CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

212608Orig1s007

Trade Name:	**AYVAKIT**
Generic or Proper Name:	avapritinib
Sponsor:	BLUEPRINT MEDICINES CORP
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 AsvSM. AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SMAHN), 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

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 212608/S-007

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 December 16, 2020, 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 change for Ayvakit (avapritinib):

- New indication for the treatment of adult patients with mast cell leukemia (MCL).

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 changes not included in the enclosed labeling.

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]

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

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-007**." 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.

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.*[3]

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

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

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, call Rachel McMullen, Senior Regulatory Project Manager, at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Division Director
Division of Hematologic Malignancies I
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:
- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

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

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06/16/2021 02:19:53 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212608Orig1s007

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 ≥ 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 ≥ 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)]*.

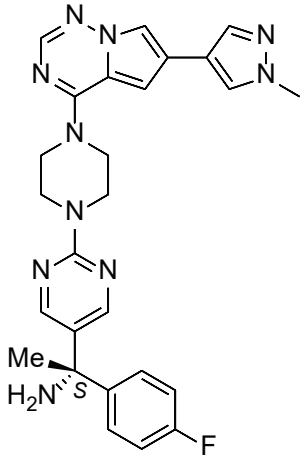
8.7 Hepatic Impairment

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:

212608Orig1s007

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review
Clinical Microbiology/Virology

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplement (SE-1)
Application Number(s)	NDA 212608 / S-007
Priority or Standard	Priority
Submit Date	December 16, 2020
Received Date	December 16, 2020
PDUFA Goal Date	June 16, 2021
Division/Office	Division of Hematologic Malignancies I (DHM I) Office of Oncologic Diseases
Review Completion Date	May 20, 2021
Established/Proper Name	Avapritinib
Trade Name	AYVAKIT
Pharmacologic Class	Protein kinase inhibitor
Code name	L01EX18
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) (b) (4)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Mast cell leukemia: 780841002
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s)	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 AdvSM patients with platelet counts of less than 50 X 10^9/L
Recommended SNOMED CT Indication Disease Term for each Indication	Mast cell leukemia: 780841002
Recommended Dosing Regimen	200 mg orally once daily

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Rachel McMullen, MPH, MHA
Nonclinical Reviewer	Refer to S-006 review
Nonclinical Team Leader	Refer to S-006 review
Office of Clinical Pharmacology Reviewer(s)	Refer to S-006 review
Office of Clinical Pharmacology Team Leader(s)	Refer to S-006 review
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Associate Director for Labeling	Elizabeth Everhart, MSN, RN, ACNP
Cross-Disciplinary Team Leader	Lori Ehrlich, M.D., Ph.D.
Division Director (DHOT)	Refer to S-006 review
Division Director (OCP)	Refer to S-006 review
Division Director (OHOP)	R. Angelo de Claro, M.D.
Office Director (or designated signatory authority)	R. Angelo de Claro, M.D.

Additional Reviewers of Application

OPQ	Refer to S-006 review

OPQ=Office of Pharmaceutical Quality

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AdvSM	advanced systemic mastocytosis
AE	adverse event
AR	adverse reaction
ASM	aggressive systemic mastocytosis
BPCA	Best Pharmaceuticals for Children Act
BM	bone marrow
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	clinical improvement
CMC	chemistry, manufacturing, and controls
CR	complete response
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DHMI	Division of Hematologic Malignancies I
DHOT	Division of Hematology Oncology Toxicology
DLT	dose limiting toxicity
DMC	data monitoring committee
DNH	Division of Non-Malignant Hematology
DOR	duration of response
DO3	Division of Oncology 3
ECG	electrocardiogram
eCTD	electronic common technical document
EOS	end of study
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
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
GIST	gastrointestinal stromal tumor
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug

ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
MC	mast cell
MCL	mast cell leukemia
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
mIWG-MRT-ECNM	modified International Working Group-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
OCHEN	Office of Cardiology, Hematology, Endocrinology, and Nephrology
OCS	Office of Computational Science
ODAC	Oncology Drug Advisory Committee
OPQ	Office of Pharmaceutical Quality
OOD	Office of Oncologic Disease
ORR	overall response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PDGFRA	platelet-derived growth factor receptor alpha
PBRER	Periodic Benefit-Risk Evaluation Report
PD	disease progression
PFS	progression free survival
PI	prescribing information
PK	pharmacokinetics
PMC	post marketing commitment
PMR	post marketing requirement
PO	*per os*, or by mouth
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PR	partial response
PRO	patient reported outcome
PSUR	Periodic Safety Update report
QD	daily
RAC	Response Assessment Committee
RAC-RE	Response Assessment Committee Response-Evaluable

REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SGE	special government employee
SM	systemic mastocytosis
SM-AHN	systemic mastocytosis with an associated hematological neoplasm
sNDA	supplemental new drug application
SOC	standard of care
SSC	study steering committee
SSM	smoldering systemic mastocytosis
TEAE	treatment emergent adverse event
US	United States
USPI	US Package Insert (or label)
WHO	World Health Organization
WRO	written response only

1 Executive Summary

1.1. Product Introduction

Avapritinib (proprietary name, AYVAKIT) is an orally bioavailable, small molecule tyrosine kinase inhibitor of platelet-derived growth factor receptor alpha (PDGFRA) and KIT activation loop mutants. Avapritinib is currently approved in unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations. A supplemental NDA is submitted to support an 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). This review is for the mast cell leukemia indication. The review team recommends regular approval of avapritinib for the treatment of adult patients with mast cell leukemia. The proposed dose and schedule is 200 mg orally once daily and continued until disease progression or unacceptable toxicity.

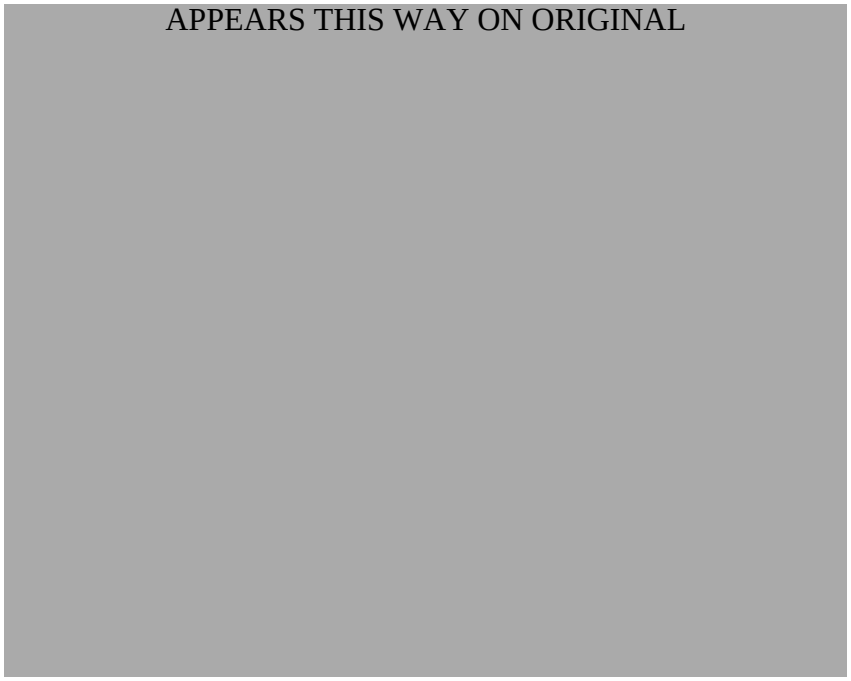
1.2. Conclusions on the Substantial Evidence of Effectiveness

The submitted data meet the evidentiary standard of effectiveness for adult patients with previously treated or untreated MCL.

The efficacy evaluation is based on analysis of pooled data from 2 studies (BLU-285-2101 and BLU-285-2202). In a combined cohort of patients with MCL across the studies, the primary efficacy endpoint is overall response rate (ORR) per modified International Working Group-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis (mIWG-MRT-ECNM) criteria including complete remission (CR), complete remission with partial hematologic recovery (CRh), and partial remission (PR). The endpoint of interest for approval for MCL is complete remission (CR). The Response Assessment Committee Response-Evaluable (RAC-RE) analysis population of patients with MCL consists of 17 patients treated across all doses and 10 patients treated at the proposed 200 mg daily dose. While avapritinib was previously approved at a higher dose (300 mg/day) in gastrointestinal stromal tumors (GIST), safety considerations in a different disease model led to the selection of the 200 mg dose in AdvSM. In the 17 patientswith MCL who were efficacy evaluable at all dose levels (60 mg to 400 mg), the adjudicated ORR was 47.1% with a CR rate of 17.6%. In the10 patients with MCL treated at only the 200 mg dose level, the ORR was 40% with no CRs observed at the 200 mg dose level. One CR was observed in a patient treated with a starting dose of 60 mg, resulting in a CR rate of 9% and ORR of 45% in 11 patients with MCL treated at 200 mg or less. The durations of response for each PR were 3.9+, 4.5+, 17.3+, and 21.6 months, with + indicating ongoing response at the time of data cutoff.

While the 4 PR are supportive of drug activity in MCL, PR is not considered an acceptable early predictor of clinical benefit in acute leukemias. The sample size of 10 patients treated at the proposed 200 mg dose level is small. Careful consideration of the 1 reported CR at the 60 mg dose level is supportive, however.

Given the rarity and fatal clinical course of MCL, the clinically meaningful activity of avapritinib supports a recommendation of regular approval.



1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Efficacy

Determination of efficacy is derived from a pooled analysis of two studies: BLU-285-2101, a phase 1 open-label trial in patients with AdvSM and relapsed or refractory myeloid malignancies, and BLU-285-2202, an open-label, single-arm, phase 2 study in AdvSM. A total of 23 patients with MCL were treated across multiple dose levels on both studies. While different response assessment tools exist in MCL, the primary endpoint was ORR in response-evaluable patients per mIWG-MRT-ECNM criteria. The RAC-RE analysis population of patients with MCL consists of 17 patients treated across all doses and 10 patients treated at the proposed 200 mg daily dose. In the 17 patients with MCL who were efficacy evaluable treated across all dose levels, the ORR is 47.1%, with CR rate of 17.6%. At the 200 mg dose level, the ORR in 10 patients was 40%, with no CR. One patient treated at a starting dose of 60 mg achieved a CR. Unlike other AdvSM cohorts, MCL is a leukemia where PR data is insufficient to demonstrate efficacy. While CRs were also reported at higher doses, safety concerns preclude the use of higher doses, and efficacy information at higher doses will not be included. The CR at a dose lower than the proposed dose is supportive of efficacy of this agent.

Safety

Multiple dose levels were explored in the two supporting clinical trials with 148 patients treated across all dose levels in the total safety population, including 81 patients with AdvSM treated at the 200 mg dose level. The overall safety data set is reported in the prescribing information and analyzed in the Division of Non-Malignant Hematology (DNH) responsible for the broader AdvSM indication. Safety analysis of the MCL cohort treated at the proposed dose level of 200 mg/day did not identify any unique safety signals. Intracranial hemorrhage was not observed in the MCL cohort. The MCL cohort did not demonstrate an increased rate of cognitive effects relative to the overall AdvSM population. The risk profile of avapritinib in MCL does not meaningfully differ from that of the overall AdvSM. Due to the risk of intracranial hemorrhage observed in the overall AdvSM cohort with an apparent increased incidence in patients with low platelets, the indication is limited to patients with platelet counts of greater than 50 X 10^9/L.

Overall Benefit-Risk Assessment for the Recommended Indication

MCL is a rare and fatal malignancy with limited treatment options. Midostaurin was approved in 2017 for AdvSM (including MCL). In the MCL cohort (n=21) treated with midostaurin, the CR rate per modified IWG-MRT-ECNM consensus criteria was 5% with an ORR (CR+PR) of 19% (95% CI: 5, 42) Cladribine and interferon have been used off label, and imatinib is approved for a small subset of patients with AdvSM that does not include MCL. The efficacy results of avapritinib for patients with MCL are clinically meaningful, with an overall favorable benefit-risk profile. Given the rarity of the disease and poor prognosis, the review team recommends regular approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• MCL is rare and fatal.	• Patients with MCL have unmet medical needs.
Current Treatment Options	• There is 1 FDA approved therapy for MCL: midostaurin (RYDAPT, approved 2017). • Cladribine and interferon are used off-label. • Imatinib indicated for small subset of AdvSM (not including MCL).	• Immediate need exists for additional treatment options for patients with MCL.
Benefit	• Efficacy was evaluated on analysis of pooled data from 2 studies: BLU-285-2101 and BLU-285-2202. Both studies were open-label studies exploring doses from 60 mg to 400 mg in 23 patients with MCL. Of those 23 patients, 17 were considered response-evaluable per the response assessment committee, and 10 were treated at the proposed 200 mg dose level. • The primary efficacy endpoint of the study was overall response rate (ORR) per mIWG-MRT-ECNM criteria. Note that in MCL, PR is insufficient to demonstrate efficacy, and efficacy is based on CR. • In the 17 patients with MCL in the response evaluable population treated across all doses, ORR was 47.1% (8 patients consisting of 3 CR and 5 PR). • In the 10 patients with MCL in the response evaluable population treated at the proposed 200 mg dose, ORR was 40% (4 patients consisting of 4 PR and 0 CR). For the 4 patients with PR, median time to response was 2.1 months. The durations of response for each PR were 3.9+, 4.5+, 17.3+, and 21.6 months, with 3 of the 4 patients with ongoing response.	• The treatment effect of avapritinib, based on overall response rate at the proposed dose, and a complete response at a lower dose, is clinically meaningful in patients with MCL.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• When considering other dose levels, 1 CR was observed at 60 mg dose level, (b) (4)	
Risk and Risk Management	• Safety analysis of the MCL cohort treated at the proposed dose level of 200 mg/day did not identify any unique safety signals. No events of intracranial hemorrhage occured in the MCL cohort. The MCL cohort did not demonstrate an increased rate of cognitive effects relative to the overall AdvSM population. The risk profile of avapritinib in MCL does not meaningfully differ from that of the overall AdvSM population and is reported jointly.	• The overall risk profile of avapritinib at the proposed dose and schedule is acceptable in the intended population. • The benefit-risk profile of avapritinib is favorable in the intended population.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☑	**The patient experience data that were submitted as part of the application include:**			
	□	Clinical outcome assessment (COA) data, such as		
		☑	Patient reported outcome (PRO) *QoL assessed by PRO questionnaires included in the broad AdvSM analysis as a secondary endpoint.	Refer to Supplement 6.
		□	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.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	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.**			

X _____

Cross Discipline Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

Systemic mastocytosis (SM) comprises a heterogeneous group of disorders characterized by excessive accumulation of mast cells (MC) in bone marrow and other extracutaneous tissues (Akin, 2004; Valent, 2004; Arber, 2016). 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 (Valent, 2004; Lim, 2009; Méni, 2015). SM can be broadly categorized as either indolent and smoldering SM or advanced SM (AdvSM). Patients with AdvSM and smoldering systemic mastocytosis (SSM) suffer from a wide variety of severe and unpredictable symptoms and reduced quality of life. AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL) (Pardanani, 2006).

SM Diagnosis and Classification

The formal diagnosis of SM is based on pathologic and laboratory criteria established by the WHO (Swerdlow, 2017). A diagnosis of SM can be made with the documentation of multifocal dense infiltrates of neoplastic MCs in bone marrow and/or other extracutaneous organs (major criterion) and at least 1 of the following minor criteria:

1) Atypical MC morphology in bone marrow and/or extracutaneous tissues
2) Presence of the KIT D816 mutation in bone marrow, blood or other extracutaneous organ
3) Abnormal expression of CD25 with or without CD2 on MCs in bone marrow, blood or other extracutaneous organ
4) Elevated serum tryptase levels

If the major criterion is not present, a diagnosis of SM can still be made if 3 of the 4 minor criteria are fulfilled (Pardanani, 2015).

Systemic mastocytosis can be broadly divided into advanced and non-advanced disease, based on the degree of organ infiltration (B-findings) and organ damage (C-findings) present, as well as the presence of adverse pathological features (Swerdlow, 2017).

Patients with AdvSM (comprising 5% to 10% of patients with SM) have adverse clinicopathological features and poor OS, even with available therapies. These adverse features include organ damage due to MC infiltration (C-findings), co-presence of an associated hematologic neoplasm (AHN), and/or excess MCs in the marrow aspirate. C-findings are heterogeneous and may occur throughout the body. Systemic mastocytosis with C-findings, but without additional adverse pathological features, is rare, and known as advanced SM (ASM), which has a median OS of 41 to 68 months (Pardanani, 2009).

Table 1: B and C Findings in SM

B-Findings	C-Findings
1) High mast cell burden (shown on bone marrow biopsy): and > 30% infiltration of cellularity by mast cells (focal, dense aggregate) and serum total tryptase > 200 ng/mL 2) Signs of dysplasia or myeloproliferation in non-mast cell lineages(s), but criteria are not met for a definitive diagnosis of an associated hematological neoplasm, with normal or only slightly abnormal blood counts 3) Hepatomegaly with impairment of liver function, palpable splenomegaly with hypersplenism and/or lymphadenopathy on palpation or imaging	1. Bone marrow dysfunction caused by neoplastic mast cell infiltration, manifested by ≥ 1 cytopenia: ANC < 1.0 x 10^9/L, Hgb < 10 g/dL and/or platelet count < 100 x 10^9/L 2. Palpable hepatomegaly with impairment of liver function, ascites and/or portal hypertension 3. Skeletal involvement, with large osteolytic lesions with or without pathological fractures (pathologic fractures causes by osteoporosis do not qualify as a C-finding) 4. Palpable splenomegaly with hypersplenism 5. Malabsorption with weight loss due to gastrointestinal mast cell infiltrates

Source: Modified from Swerdlow, 2016 and Arber, 2016

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**

Source: Modified from Swerdlow, 2016 and Arber, 2016

Table 3: Overview of Prevalence and Incidence of Mastocytosis

Disease		Annual incidence per 10,000	Prevalence per 10,000	References
Systemic mastocytosis (SM)		0.021-0.089	0.959-5	Cohen et al, 2014; Marton et al, 2016; Orphanet, 2020
Non-advanced SM	ISM	0.073	0.824-0.9	Marton et al, 2016; Orphanet, 2020
	SSM	-	0.13 (ISM+SSM)	van Doormaal et al, 2013
AdvSM	SM-AHN	0.004	0.031	Cohen et al, 2014

	ASM	0.001	0.009-0.09	Cohen et al, 2014; Orphanet, 2020
	MCL	0.001	0.000	Cohen et al, 2014

Source: Modified from Swerdlow, 2016 and Arber, 2016

Patients with both nonadvanced and advanced SM suffer from a wide variety of severe and unpredictable symptoms and reduced quality of life. Patients have limited treatment options, and the low awareness of SM can result in diagnosis being delayed for several years, suboptimal patient care, and exacerbation of the high unmet medical need in this population.

MCL

MCL is a highly aggressive SM variant with a median survival of 2 months to 23 months, the poorest prognosis among SM subtypes (Swerdlow, 2017; Jawhar, 2017). MCL is a rare disease with an annual incidence of 0.001 cases per 10,000 people. MCL is defined by the presence of ≥ 20% mast cells in a bone marrow smear. In contrast to other subtypes of advanced systemic mastocytosis, MCL diagnosis does not require B findings (which indicate a high burden of MCs and expansion of the neoplastic process into multiple hematopoietic lineages, but no evidence of organ damage) or C findings (organ damage produced by MC infiltration) (Valent, 2004).

2.2. Analysis of Current Treatment Options

Available Therapies

Patients with AdvSM have limited treatment options (Valent, 2010). In AdvSM, current recommended therapies include midostaurin (approved in US and EU), cladribine, interferon (both used off-label), and imatinib (approved in the US for only a very small subset of ASM patients without the D816V KIT mutation or with unknown KIT mutational status) (Kluin-Nelemans, 2003; Pardanani, 2003; Aichberger, 2008; Vega, 2009; Ustun, 2014). Despite the approval of midostaurin for AdvSM in 2017, cladribine is still recommended in patients needing rapid debulking, or in those who have to discontinue midostaurin due to toxicity mediated by off-target kinase inhibition. Some experts recommend interferon in patients with more slowly progressive disease (Tefferi, 2001; Lim, 2009; Radojković, 2011; Barete, 2015). Allogeneic hematopoietic stem cell transplantation may be considered, although its value in SM is questionable (Ustun, 2014).

Mast cell burden has proven very difficult to eradicate with current therapies, and thus improvement of symptoms of organ damage, rather than MC burden reduction, has historically been the endpoint used in assessing response in AdvSM (Tefferi, 2004). Currently used treatments improve organ damage in 35% to 70% of patients (per "Valent consensus" criteria), but these responses are often not durable and complete remission is rare (Tremblay, 2015).

Currently used systemic therapies are often associated with significant, sometimes life-threatening side effects. In the case of interferon-α, one-third of patients experience depression, and the adverse effects of therapy can be similar to the symptoms of mastocytosis. For cladribine, nearly half of patients experience Grade 3 or 4 neutropenia, and 80% experience prolonged lymphopenia, increasing the risk of life-threatening opportunistic infections (Kluin-Nelemans, 2003).

Midostaurin

Midostaurin is a multikinase inhibitor that was approved for FLT3-mutated AML and is the only agent approved specifically for all subtypes of AdvSM (Midostaurin USPI). It was approved by the FDA in April 2017 as Rydapt and by the European Medicines Agency (EMA) in September 2017 based on the open-label, single-arm, phase 2 D2201 clinical study in 116 patients (89 evaluable for primary efficacy analysis) with AdvSM and an open-label, single-arm, investigator-sponsored, phase 2 study in 26 patients with AdvSM.

In the D2201 study, midostaurin improved MC-related organ damage for at least 8 weeks (confirmed responses per modified "Valent consensus" criteria) in 60% of patients with AdvSM; however, many of these responses involved only minor or partial improvement (15%) in organ damage and no complete remissions were reported.

The clinical significance of responses involving only minor and partial improvements in organ damage was criticized by SM experts, and responses after 6 months on midostaurin per "Valent consensus" criteria were not significantly associated with improved OS in a landmark analysis (p-value=0.18) (DeAngelo, 2018). The response rate cited in the midostaurin US package insert (USPI) is only 21% using modified Valent criteria (ICR+CR only) and 17% using IWG-MRT-ECNM criteria (CR+PR only) with rare complete responses (2%). Per modified Valent criteria, response (CR+ICR) at 6 cycles in the MCL cohort (n=16) was 25%. Note, the USPI specifies that in the MCL cohort, efficacy was based on the CR results by mIWG-MRT-ECNM criteria with a CR rate of 5% and ORR of 19%.

Midostaurin is associated with frequent gastrointestinal side effects, including nausea (82%, 6% Grade ≥ 3) and vomiting (68%, 6% Grade ≥ 3), and treatment with prophylactic antiemetics is recommended. In addition, there is associated pulmonary toxicity including dyspnea (23%, 7% Grade ≥ 3) and pneumonia (10%, 8% Grade ≥ 3). Treatment discontinuation due to adverse events (AE) occurred in 21% of patients (Midostaurin USPI; DeAngelo, 2018; Gotlib, 2016).

Response Assessment

Multiple criteria exist to assess response in SM (Valent, 2003; Valent, 2007). The generalizability of findings in clinical trials in SM is limited by the heterogeneity of which response criteria is used.

In the Valent response criteria for AdvSM, published in 2003 and supported in a 2007 consensus statement, the status of C-findings is the fundamental basis for response assessment. Major response (MR) requires normalization of at least 1 C-finding, with subcategories of MR based on the degree of reduction in mast cell infiltrates, serum tryptase levels, and SM-associated organomegaly. PR requires incomplete regression of at least 1 C-finding.

The Valent criteria have notable limitations including:

- Responses in C-findings such as ascites and bone lesions are difficult to quantify, leading to potential interobserver variability.
- Patients with baseline laboratory values just outside normal range can achieve MR with modest improvement in disease burden.
- Criteria for baseline transfusion dependence and response are not defined.
- The minimal required DOR is unclear.
- Manifestations of organ damage caused by the SM component vs the AHN can overlap.

- Distinguishing cytopenias from bone marrow infiltration vs from other causes (such as hypersplenism, bone marrow fibrosis, and myelosuppression from prior therapy) can prove difficult.

The criticisms of the Valent criteria led to the development of the IWG-MRT-ECNM criteria, which more robustly define evaluable C-findings, count only full resolution of C-findings, and require a longer, 12-week, confirmation of response (Gotlib, 2013). The following table details the modified IWG-MRT-ECNM, the criteria used to assess response in this efficacy analysis of avapritinib, as well as a comparison of the various response criteria used in AdvSM. Note, CR with partial hematologic recovery (CRh) was not defined in the IWG-MRT-ECNM (Gotlib, 2013) publication but was added by the Applicant as a potential measure of clinical benefit following prior discussions with FDA. The Applicant also presented an analysis of response by Pure Pathologic Response (PPR) Criteria, which define responses based on mast cell burden determines the response. Comparison of response assessment criteria is shown in Table 5. This efficacy analysis does not consider PPR criteria, however, as this is a novel response criteria which has not been shown to correlate with clinical benefit.

Table 4: Modified IWG-MRT-ECNM Consensus Response Criteria in Advanced Systemic Mastocytosis

Response	Criteria for Response

Complete remission (CR)[a]	Requires all 4 of the following criteria, and response duration must be ≥12 weeks:
	• No presence of compact neoplastic MC aggregates in the BM or other biopsied extracutaneous organ
	• Serum tryptase level < 20 ng/mL[b]
	• Peripheral blood count remission defined as:
	  • ANC ≥ 1×10^9/L with normal differential (absence of neoplastic MCs and blasts < 1%) *and*
	  • Platelet count ≥100×10^9/L *and*
	  • Hgb level ≥11 g/dL.
	• Complete resolution of hepatosplenomegaly (spleen length ≤ 12 cm and liver length ≤ 18 cm by MRI or CT scan if MRI is not feasible) and all biopsy-proven or suspected SM-related organ damage (C-findings)

CR with partial recovery of peripheral blood counts (CRh)[a]	Requires all criteria for CR be met and response duration must be ≥12 weeks; however, patient may have residual cytopenias. The following minimum recovery of peripheral blood counts is required: • ANC > 0.5×10^9/L with normal differential (absence of neoplastic MCs and blasts < 1%) *and* • Platelet count > 50×10^9/L *and* • Hgb level > 8.0 g/dL

<table>
<tr><td>Partial remission (PR)[a]</td><td colspan="2">Requires all 3 of the following criteria, and response duration must be ≥ 12 weeks, in the absence of CR/CRh and PD:
• Reduction by ≥ 50% in neoplastic MCs in the BM[d] and/or other extracutaneous organ at biopsy demonstrating eligible SM-related organ damage
• Reduction of serum tryptase level by ≥ 50%[b]
• Resolution of 1 or more biopsy-proven or suspected SM-related organ damage (C-finding[s])[c]</td></tr>
<tr><td>Clinical improvement (CI)[a]</td><td colspan="2">Response duration must be ≥ 12 weeks
Requires 1 or more of the nonhematologic and/or hematologic response criteria to be fulfilled in the absence of CR, CRh, PR, or PD</td></tr>
<tr><td>Stable disease (SD)</td><td colspan="2">Not meeting criteria for CR/CRh, PR, CI, or PD</td></tr>
<tr><td rowspan="6">Progressive disease (PD)[e]</td><td colspan="2">Requires at least 1 element from the criteria below; duration must be ≥4 weeks:</td></tr>
<tr><td>Baseline</td><td>Postbaseline</td></tr>
<tr><td>Any Grade 2 nonhematologic organ damage</td><td>• Worsening by 1 grade and
• Minimum 100% increase (doubling) of laboratory abnormality</td></tr>
<tr><td>Grade ≥ 2 albumin</td><td>• Worsening by 1 grade and
• Decrease by ≥ 0.5 g/dL</td></tr>
<tr><td>Grade ≥ 3 nonhematologic organ damage</td><td>Minimum 100% increase (doubling) of laboratory abnormality</td></tr>
<tr><td>Grade ≥ 2 transfusion-independent anemia or thrombocytopenia</td><td>New transfusion dependence at 8 weeks of ≥ 4 units of PRBCs or platelets</td></tr>
<tr><td>Grade ≥ 3 neutropenia</td><td>• > 50% decrease in neutrophil count and</td></tr>
<tr><td>Response</td><td colspan="2">Criteria for Response</td></tr>
<tr><td rowspan="3"></td><td></td><td>• Absolute decrease of neutrophil count of ≥ 0.25 x 10^9/L and Grade 4 (< 0.5 x 10^9/L)</td></tr>
<tr><td>Baseline spleen size of not palpable or < 5 cm</td><td>• Development of at least 10 cm palpable symptomatic splenomegaly or
• Increase in spleen volume ≥ 25%</td></tr>
<tr><td>Splenomegaly ≥ 5 cm</td><td>• > 50% worsening and
• Development of ≥ 10 cm of palpable symptomatic splenomegaly compared with the baseline value or
• Increase in spleen volume ≥ 25%</td></tr>
<tr><td>Loss of response (LOR)</td><td colspan="2">Loss of a documented CR/CRh, PR, or CI that must be for ≥ 8 weeks. Downgrading of CR/CRh to PR or PR to CI is considered as such but is not considered a LOR unless CI is also lost for a minimum of 8 weeks. The baseline value for LOR is the pretreatment measurement(s) and not the nadir values during response.</td></tr>
</table>

Source: Adapted from Gotlib et al, 2013

Table 5: Comparison of IWG-MRT-ECNM, Modified IWG-MRT-ECNM, and PPR Criteria

Assessment	IWG-MRT-ECNM Criteria		PPR Criteria [c]
	Published [a]	Modified [b]	
Evaluable C-findings			
Inclusion of patients without evaluable C-findings	Only MCL	Only MCL	All SM patients
Symptomatic splenomegaly	Symptoms of discomfort and/or early sateity	Symptoms not required	NA
Splenomegaly	> 5 cm below LCM	≥ 5 cm below LCM	NA
Medically documented weight loss of ≥10% over 24 weeks	NA	Removed as per FDA feedback	NA
Response Categories			
Complete remission with full or partial hematologic recovery (CR or CRh)			
Elimination of BM MC aggregates	Yes	Yes	Yes
Serum tryptase < 20 ng/mL	Yes	Yes	Yes
Full recovery of peripheral blood required for CR/mCR	Yes	Yes	Yes
Partial recovery of peripheral blood required for CRh/mCRh	NA	Yes	Yes
Attribution of C-findings to SM, with resolution of all of them	Yes, except for MCL with no C-findings	Yes, except for MCL with no C-findings	NA
Partial remission (PR)			
≥ 50% reduction in BM MC and serum tryptase required for PR	Yes	Yes	Yes
Attribution of C-findings to SM, with resolution of one or more of them	Yes, except for MCL with no C-findings	Yes, except for MCL with no C-findings	NA
Clinical improvement (CI)			
CI as a response category	Yes, but not included in ORR for FDA	Yes, but not included in ORR for FDA	No
Progressive disease (PD)			
PD due to worsening C-findings	Yes, with 8-week confirmation	Yes, with 4-week confirmation	NA
PD due to transformation to AML	Yes	Yes	Yes

Source: CSR BLU-285-2101, Table 10

Table 6: Summary of Treatment Relevant to Proposed Indication in the MCL Cohort

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
RYDAPT (Midostaurin)	ASM SM-AHN MCL	2017	100 mg PO daily (with food)	N = 16 CR+ICR by 6 cycles by modified Valent criteria = 4 (25%) (95% CI: 7, 52) Median DOR = NR Median Time to CR+ICR in months: 0.3 (95% CI: 0.1, 0.5) ORR by 6 cycles by mIWG-MRT-ECNM criteria = 4 (19%) (95% CI: 5, 42)	Embryofetal toxicity; pulmonary toxicity; CYP3A4 interactions. AEs ≥ 20% : nausea, vomiting, diarrhea, edema, musculoskeletal pain, abdominal pain, fatigue, upper respiratory tract infection, constipation, pyrexia, headache, and dyspnea
GLEEVEC (Imatinib)	ASM without the D816V c-Kit mutation or with cKit mutational status unknown	2006	100 mg/day if associated with eosinophilia, or 400 mg/day	Of 28 patients treated for ASM, *no MCL is identified*.	Most frequently reported AEs: reactions were diarrhea, nausea, ascites, muscle cramps, dyspnea, fatigue, peripheral edema, anemia, pruritus, rash and lower respiratory tract infection.
Cladribine	Off-label use				
Interferon	Off-label use				

Source: FDA review

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

- AYVAKIT was approved January 9, 2020 (NDA 212608) 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. Development in GIST was conducted under IND 125379. The initial review and approval of avapritinib for metastatic GIST with exon 18 mutation was conducted by the Division of Oncology 3 (DO3).

- Avapritinib's development in systemic mastocytosis has been conducted under IND 124159 (Office of Cardiology, Hematology, Endocrinology, and Nephrology [OCHEN]/Division of Nonmalignant Hematology [DNH]). Orphan Drug Designation and Breakthrough Drug Designation granted for the proposed indications as follows:

Table 7: Orphan Drug Designation and Breakthrough Designation of Avapritinib in SM

Date Granted	Designation	Indication
January 21, 2016	Orphan Drug Designation	Mastocytosis
October 12, 2018	Breakthrough Designation (BTD)	Advanced systemic mastocytosis (AdvSM) including ASM, SM-AHN, and MCL
December 23, 2020	Breakthrough Designation (BTD)	Moderate to severe indolent systemic mastocytosis (ISM)

3.2. Summary of Presubmission/Submission Regulatory Activity

The following table summarizes regulatory interactions with OCHEN:

Table 8: Prior Regulatory Interactions with OCHEN

Date	Interaction	Summary
September 04, 2015	Study may proceed letter	Issued for phase 1 study of AdvSM and relapsed/ refractory myeloid malignancies

[redacted] (b) (4)		
March 21, 2018	End-of-Phase 1 (Type B) Meeting, Clinical	Applicant sought agreement of the non-clinical safety package to support a clinical study in ISM/SSM, the design of the Phase 2 studies in AdvSM and ISM/SSM patients as registration-enabling studies
[redacted] (b) (4)		
February 27, 2019	Multidisciplinary BTD (Type B) Meeting	Discussion of the acceptability of data from ongoing BLU-285-2101 study of avapritinib in patients with AdvSM (ASM, SM-AHN, and MCL) in support of a sNDA
August 27, 2019	Pre-sNDA Meeting	Discussion of the acceptability of using data from ongoing BLU-285-2101 study of avapritinib in patients with AdvSM in support of an sNDA to be [redacted] (b) (4)
[redacted] (b) (4)		
January 08, 2020	Informal teleconference	Discussion on acceptable data package for planned sNDA submission including pooled data from both studies, BLU-285-2101 and BLU-285-2202 interim analysis.

The following is a regulatory summary following submission of the efficacy supplement under review by DHMI:

- On December 16, 2020, FDA received NDA 212608 S-006 (SD 80), a new efficacy supplement intended to support an indication of advanced systemic mastocytosis (AdvSM) [redacted] (b) (4) AdvSM includes patients with

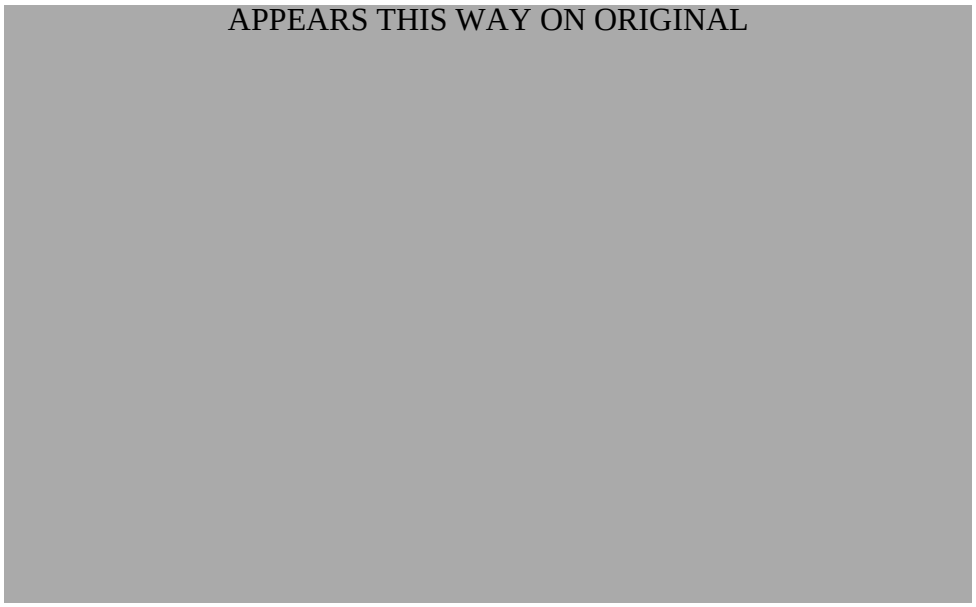
aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).

- Following initial review of the efficacy supplement, determination was made to split S-006 into the following two efficacy supplements: NDA 212608 Supplement S-006 (ASM, SM-AHN) and S-007 (MCL), letter dated January 25, 2021. The purpose of the administrative split was to permit independent review of the application by each review division (S-006 by OCHEN/DNH and S-007 by OOD/DHMI).

3.3. Foreign Regulatory Actions and Marketing History

- On March 3, 2021, the European Medicines Agency (EMA) has validated a 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.

- Avapritinib was previously approved for the indication in GIST by the EMA on September 24, 2020.



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

4.1. Office of Scientific Investigations (OSI)

Not applicable. Clinical inspections were not conducted for this sNDA.

4.2. Product Quality

Product quality information was reviewed under S-006.

4.3. Clinical Microbiology

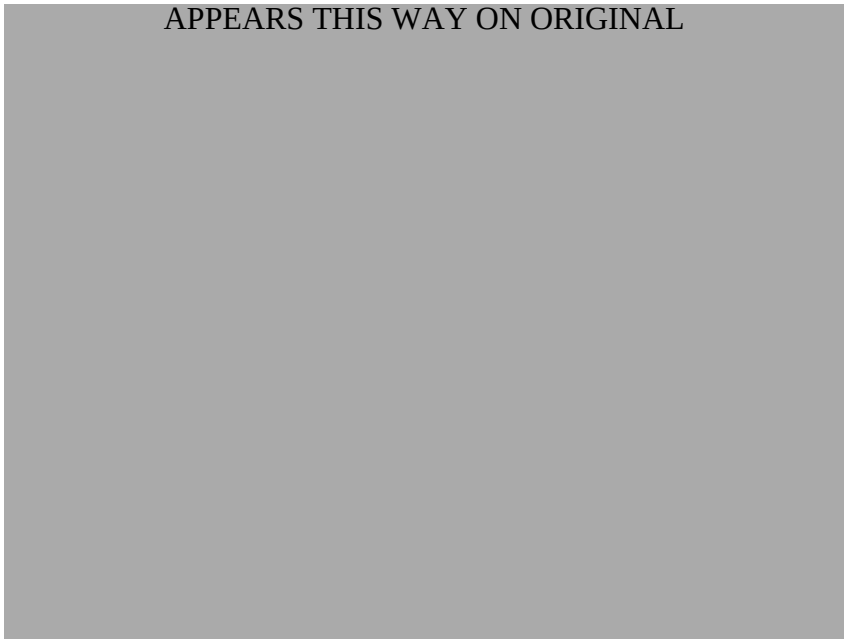
Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable. No devices or companion diagnostics are needed for this indication.

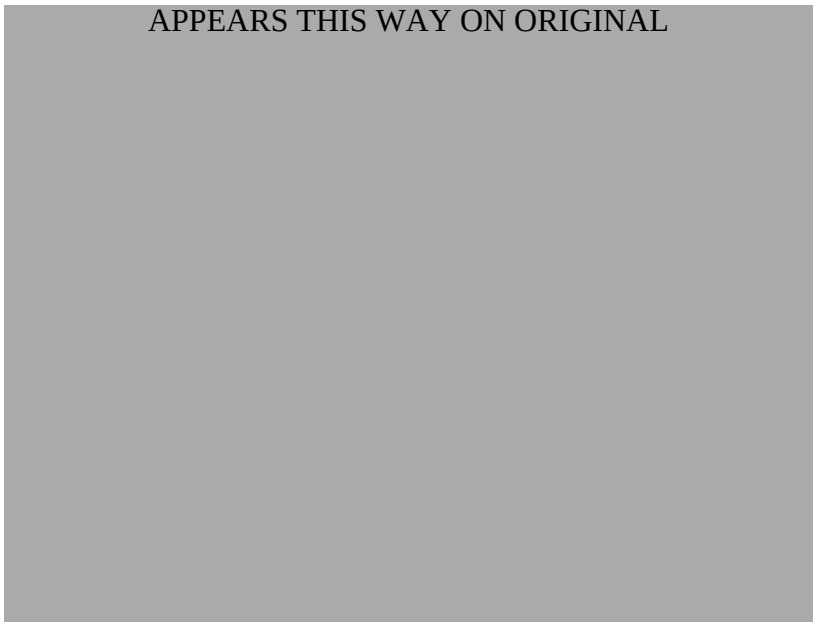
5 Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology and toxicology studies supporting the initial approval and labeling for avapritinib were reviewed under the Multidisciplinary Review and Evaluation for the original submission of NDA 212608. Additional studies to support Supplements 6 and 7 have been reviewed under Supplement 6.



6 Clinical Pharmacology

Clinical pharmacology review for Supplements 6 and 7 has been provided separately. The Office of Clinical Pharmacology stated that the NDA is approvable from a clinical pharmacology perspective.



7 Sources of Clinical Data and Review Strategy

The clinical review considered pooled efficacy data from combined clinical datasets from studies BLU-285-2101 and BLU-285-2202, provided in the Applicant's Integrated Summary of Efficacy dataset. Due to similar inclusion criteria for the MCL cohort across both trials, it was reasonable to combine the datasets for pooled efficacy analysis.

For the safety evaluation, pooled data from both clinical studies BLU-285-2101 and BLU-285-2202 was provided in the Applicant's Integrated Summary of Safety dataset. Safety analysis was performed comparing the population of patients with MCL with the overall study population to consider if unique safety signals were present in the MCL cohort. As no unique safety signals were identified, our review team recommended that safety in the MCL population be analyzed and presented jointly with the larger AdvSM population reviewed in Supplement 6.

7.1. Table of Clinical Studies

Table 9: Listing of Clinical Trials Relevant to this sNDA

Trial	Trial Design	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
BLU-285-2101 "EXPLORER" NCT02561988	Phase 1, single-arm, open-label, dose-escalation	Part 1: 3 + 3 dose escalation 30 to 400 mg QD Part 2: Initially avapritinib 300 mg QD (RP2D), changed to 200 mg QD	1: Safety, MTD, RP2D	13 MCL patients Overall: Part 1: 32 patients Part 2: 54 patients	ASM SM-AHN MCL R/R myeloid malignancies	11 sites across 2 countries (US and UK)
BLU-285-2202 "PATHFINDER" NCT03580655	Phase 2, single-arm, open-label	Cohort 1 and 2: 200 mg QD (100 mg QD for patients with platelet counts from 25,000 to 50,000/µL at baseline)	1: ORR	10 MCL patients Cohort 1: 55 patients Cohort 2: 7 patients	ASM SM-AHN MCL	32 sites across 12 countries
BLU-285-1101 "NAVIGATOR" NCT02508532	Two-part, open-label, dose-escalation and dose-expansion, phase 1 study	Starting dose of 30 mg PO daily dosing (28-day cycle), escalated to MTD/RP2D	MTD (400 mg/day) RP2D (300 mg/day)	46 patients in dose escalation; 36 patients in dose expansion	Unresectable GIST or other advanced solid tumor	17 sites across 9 countries
BLU-285-1303 "VOYAGER" NCT03465722	Phase 3, open-label, randomized	300 mg PO daily + regorafenib 160 mg PO daily (days 1-21 of 28-day cycle)	1:PFS per RECIST 1.1 2: ORR, OS, EORTC-QLQ-30		Unresectable/ metastatic GIST	114 sites across 17 countries

Source: FDA Review, adapted from Applicant's Integrated Summary of Efficacy

7.2. Review Strategy

The clinical review was conducted by one primary reviewer with the assistance of one team leader. No DHMI statistical review was conducted as statistics were only descriptive for the MCL cohort and the MCL cohort reviewed by DHMI was of limited size. Refer to the review for S-006 for statistical evaluation in the overall AdvSM population. A pooled dataset from studies BLU-285-2101 and BLU-285-2202 served as the basis for the review. Data reviewed included the ISS, summary of clinical safety (SCS), summary of clinical efficacy (SCE), individual clinical study reports (CSRs), patient narratives, and information requests (IRs). JMP15 was used to reproduce key analyses, based on data analysis datasets, and to conduct additional exploratory analyses. MAED was used for safety analysis.

Efficacy claims are based on the results from two studies: BLU-285-2101 and BLU-285-2202. Study design is presented separately for each study. Efficacy results are presented from analysis of pooled data set and are limited to the MCL population for this review. The criteria used to define the Response Assessment Committee Response-Evaluable (RAC-RE) population were the same for both studies. Selection of the RAC-RE population is in accordance with the pre-specified primary efficacy endpoint for both studies (mIWG assessed by the RAC) and was uniform between Supplements 006 and 007.

8 Statistical and Clinical and Evaluation

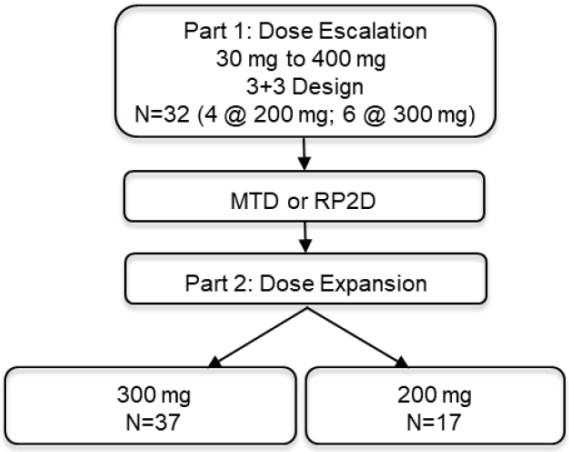
8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. BLU-285-2101 "EXPLORER"

Overview

BLU-285-2101 is an open-label, phase 1 study of orally dosed avapritinib in adult patients with AdvSM and relapsed or refractory myeloid malignancies. Study endpoints included safety, tolerability, PK, pharmacodynamics, and efficacy. The study contained two parts. Part 1 was a dose escalation portion to evaluate safety and tolerability of avapritinib in patients with a local diagnosis of AdvSM or other relapsed or refractory myeloid malignancies. Part 2 further evaluated safety, PK, pharmacodynamics, and efficacy assessed per mIWG-MRT-ECNM response criteria. Part 2 enrolled patients with a WHO diagnosis of AdvSM. Diagnosis and response assessments were determined by a central review committee. At the time of submission of the supplement, Part 1 is complete, and Part 2 is ongoing. Note, the efficacy analysis was performed on the RAC-RE population.

Figure 1: Study Schema of BLU-285-2101



Source: CSR BLU-285-2101

Part 1: Dose Escalation (with Enrichment)

Primary objectives of Part 1 were determination of MTD, RP2D, and safety/tolerability of avapritinib. Part 1 enrolled patients with a local diagnosis of AdvSM or relapsed or refractory myeloid malignancy. Patients had a confirmed diagnosis of 1 of the following, based on WHO diagnostic criteria:

- ASM
- SM-AHN and ≥ 1 C-finding attributable to SM. The AHN was to be myeloid, with the following exceptions that were excluded: AML, very high- or high-risk MDS as defined by the IPSS-R, and Philadelphia chromosome-positive malignancies
- MCL
- Histologically or cytologically-confirmed myeloid malignancy that was relapsed or refractory to standard treatments (excluding AML, very high- or high-risk MDS, and Philadelphia chromosome-positive malignancies), and other relapsed or refractory potentially avapritinib-responsive hematologic neoplasms (e.g., evidence of aberrant KIT or PDGFR signaling).

A standard 3+3 dose escalation design was employed. The first cohort of 3 patients received avapritinib at a starting dose of 30 mg PO daily. Cohorts were expanded to include 6 patients if a DLT occurred, with replacement of non-evaluable patients. Additional accrual to dose levels determined to be tolerable was allowed in enrichment cohorts. There were 32 patients enrolled in Part 1 of the study across 7 dose cohorts. No DLTs were reported in the 30, 100, 130, 200, or 300 mg dose cohorts.

The MTD was not reached up to doses of 400 mg PO daily, and doses above 400 mg PO daily were not evaluated because Study BLU-285-1101 in patients with GIST identified an MTD of 400 mg PO daily. In Study BLU-285-2101, the 400 mg PO daily dose was not well tolerated in patients with SM long term, as evidenced by frequent dose reductions in later cycles. Evidence of activity of avapritinib, based on decreasing MC burden, including BM MC, and serum tryptase, and reduction in spleen volume, were observed in the lower dose cohorts.

Based on safety, PK, pharmacodynamics, and antitumor activity, 300 mg PO daily was determined to be the RP2D for Part 2. Investigators initially were permitted to dose escalate patients stepwise (up to 400 mg PO daily) to potentially increase antitumor activity, provided the prior dose level was tolerated for ≥ 2 cycles (i.e., no treatment-related AEs Grade ≥ 3 were reported).

Part 2: Expansion

Patients enrolled in Part 2 of the study had 1 of the following confirmed diagnoses based on WHO diagnostic criteria: ASM, SM-AHN, or MCL. Patients were enrolled based on local diagnosis, which was retrospectively confirmed by an independent central pathologist and central committee adjudication. This confirmation was not required for study entry.

At the initial Part 2 study design, groups of patients with specific target enrollment by AdvSM subtypes (i.e., ASM, SM-AHN, and MCL) were defined and treated at the RP2D of 300 mg PO daily.

While efficacy was supported across all dose levels, safety data suggested improved tolerability at the 200 mg PO daily dose level. A second expansion cohort (Cohort 2) with a starting dose of 200 mg QD was added in Part 2 enrolling patients with AdvSM (regardless of subtype) who had ≥ 1 measurable C-finding by mIWG-MRT-ECNM criteria. This change was introduced with Protocol Amendment 6. With Protocol Amendment 7, all patients newly enrolling into Cohort 1 received a starting dose of 200 mg QD.

As of the data cutoff date, 54 patients had been enrolled in Part 2 of the study. Of these, 37 patients received avapritinib at the RP2D of 300 mg QD and 17 patients received avapritinib at a starting dose of 200 mg QD (in addition to the 4 patients enrolled in Part 1 of the study).

Study Endpoints

The primary endpoints were to determine the MTD, RP2D, and the overall safety profile of avapritinib. Sensitivity analyses were conducted for ORR using modified and nonmodified algorithm-IWG responses, Investigator-assessed responses based on mIWG-MRT-ECNM criteria, and for pathologic ORR using PPR criteria.

Secondary efficacy endpoints included:

- Adjudicated ORR (CR + CRh + PR + CI) based on mIWG-MRT-ECNM criteria
- DOR
- Changes in levels of serum tryptase
- Changes in KIT D816V mutant allele fraction
- Changes in spleen and liver volume by central radiology assessment
- Changes in PROs as assessed by the AdvSM-SAF, PGIS, and EORTC QLQ-C30 instruments (Part 2 only).

Exploratory efficacy endpoints included PFS, OS, and changes in KIT mutation burden (e.g., D816V) in BM. Additionally, TTR, EFS, and changes in BM MCs by central pathology assessment were analyzed.

Central Adjudication of Diagnosis and Response Assessment

Central adjudication of C-findings was performed by a RAC to ensure consistency. Further, central pathological review of bone marrow samples, central radiology reads of spleen assessments and central laboratory measurement of serum tryptase, assessments were implemented to ensure consistency across this multicenter study. These centrally assessed results were used by RAC for adjudication of diagnosis and disease response.

Central review of diagnosis at baseline was performed retrospectively and was not required for study entry. Only patients central diagnosed with AdvSM were included in the population for the primary efficacy analyses by modified IWG-MRT-ECNM criteria. Response assessment per central review was performed using data from every visit.

A central laboratory analyzed KIT D816V mutant allele burden in the peripheral blood or BM using PCR and next-generation sequencing at baseline and postbaseline.

A RAC was formed with SM expert investigators and the independent central pathologist to provide consistent assessment of diagnosis using WHO criteria for diagnosis and subclassification of SM. The RAC assessed disease response per mIWG-MRT-ECNM criteria. The diagnosis of SM and its subtype was based on clinicopathological features defined within the WHO criteria. To ensure consistency of diagnosis, the RAC reviewed every enrolled patient's central pathology and clinical documentation of WHO B- and C-findings.

Efficacy per IWG-MRT-ECNM criteria was a secondary endpoint defined in the original protocol. Modified IWG-MRT-ECNM criteria were later introduced to address issues arising from the implementation of newly published IWG-MRT-ECNM criteria, and all patient data were retrospectively adjudicated with the modified criteria. Each of these criteria were applied to patients in the RAC-RE population. The RAC-RE population is a subset of the safety population who have a central diagnosis of AdvSM, have an evaluable C-finding at baseline (or MCL where no C-finding is necessary) and adequate follow up for response assessment. In addition to response assessments provided by investigators and the RAC, a computer algorithm was implemented to derive response per the mIWG-MRT-ECNM response criteria (referred to as algorithm-mIWG response). The computer algorithm used the same source data as the RAC, as well as the RAC-adjudicated diagnosis, and the same version of mIWG-MRT ECNM response criteria. Pure pathologic responses (PPR) were derived according to pure pathologic response criteria by a computer algorithm. Because PPR does not include the C-findings, it can be applied to all patients with measurable MC burden.

Sample Size and Statistical Methods

It was expected that approximately 25 patients would be enrolled in Part 1. The planned enrollment of Part 1 was predicated upon the observed safety profile, which determined the number of patients per dose cohort, as well as the number of dose escalations required to achieve the MTD or identify the RP2D.

In Part 2, approximately 45 patients were planned for Cohort 1 at a starting dose of 300 mg PO daily (RP2D); subsequently, approximately 10 patients were planned for Cohort 2 at a starting dose of 200 mg PO daily. With 55 patients, there is approximately 94% probability of observing an AE that occurs at a frequency of ≥ 5%.

Analysis Population

The following analysis populations were evaluated and used for presentation and analyses of efficacy data:

- Safety Population: All patients who received ≥ 1 dose of avapritinib.
- RAC-RE Population: All patients who received ≥ 1 dose of avapritinib, had AdvSM per WHO criteria as adjudicated by RAC, are deemed evaluable per mIWG-MRT-ECNM criteria at baseline as assessed by RAC review, and had 1 of the following conditions:
    - ≥ 2 complete postbaseline BM biopsy assessments, and had been on study for ≥ 6 cycles (6 x 28 = 168 days)
    - had an EOS Visit.
- PPR Evaluable Population: All patients who received ≥ 1 dose of avapritinib, had SM per WHO criteria as adjudicated by RAC, and had 1 of the following conditions:
    - ≥ 2 complete postbaseline BM biopsy assessments, and had been on study for ≥ 6 cycles (6 x 28 = 168 days)
    - had an EOS Visit.

The primary analysis population for efficacy was the RAC-RE population, which was used for analyses of RAC-adjudicated response, DOR, and PFS. Further, the RAC-RE population was used for primary efficacy population due to the RAC-adjudication of diagnosis and confirmation of evaluability of response (i.e., removed non-AdvSM patients initially diagnosed by local principal Investigator as having AdvSM).

Response by mIWG-MRT-ECNM criteria was not assessed in patients without C-findings (i.e., patients who did not have AdvSM, or AdvSM patients that lacked an evaluable C-finding) or patients lacking sufficient follow up for adjudication.

8.1.2. BLU-285-2202 "PATHFINDER"

Overview

Study BLU-285-2202 is an open-label, single-arm, phase 2 study evaluating 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)

- Cohort 2: AdvSM patients who were not considered eligible for an adjudicated mIWG-MRT-ECNM.

Patients in Cohort 1 support the primary objective of determining ORR per mIWG-MRT-ECNM criteria. Both cohorts are included in the analyses of secondary and exploratory efficacy objectives. Treatment doses ranged from 100 mg daily to 300 mg daily. Study schema is shown in Figure 2 below.

Single-Arm Design

Study BLU-285-2202 was designed to obtain additional safety and efficacy data at the recommended avapritinib dose of 200 mg QD in patients with AdvSM.

Study Endpoints

The primary efficacy endpoint was adjudicated ORR (CR+CRh + PR + CI) based on mIWG-MRT-ECNM criteria, confirmed 12 weeks after initial response in patients in Cohort-1 only. Sensitivity analyses were conducted for ORR using algorithm-IWG-MRT-ECNM responses and investigator-assessed responses based on mIWG-MRT-ECNM criteria, and for pathologic ORR using PPR criteria.

Secondary endpoints included:

- Mean change from baseline in AdvSM-SAF TSS (a PRO assessment tool)
- Local Investigator-assessed ORR (CR + CRh + PR + CI) based on mIWG-MRT-ECNM
- ORR (CR + CRh + PR) based on PPR criteria
- Time to event outcomes (TTR, DOR, PFS, and OS)
- CR + CRh + PR and CBR (CR + CRh + PR + CI + SD) based on mIWG-MRT-ECNM
- ORR and other clinical outcome measures (DOR, PFS, and OS) analyzed by prior therapy and by genotype
- Changes in BM MCs, serum tryptase, KIT D816V mutation burden in PB and BM, spleen and liver volume

- Changes in AdvSM-SAF domain and individual symptom score
- Changes in PROs as assessed by the AdvSM-SAF, PGIS and EORTC QLQ-C30 (global health status, functional scales, and symptom scales/items) scores.

Exploratory endpoints included changes in: transfusion dependent anemia and thrombocytopenia, bone density, cutaneous disease in patients with mastocytosis in skin, BSC medication use as well as evaluation of other mutations in PB and BM EFS, correlations between efficacy or safety endpoints with AdvSM-SAF and EORTC QLQ-C30.

Central Adjudication of Diagnosis and Response Assessment

To promote consistency across multiple study sites, central adjudication of C-findings was performed by a study steering committee (SSC), like the RAC of the BLU-285-2101 study. Central pathological review was performed for bone marrow samples. Central radiology review was performed for spleen assessments. Central laboratory review was performed for measurement of serum tryptase.

In contrast to the BLU-285-2101 study, in which a local diagnosis of AdvSM was used for eligibility, a central diagnosis and evaluable C-findings at baseline were prospectively established by the central pathologist and SSC during screening.

SM response was assessed by the SSC using the mIWG-MRT-ECNM criteria. Other metrics for response assessment included algorithmic assessment of the IWG-MRT-ECNM as well as by PPR criteria.

Sample Size and Statistical Analysis Plan

The sample size of approximately 63 patients in Cohort 1 was estimated based on the primary objective and was intended to provide 93.5% power at the 1-sided significance level of 0.025 for testing the assumption of the null hypothesis ORR of 28% vs the alternative ORR 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. This sample size also allowed statistical testing of the key secondary objective and was intended to provide > 90% power at the 1-sided significance level of 0.025 for testing the assumption of the null hypothesis mean change of total symptom score (TSS) ≥ 0 vs the alternative mean change of TSS ≤ −10. Note, the TSS is derived from a 10-item symptom assessment tool. All treated patients in Cohort 1 and Cohort 2 were included in the analysis. Testing for this key secondary endpoint was sequential to ensure control of the study wise type I error rate (i.e., it was only performed when the null hypothesis for the primary objective was rejected). The non-mIWG-MRT-ECNM evaluable cohort (Cohort 2) of approximately 40 patients, for a total of 103, was intended for an approximate 88% probability of observing ≥ 1 AE at 2% frequency, instead of 3.5% frequency with 60 patients.

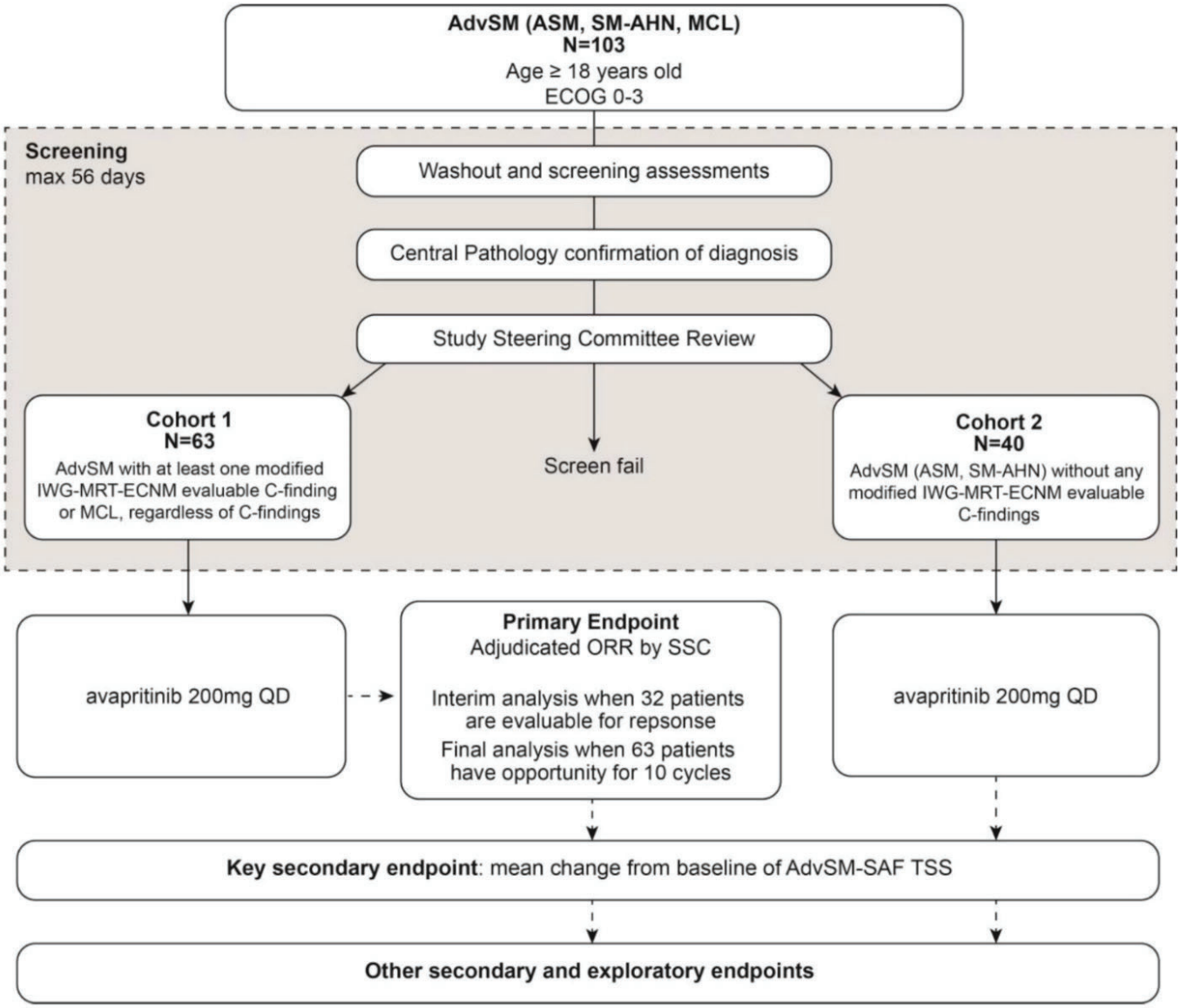
Analysis Populations

Three analysis populations were evaluated in the study: safety population, Response Evaluable (RE, equivalent to the BLU-285-2101 RAC-RE) population, PPR Evaluable population. Populations are defined as follows:

- Safety Population: All patients who received ≥ 1 dose of avapritinib.
- RAC-RE Population: All patients who received ≥ 1 dose of avapritinib, had AdvSM per WHO criteria as adjudicated by RAC, are deemed evaluable per mIWG-MRT-ECNM criteria at baseline as assessed by RAC review, and had 1 of the following conditions:
    - ≥ 2 complete postbaseline BM biopsy assessments, and had been on study for ≥ 6 cycles (6 x 28 = 168 days)
    - had an EOS Visit.
- PPR Evaluable Population: All patients who received ≥ 1 dose of avapritinib, had SM per WHO criteria as adjudicated by RAC, and had 1 of the following conditions:
    - ≥ 2 complete postbaseline BM biopsy assessments, and had been on study for ≥ 6 cycles (6 x 28 = 168 days)
    - had an EOS Visit.

The RE population was used for the primary efficacy analysis, and all secondary efficacy analyses related to response, such as objective response, TTR, DOR, PFS, CI rate, and CBR (CR + CRh + PR + CI + SD) based on mIWG-MRT-ECNM. The safety population was used for the key secondary analysis, PRO analyses, and efficacy analyses that were not based on mIWG-MRT-ECNM response criteria. The PPRE population was used as analysis population for pure pathologic response, such as objective response rate, TTR, DOR, PFS.

Figure 2: Study Schema of BLU-285-2202



Source: CSR BLU-285-2202, Figure 2

8.1.3. Study Results

Study results are presented from the pooled analysis of patients with MCL in the RAC-RE population at the proposed 200 mg oral daily dose level and doses lower than 200 mg.

Compliance with Good Clinical Practices

The Applicant stated that study was conducted in compliance with Good Clinical Practice.

Financial Disclosure

Of the over 100 investigators and sub-investigators, only 3 had reportable interests where were properly disclosed. The financial disclosure information did not raise concerns about data integrity.

Data Quality and Integrity

The Applicant described methods of assuring data quality and integrity, including data verification at all sites and auditing of the data to monitor consistency.

Protocol Amendments

Study BLU-285-2101 contained 9 protocol amendments and study BLU-285-2202 contained 8 protocol amendments. Notable modifications included changes to the starting dose with adjustments for platelet level; the enrollment of patients without C-findings; the enrollment of midostaurin naïve patients.

Protocol Violations/Deviations

Study BLU-285-2101: No patient was excluded from any analysis population due to a protocol deviation. There were 45 patients (52.3%) who had a total of 124 protocol deviation during the study that were considered "major" and required reporting to the Applicant for review. The most common major protocol deviation was related to study conduct and procedures (36 patients, 41.9%). Such protocol deviations were driven by the large number and variety of assessments required to adjudicate response by mIWG-MRT-ECNM criteria and a large number of missed study visits due to restrictions imposed by the COVID-19 pandemic. The observed protocol deviations were considered unlikely to affect the study efficacy or safety conclusions.

Study BLU-285-2202: No patient was excluded from any analysis population due to a protocol deviation. A total of 39 (62.9%) patients in the all doses group had ≥ 1 major deviation. The most common protocol deviation was failure to comply with study procedures (45.2%), followed by study treatment dosing errors (14.5%). All other major protocol deviations occurred in < 5% of patients. The observed protocol deviations were considered unlikely to affect the study efficacy or safety conclusions.

Patient Disposition

Patient dispositions are provided for the entire pooled analysis population. The MCL cohort was not separated from the greater AdvSM population. The data presented is the Applicant's analysis.

Table 10: Patient Dispositions

Disposition Category	Pooled 2101+2202	
	200 mg (N=44)	All Doses (N=85)
Discontinued from treatment	13 (29.5)	36 (42.4)
Continuing on treatment	31 (70.5)	49 (57.6)
Discontinued from study	11 (25.0)	29 (34.1)
Reasons for discontinuation of treatment		
Disease progression	5 (11.4)	16 (18.8)
AML	2 (4.5)	7 (8.2)
Adverse event(s)	6 (13.6)	13 (15.3)
Related	2 (4.5)	6 (7.1)
Death	0	0
Withdrew consent	2 (4.5)	3 (3.5)
Investigator's decision	0	3 (3.5)
Administrative/ other	0	1 (1.2)
Reasons for discontinuation from study		
Disease progression	0	0
Adverse event(s)	0	1 (1.2)
Death	8 (18.2)	19 (22.4)

Source: Adapted from ISE Table 14.1.2.1.2

Table 11: Demographic Characteristics for Patients with MCL Treated with Avapritinib in the RAC Adjudicated (mIWG) Efficacy Evaluable Population from Pooled Study Analysis

	200 mg dose level	**All dose levels**
	n = 10	*n = 17*
	# Patients, n (Percentage, %)	# Patients, n (Percentage, %)
Study		
BLU-285-2101	6 (60%)	13 (76%)
BLU-285-2202	4 (40%)	4 (24%)
Geographic Location		
Europe		
Great Britain	2 (20%)	2 (12%)
Italy	1 (10%)	1 (6%)
North America		
United States	6 (60%)	13 (76%)
Canada	1 (10%)	1 (6%)
Age		
<65 years	8 (80%)	13 (76%)
>=65 years	2 (20%)	4 (24%)
Gender		
Male	8 (80%)	10 (59%)
Female	2 (20%)	7 (41%)
Race and Ethnicity		
White	10 (100%)	14 (82%)
Non-Hispanic	10 (100%)	16 (94%)
Prior Anti-Neoplastic Therapy		
Yes	8 (80%)	12 (71%)
No	2 (20%)	5 (29%)
Prior Midostaurin Use		
Yes	4 (40%)	7 (41%)
No	6 (60%)	10 (59%)
Nadir Platelet >= 50K		
Yes	9 (90%)	15 (88%)
No	1 (10%)	2 (12%)
ECOG Performance Status		

0	3 (30%)	5 (29%)
1	5 (50%)	9 (53%)
2	2 (20%)	3 (18%)

Source: FDA review

Efficacy Data

The Applicant's initial presentation of efficacy included all dose levels while FDA assessment of efficacy was limited to the proposed 200 mg dose level. Efficacy from the pooled data analysis is shown below.

Table 12: Efficacy Results for Patients with MCL treated with Avapritinib at the Recommended Dose 200 mg dose level in the RAC Adjudicated Response (mIWG) Efficacy Evaluable Population from Pooled Study Analysis

MCL, RAC Adjudicated Response (mIWG)	200 mg dose n=10	Doses up to 200 mg n=11
	n (%)	*n (%)*
ORR (CR+PR)	**4 (40%)**	**5 (45%)**
(95% CI)		(17,77)
CR	0 (0%)	1 (9%)
(95% CI)		(0,41)
PR	4 (40%)	4 (36%)
(95% CI)		(11,69)
SD	5 (50%)	5 (45%)
PD	1 (10%)	1 (9%)

Source: FDA review

Note, there are no CR observed at the 200 mg dose level. The DOR for the CR at 60 mg was 7.6 months and ongoing as of the data cutoff of May 1, 2020. The DOR for each PR were 3.9+, 4.5+, 17.3+, and 21.6 months; 3 of the 4 reported PR DOR metrics were censored as they are still ongoing. Kaplan-Meier DOR estimates were not informative. In contrast, note the following table of efficacy in all dose levels.

Table 13: Adjudicated Best Response by mIWG-MRT-ECNM Criteria in MCL (RAC-RE Population, Pooled All Doses)

Parameter	MCL N=17
ORR (CR + CRh + PR + CI), n (%)	10 (58.8)
95% confidence interval	(32.9, 81.6)
CR+CRh+PR, n (%)	**8 (47.1)**
95% confidence interval	(23.0, 72.2)
CR+CRh, n (%)	3 (17.6)
95% confidence interval	(3.8, 43.4)
CR	**3 (17.6)**
CRh	0
PR	5 (29.4)
CI	2 (11.8)
SD	6 (35.3)
PD	1 (5.9)
NE	0

Source: Adapted from ISE Table 14.2.1.1

8.1.3 Integrated Review of Effectiveness

The proposed indication in mast cell leukemia is supported by efficacy data from EXPLORER (NCT02561988) and PATHFINDER (NCT03580655), two multi-center, single-arm, open-label clinical trials. EXPLORER, also known as study BLU-285-2101, is a phase 1, open-label study designed to evaluate the safety, tolerability, PK, pharmacodynamics, and efficacy of avapritinib, administered orally, in adult patients with advanced systemic mastocytosis (AdvSM) and relapsed or refractory myeloid malignancies. PATHFINDER, also known as BLU-285-2202, is a phase 2, open-label, single-arm study evaluating the efficacy and safety of avapritinib in patients with a WHO diagnosis of AdvSM. Both studies in patients with AdvSM were conducted in countries in Europe and North America.

Response-evaluable patients include those with a confirmed diagnosis of AdvSM (specifically MCL for our review population) per World Health Organization (WHO) and deemed evaluable by modified 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.

The primary efficacy outcome measure per the study design was ORR per modified IWG-MRT-ECNM criteria in the AdvSM population. However, in acute leukemia such as MCL, the Agency considers the CR rate for approval. In the 17-patient efficacy evaluable population that includes patients with MCL treated across all dose levels, the Applicant reported ORR of 8 patients, or 47.1%. When our review considered only those patients treated at the 200 mg dose level (n=10), ORR was 4 patients, or 40%. Additionally, while 3 CR were noted in the Applicant's efficacy evaluation at all doses, no CR were reported at the 200 mg dose level. One CR occurred in a patient treated at doses lower than 200 mg and was included in the overall assessment of avapritinib in MCL.

Consider the following analysis of all patients with MCL treated at all dose levels and using response assessment criteria including:

- Algorithm Pure Pathologic Response (molecular):
- Algorithm Pure Pathologic Response (morphologic):
- Algorithm mIWG:
- RAC Adjudicated Response (mIWG):
- Investigator-assessed Response (mIWG): Varies from RAC adjudicated using same criteria, but not centrally assessed.

Refer to **Table 14** for a comparison of response criteria.

Table 14: Efficacy in Patients with MCL Treated with Avapritinib at All Doses Levels Compared by Response Assessment Criteria

STUDY	SUBJECT ID	Treatment Dose	Algorithm Pure Pathologic Response (molecular)	Algorithm Pure Pathologic Response (morphologic)	Algorithm-IWG Response	Algorithm-mIWG Response	Investigator Assessed Response (mIWG)	RAC Adjudicated Response (mIWG)
BLU-285-2101	(b) (6)	200 mg	mCR	mCR	PR	PR	CR	PR
BLU-285-2101		200 mg	mCR	mCR	CR	CR	PR	PR
BLU-285-2101		200 mg	mPR	mPR	PR	PR	SD	SD
BLU-285-2101		200 mg	SD	SD	SD	SD	SD	SD
BLU-285-2101		200 mg	SD	SD	SD	SD	CI	SD
BLU-285-2101		200 mg	mPR	mPR	PR	PR	CI	PR
BLU-285-2202		200 mg	SD	SD	CI		SD	SD
BLU-285-2202		200 mg	SD	SD	SD		SD	SD
BLU-285-2202		200 mg	mPR	mPR	PR		PR	PR
BLU-285-2202		200 mg	SD	SD	SD		SD	PD
BLU-285-2101		300 mg	SD	SD	SD	CI	SD	CI
BLU-285-2101		300 mg	SD	SD	CI	CI	SD	CI
BLU-285-2101		300 mg	SD	SD	CI	CI	SD	SD
BLU-285-2101		300 mg	mCR	mCR	CR	CR	CR	CR
BLU-285-2101		300 mg	moCRh	mCRh	CR	CR	PR	PR
BLU-285-2101		400 mg	mCR	mCR	CR	CR	CR	CR
BLU-285-2101		60 mg	moCR	mCR	CR	CR	CR	CR

Source: FDA review
Note, gray highlighting indicates patients who achieved a CR by RAC adjudicated mIWG criteria.

While no CR were observed at the 200 mg, 1 CR was observed at the 60 mg dose (b) (4) (b) (4) Responses at doses at or below the recommended dose of 200 mg were considered supportive while responses above the recommended dose were not considered.

Clinical information request was sent to the Applicant on March 31, 2021 to better understand the response data and consider why CRs at the 200 mg dose level per other assessment criteria were not considered a CR per the RAC Adjudicated Response Criteria (pre-specified efficacy endpoint). The IR stated:

> Our efficacy analysis shows that among patients with mast cell leukemia treated at the 200 mg dose level (n=10), there was a best response determination of 4 PR and no CR when evaluated by RAC Adjudicated Response (mIWG). When considering other response criteria, patient BLU-285-2101 (b) (6) achieved CR by investigator assessed mIWG and mCR by molecular and morphologic algorithm Pure Pathologic Response Criteria, but a PR by algorithm-IWG, algorithm-mIWG, and RAC adjudicated response. A second patient, BLU-285-2101 (b) (6) achieved CR by algorithm-IWG and algorithm-mIWG, mCR by molecular and morphologic algorithm Pure Pathologic Response Criteria, but PR by investigator assessed mIWG and RAC adjudicated response.

The Agency additionally requested detailed information on the criteria for each response determination (including CBC, bone marrow findings, serum tryptase, c-kit mutation level, spleen and liver size, C-findings, if applicable, etc.), the best response determination, date of best response, and duration of response. Additionally, the IR requested an explanation of the

discrepancy between algorithm-mIWG and RAC-mIWG which used the same source data, and the reason for missing algorithm-mIWG in the response dataset for 4 patients.

The Applicant advised that discrepancies arose when a response was not able to be confirmed, known as the "carry forward rule." In general, the pre-specified RAC adjudicated mIWG responses were concordant with the algorithmic mIWG sensitivity analysis. In each case of discordance, the RAC adjudicated response was lesser (i.e. PR instead of CR, SD instead of PR), due to the more stringent and conservative assessment of confirmation applied by the committee. Therefore, the efficacy analysis (and corresponding labeling) reflected a conservative approach to the determination of efficacy.

The information request also asked for supplemental information to better understand the case of the patient who achieved CR per RAC adjudicated response and was treated at a lower dose level (60 mg). The clinical review team queried if any factors may have contributed to the response at a lower dose level, and if there was late response compared to the median time to response. For example, did the patient receive any additional disease modifying therapy such as a HSCT prior to the response? The Applicant advised no antecedent treatment or HSCT that may have contributed to the response. While the patient started treatment on the 60 mg dose, treatment was escalated to 100 mg daily, with a brief escalation to 200 mg daily. The patient achieved a PR by RAC assessment over 22 cycles, and a CR by RAC assessment, 12 cycles, thereafter. The patient received no additional disease-modifying therapy. This additional information allowed the clinical review team to conclude that the 1 CR at the lower treatment dose was supportive of efficacy.

Note, while PRO results were provided for the broad AdvSM indication, (b) (4) (b) (4) Please refer to the PRO assessment in Supplement 6 for further details.

8.1.4 Integrated Assessment of Effectiveness

Analysis of pooled data from studies BLU-285-2101 and BLU-285-2202 meets the evidentiary standard to recommend regular approval of avapritinib for patients with MCL.

In 17 efficacy-evaluable patients with MCL treated across all dose levels in both studies, there were 3 CR (17.6%) and 5 PR (29.4%). The proposed dose of avapritinib in MCL is 200 mg oral daily, and when doses greater than 200 mg are excluded, the CR rate is 9% (1/11) and CR+PR is 45% (5/11). This response data is supportive of drug activity.

Limitations include the small sample size treated at the recommended dose (n=10) and the lack of CR at that dose. In acute leukemia, only CR are considered sufficient responses for efficacy, and no CR were observed at the 200 mg dose. Because 1 of the 3 CR was observed at a dose level below the recommended 200 mg dose, the clinical review team accepted this as adequate confirmation of drug efficacy. Review of response data by other response criteria addressed by the Applicant in their response to IR was also supportive.

While the Applicant argued that the [redacted](b) (4) should be included in the labeling, the review team does not agree that it is appropriate to report [redacted](b) (4) where safety has not been established.

8.2 Review of Safety

8.2.1 Safety Review Approach

The safety database to support this indication expansion consists of 2 studies in patients with AdvSM and updated safety data from 2 studies in patients with GIST. A comprehensive safety review was performed for the entire safety data set as part of Supplement 6, with select sections from the Applicant's Integrated Summary of Safety considered in section 8.2 (Review of Safety).

DHMI performed an additional limited safety analysis via MAED to assess safety in the MCL cohort and to determine if there were unique safety signals in MCL cohort when compared to the greater AdvSM population.

Adverse reactions occurring in ≥ 10% of patients in the MCL safety cohort at the recommended dose are summarized below in Table 15.

Given the similarity between the datasets, it was determined that safety in MCL would be considered jointly as part of the comprehensive safety analysis performed for the broad AdvSM indication. The joint presentation of safety is reflected in the proposed US package insert.

8.2.2 Review of the Safety Database

Overall Exposure

Safety analysis presented the Applicant's Integrated Summary of Safety included an overall safety population which includes all patients who received ≥ 1 dose of avapritinib. All Applicant analyses were based on the safety population and/or its subgroups, unless otherwise specified. Study BLU-285-2101 enrolled 86 patients with AdvSM and Study BLU-285-2202 enrolled 62 patients with AdvSM. Study BLU-285-1101 enrolled 250 patients with GIST. Study BLU-285-1303 enrolled 473 patients with advanced GIST. A total of 148 AdvSM patients received ≥ 1 dose of avapritinib and 81 AdvSM patients received ≥ 1 dose of avapritinib at a starting dose of 200 mg QD.

In the MCL cohort, 23 patients were treated across all dose levels and 16 patients were treated at the recommended dose of 200 mg.

Adequacy of the safety database

The safety database is adequate.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No data integrity or submission quality issues were identified.

Categorization of Adverse Events

Safety parameters evaluated include AEs, AESIs, SAEs, deaths, and clinical laboratory assessments. The Applicant provided accurate definitions of AEs and serious adverse events (SAEs) in the protocol.

Medical history and all AEs were coded to SOC and PT by using the MedDRA version 18.1. Intensity of AEs was graded according to the NCI CTCAE, version 4.03 for Studies BLU-285-2101, BLU-285-1101, and BLU-285-1303 (patients enrolled before Amendment 2) and version 5.0 for Studies BLU-285-2202 and BLU-285-1303 (patients enrolled after Amendment 2). Concomitant medications were coded to anatomic therapeutic chemical classification and preferred drug name by using the WHO Drug Dictionary Enhanced, March 2019 version.

Treatment-emergent AEs were defined as any AE that started after administration of the first dose of avapritinib through 30 days after the last dose of avapritinib. In addition, in studies BLU-285-2101 and BLU-285-1101, AEs occurring more than 30 days after the last dose were also collected if considered treatment-related by the Investigator.

8.2.4 Safety Results

Deaths

As described in the Applicant's Integrated Summary of Safety and updated in the 120-day Safety Report, in the entire safety population (including GIST), 74 (9.3%) patients treated with avapritinib died during the study due to AEs. Most deaths were related to the patients' underlying disease. The most common PT leading to death was disease progression (25 patients, 3.1%).

In patients with AdvSM treated *at all doses*, 12 (6.4%) patients died during the study due to AEs. Most deaths were related to the patients' underlying disease. No specific AE leading to death was reported in more than 1 patient. The incidence of AEs leading to death was slightly lower for AdvSM patients than for GIST patients treated at all doses (10.2%). One patient (<1%) died due to a related AE of hemorrhage intracranial.

In patients with AdvSM treated *at the 200 mg dose*, 6 (5.0%) died during the study due to AEs. During the update period, there were 3 new patient deaths from the following causes: acute kidney injury, erosive gastritis, and intra-abdominal hemorrhage. No specific AE leading to death was reported in more than 1 patient. No patients died due to a related AE. The incidence of AEs leading to death was slightly lower for AdvSM patients treated at 200 mg daily than for AdvSM patients treated at ≥ 300 mg daily (10.0%).

There were 3 on-study deaths in patients with MCL. In the MCL cohort treated *at the 200 mg dose*, 1 (6.3%) died due to erosive gastritis considered not related to avapritinib. This case is described in the 120-day safety report below. The other 2 deaths in patients with MCL both occurred at the 300 mg dose level. In these two patients, death was a consequence of disease progression, and not an adverse event.

Serious Adverse Events

In the AdvSM cohort treated *at all doses*, 92.6% experienced AEs related to avapritinib, 59% experienced Grade ≥ 3 related AEs, 46.3% experienced SAEs, and 17% experienced related SAEs.

- The most common AE (reported in > 20% of patients) was periorbital edema (52.1%), followed by peripheral edema (40.4%), anemia (39.9%), thrombocytopenia (36.7%), diarrhea (32.4%), nausea (30.3%), fatigue (25.5%) and vomiting (25%).

- The most common related SAEs (reported in > 1% of patients) were subdural hematoma (2.7%), anemia (2.1%), followed by ascites, intracranial hemorrhage, and pleural effusion (1.6% each), and finally GI hemorrhage and hemorrhage (1.1% each); all other related SAEs occurred in ≤ 1% of patients.

In the AdvSM cohort treated *at the 200 mg dose*, 90.1% experienced AEs related to avapritinib,

52.1% experienced Grade ≥ 3 related AEs, 32.2% experienced SAEs, and 11.6% experienced related SAEs.

- The most common AE (reported in > 20% of patients) was periorbital edema and (each 39.7%), followed by anemia (28.9%), thrombocytopenia (34.7%), diarrhea (24%), and nausea (22.3%).

- The most common related SAEs (reported in > 1% of patients) were subdural hematoma (2.5%) and anemia (1.7%); all other related SAEs occurred in ≤ 1% of patients.

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 QD compared with patients treated at ≥ 300 mg QD.

In the MCL cohort treated *at the 200 mg dose* (n=16), AEs of all grades and AEs ≥ grade 3 occurring in at least 10% of patients are shown in Table 15.

In patients with MCL treated at all dose levels (n=23), 14 (61%) patients experienced SAEs and 3 (13%) patients experienced *related* SAEs.

In MCL patients treated *at the 200 mg dose* (n=16), 8 patients (50%) experienced SAEs and 2 (12.5%) patients experienced *related* SAEs.

One unrelated SAE was reported at the lower 60 mg dose level; there were no related SAEs at lower dose levels.

FDA comparison of safety between the MCL cohort (n = 16) and non-MCL cohort (n = 64) at the recommended dose showed non-significant differences in AE rates limited to increased risk of oral herpes (18.75% MCL vs 0% Non-MCL AdvSM), dry lips (12.5% MCL vs 0% Non-MCL AdvSM), dyspepsia (18.75% MCL vs 3.1% Non-MCL AdvSM), and pyrexia (25% MCL vs 3.1% Non-MCL AdvSM).

Table 15: Adverse Reactions (≥ 10%) in AdvSM Patients Receiving AYVAKIT at 200 mg dose level

Adverse Reactions	MCL n=16		AdvSM (Non-MCL) n=64	
	All Grades %	**Grades 3-5 %**	**All Grades %**	**Grades 3-5 %**
General				
Edema - Peripheral	50	0	48.44	3.13
Edema - Periorbital	31.25	0	40.63	3.13

Edema - Face	18.75	0	9.38	0
Swelling face	12.5	0	3.13	0
Pyrexia	25	0	3.13	0
Fatigue	18.75	6.25	18.75	3.13
Gastrointestinal				
Diarrhea	31.25	6.25	26.56	0
Abdominal pain	18.75	0	10.94	1.56
Dyspepsia	18.75	0	3.13	1.56
Nausea	18.75	0	25	1.56
Melaena	12.5	6.25	1.56	0
Vomiting	12.5	6.25	18.75	1.56
Hematologic				
Anemia	43.75	25	29.69	18.75
Platelet count decreased	18.75	6.25	10.94	9.38
Thrombocytopenia	18.75	6.25	39.06	17.19
Nervous system				
Confusional state	12.5	0	1.56	0
Depressed mood	12.5	0	1.56	0
Dizziness	12.5	0	12.5	0
Headache	12.5	0	15.63	0
Insomnia	12.5	0	4.69	0
Respiratory, thoracic, and mediastinal				
Epistaxis	25	0	7.81	0
Skin and subcutaneous tissue				
Lip dry	12.5	0	0	0
Pruritus	12.5	0	6.25	0
Metabolism and nutrition				
Decreased appetite	18.75	0	4.69	0
Hypokalemia	12.5	0	4.69	0
Hypomagnesemia	12.5	0	3.13	1.56
Infections and infestations				
Oral herpes	18.75	0	0	0

Source: FDA review

Dropouts and/or Discontinuations Due to Adverse Effects

In the AdvSM cohort treated *at all doses*, 17% experienced AEs leading to permanent discontinuation of study drug (including "disease progression" reported as an AE term and AEs that represented symptoms of disease progression).

In the AdvSM cohort treated *at the 200 mg dose*, 12.4% experienced AEs leading to permanent discontinuation of study drug.

The incidence of AEs (both treatment-related and overall) leading to permanent discontinuation of study drug for AdvSM patients treated at 200 mg QD was lower than for AdvSM patients treated at ≥ 300 mg QD.

Significant Adverse Events

Adverse events of special interest were identified by evaluating the evolving safety profile for avapritinib and determining the clinical significance of the reported AEs based on medical review of the type of event as well as its frequency, severity, and relatedness to avapritinib. The following AESIs were identified:

- Intracranial bleeding consisting of the following PTs: Hemorrhage intracranial, Cerebral hemorrhage, and Subdural hematoma. In patients with MCL treated at the 200 mg dose level, there were no cases of hemorrhage intracranial, cerebral hemorrhage, or subdural hematoma. In patients with MCL treated at all dose levels, there was 1 case of intracranial hemorrhage (300 mg dose level).

- Cognitive effects consisting of the following PTs: 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 MCL treated at the 200 mg dose level (n=16), 5 (31%) patients experienced cognitive effects including: 1 patient with low mood and emotional breakdown, 1 patient with memory impairment and confusion, 1 patient with confusion, 1 patient with depression, and 1 patient with sleep disorder. When considering MCL patients treated at all dose levels (n=23), 10 patients (43%) experienced cognitive effects. Note, a comparison of cognitive effects in the MCL cohort and non-MCL cohort is presented in section 8.2.5.2 that define cognitive effects using the grouped terms defined in the proposed US package insert. Here, cognitive effects are defined more expansively using the PTs included in the Sponsor's 120-day safety analysis. This discrepancy accounts for the difference in rate of cognitive effects between the two sections.

Laboratory Findings

Table 16: Proportion of Patients with Shifts in Selected Serum Chemistry Parameters from Grade ≤ 2 at Baseline to Grade ≥ 3 at Worst Value on Study

Parameter	AdvSM		
	200 mg N=81 n (%)	≥ 300 mg N=50 n (%)	All N=148 n (%)
ALP increased	4/81 (4.9)	3/50 (6.0)	11/148 (7.4)
Phosphate decreased	1/81 (1.2)	6/50 (12.0)	9/148 (6.1)
Bilirubin increased	2/81 (2.5)	4/50 (8.0)	8/148 (5.4)
Potassium decreased	3/81 (3.7)	3/50 (6.0)	6/148 (4.1)
AST increased	1/81 (1.2)	2/50 (4.0)	3/148 (2.0)
ALT increased	1/81 (1.2)	1/50 (2.0)	2/148 (1.4)

Source: Applicant's Summary of Clinical Safety

Table 17: Proportion of Patients with Shifts in Selected Hematology Parameters from Grade ≤ 2 at Baseline to Grade ≥ 3 at Worst Value on Study

Parameter	AdvSM		
	200 mg N=81 n (%)	≥ 300 mg N=50 n (%)	All N=148 n (%)
Hemoglobin decreased	18/81 (22.2)	24/50 (48.0)	44/148 (29.7)
Platelets decreased	16/81 (19.8)	13/50 (26.0)	35/148 (23.6)
Neutrophils decreased	18/81 (22.2)	11/50 (22.0)	34/148 (23.0)
Lymphocytes decreased	9/81 (11.1)	12/50 (24.0)	25/148 (16.9)
Leukocytes decreased	8/81 (9.9)	9/50 (18.0)	21/148 (14.2)

Source: Applicant's Summary of Clinical Safety

Vital Signs

There were no AEs related to vital sign measurements that were reported by ≥ 10% of patients with AdvSM treated at 200 mg QD. The observed changes in vital signs measurements seen for AdvSM patients treated at 200 mg QD were similar to those seen for GIST patients treated at all doses.

Electrocardiograms (ECGs) and QT

Table 18: Summary of Cardiac Adverse Events by Preferred Term

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

Source: Applicant's Summary of Clinical Safety

120-Day Safety Report

The 120-day safety report was reviewed, and adverse events were not reported by subgroup. In the 120-day safety report, one death was reported in a patient with MCL in study BLU-285-2202. Patient (b) (6) was a 67-year-old male with MCL who had a fatal event of erosive gastritis. The patient's relevant medical history included hemorrhagic gastritis and his concomitant medications included famotidine and metoclopramide. Dosing of avapritinib was initiated at 200 mg QD on (b) (6). On (b) (6) the patient experienced an SAE of erosive gastritis, which required hospitalization. On admission the patient was vomiting and antiemetics were given. Endoscopy confirmed erosive gastritis. There was no active bleeding (hematemesis or other clinical manifestations) prior to endoscopy. A gastric biopsy was taken and the report showed fragments of transitional type gastric mucosa with foveolar hyperplasia, diffuse angioectasia, and mild glandular atrophy. On (b) (6) avapritinib was interrupted and on (b) (6) it was restarted at a lower 100 mg QD dose. The same day, omeprazole 40 mg continuous IV infusion was started. On (b) (6) (b) (6) the patient died, with the likely cause of death reported as erosive gastritis. The Investigator assessed the event as not related to avapritinib.

8.2.5 Analysis of Submission-Specific Safety Issues

8.2.5.1 Intracranial Bleeding

Throughout the clinical development of avapritinib in patients with 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 with GIST (1.8%).

Severe thrombocytopenia (platelet count < 50,000/µL) was identified as the primary risk factor for intracranial bleeding in AdvSM. An avapritinib starting dose of ≥ 300 mg QD was considered as contributing to the risk of intracranial bleeding. Risk mitigation strategies were implemented for all AdvSM patients to minimize the risk for intracranial bleeding. These measures included exclusion of patients with a platelet count < 50,000/µL at baseline, monitoring of platelet count at every treatment cycle, detailed guidance on dose modification, and defining the starting dose of avapritinib to be 200 mg QD. Additionally, to mitigate against a second bleed, patients who experienced an intracranial bleed of any toxicity grade permanently discontinued avapritinib treatment. With such risk minimization measures, the intracranial bleeding incidence was reduced to 2.6% in AdvSM patients who did not have pre-existing severe thrombocytopenia and were treated at a starting dose of 200 mg QD. In patients with AdvSM treated at 200 mg, there were 3 (3.7%) reported events of intracranial bleeding (all SAEs).

Of note, no patients with MCL treated at the recommended dose level experienced an intracranial hemorrhage. One patient with MCL treated at the 300 mg dose level experienced an intracranial hemorrhage, considered an unrelated SAE.

8.2.5.2 Cognitive Effects

Overall, cognitive effects were reported in 39.3% of patients treated with avapritinib, including 27.7% of AdvSM patients. The incidence of cognitive effects in AdvSM patients treated at 200 mg QD (16.5%) was less than the 27.7% observed in AdvSM patients treated at all doses. No AdvSM patients treated at 200 mg daily reported serious events of cognitive effects. One patient (< 1%) reported cognitive disorder that led to permanent discontinuation of study treatment

Of note, a comparison of cognitive effects using the grouped terms included in the USPI showed 12.5% in the MCL cohort experienced cognitive AEs compared to 13.9% in the AdvSM cohort without MCL. Cognitive effects include memory impairment, cognitive disorder, confusional state, delirium, and disorientation.

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

PRO analyses conducted for the overall safety set with Supplement 6.

8.2.7 Safety Analyses by Demographic Subgroups

Prior Midostaurin Exposure

Among the 81 AdvSM patients treated at 200 mg QD, 42 patients (51.9%) had received prior midostaurin. The incidence of AEs overall was the same (100%) for patients who had received prior midostaurin or not and the incidence of related AEs was similar (95.2% vs 92.3%).

Table 19: Summary of the Events with a Difference in Incidence of ≥ 10% Between Prior Midostaurin Groups for Adverse Events Reported in ≥ 20% of AdvSM Patients Treated at 200 mg QD

	Prior Midostaurin		
Preferred Term	**Yes N=42 n (%)**	**No N=39 n (%)**	**Total N=81 n (%)**
Edema peripheral	23 (54.8)	16 (41.0)	39 (48.1)
Periorbital edema	12 (28.6)	20 (51.3)	32 (39.5)

Source: Applicant's Summary of Clinical Safety

8.2.8 Specific Safety Studies/Clinical Trials

Not applicable.

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No new data to is presented.

Human Reproduction and Pregnancy

There are no data in pregnant women exposed to avapritinib, the secretion of avapritinib in human milk or its effects on the breastfed infant, or on milk production to assess the risks.

Pediatrics and Assessment of Effects on Growth

No pediatric data is presented.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No cases of overdose have been reported. The highest dose of avapritinib studied clinically is 600 mg PO QD. Adverse reactions observed at this dose were consistent with the safety profile at 300 or 400 mg QD.

There is no known antidote for avapritinib overdose. In the event of suspected overdose, avapritinib dosing should be interrupted and supportive care instituted. Based on the large volume of distribution of avapritinib and extensive protein binding, dialysis is unlikely to result in significant removal of avapritinib.

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Avapritinib was approved in the US on 09 January 2020 by the 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. Postmarketing 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 postmarketing setting.

Expectations on Safety in the Postmarket Setting

None.

8.2.11 Integrated Assessment of Safety

Safety analysis presented by the Applicant did not consider the individual populations within the AdvSM population. DHMI clinical review team performed independent safety analysis using MAED and considered patients with MCL at the proposed dose level of 200 mg. The safety population included x patients with MCL who were treated at 200 mg and all doses, and included patients who were not efficacy evaluable. Adverse reactions occurring in greater or equal to 10% of patients are summarized in Table 15. In patients treated at the 200 mg proposed dose level, most adverse events were grade 1 or 2. Adverse events grade 3 and above were uncommon and limited to: fatigue (6%), diarrhea (6%), melena (6%), and vomiting (6%).

The risk profile in MCL was not unique relative to the non-MCL cohort, however, and no safety signals were identified.

No intracranial hemorrhage was identified in the MCL cohort and the rate of cognitive effects was similar in the MCL cohort compared to the non-MCL cohort.

8.3 Statistical Issues

None

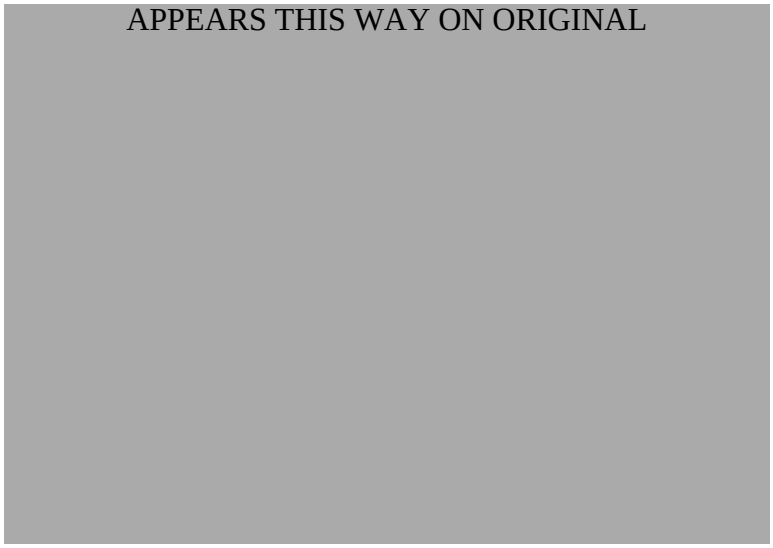
8.4 Conclusions and Recommendations

The recommended starting dose of avapritinib in patients with MCL is 200 mg daily. This is based on analyses of safety and efficacy. Additional safety analysis of the comprehensive safety data set for the broad AdvSM population is presented in Supplement 6 and will form the basis of the presentation of safety data in the USPI. No safety issues were identified in patients with MCL treated with avapritinib at the 200 mg recommended dose level.

X	X
Primary Clinical Reviewer	Clinical Team Leader

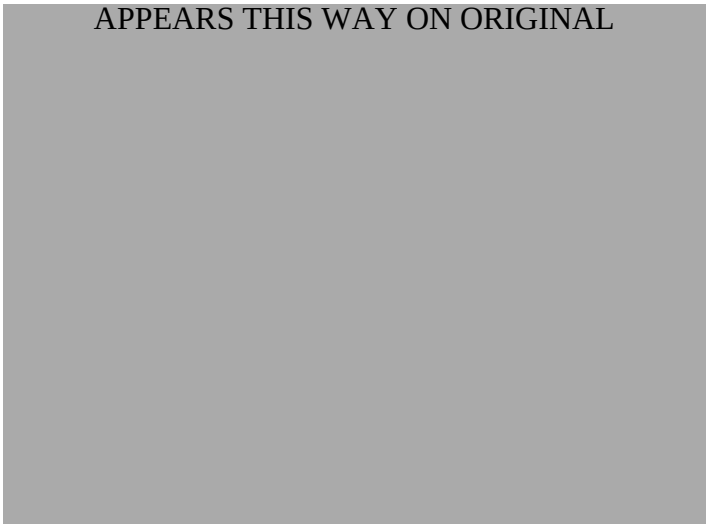
9 Advisory Committee Meeting and Other External Consultations

Avapritinib was not presented to the Oncologic Drug Advisory Committee or other external consultants.



10 Pediatrics

Pediatric data was not included in the supplement. The Applicant was granted Orphan Designation for avapritinib for the treatment of patients with systemic mastocytosis (including MCL), and therefore is exempt from pediatric studies under the Pediatric Research Equity Act (PREA).



11 Labeling Recommendations

11.1 Prescription Drug Labeling

The following recommendations for the avapritinib USPI included:

Indication:

- Regular approval of avapritinib for the treatment of adult patients with MCL (to be included along with the broader indication for AdvSM).

Dosing and Administration:

- 200 mg orally daily

Efficacy:

- Present efficacy in MCL in the RAC-RE analysis data set according to mIWG-MRT-ECNM response criteria at the recommended dose of 200 mg orally daily.
- (b) (4)

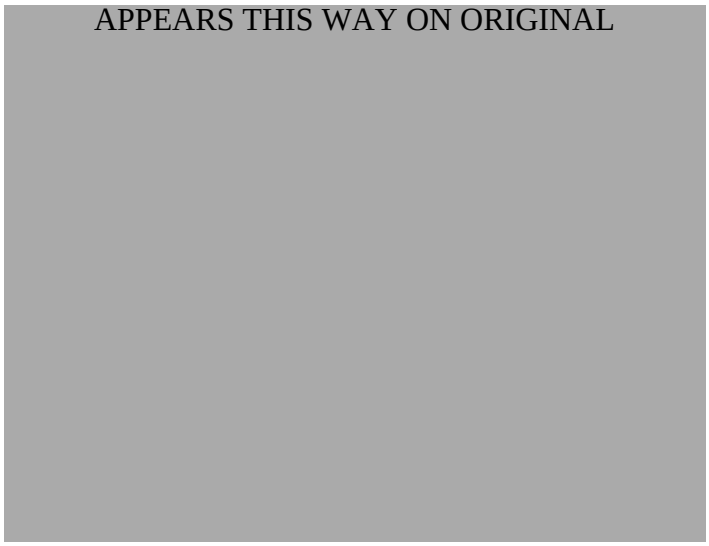
Refer also to separate review from Elizabeth Everhart (OOD Associate Director for Labeling).

11.2 Patient Labeling

Patient labeling was revised to be consistent with the changes to the USPI.

12 Risk Evaluation and Mitigation Strategies (REMS)

DHMI does not recommend a REMS for avapritinib. Based on the risk/benefit profile of avapritinib, safety issues can be adequately managed through appropriate labeling and routine post-marketing surveillance.



13 Postmarketing Requirements and Commitment

For the MCL indication, DHMI clinical review does not recommend a postmarketing requirement or postmarketing commitment.

Note, DNH has advised they will be recommending postmarketing requirements, which DHMI has reviewed with no further comments. Refer to action letter for S-006.

14 Division Director (DHOT)

X

15 Division Director (OCP)

X

16 Division Director (OB) Comments

X

17 Division Director (Clinical) Comments

X

18 Office Director (or designated signatory authority) Comments

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

19 Appendices

19.1 References

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19.2 Financial Disclosure

Financial certification and disclosure records were submitted (section 1.3.4) as part of the supplement with attestation from the Applicant's Chief Financial Officer.

Three investigators are listed on the financial disclosure records along with cumulative disclosure amounts, the nature of the disclosure, and steps taken to minimize bias. A comprehensive list of the remaining study investigators without financial interest is also included.

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: > 100 investigators were identified. Only 3 investigators noted relevant financial disclosures		
Number of investigators who are Applicant 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)): - (b) (6) – Dislosure Amount (b) (6) - (b) (6) – Disclosure Amount (b) (6) - (b) (6) – Disclosure Amount (b) (6) Applicant of covered study: Blueprint Medicines		
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): 7		
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/

RACHEL S MCMULLEN
06/09/2021 10:16:05 AM

PETER J DEMARIA
06/09/2021 10:19:15 AM

LORI A EHRLICH
06/09/2021 10:20:41 AM

ROMEO A DE CLARO
06/16/2021 07:47:37 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212608Orig1s007

CLINICAL REVIEW(S)

MEMORANDUM

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) (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 4 in Section 6 and the events for these PTs were rarely Grade ≥ 3.

Additional Comments:

- DO3 recommended (b) (4) (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:

212608Orig1s007

PRODUCT QUALITY 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) a new manufacturing (b) (4) (b) (4) 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).

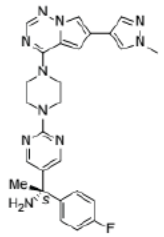
6. **Name and Address of Applicant**:
Blueprint Medicines Corporation
45 Sidney Street
Cambridge, MA, USA 02139

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) into 100 mg, 200 mg, or 300 mg tablets which are film coated and printed before packaging into HDPE bottles with 0.5 g desiccant (b) (4). The drug substance, avapritinib, is currently manufactured (b) (4) approved S-003). The drug product (100 mg, 200 mg, 300 mg tablets) is currently manufactured (b) (4). The 100 mg, 200 mg, and 300 mg tablets are manufactured (b) (4) for all dosage strengths. The manufacturing process (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 (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) (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) 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) (b) (4). The equipment is similar with the exception of (b) (4) (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) (b) (4) (b) (4) The same primary packaging site as is 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 (b) (4) batches (clinical and registration) of 25 mg tablets, and (b) (4) 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 (b) (4) for clinical studies, but will not be manufactured (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 (b) (4). 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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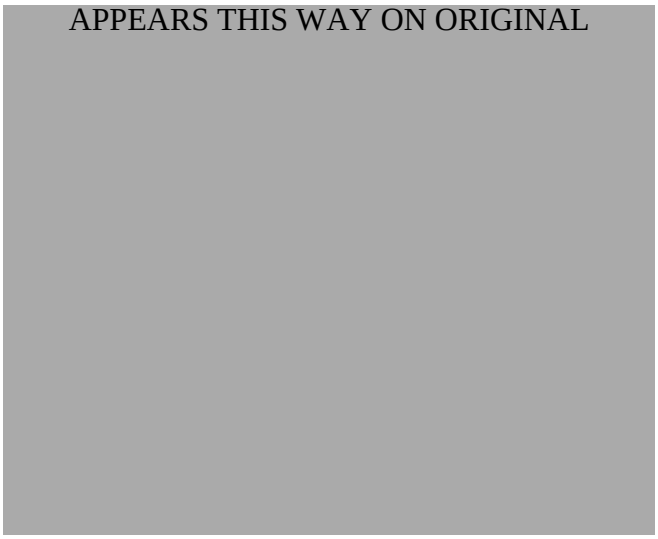

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212608Orig1s007

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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) (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.

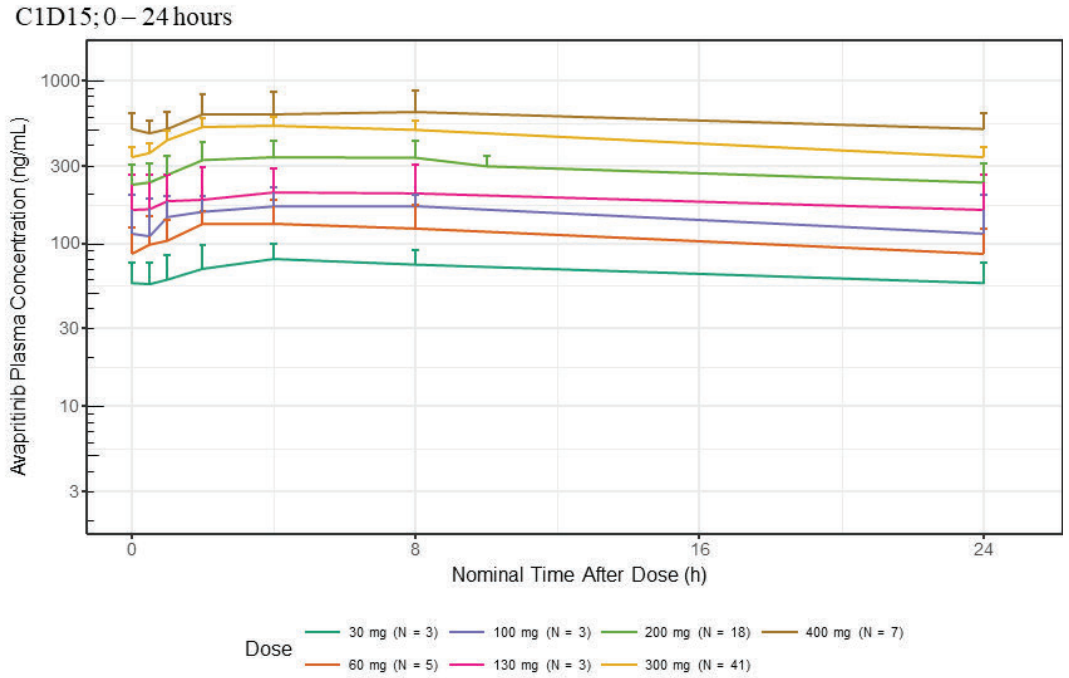
Dose Selection Rationale

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

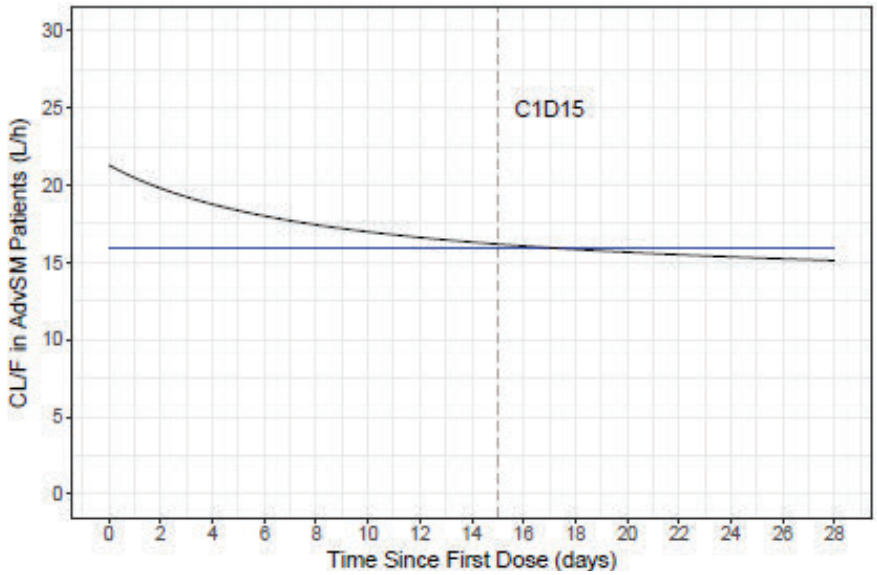
The final model retained the same structure as the base model. The final model contained all of the parameters included in the base model as well as a small number of new fixed-effect parameters. The lean body weight effect on V/F and PPI comedication effect on F1 were included in the final model with 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

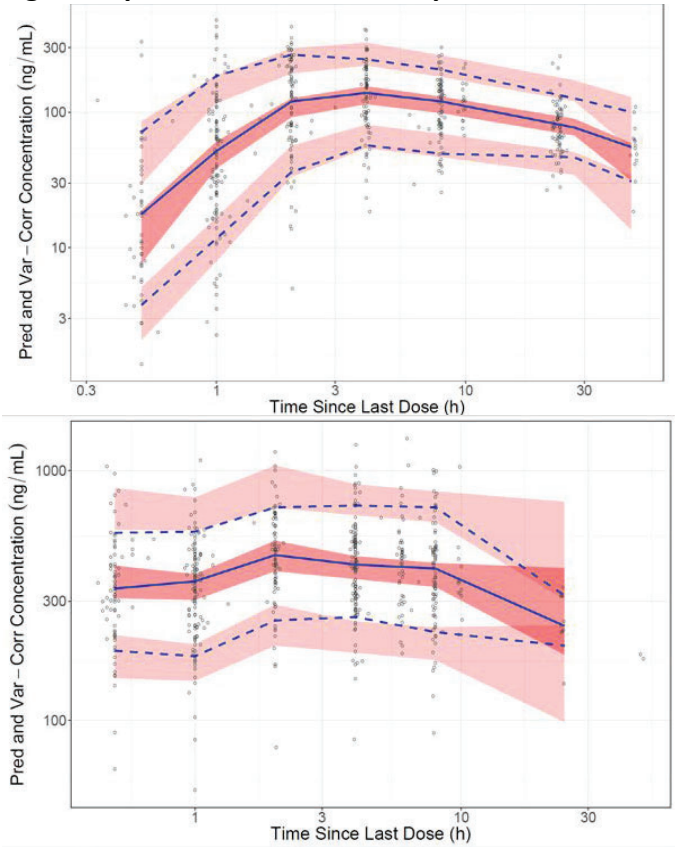


Black line represents the typical CL/F of patients with SM as estimated from the final model, and the blue line represents the typical CL/F of healthy volunteers or patients with GIST (15.9 L/h). Dashed vertical line denotes time at Cycle 1, Day 15.
AdvSM = advanced systemic mastocytosis; C1D15 = Cycle 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)



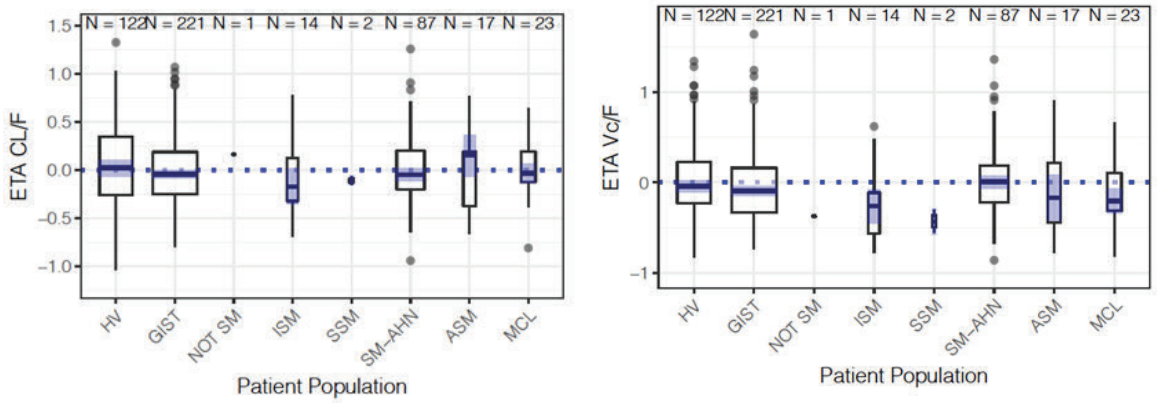
Top: Cycle 1 Day 1; Bottom: Cycle 1 Day 15 (steady-state). Open circles = individual observed, dashed blue lines = observed 10th & 90th percentiles of the observed data, solid blue line = observed median concentration, shaded red area = 95% prediction interval around the model predicted 10th, 50th, & 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

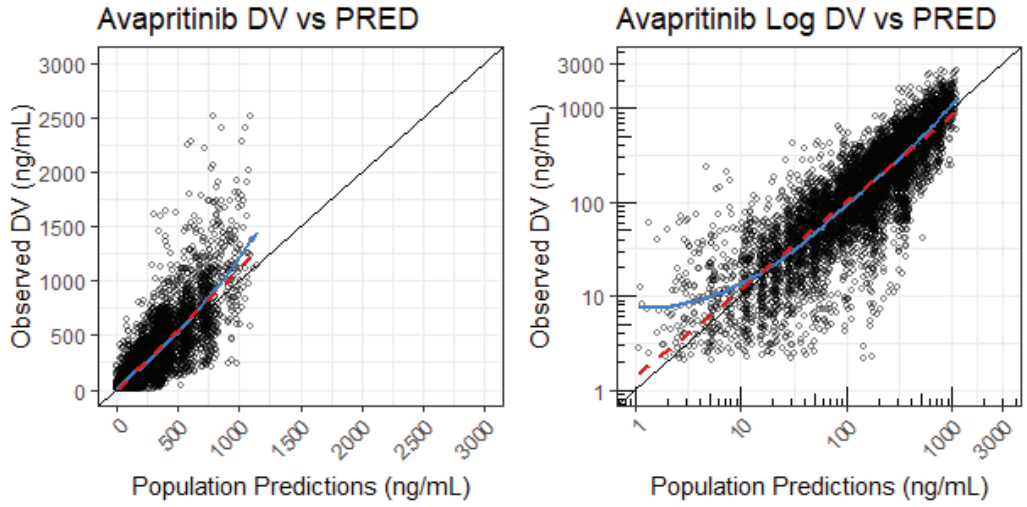
Fixed-Effects Parameters					
Parameter Name	**Description (units)**	**Estimate**	**SE**	**RSE (%)**	**Confidence Interval (95%)**
tvKTRT	Typical value of transit absorption constant for tablets (1/h)	3.31	0.0469	1.417	3.218 - 3.402
tvKTRC	Typical value of transit absorption constant for	3.79	0.0888	2.343	3.616 - 3.964

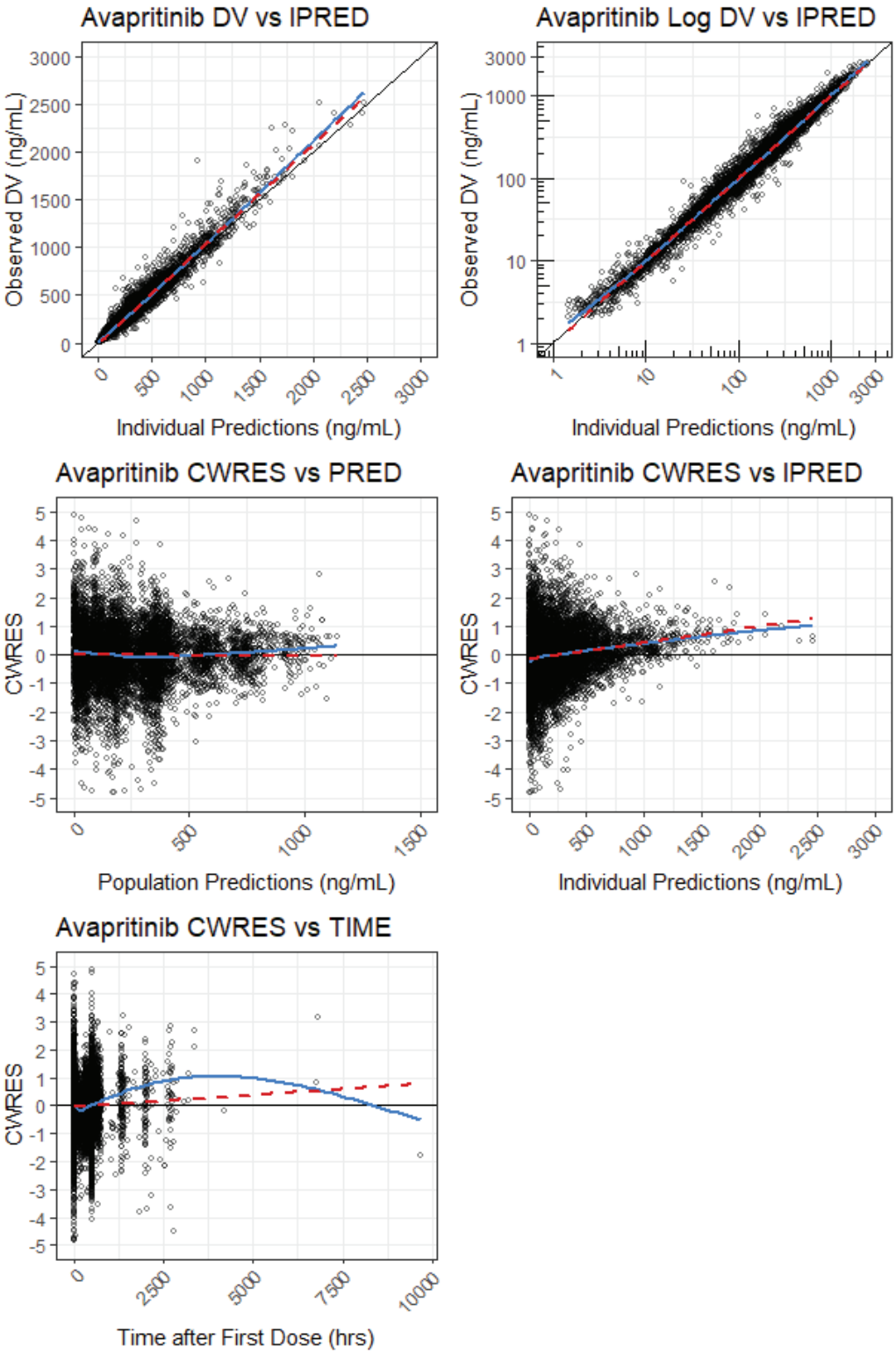
	capsules (1/h)				
tvCL	Typical value of clearance (L/h)	15.9	0.433	2.723	15.05 - 16.75
tvV	Typical value of central volume of distribution (L)	988	22.4	2.267	944.1 - 1032
SM_F	Effect of SM subject status on relative bioavailability	0.656	0.0337	5.137	0.5899 - 0.7221
tvV2	Typical value of peripheral 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

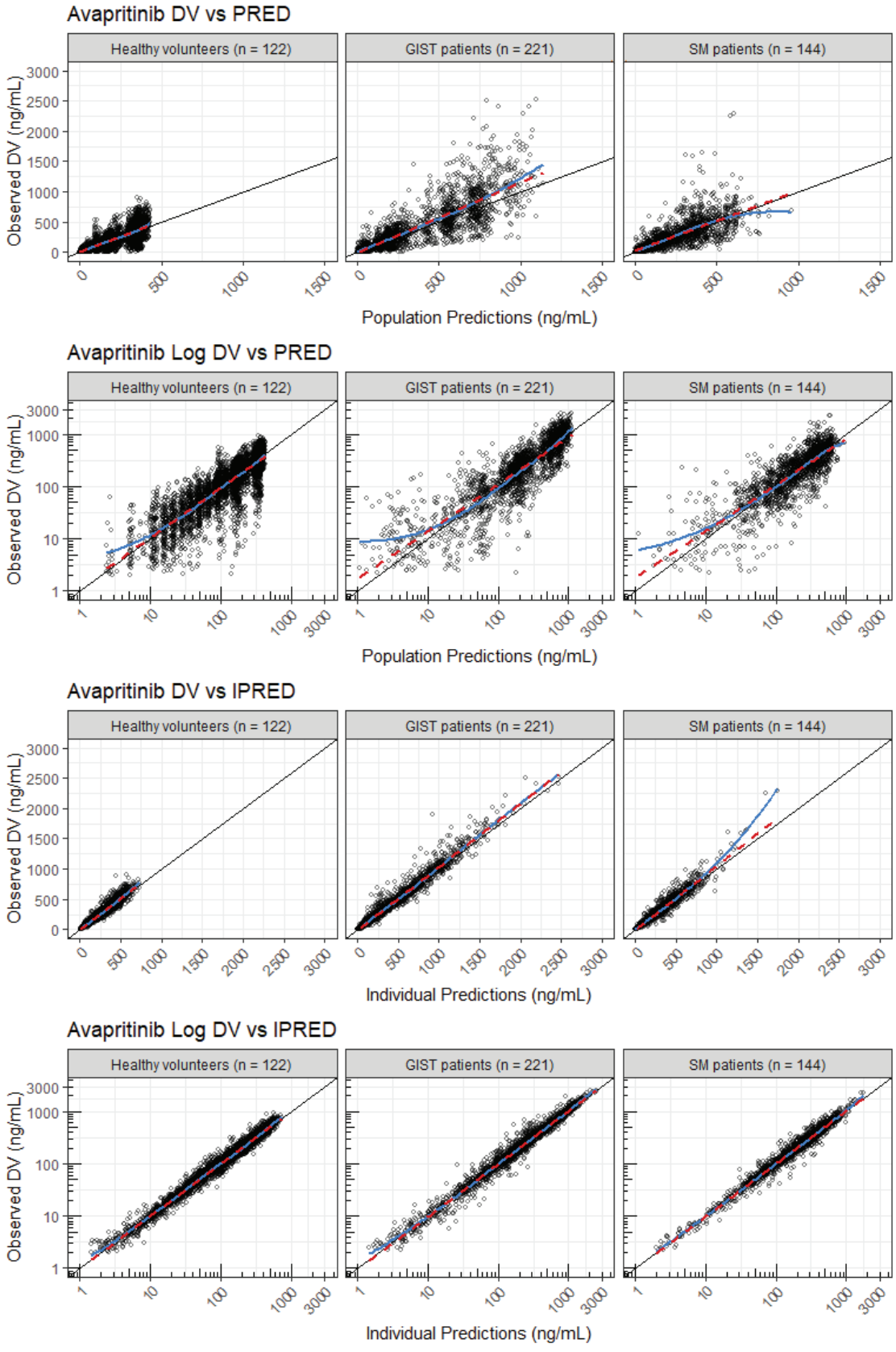
Figure 5. Goodness of Fit Plots for Final Model

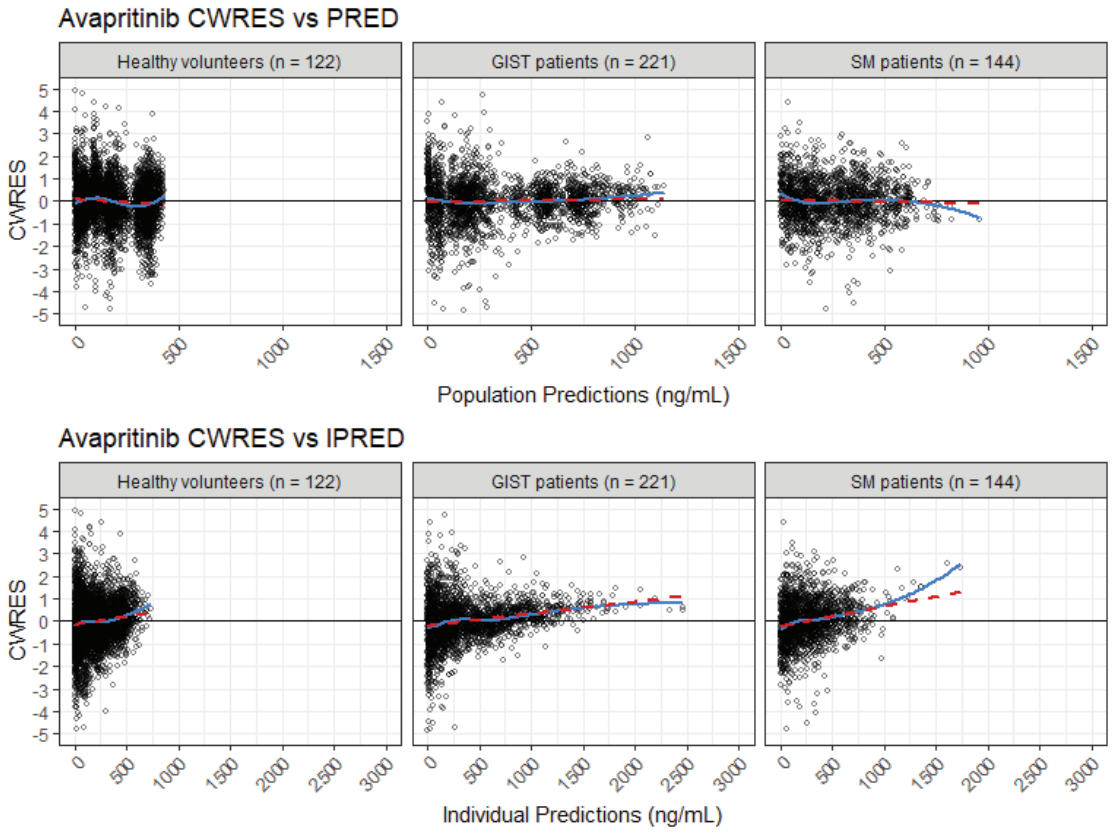




Loess in solid blue; Linear regression in dashed red. Avapritinib LLOQ=2 ng/mL.
CWRES=conditional weighted residuals; DV = observed concentration; hrs = hours; IPRED=individual prediction of concentration; LLOQ = lower limit of quantification; PRED=population prediction of concentration.
Source: Reviewer Analysis

Figure 6. Goodness of fit Plots for the Final Model According to Subject Status



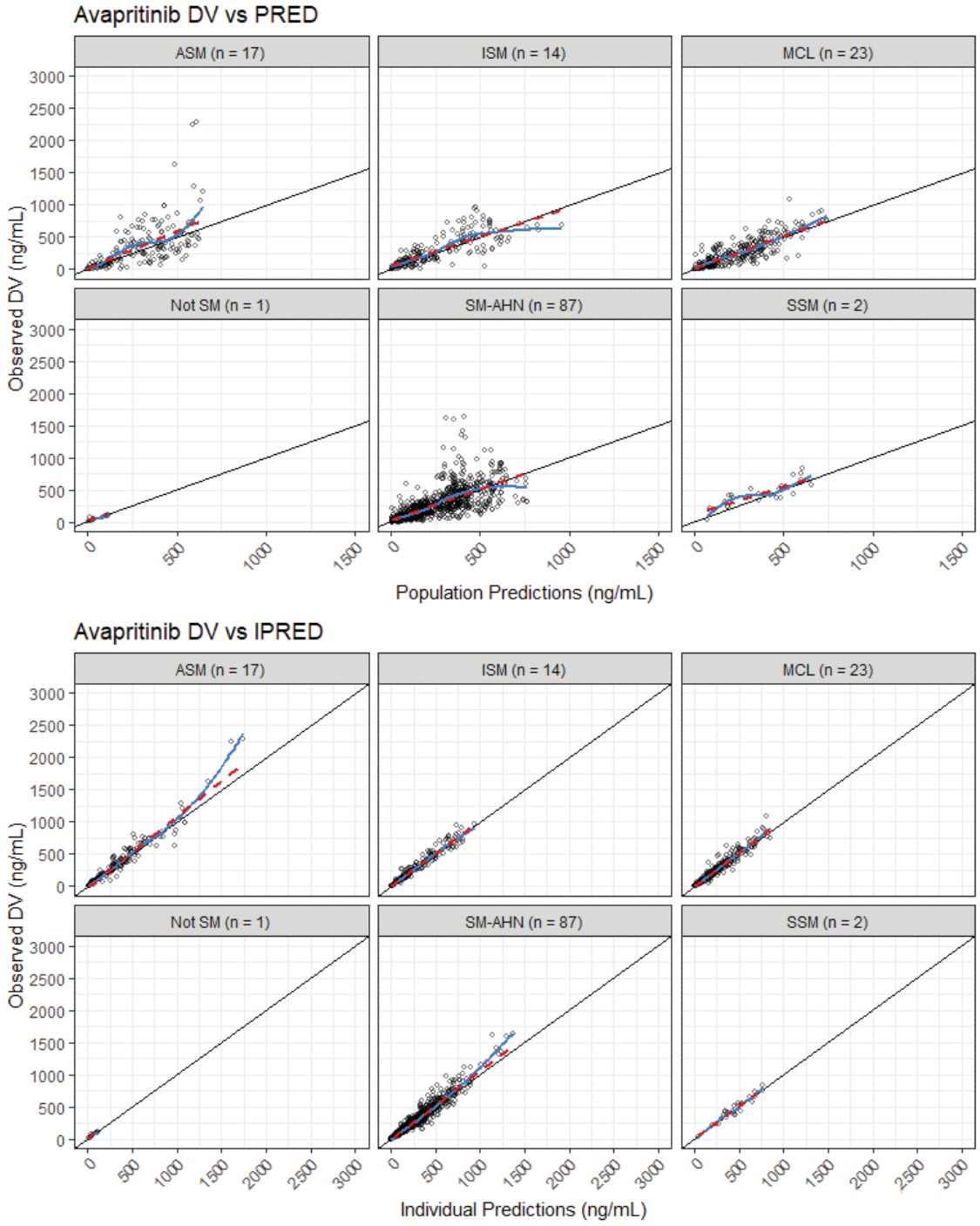


Loess in solid blue; Linear regression in dashed red. Avapritinib LLOQ=2 ng/mL.
CWRES=conditional weighted residuals; DV = observed concentration; hrs = hours; GIST = gastrointestinal stromal tumor; IPRED=individual prediction of concentration; LLOQ = lower limit of quantification; PRED=population prediction 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**.

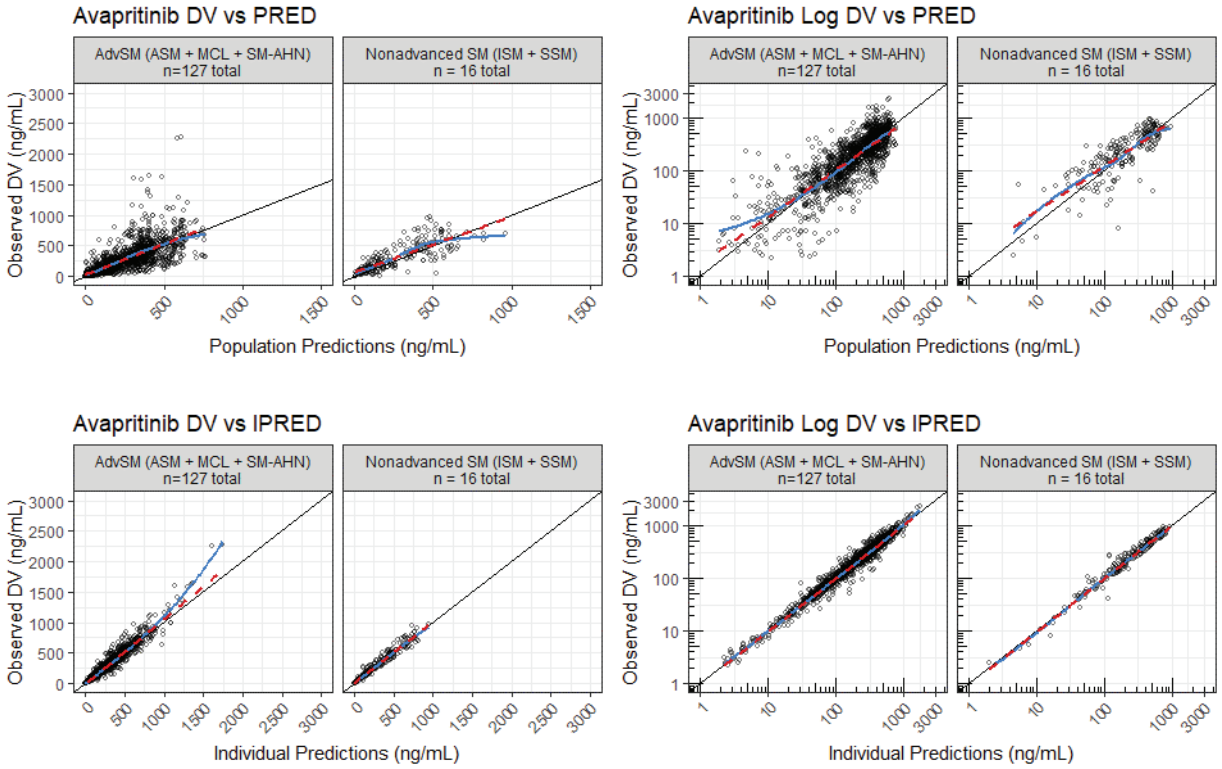
The sample sizes of patients with ASM (n=17), ISM (n=14), and MCL (n=23) were much smaller than the sample size of patients with SM-AHN (n=87). There were also not enough data in subjects with SSM (n=2) to evaluate the GOF in this subgroup. There was a slight tendency to under-predict higher observed 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



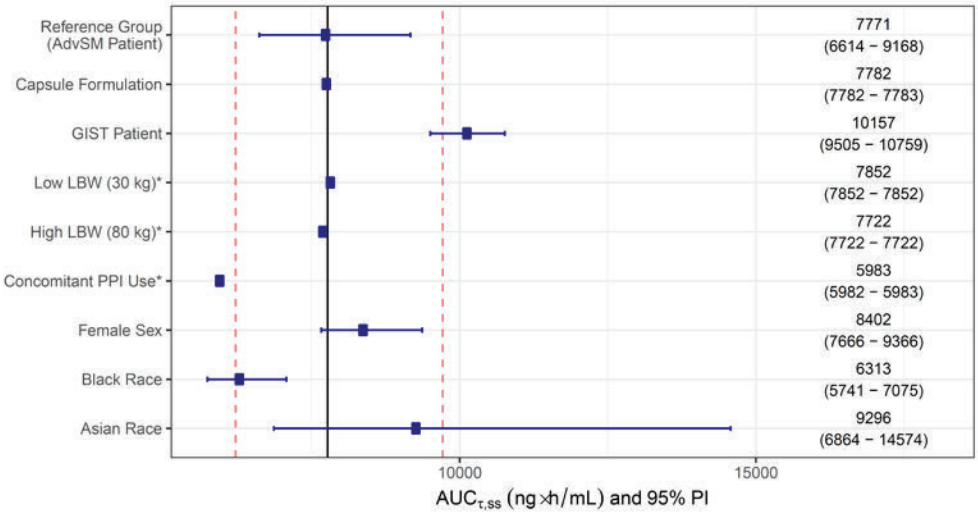
Loess in solid blue; Linear regression in dashed red. Avapritinib LLOQ=2 ng/mL.
AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; DV = observed concentration; IPRED=individual prediction of concentration; ISM = indolent systemic mastocytosis; MCL = mast cell leukemia; PRED=population 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.

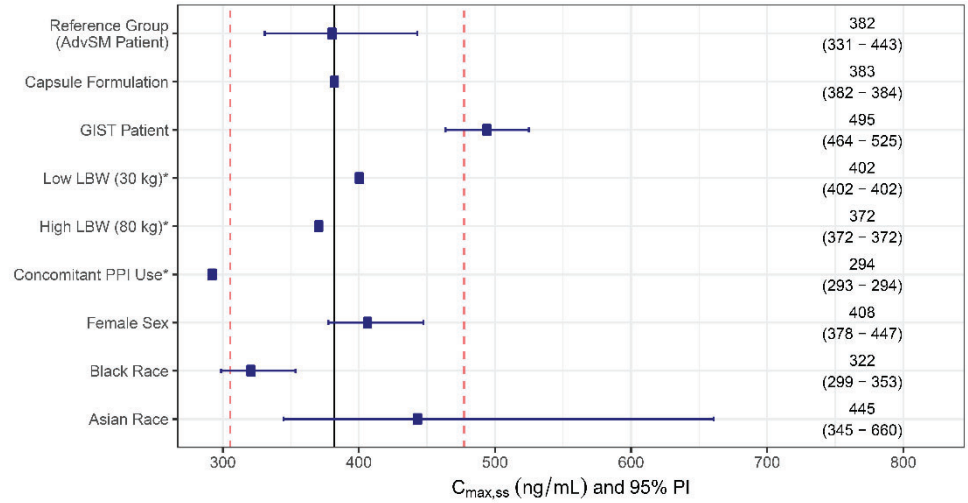
Figure 9. Model Predicted Effect of Covariates on Change in $AUC_{0\text{-}tau,ss}$



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

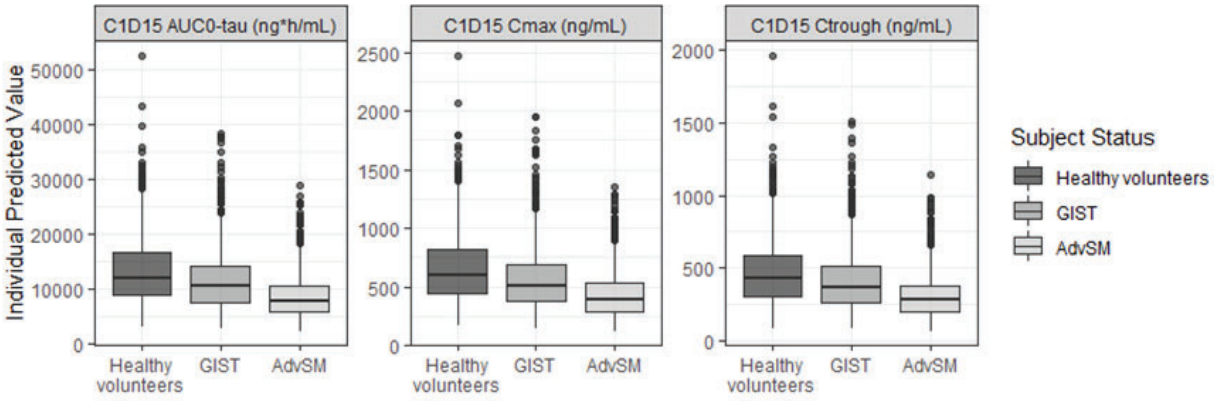
The Reviewer used final population PK model and the Applicant's final parameter estimates to simulate avapritinib exposure over time. There was no significant discordance between the Applicant's simulation results and the Reviewer's simulation results. The reviewer agrees with Applicant's conclusion 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.*

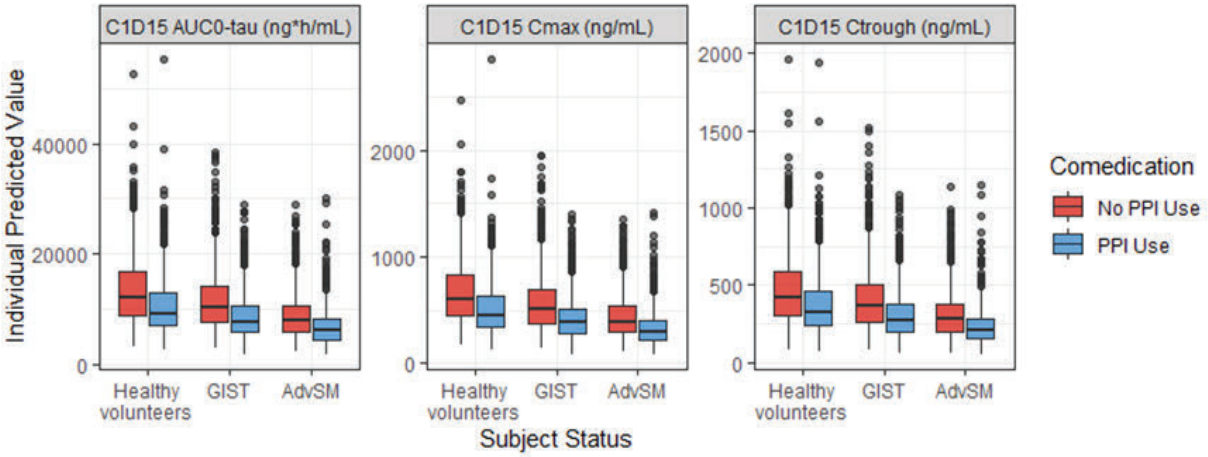
The final population PK model included covariate effects of Asian (n=25/487 total) and Black (n=26/487) race on CL/F, although the final estimate of the 95% CI for the effect of Asian race on CL/F (0.492 – 1.178) was relatively wide and included the null hypothesis that Asian race had no effect. Predicted 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



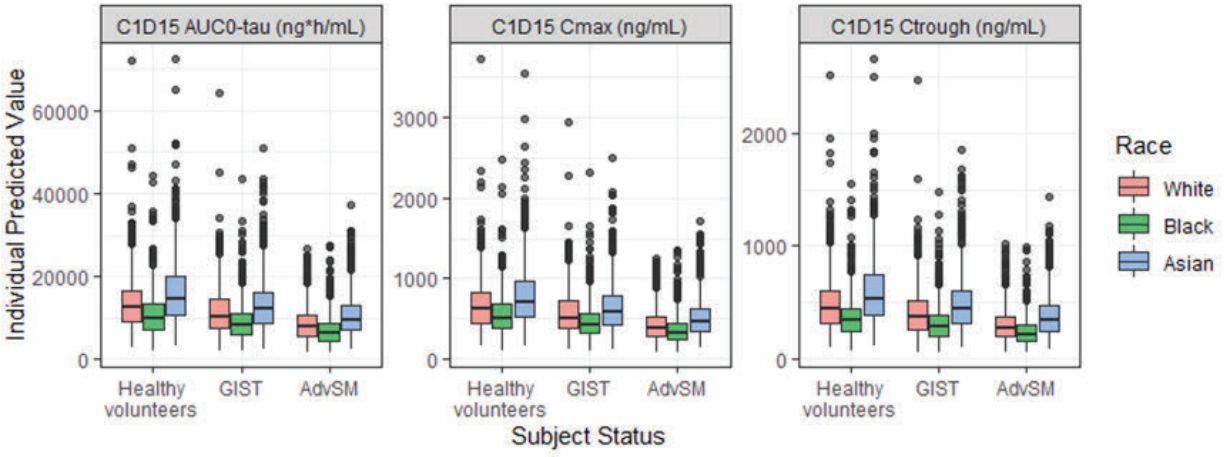
AdvSM = advanced systemic mastocytosis; $AUC_{0\text{-}tau}$ = area under the concentration-versus-time curve from time after last dose 0 to 24 hours; C1D15 = Cycle 1 Day 15; C_{max} = predicted maximum concentration; C_{trough} = predicted predose concentration; GIST = gastrointestinal stromal tumor. 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									

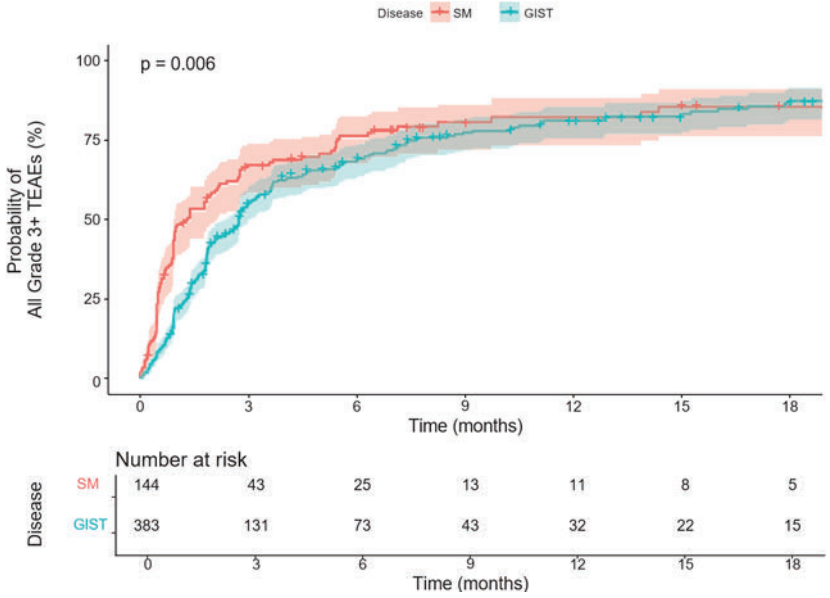
		Subject Status/Disease Subtype							
Covariate	**Statistic**	**GIST**	**MCL**	**ASM**	**SM-AHN**	**ISM**	**SSM**	**Not SM**	**TOTAL**
Yes	N (%)	69 (18%)	5 (21.7%)	4 (23.5%)	14 (16.1%)	4 (28.6%)	0	0	96 (18.2%)
No	N (%)	314 (82%)	18 (78.3%)	13 (76.5%)	73 (83.9%)	10 (71.4%)	2 (100%)	1 (100%)	431 (81.8%)
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

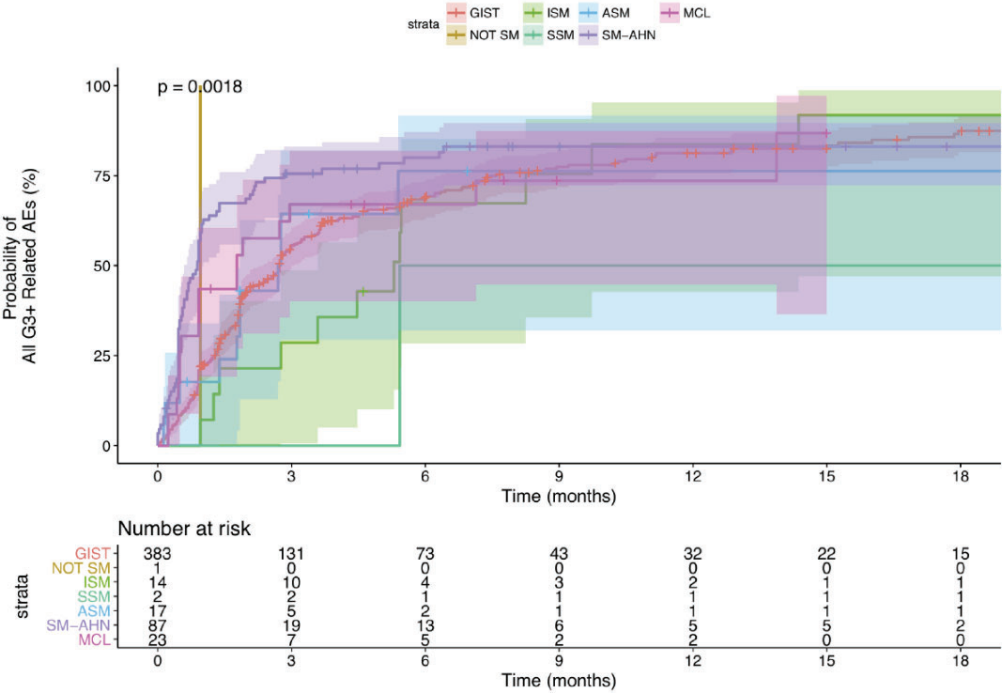
When subjects with GIST were compared to subjects with SM, subjects with SM had a faster onset of grade 3+ TEAEs (**Figure 14**). Probability of a grade 3+ TEAE by 6 months of treatment was higher in the 4th quartile of avapritinib $C_{average}$ (78% with 95% CI of 70 – 84%) compared to the 1st quartile (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

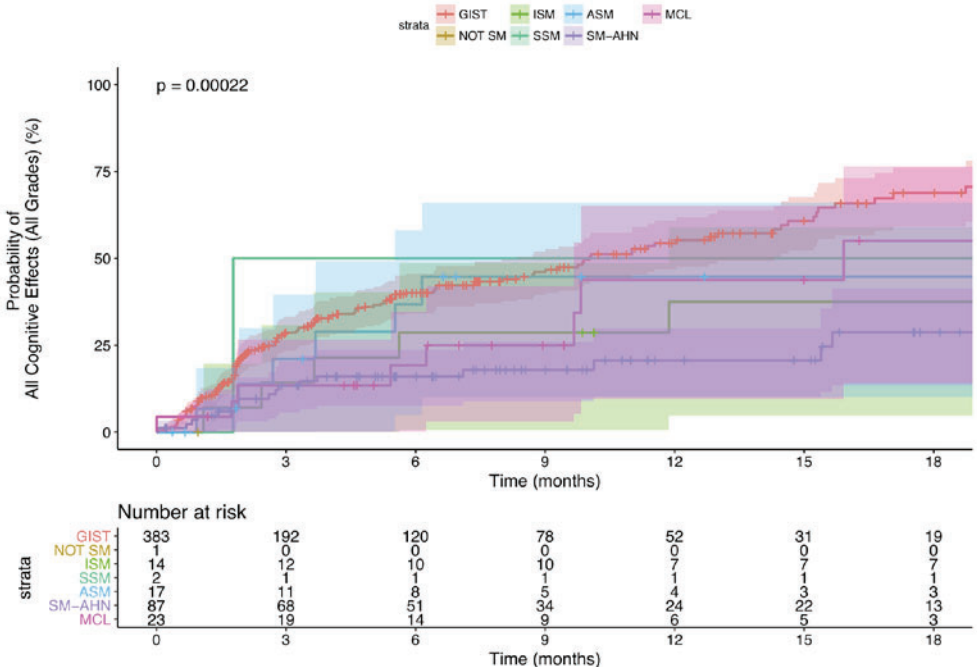
Figure 15. Time to Grade 3+ TEAEs versus Disease Status and Subtype



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

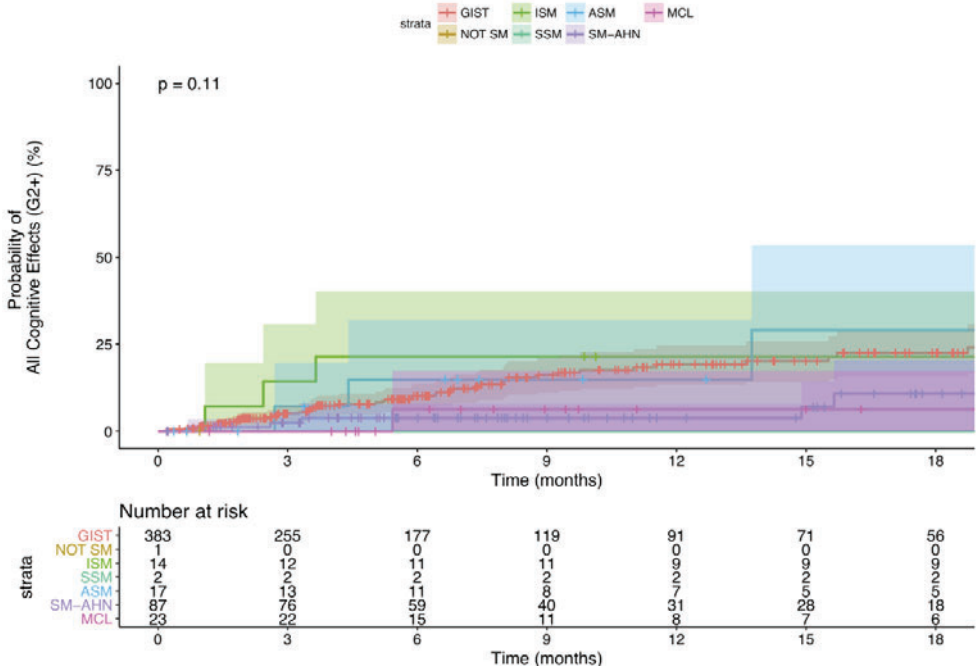


Solid lines represent Kaplan-Meier curves, shaded areas represent 95% confidence intervals, and p-value is derived from a log-rank test. Note: plot truncated at 18 months.

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

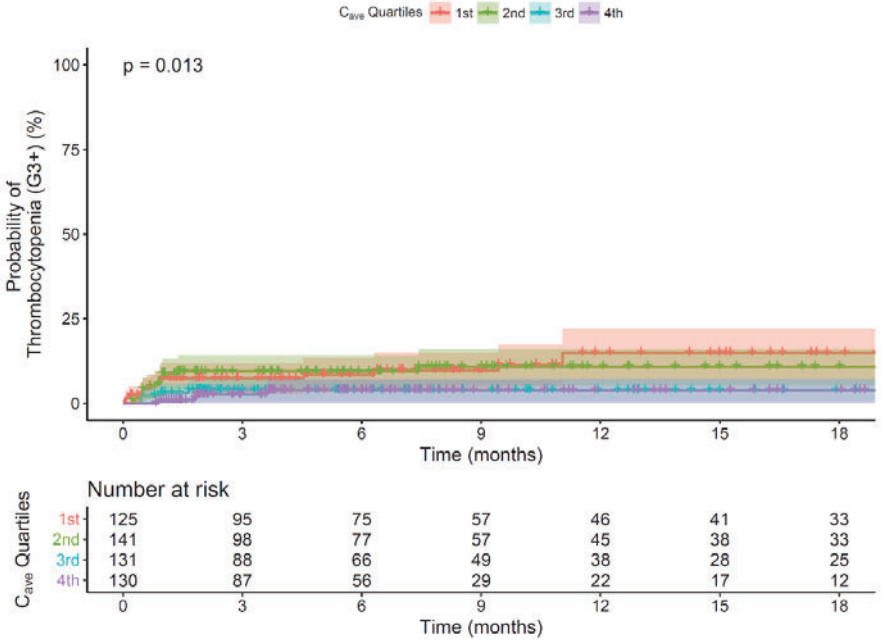


Solid lines represent Kaplan-Meier curves, shaded areas represent 95% confidence intervals, and p-value is derived from a log-rank test. Note: plot truncated at 18 months.
ASM = aggressive systemic mastocytosis; GIST = gastrointestinal stromal tumor; ISM = indolent systemic mastocytosis; MCL = mast cell 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

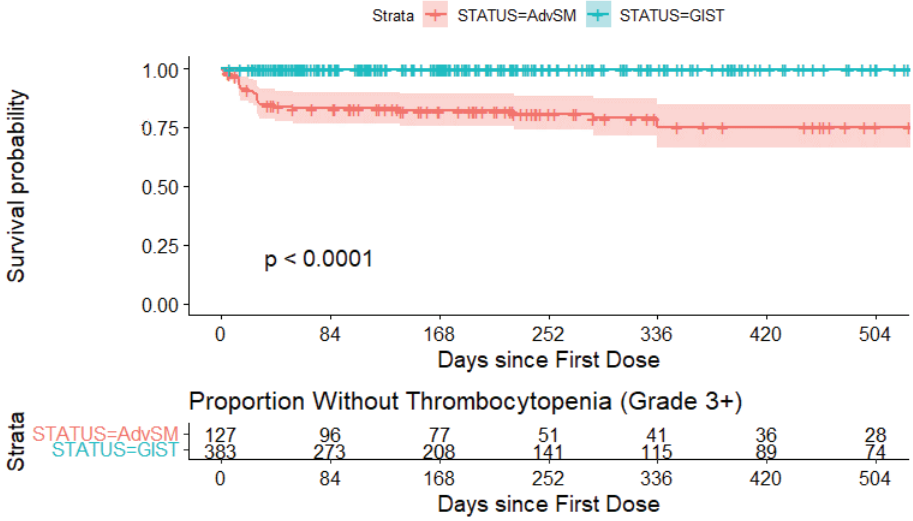
Reviewer Comments

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****.*

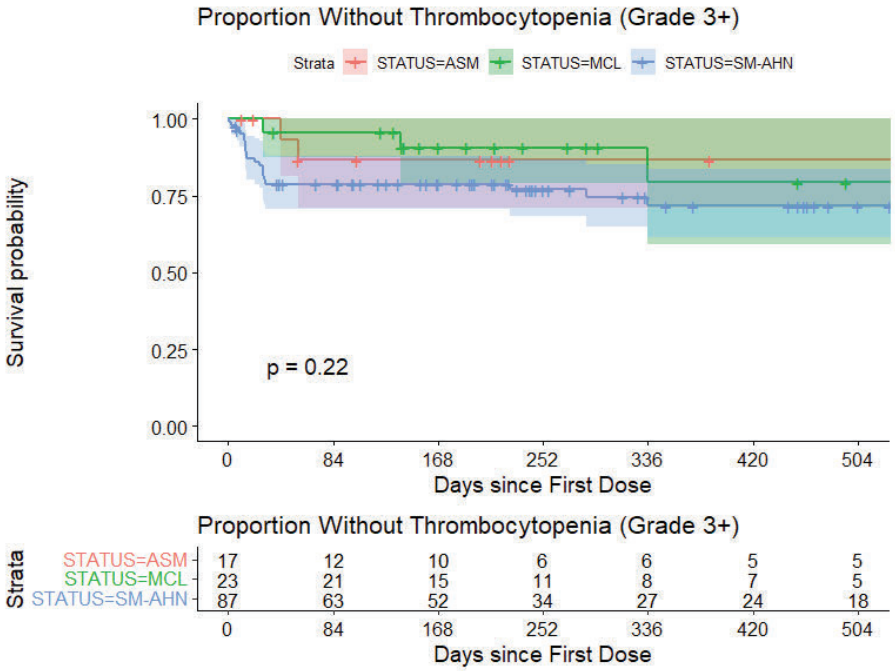
The Applicant's proposed dosage modification recommending that avapritinib dosing be interrupted in patients with AdvSM who have a platelet count fall below 50 x 10^9/L, and that avapritinib should only be resumed once platelet count is ≥50 x 10^9/L. The proposed dosage modification for thrombocytopenia 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

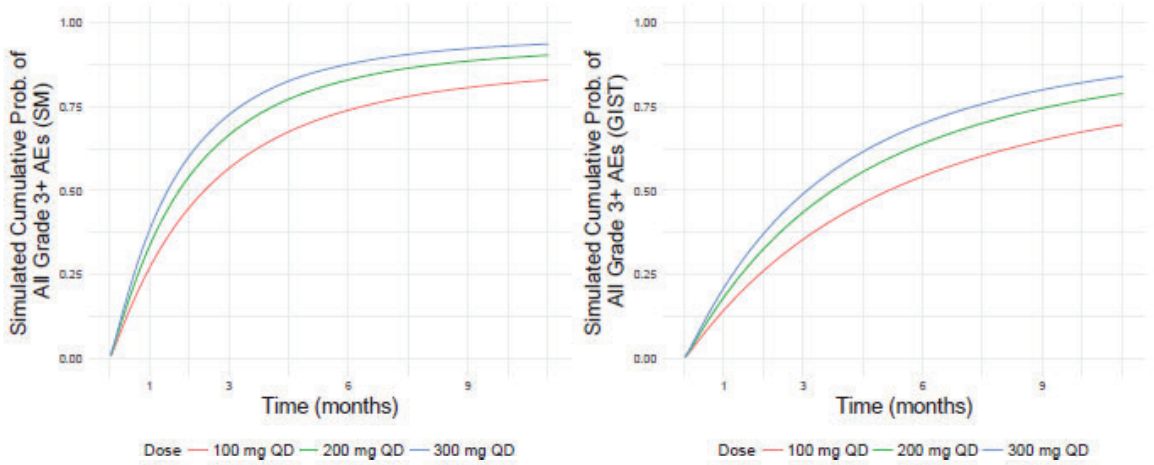
The final E-R time-to-event (TTE) models for safety were used to predict the cumulative probability of safety outcomes for 100 mg QD, 200 mg QD, and 300 mg QD dosing regimens in datasets of 1000 subjects created by resampling with replacement from GIST studies (BLU-285-1101 and BLU-285-1303) and SM studies (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.

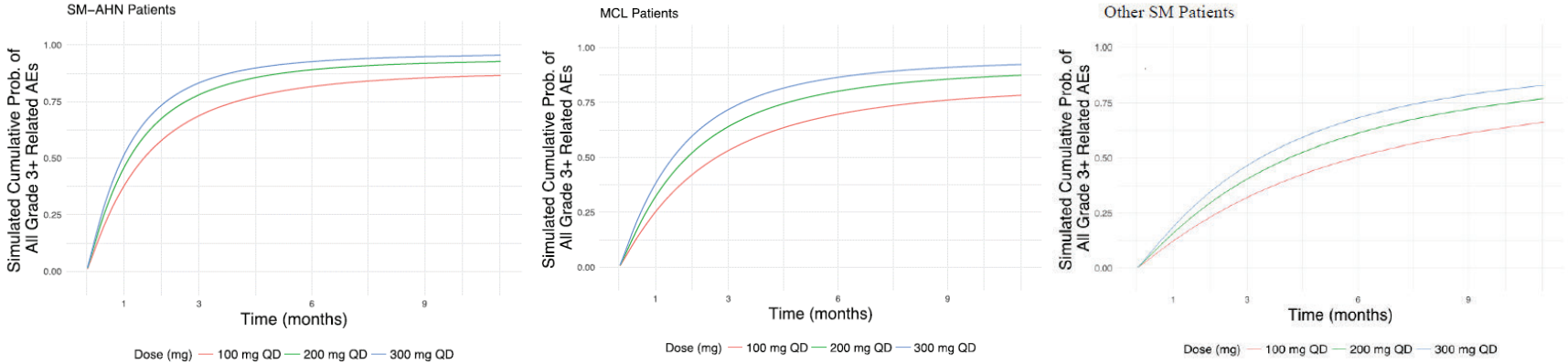
Similarly, there was not a clinically significant difference in predicted cumulative probability of grouped grade 2+ edema TEAEs at 12 months after first dose between 100 mg QD, 200 mg QD, and 300 mg QD dosing regimens (**Figure 23**).

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

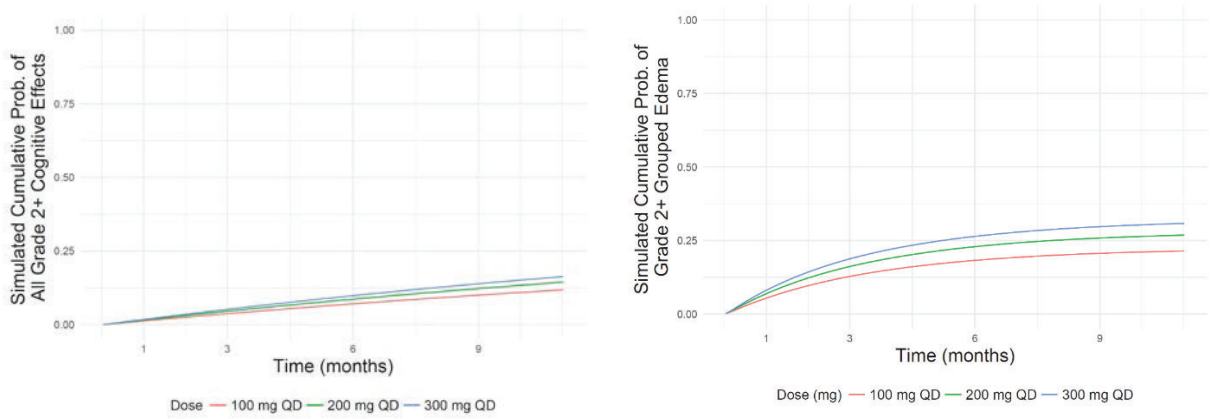


Other SM = Patients with ASM, SSM, or ISM. Exposure was simulated in 1000 virtual subjects resampled from safety dataset according to SM subtype. Solid lines represent median cumulative probability of grade 3+ treatment-emergent adverse events.

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).

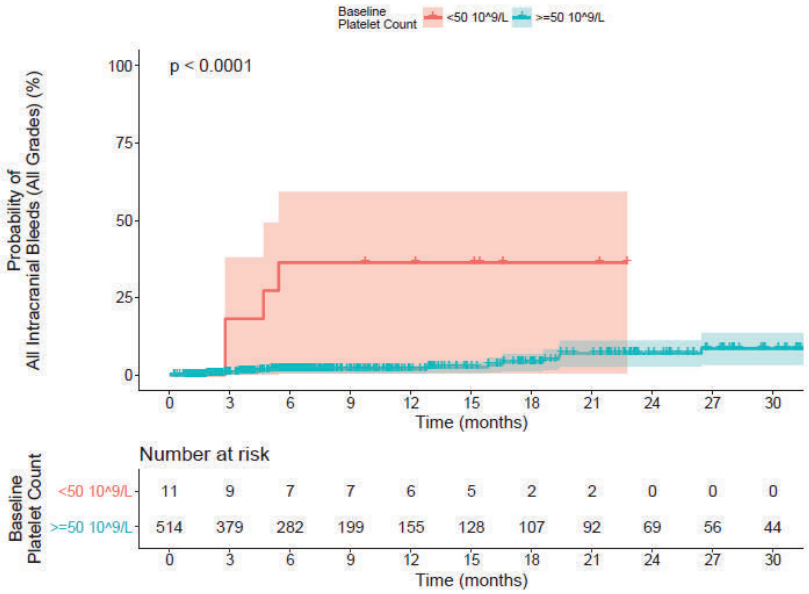
Although intracranial bleed risk was not significantly associated with avapritinib exposure quartile, both baseline platelet count and time-varying platelet count were found to have significant associations with intracranial bleed incidence. Out of 11 subjects with baseline platelet count $<50 \times 10^9$/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

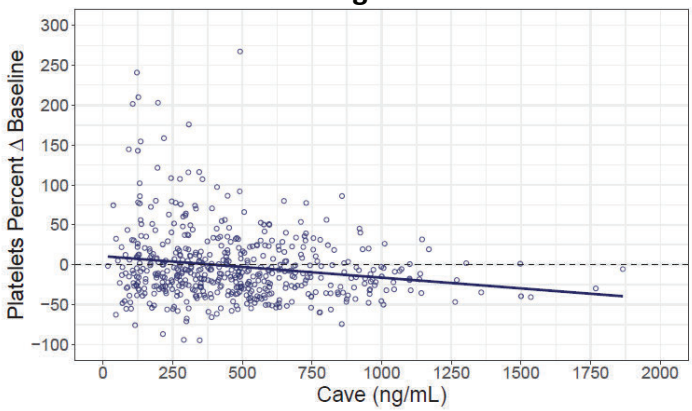
(**Figure 25**) between $C_{average}$ and percent change from platelet baseline nor between $C_{average}$ and platelet nadir in the first 2 months of therapy.

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.*

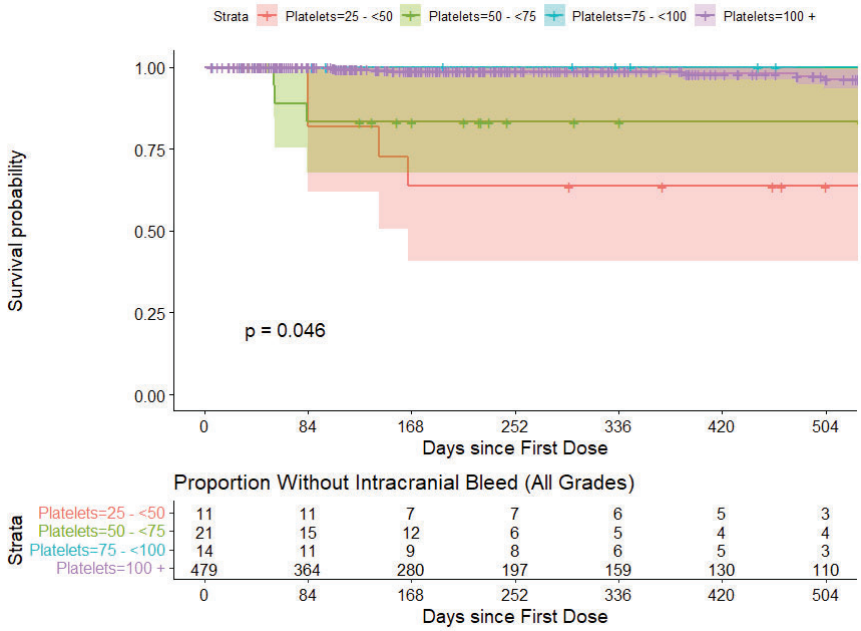
In order to assess the relationship between intracranial bleeding and additional baseline platelet count cutoffs, Kaplan-Meier curves were plotted in **Figure 26** *for baseline platelet count categories of 25 to <50 × 10^9/L (n = 11), 50 to <75 × 10^9/L (n = 21), 75 to <100 × 10^9/L (n = 14), and ≥100 × 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%)

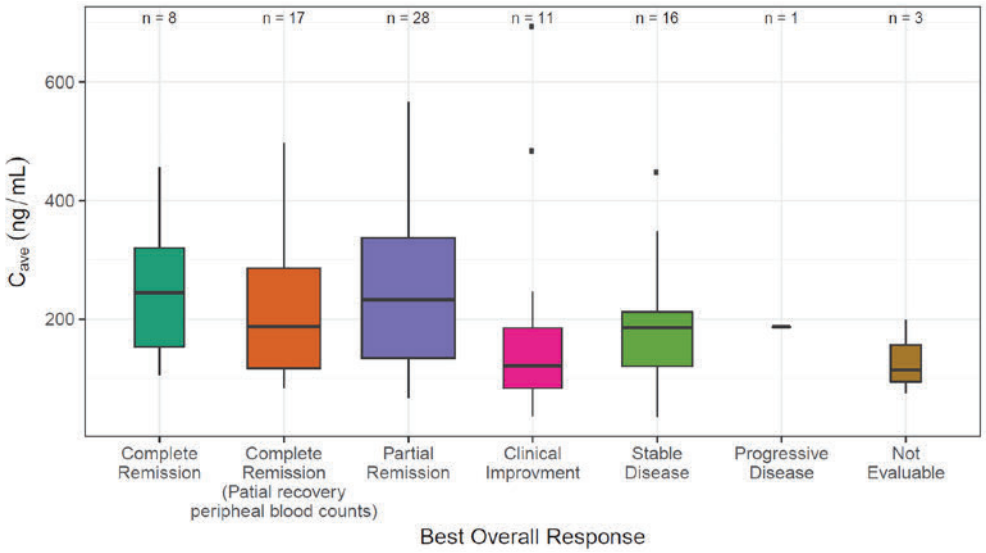
ASM = aggressive systemic mastocytosis; eGFR = estimated glomerular filtration rate; GIST = gastrointestinal stromal tumor; MCL = mast cell leukemia; PK = pharmacokinetic; PPI = proton pump inhibitor; PPRE = pure pathologic response-evaluable; RAC-RE = Response Assessment Committee response evaluable; 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).

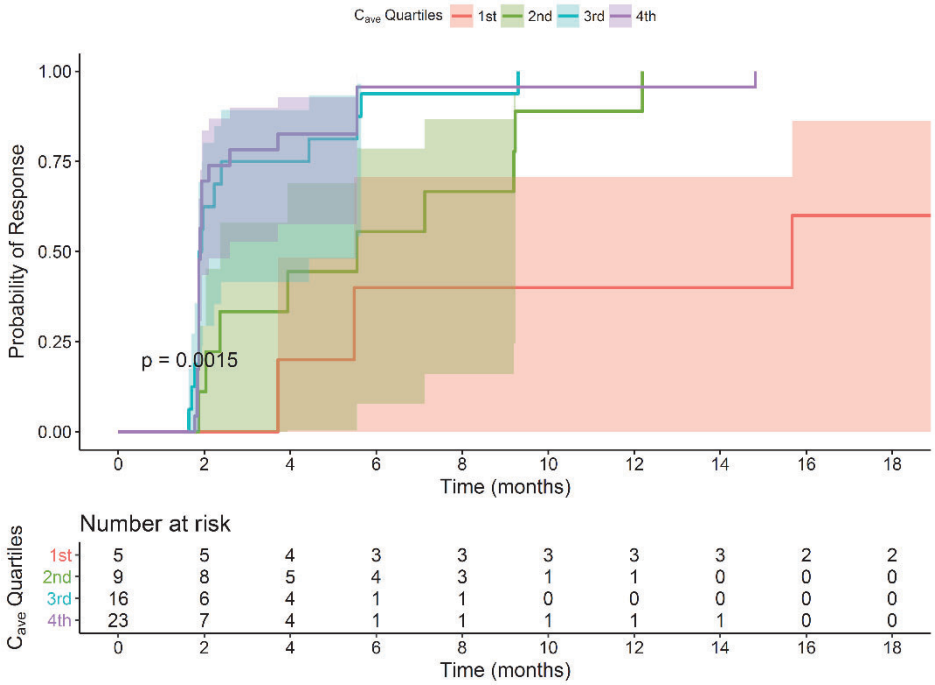
Graphical analysis was performed for all efficacy endpoints. Statistical comparison of efficacy by $C_{average}$ quartiles using a log-rank test was performed for all efficacy endpoints except for BOR and mBOR. The BOR according to exposure is presented in **Figure 27**. The TTR according to exposure 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, although the small number of patients with SSM (n = 2 in the efficacy population) made it difficult to assess the true response for that subtype.

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**).

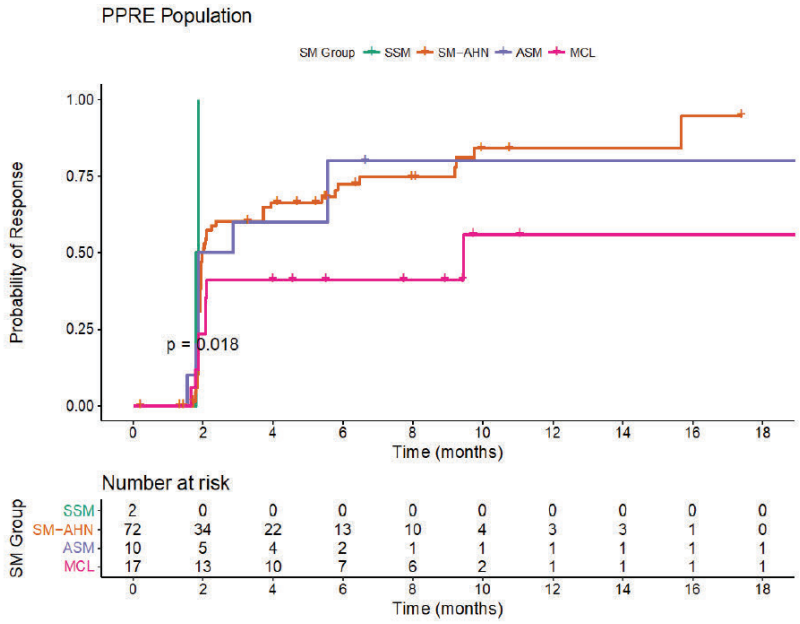
Table 14. Best Overall Response and Best Overall Morphologic Response by SM Subtype

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%)

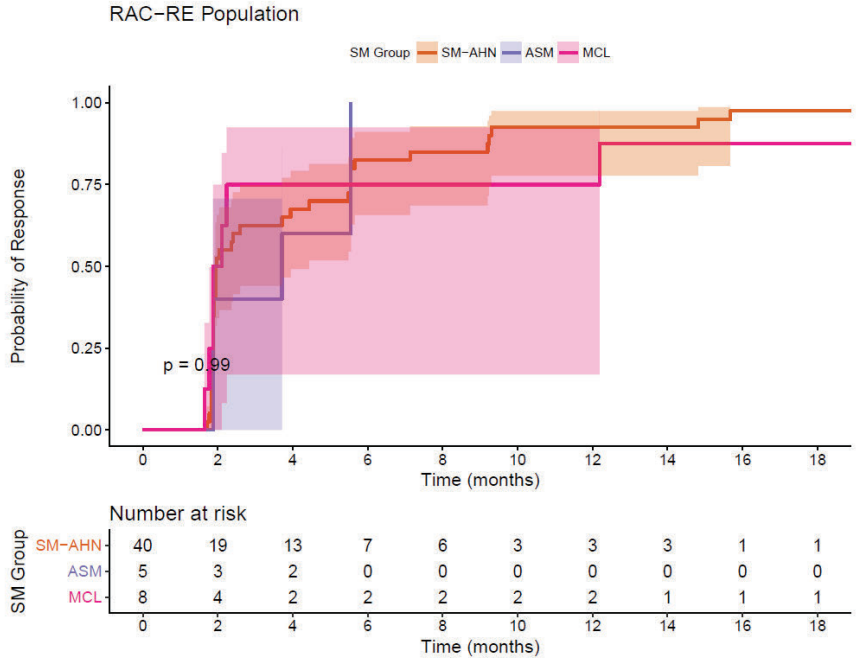
ASM = aggressive systemic mastocytosis; BOR = best overall response; mBOR = best overall morphologic response; MCL = mast cell leukemia; PPRE = pure pathologic response-evaluable; RAC-RE = Response Assessment Committee response evaluable; SM = systemic mastocytosis; SM-AHN = systemic mastocytosis with 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

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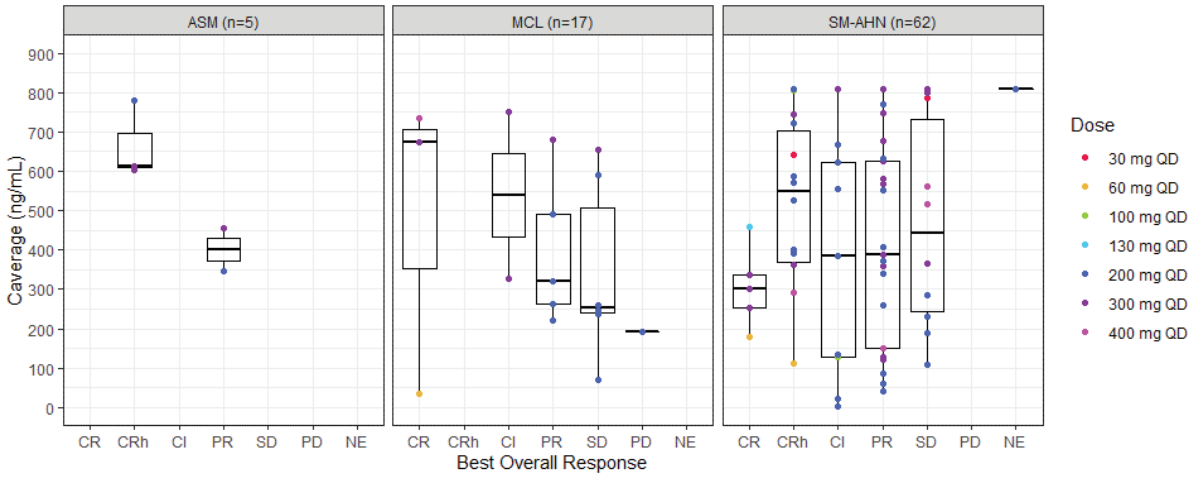
*Exposure is summarized according to SM subtype and BOR in **Figure 31.** The small number of subjects with ASM in the RAC-RE population (n = 5) is a limitation, but all three ASM subjects with best overall response of CRh have higher $C_{average}$ values than the two ASM subjects with best overall response 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).*

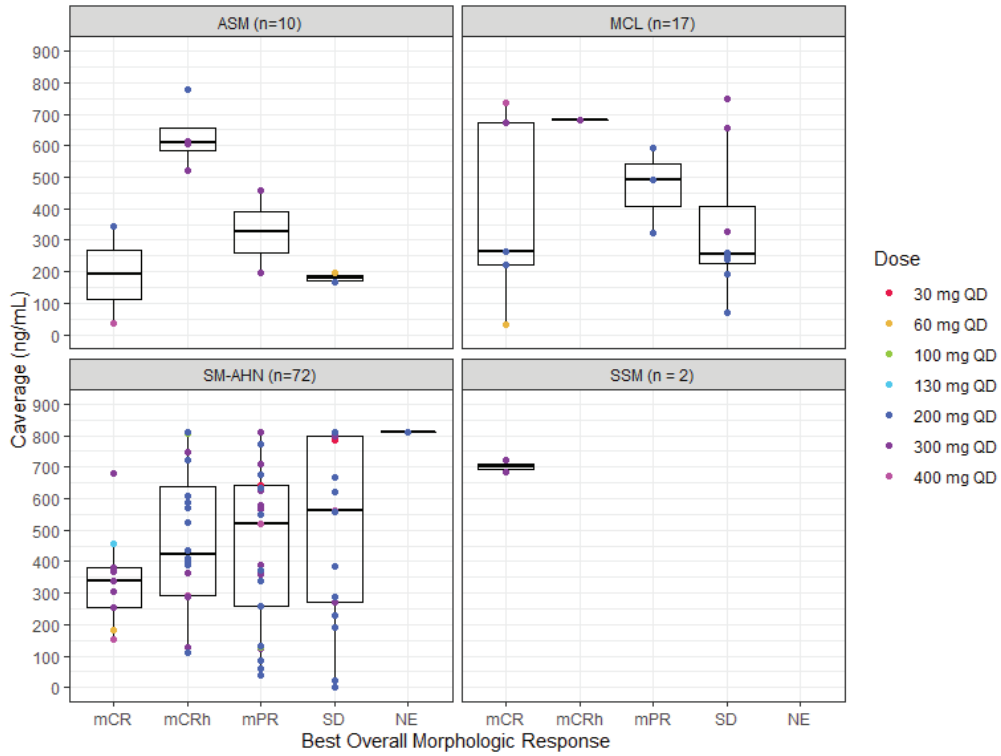
Although certain SM subtypes had small sample sizes for evaluation of BOR or mBOR, the $C_{average}$ values largely overlapped between SM subtypes. Individual $C_{average}$ also overlapped considerably between BOR and mBOR categories within each SM subtype and overall.

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

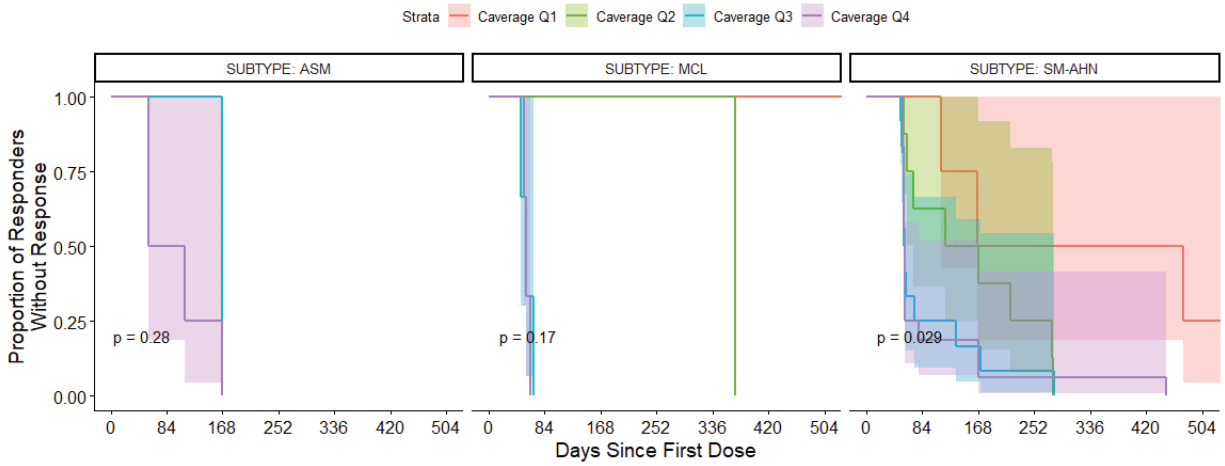


Points represent individual $C_{average}$. Best Overall Morphologic Response included Complete Morphologic Remission (mCR), mCR with Partial Recovery of Peripheral Blood Counts (mCRh), Morphologic Partial Remission (mPR), Stable Disease (SD), Progressive Disease (PD), and Not Evaluable (NE).

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

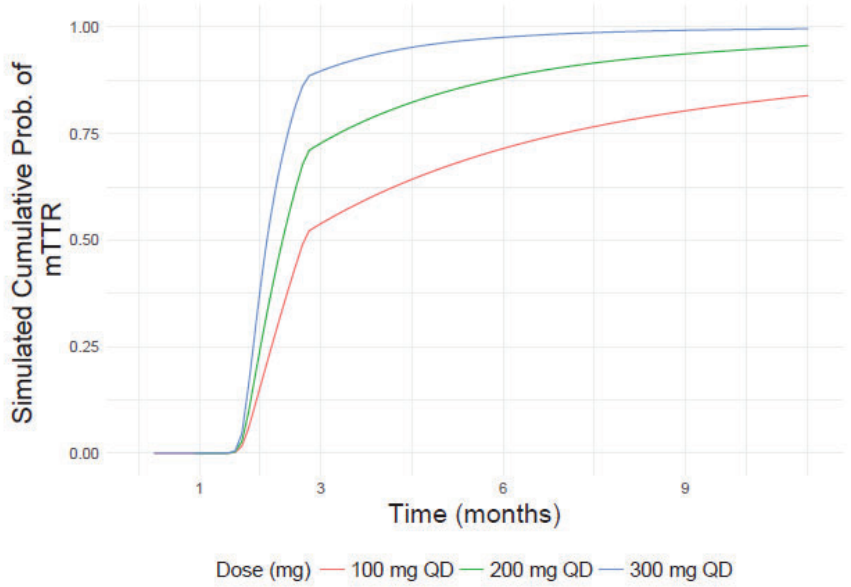
Parameter	Estimate	%RSE	95% Confidence Interval
Baseline hazard (log scale)	-8.56	2.92	(-9.05,-8.07)
T50 (hours)	1238	2.17	(1185,1290)
Hill coefficient	37	24.2	(19.4,54.5)
Slope for Daily $C_{average}$ (ng/mL)	0.00311	13	(0.00232,0.0039)
γ1 (≤84 days of treatment)	0.65	28.1	(0.29,1.01)
γ2 (>84 days of 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)

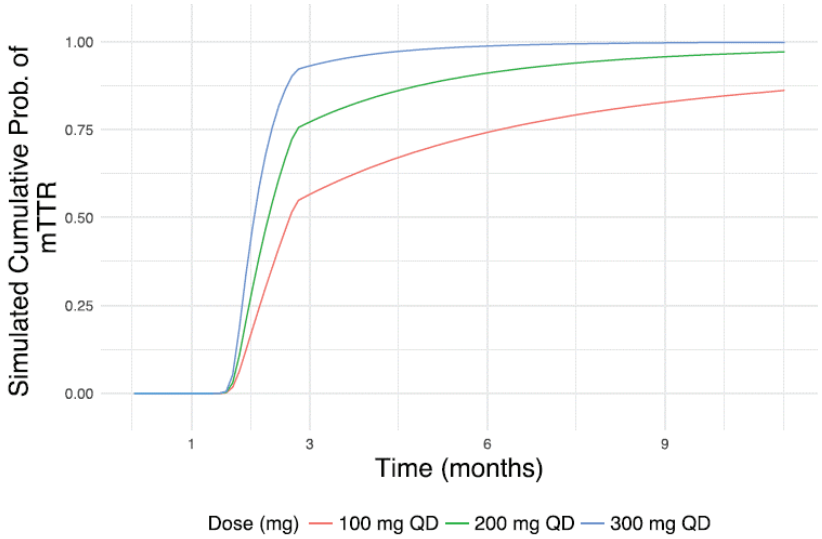


Exposure was simulated for each dose in 1000 virtual subjects with ASM, MCL, SM-AHN, and SSM resampled from BLU-285-2101 and BLU-285-2202. Solid lines represent median cumulative probability of morphologic response.
ASM = aggressive systemic mastocytosis; MCL = mast cell leukemia; mTTR = time to morphologic 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.

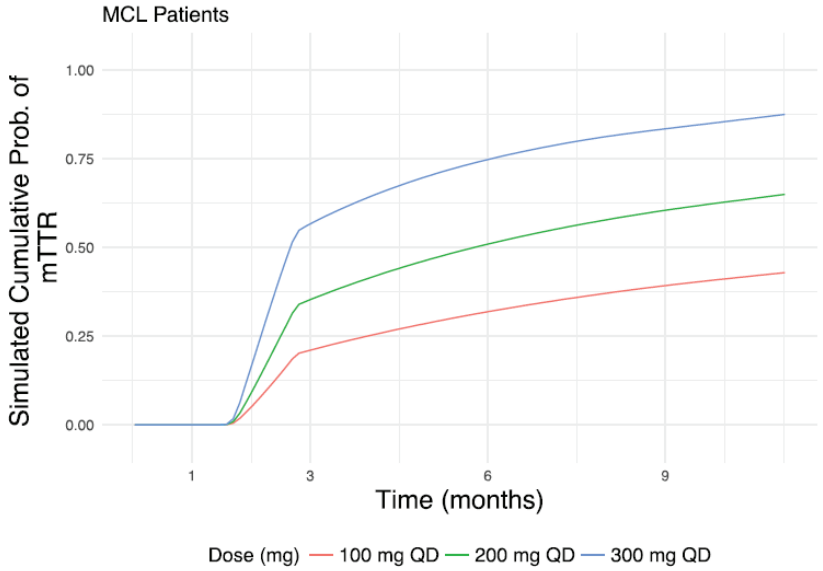
Subjects with MCL were predicted to have a lower rate of morphologic response compared to other AdvSM subtypes. **Figure 36** shows results from the simulation of patients with MCL, which predicts a median cumulative probability of morphologic response above 25% by 3 months after first dose with 200 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

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The simulations performed by the Applicant utilized virtual populations resampled from Studies BLU-285-2101 and BLU 285-2202, and (b) (4) (b) (4)

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) (b) (4) (b) (4) *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. (b) (4) 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.

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/

ROBYN E KONICKI
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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) (b) (4) (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 [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] is shown below (Table 1):

Table 1. Comparison of Avapritinib Tablet formulations manufactured at [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]	
	Percent of Blend (w/w)	
Avapritinib	[redacted]	
Microcrystalline cellulose [redacted]		
Microcrystalline cellulose [redacted]		
Copovidone		
Croscarmellose sodium		
Magnesium stearate [redacted]		
Total (core tablet)		
[redacted] White film coating		
[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)	64
25 mg Batch CFXKG	100 mg Batch 19J28G (b) (4)	72
50 mg Batch CDZGF	100 mg Batch 19J28G	54
100 mg Batch CDSPP	100 mg Batch 19J28G	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*)

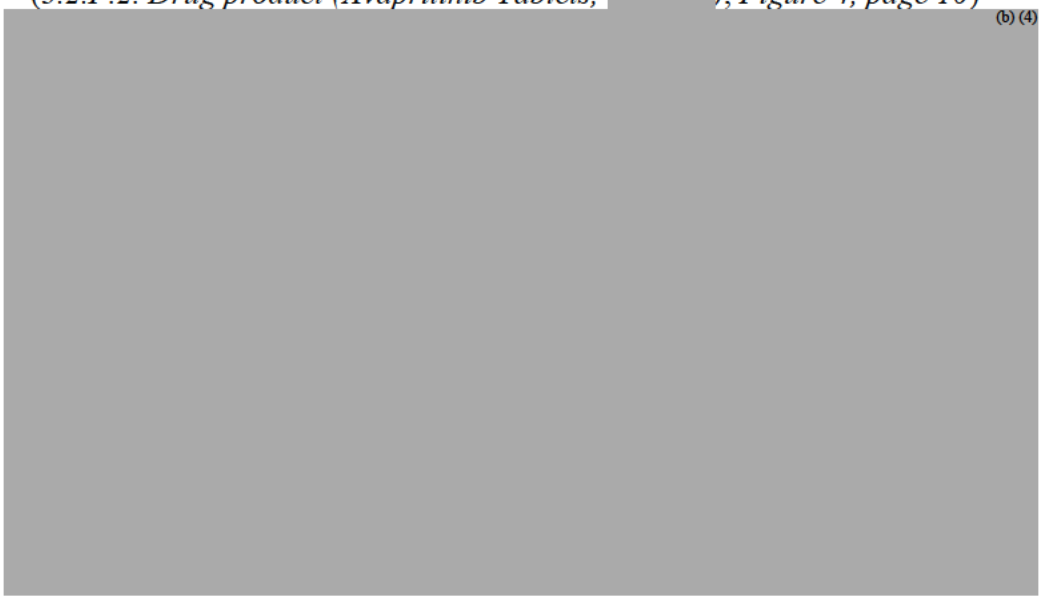


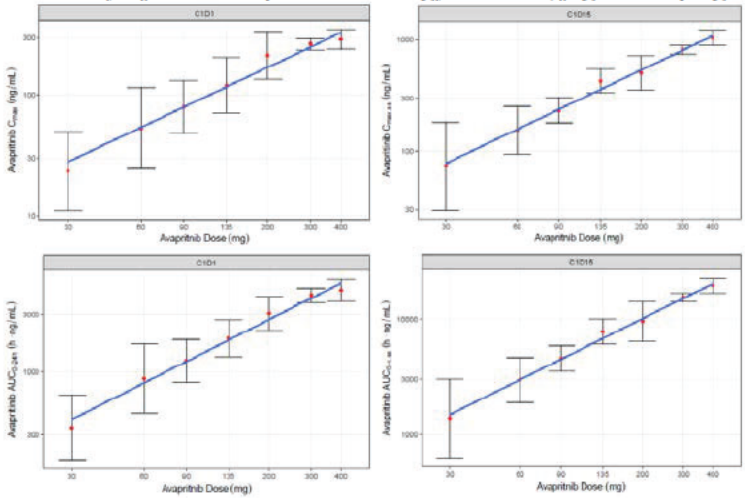
Figure 4. Comparative dissolution profiles in pH 6.8 buffer media (SIF)
(*3.2.P.2. Drug product (Avapritinib Tablets, (b) (4)), Figure 7, page 12*)

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 (b) (4) (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)	64
25 mg Batch CFXKG	100 mg Batch 19J28G (b) (4)	72
50 mg Batch CDZGF	100 mg Batch 19J28G	54
100 mg Batch CDSPP (b) (4)	100 mg Batch 19J28G	76
100 mg Batch 19E27G (b) (4) (b) (4)	100 mg Batch 19J28G	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 [redacted]. 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 [redacted]% in 15 minutes, NLT [redacted]% (Q) in 60 minutes) for the newly proposed lower strength s 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 [redacted] (approved) and [redacted] (newly proposed). The submitted dissolution data from the stability batches manufactured at [redacted] 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 [redacted]% in 15 minutes NLT [redacted]% (Q) in 60 minutes

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212608Orig1s007

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) (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:

- DNH removed the (b) (4) (b) (4)
- Throughout the labeling, the term (b) (4) was revised to "Advanced Systemic Mastocytosis" to reflect the removal of (b) (4)
- DNH relocated the Applicant's inserted (b) (4) (b) (4) from Section (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 (b) (4).
- 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 more narrow 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 broader population (n=148 patients with systemic mastocytosis) for the Warnings and Precautions section to provide a larger 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 (b) (4) (b) (4) (b) (4) 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 (b) (4).
- The review team asked the Applicant to revise the efficacy table (b) (4) (b) (4) and to update the rates presented for background and demographics to reflect this population.

- The review team removed [redacted]
- 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 [redacted] text remain in section [redacted] based upon edits to sections [redacted].

Regulatory Recommendation: This NDA is recommended for approval upon completion of labeling negotiations.

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/s/

VIRGINIA E KWITKOWSKI
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Office of Oncologic Diseases Associate Director for Labeling Review of the Prescribing Information

Product Title	AYVAKIT (avapritinib) tablets, for oral use
Applicant	Blueprint Medicines Corporation
Application/Supplement Number	sNDA 212608/S-7
Is Proposed Labeling in Old Format?	N
Is Labeling Being Converted to PLR?	N
Is Labeling Being Converted to PLLR?	N
Approved Indication(s)	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
Date FDA Received Application	December 16, 2020
Review Classification	P
PDUFA Goal Date	June 16, 2021
Review Date	5/25/2021
Reviewer	Elizabeth Everhart, MSN, RN, ACNP, ADL (acting)

This Associate Director for Labeling (ADL) memo documents recommendations for section 14.2 of the U.S. Prescribing Information (USPI) for Ayvakit (avapritinib) for supplement 7.

Background: Ayvakit (avapritinib) was initially approved in 2020 for the treatment of GIST. The Applicant submitted an efficacy supplement to propose a new indication for Mast Cell Leukemia (MCL). The applicant included efficacy results for patients enrolled in a clinical study who received starting doses ranging from 30 mg to 400 mg, 0.15 – 2 times the recommended dose of 200 mg, in text describing the clinical trial, as well as in the efficacy results table.

Per 21 CFR 201.57(c)(15)(i), information in section 14, Clinical Studies, must not imply or suggest indications or uses or dosing regimens not stated in the "Indications and Usage" or "Dosage and Administration" sections. Therefore, FDA added language to qualify the doses used in the study other than the recommended dosage by adding "x times recommended dosage".

In this rare disease state, FDA permitted analysis of pooled efficacy results for doses up to 200 mg (i.e., the recommended dose). (b) (4)

(b) (4)

At the time of this memo, labeling negotiations were ongoing. See the final approved USPI for AYVAKIT accompanying the approval letter for agreed upon labeling.

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/s/

ELIZABETH E EVERHART
05/25/2021 11:43:21 AM

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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BARBARA A FULLER
04/13/2021 08:57:10 AM

LASHAWN M GRIFFITHS
04/13/2021 09:04:59 AM

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) (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" as the stated (b) (4) (b) (4)

    2. We recommend relocating (b) (4) (b) (4) to *Section 2.5 Dosage Modifications for Adverse Reactions* as the (b) (4) (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 dosing information presented in the table [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] the starting dosage 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) (b) (4) • *Limitations of Use: AYVAKIT is not recommended for the treatment of AdvSM* (b) (4) (b) (4) *patients 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:*** (b) (4) ***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.

Carton Labeling

(b) (4)

1 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