady-state AUC over the dosing interval ($AUC_{0\text{-}tau,ss}$) and maximum concentration at steady-state ($C_{max,ss}$) are presented in **Figure 9** and **Figure 10**, respectively.

For the 200 mg once daily dosing, subjects with GIST were predicted to have >25% higher median $AUC_{0\text{-}tau,ss}$ and >25% higher median $C_{max,ss}$ compared to subjects with AdvSM. Concomitant PPI use was predicted to result in a >20% decrease in both median $AUC_{0\text{-}tau,ss}$ and median $C_{max,ss}$ in subjects with AdvSM. There were no significant differences in predicted exposure for formulation (tablets versus capsules), low lean body weight (30 kg), high lean body weight (80 kg), female sex, Black or African-American race, or Asian race compared to the reference virtual population of White, male subjects with AdvSM and a lean body weight of 55.6 kg.

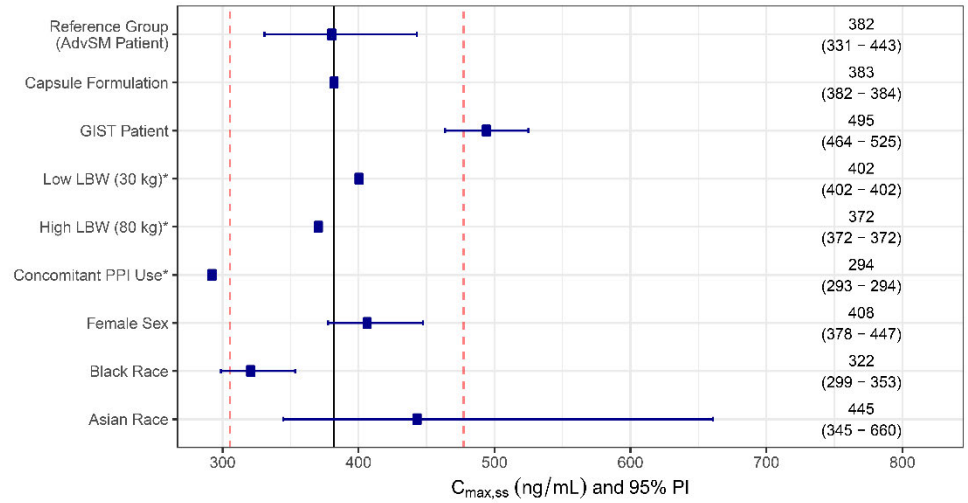
Figure 9. Model Predicted Effect of Covariates on Change in $AUC_{0\text{-}tau,ss}$



The solid black line represents the median of the reference group, defined as a White male patient with AdvSM of LBW 55.6 kg, receiving 200 mg avapritinib (tablet) QD in a fasted condition, sampled every hour on Day 15 (steady state). Dashed red lines represent the 80-125% range of the reference group. Blue dots and error bars represent the median and 95% (2.5th to 97.5th percentiles of the simulations) prediction intervals (PI) of the covariate effect based on 1000 simulated subjects within each group with uncertainty on the fixed effect. Note: healthy volunteers are not included in the plot.

Source: Figure 34 from Applicant's Population PK Report

Figure 10. Model Predicted Effect of Covariates on Change in $C_{max,ss}$



The solid black line represents the median of the reference group, defined as a White male patient with AdvSM of lean body weight of 55.6 kg, receiving 200 mg avapritinib (tablet) QD in a fasted condition, sampled every hour on Day 15 (steady state). Dashed red lines represent the 80-125% range of the reference group. Blue dots and error bars represent the median and 95% (2.5th to 97.5th percentiles of the simulations) prediction intervals (PI) of the covariate effect based on 1000 simulated subjects within each group with uncertainty on the fixed effect. Note: healthy volunteers are not included in the plot.

Source: Figure 36 from Applicant's Population PK Report

Reviewer Comments

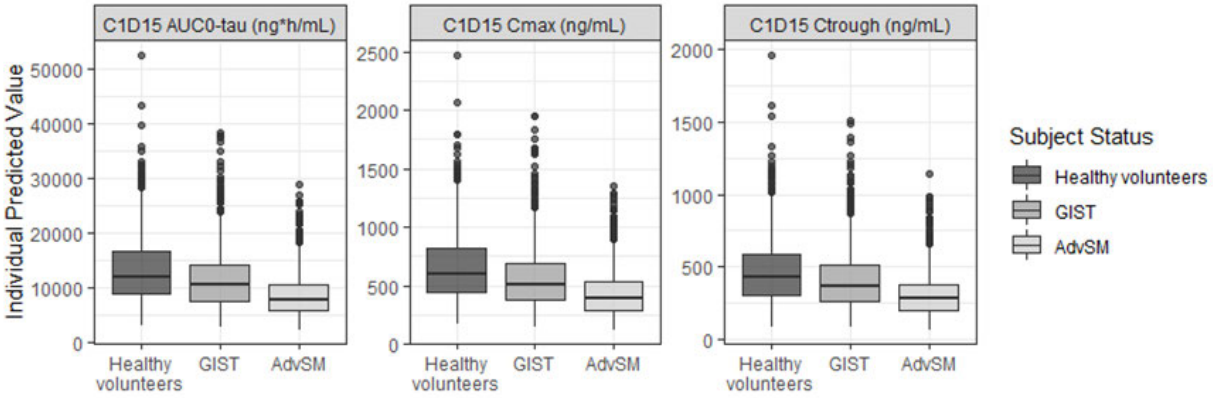
The Reviewer used final population PK model and the Applicant's final parameter estimates to simulate avapritinib exposure over time. There was no significant discordance between the Applicant's simulation results and the Reviewer's simulation results. The reviewer agrees with Applicant's conclusion that no dose adjustment is needed based on race or PPI use.

Subjects with AdvSM were predicted to have lower exposure than healthy volunteers or patients with GIST, as shown in ***Figure 11.*** *After the dose given on Cycle 1 Day 15 (C1D15), patients with AdvSM were predicted to have a 23% lower median $C_{max,ss}$, 25% lower median trough concentration at steady-state ($C_{trough,ss}$), and 24% lower median $AUC_{0\text{-}tau,ss}$ compared to patients with GIST.*

Comedication with a PPI was predicted to result in lower avapritinib exposure, as shown in ***Figure 12****. Virtual AdvSM subjects with five or more consecutive days of PPI use prior to PK sampling were predicted to have 23% lower median $C_{max,ss}$, 24% lower median $C_{trough,ss}$, and 24% lower median $AUC_{0\text{-}tau,ss}$ compared to virtual AdvSM subjects without PPI use. This is not expected to result in a clinically significant difference in exposure.*

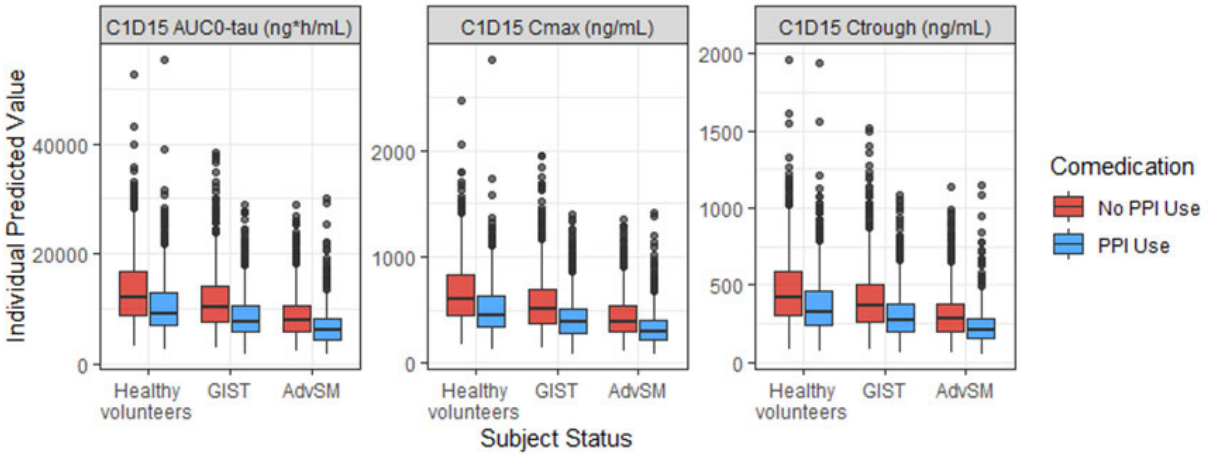
The final population PK model included covariate effects of Asian (n=25/487 total) and Black (n=26/487) race on CL/F, although the final estimate of the 95% CI for the effect of Asian race on CL/F (0.492 – 1.178) was relatively wide and included the null hypothesis that Asian race had no effect. Predicted PK exposure parameters from the simulation of subject race are presented in ***Figure 13****, which shows that the effect of race had a larger impact on predicted $C_{trough,ss}$ compared to $C_{max,ss}$ or $AUC_{0\text{-}tau,ss}$.*

Figure 11. Simulated Avapritinib Exposure for 200 mg Once Daily Dosing in Virtual Healthy Volunteers, Virtual Patients with GIST, and Virtual Patients with AdvSM



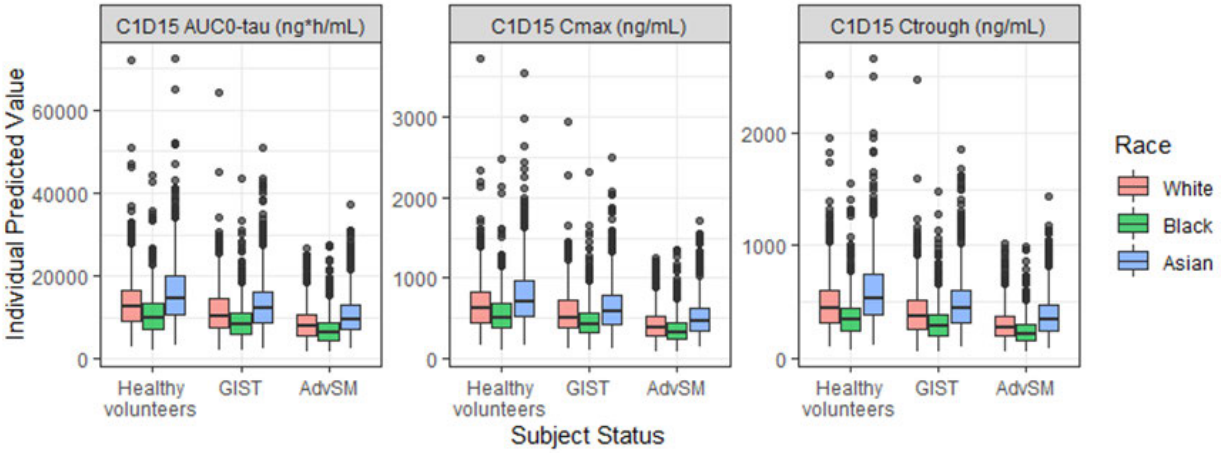
AdvSM = advanced systemic mastocytosis; $AUC_{0\text{-}tau}$ = area under the concentration-versus-time curve from time after last dose 0 to 24 hours; C1D15 = Cycle 1 Day 15; C_{max} = predicted maximum concentration; C_{trough} = predicted predose concentration; GIST = gastrointestinal stromal tumor. Simulation contained 1000 replicates for each subject status assuming a male subject with a lean body weight of 55.6 kg, receiving 200 mg avapritinib (as tablet formulation) once daily and using the Applicant's final population PK model. Points represent outliers.
Source: Reviewer Analysis

Figure 12. Simulated Avapritinib Exposure for 200 mg Once Daily Dosing According to PPI Comedication Status



AdvSM = advanced systemic mastocytosis; $AUC_{0\text{-}tau}$ = area under the concentration-versus-time curve from time after last dose 0 to 24 hours; C1D15 = Cycle 1 Day 15; C_{max} = predicted maximum concentration; C_{trough} = predicted predose concentration; GIST = gastrointestinal stromal tumor; PPI = proton pump inhibitor.
Solid lines represent a simulated median concentration-time profile assuming a White male subject with a lean body weight of 55.6 kg, receiving 200 mg avapritinib (as tablet formulation) once daily. Shaded regions represent 10th to 90th percentiles. Simulation contained 1000 replicates for each unique combination of comedication status and subject status using the Applicant's final population PK model. PPI use defined as 5 or more days of continuous PPI administration prior to PK sampling.
Source: Reviewer Analysis

Figure 13. Simulated Avapritinib Exposure for 200 mg Once Daily Dosing According to Subject Race



AdvSM = advanced systemic mastocytosis; $AUC_{0\text{-}tau}$ = area under the concentration-versus-time curve from time after last dose 0 to 24 hours; C1D15 = Cycle 1 Day 15; C_{max} = predicted maximum concentration; C_{trough} = predicted predose concentration; GIST = gastrointestinal stromal tumor.
Simulation contained 1000 replicates for each unique combination of race and subject status assuming a male subject with a lean body weight of 55.6 kg, receiving 200 mg avapritinib (as tablet formulation) once daily and using the Applicant's final population PK model. Points represent outliers.
Source: Reviewer Analysis

4.2 Exposure-Response Analysis

The primary objectives of the applicant's analysis were to:

- Graphically evaluate the effect of avapritinib exposure on measures of efficacy (in AdvSM patients) and safety (in AdvSM and GIST patients).
- Develop time to event (TTE) exposure-response (E-R) models for selected measures of efficacy (in AdvSM patients) and safety (in AdvSM and GIST patients).
- Simulate TTE profiles of selected measures of efficacy (in virtual AdvSM patients) and safety (in virtual AdvSM and GIST patients).

4.2.1 Analysis of Safety

The exposure-response analysis of safety used data from 144 SM subjects and 383 GIST subjects (n=527 total). The population PK model was used to predict individual daily $AUC_{0\text{-}24}$ for every day up to the date of the first occurrence of the AE of interest, which was used to calculate cumulative AUC up to the first occurrence of the AE of interest ($AUC_{cumulative}$). The E-R safety analysis used $C_{average}$ as the metric of exposure, which was calculated as $AUC_{cumulative}$ over time to first occurrence of the AE of interest. Subjects who did not experience an AE of interest would have $C_{average}$ equal to the $AUC_{cumulative}$ over time to end of study participation or up to 2 days following last exposure to treatment (whichever occurred first).

Avapritinib subject covariates are summarized for the exposure-safety dataset in **Table 7**. Subjects with GIST had higher median baseline platelet count compared to subjects with SM (all subtypes). None of the 381 GIST subjects had a baseline platelet count less than 100×10^9/L, while 11 out of 144 SM subjects (7.6%) had a baseline platelet count less than 50×10^9/L and 35 out of 144 SM subjects (24.3%) had a baseline platelet count less than 100×10^9/L.

Table 7. Summary of Subject Covariates in the Exposure-Safety Dataset According to Disease Status and Subtype

		Subject Status/Disease Subtype							
Covariate	**Statistic**	**GIST**	**MCL**	**ASM**	**SM-AHN**	**ISM**	**SSM**	**Not SM**	**TOTAL**
Number of Subjects		**383**	**23**	**17**	**87**	**14**	**2**	**1**	**527**
Study									
BLU-285-1101	N (%)	221 (57.7%)	0	0	0	0	0	0	221 (41.9%)
BLU-285-1303	N (%)	162 (42.3%)	0	0	0	0	0	0	162 (30.7%)
BLU-285-2101	N (%)	0	13 (56.5%)	8 (47.1%)	48 (55.2%)	14 (100%)	2 (100%)	1 (100%)	86 (16.3%)
BLU-285-2202	N (%)	0	10 (43.5%)	9 (52.9%)	39 (44.8%)	0	0	0	58 (11%)
Baseline Weight (kg)	N	383	23	17	87	14	2	1	527
	Mean	76.5	77.9	75.1	72.6	76.2	60.3	115.8	75.9
	CV (%)	26.4	20.7	21.8	21.3	25.1	19.9	-	25.4
	Median	74	78	72.3	70.2	74.4	60.3	115.8	73.8
	Minimum	39.5	51.5	53.9	42.5	48.5	51.9	115.8	39.5
	Maximum	156.3	103.1	105.5	106	104	68.8	115.8	156.3
Age Group									
≥65 years	N (%)	153 (39.9%)	6 (26.1%)	10 (58.8%)	63 (72.4%)	2 (14.3%)	0	1 (100%)	235 (44.6%)
< 65 years	N (%)	230 (60.1%)	17 (73.9%)	7 (41.2%)	24 (27.6%)	12 (85.7%)	2 (100%)	0	292 (55.4%)
Race Group									
White	N (%)	268 (70%)	19 (82.6%)	15 (88.2%)	78 (89.7%)	11 (78.6%)	2 (100%)	1 (100%)	394 (74.8%)
Non-White	N (%)	80 (20.9%)	2 (8.7%)	1 (5.9%)	7 (8%)	1 (7.1%)	0	0	91 (17.3%)
Unknown	N (%)	35 (9.1%)	2 (8.7%)	1 (5.9%)	2 (2.3%)	2 (14.3%)	0	0	42 (8%)
Sex									
Female	N (%)	136 (35.5%)	8 (34.8%)	9 (52.9%)	38 (43.7%)	10 (71.4%)	2 (100%)	0	203 (38.5%)
Male	N (%)	247 (64.5%)	15 (65.2%)	8 (47.1%)	49 (56.3%)	4 (28.6%)	0	1 (100%)	324 (61.5%)
Baseline Platelets (10^9/L)	N	381	23	17	87	14	2	1	525
	Mean	303.9	178.6	228.9	159.4	254.2	234	79	270
	CV (%)	42.3	57.4	50	74.8	20.1	0	-	50.5
	Median	278	162	207	123	264.5	234	79	256
	Minimum	105	28	68	28	164	234	79	28
	Maximum	871	504	454	606	324	234	79	871
Baseline Platelet Category									
<50 × 10^9/L	N (%)	0	2 (8.7%)	0	9 (10.3%)	0	0	0	11 (2.1%)
50 × 10^9/L - <100 × 10^9/L	N (%)	0	2 (8.7%)	3 (17.6%)	29 (33.3%)	0	0	1 (100%)	35 (6.7%)
100 × 10^9/L - <150 × 10^9/L	N (%)	18 (4.7%)	4 (17.4%)	1 (5.9%)	13 (14.9%)	0	0	0	36 (6.9%)
150 × 10^9/L and up	N (%)	363 (95.3%)	15 (65.2%)	13 (76.5%)	36 (41.4%)	14 (100%)	2 (100%)	0	443 (84.4%)
Baseline Anti-thrombotic Medication Use									

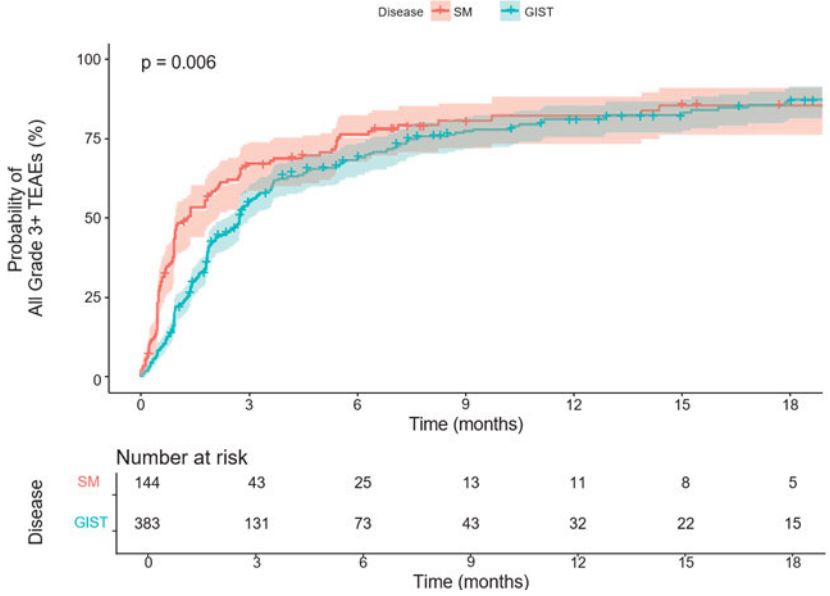
		Subject Status/Disease Subtype							
Covariate	**Statistic**	**GIST**	**MCL**	**ASM**	**SM-AHN**	**ISM**	**SSM**	**Not SM**	**TOTAL**
Yes	N (%)	69 (18%)	5 (21.7%)	4 (23.5%)	14 (16.1%)	4 (28.6%)	0	0	96 (18.2%)
No	N (%)	314 (82%)	18 (78.3%)	13 (76.5%)	73 (83.9%)	10 (71.4%)	2 (100%)	1 (100%)	431 (81.8%)
Baseline APPT Grade									
APTT Grade <1	N (%)	350 (91.4%)	18 (78.3%)	14 (82.4%)	51 (58.6%)	13 (92.9%)	2 (100%)	1 (100%)	449 (85.2%)
APTT Grade ≥1	N (%)	33 (8.6%)	5 (21.7%)	3 (17.6%)	36 (41.4%)	1 (7.1%)	0	0	78 (14.8%)
Baseline INR Grade									
INR Grade <1	N (%)	344 (89.8%)	8 (34.8%)	12 (70.6%)	36 (41.4%)	13 (92.9%)	2 (100%)	0	415 (78.7%)
INR Grade ≥1	N (%)	39 (10.2%)	15 (65.2%)	5 (29.4%)	51 (58.6%)	1 (7.1%)	0	1 (100%)	112 (21.3%)
Midostaurin Use									
No prior midostaurin	N (%)	383 (100%)	11 (47.8%)	10 (58.8%)	52 (59.8%)	12 (85.7%)	2 (100%)	1 (100%)	471 (89.4%)
Prior midostaurin use	N (%)	0	12 (52.2%)	7 (41.2%)	35 (40.2%)	2 (14.3%)	0	0	56 (10.6%)

AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; GIST = gastrointestinal stromal tumor; ISM = indolent systemic mastocytosis; MCL = mast cell leukemia; SM = systemic mastocytosis; SM-AHN = systemic mastocytosis with associated hematological neoplasm; SSM = smoldering systemic mastocytosis.
Source: Reviewer Analysis of Applicant's Datasets

4.2.1.1 Analysis of Safety by Patient Subgroups and Exposure Quartiles

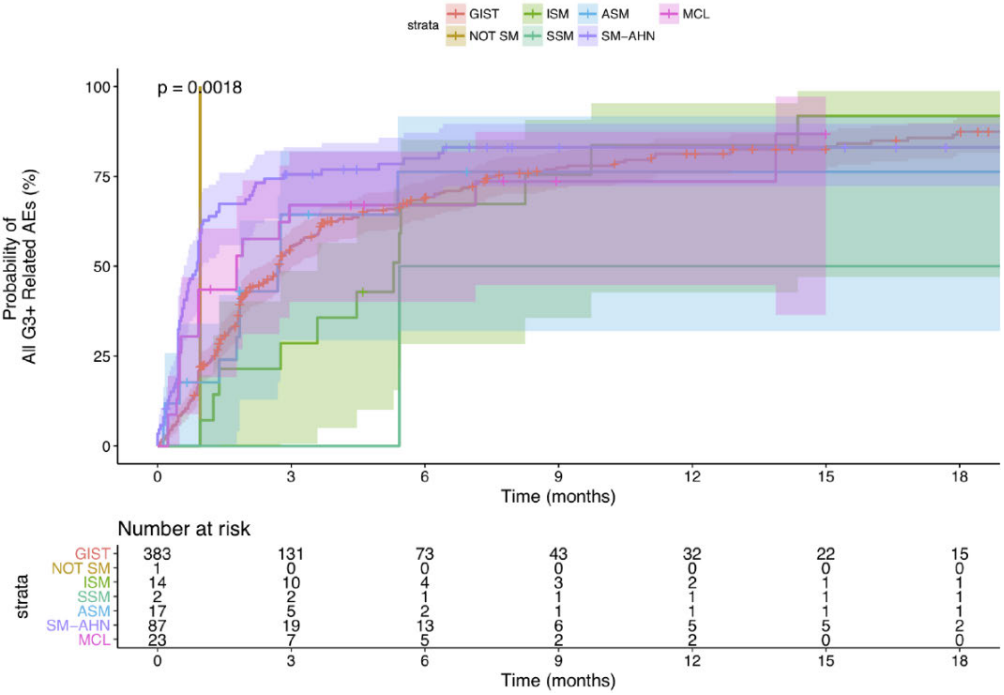
When subjects with GIST were compared to subjects with SM, subjects with SM had a faster onset of grade 3+ TEAEs (**Figure 14**). Probability of a grade 3+ TEAE by 6 months of treatment was higher in the 4th quartile of avapritinib $C_{average}$ (78% with 95% CI of 70 – 84%) compared to the 1st quartile (58% with 95% CI of 47 – 67%). The difference in onset of grade 3+ TEAEs appears to be largely driven by the shorter onset in subjects with SM-AHN subtypes of SM. (**Figure 15**).

Figure 14. Time to All Grade 3+ TEAEs versus Disease Status



Solid lines represent Kaplan-Meier curves, shaded areas represent 95% confidence intervals, and p-value is derived from a log-rank test. Note: plot truncated at 18 months.
GIST = gastrointestinal stromal tumor; SM = systemic mastocytosis; TEAE = treatment-emergent adverse events.
Source: Figure 27 from Applicant's Exposure-Response Analysis with correction to axis label and SM subgroup name

Figure 15. Time to Grade 3+ TEAEs versus Disease Status and Subtype



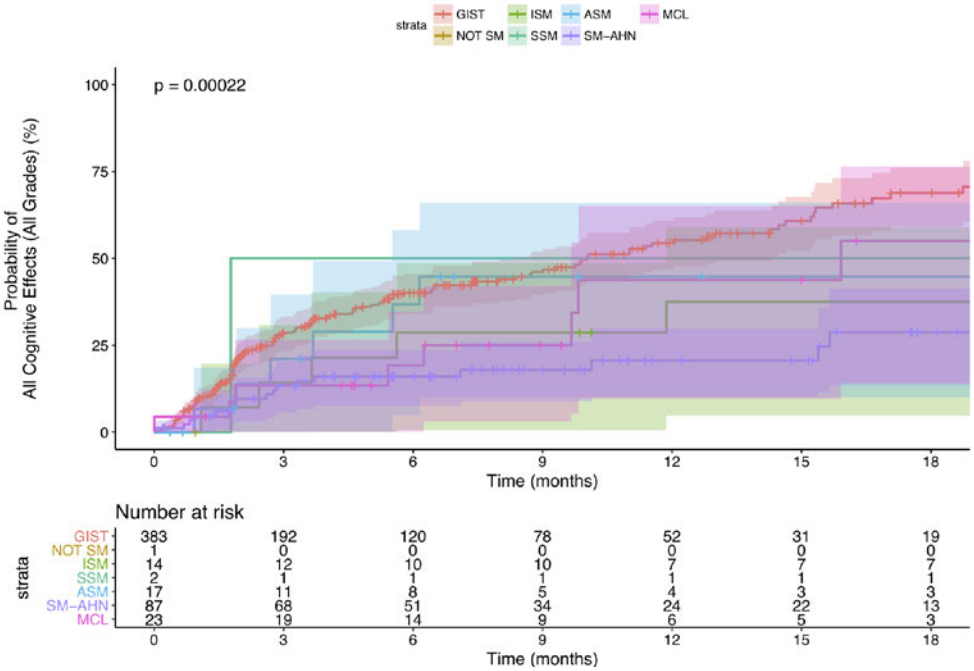
Solid lines represent Kaplan-Meier curves, shaded areas represent 95% confidence intervals, and p-value is derived from a log-rank test. Note: plot truncated at 18 months.

ASM = aggressive systemic mastocytosis; GIST = gastrointestinal stromal tumor; ISM = indolent systemic mastocytosis; MCL = mast cell leukemia; SM = systemic mastocytosis; SM-AHN = systemic mastocytosis with associated hematologic neoplasm; SSM = smoldering systemic mastocytosis; TEAE = treatment-emergent adverse events.

Source: Page 3 of Applicant's Response to FDA 23 February 2021 Information Request

Increased avapritinib exposure quartile was significantly ($p < 0.05$) associated with faster onset of pooled cognitive effects (all grades, grade 2+), cognitive disorders (all grades), memory impairment (all grades), amnesia (grade 2+), edema (grade 2+), and pleural effusion (grade 2+). However, grade 2+ amnesia was only experienced by 5/527 subjects in the E-R safety dataset and the small number of subjects makes it difficult to compare risk by exposure. When SM subtype was investigated, there were also trends where subjects with SM-AHN had a slower onset of cognitive effects (all grades) (**Figure 16**) and subjects with SM-AHN or MCL had a slower onset of cognitive effects (grade 2+) (**Figure 17**) compared to subjects with GIST; however, all other SM subtypes had overlapping confidence intervals with GIST patients.

Figure 16. Time to All Grade Cognitive Effects versus Disease Status and Subtype

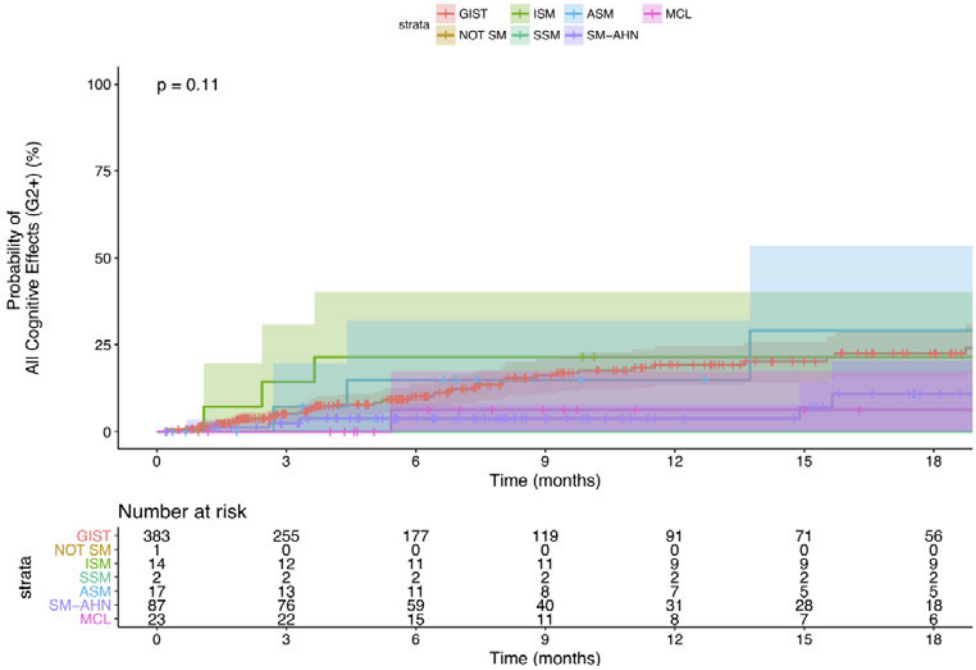


Solid lines represent Kaplan-Meier curves, shaded areas represent 95% confidence intervals, and p-value is derived from a log-rank test. Note: plot truncated at 18 months.

ASM = aggressive systemic mastocytosis; GIST = gastrointestinal stromal tumor; ISM = indolent systemic mastocytosis; MCL = mast cell leukemia; SM = systemic mastocytosis; SM-AHN = systemic mastocytosis with associated hematologic neoplasm; SSM = smoldering systemic mastocytosis.

Source: Page 7 of Applicant's Response to FDA 23 February 2021 Information Request

Figure 17. Time to Grade 2+ Cognitive Effects versus Disease Status and Subtype

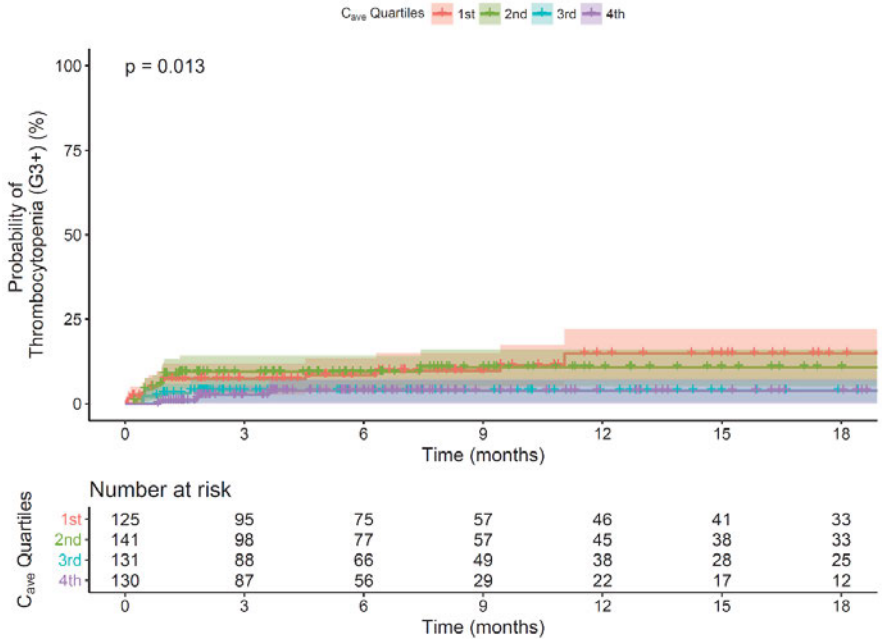


Solid lines represent Kaplan-Meier curves, shaded areas represent 95% confidence intervals, and p-value is derived from a log-rank test. Note: plot truncated at 18 months.
ASM = aggressive systemic mastocytosis; GIST = gastrointestinal stromal tumor; ISM = indolent systemic mastocytosis; MCL = mast cell leukemia; SM = systemic mastocytosis; SM-AHN = systemic mastocytosis with associated hematologic neoplasm; SSM = smoldering systemic mastocytosis.
Source: Page 8 of Applicant's Response to FDA 23 February 2021 Information Request

Increased avapritinib exposure quartile was also significantly associated with slower onset of thrombocytopenia (all grades and grade 3+). Overall, 91/527 subjects experienced thrombocytopenia (all grades) and 39/527 experienced grade 3+ thrombocytopenia as an AE at any time. The Applicant suggested this finding could be due to the association between disease status (GIST versus SM) and dosing/exposure, as thrombocytopenia is expected to be more common in subjects with SM and subjects with SM generally had lower avapritinib exposure. The Kaplan-Meier plot for grade 3+ thrombocytopenia is shown in **Figure 18**.

Notably, there were no trends in the incidence of intracranial bleeding (all grades) across avapritinib exposure quartiles at any time point (**Table 8**). However, there were relatively few subjects who experienced an intracranial bleed (18 out of 527 total) which may limit the ability of the analysis to identify exposure-response relationships with this safety endpoint.

Figure 18. Probability of Grade 3+ Thrombocytopenia by Quartiles of Avapritinib Exposure



Solid lines represent Kaplan-Meier curves, shaded areas represent 95% confidence intervals, and p-value is derived from a log-rank test. Note: plot truncated at 18 months. C_{ave} = individual average predicted concentration.
Source: Figure 44 from Applicant's Exposure-Response Analysis

Table 8. Probability of Intracranial Bleeds (All Grades) by Quartiles of Avapritinib Exposure

Month	$C_{average}$ Quartile	Probability	95% Confidence Interval	Cumulative Events
3	1	0.02	0 - 0.04	2
3	2	0.01	0 - 0.03	1
3	3	0	0 - 0	0
3	4	0.02	0 - 0.05	2
6	1	0.04	0 - 0.07	4
6	2	0.02	0 - 0.04	2
6	3	0.01	0 - 0.04	1
6	4	0.05	0 - 0.09	4
9	1	0.04	0 - 0.07	4
9	2	0.02	0 - 0.04	2
9	3	0.01	0 - 0.04	1
9	4	0.05	0 - 0.09	4
12	1	0.04	0 - 0.07	4
12	2	0.02	0 - 0.04	2
12	3	0.01	0 - 0.04	1
12	4	0.05	0 - 0.09	4
18	1	0.04	0 - 0.07	4
18	2	0.04	0 - 0.1	3
18	3	0.07	0 - 0.16	3
18	4	0.05	0 - 0.09	4

If a subject had 2 or more intracranial bleed events, the subject was counted only once at the occurrence of the first intracranial bleed event. $C_{average}$ was calculated as the cumulative AUC over time to first occurrence of intracranial bleed in subjects who experienced intracranial bleed, or as the cumulative AUC over time to end of study participation or up to 2 days after last exposure to treatment (whichever occurred first) in subjects who did not experience intracranial bleed. $C_{average}$ = individual average predicted concentration.
Source: Table 40 from Applicant's Exposure-Response Analysis

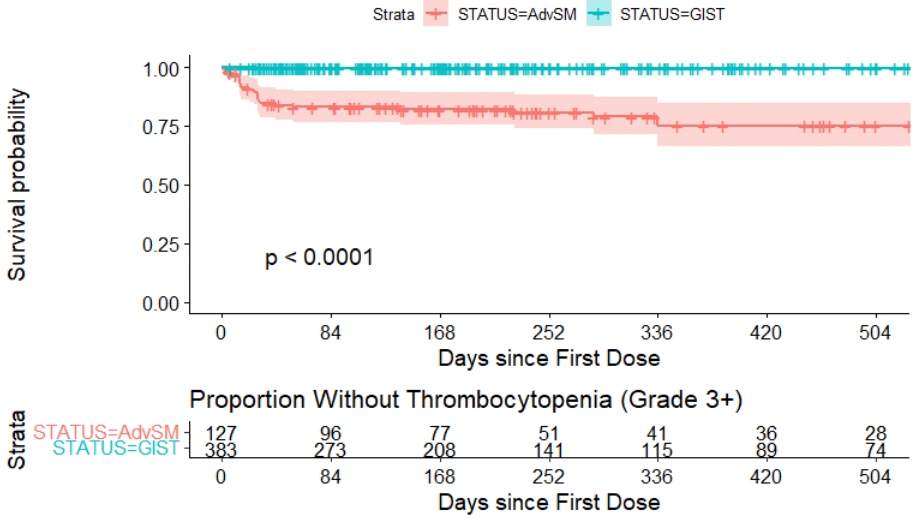
Reviewer Comments

Thrombocytopenia incidence was also assessed according to disease subtype. Subjects with AdvSM (including ASM, SM-AHN, and MCL) had significantly faster onset and higher incidence of thrombocytopenia (both all grades and grade 3+). The Kaplan-Meier curve for proportion of AdvSM and GIST subjects without grade 3+ thrombocytopenia is shown in ***Figure 19****.*

In the subgroup of subjects with AdvSM, neither onset of thrombocytopenia (both all grades and grade 3+) nor incidence at 18 months differed significantly according to SM subtype. The Kaplan-Meier curve for proportion of ASM, SM-AHN, and MCL subjects without grade 3+ thrombocytopenia is shown in ***Figure 20****.*

The Applicant's proposed dosage modification recommending that avapritinib dosing be interrupted in patients with AdvSM who have a platelet count fall below 50 x 10^9/L, and that avapritinib should only be resumed once platelet count is ≥50 x 10^9/L. The proposed dosage modification for thrombocytopenia was not recommended for GIST, which is reasonable given that thrombocytopenia (both all grades and grade 3+) and intracranial bleeding are much more likely to occur in subjects with AdvSM compared to GIST.

Figure 19. Proportion of Subjects Without Grade 3+ Thrombocytopenia versus Disease Subtype (AdvSM versus GIST)

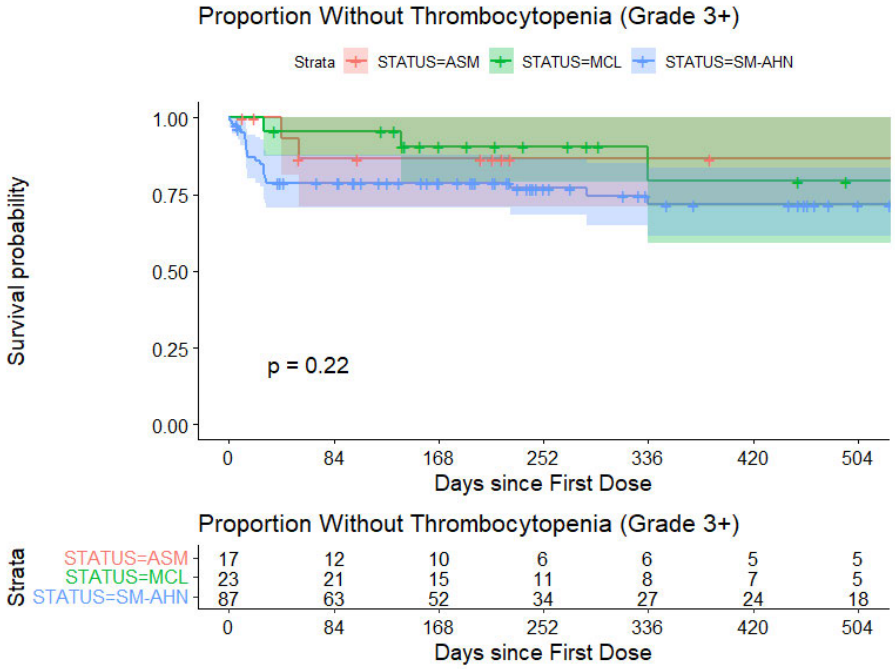


Solid lines represent Kaplan-Meier curves. Shaded areas represent 95% confidence intervals. Note: plot truncated at 504 days. AdvSM includes ASM, SM-AHN, and MCL. Survival probability refers to probability of not experiencing grade 3+ thrombocytopenia.

AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; GIST = gastrointestinal stromal tumor; MCL = mast cell leukemia; SM-AHN = systemic mastocytosis with associated hematological neoplasm.

Source: Reviewer Analysis of Applicant's Datasets

Figure 20. Proportion of Subjects Without Grade 3+ Thrombocytopenia versus AdvSM Subtype (ASM versus SM-AHN versus MCL)



Solid lines represent Kaplan-Meier curves. Shaded areas represent 95% confidence intervals. Note: plot truncated at 504 days. Survival probability refers to probability of not experiencing grade 3+ thrombocytopenia.
AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; MCL = mast cell leukemia; SM-AHN = systemic mastocytosis with associated hematological neoplasm.
Source: Reviewer Analysis of Applicant's Datasets

4.2.1.2 Exposure-Safety Model Development and Results

Subject covariates were evaluated with the TTE models, including disease status (AdvSM or GIST), disease status with SM subtype (ASM, ISM, SM-AHN, SSM/non-SM, MCL, or GIST), gender, race, body weight, age group (<65 years or ≥65 years), region of the world, and prior midostaurin use. The TTE models for intracranial bleeding also evaluated the covariates of baseline platelet count, time-varying platelet count, platelet transfusion before C1D1 (yes or no), anti-thrombotic medication use, and elevated INR/APTT.

E-R modeling found significant relationships between increased avapritinib exposure and increased risk of grade 3+ TEAEs, cognitive effects (both grade 2+ and any grade) and edema TEAEs (grade 2+). No relationship between exposure and intracranial bleeding (any grade) was identified. However, intracranial bleeding was significantly related to baseline platelet count and time-varying platelet count.

Increased avapritinib exposure was associated with higher risk of grade 3+ TEAEs, and the final model with best fit for grade 3+ TEAEs also included covariate effects of SM-AHN and MCL subtypes of SM on baseline hazard and on the shape parameter. Subjects with the SM-AHN or MCL subtype of SM were predicted to have higher risk of grade 3+ TEAEs and higher rate of grade 3+ TEAE onset. The risk was higher with SM-AHN compared to MCL; however, MCL had a larger sample size (n=23) compared to SM-AHN (n=7). Compared to subjects with GIST, subjects

with SM-AHN and MCL had a significantly faster onset of grade 3+ TEAEs (hazard ratio [HR] 2.57 [95% CI 1.92 to 3.45] for SM-AHN; HR 1.77 [95% CI 1.07 to 2.94] for MCL). The final grade 3+ TEAE model is presented in **Table 9.**

The final grade 3+ TEAE model resulted in better fit compared to the model that included a disease state effect for all SM patients pooled together, which predicted a higher risk of grade 3+ TEAEs relative to GIST patients. This suggests that higher incidence of grade 3+ TEAEs in SM patients relative to GIST patients is largely driven by the SM-AHN and MCL subtypes.

Table 9. Applicant's Final Exposure-Response Model for Grade 3+ TEAEs

Parameter	Estimate	95% Confidence Interval
Baseline hazard (log scale)	-10.8	(-11.4, -10.2)
Shape parameter	-0.000115	(-0.000154, -0.0000761)
Exponent for $C_{average}$ (ng/mL)	0.16	(0.13, 0.19)
SM-AHN effect on baseline hazard	1.34	(0.97, 1.70)
MCL effect on baseline hazard	0.88	(0.22, 1.55)
SM-AHN effect on shape parameter	-0.000269	(-0.000459, -0.0000787)
MCL effect on shape parameter	-0.000162	(-0.000423, 0.0000989)

$C_{average}$ = individual average predicted concentration; MCL = mast cell leukemia; SM-AHN = systemic mastocytosis with associated hematological neoplasm; TEAE = treatment-emergent adverse event.
Source: Page 4 of Applicant's Response to FDA 23 February 2021 Information Request

4.2.1.3 Exposure-Response Simulations of Safety

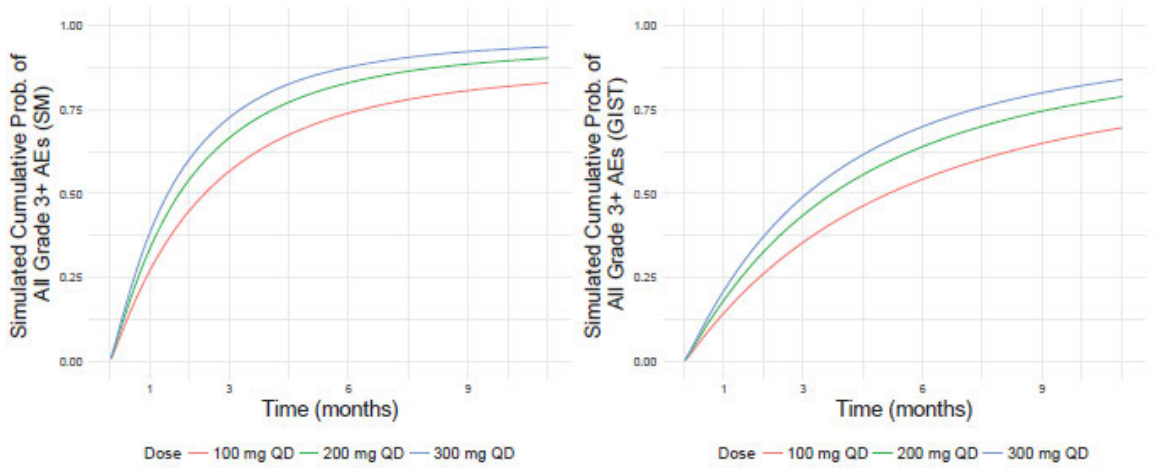
The final E-R time-to-event (TTE) models for safety were used to predict the cumulative probability of safety outcomes for 100 mg QD, 200 mg QD, and 300 mg QD dosing regimens in datasets of 1000 subjects created by resampling with replacement from GIST studies (BLU-285-1101 and BLU-285-1303) and SM studies (BLU-285-2101 and BLU-285-2202). Exposure (avapritinib $C_{average}$) was predicted by the final population PK model.

Figure 21 shows the simulation of grade 3+ TEAEs for patients with SM and for patients with GIST. The same dose is predicted to have a faster rate of grade 3+ TEAE onset in patients with SM compared to patients with GIST. **Figure 22** shows results from simulations performed by SM subtype, which compare MCL versus SM-AHN versus other SM subtypes (ASM, SSM, and ISM). The rate of grade 3+ TEAE onset was predicted to be faster in patients with MCL and with SM-AHN compared to other subtypes of SM. The cumulative probability of experiencing a grade 3+ TEAE by 12 months does not differ significantly between these SM subtypes, but patients with MCL and SM-AHN have higher cumulative probabilities of grade 3+ TEAEs at earlier time points. This could be related to the higher rate of disease-related cytopenias that were observed with the MCL and SM-AHN subtypes compared to other subtypes of SM.

The cumulative probability of pooled cognitive effects (any grade) was associated with exposure and increased with dose from 100 mg QD to 200 mg QD to 300 mg QD. However, the differences in this safety endpoint appear largely due to grade 1 cognitive effect. There was not a significant a difference in predicted cumulative probability of grade 2+ cognitive effects at 12 months after first dose between 100 mg QD, 200 mg QD, and 300 mg QD dosing regimens (**Figure 23**), potentially due to relatively low incidence rates in the E-R safety population.

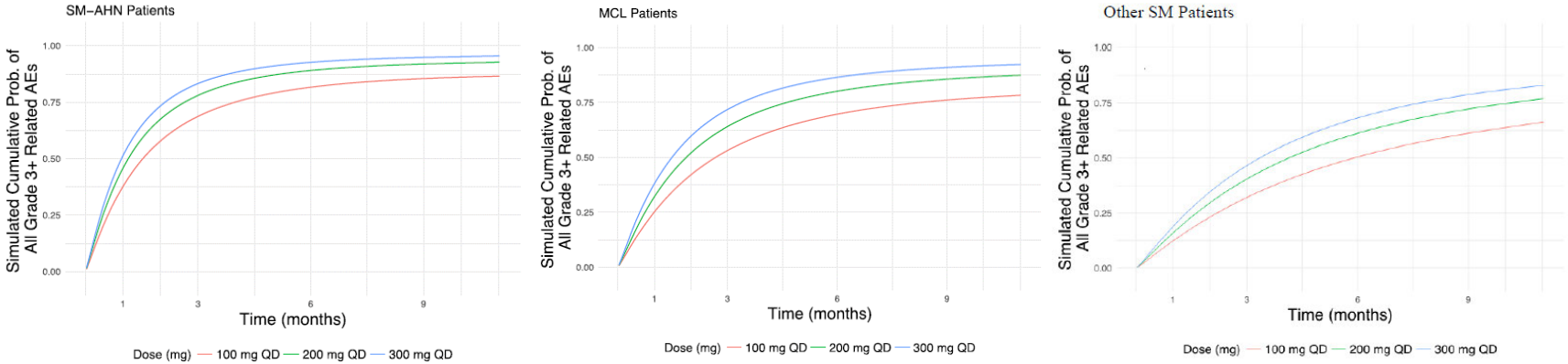
Similarly, there was not a clinically significant difference in predicted cumulative probability of grouped grade 2+ edema TEAEs at 12 months after first dose between 100 mg QD, 200 mg QD, and 300 mg QD dosing regimens (**Figure 23**).

Figure 21. Simulated Time to Grade 3+ TEAEs in Patients with SM (left) or GIST (right) from Model-Predicted Exposure



Exposure was simulated in 1000 virtual subjects resampled from safety dataset according to disease status. Solid lines represent median cumulative probability of grade 3+ TEAEs.
GIST = gastrointestinal stromal tumor; QD = once daily; SM = systemic mastocytosis; TEAE = treatment-emergent adverse event.
Source: Figure 58 from Applicant's Exposure-Response Analysis

Figure 22. Simulated Time to Grade 3+ TEAEs in Patients with SM-AHN (left), MCL (middle), or Other Subtypes of SM (right) from Model-Predicted Exposure

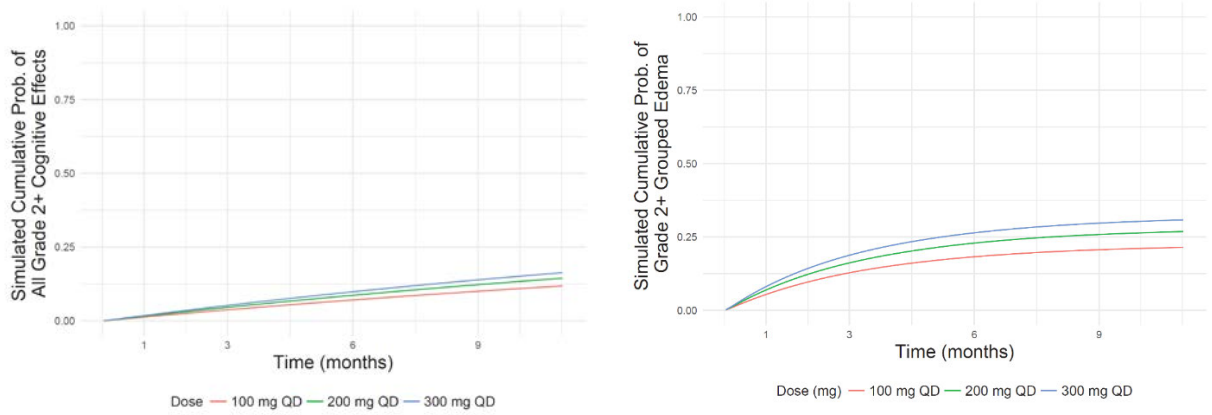


Other SM = Patients with ASM, SSM, or ISM. Exposure was simulated in 1000 virtual subjects resampled from safety dataset according to SM subtype. Solid lines represent median cumulative probability of grade 3+ treatment-emergent adverse events.

ASM = aggressive systemic mastocytosis; ISM = indolent systemic mastocytosis; MCL = mast cell leukemia; QD = once daily; SM = systemic mastocytosis; SM-AHN = systemic mastocytosis with associated hematologic neoplasm; SSM = smoldering systemic mastocytosis; TEAE = treatment-emergent adverse events.

Source: Figure 6, Figure 7, and Figure 8 from Applicant's Response to FDA 19 March 2021 Information Request

Figure 23. Simulations for Pooled Grade 2+ Cognitive Effects and Grade 2+ Edema



Solid lines represent median cumulative probability of treatment-emergent adverse events.
Source: Figure 60 and Figure 62 from Applicant's Exposure-Response Analysis

Reviewer Comments

Although the risks of grade ≥3 TEAEs, grade ≥2 cognitive effects, and grade ≥2 edema events are higher with increased dose, E-R safety modeling and simulation supports the conclusion that avapritinib 200 mg once daily has an acceptable safety profile in subjects with AdvSM.

4.2.1.4 Intracranial Bleed Analysis by Baseline Platelet Count

Intracranial bleeding events (all grades) occurred in 18/527 (3.4%) total subjects in the E-R safety dataset. GIST subjects experienced 7 intracranial bleeding events (out of 383 total subjects with GIST), AdvSM subjects experienced 10 intracranial bleeding events (out of 127 total subjects with ASM, MCL, or SM-AHN), and non-advanced SM subjects experienced 1 intracranial bleeding event (out of 16 total subjects with ISM or SSM).

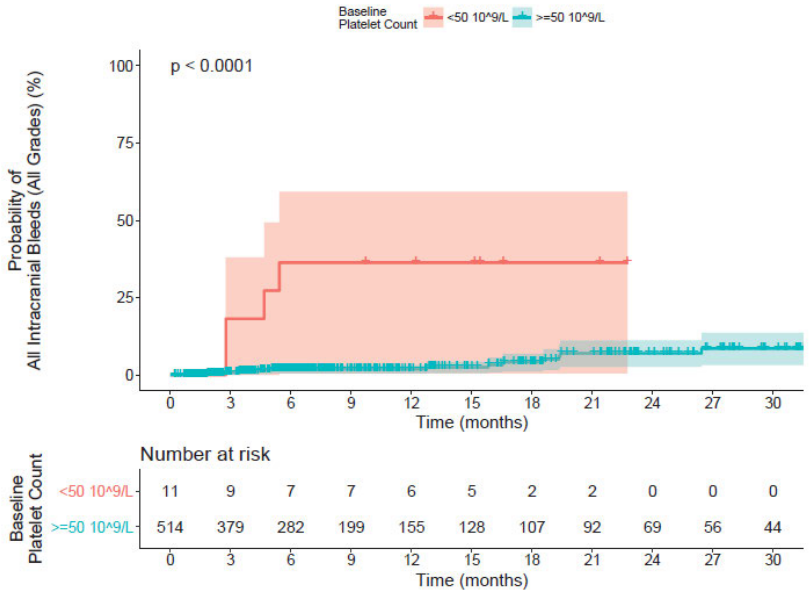
Although intracranial bleed risk was not significantly associated with avapritinib exposure quartile, both baseline platelet count and time-varying platelet count were found to have significant associations with intracranial bleed incidence. Out of 11 subjects with baseline platelet count $<50 \times 10^9$/L, intracranial bleeding occurred in 4/11 (36.4%) subjects. All subjects with baseline platelet count $<50 \times 10^9$/L were subjects with AdvSM (2 subjects with MCL and 9 subjects with SM-AHN). **Figure 24** shows the Kaplan-Meier curves for subjects with baseline platelet count $\geq 50 \times 10^9$/L (n = 514) versus $<50 \times 10^9$/L (n = 11). Subjects with baseline platelet count $<50 \times 10^9$/L had a significantly higher incidence of intracranial bleeding events.

Additionally, out of 11 subjects with SM who experienced an intracranial bleed event (1 subject with ASM, 8 subjects with SM-AHN, 1 subject with MCL, and 1 subject with SSM), 9/11 (81.8%) also experienced a platelet count $<50 \times 10^9$/L during treatment. There was no association with baseline platelet count or thrombocytopenia during treatment and intracranial bleeding events in subjects with GIST.

Because of the association between platelet count and intracranial bleeding, $C_{average}$ was investigated for relationships with platelets. The Applicant found no clear relationship

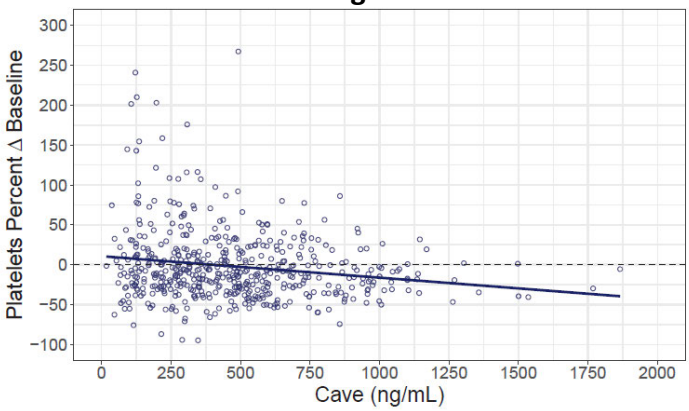
(**Figure 25**) between $C_{average}$ and percent change from platelet baseline nor between $C_{average}$ and platelet nadir in the first 2 months of therapy.

Figure 24. Time to All Intracranial Bleeds versus Baseline Platelet Count



Solid lines represent Kaplan-Meier curves, shaded areas represent 95% CIs, and the p-value is derived from a log-rank test. Note: 22 patients in the ISS dataset experience an ICB, however 2 events occurred in patients >2 days after their last exposure to avapritinib and were excluded, and 2 events occurred in patients without valid PK.
Source: Figure 37 from Applicant's Exposure-Response Analysis

Figure 25. Platelet Percent Change from Baseline versus $C_{average}$ in the E-R Safety Dataset



Solid lines represent linear trend. $C_{average}$ = individual average predicted concentration
Source: Figure 47 from Applicant's Exposure-Response Analysis

Reviewer Comments

Because neither baseline platelet count nor low platelet count during treatment were associated with intracranial bleeding events in patients with GIST, it is acceptable not to include subjects

with GIST in the proposed recommendation to interrupt avapritinib dosing in patients with platelet count <50 × 10^9/L.

*The number of intracranial bleed events (any grade) according to baseline platelet count and disease status is presented in **Table 10**. Subjects with AdvSM were much more likely to have low baseline platelet counts (<50 × 10^9/L, <75 × 10^9/L, or <100 × 10^9/L) compared to subjects with GIST, which is to be expected as AdvSM is a clonal mast cell neoplasm with infiltration of bone marrow. Because of this, it is acceptable not to include subjects with GIST in the proposed recommended limitation of use based on baseline platelet count.*

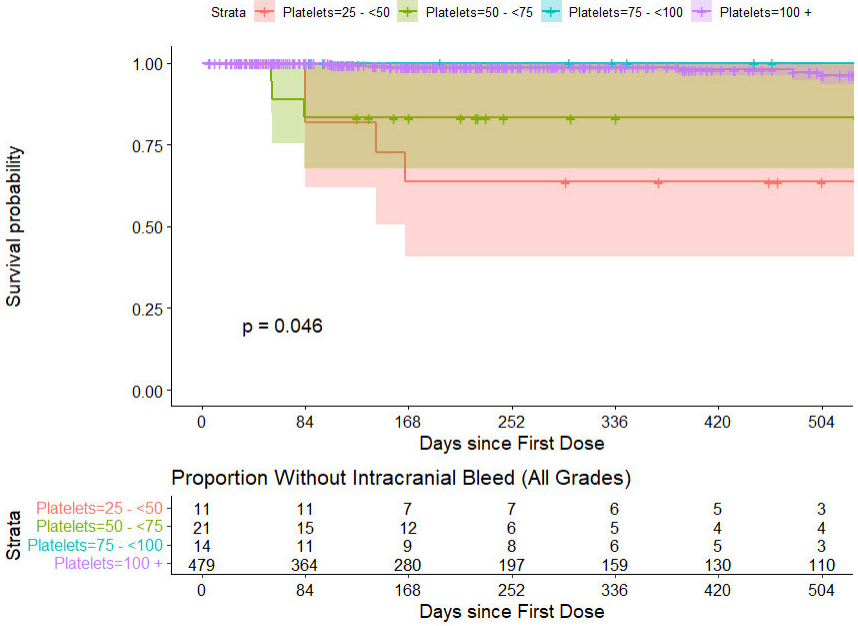
In order to assess the relationship between intracranial bleeding and additional baseline platelet count cutoffs, Kaplan-Meier curves were plotted in **Figure 26** *for baseline platelet count categories of 25 to <50 × 10^9/L (n = 11), 50 to <75 × 10^9/L (n = 21), 75 to <100 × 10^9/L (n = 14), and ≥100 × 10^9/L (n = 479). Subjects with lower baseline platelet count were significantly more likely to experience an intracranial bleeding event compared to subjects with higher baseline platelet count. Subjects with baseline platelet count of 25 to <50 × 10^9/L had higher incidence of intracranial bleeding compared to subjects with baseline platelet counts ≥50 × 10^9/L. This supports the conclusion that avapritinib should not be recommended for treatment in subjects with AdvSM who have baseline platelet count <50 × 10^9/L due to high risk of intracranial bleeding events.*

Table 10. Intracranial Bleed Event Incidence (All Grades) in the Exposure-Response Safety Population According to Baseline Platelet Count and Disease Status (AdvSM versus GIST)

	ASM		SM-AHN		MCL		AdvSM (ASM + MCL + SM-AHN)		GIST	
	n	n (%) with ICB	n total	n (%) with ICB	n	n (%) with ICB	n	n (%) with ICB	n	n (%) with ICB
All Subjects	17	1 (5.9%)	87	8 (9.2%)	23	1 (4.3%)	127	10 (7.9%)	383	7 (1.8%)
Baseline Platelet Count										
25 × 10^9/L - <50 × 10^9/L	0	-	9	3 (33.3%)	2	1 (50%)	11	4 (36.4%)	0	-
50 × 10^9/L - <75 × 10^9/L	2	1 (50%)	17	3 (17.6%)	2	0 (0%)	21	4 (19%)	0	-
75 × 10^9/L - <100 × 10^9/L	1	0 (0%)	12	1 (8.3%)	0	-	13	1 (7.7%)	0	-
100 × 10^9/L and up	14	0 (0%)	49	1 (2%)	19	0 (0%)	82	1 (1.2%)	381	7 (1.8%)
Missing platelet count	0	-	0	-	0	-	0	-	2	0 (0%)

AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; GIST = gastrointestinal stromal tumor; ICB = intracranial bleed; MCL = mast cell leukemia; n = number of subjects; SM-AHN = systemic mastocytosis with associated hematological neoplasm.
Source: Reviewer Analysis of Applicant's Datasets

Figure 26. Proportion of Subjects Without Intracranial Bleed Events (All Grades) versus Baseline Platelet Count Categories



Solid lines represent Kaplan-Meier curves, shaded areas represent 95% confidence intervals, and the p-value is derived from a log-rank test. Platelet counts refer to baseline platelet count values (number of platelets x 10^9/L). Survival probability refers to probability of not experiencing an intracranial bleed event.
Source: Reviewer Analysis of Applicant's Datasets

4.2.1.5 Reviewer's Independent Analysis of Safety

Introduction

The reviewer conducted additional analyses in order to verify the Applicant's final TTE safety models and the Applicant's covariate analyses.

Methods

Dataset handling and generation of diagnostics and other plots was conducted using R version 4.0.2. NONMEM version 7.3 was used for model analysis. Datasets were provided by the Applicant for each safety endpoint that was investigated in a model. Additional models were developed by editing the final model control file provided by the Applicant.

Results

Additional TTE models were tested using the Applicant's final TTE model as a reference for respective safety endpoints. Key models in the analyses are summarized in **Table 11**, and any changes from the reference model structure are in the model description.

Table 11. Summary of Independent Review Grade 3+ TEAE TTE Model Runs

Run number	Model description	OFV	dOFV	Comments
Reference	Applicant's final model with SM-AHN effects on baseline hazard and shape AND MCL effects on baseline hazard and shape	6956.5	-	Highest RSE is 82.1% (MCL effect on shape); MCL effect on shape parameter final estimate has 95% CI of which contains zero (-4.23E-04 to 9.87E-05).
002	Removed separate SM-AHN and MCL effects; added SM-AHN/MCL effect on baseline hazard plus SM-AHN/MCL effect on shape	6958.2	+1.7	Highest RSE is 32.4% (SM-AHN/MCL effect on shape); 95% CI does not include zero for any parameter.
003	Removed MCL effects on baseline hazard and shape	6962.4	+5.9	Highest RSE is 36.5% (SM-AHN effect on shape).
004	Removed MCL effect on shape	6958.2	+1.8	Highest RSE is 45.8% (MCL on base hazard).
005	Removed SM-AHN and MCL effects on shape	6970.0	+13.5	Highest RSE is 45.3% (MCL on base hazard).

Source: Reviewer Analysis

The Applicant's final model and the model in run 002 appear acceptable. Run 002 removed the separate estimates for effects of SM-AHN and MCL. Although the run 002 OFV increased slightly compared to the reference model, run 002 does not have any parameters with a 95% CI that includes the null hypothesis of zero. The results of run 002 suggest that there is no significant difference in rate of grade 3+ TEAE onset between SM-AHN and MCL patients. However, the Applicant's final model and the Reviewer's independent analysis both demonstrate that rate of grade 3+ TEAE onset is significantly higher in patients with SM-AHN or MCL compared to patients with GIST or other SM subtypes.

4.2.2 Analysis of Efficacy

The overall efficacy population consisted of 127 subjects with ASM, SM-AHN, MCL, or SSM with both efficacy data and PK data, although not all subjects had data for all efficacy endpoints. Two sub-populations of efficacy were used for exposure-response analysis. The Response Assessment Committee Response-Evaluable (RAC-RE) population consisted of 84 subjects with a RAC-adjudicated diagnosis of SM-AHN, ASM, or MCL. The Pure Pathologic Response-Evaluable (PPRE) population consisted of 101 subjects with a RAC-adjudicated diagnosis of SSM, SM-AHN, ASM, or MCL. Covariates for the RAC-RE population and the PPRE population are summarized in **Table 12**. The RAC-RE population served as the primary analysis population for efficacy.

The final avapritinib population PK model was used to predict daily $AUC_{0\text{-}24}$ and cumulative AUC from time of first dose to time of event ($AUC_{cumulative}$). The $C_{average}$ was calculated as the $AUC_{cumulative}$ divided by the time to event, and $C_{average}$ served as the exposure metric for exposure-response analyses.

Table 12. Summary of Subject Covariates in the Exposure-Efficacy Datasets

Covariate	Statistic	Efficacy Population	PPRE sub-population	RAC-RE sub-population
	Total (n)	**127**	**101**	**84**
SM Subtype	MCL [n (%)]	23 (18.1 %)	17 (16.8 %)	17 (20.2 %)
	ASM [n (%)]	16 (12.6 %)	10 (9.9 %)	5 (6.0 %)
	SM-AHN [n (%)]	86 (67.7 %)	72 (71.3 %)	62 (73.8 %)
	SSM [n (%)]	2 (1.6 %)	2 (2.0 %)	0
Dose	30 mg once daily [n (%)]	3 (2.4%)	3 (3%)	3 (3.6%)
	60 mg once daily [n (%)]	4 (3.1%)	4 (4%)	3 (3.6%)
	100 mg once daily [n (%)]	3 (2.4%)	2 (2%)	2 (2.4%)
	130 mg once daily [n (%)]	1 (0.8%)	1 (1%)	1 (1.2%)
	200 mg once daily [n (%)]	74 (58.3%)	49 (48.5%)	43 (51.2%)
	300 mg once daily [n (%)]	36 (28.3%)	36 (35.6%)	27 (32.1%)
	400 mg once daily [n (%)]	6 (4.7%)	6 (5.9%)	5 (6%)
Age (years)	Mean (SD)	65.8 (10.9)	65.1 (10.6)	64.7 (11)
	Median	68	67	66.5
	Min - Max	31 - 85	34 - 85	34 - 85
Sex	Male [n (%)]	72 (56.7%)	57 (56.4%)	47 (56%)
	Female [n (%)]	55 (43.3%)	44 (43.6%)	37 (44%)
Race	White	112 (88.2%)	94 (93.1%)	78 (92.9%)
	Black or African-American	1 (0.8%)	1 (1%)	1 (1.2%)
	Asian	3 (2.4%)	2 (2%)	2 (2.4%)
	Other	11 (8.7%)	4 (4%)	3 (3.6%)
Body Weight (kg)	Mean (SD)	73.9 (15.8)	74.7 (15.6)	76 (15.4)
	Median	71	73.8	76.7
	Min - Max	42.5 - 106	42.5 - 104.7	42.5 - 104.7
Lean Body Weight (kg)	Mean (SD)	51.7 (11.6)	52.1 (11.6)	52.7 (11.5)
	Median	53.1	53.1	53.3
	Min - Max	29.6 - 74.3	29.6 - 71.7	29.6 - 71.7
Creatinine Clearance (mL/min)	Mean (SD)	91.2 (37.5)	93.8 (37.3)	98.3 (38.7)
	Median	85.2	90.3	95.9
	Min - Max	34.2 - 214.9	34.2 - 214.9	34.2 - 214.9
Estimated Glomerular Filtration Rate (mL/min/1.73 m^2)	Mean (SD)	88.7 (31.9)	90 (33.5)	92.8 (35.3)
	Median	86.5	86.5	89.2
	Min - Max	41.9 - 273.1	41.9 - 273.1	43.4 - 273.1
Renal function category (eGFR)	Normal [n (%)]	57 (44.9%)	45 (44.6%)	41 (48.8%)
	Mild Dysfunction [n (%)]	51 (40.2%)	44 (43.6%)	33 (39.3%)
	Moderate Dysfunction [n (%)]	19 (15%)	12 (11.9%)	10 (11.9%)
Hepatic Function Category	Normal [n (%)]	103 (81.1%)	82 (81.2%)	66 (78.6%)
	Mild Dysfunction [n (%)]	17 (13.4%)	13 (12.9%)	12 (14.3%)
	Moderate Dysfunction [n (%)]	7 (5.5%)	6 (5.9%)	6 (7.1%)
Prior Midostarin Use	No prior midostaurin [n (%)]	73 (57.5%)	63 (62.4%)	51 (60.7%)
	Prior midostaurin [n (%)]	54 (42.5%)	38 (37.6%)	33 (39.3%)
PPI Use	No PPI use ≥14 days prior to any PK samples [n (%)]	71 (55.9%)	62 (61.4%)	52 (61.9%)
	PPI use between 5-14 days prior to ≥1 PK sample [n (%)]	3 (2.4%)	2 (2%)	2 (2.4%)
	PPI use for ≥5 days prior to ≥1 PK sample [n (%)]	53 (41.7%)	37 (36.6%)	30 (35.7%)

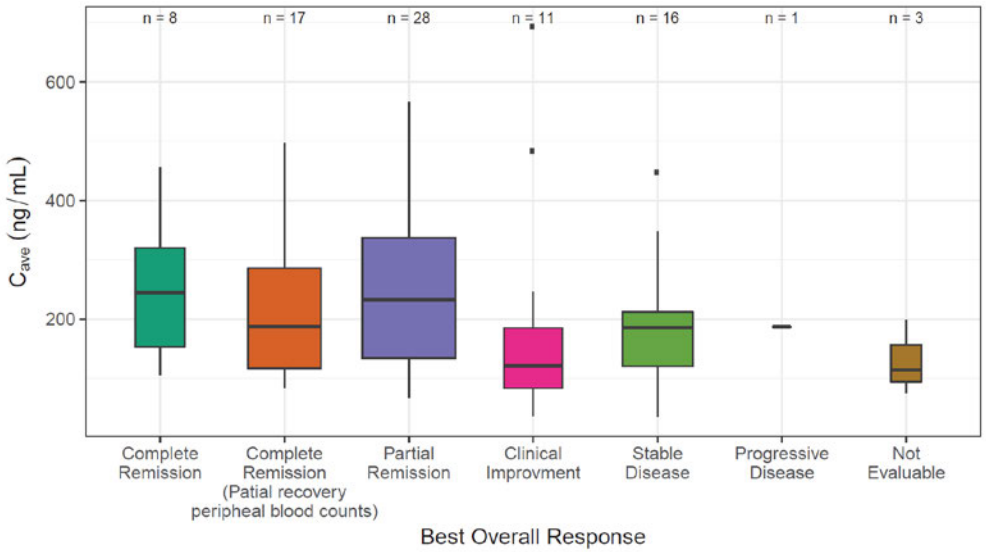
ASM = aggressive systemic mastocytosis; eGFR = estimated glomerular filtration rate; GIST = gastrointestinal stromal tumor; MCL = mast cell leukemia; PK = pharmacokinetic; PPI = proton pump inhibitor; PPRE = pure pathologic response-evaluable; RAC-RE = Response Assessment Committee response evaluable; SM = systemic mastocytosis; SM-AHN = systemic mastocytosis with associated hematological neoplasm; SSM = smoldering systemic mastocytosis.
Source: Reviewer Analysis of Applicant's Datasets

4.2.2.1 Exposure-Response Analysis of Efficacy

The PPRE population (n=101) was used for E-R analysis of Best Overall Morphologic Response (mBOR), Duration of Morphologic Response (mDOR), Time to Morphologic Response (mTTR), and Time to Complete Morphologic Remission (mTTCR).
The RAC-RE population (n=84) was used for the primary E-R analysis of Best Overall Response (BOR), Progression-Free Survival (PFS), Duration of Response (DOR), Time to Response (TTR), and Time to Complete Remission (TTCR).

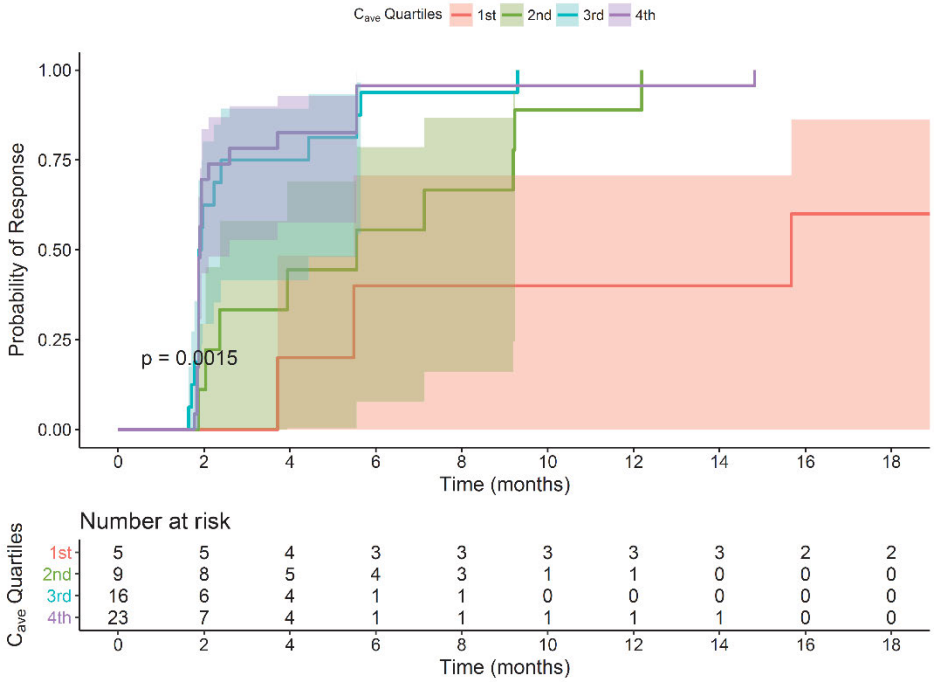
Graphical analysis was performed for all efficacy endpoints. Statistical comparison of efficacy by $C_{average}$ quartiles using a log-rank test was performed for all efficacy endpoints except for BOR and mBOR. The BOR according to exposure is presented in **Figure 27**. The TTR according to exposure quartile is presented in **Figure 28**. A summary of the Applicant's E-R analyses of efficacy is presented in **Table 13;** significant relationships between higher exposure and higher response were identified for TTR, mTTR, time to complete remission, and time to complete morphologic remission.

Figure 27. Best Overall Response versus Exposure: RAC Adjudicated Responses in the RAC-RE Population



C_{ave} = individual predicted average concentration; RAC-RE = Response Assessment Committee response evaluable.
Source: Figure 9 from Applicant's Exposure-Response Analysis

Figure 28. Time to Response versus Exposure: RAC Adjudicated Responses in the RAC-RE Population



Solid lines represent Kaplan-Meier curves, shaded areas represent 95% confidence intervals, and p-value is derived from a log-rank test. Note: plot truncated at 18 months.
C_{ave} = individual predicted average concentration; RAC-RE = Response Assessment Committee response evaluable.
Source: Figure 14 from Applicant's Exposure-Response Analysis

Table 13. Summary of Efficacy Endpoints in Applicant's Exposure-Response Graphical Analysis

Efficacy Endpoint	Exposure Metric	Population Analyzed	Exposure-Response Analysis Result
Best Overall Response[a]	$C_{average}$ (continuous)	RAC-RE (n=84)	No statistical comparison performed; no significant trends.
Best Overall Morphologic Response[b]	$C_{average}$ (continuous)	PPRE (n=101)	No statistical comparison performed; no significant trends.
Progression-Free Survival	$C_{average}$ (quartiles)	RAC-RE (n=84)	No significant difference between exposure quartiles.
Duration of Response	$C_{average}$ (quartiles)	RAC-RE (n=84)	No significant difference between exposure quartiles.
Duration of Morphologic Response	$C_{average}$ (quartiles)	PPRE (n=101)	No significant difference between exposure quartiles.
Time to Response	$C_{average}$ (quartiles)	RAC-RE (n=84)	Higher exposure was associated with faster response (p=0.0015).
Time to Morphologic Response	$C_{average}$ (quartiles)	PPRE (n=101)	Higher exposure was associated with faster morphologic response (p<0.0001).
Time to Morphologic Response	$C_{average}$ (continuous)	PPRE (n=101)	Higher exposure was associated with faster morphologic response in E-R model.
Time to Complete Remission	$C_{average}$ (quartiles)	RAC-RE (n=84)	Higher exposure was associated with faster complete remission (p=0.00065).
Time to Complete	$C_{average}$	PPRE	Higher exposure was associated with faster

Morphologic Remission	(quartiles)	(n=101)	complete morphologic remission (p=0.021).

[a]Best Overall Response included Complete Remission (CR), CR with Partial Recovery of Peripheral Blood Counts (CRh), Partial Remission (PR), Clinical Improvement (CI), Stable Disease (SD), Progressive Disease (PD), and Not Evaluable (NE) using mIWG criteria.

[b]Best Overall Morphologic Response included Complete Morphologic Remission (mCR), mCR with Partial Recovery of Peripheral Blood Counts (mCRh), Morphologic Partial Remission (mPR), Clinical Improvement (CI), Stable Disease (SD), Progressive Disease (PD), and Not Evaluable (NE) using Pure Pathologic Response criteria.

$C_{average}$ = individual predicted average concentration; mIWG = Modified International Working Group; PPRE = pure pathologic response-evaluable; RAC-RE = Response Assessment Committee response evaluable.

Source: Reviewer Analysis of Applicant's Exposure-Response Analysis

Analysis according to SM subtype (MCL versus ASM versus SM-AHN versus SSM) was also performed for all efficacy endpoints, (b) (4)

SM subtype did not have any clear trends with BOR or mBOR, which are summarized in **Table 14**. Additionally, there were no clear trends or associations between SM subtype and duration of response, duration of morphological response, time to response, or time to complete remission, or time to morphological complete remission.

There was a significant relationship between time to morphological response and SM subtype in the PPRE population. The probability of morphologic response (which included complete morphologic remission [mCR], mCR with partial recovery of peripheral blood counts [mCRh], and morphologic partial remission [mPR]) up to 18 months after first dose was also lower for subjects with MCL compared to subjects with ASM or SM-AHN in the PPRE population (**Figure 29**). However, time to response in the RAC-RE population (which included complete remission [CR], CR with partial recovery of peripheral blood counts [CRh], and partial remission [PR]) had no clear differences between subtypes of SM (**Figure 30**).

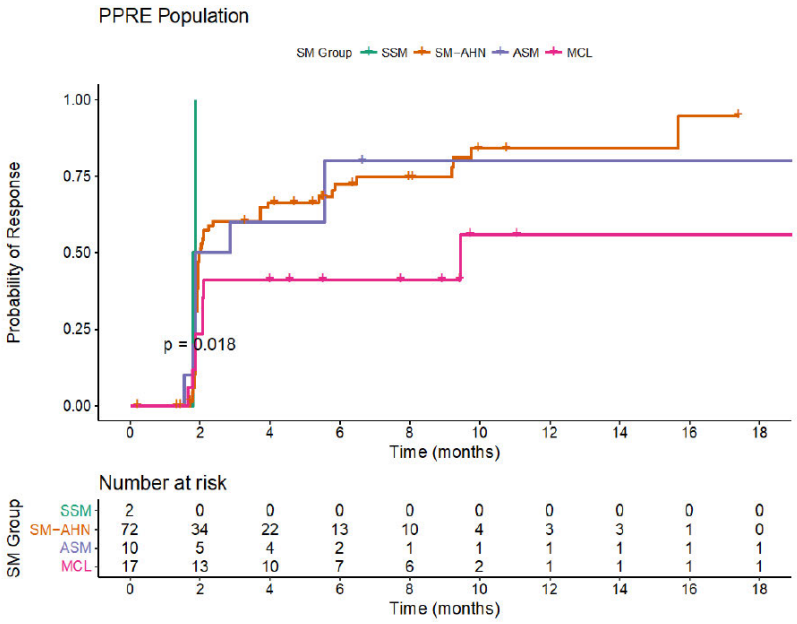
Table 14. Best Overall Response and Best Overall Morphologic Response by SM Subtype

BOR (RAC-RE Population)	**SSM (n = 0)**	**SM-AHN (n = 62)**	**ASM (n = 5)**	**MCL (n = 17)**	**Overall (n = 84)**
Complete Remission	0	5 (8.1%)	0	3 (17.6%)	8 (9.5%)
Complete Remission (Partial Recovery Peripheral Blood Counts)	0	14 (22.6%)	3 (60%)	0	17 (20.2%)
Partial Remission	0	21 (33.9%)	2 (40%)	5 (29.4%)	28 (33.3%)
Clinical Improvement	0	9 (14.5%)	0	2 (11.8%)	11 (13.1%)
Stable Disease	0	10 (16.1%)	0	6 (35.3%)	16 (19%)
Progressive Disease	0	0	0	1 (5.9%)	1 (1.2%)
Not Evaluable	0	3 (4.8%)	0	0	3 (3.6%)
mBOR (PPRE Population)	**SSM (n = 2)**	**SM-AHN (n = 72)**	**ASM (n = 10)**	**MCL (n = 17)**	**Overall (n = 101)**
Morphologic Complete Remission	2 (100%)	9 (12.5%)	2 (20%)	5 (29.4%)	18 (17.8%)
Morphologic Complete Remission (Partial Recovery Peripheral Blood Counts)	0	20 (27.8%)	4 (40%)	1 (4%)	25 (24.8%)

Morphologic Partial Remission	0	25 (34.7%)	2 (20%)	3 (17.6%)	30 (29.7%)
Clinical Improvement	0	0	0	0	0
Stable Disease	0	17 (23.6%)	2 (20%)	8 (47.1%)	27 (26.7%)
Progressive Disease	0	0	0	0	0
Not Evaluable	0	1 (1.4%)	0	0	1 (1%)

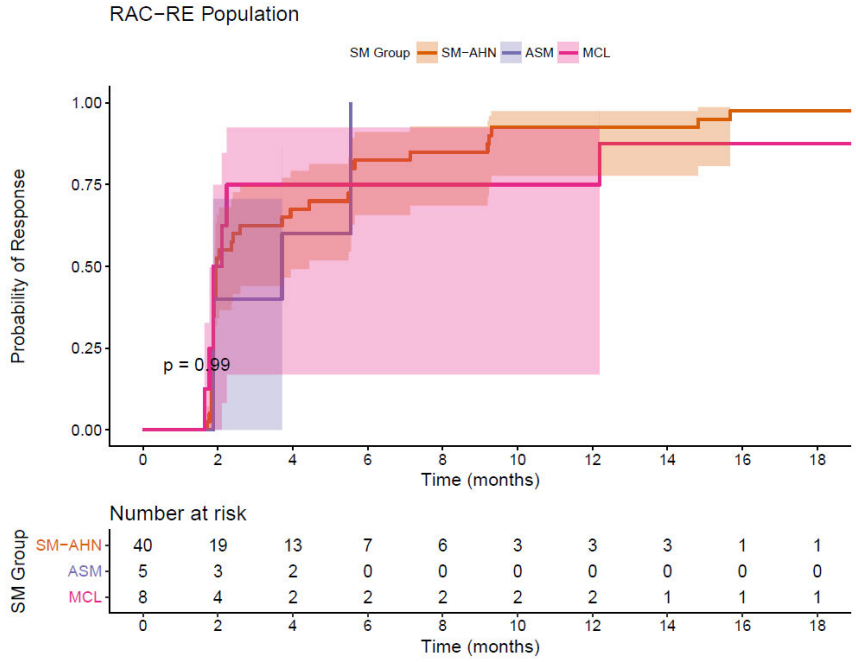
ASM = aggressive systemic mastocytosis; BOR = best overall response; mBOR = best overall morphologic response; MCL = mast cell leukemia; PPRE = pure pathologic response-evaluable; RAC-RE = Response Assessment Committee response evaluable; SM = systemic mastocytosis; SM-AHN = systemic mastocytosis with associated hematological neoplasm; SSM = smoldering systemic mastocytosis.
Source: Reviewer Analysis of Applicant's Datasets

Figure 29. Time to Morphological Response versus Disease State: PPRE Population



Solid lines represent Kaplan-Meier curves and p-value is derived from a log-rank test. Plot truncated at 18 months.
ASM = aggressive systemic mastocytosis; MCL = mast cell leukemia; PPRE = pure pathologic response-evaluable; SM = systemic mastocytosis; SM-AHN = systemic mastocytosis with associated hematological neoplasm; SSM = smoldering systemic mastocytosis.
Source: Figure 4 from Applicant's Response to FDA 19 March 2021 Information Request

Figure 30. Time to Response versus Disease State: RAC-RE Population



Solid lines represent Kaplan-Meier curves, shaded areas represent 95% confidence intervals, and p-value is derived from a log-rank test. Note: plot truncated at 18 months.
ASM = aggressive systemic mastocytosis; MCL = mast cell leukemia; RAC-RE = Response Assessment Committee response evaluable; SM = systemic mastocytosis; SM-AHN = systemic mastocytosis with associated hematological neoplasm.
Source: Appendix page 16 of Applicant's Response to FDA 19 March 2021 Information Request

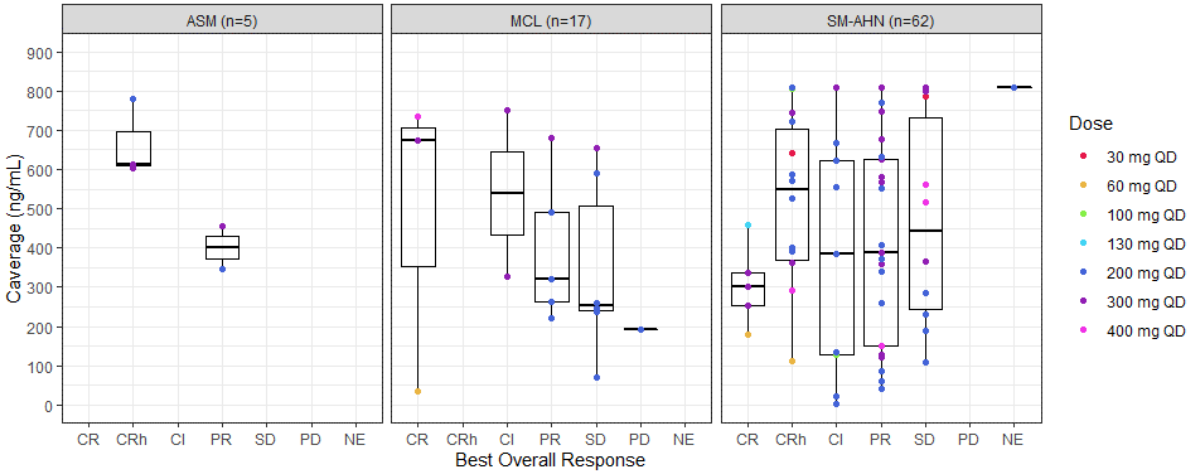
Reviewer Comments

*Exposure is summarized according to SM subtype and BOR in **Figure 31.** The small number of subjects with ASM in the RAC-RE population (n = 5) is a limitation, but all three ASM subjects with best overall response of CRh have higher $C_{average}$ values than the two ASM subjects with best overall response of PR. Additionally, there is a trend in subjects with MCL (n=17) where median $C_{average}$ in subjects with CR was higher than the median $C_{average}$ of any other response.*

*Exposure according to SM subtype and mBOR is shown in **Figure 32**. Unlike best overall response in MCL patients in the RAC-RE population, there is no clear trend between median $C_{average}$ and best overall morphologic response in MCL patients in the PPRE population. There is also no clear trend between morphologic response and $C_{average}$ in subjects with ASM, with relatively few ASM subjects (n = 10).*

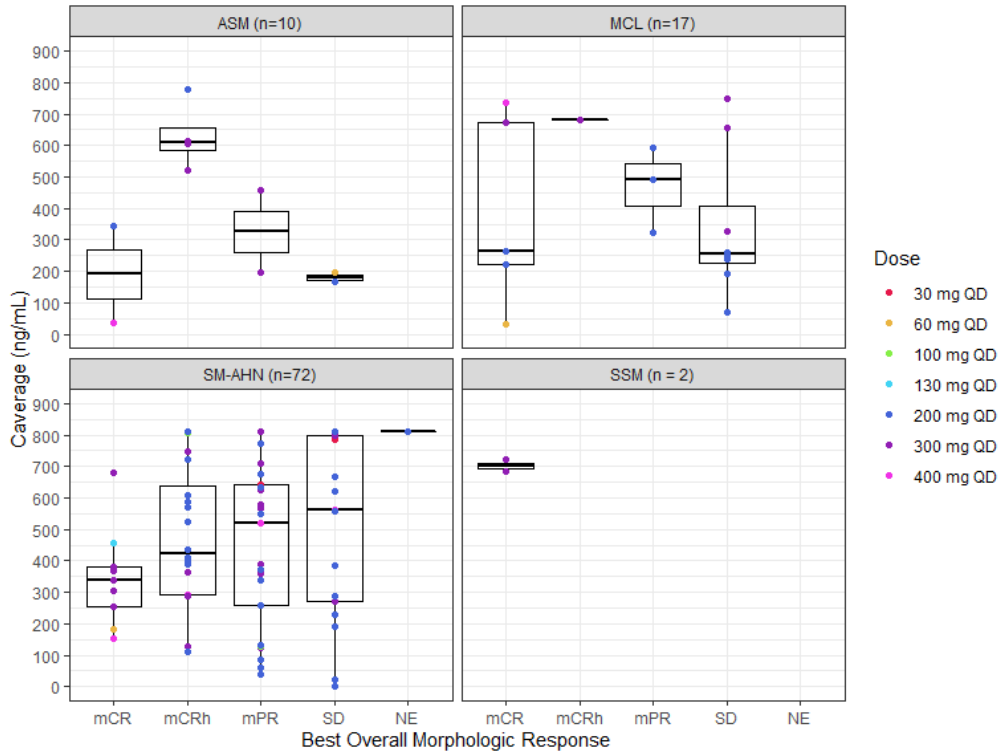
Although certain SM subtypes had small sample sizes for evaluation of BOR or mBOR, the $C_{average}$ values largely overlapped between SM subtypes. Individual $C_{average}$ also overlapped considerably between BOR and mBOR categories within each SM subtype and overall.

Figure 31. Best Overall Response by SM Subtype in the RAC-RE Population



Points represent individual $C_{average}$. Best Overall Response included Complete Remission (CR), CR with Partial Recovery of Peripheral Blood Counts (CRh), Partial Remission (PR), Clinical Improvement (CI), Stable Disease (SD), Progressive Disease (PD), and Not Evaluable (NE).
ASM = aggressive systemic mastocytosis; $C_{average}$ = individual average predicted concentration; MCL = mast cell leukemia; QD = once daily; RAC-RE = Response Assessment Committee response evaluable; SM = systemic mastocytisis; SM-AHN = systemic mastocytosis with associated hematological neoplasm.
Source: Reviewer Analysis of Applicant's Datasets

Figure 32. Best Overall Morphologic Response by SM Subtype in the PPRE Population

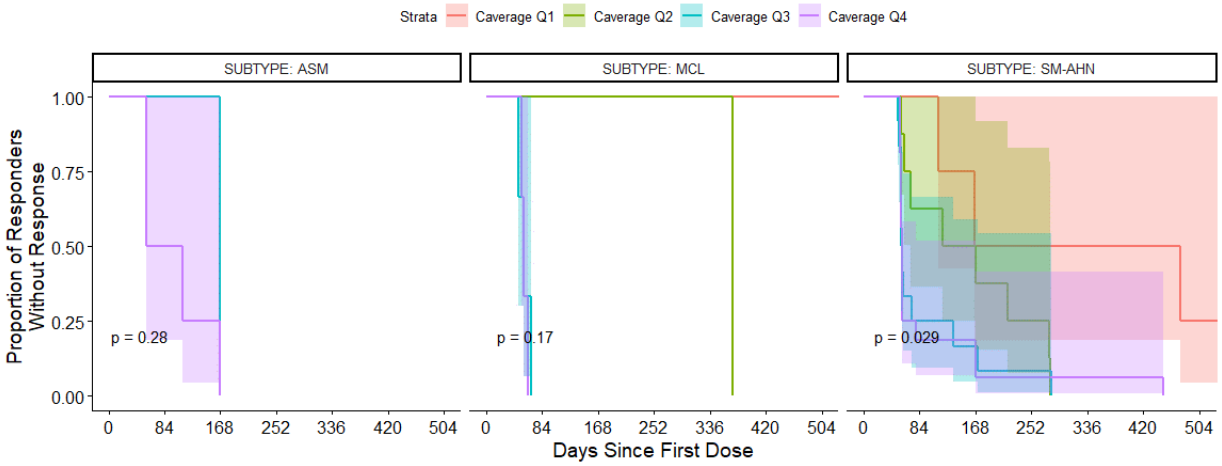


Points represent individual $C_{average}$. Best Overall Morphologic Response included Complete Morphologic Remission (mCR), mCR with Partial Recovery of Peripheral Blood Counts (mCRh), Morphologic Partial Remission (mPR), Stable Disease (SD), Progressive Disease (PD), and Not Evaluable (NE).

ASM = aggressive systemic mastocytosis; $C_{average}$ = individual average predicted concentration; MCL = mast cell leukemia; PPRE = pure pathologic response-evaluable; QD = once daily; SM = systemic mastocytosis; SM-AHN = systemic mastocytosis with associated hematological neoplasm; SSM = smoldering systemic mastocytosis.
Source: Reviewer Analysis of Applicant's Datasets

Higher avapritinib exposure was associated with faster time to response in the RAC-RE population, which included all SM subtypes. There were a limited number of subjects with ASM (n=5) and MCL (n=17) in the RAC-RE population, which made it difficult to conclude the relationships with exposure in those SM subtypes. A total of 53 subjects in the RAC-RE population (out of 84 total) responded, which included 5 subjects with ASM, 8 subjects with MCL, and 40 subjects with SM-AHN. ***Figure 33*** *shows TTR for each SM subtype. Higher avapritinib* $C_{average}$ *quartile was associated with faster time to response in subjects with SM-AHN. There was not a statistically significant trend between TTR and exposure quartile for ASM or MCL, although this is likely due to limited numbers of subjects.*

Figure 33. Time to Response versus Quartiles of $C_{average}$: RAC-RE Population According to AdvSM Subtype



Solid lines represent Kaplan-Meier curves, shaded areas represent 95% confidence intervals, and p-value is derived from a log-rank test. Note: plot truncated at 504 days.
53/84 subjects in the RAC-RE dataset responded to treatment. 5/5 subjects with ASM, 8/17 subjects with MCL, and 40/62 subjects with SM-AHN in the RAC-RE dataset responded to treatment.
AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; $C_{average}$ = individual average predicted concentration; MCL = mast cell leukemia; Q = quartile; RAC-RE = Response Assessment Committee response evaluable; SM-AHN = systemic mastocytosis with associated hematological neoplasm.
Source: Reviewer Analysis of Applicant's Datasets

4.2.2.2 Exposure-Efficacy Model Development and Results

Time-to-event modeling was performed for the mTTR endpoint of efficacy in the PPRE population. The final exposure-response model for mTTR is described in **Table 15**.

The final model included a significant effect of avapritinib exposure where higher $C_{average}$ was associated with higher morphological response and a significant effect of MCL where patients with MCL were predicted to have lower incidence of morphological response compared to subjects with ASM, SM-AHN, or SSM. The final model also included separate Gompertz shape parameters (γ1 and γ2) for treatment durations of ≤84 days (3 cycles or fewer) and >84 days (greater than 3 cycles).

Baseline covariates of gender, race, body weight, age group (≤65 years or >65 years), region of the world, baseline bone marrow mast cells, baseline serum tryptase, and prior midostaurin use were investigated but none were significant.

Subjects with MCL were predicted to have lower incidence of response independent of effects from daily $C_{average}$ and duration of treatment (≤84 days versus >84 days). However, higher exposure was associated with higher response in all SM subgroups, including MCL.

Table 15. Applicant's Parameter Estimates from the Final Time-to-Event Exposure-Response Model for Morphological Time to Response

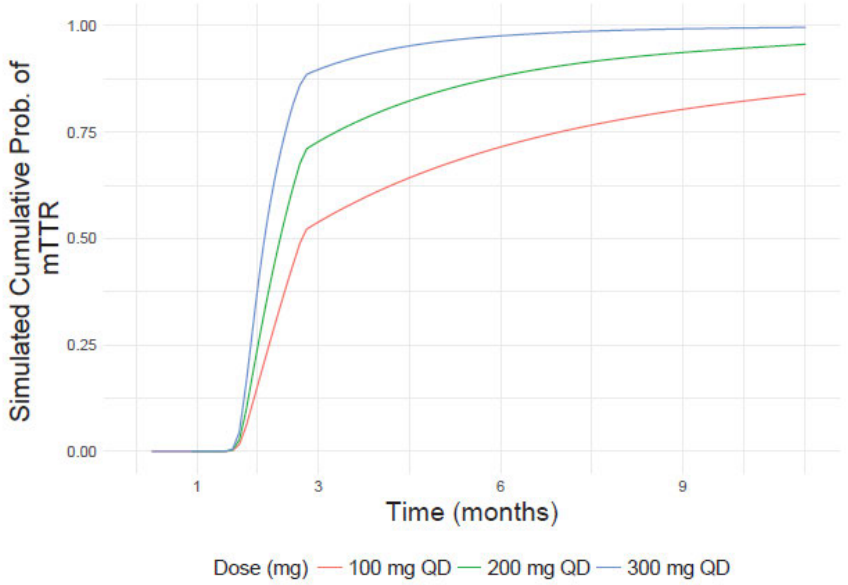
Parameter	Estimate	%RSE	95% Confidence Interval
Baseline hazard (log scale)	-8.56	2.92	(-9.05,-8.07)
T50 (hours)	1238	2.17	(1185,1290)
Hill coefficient	37	24.2	(19.4,54.5)
Slope for Daily $C_{average}$ (ng/mL)	0.00311	13	(0.00232,0.0039)
γ1 (≤84 days of treatment)	0.65	28.1	(0.29,1.01)
γ2 (>84 days of treatment)	-0.1213 (fixed)	-	-
MCL versus ASM/SM-AHN/SSM	-1.27	29	(-1.99,-0.55)

ASM = aggressive systemic mastocytosis; $C_{average}$ = individual average predicted concentration; MCL = mast cell leukemia; RSE = residual standard error; SM-AHN = systemic mastocytosis with associated hematological neoplasm; SSM = smoldering systemic mastocytosis; T50 = time corresponding to half the maximal hazard.
Source: Table 13 from Applicant's Exposure-Response Analysis

4.2.2.3 Exposure-Response Simulations of Time to Morphologic Response

The final mTTR exposure-response model was used to predict the cumulative probability of the efficacy outcome for 100 mg QD, 200 mg QD, and 300 mg QD dosing regimens in virtual populations of 1000 subjects resampled with replacement from two SM studies (BLU-285-2101 and BLU-285-2202). Individual exposure (avapritinib $C_{average}$) was predicted by the final population PK model. **Figure 34** shows the median cumulative probability of morphologic response simulated inpatients with SM.

Figure 34. Simulation of Morphologic Response from Model-Predicted Exposure in Patients with Systemic Mastocytosis (ASM, MCL, SM-AHN, and SSM Subtypes)

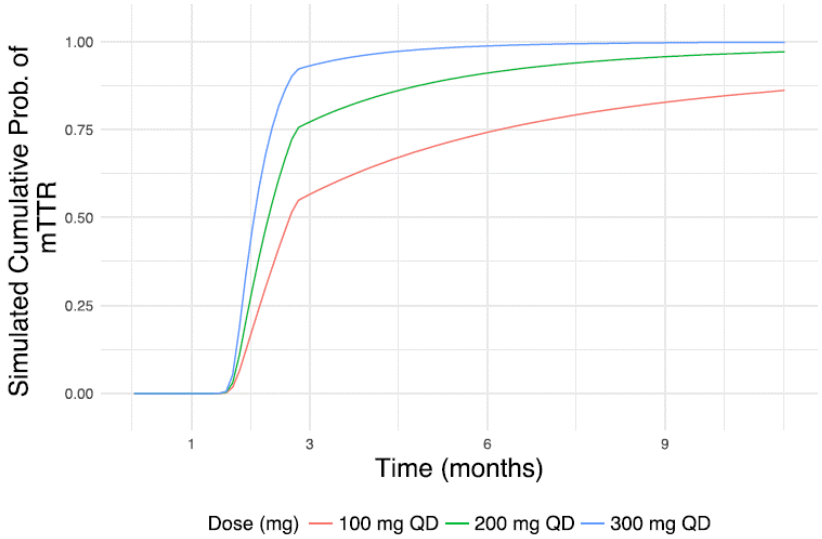


Exposure was simulated for each dose in 1000 virtual subjects with ASM, MCL, SM-AHN, and SSM resampled from BLU-285-2101 and BLU-285-2202. Solid lines represent median cumulative probability of morphologic response.
ASM = aggressive systemic mastocytosis; MCL = mast cell leukemia; mTTR = time to morphologic response; QD = once daily; SM = systemic mastocytosis; SM-AHN = systemic mastocytosis with associated hematological neoplasm; SSM = smoldering systemic mastocytosis.
Source: Figure 56 from Applicant's Exposure-Response Analysis

The mTTR was also simulated according to SM subtype. **Figure 35** shows the median cumulative probability of morphologic response from the simulation of patients with ASM, SM-AHN, and SSM, which predicts a cumulative probability of morphologic response above 75% by 3 months of dosing with 200 mg QD. After 12 months of treatment, cumulative probability of morphologic response in subjects with ASM/SM-AHN/SSM is not significantly different between 200 mg QD and 300 mg QD.

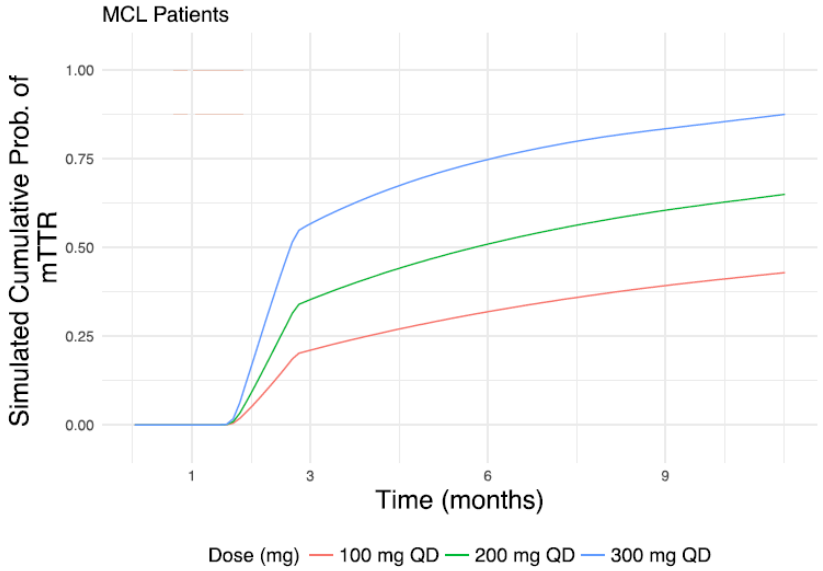
Subjects with MCL were predicted to have a lower rate of morphologic response compared to other AdvSM subtypes. **Figure 36** shows results from the simulation of patients with MCL, which predicts a median cumulative probability of morphologic response above 25% by 3 months after first dose with 200 mg QD. Unlike subjects with ASM/SM-AHN/SSM, subjects with MCL are predicted to have a difference in morphologic response of greater than 20% at 12 months between 200 mg QD and 300 mg QD dosing, indicating potential better efficacy with 300 mg QD.

Figure 35. Simulation of Cumulative Morphologic Response from Model-Predicted Exposure in Patients with ASM, SM-AHN, or SSM



Exposure was simulated for each dose in 1000 virtual subjects with ASM, SM-AHN, or SSM resampled from BLU-285-2101 and BLU-285-2202. Solid lines represent median cumulative probability of morphologic response.
ASM = aggressive systemic mastocytosis; mTTR = time to morphologic response; QD = once daily; SM = systemic mastocytosis; SM-AHN = systemic mastocytosis with associated hematological neoplasm; SSM = smoldering systemic mastocytosis.
Source: Figure 5 from Applicant's Response to FDA 19 March 2021 Information Request

Figure 36. Simulation of Cumulative Morphologic Response from Model-Predicted Exposure in Patients with MCL



Exposure was simulated for each dose in 1000 virtual subjects with MCL resampled from BLU-285-2101 and BLU-285-2202. Solid lines represent median cumulative probability of morphologic response.
MCL = mast cell leukemia; mTTR = time to morphologic response; QD = once daily.
Source: Figure 5 from Applicant's Response to FDA 19 March 2021 Information Request

Reviewer Comments

The simulations performed by the Applicant utilized virtual populations resampled from Studies BLU-285-2101 and BLU 285-2202, (b) (4) [redacted]

In the PPRE population used to develop the mTTR model, subjects had SM-AHN were the majority (n = 72/101) and the second largest SM subtype was MCL (n = 17/101). The relatively small sample size of subjects with ASM (n = 10/101) (b) (4) [redacted] *. The lower incidence of morphologic response is congruent with clinical knowledge that MCL is a more severe form of AdvSM than ASM or SM-AHN.*

The simulation of subjects with ASM, SM-AHN, and SSM supports the conclusion that avapritinib 200 mg once daily is an acceptable dosing regimen for subjects with ASM or SM-AHN in terms of efficacy. Although morphologic response rates are predicted to be lower in subjects with MCL compared to other subtypes of AdvSM (ASM and SM-AHN), there is still a positive association between avapritinib exposure and response in subjects with MCL. Higher rates of morphologic response may be expected with 300 mg QD compared to 200 mg QD in subjects with MCL, while the conclusion is limited by the relatively limited number of patients with MCL in Studies BLU-285-2101 and BLU 285-2202.

4.3 Listing of analyses codes and output files

Codes and output files for this review are listed with location in **Table 16**.

Table 16. Analysis Codes and Output Files

File.Name	Description	Location
run881.mod and run881.lst	Model control file and results from Reviewer run of Applicant's final popPK model.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Avapritinib_sNDA212608_S006_S007_REK\PPK_Analyses\Final_model\nmfe_run881_001
"Population_PK_Review_Template_NDA212608" .rmd and .docx files	R markdown code and .docx output for analyzing popPK dataset, popPK model, E-R safety dataset, and E-R efficacy dataset; code for **Table 3**, **Table 6**, **Table 7**, **Table 12**, **Figure 5**, **Figure 6**, **Figure 7**, **Figure 8**, **Figure 31**, and **Figure 32**.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Avapritinib_sNDA212608_S006_S007_REK\FDA_Reviews
"Sim_datasets_and_results" .rmd and .docx files	R markdown code and .docx output for virtual population dataset generation and PK simulation results; code for **Figure 11**, **Figure 12**, and **Figure 13**.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Avapritinib_sNDA212608_S006_S007_REK\PPK_Analyses\Simulations
sim1001.mod and sim1001.lst	Model control file and .lst output from Reviewer simulations for disease state and	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\

	PPI use (500 subproblems with random seed 76890); refer to "Sim_datasets_and_results" for relevant code and figures.	Avapritinib_sNDA212608_S006_S007_REK\PPK_Analyses\Simulations\PPI_sim\nmfe_sim1001_001
sim2001.mod and sim2001.lst	Model control file and .lst output from Reviewer simulations for disease state and PPI use (500 subproblems with random seed 83752); refer to "Sim_datasets_and_results" for relevant code and figures.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Avapritinib_sNDA212608_S006_S007_REK\PPK_Analyses\Simulations\PPI_sim\nmfe_sim2001_001
sim1001.mod and sim1001.lst	Model control file and .lst output from Reviewer simulations for racial category (500 subproblems with random seed 76890); refer to "Sim_datasets_and_results" for relevant code and figures.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Avapritinib_sNDA212608_S006_S007_REK\PPK_Analyses\Simulations\Race_sim\nmfe_sim1001_001
sim2001.mod and sim2001.lst	Model control file and .lst output from Reviewer simulations for racial category (500 subproblems with random seed 29867); refer to "Sim_datasets_and_results" for relevant code and figures.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Avapritinib_sNDA212608_S006_S007_REK\PPK_Analyses\Simulations\Race_sim\nmfe_sim2001_001
"Visualization_of_final_TTE_models" .rmd and .docx files	R markdown code and .docx output for assessment of safety and efficacy TTE data and TTE models; summarizing ICB events by platelet count; code for **Table 10**, **Figure 19**, **Figure 20**, **Figure 26**, and **Figure 33**.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Avapritinib_sNDA212608_S006_S007_REK\ER_Analyses
run001.mod and .lst through run005.mod and .lst	Reviewer's independent analysis for grade 3+ TEAE E-R modeling; corresponds to **Table 11**.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Avapritinib_sNDA212608_S006_S007_REK\ER_Analyses\TTE_Safety_Grade3plusAEs_Caverage\Indep_review

4.4 References

1. Model Answers R&D Pty Ltd. Pharmacokinetic Analysis (NCA) of Avapritinib (BLU-285) and its Metabolites, BLU111207 and BLU111208 in Study BLU-285-2101: A Phase 1 Study of BLU-285 in Patients with Advanced Systemic Mastocytosis (AdvSM) and Relapsed and Refractory Myeloid Malignancies. October, 2020.

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Office of Pharmaceutical Quality/Office of New Drug Products/Division of Biopharmaceutics **BIOPHARMACEUTICS REVIEW**			
Application No.:	NDA-212608-SUPPL-7	**Primary Reviewer:** Kevin Wei, Ph.D.	
Submission Date:	12/16/2020 (0058/80)		
Division:	S-006/DNH; S-007/DHM1	**Acting Biopharmaceutics Lead:** Om Anand, Ph.D.	
Applicant:	Blueprint Medicines		
Trade Name:	AYVAKIT®	**Biopharmaceutics Branch Chief:** Angelica Dorantes, Ph.D.	
Established Name:	Avapritinib Tablets		
Indication:	Metastatic gastrointestinal stromal tumor (GIST) *Advanced systemic mastocytosis (AdvSM) (b) (4) (b) (4) (S-006, administered by DNH) *Mast cell leukemia (MCL) (S-007, administered by DHM1). (**newly proposed indications*)		
Formulation/ strengths	**25***, **50***, 100, 200, 300 mg (**newly proposed strengths*)	**Date Assigned:**	01/21/2021
Route of Administration	Oral Tablets (IR)	**Type of Submission:** Efficacy/CMC Supplements	
Type of Review:	PAS (SUPPL-6 and 7)		
Recommendation	**Approval**		

BIOPHARMACEUTICS REVIEW SUMMARY:

This is a Review of Biopharmaceutics information/data (seq. 0058/80) supporting two Prior Approval Supplements (PASs) to the Original NDA (S-006 and S-007)[1]. The Applicant proposed two additional strengths (25 and 50 mg) (S-007) to be added to the marketed Avapritinib Tablets, 100, 200, and 300 mg with a biowaiver request, and a new drug product manufacturing site (S-007) at (b) (4) using the same (b) (4) (b) (4) as used for the currently marketed strengths (S-007).

This Biopharmaceutics Review focuses on the evaluation on the adequacy of the overall information/data supporting (i) dissolution method and acceptance criterion as a quality control (QC) test for the two newly proposed strengths, (ii) biowaiver request[2] for the two newly proposed strengths (seq. 0058/080, Module *1.12.15*) and (iii) bridging the products manufactured at (b) (4) (new manufacturing site) to (b) (4) (approved manufacturing site for 100, 200, and 300 mg strengths).

Background

AYVAKIT® (Avapritinib) Tablet, 100, 200, and 300 mg, was approved on 01/09/2020, for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRα) exon

[1] \\cdsesub1\evsprod\nda203469\0262\m1\us\2020-07-01-cover-letter-sn-0262.pdf
[2] \\CDSESUB1\evsprod\nda203469\0275\m1\us\waiver-in-vivo-bioavail-stud-req.pdf

18 mutation, including PDGFRα D842V mutation. In the current submissions (S-006 and 007), the Applicant proposed two new indications for: i) advanced systemic mastocytosis (AdvSM) [redacted] (NDA-212608-SUPPL-6); ii) mast cell leukemia (MCL) (NDA-212608-SUPPL-7). The clinical studies supporting the new indication for AdvSM [redacted] (S-006) will be reviewed by DNH and the clinical studies supporting the new indication for MCL (S-007) will be reviewed by DHM1.

Submission

Formulation and manufacturing sites

Avapritinib Tablets are formulated as immediate release (IR) oral tablets. The two newly proposed strengths (25 and 50 mg) are compositional proportional in active and inactive ingredients and manufactured using an identical [redacted] as the previously approved strengths (100, 200, and 300 mg). According to the Applicant, the manufacturing process was transferred from [redacted] (approved manufacturing site for 100, 200, and 300 mg) to [redacted] in 2019. The commercial products at [redacted] (25 and 50 mg) are debossed and not printed. The previous clinical batches (25 and 100 mg) manufactured at [redacted] and at [redacted] are coated but are not printed or debossed. A comparison of the drug products manufactured at [redacted] and [redacted] is shown below (Table 1):

Table 1. Comparison of Avapritinib Tablet formulations manufactured at [redacted] and [redacted]

(3.2.P.2. Drug product (Avapritinib Tablets, [redacted]), Table 1, page 4)

Component	Tablet Formulation	
	100 mg, 200 mg, 300 mg and 400 mg [1]	25 mg, 50 mg and 100 mg [2]
	Manufacturer	
	[redacted]	[redacted]
	Percent of Blend (w/w)	
Avapritinib	[redacted]	
Microcrystalline cellulose [redacted]		
[redacted]		
Copovidone		
Croscarmellose sodium		
Magnesium stearate [redacted]		
Total (core tablet)	100%	100%
[redacted] film coating	[redacted]	
[redacted]		

1 The 400 mg strength at [redacted] is not commercialized
2 The 100 mg strength at [redacted] is not intended for commercialization
3 [redacted] printing ink is not used for the tablets manufactured at [redacted]; the 25 mg and 50 mg tablets are debossed and the 100 mg tablets are not printed or debossed

Dissolution method and acceptance criterion:

The Applicant proposed to implement the same QC dissolution method and acceptance criteria (see below) for the newly proposed strengths (25 and 50 mg) as those approved for the other approved strengths (100, 200, and 300 mg).

Apparatus	Speed	Medium	Volume	Acceptance Criterion(a)
USP 2 (Paddle)	75 rpm	0.5% w/w CTAB in 50 mM sodium acetate, pH 5.0	900 mL	NLT (b)(4)% in 15 minutes NLT (b)(4)% (Q) in 60 minutes

The submitted dissolution profile/data

The Applicant submitted the comparative dissolution profiles between 25 mg, 50 mg and 100 mg strengths manufactured at (b)(4) versus the 100 mg strength manufactured at (b)(4) (approved manufacturing site), using the proposed QC dissolution method and in pH 1.2 (simulated gastric fluid, without enzymes), 4.5 (50 mM acetate) and pH 6.8 (simulated intestinal fluid, without enzymes) buffer media. The information for the batches used in the comparative dissolution studies is shown below (table 2):

Table 2. Comparison of manufacturing information for representative batches
(3.2.P.2. Drug product (Avapritinib Tablets, (b)(4)), Table 3, page 6)

(b)(4)

Figure 1. Comparative dissolution profiles using the QC dissolution method
(3.2.P.2. Drug product (Avapritinib Tablets, (b) (4)), Figure 1, page 7)

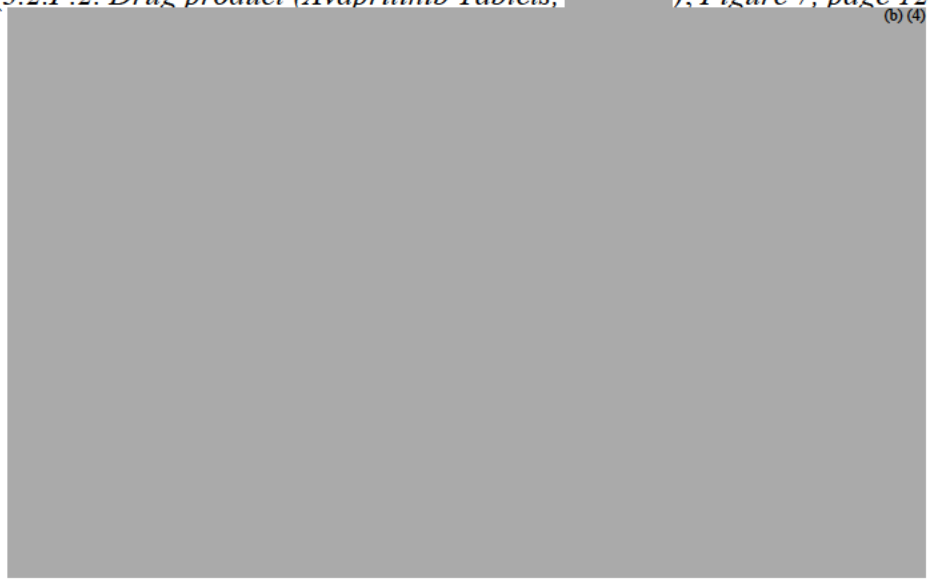
Test	Reference	*f2* Similarity Factor
25 mg Batch CFXKG ((b) (4))	50 mg Batch CDZGF ((b) (4))[1]	64
25 mg Batch CFXKG ((b) (4))	100 mg Batch 19J28G ((b) (4))[2]	72
50 mg Batch CDZGF ((b) (4))[1]	100 mg Batch 19J28G ((b) (4))[2]	54
100 mg Batch CDSPP (b) (4))	100 mg Batch 19J28G ((b) (4))[2]	76

[1]Note: n=6 units was used to calculate similarity factor for this batch
[2]Note: n=12 units was obtained for this batch by combining release data (n=6) with T=0 stability data of the packed product (n=6).

Figure 2. Comparative dissolution profiles in pH 1.2 media (SGF)
(3.2.P.2. Drug product (Avapritinib Tablets, (b) (4)), Figure 3, page 9)

Figure 3. Comparative dissolution profiles in pH 4.5 buffer media (50 mM Acetate)
(*3.2.P.2. Drug product (Avapritinib Tablets, (b) (4)), Figure 4, page 10*)

Figure 4. Comparative dissolution profiles in pH 6.8 buffer media (SIF)
(*3.2.P.2. Drug product (Avapritinib Tablets, (b) (4)), Figure 7, page 12*)

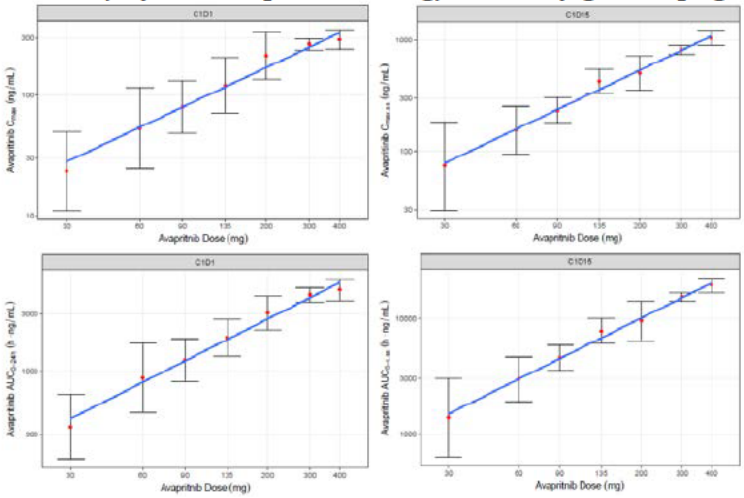


Biowaiver request

The Applicant submitted a biowaiver request for the newly proposed lower strengths (25 and 50 mg) (seq. 0058/080, Module 1.12.15). The pharmacokinetics (PK) and dose proportionality of Avapritinib Tablets from 30 mg to 400 mg was established in the dose escalation study BLU-285-1101. According to the Applicant, the proposed dosing for avapritinib is 200 mg q.d. and the newly proposed lower strengths are proposed to be used only in dose adjustment.

Figure 5. Dose proportionality of Avapritinib (C_{max} and AUC) following administration of avapritinib in patients with GIST (Study BLU-285-1101)

(2.7.2 Summary of clinical pharmacology studies, figure 4, page 34)



In addition, the Applicant has submitted comparative dissolution profiles between 25, 50 and 100 mg tablets manufactured at (b) (4) versus the 100 mg tablets manufactured at (b) (4) (with DS from two approved DS manufacturers[3]) using the QC method and in pH 1.2, 4.5 and 6.8 buffer media (see above section of the review).

Figure 6. Dissolution profile comparisons for Avapritinib Tablets 25, 50, and 100 mg manufactured at two different sites (using the QC dissolution method (n=12))

(1.12.15. Request for waiver of in vivo Bioavailability Studies, figure 1, page 5)

(b) (4)

Test	Reference	f_2 Similarity Factor
25 mg Batch CFXKG (b) (4)	50 mg Batch CDZGF (b) (4) [a]	64
25 mg Batch CFXKG (b) (4)	100 mg Batch 19J28G (b) (4) [b]	72
50 mg Batch CDZGF (b) (4) [a]	100 mg Batch 19J28G (b) (4) [b]	54
100 mg Batch CDSPP (b) (4)	100 mg Batch 19J28G (b) (4) [b]	76
100 mg Batch 19E27G (b) (4) (b) (4) [a]	100 mg Batch 19J28G (b) (4) [b]	57

[3] https://panorama.fda.gov/internal/document/preview?versionID=5f77892f00793b2d759e065e609dde28&ID=5f0eff5500733be7dfc3a9184e4d912a

Reviewer's Assessment: SATISFACTORY

Based on the information submitted, the newly proposed lower strengths and approved strengths are dose proportional in active and inactive ingredients and they are manufactured from an identical (b) (4). Implementation of the same dissolution method [USP Apparatus II Paddle at 75 rpm, 900 mL of pH=5.0, 50 mM sodium acetate containing 0.5% w/w CTAB] and acceptance criteria (NLT (b) (4)% in 15 minutes, NLT (b) (4)% (Q) in 60 minutes) for the newly proposed lower strength as those for the approved strengths is deemed acceptable. The submitted dissolution profiles using the proposed QC dissolution method and in pH 1.2, 4.5 and pH 6.8 buffer media showed comparable dissolution profiles between the drug products manufactured at (b) (4) (approved) and (b) (4) (newly proposed). The submitted dissolution data from the stability batches manufactured at (b) (4) showed no dissolution trend or out-of-specification (OOS) under long-term (25°C/60%RH) and accelerated (40°C/75%RH) conditions. The submitted biowaiver request for the newly proposed strengths was based on: i) proportional similarity of the formulations across all strengths; ii) established linear/dose proportional pharmacokinetics over a dose range of 30 to 400 mg; iii) comparable dissolution profiles (f_2>50) to the approved strengths.

Overall, this Reviewer considers that sufficient data/information were submitted to support the biowaiver request for the newly proposed lower strengths (25 and 50 mg). Therefore, the biowaiver request is granted per 21 CFR 320.22(d)(2).

RECOMMENDATION:

From a Biopharmaceutic perspective, NDA-212608-SUPPL-6 and -7 for AYVAKIT® (Avapritinib) Tablets, 25 and 50 mg are **ADEQUATE** and recommended for **Approval**.

Refer to the CMC review for the evaluation of additional information to support the proposed changes.

The approved dissolution method and acceptance criteria for NDA-212608, AYVAKIT® (Avapritinib) Tablets, 25, 50, 100, 200, 300 mg are as follows:

Apparatus	Speed	Medium	Volume	Acceptance Criterion(a)
USP 2 (Paddle)	75 rpm	0.5% w/w CTAB in 50 mM sodium acetate, pH 5.0	900 mL	NLT (b) (4)% in 15 minutes NLT (b) (4)% (Q) in 60 minutes

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212608Orig1s006

OTHER REVIEW(S)

Division of Nonmalignant Hematology Products
Associate Director for Labeling Review of the Prescribing Information

Product Title	AYVAKIT™ (avapritinib) tablets, for oral use
Applicant	Blueprint
Application/Supplement Number	NDA 212608, S-006 & S-007
Is Proposed Labeling in Old Format? (Y/N)	N
Is Labeling Being Converted to PLR? (Y/N)	N
Is Labeling Being Converted to PLLR? (Y/N)	N
Approved Indication(s)	Ayvakit is a kinase inhibitor indicated for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) haboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations.
Date FDA Received Application	12/16/2020
Review Classification (Priority/Standard)	Priority
Action Goal Date	06/16/2021
Review Date	05/26/2021
Reviewer	Virginia Kwitkowski, MS, ACNP-BC

This Associate Director for Labeling (ADL) review provides recommendations on the content and format of the prescribing information (PI) to help ensure that PI:

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements[1]
- Is consistent with labeling guidance recommendations[3] and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

Background: Blueprint submitted this efficacy supplement to add a new indication for adult patients with advanced systemic mastocytosis (AdvSM) [redacted] (b) (4) Of note, AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematologic neoplasm (SM-AHN), as well as mast cell leukemia (MCL), an indication that is regulated by DHM1, a Division within OOD. This supplement also sought to add additional tablet strengths of 25 mg and 50 mg as well as a new manufacturing site. Because the MCL indication is regulated by OOD and the other sought indications are regulated by DNH/OCHEN, an administrative split was conducted, designating that S-006 would be for Advanced Systemic Mastocytosis (AdvSM) and that S007 would be for MCL.

[1] See *January 2006 Physician Labeling Rule*; 21 CFR 201.56 and 201.57; and *December 2014 Pregnancy and Lactation Labeling Rule* (the PLLR amended the PLR regulations). For applications with labeling in non-PLR "old" format, see 21 CFR 201.56(e) and 201.80.
[3] See *PLR Requirements for PI* website for PLR labeling guidances.

Reviewer Comments: Seven multi-disciplinary interdivisional (DNH & DHM1) labeling meetings were held for this application. One internal meeting was held to prepare for a Sponsor teleconference that was held on 5/18/21 to discuss the efficacy table (b) (4) and male infertility statement.
The first round of labeling negotiations were sent to the Applicant on 4/23/2021 with a response date of 4/29/21 requested. After the meeting, the Applicant submitted revised labeling on 5/21. At this time, the review team is reviewing those edits.

Summary of Major Revisions:

- (b) (4)
- Throughout the labeling, the term "(b) (4)" was revised to "Advanced Systemic Mastocytosis" to reflect (b) (4).
- DNH relocated the Applicant's (b) (4) from Section (b) (4) (titled (b) (4)) to the more relevant subsection of 2.5 (titled "Dose Modifications for Adverse Reactions).
- In subsection 2.6 (titled Concomitant Use of Strong or Moderate CYP3A Inhibitors), DMEPA recommended to split out the two indications (GIST & AdvSM).
- In the Warnings and Precautions section, the warnings were revised to include a succinct description of the adverse reaction and outcome, based upon the recommendations in the Warnings and Precautions guidance. Rates were added where missing. Text in passive voice was revised to active voice.
- The review team selected a (b) (4) population for the Adverse Reactions section of 80 patients with AdvSM who received the recommended 200 mg dosage once daily.
- The review team selected a (b) (4) population (n=148 patients with systemic mastocytosis) for the Warnings and Precautions section to provide a (b) (4) population to identify rarer events. The populations are described at the beginning of section 6 (Warnings & Precautions population) and at the beginning of the AdvSM section of 6.1)Adverse Reactions population).
- The review team recommended the removal of the incidence rates for each event listed in the "Clinically relevant adverse reactions occurring in <10% of patients" section below the main adverse reactions table because there was already a cutoff in the subheading. This recommendation was rejected multiple times by the Applicant and ultimately agreed upon to maintain consistency with the list in the GIST section of labeling.
- The review team added qualifiers (disclaimers) in text wherever an unapproved dose was mentioned.
- The Clinical Pharmacology team edited the Clinical Pharmacology section (12) to include safety endpoints with significant exposure-response (E-R) relationships, the dose range for the E-R safety analysis, and a statement on the E-R relationship.
- The Pharmacology/Toxicology team added a summary of the impairment of fertility nonclinical evidence to section 13.1.
- The Clinical team added to section 14 the basis for efficacy, a definition of the IWG-MRT-ECNM criteria, and clinically relevant inclusion criteria.
- I removed references to "(b) (4)" per the Clinical Studies Section of Labeling guidance (because (b) (4).
- The review team asked the Applicant to revise the efficacy table (b) (4) and to update the rates presented for background and demographics to reflect this population.

- The review team removed [redacted] (b) (4) from Section 14 (titled Clinical Studies) [redacted] (b) (4) .
- We inserted a list of symptoms of intracranial hemorrhage to section 17 to simply patient counseling on this risk.
- The Pharm Tox team requested that infertility text remain in section 17 based upon edits to sections 8.3 and 13.1.

Regulatory Recommendation: This NDA is recommended for approval upon completion of labeling negotiations.

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CLINICAL INSPECTION SUMMARY

Date	May 21, 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	Andrew Dmytrijuk, M.D., Medical Officer Qin Ryan, M.D., Medical Officer Albert Deisseroth, M.D., Ph.D., Deputy Division Director Brittany Garr-Colon, Regulatory Project Manager Division of Non-Malignant Hematology (DNH)/OCHEN
NDA	NDA 212608 S-006
Applicant	Blueprint Medicines Corporation
Drug	Avapritinib (Ayvakit®)
NME	No
Division Classification	Kinase inhibitor that targets KIT D816V and other KIT exon17 mutations
Proposed Indication	Treatment of advanced systemic mastocytosis (b) (4)
Review Type	Priority
Consultation Request Date	March 9, 2021
Summary Goal Date	May 15, 2021 (original), May 24, 2021 (Extension)
Action Goal Date	June 16, 2021
PDUFA Date	June 16, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from two studies (BLU-285-2101 and BLU-285-2202) were submitted to the Agency in support of a supplemental New Drug Application (NDA 212608 S-006) for avapritinib (Ayvakit®), proposed for treatment of patients with advanced systemic mastocytosis (b) (4) A single clinical investigator site (Daniel DeAngelo, M.D.) and the sponsor (Blueprint Medicines Corporation) were inspected to support the review of NDA 212608 S-006.

Based on the results of these inspections, Study BLU-285-2101 and BLU285-2202 appear to have been conducted adequately, and the data generated from Dr. DeAngelo and the sponsor appear to be acceptable in support of this NDA for the proposed indication.

II. BACKGROUND

Systemic mastocytosis (SM) is a clonal disorder of neoplastic mast cells (MCs). The disease composite, (a) aggressive systemic mastocytosis (ASM), (b) systemic mastocytosis (SM) with associated hematologic neoplasm (SM-AHN), and (c) mast cell leukemia (MCL), referred to as advanced systemic mastocytosis (Advanced SM). Systemic mastocytosis is a rare, clonal mast cell neoplasm driven by the KIT D816V mutation, which occurs in 93% of patients with systemic mastocytosis.

Avapritinib as a kinase inhibitor targets KIT D816V and other KIT exon17 mutations. AYVAKIT™ was approved in 2020 for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) and marketed as 100 mg, 200 mg and 300 mg film-coated tablets for oral administration.

The proposed indication of avapritinib in this supplement is for the treatment of advanced systemic mastocytosis (b) (4) Blueprint is seeking regulatory approval for two additional avapritinib tablet strengths, 25 mg and 50 mg, in the current sNDA. Avapritinib received Breakthrough Therapy Designation for the treatment of patients with advanced systemic mastocytosis and Orphan Drug Designation (ODD #15-5065) for the treatment of mastocytosis.

Study BLU-285-2101

Study BLU-285-2101 was a Phase 1, open-label study designed to evaluate the safety, tolerability, PK, pharmacodynamic, and antineoplastic activity (efficacy) of avapritinib, administered orally, in adult patients with advanced systemic mastocytosis and relapsed or refractory myeloid malignancies. This 2-part study included dose escalation (Part 1) and expansion (Part 2) to evaluate safety and tolerability, and to assess the clinical efficacy of avapritinib at the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D).

The primary study objective of this study was to determine the MTD and RP2D of avapritinib, and to determine safety and patient tolerability. Analyses were performed for the Response Assessment Committee Response-Evaluable (RAC-RE) and Pure pathologic response-evaluable (PPRE) populations. The primary efficacy endpoints were RAC-adjudicated Overall Response Rate (complete response + complete response with incomplete blood count recovery +partial response + Clinical Improvement [that is, CR+CRh+PR+CI]) and complete response + complete response with incomplete blood count recovery + partial response [that is, CR+CRh+PR], percentage of patients based on International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis (IWG-MRT-ECNM) criteria. The IWG-MRT-ECNM criteria were derived from the published IWG-MRT-ECNM criteria and modified in consultation with experts and regulatory authorities.

Ten of 11 study centers that were screened enrolled subjects, including 71 patients in the United States and 15 patients in Europe (United Kingdom). The first patient first dose was on March 10, 2016. The date the last patient completed as per data cutoff date for safety, efficacy, and pharmacokinetic (PK) analyses was on May 27, 2020.

Study BLU-285-2202

Study BLU-285-2202 was an open-label, single-arm, Phase 2 study designed to evaluate efficacy and safety of avapritinib in patients with a WHO diagnosis of advanced systemic mastocytosis (AdvSM), including patients with (a) aggressive systemic mastocytosis (ASM), (b) systemic mastocytosis (SM) with associated hematologic neoplasm (SM-AHN), and (c) mast cell leukemia (MCL).

Patients with a centrally confirmed WHO diagnosis of advanced systemic mastocytosis (AdvSM) were enrolled into 1 of 2 cohorts: Cohort 1: Advanced systemic mastocytosis patients with at least one modified IWG-MRT-ECNM (mIWG-MRT-ECNM) criteria for evaluable disease or have mast cell leukemia, as determined by the Study Steering Committee, and Cohort 2: Advanced systemic mastocytosis patients who were not considered eligible for an adjudicated response and were confirmed centrally to have aggressive systemic mastocytosis (ASM), systemic mastocytosis (SM) with associated hematologic neoplasm (SM-AHN), but were lacking an evaluable C-finding as determined by the Study Steering Committee.

The primary study objective was to determine adjudicated ORR [CR+CRh+PR+CI] (that is, complete response [CR] + complete response with partial recovery of peripheral blood counts [CRh] + partial response [PR] + clinical improvement [CI]), based on mIWG-MRT-ECNM consensus response criteria in patients with advanced systemic mastocytosis treated with avapritinib and enrolled in Cohort 1.

The primary study endpoint was adjudicated overall response rate ORR [CR+CRh+PR+CI], (that is, complete response [CR] + complete response with partial recovery of peripheral blood counts [CRh] + partial response [PR] + clinical improvement [CI]), based on mIWG-MRT-ECNM criteria, confirmed 12 weeks after initial response in patients in Cohort 1.

At the time of data cutoff, 18 sites offered data for the submitted application clinical study report, including 10 sites in North America and 8 sites in Europe. The first patient (Cycle 1 Day 1) enrolled on November 21, 2018. The last patient enrolled (Cycle 1 Day 1) before the cut-off date for interim analysis was June 17, 2020. The cut-off date for analysis was June 23, 2020.

III. RESULTS (by site)

1. **Daniel Joseph DeAngelo, M.D./Site 004**
   Dana Farber Cancer Institute
   450 Brookline Avenue, D2050
   Boston, MA 02215

   The on-site inspection was conducted from April 12 to 16, 2021.

For Study BLU-285-2101, a total of 14 subjects were screened and 14 subjects were enrolled (six study subjects in Part 1 and eight patients in Part 2). Five subjects discontinued due to disease progression, one subject discontinued due to persistent pancytopenia, one study patient discontinued due to progressive dementia, and a single study participant discontinued due to transplant. Six subjects completed the study. The study is ongoing.

For Study BLU-285-2202, a total of 15 subjects were screened and 13 subjects enrolled. Eleven study subjects completed the study. Of the two study patients who discontinued, one subject died, one subject went off-treatment due to thrombocytopenia.

Records reviewed included but were not limited to: investigator agreements, financial disclosure forms, Institutional Review Board (IRB) approvals and documentation, delegation log, screening and enrollment log, monitoring log and monitoring reports, electronic case report forms (eCRFs), subject source records, test article control records, adverse event/serious adverse event documentation, and informed consent documentation.

Source records for 14 enrolled study patients in Study BLU-285-2101 and 13 patients in Study BLU-285-2202 at Dr. DeAngelo's site were reviewed and compared with the submitted data listings for the site. The primary efficacy endpoint data (such as hypoalbuminemia splenomegaly, transfusion-independent subjects, related "C-findings") were verified against the data line listings. No discrepancies were noted. There was no under-reporting of serious adverse events. A FDA Form 483 (List of Inspectional Observations) was not issued at the close of the inspection.

2. **Blueprint Medicines Corporation**
45 Sidney Street
Cambridge, MA 02139

The on-site inspection was conducted from May 3 to May 7, 2021.

An onsite inspection assessed Blueprint Medicine's responsibilities for oversight of Study BLU-285-2101 and Study BLU-285-2202.

The inspection included a review of the organizational charts, investigator agreements, transfer of obligations, financial disclosures with the sponsor, study master file, assessment of selection of clinical study site investigators, and selection of clinical study monitors and their training records. Standard operating procedures were evaluated, principally concerning clinical site monitoring, data collection, and handling of adverse event data.

Clinical study conduct in two clinical investigative sites (Dr. DeAngelo/Site 2002 and Dr. Gotlib/Site 2008, for both Study BLU-285-2101 and Study BLU-285-2202) were found to be adequate. Sponsor's clinical trial oversight were found to be appropriate. No underreporting of significant adverse events (SAEs) to the Agency was noted. FDA did not encounter any barriers during the sponsor site audit. In general, study procedures, recordkeeping and reporting procedures were adequate.

A FDA Form 483 (List of Inspectional Observations) was not issued at the close of the sponsor inspection. Monitoring appeared to be adequate. Sponsor maintained adequate study oversight of the two clinical studies.

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

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

Memorandum

Date: April 15, 2021

To: Brittany Garr-Colon, MPH, Regulatory Project Manager
Division of Non-Malignant Hematology (DNH)

From: Emily Dvorsky, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for AYVAKIT™ (avapritinib) tablets, for oral use

NDA: 212608/Supplements 6 & 7

In response to DNH's consult request dated January 25, 2021, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for AYVAKIT™ (avapritinib) tablets, for oral use. These supplements (S-006 & S-007) provide for the addition of the indication for the treatment of adult patients with advanced Systemic Mastocytosis.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DNH (Garr-Colon) on April 6, 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 on April 13, 2021.

Thank you for your consult. If you have any questions, please contact Emily Dvorsky at (240)402-4256 or Emily.Dvorsky@fda.hhs.gov.

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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:	April 13, 2021
To:	Brittany Garr-Colón, MPH Regulatory Project Manager **Division of Non-Malignant Hematology (DNH)**
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:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Emily Dvorsky, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	AYVAKIT (avapritinib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 212608
Supplement Number:	S-006 and S-007
Applicant:	BluePrint Medicines Corporation

1 INTRODUCTION

On December 16, 2020, BluePrint Medicines Corporation submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy for their New Drug Application (NDA) 212608/S-006 and S-007 for AYVAKIT (avapritinib) tablets, for oral use. With these supplements, the Applicant seeks approval for the additional indication for the treatment of adult patients with advanced systemic mastocytosis (AdvSM) (b) (4) AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL). The Applicant is also seeking approval of two additional tablet strengths (25 mg and 50 mg). For administrative purposes, the supplements have been designated as follows:

- NDA 212608/S-006: Patients with aggressive systemic mastocytosis (ASM), and systemic mastocytosis with an associated hematological neoplasm (SM-AHN).
- NDA 212608/S-007: Mast cell leukemia (CML)

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 Non-Malignant Hematology Products (DNH) on January 25, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for AYVAKIT (avapritinib) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft AYVAKIT (avapritinib) tablets, for oral use PPI received on December 16, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 6, 2021.
- Draft AYVAKIT (avapritinib) tablets, for oral use Prescribing Information (PI) received on December 16, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 6, 2021.

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)

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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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
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:	March 23, 2021
Requesting Office or Division:	Division of Non-Malignant Hematology (DNH) and Division of Hematologic Malignancies 1 (DHM1)
Application Type and Number:	NDA 212608/S-006 and S-007
Product Name and Strength:	Ayvakit (avapritinib) tablets 100 mg, 200 mg, and 300 mg *Proposed: 25 mg and 50 mg*
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Blueprint Medicines (Blueprint)
FDA Received Date:	December 16, 2020
OSE RCM #:	2021-2744 and 2021-193
DMEPA Safety Evaluator:	Stephanie DeGraw, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1. REASON FOR REVIEW

Blueprint Medicines submitted a Prior Approval Supplement (PAS) to NDA 212608 for Ayvakit (avapritinib) on December 16, 2020 proposing a new indication for the treatment of adult patients with advanced systemic mastocytosis (AdvSM) (b) (4) The supplement was split into PAS 006 and PAS 007 as the proposed indication requires review by two therapeutic review teams: Division of Nonmalignant Hematology (DNH) and Division of Malignant Hematology 1 (DHM1). Additionally, Blueprint is seeking approval for two additional strengths, 25 mg and 50 mg, to accommodate certain dosing for the new indication. We evaluated the proposed Prescribing Information (PI), Patient Information (PPI), container labels, and carton labeling for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND INFORMATION

Ayvakit (avapritinib) was approved under NDA 212608 on January 9, 2020, as a kinase inhibitor indicated for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations. Ayvakit is currently available in 100 mg, 200 mg, 300 mg oral tablets.

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 Label and Labeling 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 post-market safety surveillance

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Blueprint Medicines submitted the PAS for the proposed indication of the treatment of adult patients with AdvSM (b) (4) AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL). DNH is reviewing the labeling related to systemic mastocytosis (SM) (PAS

006), while DHM1 is reviewing the labeling related to mast cell leukemia (MCL) (PAS 007). DNH and DHM1 will be conducting their reviews together, as such, we provide our evaluation of both supplements together in this review.

Additionally, Blueprint is seeking approval for 2 additional strengths, 25 mg and 50 mg, to accommodate the dosing for the new indication. Blueprint noted that the new strengths will be manufactured at a new manufacturing site, (b) (4).

We performed a risk assessment of the proposed PI, PPI, container labels, and carton labeling to identify deficiencies that may lead to medication errors and other areas of improvement.

Our review of the proposed container labels and carton labeling for the proposed new strengths determined they are similar to the currently available 100 mg, 200 mg, and 300 mg container labels and carton labeling with regard to information provided, format, font style, and graphic element (e.g., circle design at the bottom of the labels); however, there are some minor exceptions. Most notably, the proposed container labels and carton labeling utilize new colors to highlight the new strengths (i.e., dark blue for 25 mg and light gray for 50 mg). Additionally, the container labels and carton labeling contain new manufacturer information. We did not identify any safety concerns associated with these revisions.

Our review of the PI identified areas that can be modified to improve the clarity of the information presented. We provide recommendations for the division below.

Our review of the PPI determined it is acceptable from a medication error perspective and as such, we have no concerns or recommendations at this time.

4. CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI can be improved to increase clarity of important information to promote the safe use of the product. We provide our recommendations in Section 4.1 below. We conclude the proposed Patient Information (PPI), container labels, and carton labeling are acceptable from a medication error perspective. Thus, we have no recommendations for the container labels and carton labeling at this time. We defer to the Patient Labeling Team for recommendations for the for the PPI.

4.1 RECOMMENDATIONS FOR THE DIVISION

Prescribing Information

A. Recommended Dosage for SM [2.3]
    1. We recommend revising the word "(b) (4)" in the first sentence to read "dosage" (b) (4)

    2. We recommend relocating (b) (4) to *Section 2.5 Dosage Modifications for Adverse Reactions* as (b) (4).

B. Dosage Modifications for Adverse Reactions [2.5]

1. We recommend revising "[redacted]" in the column headings of Table 2 to read "Recommended Dosage" as the [redacted] Alternatively, "[redacted]" may be deleted from the column headings.

2. We recommend adding the frequency "once daily" in the 2nd and 3rd column headings in Table 2 so the full dosage is stated.

C. Concomitant Use of Strong or Moderate CYP3A Inhibitor [2.6]

1. We recommend revising the information describing reduced starting dosages to separate out the two indications. For example, revise to read:

> Avoid concomitant use of AYVAKIT with strong or moderate CYP3A inhibitors. If concomitant use with a moderate CYP3A inhibitor cannot be avoided, [redacted] of AYVAKIT is as follows *[see Drug Interactions (7.1)]*:
>
> - GIST: [redacted] 100 mg orally once daily [redacted]
> - AdvSM [redacted] 50 mg orally once daily [redacted]

APPENDICES: METHODS & RESULTS FOR MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ayvakit received on December 16, 2020 from Blueprint Medicines.

Table 2. Relevant Product Information for Ayvakit

Initial Approval Date	January 9, 2020
Active Ingredient	avapritinib
Indication	Gastrointestinal Stromal Tumor (GIST) • the treatment of adults with unresectable or metastatic GIST harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations. ***PROPOSED:*** (b) (4) • *the treatment of adult patients with advanced systemic mastocytosis (AdvSM)* (b) (4) • *Limitations of Use: AYVAKIT is not recommended for the treatment of AdvSM* (b) (4) *with platelet counts of less than 50 X 10^9/L.*
Route of Administration	oral
Dosage Form	tablet
Strength	100 mg, 200 mg, and 300 mg ***PROPOSED:*** *25 mg and 50 mg*
Dose and Frequency	GIST: 300 mg orally once daily (see dose modifications/reductions below) ***PROPOSED:*** *SM: 200 mg orally once daily* (see dose modifications/reductions below) ***PROPOSED:*** (b) (4) (b) (4)

Recommended Dose Reductions for AYVAKIT for Adverse Reactions

Dose Reduction	GIST (starting dosage 300 mg)*	***PROPOSED:*** (b) (4) ***(starting dosage 200 mg)****
First	200 mg once daily	*100 mg once daily*
Second	100 mg once daily	*50 mg once daily*
Third	-	*25 mg once daily*

*Permanently discontinue AYVAKIT in GIST patients who are unable to tolerate a dose of 100 mg once daily.

***Permanently discontinue AYVAKIT in* (b) (4) *patients who are unable to tolerate a dose of 25 mg once daily.*

<table>
<tr><td></td><td>Recommended Dosage Modifications for AYVAKIT for Adverse Reactions
<table>
<tr><th>Adverse Reaction</th><th>Severity*</th><th>Dosage Modification</th></tr>
<tr><td>Intracranial Hemorrhage [see Warnings and Precautions (5.1)]</td><td>Any grade</td><td>Permanently discontinue AYVAKIT.</td></tr>
<tr><td rowspan="3">Cognitive Effects [see Warnings and Precautions (5.2)]</td><td>Grade 1</td><td>Continue AYVAKIT at same dose or reduced dose or withhold until improvement to baseline or resolution. Resume at same dose or reduced dose.</td></tr>
<tr><td>Grade 2 or Grade 3</td><td>Withhold AYVAKIT until improvement to baseline, Grade 1, or resolution. Resume at same dose or reduced dose.</td></tr>
<tr><td>Grade 4</td><td>Permanently discontinue AYVAKIT.</td></tr>
<tr><td>Other [see Adverse Reactions (6.1)]</td><td>Grade 3 or Grade 4</td><td>Withhold AYVAKIT until improvement to less than or equal to Grade 2. Resume at same dose or reduced dose, as clinically appropriate.</td></tr>
</table>
*Severity as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0</td></tr>
<tr><td>How Supplied</td><td>AYVAKIT (avapritinib) tablets are supplied as follows:
PROPOSED: 25 mg, round, white film-coated tablet with debossed text. One side reads “BLU” and the other side reads “25”; available in bottles of 30 tablets (NDC 72064-125-30).
PROPOSED: 50 mg, round, white film-coated tablet with debossed text. One side reads “BLU” and the other side reads “50”; available in bottles of 30 tablets (NDC 72064-150-30).
100 mg, round, white film-coated tablet, printed with blue ink “BLU” on one side and “100” on the other side; available in bottles of 30 tablets (NDC 72064-110-30).
200 mg, capsule shaped, white film-coated tablet, printed with blue ink “BLU” on one side and “200” on the other side; available in bottles of 30 tablets (NDC 72064-120-30).
300 mg, capsule shaped, white film-coated tablet, printed with blue ink “BLU” on one side and “300” on the other side; available in bottles of 30 tablets (NDC 72064-130-30).</td></tr>
<tr><td>Storage</td><td>Store at 20°C to 25°C (68°F to 77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 8, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, “Ayvakit” and “212608”. Our search identified 3 previous labeling reviews, and we confirmed that our previous recommendations were implemented.

Reviewer	Document Title	Application	Date	RCM No.
Stewart, J.	Label and Labeling Review Memo for Ayvakit	NDA 212608	2019 DEC 31	2019-1281-2
Stewart, J.	Label and Labeling Review Memo for Ayvakit	NDA 212608	2019 DEC 10	2019-1281-1
Stewart, J.	Label and Labeling Review for Ayvakit	NDA 212608	2019 OCT 29	2019-1281

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 post-market medication error data, we reviewed the following Ayvakit labeling submitted by Blueprint Medicines on December 16, 2020:

- Container Labels
- Carton Labeling
- Prescribing Information and Patient Information (image not shown) \\CDSESUB1\evsprod\nda212608\0058\m1\us\ayvakit-uspi-advsm-redline-comments-14-dec-2020.docx

Container Labels

(b) (4)

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

2 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

STEPHANIE L DEGRAW
03/23/2021 11:46:25 AM

HINA S MEHTA
03/25/2021 10:57:39 AM