# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

## *APPLICATION NUMBER:*

## 212608Orig1s013

| | |
|---|---|
| ***Trade Name:*** | AYVAKIT |
| ***Generic or Proper Name:*** | avapritinib |
| ***Sponsor:*** | Blueprint Medicines Corporation |
| ***Approval Date:*** | May 22, 2023 |
| ***Indication:*** | Ayvakit is a kinase inhibitor indicated for:<br>Gastrointestinal Stromal Tumor (GIST)<br>• 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.<br>Advanced Systemic Mastocytosis (AdvSM)<br>• 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).<br>• 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.<br>Indolent Systemic Mastocytosis (ISM)<br>• the treatment of adult patients with ISM.<br>• Limitations of Use: Ayvakit is not recommended for the treatment of patients with ISM with platelet counts of less than 50 X $10^9$/L. |

# CENTER FOR DRUG EVALUATION AND RESEARCH

# 212608Orig1s013

## CONTENTS

## Reviews / Information Included in this NDA Review.

| | |
|---|---|
| **Approval Letter** | **X** |
| **Other Action Letters** | |
| **Labeling** | **X** |
| **REMS** | |
| **Summary Review** | **X** |
| **Officer/Employee List** | |
| **Office Director Memo** | |
| **Cross Discipline Team Leader Review** | |
| **Medical Review(s)** | |
| **Chemistry Review(s)** | **X** |
| **Environmental Assessment** | |
| **Pharmacology Review(s)** | |
| **Statistical Review(s)** | |
| **Microbiology / Virology Review(s)** | |
| **Clinical Pharmacology/Biopharmaceutics Review(s)** | |
| **Other Reviews** | **X** |
| **Risk Assessment and Risk Mitigation Review(s)** | |
| **Proprietary Name Review(s)** | |
| **Administrative/Correspondence Document(s)** | |

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 212608Orig1s013

# APPROVAL LETTER

NDA 212608/S-013

**SUPPLEMENT APPROVAL**
**FULFILLMENT OF POSTMARKETING REQUIREMENT**

Blueprint Medicines Corporation
Attention: Elisabeth Garrison, Pharm.D, MS
Associate Director, Global Regulatory Sciences
45 Sidney Street, Suite 200
Cambridge, Massachusetts 02139

Dear Dr. Garrison:

Please refer to your supplemental new drug application (sNDA) dated and received on November 22, 2022, and your amedments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ayvakit (avapritinib) tablets.

This Prior Approval supplemental new drug application provides for a new indication of indolent systemic mastocytosis (ISM).

## APPROVAL & LABELING

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

## CONTENT OF LABELING

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

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).

## 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.

## FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submission dated November 22, 2022, containing the final report for the following postmarketing requirement listed in the January 9, 2020, approval letter.

3781-3 Complete a pharmacokinetic trial to determine an appropriate dose of avapritinib in patients with severe hepatic impairment in accordance with the FDA Guidance for Industry titled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling” found at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072123.pdf.

We have reviewed your submission and conclude that the above requirement was fulfilled.

This completes all of your postmarketing requirements and postmarketing commitments acknowledged in our January 9, 2020, letter. You are not required to report on the status of closed (released or fulfilled) PMRs/PMC in your annual report required under 21 CFR 314.81(b)(2)(vii) of the FD&CA.

## 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]

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]

## PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

## REPORTING REQUIREMENTS

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

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, call Bijal Patel, Regulatory Project Manager, at 240-402-4829 or email at bijal.patel1@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Ann T. Farrell, MD
Director
Division of Nonmalignant Hematology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

---

**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/

---

ANN T FARRELL
05/22/2023 01:29:45 PM

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 212608Orig1s013

# 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) | 5/2023 |
| Dosage and Administration (2) | 5/2023 |
| Warnings and Precautions (5) | 5/2023 |

**----------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, 2.2)

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)

Indolent Systemic Mastocytosis (ISM)

- the treatment of adult patients with ISM. (1.3)
- Limitations of Use: AYVAKIT is not recommended for the treatment of patients with ISM 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. (2.2)
- GIST: The recommended dosage is 300 mg orally once daily. (2.2)
- AdvSM: The recommended dosage is 200 mg orally once daily. (2 3)
- ISM: The recommended dosage is 25 mg orally once daily. (2.4)
- Patients with severe hepatic impairment (Child-Pugh Class C): reduce dose of AYVAKIT. (2.7)

**----------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. In patients with GIST, AdvSM, or ISM 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)
- Photosensitivity: May cause photosensitivity reactions. Advise patients to limit direct ultraviolet exposure. (5.3)
- 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. (5.4, 8.1, 8.3)

**----------ADVERSE REACTIONS----------**

The most common adverse reactions are:

- GIST (≥20% incidence): edema, nausea, fatigue/asthenia, cognitive impairment, vomiting, decreased appetite, diarrhea, increased lacrimation, abdominal pain, constipation, rash, dizziness, and hair color changes. (6.1)
- AdvSM (≥20% incidence): edema, diarrhea, nausea, and fatigue/asthenia. (6.1)
- ISM (≥10% incidence): eye edema, dizziness, peripheral edema and flushing. (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 in patients with GIST or AdvSM. (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: 5/2023**

**FULL PRESCRIBING INFORMATION: CONTENTS***


**1 INDICATIONS AND USAGE**
1.1 PDGFRA Exon 18 Mutation-Positive Unresectable or Metastatic Gastrointestinal Stromal Tumor (GIST)
1.2 Advanced Systemic Mastocytosis (AdvSM)
1.3 Indolent Systemic Mastocytosis (ISM)
**2 DOSAGE AND ADMINISTRATION**
2.1 Recommended Administration
2.2 GIST Harboring PDGFRA Exon 18 Mutations
2.3 Advanced Systemic Mastocytosis
2.4 Indolent Systemic Mastocytosis
2.5 Dosage Modifications for Adverse Reactions
2.6 Concomitant Use of Strong or Moderate CYP3A Inhibitors
2.7 Dose Modifications for Severe Hepatic Impairment
**3 DOSAGE FORMS AND STRENGTHS**
**4 CONTRAINDICATIONS**
**5 WARNINGS AND PRECAUTIONS**
5.1 Intracranial Hemorrhage
5.2 Cognitive Effects
5.3 Photosensitivity
5.4 Embryo-Fetal Toxicity
**6 ADVERSE REACTIONS**
6.1 Clinical Trials Experience
**7 DRUG INTERACTIONS**
7.1 Effects of Other Drugs on AYVAKIT
7.2 Effects of AYVAKIT on Other Drugs
**8 USE IN SPECIFIC POPULATIONS**
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
**11 DESCRIPTION**
**12 CLINICAL PHARMACOLOGY**
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
**13 NONCLINICAL TOXICOLOGY**
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
**14 CLINICAL STUDIES**
14.1 Gastrointestinal Stromal Tumors
14.2 Advanced Systemic Mastocytosis
14.3 Indolent Systemic Mastocytosis
**16 HOW SUPPLIED/STORAGE AND HANDLING**

## 17 PATIENT COUNSELING INFORMATION

*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 (2.2)]*.

## 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)]*.

## 1.3 Indolent Systemic Mastocytosis (ISM)

AYVAKIT is indicated for the treatment of adult patients with indolent systemic mastocytosis (ISM).

Limitations of Use:

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

# 2 DOSAGE AND ADMINISTRATION

## 2.1 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.

## 2.2 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.

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 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.

## 2.4 Indolent Systemic Mastocytosis

The recommended dosage of AYVAKIT is 25 mg orally once daily in patients with ISM.

## 2.5 Dosage Modifications for Adverse Reactions

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

**Table 1: Recommended Dosage Reductions for AYVAKIT for Adverse Reactions**

| Dose Reduction Level | Dosage in patients with GIST* | Dosage in patients with AdvSM† |
|---|---|---|
| First dose reduction | 200 mg once daily | 100 mg once daily |
| Second dose reduction | 100 mg once daily | 50 mg once daily |
| Third dose reduction | - | 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 $50 \times 10^9$/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 and 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

For ISM, avoid concomitant use of AYVAKIT with strong or moderate CYP3A inhibitors.

### 2.7 Dosage Modifications for Severe Hepatic Impairment

A modified starting dosage of AYVAKIT is recommended for patients with severe hepatic impairment (Child-Pugh Class C) *[see Use in Specific Populations (8.7)]:*

- GIST: 200 mg orally once daily
- AdvSM: 100 mg orally once daily
- ISM: 25 mg orally every other day

## 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 with GIST or AdvSM who received AYVAKIT in clinical trials. No events of intracranial hemorrhage occurred in the 246 patients with ISM who received any dose of AYVAKIT in the PIONEER study.

Monitor patients closely for risk factors of intracranial hemorrhage which may include history of vascular aneurysm, intracranial hemorrhage or cerebrovascular accident within the prior year, concomitant use of anticoagulant drugs, or thrombocytopenia.

Symptoms of intracranial hemorrhage may include headache, nausea, vomiting, vision changes, or altered mental status. Advise patients to seek immediate medical attention for signs or symptoms of intracranial hemorrhage.

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 33% of the 995 patients with GIST, AdvSM or ISM who received AYVAKIT in clinical trials. These adverse reactions were managed with dose interruption and/or reduction when needed.

Overall, 10% led to dose interruptions, 7% led to dose reductions and 2.2% led to permanent discontinuation of AYVAKIT treatment in patients with GIST, AdvSM or ISM.

Depending on the severity and indication, 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)]*.

*Indolent Systemic Mastocytosis*

Cognitive adverse reactions occurred in 7.8% of patients with ISM who received AYVAKIT + best supportive care versus 7% of patients who received placebo + best supportive care in the PIONEER study; <1% were Grade 3. The median time to onset of the first cognitive adverse reaction was 2.3 months (range: 0 to 5.4 months). Median time to improvement to Grade 1 or complete resolution was 2.1 months (range: 0.4 to 2.1 months).

*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.

*Advanced Systemic Mastocytosis*

Cognitive adverse reactions occurred in 28% of 148 patients with AdvSM 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 Photosensitivity

AYVAKIT may cause photosensitivity reactions. In all patients treated with AYVAKIT in clinical trials (n=1049), photosensitivity reactions occurred in 2.5% of patients. Advise patients to limit direct ultraviolet exposure during treatment with AYVAKIT and for one week after discontinuation of treatment.

## 5.4 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 31.4, 6.3 and 2.7 times

the human exposure based on area under the curve (AUC) at the 25 mg, 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)]*
- Photosensitivity *[see Warnings and Precautions (5.3)]*

## 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 25 mg to 600 mg orally once daily in 995 patients enrolled in one of five clinicals trials conducted in patients with advanced malignancies and systemic mastocytosis, including NAVIGATOR, EXPLORER, PATHFINDER and PIONEER *[see Clinical Studies (14.1, 14.2, 14.3)].* These patients included 601 patients with GIST, 148 patients with AdvSM and 246 patients with ISM. Among the 995 patients receiving AYVAKIT, 54% were exposed for 6 months or longer and 26% 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, increased lacrimation, abdominal pain, constipation, rash, dizziness, and hair color changes. Table 5 summarizes the adverse reactions observed in NAVIGATOR.

**Table 5. 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 | 0 |
| **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 6 summarizes the laboratory abnormalities observed in NAVIGATOR.

**Table 6. 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 7 summarizes the adverse reactions observed in EXPLORER and PATHFINDER.

**Table 7. 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 8 summarizes the laboratory abnormalities observed in EXPLORER and PATHFINDER.

**Table 8. 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 |

Other Clinically Relevant Adverse Reactions in <10% of patients

In the pooled GIST and AdvSM safety populations, photosensitivity occurred in 2.5% of patients *[see Warnings and Precautions (5.3)]*.

Indolent Systemic Mastocytosis

The safety of AYVAKIT in patients with ISM was evaluated in PIONEER *[see Clinical Studies (14.3)]*. Patients received AYVAKIT 25 mg orally once daily with best supportive care (n = 141) or placebo once daily with best supportive care (n = 71).

Serious adverse reactions occurred in 1 patient (0.7%) who received AYVAKIT due to pelvic hematoma.

Permanent discontinuation of AYVAKIT due to an adverse reaction occurred in 1 patient (0.7%) due to dyspnea and dizziness.

Dosage interruptions of AYVAKIT due to an adverse reaction occurred in 5% of patients. Adverse reactions which required dosage interruption included dizziness, blood alkaline phosphatase increased, dyspnea, face edema, pelvic hematoma, liver transaminase increased and respiratory tract infection (1 patient each).

Table 9 summarizes the frequency of adverse reactions in the PIONEER study. The most common adverse reactions (≥ 10%) in the AYVAKIT group were eye edema, dizziness, peripheral edema and flushing. Of all adverse reactions, 55% were Grade 1, 38% were Grade 2 and 7% were Grade 3. Among patients with edema adverse reactions, 95% were Grade 1 and 5% were Grade 2. Among patients with hemorrhage adverse reactions, 86% were Grade 1 and 14% were Grade 2.

**Table 9. Adverse Reactions Occurring in AYVAKIT-Treated Patients with Indolent Systemic Mastocytosis During PIONEER Trial**

| Adverse Reactions[a, b] | AYVAKIT (25 mg once daily) + BSC N=141 % | Placebo + BSC N=71 % |
|---|---|---|
| Eye edema[c] | 13 | 7 |
| Dizziness[d] | 13 | 10 |
| Peripheral edema[d] | 12 | 6 |
| Flushing[d] | 11 | 4 |
| Respiratory tract infection[e] | 8 | 1 |
| Face edema | 7 | 1 |
| Rash[d] | 6 | 4 |
| Liver transaminase increased[d] | 6 | 3 |
| Insomnia | 6 | 3 |
| Hematoma[f] | 6 | 1 |
| Blood alkaline phosphatase increased | 6 | 1 |
| Hemorrhage[g] | 5 | 3 |

Abbreviations: BSC=best supportive care

[a] Adverse reactions that occurred in ≥5% of AYVAKIT-treated patients and ≥2% more than placebo-treated patients.

[b] Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

[c] Eye edema includes periorbital edema, eye edema, swelling of eyelid, orbital edema, eye swelling, eyelid edema and eyelid ptosis.

[d] Term includes several similar terms.

[e] Respiratory tract infection includes pneumonia, upper respiratory tract infection, bronchitis and respiratory tract infection.

[f] Hematoma includes contusion, hematoma and pelvic hematoma.

[g] Hemorrhage includes epistaxis, gingival bleeding, hematochezia, rectal hemorrhage, retinal hemorrhage.

Clinically relevant adverse reactions occurring in <5% of patients were:

*Skin and subcutaneous tissue:* photosensitivity (2.8%)

# 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 rats during the period of organogenesis was teratogenic and embryotoxic at exposure levels approximately 31.4, 6.3 and 2.7 times the human exposure based on AUC at the 25 mg, 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 31.4, 6.3 and 2.7 times the human exposure based on AUC at the 25 mg, 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 impair female fertility. These findings were not reversible within a two month recovery period *[see Nonclinical Toxicology (13.1)]*.

Males

Based on findings from animal studies, AYVAKIT may impair male fertility. These findings were not reversible within a two month recovery period *[see Nonclinical Toxicology (13.1)]*.

## 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. Of the 141 patients with ISM who received AYVAKIT in PIONEER, 6% were 65 years or older, while <1% 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

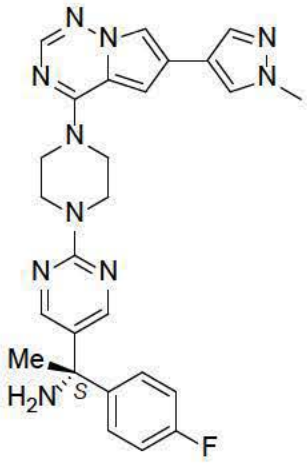
No dose adjustment is recommended for patients with mild or moderate renal impairment [creatinine clearance (CLcr) 30 to 89 mL/min estimated by Cockcroft-Gault]. The recommended dose of AYVAKIT has not been established for patients with severe renal impairment (CLcr 15 to 29 mL/min) or end-stage renal 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. Unbound $AUC_{0\text{-}INF}$ was 61% higher in subjects with severe hepatic impairment (Child-Pugh Class C) as compared to matched healthy subjects with normal hepatic function. A lower starting dose is recommended in patients with severe hepatic impairment *[see Dosage and Administration (2.7)]*.

## 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

*Gastrointestinal Stromal Tumors or Advanced Systemic Mastocytosis*

Based on the data from four clinicals trials conducted in patients with advanced malignancies and AdvSM, 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 doses of 300 mg or 400 mg (12 to 16 times the lowest recommended 25 mg dose, 1.33 times the highest 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 approximately proportionally over the dose range of 25 mg to 400 mg once daily. Steady state concentrations of avapritinib were reached prior to day 15 following daily dosing. Steady state pharmacokinetic parameters per recommended dosing regimen are described in Table 10.

**Table 10. Steady State Pharmacokinetic Parameters of AYVAKIT Following Different Dosing Regimen**

| Pharmacokinetic Parameters | 25 mg once daily (ISM) | 200 mg once daily (AdvSM) | 300 mg once daily (GIST) |
|---|---|---|---|
| $C_{max}$ (ng/mL) Geometric Mean (CV%) | 70.2 (47.8 %, n=9) | 377 (62%, n=18) | 813 (52%, n=110) |

| | | | |
|---|---|---|---|
| $AUC_{0\text{-}24h}$ (h•ng/mL) Geometric Mean (CV%) | 1330 (49.5 %, n = 9) | 6600 (54%, n=16) | 15400 (48%, n=110) |
| Mean accumulation ratio of $AUC_{0\text{-}24h}$ | 4.06 (n=9) | 6.41 (n=9) | 3.82 (n=34) |

Abbreviations: CV%=coefficient of variation

Absorption

The median time to peak concentration ($T_{max}$) ranged from 2 to 4 hours following single doses of avapritinib.

*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 (CV %) apparent volume of distribution of avapritinib is 1310 L (51.5%) at 300 mg in patients with GIST, 1900 L (43.2%) at 200 mg in patients with AdvSM, and 1400 L (59.1%) at 25 mg in patients with ISM. 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 to 57 hours in patients with GIST, 20 to 39 hours in patients with AdvSM, and 38 to 45 hours in patients with ISM. The steady state mean (CV%) apparent oral clearance of avapritinib is 21.8 L/h (54.9%) at 300 mg in patients with GIST, 40.3 L/h (86.0%) at 200 mg in patients with AdvSM, and 21.6 L/h (58.1%) at 25 mg in patients with ISM.

*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 ($CL_{cr}$ 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. In a dedicated hepatic impairment study following a single oral dose administration of 100 mg avapritinib, the mean unbound AUC was 61% higher in subjects with severe hepatic impairment (Child-Pugh Class C) as compared to matched healthy subjects with normal hepatic function. The effect of severe renal impairment ($CL_{cr}$ 15 to 29 mL/min) and end-stage renal disease ($CL_{cr}$ < 15 mL/min) 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 Dosage and Administration (2.6), 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 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

Avapritinib was not mutagenic in a 6-month transgenic mouse study up to the highest dose evaluated at 20 mg/kg/day. 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.

There were no direct effects on fertility in rats of either sex in a dedicated fertility and early embryonic development study. Avapritinib may impair spermatogenesis and adversely affect early embryogenesis. Reduction in sperm production and testicular weight were observed in rats and hypospermatogenesis in dogs administered avapritinib at exposure of 8.7 times and 0.5 time the 300 mg human dose, respectively. Avapritinib partitioned into seminal fluids up to 0.2 times the concentration found in human plasma at 300 mg. In female rats there was an increase in pre-implantation loss at exposure of 5.4 times the human exposure at 300 mg and in early resorptions at exposure 2.7 times the human exposure at 300 mg with an overall decrease in viable embryos. Cystic degeneration of corpora lutea and vaginal mucification was also observed in female rats administered avapritinib for up to 6 months at exposure 1.3 times the human exposure based on AUC at the 300 mg dose.

### 13.2 Animal Toxicology and/or Pharmacology

In repeat dose toxicology studies, administration of avapritinib to rats for up to 28 days and to dogs for up to 3 months resulted in tremors at doses greater than or equal to 100 mg/kg/day or 30 mg/kg/day (approximately 8 and 1.5 times the human exposure based on AUC at the 300 mg dose). Hemorrhage in the brain and spinal cord occurred in dogs at doses greater than or equal to 15 mg/kg/day (approximately 9.0, 1.8, or 0.8 times the human exposure based on AUC at the 25 mg, 200 mg. or 300 mg dose, respectively) and choroid plexus edema in the brain occurred in dogs at doses greater than or equal to 7.5 mg/kg/day (approximately 4.7, 1 or 0.4 times the human exposure based on AUC at the 25 mg, 200 mg or 300 mg dose, respectively), 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 11.

**Table 11. 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

+ 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 12.

**Table 12. 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).

## 14.3 Indolent Systemic Mastocytosis

The efficacy of AYVAKIT was demonstrated in PIONEER (NCT03731260), a randomized, double-blind, placebo-controlled trial conducted in adult patients with Indolent Systemic Mastocytosis (ISM) based on World Health Organization (WHO) classification. Enrolled patients had moderate to severe symptoms

despite receiving at least 2 symptom directed therapies. Patients were randomized to receive 25 mg AYVAKIT orally once daily with best supportive care versus placebo with best supportive care. The treatment duration was over a 24-week period, during the randomized portion of the study.

Efficacy was based on the absolute mean change from baseline to Week 24 in the Indolent Systemic Mastocytosis-Symptom Assessment Form (ISM-SAF) total symptom score (TSS). The ISM-SAF is a patient-reported outcome measure assessing ISM signs and symptoms: abdominal pain, nausea, diarrhea, spots, itching, flushing, bone pain, fatigue, dizziness, headache, brain fog. Scores ranged from 0 ("none") to 10 ("worst imaginable"). The item scores were summed to calculate a daily ISM-SAF TSS (range 0-110), with higher scores indicating greater symptom severity. A biweekly average ISM-SAF TSS was used to evaluate efficacy endpoints.

Additional supportive results included the proportion of AYVAKIT-treated patients achieving ≥50% reduction from baseline through Week 24 in TSS compared to placebo. Objective measures of mast cell burden were assessed including the proportion of AYVAKIT-treated patients with a ≥50% reduction from baseline through Week 24 in serum tryptase, peripheral blood KIT D816V allele fraction and bone marrow mast cells.

The median age of the patients who received AYVAKIT was 50 years (range: 18 to 77 years), 71% were female, 77% were White, <1% were Asian, 3% had other race and 19% had missing race. Ethnicities included 4% Hispanic or Latino. KIT D816V mutations were identified in 93% of patients. At baseline, the mean TSS was 50.17 (standard deviation: 19.15), the median serum tryptase level was 38.40 ng/mL, the median KIT D816V mutant allele fraction was 0.39% by ddPCR and the median bone marrow mast cell infiltrate was 7%. Study population characteristics were similar in the placebo group.

The majority of patients who received AYVAKIT (99.3%) or placebo (100%) received concomitant best supportive care at baseline (median of 3 therapies in the AYVAKIT group and 4 in the placebo group). The most common therapies in the AYVAKIT group were H1 antihistamines (97%), H2 antihistamines (66%), leukotriene inhibitors (35%) and cromolyn sodium (30%).

Efficacy results are summarized in Tables 13 and 14.

**Table 13. Efficacy Results for Patients with ISM in PIONEER at Week 24**

| **Efficacy Parameter** | **AYVAKIT (25 mg once daily) + BSC N=141** | **Placebo + BSC N=71** | **2-sided p-value** |
|---|---|---|---|
| **Absolute Mean change in the ISM-SAF TSS[1]** | | | |
| Change from baseline (95% CI) | -15.33 (-18.36, -12.31) | -9.64 (-13.61, -5.68) | 0.012 |
| Difference from placebo (95% CI) | -5.69 (-10.16, -1.23) | | |

| | | | |
|---|---|---|---|
| **% of patients achieving ≥50% reduction in the ISM-SAF TSS[2]** (95% CI) | 25<br>(17.9, 32.8) | 10<br>(4.1, 19.3) | 0.009 |

Abbreviations: BSC=best supportive care; CI=confidence interval; ISM-SAF= Indolent Systemic Mastocytosis-Symptom Assessment Form TSS=Total Symptom Score
[1]Markov chain Monte Carlo simulation was used to impute the missing values at Baseline or C7D1.
[2]Patients with missing values at Baseline or C7D1 were counted in the denominator but not numerator.

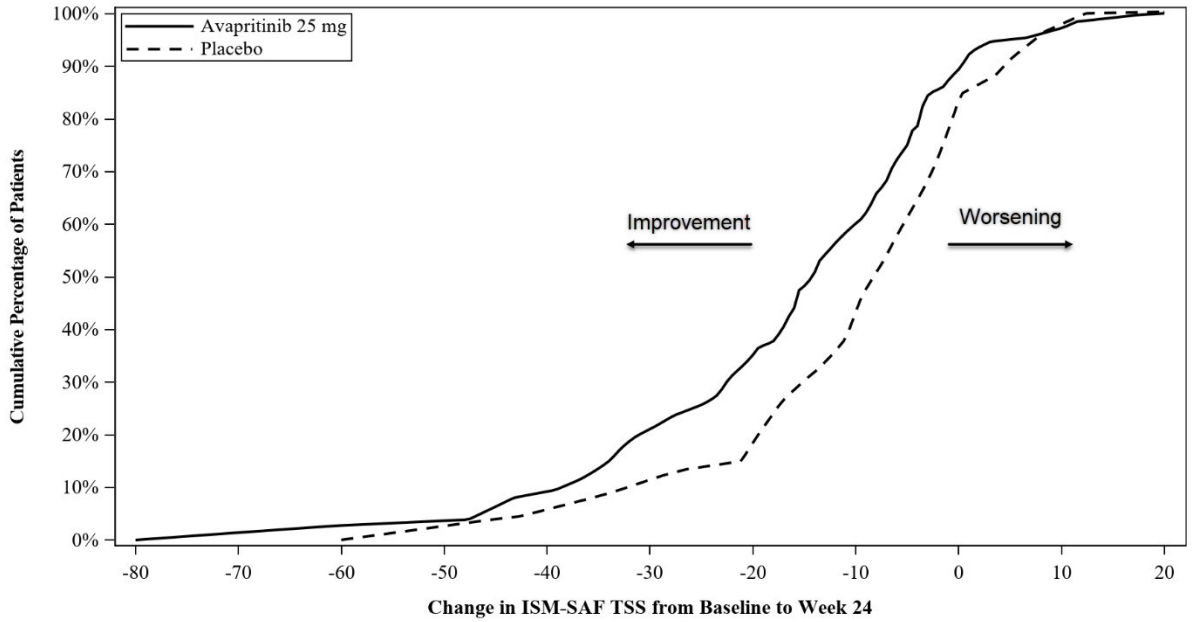
**Table 14. Efficacy Results Related to Mast Cell Burden for Patients with ISM in PIONEER at Week 24**

| Efficacy Parameter | AYVAKIT (25 mg once daily) + BSC | Placebo + BSC | 2-sided p-value |
|---|---|---|---|
| **% of patients with a ≥50% reduction in serum tryptase** (95% CI) | N=141<br>**53.9**<br>(45.3, 62.3) | N=71<br>**0**<br>(0.0, 5.1) | <0.0001 |
| **% of patients with a ≥50% reduction in peripheral blood KIT D816V allele fraction or undetectable** (95% CI) | N=118<br>**67.8**<br>(58.6, 76.1) | N=63<br>**6.3**<br>(1.8, 15.5) | <0.0001 |
| **% of patients with a ≥50% reduction in bone marrow mast cells or no aggregates** (95% CI) | N=106<br>**52.8**<br>(42.9, 62.6) | N=57<br>**22.8**<br>(12.7, 35.8) | <0.0001 |

Abbreviations: BSC=best supportive care; CI=confidence interval

To aid in the interpretation of the ISM-SAF TSS absolute mean change from baseline results, the proportion of patients reporting less than or equal to any particular level of change in the ISM-SAF TSS from baseline to Week 24 is depicted in a cumulative distribution function plot as shown in Figure 1.

**Figure 1: Cumulative Proportion of Patients with ISM in PIONEER Reporting Change in ISM-SAF TSS From Baseline to Week 24**




# 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)]*.

Photosensitivity

Inform patients that there is a potential risk of photosensitivity reactions with AYVAKIT. Advise patients to limit direct ultraviolet exposure by using sunscreen and protective clothing during treatment with AYVAKIT *[see Warnings and Precautions (5.3)]*.

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 (5.4), 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 at 200 mg or 300 mg *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*. Advise males of reproductive potential that AYVAKIT may decrease sperm production at 200 mg or 300 mg *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*.

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 (2.1)]*.

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).
- indolent systemic mastocytosis (ISM).

  AYVAKIT is not recommended for the treatment of ISM 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 a history of bulging or weakening of a blood vessel wall (aneurysm) or bleeding in your brain
- history of stroke within the last year
- have low platelet counts
- have or have had liver problems
- 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.

**Especially tell your healthcare provider** if you take medicines that prevent blood clots.

**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.
- AYVAKIT is usually taken 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.
- Your skin may be sensitive to the sun or other forms of light (photosensitivity) during treatment with AYVAKIT. Avoid or limit exposure to direct sunlight, sunlamps, and other sources of ultraviolet radiation during treatment and for 1 week after stopping treatment with AYVAKIT. Use sunscreen or wear clothes that cover your skin if you need to be out in the sun.

**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, nausea, vomiting, vision changes, drowsiness, dizziness, confusion, or severe weakness on one or more side of your body. Bleeding in the brain has not been seen in people treated with AYVAKIT for ISM.

  If you have AdvSM, your healthcare provider will check your platelet counts before and during treatment with AYVAKIT.
- **Cognitive effects.** Cognitive side effects can happen during treatment 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
- **Skin sensitivity to sunlight (photosensitivity)**. See **"What should I avoid while taking AYVAKIT?"**

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

- fluid retention or swelling
- nausea
- tiredness or weakness
- trouble thinking
- 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 or weakness
- changes in certain blood tests

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

- swelling around your eyes
- dizziness
- swelling of your arms and legs
- flushing

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 males. 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: May/2023

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 212608Orig1s013

# SUMMARY REVIEW

# Integrated Review

**Table 1. Application Information**

| | |
|---|---|
| **Application type** | Efficacy Supplement |
| **Application number(s)** | 212608/S-013 |
| **Priority or standard** | Priority |
| **Submit date(s)** | 11/22/2022 |
| **Received date(s)** | 11/22/2022 |
| **PDUFA goal date** | 5/22/2023 |
| **Division/office** | Division of Nonmalignant Hematology (DNH) |
| **Review completion date** | Electronic Stamp |
| **Established/proper name** | Avapritinib |
| **Proprietary name** | AYVAKIT® |
| **Pharmacologic class** | tyrosine kinase inhibitor |
| **Other product name(s)** | N/A |
| **Applicant** | BLUEPRINT MEDICINES CORP |
| **Dosage form(s)/formulation(s)** | TABLET |
| **Dosing regimen** | 25 mg orally once daily |
| **Applicant-proposed indication(s)/ population(s)** | The treatment of adult patients with indolent systemic mastocytosis (ISM) |
| **SNOMED CT code for proposed indication disease term(s)[1]** | Click or tap to enter text. |
| **Regulatory action** | Approval |
| **Approved dosage (if applicable)** | 25 mg orally once daily |
| **Approved indication(s)/ population(s) (if applicable)** | For the treatment of adult patients with indolent systemic mastocytosis (ISM) |
| **SNOMED CT code for approved indication disease term(s)1** | Click or tap to enter text. |

[1] For internal tracking purposes only.
Abbreviations: ISM, indolent systemic mastocytosis; PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

## Table of Contents

Table of Tables ..... v
Table of Figures ..... viii
Glossary ..... x
I. Executive Summary ..... 12
1. Summary of Regulatory Action ..... 12
2. Benefit-Risk Assessment ..... 14
2.1. Benefit-Risk Framework ..... 14
2.2. Conclusions Regarding Benefit-Risk ..... 17
II. Interdisciplinary Assessment ..... 18
3. Introduction ..... 18
3.1. Review Issue List ..... 20
3.1.1. Key Efficacy Review Issues ..... 20
3.1.1.1. Prespecified Primary Analysis Population for the Primary Endpoint Was Not Based on the Intent-to-Treat Population ..... 20
3.1.1.2. Fitness for Purpose of ISM-SAF To Support the Primary and Key Secondary Efficacy Endpoints ..... 20
3.1.1.3. Clinical Meaningfulness of ISM-SAF TSS for the Primary and Key Secondary Efficacy Endpoints ..... 20
3.1.2. Key Safety Review Issues ..... 20
3.1.2.1. Risk of Intracranial Hemorrhage ..... 20
3.2. Approach to the Clinical Review ..... 20
4. Patient Experience Data ..... 22
5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology ..... 23
5.1. Nonclinical Assessment of Potential Effectiveness ..... 23
5.2. Clinical Pharmacology/Pharmacokinetics ..... 25
6. Efficacy (Evaluation of Benefit) ..... 27
6.1. Assessment of Dose and Potential Effectiveness ..... 27
6.2. Clinical Studies Intended to Demonstrate Efficacy ..... 27
6.2.1. Study BLU-285-2203 (Study 2203) ..... 27
6.2.1.1. Design, Study ..... 27
6.2.1.2. Statistical Analysis Plan, Study 2203 Part 2 ..... 32
6.2.1.3. Results of Analyses, Study 2203 Part 2 ..... 36
6.3. Key Efficacy Review Issues ..... 49
6.3.1. Prespecified Primary Analysis Population for the Primary Endpoint Was Not Based on the Intent-to-Treat Population ..... 49

6.3.2. Fitness for Purpose of ISM-SAF To Support the Primary and Key Secondary Efficacy Endpoints....50
6.3.3. Clinical Meaningfulness of ISM-SAF TSS for the Primary and Key Secondary Efficacy Endpoints....53
7. Safety (Risk and Risk Management)....63
7.1. Potential Risks or Safety Concerns Based on Nonclinical Data....63
7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors....64
7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience....64
7.3.1. Adverse Events Identified in Postmarket Experiences....64
7.3.2. Expectations on Safety....65
7.3.3. Additional Safety Issues From Other Disciplines....65
7.4. FDA Approach to the Safety Review....65
7.5. Adequacy of the Clinical Safety Database....66
7.6. Safety Results....67
7.6.1. Safety Results, Study 2203....67
7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Pooled Analyses....67
7.6.1.2. Deaths, Study 2203....69
7.6.1.3. Serious Treatment-Emergent Adverse Events, Study 2203....69
7.6.1.4. Adverse Events Leading to Treatment Discontinuation, Study 2203....73
7.6.1.5. Treatment-Emergent Adverse Events, Study 2203....77
7.6.1.6. Laboratory Findings....89
7.6.1.7. Assessment of Drug-Induced Liver Injury, Study 2203....91
7.6.1.8. Vital Signs Analyses, Study 2203....92
7.6.1.9. Subgroup Analyses, Study2203....95
7.7. Key Safety Review Issues....96
7.7.1. Risk of Intracranial Hemorrhage....96
8. Therapeutic Individualization....97
8.1. Intrinsic Factors....97
8.2. Extrinsic Factors....98
8.3. Plans for Pediatric Drug Development....98
8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential....99
9. Product Quality....100
9.1. Device or Combination Product Considerations....100

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review ....100
11. Advisory Committee Summary ....100
III. Additional Analyses and Information ....100
12. Summary of Regulatory History ....100
13. Pharmacology Toxicology ....101
13.1. Summary Review of Studies Submitted With the Investigational New Drug Application ....101
13.2. Individual Reviews of Studies Submitted With the New Drug Application ....101
14. Clinical Pharmacology ....109
14.1. In Vitro Studies ....109
14.2. In Vivo Studies ....109
14.3. Bioanalytical Method Validation and Performance ....110
14.4. Immunogenicity Assessment—Impact of Pharmacokinetic/Pharmacodynamic, Efficacy, and Safety ....112
14.5. Pharmacometrics Assessment ....112
14.6. Pharmacogenetics ....128
15. Study Design ....128
16. Efficacy ....136
16.1. Patient-Reported Outcome Instruments for Primary and Key Secondary Efficacy Endpoints ....137
16.1.1. ISM-SAF ....137
16.1.2. Anchor Scales Used for Evaluation of Meaningful Within-Subject Score Change ....141
17. Clinical Safety ....142
18. Clinical Virology ....146
19. Clinical Microbiology ....147
20. Mechanism of Action/Drug Resistance ....147
21. Other Drug Development Considerations ....147
22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections) ....147
23. Labeling: Key Changes and Considerations ....148
23.1. Approved Labeling Types ....149
24. Postmarketing Requirements and Commitments ....150
25. Financial Disclosure ....150
26. References ....150
27. Review Team ....152
27.1. Reviewer Signatures ....152

## Table of Tables

Table 1. Application Information ....i
Table 2. Benefit-Risk Framework....14
Table 3. Pharmacologic Therapies Used Off-Label for Symptomatic Treatment of ISM ....19
Table 4. Clinical Trials Submitted[1] in Support of Efficacy and Safety Determinations for Avapritinib ....21
Table 5. Patient Experience Data Submitted or Considered....22
Table 6. Summary of Clinical Pharmacology and Pharmacokinetics....25
Table 7. BSC Medications ....31
Table 8. Subject Disposition, Study BLU-285-2203 Part 2—Intent-to-Treat Population ....37
Table 9. Demographic and Baseline Characteristics, Study BLU-285-2203 Part 2—Intent-to-Treat Population....37
Table 10. Additional Baseline Characteristics, Study BLU-285-2203 Part 2—Intent-to-Treat Population ....38
Table 11. Analyses Results for the Primary Endpoint (Mean Change in TSS), Study BLU-285-2203 Part 2 ....41
Table 12. Analyses Results for the Applicant's Proposed Key Secondary Endpoints, Study BLU-285-2203 Part 2—Intent-to-Treat Population ....47
Table 13. Analyses Results for the Applicant's Proposed Key Secondary Endpoints, Study BLU-285-2203 Part 2—Per-Protocol Population....48
Table 14. Summary of Proposed Anchor Scales for ISM-SAF ....56
Table 15. 1-Category and 2-Category Improvement on the PGIS Scale ....58
Table 16. Category Change (n [%]) in the PGIS Scale From Baseline to C7D1 by Baseline PGIS Category, Study BLU-285-2203 Part 2 ....58
Table 17. Absolute Change From Baseline to C7D1 in the ISM-SAF TSS by Baseline PGIS for Subjects Who Achieved a 1-Category Improvement on PGIS, Study BLU-285-2203 Part 2 ....60
Table 18. Absolute Change From Baseline to C7D1 in the ISM-SAF TSS by Baseline PGIS for Subjects Who Achieved a 2-Category Improvement on PGIS Scale, Study BLU-285-2203 Part 2 ....60
Table 19. Percent Change From Baseline to C7D1 in the ISM-SAF TSS by Baseline PGIS for Subjects Who Achieved a 1-Category Improvement on the PGIS Scale, Study BLU-285-2203 Part 2 ....62

Table 20. Percent Change From Baseline to C7D1 in the ISM-SAF TSS by Baseline PGIS for Subjects Who Achieved a 2-Category Improvement on the PGIS Scale, Study BLU-285-2203 Part 2 ....63

Table 21. Duration of Exposure, Safety Population, Study BLU-285-2203 Overall (Parts 1/2/3)....66

Table 22. Duration of Exposure, Safety Population, Study BLU-285-2203 Part 2....67

Table 23. Overview of Adverse Events, Safety Population, Study BLU-285-2203 Part 2....67

Table 24. Overview of Adverse Events, Safety Population, Study BLU-285-2203 Overall (Parts 1/2/3)....68

Table 25. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Study BLU-285-2203 Part 2 ....69

Table 26. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Study BLU-285-2203 Overall (Parts 1/2/3)....71

Table 27. Subjects With Serious Adverse Events by System Organ Class, FDA Medical Query (Narrow), and Preferred Term, Occurring in at Least 2% of Subjects in Any Arm, Safety Population, Study BLU-285-2203 Overall (Parts 1/2/3) ....73

Table 28. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Study BLU-285-2203 Part 2 ....74

Table 29. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class, FDA Medical Query (Narrow), and Preferred Term, Safety Population, Study BLU-285-2203 Part 2....74

Table 30. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Study BLU-285-2203 Overall (Parts 1/2/3)....75

Table 31. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class, FDA Medical Query (Narrow), and Preferred Term, Safety Population, Study BLU-285-2203 Overall (Parts 1/2/3) ....76

Table 32. Subjects With Common Adverse Events Occurring at ≥2% Frequency, Safety Population, Study BLU-285-2203 Part 2....77

Table 33. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Study BLU-285-2203 Part 2....79

Table 34. Grouped Queries, Safety Population, Study BLU-285-2203 Part 2 ....81

Table 35. Adverse Reactions Occurring in Avapritinib-Treated Subjects With Indolent Systemic Mastocytosis During PIONEER Study....84

Table 36. Subjects With Common Adverse Events Occurring at ≥2% Frequency, Safety Population, Study BLU-285-2203 Overall (Parts 1/2/3) ....85

Table 37. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Study BLU-285-2203 Overall (Parts 1/2/3) .....87

Table 38. Overview of Adverse Events by Demographic Subgroup, Safety Population, Study BLU-285-2203 Part 2 .....95

Table 39. Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation .....99

Table 40. Study Summary of 26-Week Oral Carcinogenicity Study in CByB6F1/Tg rasH2 Hemizygous Mice.....101

Table 41. Study Methods of 26-Week Oral Carcinogenicity Study in CByB6F1/Tg rasH2 Hemizygous Mice.....102

Table 42. Survival Rate (%) After 26-Week Dosing of AYVAKIT in Main Study .....103

Table 43. Summary of Unscheduled Deaths of Main Study .....103

Table 44. Cause of Death and Notable Clinical Findings in Early Decedents .....104

Table 45. Organ Weight Changes (% Difference Compared to Controls) After 26-Week Dosing of Avapritinib .....105

Table 46. Tumor Types With Statistically Significant (P<0.05) Dose Response Relationships or Pairwise Comparisons of Treated Groups and Controls in Male Mice .....106

Table 47. Tumor Types With Statistically Significant (P<0.05) Dose Response Relationships or Pairwise Comparisons of Treated Groups and Controls in Female Mice .....107

Table 48. Microscopic Findings After 26-Week Dosing of Avapritinib .....107

Table 49. Toxicokinetics Parameters After AYVAKIT Dosing on Days 1 and 182.....108

Table 50. Summary of Plasma Unbound Avapritinib Pharmacokinetic Parameters Following a Single Oral Dose of Avapritinib 100 mg in Subjects With Severe Hepatic Impairment and in Matched Control Subjects With Normal Hepatic Function, Study BLU-285-0107 .....110

Table 51. Validation Summary for Determination of Avapritinib in Human Plasma, Study (b) (4)-1963 .....111

Table 52. Summary of Studies Included in the Population PK Analysis .....113

Table 53. Categorical Covariates for All Subjects in the Population PK Development Dataset.....114

Table 54. Continuous Demographic Covariates for All Subjects in the Population PK Development Dataset .....114

Table 55. Schematic of the Developed Population PK Model for Avapritinib .....119

Table 56. Summary of Model Predicted Exposure Metrics for Subjects, Study BLU-285-2203 Part 2 C1D15 .....121

Table 57. Study Schedule, Study 2203 Part 1.....129

Table 58. Study Schedule, Study 2203 Part 2 ..... 133
Table 59. WHO SM Criteria ..... 136
Table 60. Conceptual Framework for ISM-SAF ..... 137
Table 61. Subjects With Adverse Events by System Organ Class, Safety Population, Study BLU-285-2203 Part 2 ..... 143
Table 62. Listing of Subjects With Adverse Events Leading to Treatment Discontinuation From Study Drug, Safety Population, Study BLU-285-2203 Part 2 ..... 144
Table 63. Treatment-Emergent Adverse Events Leading to Drug Modification ..... 145
Table 64. Key Labeling Changes and Considerations ..... 148
Table 65. Covered Clinical Studies: Study BLU-285-2203 ..... 150
Table 66. Reviewers of Integrated Assessment ..... 152
Table 67. Additional Reviewers of Application ..... 152

## Table of Figures

Figure 1. Mechanism of Action of Avapritinib for Treatment of Advanced Systemic Mastocytosis ..... 23
Figure 2.Schematic of Mechanism of Action of Tyrosine Kinase Inhibitor Drug Class Approved by FDA for GIST Including AYVAKIT ..... 24
Figure 3. Design, Study 2203 ..... 29
Figure 4. Mean Change in ISM-SAF TSS From Baseline to C7D1 With the MCMC Imputation, Study BLU-285-2203 Part 2—Intent-to-Treat Population ..... 42
Figure 5. Tipping Point Analyses for the Primary Endpoint, Ranged -25 to -15 in the Avapritinib 25-mg Arm, Study BLU-285-2203 Part 2—Intent-to-Treat Population ..... 43
Figure 6 Tipping Point Analyses for the Primary Endpoint, Ranged 15 to 25 in the Placebo Arm, Study BLU-285-2203 Part 2—Intent-to-Treat Population ..... 43
Figure 7. Histogram of the Mean Change in ISM-SAF TSS From Baseline to C7D1, Study BLU-285-2203 Part 2 ..... 45
Figure 8. Forest Plot of Mean Change From Baseline in ISM-SAF TSS at C7D1 Across Subgroups, Study BLU-285-2203 Part 2 ..... 46
Figure 9. eCDF, Baseline ISM-SAF TSS by PGIS Category at Baseline, Study BLU-285-2203 Part 2 ..... 57
Figure 10. eCDF, Absolute Change From Baseline to C7D1 in the ISM-SAF TSS by PGIS Category of Change From Baseline, Study BLU-285-2203 Part 2 ..... 59
Figure 11. eCDF, Change in the ISM-SAF TSS From Baseline to C7D1 by Treatment Arm, Study BLU-285-2203 Part 2 ..... 61

Figure 12. eCDF, Percent Change From Baseline to C7D1 in the ISM-SAF TSS by PGIS Category of Change From Baseline, Study BLU-285-2203 Part 2 .....62

Figure 13. Mean Laboratory (Kidney Function) Data Change From Baseline Over Time, Safety Population, Study BLU-285-2203 Part 2 .....90

Figure 14. Mean Laboratory (Hematology) Data Change From Baseline Over Time, Safety Population, Study BLU-285-2203 Part 2 .....91

Figure 15. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Study BLU-285-2203 Overall (Parts 1/2/3) .....92

Figure 16. Mean and 95% Confidence Interval of Systolic Blood Pressure Over Time by Treatment Arm, Safety Population, Study BLU-285-2203 Overall (Parts 1/2/3) ..93

Figure 17. Mean and 95% Confidence Interval of Diastolic Blood Pressure Over Time by Treatment Arm, Safety Population, Study BLU-285-2203 Overall (Parts 1/2/3) .....94

Figure 18. Mean and 95% Confidence Interval of Pulse Rate Over Time by Treatment Arm, Safety Population, Study BLU-285-2203 Overall (Parts 1/2/3) .....95

Figure 19. Model Development Flowchart .....115

Figure 20. Schematic of the Developed Population PK Model for Avapritinib .....116

Figure 21. Goodness-of-Fit Plots and CWRES Plots for Final Population PK Model ...117

Figure 22. pvcVPC for the Final Population PK Model: Subjects With ISM (C1D1 & C1D15) .....118

Figure 23. Model Predicted Effect of Covariates on $AUC_{0\text{-}tau,ss}$ and $C_{max,ss}$ .....120

Figure 24. Study Design for BLU-285-2203 .....122

Figure 25. $C_{ave}$ by Treatment Arm .....123

Figure 26. ΔTSS vs. $C_{ave}$ and Model Diagnostic Plots .....124

Figure 27. TSS Change From Baseline Versus Dose .....125

Figure 28. ≥50% Reduction in TSS and Serum Tryptase From Baseline Versus $C_{ave}$ ....126

Figure 29. Grade ≥1 Edema Versus $C_{ave}$ .....127

Figure 30. Copy of Indolent Systemic Mastocytosis Symptom Assessment Form .....138

Figure 31. Patient Global Impression of Symptom Severity .....141

Figure 32. Patient Global Impression of Change .....142

# Glossary

| | |
|---|---|
| AdvSM | advanced systemic mastocytosis |
| AE | adverse event |
| AML | acute myeloid leukemia |
| ANCOVA | analysis of covariance |
| AR | adverse reaction |
| ASM | aggressive systemic mastocytosis |
| AUC | area under the concentration-time curve |
| BM | bone marrow |
| BMMC | bone marrow mast cell |
| BSC | best supportive care |
| $C_{max}$ | maximum plasma concentration |
| eCDF | empirical cumulative distribution function |
| E-R | exposure-response |
| FDA | Food and Drug Administration |
| FMQ | Food and Drug Administration Medical Dictionary for Regulatory Activities query |
| GIST | gastrointestinal stromal tumor |
| GLP-1 | glucagon-like peptide-1 |
| ICH | intracranial hemorrhage |
| IND | investigational new drug |
| ISM | indolent systemic mastocytosis |
| ITT | intent-to-treat |
| LOU | Limitation of Use |
| MAR | missing at random |
| MCL | mast cell leukemia |
| MCMC | Markov chain Monte Carlo |
| mITT | modified intent-to-treat |
| NDA | new drug application |
| NME | new molecular entity |
| OPQ | Office of Pharmaceutical Quality |
| OSI | Office of Scientific Investigations |
| PBRER | Periodic Benefit-Risk Evaluation Report |
| PDGFRA | platelet-derived growth factor receptor alpha |
| PGIC | Patient's Global Impression of Change |
| PGIS | Patient's Global Impression of Symptom Severity |
| PI | Prescribing Information |
| PK | pharmacokinetic |
| PMR | postmarketing requirement |
| PP | per protocol |
| PRO | patient-reported outcome |
| QD | once daily |
| RP2D | recommended Phase 2 dose |
| SAE | serious adverse event |

| | |
|---|---|
| SAF | symptom assessment form |
| SAP | statistical analysis plan |
| SM | systemic mastocytosis |
| SM-AHN | systemic mastocytosis with an associated hematologic neoplasm |
| SSM | smoldering systemic mastocytosis |
| TEAE | treatment-emergent adverse event |
| TKI | tyrosine kinase inhibitor |
| TSS | total symptom score |
| ULN | upper limit of normal |
| WHO | World Health Organization |

# I. Executive Summary

## 27. Summary of Regulatory Action

On November 22, 2022, Blueprint Medicines submitted NDA 212608 Supplement 0013 for avapritinib for the following indication: AYVAKIT® is a kinase inhibitor indicated for the treatment of adult patients with Indolent Systemic Mastocytosis (ISM). This application was reviewed by a multidisciplinary team. This application was given priority review because the proposed indication addresses an unmet medical need of a treatment for patients with ISM, a serious disease for which there are no approved therapies. Previously, on January 9, 2020, avapritinib was granted marketing approval 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. Also, on June 16, 2021, avapritinib was approved 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).

On January 21, 2016, avapritinib received orphan designation for the treatment of mastocytosis. On December 23, 2020, avapritinib received breakthrough therapy designation for the treatment of ISM.

This sNDA was primarily based on as single adequate and well controlled trial, Study BLU-285-2203 (Study 2203). Study 2203 was a multicenter, randomized, double-blind, placebo-controlled study in patients with symptomatic ISM despite receiving best supportive care (BSC). This study demonstrated that avapritinib in combination with BSC improves signs and symptoms of ISM based on a novel patient-reported outcome (PRO) measurement tool, the Indolent Systemic Mastocytosis-Symptom Assessment Form (ISM-SAF) total symptom score (TSS). The ISM-SAF measurement tool is made up of a 12-item questionnaire developed specifically to assess ISM signs and symptoms (abdominal pain, nausea, diarrhea, spots, itching, flushing, bone pain, fatigue, dizziness, headache, brain fog). The review team concluded that the ISM-SAF is fit for purpose and the results are representative of a clinically meaningful within-subject improvement.

Clinical, clinical pharmacology, statistical, nonclinical, and clinical outcomes assessment review teams all support approval of avapritinib for the proposed indication. The clinical data package for the ISM indication and supportive prior evidence of safety and effectiveness of the drug for the treatment of patients with AdvSM demonstrates that avapritinib has met the evidentiary bar for substantial evidence of effectiveness. The overall benefit-risk is favorable as described in the Benefit-Risk Framework table below. For detailed information supporting the basis for this approval, please refer to the detailed reviews included in this Interdisciplinary Assessment document.

Of note, this sNDA submission also fulfills postmarketing requirement (PMR) 3781-3; to complete a pharmacokinetic trial to determine an appropriate dose of avapritinib in patients with severe hepatic impairment in accordance with the FDA Guidance for Industry titled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis,

and Impact on Dosing and Labeling" found at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072123.pdf. Labeling was updated accordingly.

APPEARS THIS WAY
ON ORIGINAL

# 28. Benefit-Risk Assessment

## 28.1. Benefit-Risk Framework

**Table 2. Benefit-Risk Framework**

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of condition | • Indolent systemic mastocytosis (ISM) is a rare and chronic disease driven by the KIT D816V mutation, characterized by an abnormal proliferation of mast cells, which are immune cells that play a role in the body's response to allergens and inflammation. The prevalence of ISM is estimated to be approximately 0.8 per 10,000 people. ISM is characterized by a trigger causing inflammatory mediator release by mast cells that then can lead to a variety of symptoms related to an allergic response including anaphylaxis. Patients may experience frequent symptoms including episodes of vasodilation, hypotension, flushing, pruritus, syncope, abdominal pain, nausea, vomiting, diarrhea, fatigue, and headache. | ISM is a rare and chronic disease that can cause a variety of symptoms due to release of inflammatory mediators from mast cells which can greatly impair quality of life. |
| Current treatment options | • There are no approved therapies for the treatment of ISM. Patients are counseled to avoid triggers that may result in symptoms. Otherwise, symptoms are controlled with supportive care treatments, e.g., H1 and H2 antihistamines, antileukotrienes, cromolyn sodium, and the anti-IGE antibody omalizumab. Epinephrine is recommended for anaphylaxis. Most patients often have to receive multiple therapies to control symptoms. | There is an unmet medical need for an effective treatment for patients with ISM. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Benefit | • Study BLU-285-2203 was a randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of avapritinib in combination with BSC to placebo in combination with BSC in subjects with ISM whose symptoms were not adequately controlled by BSC. In total, 141 subjects were randomized to the avapritinib group and 71 subjects were randomized to the placebo group.<br>• Clinically meaningful within-subject improvements in signs and symptoms of ISM based on the ISM-SAF TSS were observed in the avapritinib group. The mean change from baseline to C7D1 in the ISM-SAF TSS was -15.33 for the avapritinib group compared to -9.64 for the placebo group, with a difference of -5.69 (95% CI between -10.16, -1.23 points*)*. Results were statistically significant. Improvement in signs and symptoms of ISM is clinically meaningful for patients who are symptomatic despite receiving BSC.<br>• The proportion of subjects achieving a ≥50% reduction in TSS was 25% (95% CI =17.9, 32.8) in the avapritinib group compared to 10% (95% CI =4.1, 19.3) in the placebo group.<br>• A higher proportion of subjects in the avapritinib group had >50% reduction in serum typtase, >50% reduction in peripheral blood KIT D816V allele fraction, and >50% reduction in bone marrow mast cells, compared to the placebo group, further supporting the efficacy of avapritinib for the treatment of ISM. | The benefit of avapritinib was clearly demonsrated in Study BLU-285-2203, in which avapritinib 25 mg daily in combination with BSC resulted in improved signs and symptoms of ISM as measured by the ISM-SAF TSS, a novel PRO measurement. During the review, the PRO instrument was determined to be fit-for-purpose, and results were consistent with clinically meaningful within patient symptom improvement.<br><br>Substantial evidence of effectivness of avapritinib for the treatment of ISM was based on one adequate and well controlled study, Study BLU 285-2203, and confirmatory evidence. Confirmatory evidence is provided by existing adequate and well-controlled clinical trial data that demonstrated the effectiveness of avapritinib for its other closely related approved indication, AdvSM. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Risk and risk management | • The review of safety focused on Part 2 (randomized, double-blind, placebo-controlled part for 24 weeks) of Study 2203, including 141 subjects in the avapritinib + BSC arm and 71 subjects in the placebo + BSC arm. The pooled analysis of all three parts of Study 2203 was supportive and included 226 subjects with ISM who received at least dose of avapritinib.<br>• The most common ARs (>10% of subjects) were eye edema, dizziness, peripheral edema, and flushing.<br>• Serious AR of pelvic hematoma occurred in one subject (0.7%) who received avapritinib.<br>• Discontinuation due to an AR occurred in one subject (0.7%) who received avapritinib. Dose interruptions due to adverse reactions occurred in 5% of subjects.<br>• Cognitive adverse reactions occurred in 7.8% of subjects with ISM who received avapritinib versus 7.0% of subjects who received placebo.<br>• Although no ICH events were reported among subjects in Study 2203, there is still a potential risk of ICH for subjects with ISM who develop thrombocytopenia with platelet counts below 50 x $10^9$/L for other reasons. | Overall, the safety profile of avapritinib is acceptable for the patients with ISM.<br><br>The Limitation of Use for thrombocytopenia (platelet count below 50 x $10^9$/L) should also apply to patients with ISM as it does for patients with AdvSM. |

Abbreviations: AdvSM, advanced systemic mastocytosis; AR, adverse reaction, BSC, best supportive care; ICH, intracranial hemorrhage, ISM, Indolent systemic mastocytosis, ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form, PRO, patient-reported outcome; TSS, total symptom score

## 28.2. Conclusions Regarding Benefit-Risk

Systemic mastocytosis (SM) is a rare group of disorders characterized by excessive mast cell proliferation and activation driven by the KIT D816V mutation, with accumulation of mast cells in the bone marrow, skin, and other organ sites. ISM is defined by the World Health Organization (WHO) as meeting the definition of SM but without evidence of associated clonal hematological nonmast cell lineage disease or any C-findings (see Table 59 for WHO diagnostic criteria). Despite being described as indolent, patients with ISM can be highly symptomatic, which can greatly impact quality of life. Patients have episodic and/or persistent symptoms related to mast cell activation, including anaphylaxis, hypotension, flushing, pruritus, syncope, abdominal pain, nausea, vomiting, diarrhea, fatigue among others.

There are no approved therapies for ISM, and treatment is typically aimed at prevention of triggers of anaphylaxis and symptom control with over-the-counter medications, including antihistamines.

Avapritinib, a tyrosine kinase inhibitor addresses an unmet medical need for patients by targeting the underlying driver of ISM thus decreasing signs and symptoms of ISM. This was clearly demonstrated in Study BLU-285-2203, an international, multicenter, randomized, double-blinded, placebo-controlled trial in which 141 subjects received avapritinib 25 mg daily in combination with BSC and 71 subjects received placebo in combination with BSC. Clinically meaningful within-subject improvement in signs and symptoms of ISM based on the ISM-SAF TSS were observed in the avapritinib in combination with BSC group. The mean change from baseline to C7D1 in the ISM-SAF TSS was -15.33 for the avapritinib group compared to -9.64 for the placebo group; the difference from placebo was statistically significant.

Overall, the safety profile of avapritinib 25 mg daily in Study BLU-285-2203 appears to be similar to the safety profile of avapritinib described in the approved product label for the AdvSM indication. Although no intracranial hemorrhage (ICH) events were reported among subjects in Study 2203 there is still a potential risk of ICH for patients with ISM who have thrombocytopenia for other reasons. The Limitation of Use (LoU) for thrombocytopenia (platelet count below 50 x 109/L) should also apply to patients with ISM as it does for patients with AdvSM receiving avapritinib therapy.

In summary, sNDA 212608, AYVAKIT (avapritinib), provided substantial evidence of effectiveness based on data from the clinical study BLU-285-2203 and confirmatory evidence provided from the prior approval of AdvSM. Overall, the benefit-risk profile was favorable, and risks can be adequately addressed in labeling, with a LoU included for a platelet count below 50 x 109/L. Therefore, the review team recommends the approval of avapritinib for the treatment of ISM.

# II. Interdisciplinary Assessment

## 29. Introduction

**Product Introduction**

Avapritinib (propriety name, AYVAKIT®), is a small molecule, orally bioavailable, 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 is currently approved for the treatment of adults with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations and for the treatment of adults with AdvSM.

The Applicant proposes the following new indication: the treatment of adult patients with ISM.

The proposed dosing regimen of avapritinib is 25-mg orally, once daily in patients with ISM.

**Disease Background**

Mastocytosis results from a clonal proliferation of morphologically and immunophenotypically abnormal mast cells due to a mutation of the KIT D816 V allele. With the 2016 revision of the World Health Organization (WHO) classification of myeloid neoplasms, mastocytosis is now considered a distinct disease category (Pardanani 2019). Systemic mastocytosis (SM) is comprised of five clinical subtypes, i.e., indolent systemic mastocytosis (ISM), smoldering systemic mastocytosis (SSM), aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematologic neoplasm (SM-AHN) and mast cell leukemia (MCL).

ISM is a rare condition characterized by an abnormal proliferation of mast cells, which are immune cells that play a role in the body's response to allergens and inflammation. The WHO defines ISM as meeting criteria for systemic mastocytosis (SM), with no "C" findings and without evidence of associated hematological neoplasm (refer to Table 59 for WHO diagnostic criteria). ISM is a rare and chronic disease that has a prevalence of approximately 1 in 100,000 people. ISM accounts for approximately 70% of all cases of systemic mastocytosis (SM) and about 3% of patients with ISM will progress to advanced systemic mastocytosis (Mikkelsen et al. 2014). Less than 1% of patients with ISM have transformation to the leukemic subtype (Pardanani 2013). Patients typically present in adulthood with a median age of onset around 49 years (Pardanani 2019). Patients with ISM usually have a normal life expectancy. ISM is characterized by a trigger causing inflammatory mediator release by mast cells. Triggers include heat and humidity, emotional and physical stress, alcohol, medications (e.g., aspirin, opioid analgesics, radiocontrast agents) (Pardanani 2013). Common symptoms experienced by patients with ISM include vasodilation, hypotension, flushing, pruritus, syncope, abdominal pain, nausea, vomiting, diarrhea, fatigue, and headache. Patients can be highly symptomatic, greatly impairing quality of life. Patients are also at increased risk for osteopenia and osteoporosis. Morbidity is often due to anaphylaxis which can be triggered by a variety of factors, including hymenoptera envenomation.

## Current Therapy Options

There is currently no approved therapy for ISM. The standard therapy for ISM depends on the individual's symptoms and the severity of their condition along with avoiding triggers of mast cell degranulation. In some cases, symptoms can be managed with over-the-counter antihistamines and avoidance of triggers. Currently, ISM symptoms are controlled with supportive care treatments, e.g., H1 and H2 antihistamines, antileukotrienes, cromolyn sodium and the anti-IGE antibody omalizumab (see Table 3). Anaphylaxis should be promptly treated with epinephrine (Pardanani 2013).

Imatinib (Gleevec®) approved April 18, 2003, under NDA 21588 and midostaurin (Rydapt®) approved for marketing on April 28, 2017, under NDA 207997 are two orally administered tyrosine kinase inhibitors that are indicated for the advanced systemic mastocytosis (AdvSM) subtypes. Specifically, imatinib is indicated for the treatment of adult patients with ASM without D816V c-Kit mutation determined with an FDA-approved test or with c-Kit mutational status unknown. Midostaurin is indicated for the treatment of adult patients with ASM, SM-AHN and MCL. Imatinib and midostaurin have both been reported used off-label for the treatment of ISM in patients who were refractory to other supportive treatments (Alvarez-Twose et al. 2017; van Anrooij et al. 2018).

**Table 3. Pharmacologic Therapies Used Off-Label for Symptomatic Treatment of ISM**

| Symptom<br>Treatment Line | Drug Class |
|---|---|
| Pruritus/flushing | |
| 1st line | H1-antagonist |
| 2nd line | Leukotriene antagonist |
| 3rd line | Nonsteroidal anti-inflammatory drug |
| 4th line | PUVA photochemotherapy |
| Abdominal pain, cramping, diarrhea, heartburn, nausea, vomiting | |
| 1st line | H2-antagonist |
| 2nd line | Proton pump inhibitor |
| 3rd line | Sodium cromolyn |
| 4 h line | corticosteroid |
| Headache, cognitive impairment, depression | |
| 1st line | H1-antagonist and H2-antagonist |
| 2nd line | Sodium cromolyn |
| Recurrent hypotension | |
| 1st line | Epinephrine |
| 2nd line | H1-antagonist and H2-antagonist |
| 3rd line | Corticosteroid |
| 4 h line | Cytoreductive therapy (interferon-α or 2-chlorodeoxyadenosine) |
| Osteoporosis | |
| 1st line | Bisphosphonate |
| 2nd line | Cytokine/ immunomodulatory drug |
| 3rd line | Purine nucleoside analog |

Source: Pardanani (2019)
Abbreviations: ISM, indolent systemic mastocytosis; N/A, not applicable; PUVA, Psolaren plus ultraviolet A

# 29.1. Review Issue List

## 29.1.1. Key Efficacy Review Issues

### 29.1.1.1. Prespecified Primary Analysis Population for the Primary Endpoint Was Not Based on the Intent-to-Treat Population

### 29.1.1.2. Fitness for Purpose of ISM-SAF To Support the Primary and Key Secondary Efficacy Endpoints

### 29.1.1.3. Clinical Meaningfulness of ISM-SAF TSS for the Primary and Key Secondary Efficacy Endpoints

## 29.1.2. Key Safety Review Issues

### 29.1.2.1. Risk of Intracranial Hemorrhage

# 29.2. Approach to the Clinical Review

This is a joint review. Andrew Dmytrijuk and Carrie Diamond focused on the safety and efficacy data. The Statistical team, Huan Wang and Yeh-Fong Chen focused on the efficacy data. The Patient-Focused Statistical Support team, Weimeng Wang and Lili Garrard focused on efficacy data. The Clinical Outcome Assessment team, Qing Xie and Selena Daniels focused on the efficacy data. The Clinical Data Scientist team, Adam Horin and Qunshu Zhang, focused on the supportive safety. Bo Lee and Pedro DelValle reviewed the nonclinical toxicology studies, and Anusha Ande and Doanh Tran reviewed the clinical pharmacology data.

**Table 4. Clinical Trials Submitted[1] in Support of Efficacy and Safety Determinations for Avapritinib**

| Trial Identifier | Trial Population | Trial Design | Regimen (Number Treated), Duration | Primary and Key Secondary Endpoints | No. of Patients Planned; Actual Randomized | No. of Centers and Countries |
|---|---|---|---|---|---|---|
| BLU-285-2203 | Adults with ISM | Control Type:<br>Part 1: Placebo-controlled<br>Part 2: Placebo-controlled<br>Part 3: No treatment concurrent (Single-arm)<br><br>Randomization:<br>Part 1: 1:1:1:1 Randomization (25 mg, 50 mg, 100 mg, or placebo)<br>Part 2: 2:1 Randomization (25 mg or placebo)<br>Part 3: No randomization (Single-arm)<br><br>Blinding:<br>Part 1: Double-blinded<br>Part 2: Double-blinded<br>Part 3: Open-label<br><br>Biomarkers: No biomarkers<br><br>Innovative design features: None | Drug (established name):<br>Avapritinib<br><br>Dose:<br>Part 1: 25, 50, or 100 mg<br>Part 2: 25 mg<br>Part 3: 25 mg<br><br>Number treated:<br>Part 1:<br>25 mg (N=10)<br>50 mg (N=10)<br>100 mg (N=10)<br>Placebo (N=9)<br>Part 2:<br>25 mg (N=141)<br>Placebo (N=71)<br>Part 3:<br>25 mg (N=235)<br>(Rollover from Part 2, N=201; Rollover from Part 1, N=34)<br><br>Duration (quantity and units):<br>Part 1: 12 weeks<br>Part 2: 24 weeks<br>Part 3: up to 5 years | Primary:<br>Part 2: The mean change in Indolent Systemic Mastocytosis-Symptom Assessment Form (ISM-SAF) total symptom score (TSS) from baseline to cycle 7 day 1 (C7D1), compared to placebo.<br><br>Secondary:<br>Part 2 Only:<br>• The proportion of avapritinib-treated patients with ISM with a ≥50% reduction in serum tryptase from baseline to C7D1, compared to placebo.<br>• The proportion of avapritinib-treated patients with ISM with a ≥50% reduction in peripheral blood KIT D816V allele fraction from baseline to C7D1 or undetectable (<0.02%) for patients with detectable mutation at baseline, compared to placebo.<br>• The proportion of avapritinib-treated patients with ISM achieving ≥50% reduction in ISM-SAF TSS from baseline to C7D1, compared to placebo.<br>• The proportion of avapritinib treated patients with ISM achieving ≥30% reduction in ISM-SAF TSS from baseline to C7D1, compared to placebo.<br>• The proportion of avapritinib-treated patients with a ≥50% reduction in bone marrow mast cells from baseline to C7D1 or no aggregates for patients with aggregates at baseline, compared to placebo. | Planned:<br>Part 1: 40<br>Part 2: 204<br>Part 3: 244<br><br>Actual:<br>Part 1: 39<br>Part 2: 212<br>Part 3: 235 | Centers: 42<br><br>Countries: 13 |

Source: Clinical Study Report and adsl.xpt
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
Abbreviations: C, cycle; D, day; ISM, indolent systemic mastocytosis; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; RP2D, recommended Phase 2 dose; TSS, total symptom score

# 30. Patient Experience Data

In study BLU-285-2203, the primary and secondary efficacy data were obtained from patient-reported outcomes (PROs) using the Indolent Systemic Mastocytosis-Symptom Assessment Form tool to obtain a total symptom score (TSS) before and after study drug treatment.

Other patient-reported outcomes (PROs) and quality of life (QoL) measures included were the Mastocytosis Quality of Life Questionnaire (MC-QoL), Patient's Global Impression of Symptom Severity (PGIS), 12-item Short Form Health Survey (SF-12), Patient's Global Impression of Change (PGIC), and Five-level EuroQuol 5 Dimension questionnaire (EQ-5D-5L).

**Table 5. Patient Experience Data Submitted or Considered**

| **Data Submitted in the Application - Yes** | | |
|---|---|---|
| **Check if Submitted** | **Type of Data** | **Section Where Discussed, if Applicable** |
| **Clinical Outcome Assessment Data Submitted in the Application** | | Section 32 Efficacy |
| ☒ | Patient-reported outcome | |
| ☐ | Observer-reported outcome | |
| ☐ | Clinician-reported outcome | |
| ☐ | Performance outcome | |
| **Other Patient Experience Data Submitted in the Application** | | |
| ☐ | Patient-focused drug development meeting summary | |
| ☐ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel) | |
| ☐ | Observational survey studies | |
| ☐ | Natural history studies | |
| ☐ | Patient preference studies | |
| ☐ | Other: (please specify) | |
| ☐ | If no patient experience data were submitted by Applicant, indicate here. | |
| **Data Considered in the Assessment (But Not Submitted by Applicant)** | | |
| **Check if Considered** | **Type of Data** | **Section Where Discussed, if Applicable** |
| ☐ | Perspectives shared at patient stakeholder meeting | |
| ☐ | Patient-focused drug development meeting summary report | |
| ☐ | Other stakeholder meeting summary report | |
| ☐ | Observational survey studies | |
| ☐ | Other: (please specify) | |

# 31. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

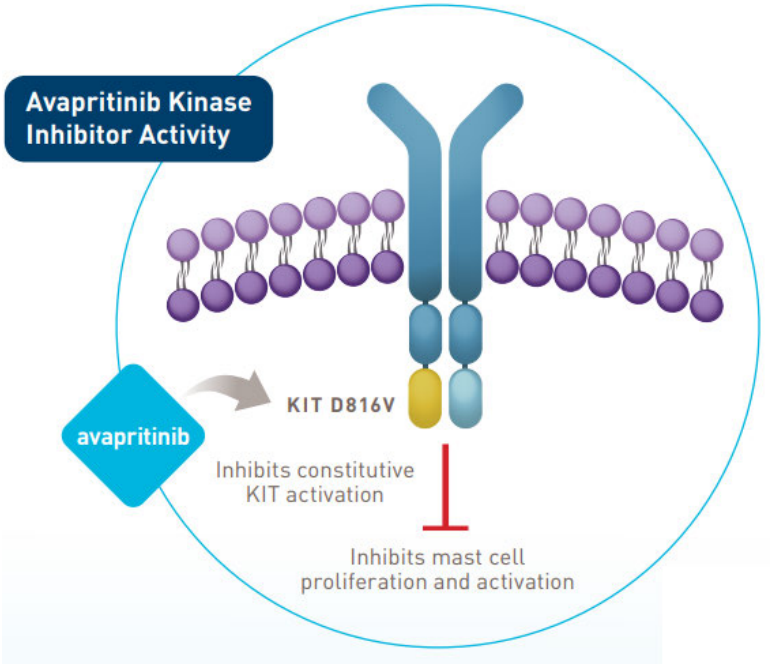
## 31.1. Nonclinical Assessment of Potential Effectiveness

Avapritinib is a tyrosine kinase inhibitor that targets platelet-derived growth factor receptor alpha (PDGFRα), PDGFRα D842 mutants, and other exon 18 mutants, as well as KIT and multiple KIT exon 11, 11/17, and 17 mutants with half maximal inhibitory concentrations ($IC_{50}$) within nanomolar range. See Figure 1 and Figure 2.

The mechanism of action of avapritinib for the indication of ISM remains the same as for the approved indication of advanced systemic mastocytosis (AdSM).

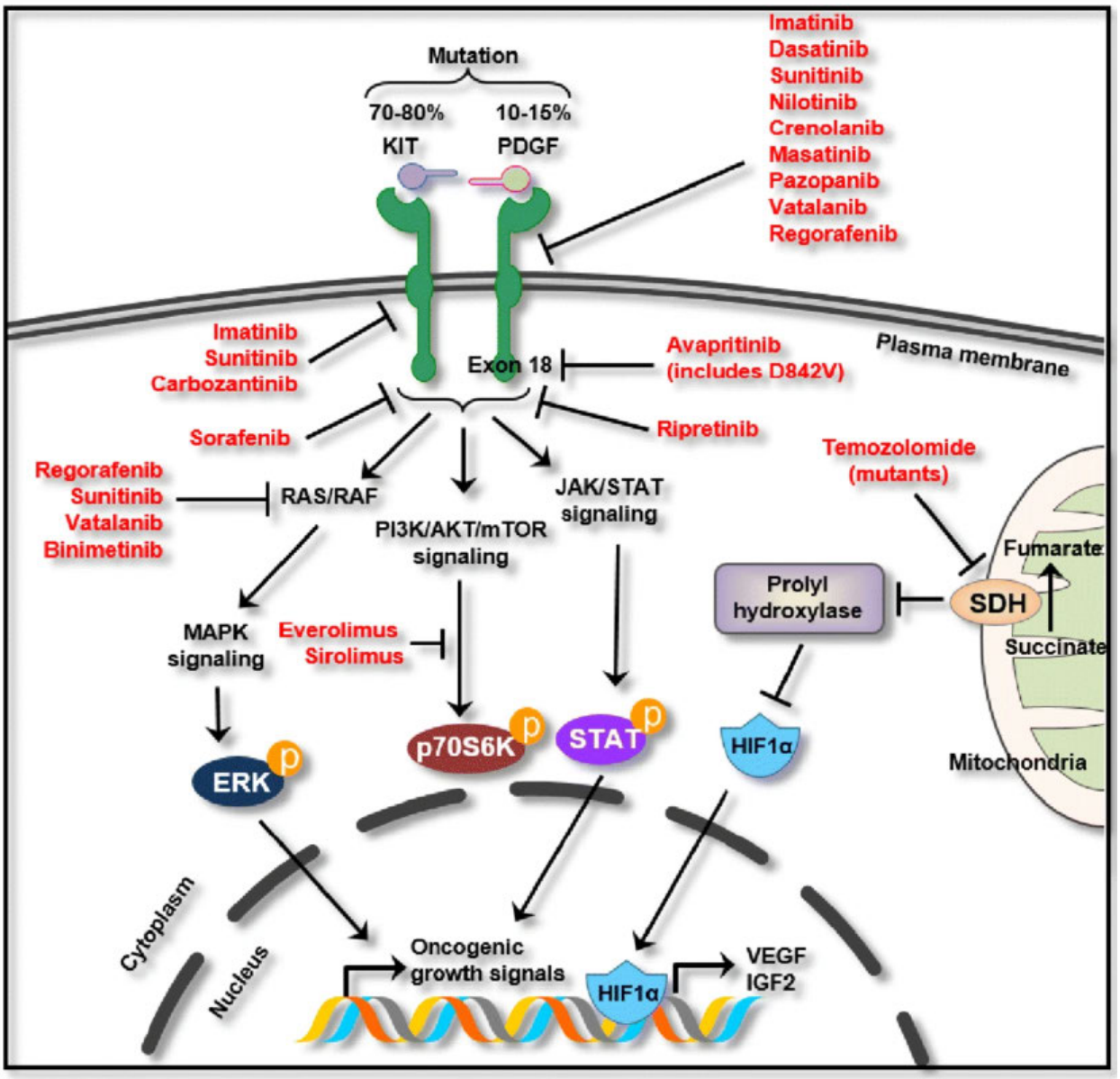
Nonclinical assessment on pharmacology and mechanism of action of avapritinib was previously reviewed and can be found in the integrated multidisciplinary review of the original NDA application.

**Figure 1. Mechanism of Action of Avapritinib for Treatment of Advanced Systemic Mastocytosis**




Source: AYVAKIT promotional material: Adv-SM-Product-Brochure

**Figure 2.Schematic of Mechanism of Action of Tyrosine Kinase Inhibitor Drug Class Approved by FDA for GIST Including AYVAKIT**




Source: Al-Share et al. (2021)
Abbreviations: GIST, gastrointestinal stromal tumor

## 31.2. Clinical Pharmacology/Pharmacokinetics

Please refer to the U.S. Prescribing Information (PI) for AYVAKIT® (avapritinib) along with original NDA multidisciplinary review for NME (DARRTS on June 14, 2019; reference ID: 4543562) and NDA multidisciplinary review for efficacy supplement, S-007 (DARRTS on December 16, 2020; reference ID: 4808725) for details on summary of clinical pharmacology and pharmacokinetics (PK). PK summary of patients with ISM and patients with severe hepatic impairment are included in Table 6 (abbreviated version).

**Table 6. Summary of Clinical Pharmacology and Pharmacokinetics**

| Characteristic | Drug Information |
|---|---|
| | ***Pharmacologic Activity*** |
| Established pharmacologic class (EPC) | Kinase inhibitor |
| | ***General Information*** |
| Bioanalysis | The bioanalytical methods used for determining plasma concentrations of avapritinib and the constituent enantiomers BLU111207 and BLU111208 of the M499 metabolite [redacted] (b) (4) in clinical studies remain unchanged. The performance of the methods was acceptable. |
| Healthy subjects versus patients | In the population PK analysis of avapritinib, patients with ISM were found to have overall exposure comparable to healthy subjects while patients with GIST and AdvSM, in contrast, had reduced bioavailability. |
| Drug exposure at steady state following the therapeutic dosing | Parameter Geo Mean (%CV) at 25 mg QD in patients with ISM<br>$AUC_{0-T,ss}$ 1330 h•ng/mL (49.5%)<br>$C_{max,ss}$ 70.2 ng/mL (47.8%) |
| Range of effective dose(s) or exposure | Avapritinib was studied from 25 to 100 mg QD in patients with ISM. |
| Dose proportionality | In patients with ISM, after single dose and repeat (QD) dosing of avapritinib, systemic exposure was dose proportional over the dose range of 25 to 100 mg. |
| Accumulation | At 25 mg QD, the steady-state geometric mean accumulation ratio (%CV), based on AUC, for avapritinib was 3.59 (54.3%) in patients with ISM. |
| Time to achieve steady-state | Steady state concentrations of avapritinib were reached prior to day 15 following daily dosing. |
| Bridge between to-be-marketed and clinical study formulations | Final formulation was used in pivotal clinical studies. |
| | ***Absorption*** |
| Food effect | The $C_{max}$ of avapritinib was increased by 59% and the $AUC_{0-INF}$ was increased by 29% when AYVAKIT was taken with a high-calorie, high-fat meal compared to those in the fasted state. Patients with ISM in Study BLU-285-2203 were administered avapritinib tablets in the fasted state. |
| Administration | Administer AYVAKIT orally on an empty stomach, at least 1 hour before or 2 hours after a meal. |

| Characteristic | Drug Information |
|---|---|
| | ***Distribution*** |
| Volume of distribution | The mean (CV %) apparent volume of distribution of avapritinib is 1400 L (59.1%) at 25 mg in patients with ISM. |
| | ***Elimination*** |
| Clearance | The steady state mean (CV%) apparent oral clearance of avapritinib is 21.6 L/h (58.1%) at 25 mg in patients with ISM. |
| Half-life | The mean plasma elimination half-life of avapritinib was 38 to 45 hours in patients with ISM. |
| | ***Intrinsic Factors and Specific Populations*** |
| Hepatic impairment | In a dedicated hepatic impairment study, the mean unbound AUC was 61% higher in subjects with severe hepatic impairment (Child-Pugh Class C) as compared to matched healthy subjects with normal hepatic function following a single oral dose administration of 100 mg avapritinib. |

Abbreviations: AdvSM, advanced systemic mastocytosis; AUC, area under the concentration-time curve, CV, coefficient of variance; GIST, gastrointestinal stromal tumor; ISM, indolent systemic mastocytosis; QD, once daily

APPEARS THIS WAY ON ORIGINAL

# 32. Efficacy (Evaluation of Benefit)

## 32.1. Assessment of Dose and Potential Effectiveness

The Applicant's proposed dosing of 25 mg once daily (QD) was evaluated in Study BLU-285-2203 in subjects with ISM. Study BLU-285-2203 is an ongoing, double-blind, placebo-controlled 3-part study to investigate the efficacy and safety of avapritinib in combination with BSC administered orally in adult subjects with ISM. In Part 1, the 25 mg QD recommended Phase 2 dose (RP2D) of avapritinib was determined based on the administration of avapritinib at doses of 25, 50, and 100 mg QD and the evaluation of efficacy, safety, and PK at each dose level. In Part 2, the efficacy of the RP2D (25 mg QD) in combination with BSC was compared with placebo in combination with BSC.

Based on exposure-response (E-R) analysis of efficacy, there was a flat E-R relationship for TSS (primary endpoint). However, faster onset and larger response rates (i.e., ≥50% reduction in serum tryptase, ≥30%, and ≥50% reductions in TSS) were identified for the treatment group compared to placebo. Based on E-R analysis of safety, higher exposure was associated with higher Grade ≥1 edema, however, this trend did not lead to discontinuations. No clear trends for other adverse events (AEs) (e.g., Grade ≥3 AEs, Grade ≥1 cognitive effects, and Grade ≥1 weight gain) were found. Doses higher than 25 mg have been studied in AdvSM and were found to be effective.

## 32.2. Clinical Studies Intended to Demonstrate Efficacy

### 32.2.1. Study BLU-285-2203 (Study 2203)

#### 32.2.1.1. Design, Study

Support for avapritinib for the treatment of ISM comes from a single trial BLU-285-2203 titled, "A 3-Part, Randomized, Double-Blind, Placebo-Controlled Phase 2 Study to Evaluate Safety and Efficacy of Avapritinib (BLU 285), a Selective KIT Mutation-Targeted Tyrosine Kinase Inhibitor, in Indolent and Smoldering Systemic Mastocytosis with Symptoms Inadequately Controlled with Standard Therapy"; (PIONEER; NCT03731260).

**Objectives**

The primary objective of each part of this 3-part trial is as follows.

- Part 1: Determine the RP2D in subjects with ISM for use in Part 2 and Part 3 of the study.

- Part 2: To determine mean change in ISM-SAF TSS from baseline to C7D1, compared to placebo.
- Part 3: Determine the long-term safety and efficacy of avapritinib in subjects with ISM.

Key secondary objectives (Part 2 only)

- To determine the proportion of avapritinib treated subjects with ISM with a ≥50% reduction in serum tryptase from baseline to C7D1, compared to placebo.
- To determine the proportion of avapritinib treated subjects with ISM with a ≥50% reduction in peripheral blood KIT D816V allele fraction from baseline to C7D1 or undetectable (<0.02%) for subjects with detectable mutation at baseline, compared to placebo.
- To determine the proportion of avapritinib treated subjects with ISM achieving ≥50% reduction in ISM-SAF TSS from baseline to C7D1, compared to placebo.
- To determine the proportion of avapritinib treated subjects with ISM achieving ≥30% reduction in ISM-SAF TSS from baseline to C7D1, compared to placebo.
- To determine the proportion of avapritinib treated subjects with ISM with a ≥50% reduction in bone marrow mast cells (MCs) from baseline to C7D1

*Clinical reviewer comment: The Agency worked with the Applicant during the IND stage to determine an optimal primary objective for Part 2 of the study to obtain meaningful PRO endpoint results. The clinical reviewer agrees with the primary and secondary objectives. See further discussion below in Section 32.2.1.2.*

**Study Design**

Study 2203 is a Phase 2, multicenter, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of avapritinib plus best supportive care (BSC) with placebo plus BSC in subjects with ISM whose symptoms are not adequately controlled by BSC. The study was conducted in three parts. In Part 1, the RP2D of avapritinib in subjects with ISM was determined. In Part 2, subjects with ISM were randomly assigned the avapritinib RP2D identified in Part 1 (avapritinib 25 mg once daily) in combination with BSC, or to matching placebo in combination with BSC. In Part 3, subjects who completed treatment in Part 1 or Part 2 of the study continued in a long-term extension part, receiving avapritinib at the RP2D in combination with BSC. See figure below for an overview of the study design.

In Part 1 of the study, approximately 40 subjects were planned to be randomly assigned to one of three dose levels of avapritinib (25 mg, 50 mg, 100 mg) plus BSC or to placebo plus BSC. Each dose-level cohort and placebo group in Part 1 was to be composed of 10 subjects. Avapritinib doses were tested in parallel: 25, 50, and 100 mg. The expected duration of subject participation in Part 1 was approximately 26 weeks, including a screening period of up to 14 weeks and a treatment period of 12 weeks.

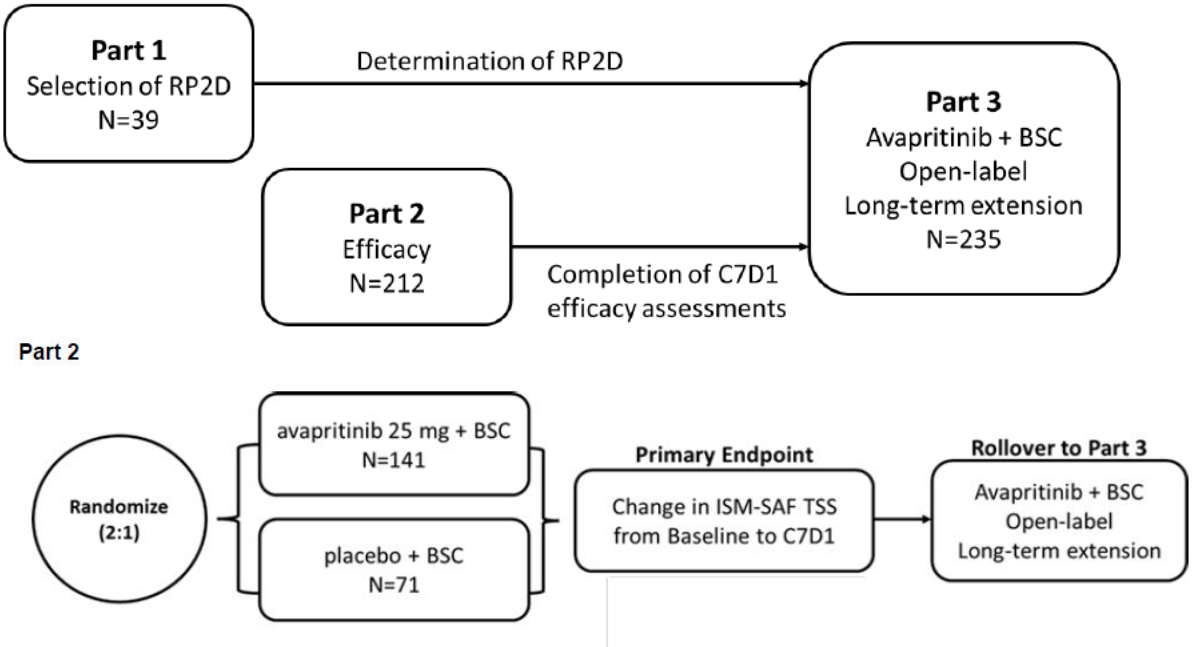
In Part 2 of the study, approximately 204 subjects were randomized (2:1 ratio) to the RP2D 25 mg avapritinib dose in combination with BSC or placebo in combination with BSC. Patients, study staff, and the Applicant were blinded to an individual patient's treatment assignment as well as the ISM-SAF TSS and all objective measures of mast cell burden (i.e., serum tryptase, KIT D816V MAF, and percent bone marrow mast cells) until Part 2 was completed.

Randomization was stratified based on serum tryptase levels at screening (<20 ng/mL versus ≥20 ng/mL). The expected duration of patient participation in Part 2 was approximately 38 weeks including a screening period of up to 14 weeks and a treatment period of at least 24 weeks. Avapritinib and placebo were each administered orally, QD, in continuous 28-day cycles. Subjects were assessed every 4 weeks through C7D1 for safety, laboratory monitoring, and QoL assessments. The ISM-SAF questionnaire was completed daily using a hand-held device.

After all subjects completed Part 1, or as each subject in Part 2 completed their C7D1 study assessments, subjects were given the opportunity to roll over to Part 3, where all subjects start or continue treatment with 25 mg avapritinib in combination with BSC in an open-label fashion. Part 3 of the study includes a treatment period up to 5 years. Part 3 of the study is ongoing.

The study schedule of events is shown Table 57.

**Figure 3. Design, Study 2203**




Source: Applicant's clinical study report (CSR)Abbreviations: RPD2 = recommended Phase 2 dose, C7D1 = cycle 7 day 1, BSC = best supportive care
Abbreviations: BSC, best supportive care; CXDX, Cycle X Day X; RP2D, recommended Phase 2 dose, ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; TSS, total symptom score.

*Clinical reviewer comment: The clinical reviewer agrees with the double-blind, placebo-controlled study design of Study 2203. A single adequate and well controlled trial is acceptable to support the indication given the rarity of the disease and strong confirmatory evidence from the prior approvals of avapritinib, in particular from the indication of AdvSM.*

## Subject Population

The key inclusion criteria were as follows:

- Age ≥18 years
- ISM as confirmed by Central Pathology Review of bone marrow biopsy, and central review of B- and C-findings by World Health Organization (WHO) diagnostic criteria (see Table 59)

- Moderate to severe symptoms based on minimum mean ISM-SAF total symptom score (TSS) over the 14-day eligibility screening period for assessment of ISM-SAF TSS and ≥1 symptom in skin or gastrointestinal domains of the ISM-SAF at baseline. Minimum ISM-SAF TSS for eligibility is ≥28
- Failed to achieve symptom control for one or more baseline symptoms measured by ISM-SAF, as determined by the Investigator, with at least two of the following symptomatic therapies administered at optimal (approved) dose and for a minimum of 28 days before starting the ISM-SAF for determination of eligibility: H1 blockers, H2 blockers, proton-pump inhibitors, leukotriene inhibitors, cromolyn sodium, corticosteroids, or omalizumab
- Symptom management optimized with symptomatic therapies, e.g., H1 and H2 blockers, and the dose must be stable for ≥14 days before starting the ISM-SAF for determination of eligibility
- Corticosteroids dose must be ≤20 mg/d prednisone or equivalent, and the dose must be stable for ≥14 days before starting the ISM-SAF for determination of eligibility
- Eastern Cooperative Oncology Group Performance Status of 0 to 2
- Subject must not have received prior treatment with avapritinib

The key exclusion criteria are as follows:

- Subject has been diagnosed with any of the following WHO SM subclassifications:
  - Cutaneous mastocytosis (CM) only, i.e., without documentation of systemic involvement
  - SM-AHN
  - ASM
  - MCL
  - MC sarcoma
- Subject meets any of the following laboratory criteria:
  - Aspartate aminotransferase or alanine aminotransferase >3.0 × upper limit of normal (ULN)
  - Total bilirubin >1.5 × ULN; >3.0 × ULN if due to Gilbert's disease
  - Albumin <1 × lower limit of normal
  - Estimated glomerular filtration rate (eGFR; calculated using the Modification of Diet in Renal Disease equation) <30 mL/min/1.73 m2 or creatinine clearance calculated by Cockcroft-Gault equation <40 mL/min
  - Absolute neutrophil count <1.5 × 109/L
  - Hemoglobin <10 g/dL
  - Platelet count <100 × 109/L

**Concomitant Medications**

Subjects continued with BSC in both treatment arms while on study. A list of permitted BSC medications is shown in the table below.

**Table 7. BSC Medications**

| Drug Class | Generic/Trade Name |
|---|---|
| H1 antihistamines | Loratidine/Claritin |
| | Diphenhydramine/Benadryl |
| | Cetirizine/Zyrtec |
| | Fexofenadine/Allegra |
| | Hydroxyzine/Vistaril/Atarax |
| | Rupatadine/Rupafin |
| | Ketotifen/Zaditor |
| H2 antihistamines | Cimetidine/Tagamet |
| | Famotidine/Pepcid |
| | Ranitidine/Zantac |
| Proton-pump inhibitors | Omeprazole/Prilosec |
| | Pantoprazole/Protonix |
| | Rabeprazole/AcipHex |
| Leukotriene inhibitors | Montelukast/Singulair |
| | Zafirlukast/Accolate |
| Corticosteroids | Prednisone/Deltasone |
| Cromolyn sodium | Cromoglicic acid/Nasalcrom/Gastrocrom |
| Anti-IgE antibody | Omalizumab/Xolair |
| Bisphosphonates for osteoporosis | Alendronate/Aledronic acid//Fosamax |
| | Risedronate/Risedronic acid/Actenol/Atelvia |
| | Ibandronate/Ibandronic acid/Boniva |
| | Pamidronic acid/Aredia |
| | Zoledronic acid/Reclast/Zometa |
| Other drugs for osteoporosis | Denosumab/Prolia |
| | Raloxifene/Evista |
| | Teriparatide/Forteo |
| Epinephrine for allergic reactions | Adrenalin/EpiPen |

Source: Protocol for study BLU-285-2203
Abbreviations: BSC, best supportive care

The following medications and procedures were prohibited during the screening period:

- Hematopoietic growth factors <14 days before starting the ISM-SAF for determination of eligibility
- Cytoreductive therapy (including midostaurin and other tyrosine kinase inhibitors (TKIs), such as masitinib) or an investigational agent <14 days, and for cladribine, interferon alpha, pegylated interferon and any antibody therapy <28 days, before starting the ISM-SAF for determination of eligibility
- Radiotherapy <14 days before starting the ISM-SAF for determination of eligibility
- Psolaren plus ultraviolet A (PUVA) therapy <14 days before starting the ISM-SAF for determination of eligibility

### 32.2.1.2. Statistical Analysis Plan, Study 2203 Part 2

**Endpoints**

The primary efficacy endpoint of part 2 of Study BLU-285-2203 is the mean change in the Indolent Systemic Mastocytosis Symptom Assessment Form total symptom score from baseline to C7D1.

The key secondary efficacy endpoints of the part 2 of the study include:

- Proportion of subjects with a ≥50% reduction in serum tryptase from baseline to C7D1
- Proportion of subjects with a ≥50% reduction in peripheral blood KIT D816V MAF from baseline to C7D1 or undetectable (<0.02%) for subjects with detectable mutation at baseline
- Proportion of subjects with ≥50% reduction in ISM-SAF TSS from baseline to C7D1
- Proportion of subjects with ≥30% reduction in ISM-SAF TSS from baseline to C7D1
- Proportion of subjects with a ≥50% reduction in bone marrow mast cell (BMMC) from baseline to C7D1 or no aggregates for subjects with aggregates at baseline

*Statistical and clinical reviewer comment: During the IND development, Study 2203 underwent multiple revisions based on feedback from the Agency. Originally, the Applicant had proposed a primary endpoint of proportion of responders, defined as at least a 30% decrease in ISM-SAF Total Symptom Score (TSS), from baseline to Cycle 7 Day 1 (C7D1). Based on advice from the Agency, the Applicant subsequently revised the primary endpoint to change from baseline to C7D1 on ISM-SAF TSS, which at the time was the third key secondary endpoint in the protocol. As described in post meeting comments in the Type B Meeting on April 1, 2022, the Agency made this recommendation because it avoided the potential power loss that could result from dichotomization of a continuous variable and it removed the threshold setting step as part of the primary analysis. The Applicant agreed with the Agency's recommendation and revised the primary endpoint accordingly. The Applicant subsequently moved the proportion of patients with a 30% or greater reduction in TSS at C7D1 and added the proportion of patients with a 50% or greater reduction in TSS at C7D1 to key secondary endpoints. The Agency expressed concern in following the review of the statistical analysis plan (SAP) submitted on June 8, 2022, stating there was insufficient evidence to support the proposed responder thresholds* (b) (4)

(b) (4). *The Agency recommended the Applicant include justification in their submission for the proposed thresholds. In the sNDA submission, the Applicant provided the following justification, "A 30% reduction in TSS was selected given that psychometric evaluation of the ISM-SAF at 12 weeks in Part 1 (Padilla et al. 2021) of BLU- 285-2203 suggested that this degree of individual reduction in the TSS represented the clinically important response, and 50% individual reduction in the TSS was specified to test a higher threshold of benefit." The clinical and statistical team did not find the Applicant's justification for the responder thresholds of 30% and 50% acceptable, therefore the review team conducted their own analysis as described in Section 32.3.3.*

**Indolent Systemic Mastocytosis-Symptom Assessment Form**

The Applicant developed the ISM-SAF (Section 42.1.1), which is a 12-item patient-reported outcome (PRO) instrument designed to assess the severity and frequency of ISM-related signs and symptoms. Sign and symptom severity items are rated on an 11-point numeric rating scale (NRS) ranging from 0 ("No [sign/symptom]") to 10 ("Worst imaginable [sign/symptom]"). Diarrhea frequency is rated by entering the number of diarrhea episodes using "plus minus" buttons. The recall period is the previous 24 hours for all items.

The ISM-SAF was administered daily using a handheld electronic diary (eDiary), beginning at least 28 days before the first dose of the study drug (C1D-28) through end of treatment (EOT), as well as during the open-label extension part of the study, unless the subject experienced unacceptable toxicity or death, or withdrew from the study for any other reason.

The ISM-SAF sign and symptom severity item scores were summed to calculate a daily ISM-SAF TSS (range 0 to 110), with higher scores indicating greater symptom severity. A biweekly average ISM-SAF TSS was used to evaluate efficacy endpoints.

If any item score is missing, the corresponding domain and TSS score will be set as missing on a given day. If a subject is missing more than 7 days of the ISM-SAF TSS within a 14-day period, the 14-day average ISM-SAF TSS will be considered as missing. Missing data for the daily and biweekly item – and domain-level scores from the ISM-SAF were not imputed.

**Analysis Populations**

The major analysis populations include the intent-to-treat (ITT) population, the per-protocol (PP) population, and the safety population.

- The ITT population included all randomized subjects, independent of whether they received the study medication or not.
- The PP population included all subjects who were randomly assigned to treatment and were confirmed to have ISM per WHO diagnostic criteria, including Central Pathology Review of bone marrow, and had no major violations of the inclusion or exclusion criteria.
- The safety population included subjects who received at least one dose of avapritinib or placebo.

**Sample Size Determination**

With a 1:2 (placebo versus avapritinib 25 mg once daily) randomization ratio, assuming the null hypothesis was the mean change of TSS of negative 10 in the placebo group, versus the

alternative hypothesis of the mean change of TSS of negative 19.7 in the avapritinib group, the standard deviation of mean change of TSS was assumed to be 20, and a 1-sided type I error rate of 0.025, a total of 204 subjects would provide >90% power using a 2-sample t-test for the primary endpoint. This sample size was also expected to provide >90% power for all key secondary endpoints.

*Statistical reviewer's comment: the assumptions were only based on the findings in Part 1 of the study with a total number of 39 patients. Therefore, the planned effect size for powering the Part 2 study may not be reliable.*

**Randomization**

Enrollment into Part 2 of the study was randomized at the ratio of 2:1 to avapritinib 25 mg QD and placebo. Randomization in Part 2 was stratified based on baseline serum tryptase level (<20 ng/mL versus ≥20 ng/mL).

**Analysis of the Primary Efficacy Endpoint**

The primary efficacy endpoint for Part 2 of the study was defined as the mean change in ISM-SAF TSS from baseline to C7D1. TSS at each day was calculated as the 14-day average of TSS prior to the day (i.e., C1D15 TSS is the 14-day average of TSS from C1D1 to C1D14). Baseline TSS was the 14-day average of TSS from C1D-14 to C1D-1.

The mean change for each treatment group was calculated for subjects in Part 2 from baseline to C7D1 and an analysis of covariance (ANCOVA) controlling for randomization stratification factor (tryptase) and baseline ISM status (moderate versus severe) was performed to compare avapritinib and placebo. The threshold for moderate versus severe ISM was prespecified in the statistical analysis plan. If fewer than five subjects were in one of the combinations of tryptase and baseline ISM status under each treatment arm, then the corresponding stratification factor was removed from the analysis. If the 1-sided p-value was <0.025, avapritinib was deemed as superior in reducing ISM symptoms compared to placebo.

The analysis of the primary efficacy endpoint used the ITT population as primary and the per-protocol population as a sensitivity analysis. Subjects with high-dose steroid use within 7 days before C7D1, or greater than 14 consecutive days at any point from C1D1 to C7D1, were excluded from the primary efficacy analysis. Subjects with either missing baseline TSS or missing C7D1 TSS were also excluded from the primary efficacy analysis.

Markov chain Monte Carlo (MCMC) simulations that imputed the missing values at baseline or C7D1 were performed as sensitivity analyses. In particular, the MCMC simulations using the missing at random (MAR) assumption were run 1000 times with a prespecified random seed of 4502139.

Subgroup analyses were conducted by using the primary analysis method in the following subgroups (if ≤ five subjects in one group, the subgroup analysis was removed).

Corresponding forest plots were provided for subgroup analyses:

- Age (<65 years, ≥65 years)
- Sex (male, female)
- Region (North America, Europe)

- Country (BEL, CAN, CHE, DEU, DNK, ESP, FRA, GBR, ITA, NLD, NOR, SWE, USA)
- Baseline ISM status (moderate versus severe)
- Baseline serum tryptase level (<20 ng/mL versus ≥20 ng/mL)
- Eastern Cooperative Oncology Group (ECOG) status (0 or 1 versus 2+)
- Prior tyrosine kinase inhibitor (TKI) therapy (Yes, No)

*Statistical reviewer's comment: the primary analysis method of the primary endpoint prespecified in the SAP was an ANCOVA model controlling for randomization stratification factor serum tryptase and baseline ISM status on the observed cases on the ITT population. Therefore, the prespecified primary analysis population was actually a modified ITT (mITT) instead of ITT. During the IND stage, the Agency informed the Applicant that the Agency did not agree with the prespecified primary analysis method because the primary analysis should be based on the ITT population. However, the Applicant did not address this comment before the sNDA submission. During the sNDA review, the Agency recommended the Applicant use the analysis result based on the ITT population and the MCMC imputation with the MAR assumption in the label and the Applicant agreed.*

**Analyses of Key Secondary Efficacy Endpoints**

The analyses of the key secondary endpoints used the ITT population primarily and were performed in the PP population as a sensitivity analysis.

The first key secondary endpoint was defined as the proportion of subjects with ≥50% reduction in serum tryptase at C7D1. If C7D1 serum tryptase value was missing, the subject was deemed as not achieving ≥50% reduction. The proportion of subjects with ≥50% reduction, including frequency, percentage, and 95% confidence interval was calculated in each treatment arm. A Cochran–Mantel–Haenszel test controlling for randomization stratification factor (tryptase) and baseline ISM status (moderate versus severe) was used to compare avapritinib and placebo.

The second key secondary endpoint was defined as the proportion of subjects with ≥50% reduction in KIT D816V MAF at C7D1 or undetectable (<0.02%) for subjects with detectable mutation at baseline. If C7D1 KIT D816V MAF value was missing, the subject was deemed as not achieving ≥50% reduction. Similar to the first key secondary endpoint, the proportion of subjects with ≥50% reduction, including frequency, percentage, and 95% confidence interval was calculated in each treatment arm. A Cochran–Mantel–Haenszel test controlling for randomization stratification factor (tryptase) and baseline ISM status (moderate versus severe) was used to compare avapritinib and placebo. As a sensitivity analysis, the same analyses were provided for the subset of subjects with baseline MAF ≥0.1%.

The percent change in TSS from baseline to C7D1 was calculated as (C7D1 TSS – Baseline TSS) / Baseline TSS. The proportion of subjects with a 50% or greater reduction in TSS at C7D1 was defined as the third key secondary endpoint. The proportion of subjects with a 30% or greater reduction in TSS at C7D1 was defined as the fourth key secondary endpoint. The proportion of subjects with ≥50% or ≥30% reduction, including frequency, percentage, and 95% confidence interval was calculated in each treatment arm. Subjects missing baseline or C7D1 TSS score were considered as not achieving either 50% or 30% reduction. A Cochran-Mantel-Haenszel test with controlling for randomization stratification factor (Serum tryptase <20 ng/mL

versus ≥20 ng/mL) and baseline ISM status (moderate versus severe) was used to compare avapritinib and placebo. If fewer than five subjects were in one of the combinations of tryptase and baseline ISM status under each treatment arm, then the corresponding stratification factor was removed from the analysis. A sensitivity analysis that excluded subjects with missing baseline TSS was performed. Complete case analyses based on subjects with a complete set of baseline and C7D1 TSS scores were also performed as sensitivity analyses.

The fifth key secondary endpoint was defined as the proportion of subjects with ≥50% reduction in bone marrow mast cell (BMMC) at C7D1 or no aggregates for subjects with aggregates at baseline. The percent change in BMMC was calculated as (C7D1 BMMC – baseline BMMC) / baseline BMMC. If baseline or C7D1 BMMC value was missing, the subject was deemed as not achieving ≥50% reduction. Similar to the first key secondary endpoint, the proportion of subjects with ≥50% reduction, including frequency, percentage, and 95% confidence interval was calculated in each treatment arm. A Cochran–Mantel–Haenszel test controlling for randomization stratification factor (tryptase) and baseline ISM status (moderate versus severe) was used to compare avapritinib and placebo.

**Multiplicity Adjustment**

The hierarchical testing strategy was used to test the primary endpoint and all five key secondary endpoints with the testing order shown below to ensure that the family-wise type I error was strongly controlled for the primary endpoint and key secondary endpoints at 1-sided alpha of 0.025.

- Mean change in the ISM-SAF TSS from baseline to C7D1
- Proportion of subjects with a ≥50% reduction in serum tryptase from baseline to C7D1
- Proportion of subjects with a ≥50% reduction in peripheral blood KIT D816V MAF from baseline to C7D1 or undetectable (<0.02%) for subjects with detectable mutation at baseline
- Proportion of subjects with ≥50% reduction in ISM-SAF TSS from baseline to C7D1
- Proportion of subjects with ≥30% reduction in ISM-SAF TSS from baseline to C7D1
- Proportion of subjects with a ≥50% reduction in bone marrow mast cell (BMMCs) from baseline to C7D1 or no aggregates for subjects with aggregates at baseline

**Interim Analyses**

No interim analysis for Part 2 was planned.

### 32.2.1.3. Results of Analyses, Study 2203 Part 2

**Data Quality and Integrity**

Data were provided electronically in the standard data format, with SDTM and ADaM. SAS programs used to create key efficacy and safety outputs for the study were submitted along with the data. The Applicant also provided a clear definition file for datasets and detailed analysis programs for assisting review. The link to the data from Study BLU-285-2203 Part 2 is \\CDSESUB1\evsprod\NDA212608\0112\m5\datasets\blu-285-2203.

### Subject Disposition

In Part 2, both the ITT and safety populations included 141 subjects in the avapritinib group and 71 subjects in the placebo group. The PP population in Part 2 included 123 subjects in the avapritinib group and 67 subjects in the placebo group.

In the avapritinib group, five subjects discontinued from Part 2 of the study: two for withdrawal of consent, one for the related adverse event, one for systemic mastocytosis clinical progression, and one based on Investigator's decision. In the placebo group, five subjects discontinued from Part 2 of the study: two for withdrawal of consent and two for other reasons. A total of 202 subjects completed Part 2 of the study.

The disposition of subjects in Part 2 of the study is shown in Table 8.

**Table 8. Subject Disposition, Study BLU-285-2203 Part 2—Intent-to-Treat Population**

| Parameter | Avapritinib 25 mg n (%) | Placebo n (%) | Total n (%) |
|---|---|---|---|
| Intent-to-Treat Population | 141 (100.0%) | 71 (100.0%) | 212 (100.0%) |
| Completed Part 2 | 136 (96.5%) | 66 (93.0%) | 202 (95.3%) |
| Discontinued in Part 2 | 5 (3.5%) | 5 (7.0%) | 10 (4.7%) |
| Adverse event | 1 (0.7%) | 0 (0.0%) | 1 (0.5%) |
| Lost to follow-up | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Death | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Progressive disease | 1 (0.7%) | 0 (0.0%) | 1 (0.5%) |
| Physician decision | 1 (0.7%) | 0 (0.0%) | 1 (0.5%) |
| Withdrawal by subject | 2 (1.4%) | 3 (4.2%) | 5 (2.4%) |
| Other | 0 (0.0%) | 2 (2.8%) | 2 (0.9%) |

Source: The Applicant's clinical study report. The results were confirmed by the statistical reviewer.

### Demographic Characteristics

Demographic and baseline characteristics of subjects (ITT population) in Part 2 of the study are shown in Table 9. For subjects in the avapritinib group, the study population characteristics were median age of 50 years (range: 18 to 77 years), 71% were female, 77% were White, and 94% had a KIT D816V mutation. At baseline, the mean TSS was 50.17 (standard deviation: 19.15), the median serum tryptase level was 38.40 ng/mL, the median KIT D816V mutant allele fraction was 0.39% by ddPCR and the median bone marrow mast cell infiltrate was 7%.

Forty-two sites enrolled subjects and entered data for this study, including 19 sites in North America, 20 sites in Europe, and 3 sites in the United Kingdom. Most study subjects enrolled were ex-U.S. participants in part 2 of the study, (i.e., 63.1% in the avapritinib 25 mg group and 60.6% in the placebo group).

In general, demographic and baseline characteristics were similar between treatment groups.

**Table 9. Demographic and Baseline Characteristics, Study BLU-285-2203 Part 2—Intent-to-Treat Population**

| Category | Avapritinib 25 mg N=141 n (%) | Placebo N=71 n (%) | Total N=212 n (%) |
|---|---|---|---|
| Age (years) | | | |
| Mean (SD) | 48.7 (11.7) | 52.2 (12.5) | 49.8 (12.1) |
| Median [min, max] | 50.0 [18.0, 77.0] | 54.0 [26.0, 79.0] | 51.0 [18.0, 79.0] |

| Category | Avapritinib 25 mg N=141 n (%) | Placebo N=71 n (%) | Total N=212 n (%) |
|---|---|---|---|
| Age group | | | |
| <65 years | 132 (93.6%) | 60 (84.5%) | 192 (90.6%) |
| ≥65 years | 9 (6.4%) | 11 (15.5%) | 20 (9.4%) |
| Sex | | | |
| Female | 100 (70.9%) | 54 (76.1%) | 154 (72.6%) |
| Male | 41 (29.1%) | 17 (23.9%) | 58 (27.4%) |
| Ethnicity | | | |
| Hispanic or Latino | 6 (4.3%) | 1 (1.4%) | 7 (3.3%) |
| Not Hispanic or Latino | 99 (70.2%) | 58 (81.7%) | 157 (74.1%) |
| Not Reported | 22 (15.6%) | 10 (14.1%) | 32 (15.1%) |
| Unknown | 14 (9.9%) | 2 (2.8%) | 16 (7.5%) |
| Race | | | |
| Asian | 1 (0.7%) | 0 (0%) | 1 (0.5%) |
| Other | 4 (2.8%) | 2 (2.8%) | 6 (2.8%) |
| Unknown | 27 (19.1%) | 8 (11.3%) | 35 (16.5%) |
| White | 109 (77.3%) | 61 (85.9%) | 170 (80.2%) |
| Height (cm) | | | |
| Mean (SD) | 169 (9.73) | 167 (9.07) | 168 (9.56) |
| Median [min, max] | 167 [152, 194] | 165 [150, 195] | 165 [150, 195] |
| Missing | 4 (2.8%) | 1 (1.4%) | 5 (2.4%) |
| Weight (kg) | | | |
| Mean (SD) | 81.1 (17.9) | 82.2 (17.8) | 81.5 (17.8) |
| Median [min, max] | 80.2 [45.0, 126] | 80.7 [44.4, 135] | 80.5 [44.4, 135] |
| BMI (kg/m$^2$) | | | |
| Mean (SD) | 28.3 (5.40) | 29.5 (5.28) | 28.7 (5.37) |
| Median [min, max] | 27.8 [17.6, 42.0] | 29.0 [19.7, 43.7] | 28.3 [17.6, 43.7] |
| Missing | 4 (2.8%) | 1 (1.4%) | 5 (2.4%) |
| Baseline ISM severity based on ISM-SAF TSS [a] | | | |
| Moderate | 52 (36.9%) | 26 (36.6%) | 78 (36.8%) |
| Severe | 87 (61.7%) | 45 (63.4%) | 132 (62.3%) |
| Missing | 2 (1.4%) | 0 (0%) | 2 (0.9%) |
| Baseline tryptase group | | | |
| <20 ng/mL | 28 (19.9%) | 15 (21.1%) | 43 (20.3%) |
| >=20 ng/mL | 113 (80.1%) | 56 (78.9%) | 169 (79.7%) |

Source: The Applicant's clinical study report. The results were confirmed by the statistical reviewer.
[a] Baseline TSS score is defined as the 14-day average of TSS from C1D-14 to C1D-1. If a subject is missing more than 7 days of score between C1D-14 and C1D-1, the baseline score is considered as missing for the subject.
Abbreviations: BMI, body mass index; ISM-SAF TSS, Indolent Systemic Mastocytosis-Symptom Assessment Form total symptom score; Max, maximum; Min, minimum; SD. standard deviation.

**Table 10. Additional Baseline Characteristics, Study BLU-285-2203 Part 2—Intent-to-Treat Population**

| Category | Avapritinib 25 mg N=141 n (%) | Placebo N=71 n (%) |
|---|---|---|
| Baseline ISM-SAF TSS[a] | | |
| Mean (SD) | 50.17 (19.145) | 52.43 (19.823) |
| Median [min, max] | 47.86 [12.1, 102.7] | 47.79 [18.0, 104.4] |
| Missing | 2 (1.4%) | 0 (0%) |
| Baseline serum tryptase (ng/mL) | | |
| Mean (SD) | 57.57 (54.371) | 67.57 (74.248) |
| Median [min, max] | 38.40 [3.6, 256.0] | 43.70 [5.7, 501.6] |

| Category | Avapritinib 25 mg N=141 n (%) | Placebo N=71 n (%) |
|---|---|---|
| Baseline KIT D816V mutation allele burden as measured by MAF using ddPCR from blood | | |
| Mean (SD) | 2.570 (6.1287) | 3.570 (7.5691) |
| Median [min, max] | 0.390 [0.00, 41.29] | 0.260 [0.00, 36.74] |
| Baseline percent bone marrow mast cells | | |
| Mean (SD) | 11.03 (11.087) | 12.23 (12.611) |
| Median [min, max] | 7.00 [1.0, 50.0] | 7.00 [1.0, 70.0] |

Source: Adapted from the Applicant's clinical study report.
[a] Baseline TSS score is defined as the 14-day average of TSS from C1D-14 to C1D-1. If a subject is missing more than 7 days of score between C1D-14 and C1D-1, the baseline score is considered as missing for the subject.
Abbreviations: ddPCR = digital-droplet polymerase chain reaction, ISM-SAF TSS, Indolent Systemic Mastocytosis-Symptom Assessment Form total symptom score; Max, maximum; Min, minimum; SD. standard deviation.

*Statistical reviewer's comment: the Agency sent an information request to the Applicant asking for clarification on why baseline TSS scores were missing for two patients for the primary endpoint. In the responses, the Applicant provided detailed information: One patient did not respond to the ISM-SAF questionnaire for all 14 days prior to the first treatment in Part 2 of the study despite being informed to complete the questionnaire daily by the site staff. The other patient did not respond to the ISM-SAF questionnaire for 11 of the 14 days prior to the first treatment in Part 2 of the study. The statistical review team determined that the Applicant's response was acceptable and did not raise additional concerns.*

*Clinical reviewer comment: Most patients (approximately 62%) had severe ISM based on the ISM-SAF TSS. The patient population is comprised of patients with ISM in need of therapy despite receiving BSC. Treatment arms were well balanced in terms of demographics. Of note, most patients in the clinical trial were Caucasian, which is consistent with the demographics of the disease. In a study by Bista et al. (2018), 425 patients with SM from the United States (U.S.) were identified in the Surveillance, Epidemiology, and End Results (SEER) Program of which, 92.5% were Caucasian.*

**Concomitant Medications**

Supportive care treatments at baseline were a median of three therapies in the avapritinib group and four therapies in the placebo group. Nearly all subjects in Part 2 of Study 2203 were treated with concomitant best supportive care treatments (i.e., 99.3% in the 25 mg avapritinib and 100.0% in the placebo group). The most commonly used BSC medications were antihistamines for systemic use (97.2% in the 25 mg avapritinib group and 100.0% in the placebo group) and drugs for peptic ulcer and gastroesophageal reflux disease (GERD) (73.8% in the 25 mg avapritinib group and 78.9% in the placebo group.

The most common concomitant medication/therapies used were viral vaccines (43.3% in the 25 mg avapritinib group and 43.7% in the placebo group), combinations of analgesics/antipyretics (36.2% in the 25 mg avapritinib group and 35.2% in the placebo group). Antidepressants and anxiolytic medications were also used similarly between the two groups (19.1% and 16.3% in the 25 mg avapritinib group; and 21.1% and 22.5% in the placebo group, respectively). The use of opioids was similar between the two treatment groups (22.0% in the 25 mg avapritinib group and 22.5% in the placebo group).

**Efficacy Results for the Primary Endpoint**

The analysis using the ANCOVA on the observed cases of the ITT population (i.e., a modified ITT population included all subjects in the ITT population without any of following: 1) missing baseline TSS, 2) missing C7D1, 3) receiving prednisone greater than 20 mg daily or equivalent within 7 days before C7D1, 4) receiving prednisone for greater than 14 consecutive days at any point from C1D1 to C7D1) showed that the least squares mean change from baseline to C7D1 in the ISM-SAF TSS was -15.58 for the avapritinib group and -9.15 for the placebo group. The difference between the groups was -6.43 with a 95% CI between -10.90 and -1.96 points. The two-sided p-value of the difference was 0.005, which was smaller than the prespecified threshold of 0.05.

The analysis based on the ITT population and the Markov chain Monte Carlo (MCMC) imputation of missing data with the MAR assumption showed similar results to the analysis based on observed cases of the ITT population: The least squares mean change from baseline to C7D1 in the ISM-SAF TSS was -15.33 for the avapritinib group and -9.64 for the placebo group. The difference between the groups was -5.69 with a 95% CI between -10.16 and -1.23 points. The two-sided p-value of the difference was 0.012, which was smaller than the prespecified threshold of 0.05.

Similar results were obtained from sensitivity analyses based on observed cases of the PP population (i.e., a modified PP population) and based on PP population with the MCMC imputation of missing data.

As recommended by the Agency during the NDA review, the Applicant also conducted sensitivity analyses based on the worst-case imputation, pattern mixture model, and tipping point analyses.

Two different worst-case imputations were performed. In both imputations, subjects with missing baseline TSS (n=2, both in the avapritinib group) are imputed with the lowest observed baseline TSS (TSS =12.071) among the Part 2 ITT population. For subjects with missing C7D1 TSS (n=14, 11 in the avapritinib group and 3 in the placebo group) two approaches were taken to determine the “worst case” scenario. In the first scenario, the worst TSS observed within each subject was imputed as the C7D1 TSS for that subject. The analysis results were similar to the ANCOVA analysis based on observed cases of the ITT population. In the second scenario, a score of 110, the highest possible TSS on the ISM-SAF PRO questionnaire, was imputed as the C7D1 TSS. For the second scenario, the point estimate of mean difference was -6.50 with a two-sided p-value of 0.079, which is higher than the significance cutoff of 0.05. However, this analysis is overly conservative because it is exceedingly unlikely that all subjects with missing TSS on C7D1 would have a TSS of 110, whereas the highest observed post baseline TSS was 105.2.

The pattern mixture model was performed by using the control-based pattern imputation, which assumed that after withdrawal from the study subjects on the avapritinib treatment arm would exhibit the same future evolution of the disease as subjects on the control arm. The analysis results were similar to the ANCOVA analysis based on observed cases of the ITT population.

The analyses results for the primary endpoint except for the tipping point analyses are summarized in Table 11. All results were consistent with the ANCOVA analysis based on

observed cases of the ITT population, except for the second scenario of the worst-case imputation which was determined to be overly conservative.

**Table 11. Analyses Results for the Primary Endpoint (Mean Change in TSS), Study BLU-285-2203 Part 2**

| Analysis Method, Analysis Population | Avapritinib 25 mg N Least Squares Mean (95% CI) | Placebo N Least Squares Mean (95% CI) | Difference Between Avapritinib and Placebo (95% CI) | 2-Sided P-value [a] |
|---|---|---|---|---|
| ANCOVA, mITT [b] | N=128<br>-15.58<br>(-18.61, -12.55) | N=65<br>-9.15<br>(-13.12, -5.18) | -6.43<br>(-10.90, -1.96) | 0.005 |
| MCMC with the MAR assumption, ITT | N=141<br>-15.33<br>(-18.36, -12.31) | N=71<br>-9.64<br>(-13.61, -5.68) | -5.69<br>(-10.16, -1.23) | 0.012 |
| ANCOVA, mPP [c] | N=112<br>-16.80<br>(-20.20, -13.40) | N=61<br>-9.27<br>(-13.61, -4.93) | -7.53<br>(-12.36, -2.70) | 0.002 |
| MCMC with the MAR assumption, PP | N=123<br>-16.63<br>(-20.01, -13.25) | N=67<br>-9.83<br>(-14.16, -5.49) | -6.80<br>(-11.62, -1.99) | 0.006 |
| Worst-case imputations 1 [d], ITT | N=141<br>-14.30<br>(-17.35, -11.26) | N=71<br>-8.32<br>(-12.26, -4.39) | -5.98<br>(-10.40, -1.56) | 0.008 |
| Worst-case imputations 2 [e], ITT | N=141<br>-10.65<br>(-15.66, -5.65 | N=71<br>-4.15<br>(-10.61, 2.32) | -6.50<br>(-13.76, 0.75) | 0.079 |
| Pattern mixture model with the MNAR assumption, ITT | N=141<br>-15.05<br>(-18.05, -12.04) | N=71<br>-9.37<br>(-13.29, -5.44) | -5.68<br>(-10.07, -1.29) | 0.011 |

Source: The Applicant's clinical study report and responses to the Agency's information requests. The results were confirmed by the statistical reviewer.

[a] Two-sided p-value is from ANCOVA model with controlling for randomization stratification factor (tryptase) and Baseline ISM status (moderate versus severe).

[b] The mITT population included all subjects in the ITT population without any of following: 1) missing baseline TSS, 2) missing C7D1, 3) receiving prednisone greater than 20 mg daily or equivalent within 7 days before C7D1, 4) receiving prednisone for greater than 14 consecutive days at any point from C1D1 to C7D1.

[c] The mPP population included all subjects in the PP population without any of following: 1) missing baseline TSS, 2) missing C7D1, 3) receiving prednisone greater than 20 mg daily or equivalent within 7 days before C7D1, 4) receiving prednisone for greater than 14 consecutive days at any point from C1D1 to C7D1.

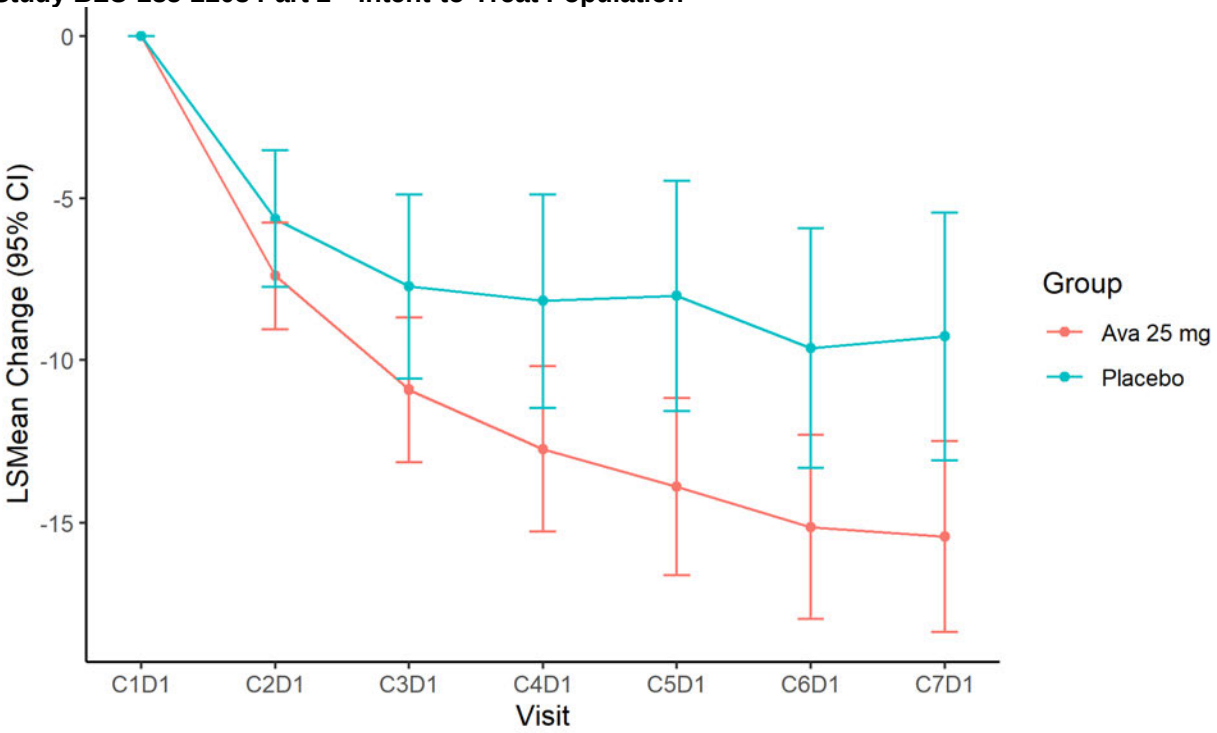
[d] Impute missing baseline TSS with the lowest observed baseline TSS among the Part 2 ITT population. Impute missing C7D1 TSS with the highest observed TSS for the subject with missing data

[e] Impute missing baseline TSS with the lowest observed baseline TSS among the Part 2 ITT population. Impute missing C7D1 TSS with 110, the highest poss ble TSS of the ISM-SAF PRO questionnaire

Abbreviations: ANCOVA, analysis of covariance; ITT, intent-to-treat; MAR, missing at random; MCMC, Markov chain Monte Carlo; mITT, modified intent-to-treat; mPP, modified per-protocol; MNAR, missing not at random; PP, per-protocol

Figure 4 shows the mean change in ISM-SAF TSS from baseline to C7D1 during the part 2 of the study with the MCMC imputation of missing data.

**Figure 4. Mean Change in ISM-SAF TSS From Baseline to C7D1 With the MCMC Imputation, Study BLU-285-2203 Part 2—Intent-to-Treat Population**

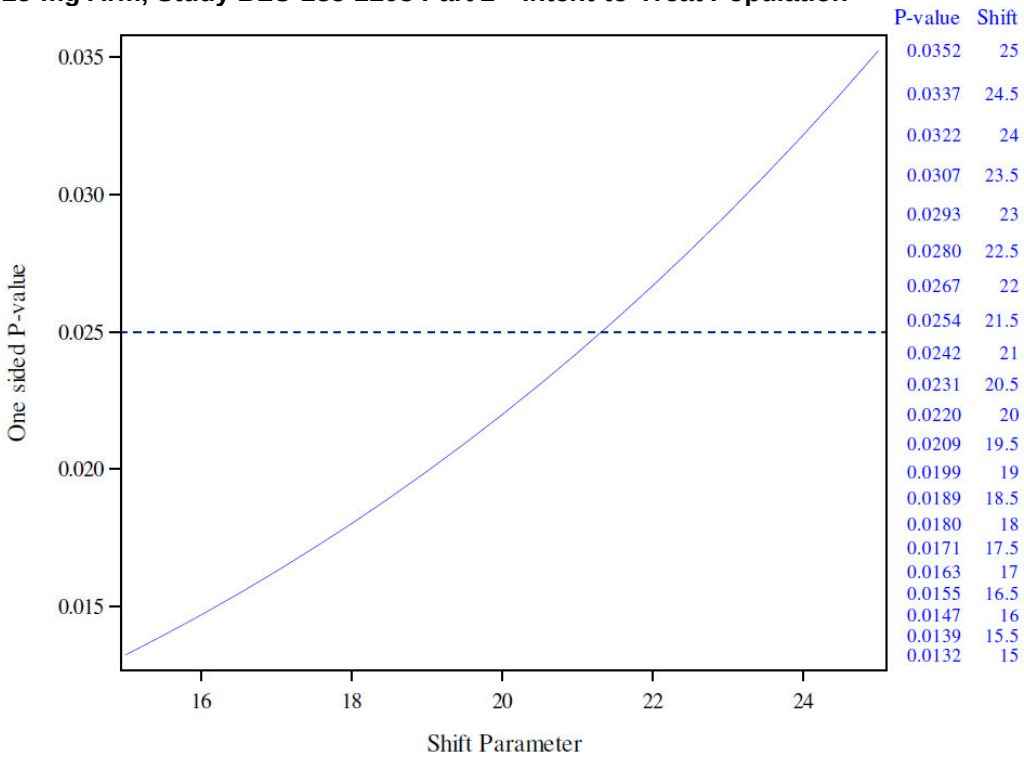



Source: The Applicant's responses to the Agency's information requests. The results were confirmed by the statistical reviewer.
Abbreviations: Ava, avapritinib ISM-SAF TSS, indolent systemic mastocytosis-symptom assessment form total symptom score; MCMC, Markov chain Monte Carlo

*Statistical reviewer's comment: The statistical review team observed overlaps in the 95% CIs of the two groups at all visits including week 24. However, due to the 2:1 randomization ratio and the lack of large enough between-group difference, the conclusion of the two confidence intervals can be different from that of the hypothesis test. After thorough and careful evaluation, the statistical review team concluded that the analysis results of the primary endpoint that assess the between-group difference at week 24 are indeed statistically significant.*

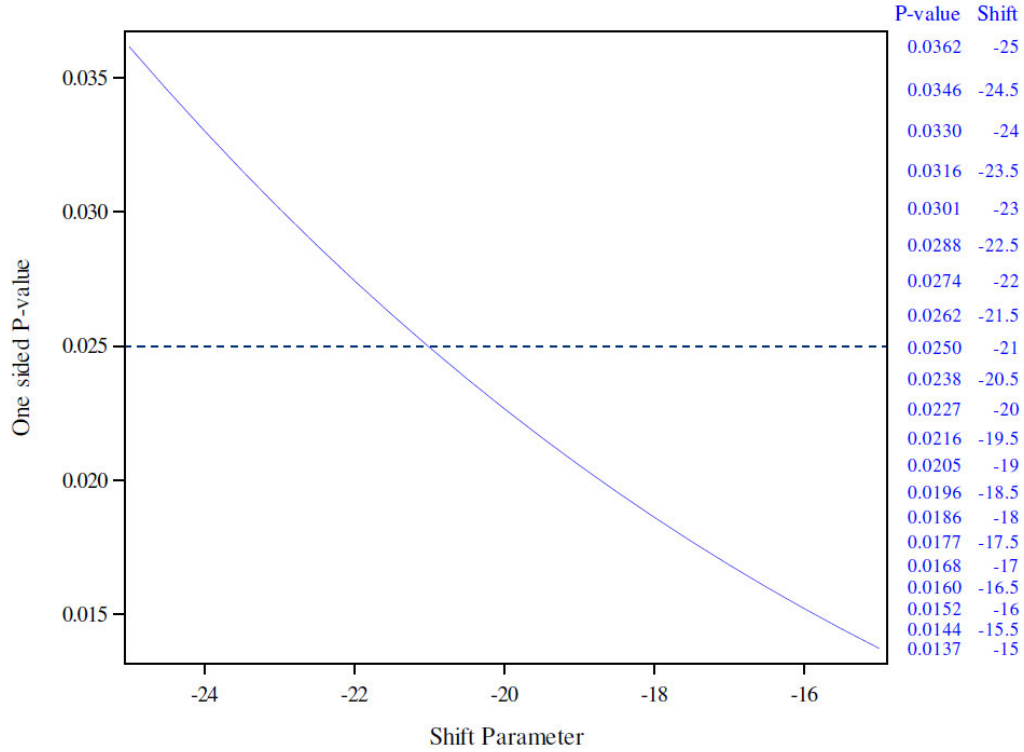
Tipping point analysis results are visualized in Figure 5 and Figure 6. The results showed that shift parameters of 21.5 or -21 must be added to the missing values in the avapritinib or placebo arms, respectively, to cause the results to tip (two-sided ANCOVA p-value change from <0.05 to >0.05). Both tipping points of ~21 are more than 3 times the treatment effect of -6.43 for the observed cases on the ITT and represent 19% of the total 110 points in the TSS scale. Because the results from the tipping point analysis are highly unlikely to occur, the results from the analyses based on the MAR assumption are considered robust.

**Figure 5. Tipping Point Analyses for the Primary Endpoint, Ranged -25 to -15 in the Avapritinib 25-mg Arm, Study BLU-285-2203 Part 2—Intent-to-Treat Population**




Source: The Applicant's responses to the Agency's information requests. The results were confirmed by the statistical reviewer.

**Figure 6 Tipping Point Analyses for the Primary Endpoint, Ranged 15 to 25 in the Placebo Arm, Study BLU-285-2203 Part 2—Intent-to-Treat Population**




Source: The Applicant's responses to the Agency's information requests. The results were confirmed by the statistical reviewer.

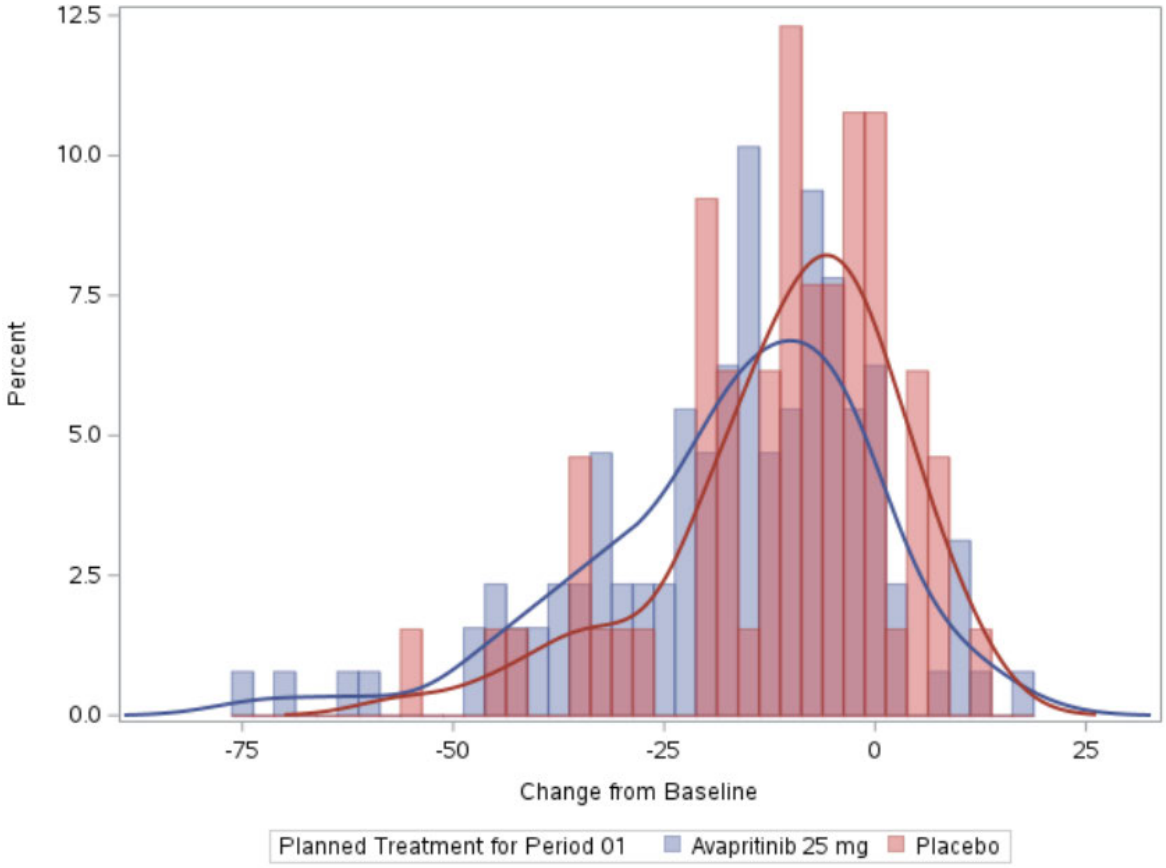
*Statistical reviewer's comment: the prespecified primary analysis method of the primary endpoint was an ANCOVA model controlling for randomization stratification factor serum tryptase and baseline ISM status on the observed cases on the ITT population, i.e., a modified ITT population, which was not agreed by the Agency during the IND stage. During the sNDA stage, the Agency recommended the Applicant use the analysis result based on the ITT population and the MCMC imputation with the MAR assumption in the label. The Agency also recommended the Applicant conduct sensitivity analyses based on the worst-case imputation, pattern mixture model, and tipping point analyses to assess results based on different missing assumptions. In addition, the Agency recommended the Applicant plot the mean change in ISM-SAF TSS from baseline to C7D1 for all patients in the ITT population by using the MCMC imputation, rather than observed patients in the ITT population.*

*The Applicant agreed and followed the Agency's recommendations.*

*The distributions of the mean changes in ISM-SAF TSS for two treatment groups are plotted in Figure 7. Comparing the density function in the placebo group, the density function in the avapritinib group shift to the left as a whole. Note that the same exercise was performed for subgroup analyses, including the subgroups by patients' baseline disease severity status (i.e., severe and moderate patients) by the statistical reviewer. Similar shifts of the distribution in the avapritinib group comparing with the placebo's distribution were observed in subgroup analyses on the primary TSS endpoints.*

*As seen from the Figure 7, there appears to be some outliers. To examine the impact of those outliers, the statistical reviewer performed a sensitivity analysis by excluding the 3 patients with extreme values of the TSS change (i.e., patients with TSS changes of -74.0, -70.6, and 17.6). The results of the sensitivity analysis remained significant with a two-sided p-value of 0.006, indicating that the statistical significance of the primary endpoint result was not caused by outliers.*

**Figure 7. Histogram of the Mean Change in ISM-SAF TSS From Baseline to C7D1, Study BLU-285-2203 Part 2**




Source: FDA analysis.

*Clinical reviewer comment: in summary, the primary endpoint results demonstrated that the mean change from baseline to C7D1 in the ISM-SAF TSS was -15.33 for the avapritinib group compared to -9.64 for the placebo group, with a difference of -5.69 (95% CI between -10.16, -1.23 points; p-value =0.012) based on the ITT population and the MCMC imputation of missing data with the MAR assumption. The statistical team conducted multiple sensitivity analysis to confirm the robustness of the primary endpoint results. A greater reduction in ISM-SAF TSS in the avapritinib group signifies improvement in ISM signs and symptoms. The difference in ISM-SAF TSS represents a clinically meaningful within-subject improvement as determined by the review team (see discussion under Section 32.3.3.)*

**Subgroup Analyses for the Primary Endpoint**

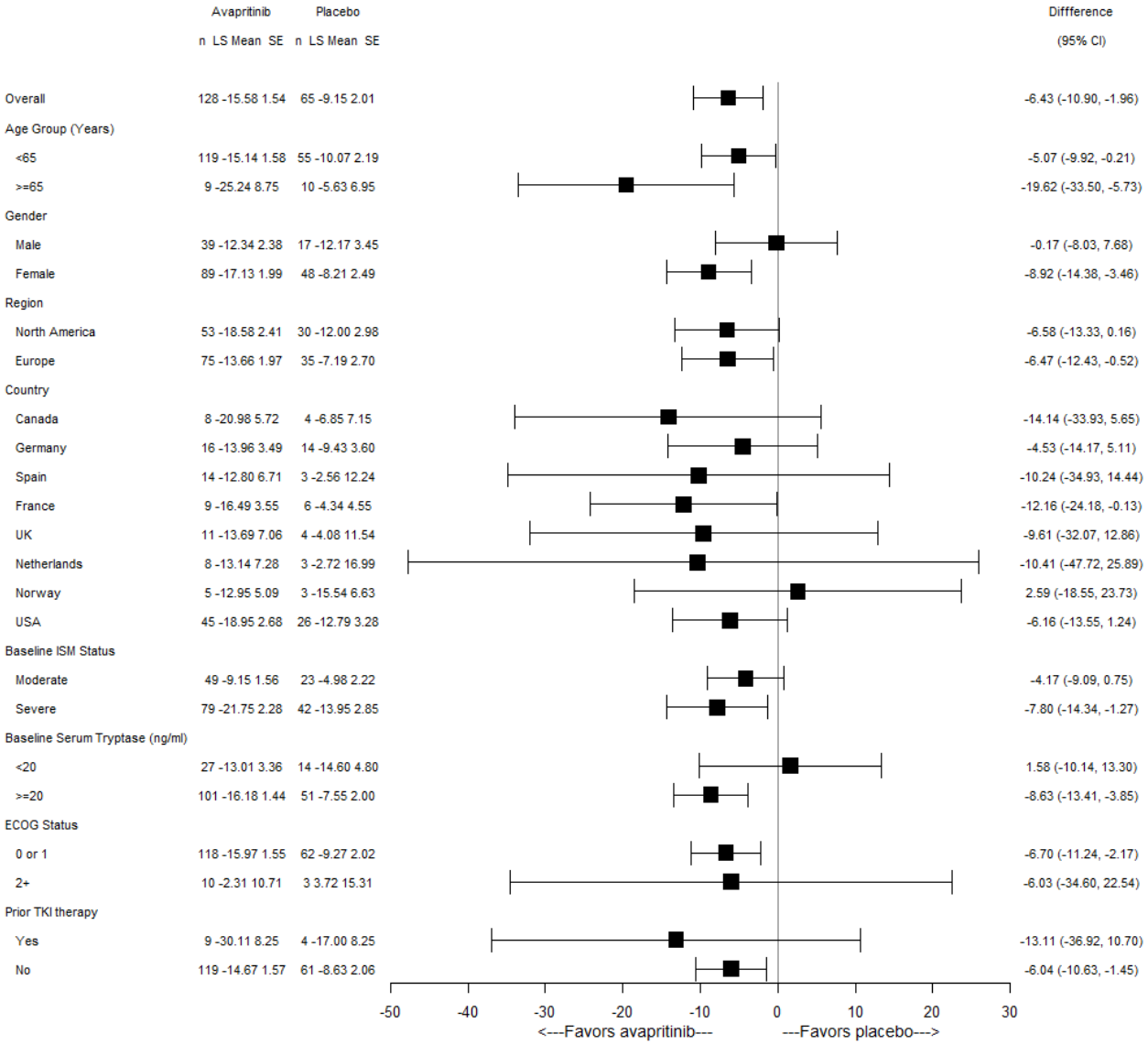
Analysis of the primary endpoint was performed for the subgroups of age (<65 years, ≥65 years), gender (male, female), region (North America, Europe), country, baseline ISM status (moderate, severe), baseline serum tryptase level (<20 ng/mL, ≥20 ng/mL), Eastern Cooperative Oncology Group Performance Scale (ECOG PS) (0 or 1, 2+), and prior tyrosine kinase inhibitor (TKI) therapy (yes, no).

The results of subgroup analyses were in general consistent with the primary analysis result as most of them favor or tend to favor avapritinib, except in subjects with baseline serum tryptase <20 ng/mL, in the country Norway, and men. However, for these three subgroups, the CIs were

wide, indicating that the estimates were associated with large variability due to the small sample sizes of the subgroups.

The forest plot of the mean change from baseline in ISM-SAF TSS at C7D1 across subgroups is shown in Figure 8.

**Figure 8. Forest Plot of Mean Change From Baseline in ISM-SAF TSS at C7D1 Across Subgroups, Study BLU-285-2203 Part 2**




Source: The Applicant's clinical study report and FDA analyses.
Abbreviations: CXDX, Cycle X Day X; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; TSS, Total symptom score; LS Mean, least squares Mean; SE, standard error; CI, confidence interval; NA, not applicable; ECOG, Eastern Cooperative Oncology Group; TKI, tyrosine kinase inhibitor.

**Efficacy Results for Key Secondary Endpoints**

The primary analyses for the Applicant's proposed key secondary endpoints were conducted on the ITT population. The results are summarized in Table 12**.**

**Table 12. Analyses Results for the Applicant's Proposed Key Secondary Endpoints, Study BLU-285-2203 Part 2—Intent-to-Treat Population**

| Key Secondary Endpoint | Avapritinib 25 mg N Least Squares Mean (95% CI) | Placebo N Least Squares Mean (95% CI) | Difference Between Avapritinib and Placebo (95% CI) [a] | Odds Ratio (95% CI) | 2-Sided P-value [b] |
|---|---|---|---|---|---|
| % of subjects with a ≥50% reduction in serum tryptase | N=141<br>53.9<br>(45.3, 62.3) | N=71<br>0<br>(0.0, 5.1) | 55.5<br>(47.2, 63.7) | NE<br>(30.59, NE) | <0.0001 |
| % of subjects with a ≥50% reduction in peripheral blood KIT D816V MAF or undetectable (95% CI) | N=118<br>67.8<br>(58.6, 76.1) | N=63<br>6.3<br>(1.8, 15.5) | 62.6<br>(52.2, 73.0) | 39.34<br>(10.93, 140.56) | <0.0001 |
| % of subjects achieving ≥50% reduction in TSS (95% CI) | N=141<br>24.8<br>(17.9, 32.8) | N=71<br>9.9<br>(4.1, 19.3) | 15.3<br>(5.3, 25.3) | 3.10<br>(1.24, 8.64) | 0.009 |
| % of subjects achieving ≥30% reduction in TSS (95% CI) | N=141<br>45.4<br>(37.0, 54.0) | N=71<br>29.6<br>(19.3, 41.6) | 16.9<br>(3.4, 30.3) | 2.07<br>(1.08, 3.99) | 0.020 |
| % of subjects with a ≥50% reduction in bone marrow mast cells or no aggregates (95% CI) | N=106<br>52.8<br>(42.9, 62.6) | N=57<br>22.8<br>(12.7, 35.8) | 33.8<br>(19.7, 47.9) | 4.74<br>(2.06, 11.45) | <0.0001 |

Source: The Applicant's clinical study report and FDA analyses.
[a] The common rate difference is from Mantel-Haenszel stratum weights controlling for randomization stratification factor (tryptase) and Baseline ISM status (moderate versus severe).
[b] Two-sided p-value is from Cochran-Mantel-Haenszel test controlling for randomization stratification factor (tryptase) and baseline ISM status (moderate versus severe).
Abbreviations: TSS, Total symptom score

At C7D1, 53.9% of subjects in the 25 mg avapritinib group (95% CI: 45.3, 62.3) versus 0% of subjects in the placebo group (95% CI: 0.0, 5.1) achieved ≥50% reduction in serum tryptase. The odds ratio was statistically significant with a 2-sided p-value<0.0001.

At C7D1, 67.8% of subjects in the 25 mg avapritinib group (95% CI: 58.6, 76.1) versus 6.3% of subjects in the placebo group (95% CI: 1.8, 15.5) achieved either ≥50% reduction in KIT D816V MAF or became undetectable (<0.02%). The odds ratio was statistically significant with a 2-sided p-value<0.0001.

At C7D1, 24.8% of subjects in the 25 mg avapritinib group (95% CI: 17.9, 32.8) versus 9.9% of subjects in the placebo group (95% CI: 4.1, 19.3) achieved ≥50% reduction in the ISM-SAF TSS. The odds ratio was statistically significant with a 2-sided p-value=0.009.

At C7D1, 45.4% of subjects in the 25 mg avapritinib group (95% CI: 37.0, 54.0) versus 29.6% of subjects in the placebo group (95% CI: 19.3, 41.6) achieved ≥30% reduction in the ISM-SAF TSS. The odds ratio was statistically significant with a 2-sided p-value=0.020.

At C7D1, 52.8% of subjects in the 25 mg avapritinib group (95% CI: 42.9, 62.6) versus 22.8% of subjects in the placebo group (95% CI: 12.7, 35.8) achieved ≥50% reduction in bone marrow mast cells or no mast cell aggregates. The odds ratio was statistically significant with a 2-sided p-value<0.0001.

The 2-sided p-values for all key secondary endpoints proposed by the Applicant were smaller than the prespecified threshold of 0.05.

The results of sensitivity analyses for the Applicant's proposed key secondary endpoints on the PP population are summarized in Table 13.

**Table 13. Analyses Results for the Applicant's Proposed Key Secondary Endpoints, Study BLU-285-2203 Part 2—Per-Protocol Population**

| Key Secondary Endpoint | Avapritinib 25 mg N Least Squares Mean (95% CI) | Placebo N Least Squares Mean (95% CI) | Difference Between Avapritinib and Placebo (95% CI) [a] | Odds Ratio (95% CI) | 2-Sided P-value [b] |
|---|---|---|---|---|---|
| % of subjects with a ≥50% reduction in serum tryptase | N=123<br>53.7<br>(44.4, 62.7) | N=67<br>0<br>(0.0, 5.4) | 56.5<br>(47.7, 65.2) | NE<br>(30.39, NE) | <0.0001 |
| % of subjects with a ≥50% reduction in peripheral blood KIT D816V MAF or undetectable (95% CI) | N=103<br>68.0<br>(58.0, 76.8) | N=61<br>6.6<br>(1.8, 15.9) | 62.2<br>(51.4, 73.0) | 41.06<br>(10.46, 146.26) | <0.0001 |
| % of subjects achieving ≥50% reduction in TSS (95% CI) | N=123<br>27.6<br>(20.0, 36.4) | N=67<br>7.5<br>(2.5, 16.6) | 20.6<br>(10.1, 31.0) | 4.53<br>(1.72, 16.75) | <0.001 |
| % of subjects achieving ≥30% reduction in TSS (95% CI) | N=123<br>48.0<br>(38.9, 57.2) | N=67<br>28.4<br>(18.0, 40.7) | 19.4<br>(5.2, 33.6) | 2.28<br>(1.16, 4.61) | 0.011 |
| % of subjects with a ≥50% reduction in bone marrow mast cells or no aggregates (95% CI) | N=91<br>51.6<br>(40.9, 62.3) | N=54<br>24.1<br>(13.5, 37.6) | 29.9<br>(15.0, 44.9) | 4.01<br>(1.69, 9.75) | <0.001 |

Source: The Applicant's clinical study report and FDA analyses.
[a] The common rate difference is from Mantel-Haenszel stratum weights controlling for randomization stratification factor (tryptase) and baseline ISM status (moderate versus severe).
[b] Two-sided p-value is from Cochran-Mantel-Haenszel test controlling for randomization stratification factor (tryptase) and baseline ISM status (moderate versus severe).
Abbreviations: TSS, Total symptom score

The sensitivity analysis results based on the PP population for the Applicant's proposed key secondary endpoints were similar and consistent with the primary analysis results.

For the KIT D816V MAF endpoint, the sensitivity analysis conducted on the subset of subjects with baseline MAF ≥0.1% showed consistent results with the primary analysis result.

For binary TSS endpoints, the sensitivity analysis that excludes subjects with missing baseline TSS and the sensitivity analysis based on subjects with a complete set of baseline and C7D1 TSS scores also showed consistent results with the primary analysis results.

*Statistical reviewer's comment: during the IND stage, the Applicant moved the binary TSS endpoint with the 30% threshold to the list of key secondary endpoints because the primary endpoint was modified to be the change from baseline on TSS per the Agency's recommendation. Besides the 30% improvement, the Applicant also added 50% improvement on TSS as a key secondary endpoint. Although both binary TSS endpoints with the 30% and 50% thresholds were prespecified in the SAP, these two key secondary endpoints were selected with inadequate rationale and justification. The Agency informed the Applicant that the Agency had concerns with the Applicant's proposed binary TSS endpoints with a 30% or 50% threshold due to insufficient evidence to support the proposed responder thresholds* (b) (4) .

*During the sNDA review,* (b) (4) *Please refer to Section 32.3.3 for further details.*

# 32.3. Key Efficacy Review Issues

## 32.3.1. Prespecified Primary Analysis Population for the Primary Endpoint Was Not Based on the Intent-to-Treat Population

**Issue**

The Agency did not agree with the prespecified primary analysis population for the primary endpoint.

**Background**

The primary analysis method of the primary endpoint prespecified in the SAP was an ANCOVA model controlling for randomization stratification factor serum tryptase and baseline ISM status on the observed cases on the ITT population. Therefore, the prespecified primary analysis population was actually a modified ITT (mITT) instead of the ITT population. During the IND stage, the Agency informed the Applicant that the Agency did not agree with the prespecified

primary analysis method because the primary analysis should be based on the ITT population. However, the Applicant did not address this comment before the sNDA submission.

**Assessment**

The difference in mean change in ISM-SAF TSS from baseline to C7D1 in the avapritinib group and placebo group were statistically significant in both the mITT and ITT populations, see Section 32.2.1.3 for further details. The Agency recommended the Applicant use the analysis result based on the ITT population and the MCMC imputation with the MAR assumption in the label. The Agency also recommended the Applicant conduct sensitivity analyses based on the worst-case imputation, pattern mixture model, and tipping point analyses to assess results based on different missing assumptions. The results of these sensitivity analysis are described in Section 32.2.1.3.

**Conclusion**

The Applicant agreed to use the analysis results based on the ITT population and the MCMC imputation with the MAR assumption in the label and results were statistically significant. The Applicant also conducted additional sensitivity analyses as recommended by the Agency. The results of all sensitivity analyses were in general consistent with the prespecified primary analysis result. The Agency's concerns about the analysis population for the primary endpoint have been addressed.

### 32.3.2. Fitness for Purpose of ISM-SAF To Support the Primary and Key Secondary Efficacy Endpoints

**Issue**

In the clinical program conducted to support this sNDA, the Applicant used the ISM-SAF instrument to assess the primary and key secondary efficacy endpoints. This section discusses whether the ISM-SAF is fit-for-purpose.

**Background**

The Applicant proposed using the ISM-SAF to assess ISM-related signs and symptoms to support the primary and key secondary efficacy endpoints (refer to Section 32.2.1.1 for a description of the instrument). In the final written response dated April 18, 2018, the FDA acknowledged that the Applicant's PRO development plan for the ISM-SAF appeared reasonable. However, the FDA communicated to the Applicant that the final data generated from their developmental activities (including psychometric evaluation) would ultimately help determine whether the ISM-SAF is fit-for-purpose to demonstrate evidence of clinical benefit and relevant labeling claims. The FDA also provided advice to help optimize measurement with the ISM-SAF (e.g., exclude nonspecific signs and symptoms, use well-defined measurement concepts).

The Applicant evaluated the other measurement properties of the ISM-SAF using Part 1 of Study BLU-285-2203. In response to their evaluation, the FDA provided Post meeting Comments via email communication dated June 10, 2020, that they were unable to comment on the reliability, validity, and score interpretability of the ISM-SAF TSS due to the small sample size (n=38) used

in Part 1 which limits interpretation of the psychometric analyses. The FDA noted that the psychometric results should be cautiously interpreted and may not be generalizable to future studies (i.e., Part 2). The FDA recommended that the Applicant confirm the psychometric properties of the ISM-SAF TSS and threshold for meaningful score change using Part 2 of Study BLU-285-2203, as a larger sample size was expected in Part 2 compared to Part 1.

In the Meeting Minutes dated October 5, 2022, the FDA recommended the Applicant to submit a PRO evidence dossier to support the adequacy of the ISM-SAF instrument.

**Assessment**

The review team assessed the Applicant's *Indolent Systemic Mastocytosis-Symptom Assessment Form (ISM-SAF): Clinical Outcome Assessment Evidence Dossier* (Version 8.0 dated October 28, 2022 (hereafter referred to as the PRO evidence dossier). The ISM-SAF was reviewed for content validity and other measurement properties.

**Content Validity**

The Applicant completed the following instrument development activities to evaluate the content validity of the ISM-SAF:

- Targeted literature review
- Expert input (four therapeutic area experts)
- Patient input (16 concept elicitation and 10 cognitive interviews)

The review team evaluated the data generated from these instrument development activities.

Both literature and input from experts and patients confirmed that the content of the ISM-SAF was mostly relevant to the patient experience with ISM. In general, the instrument was well-understood and interpreted as intended (refer to the Applicant's PRO evidence dossier for the full summary results of subjects' understanding and relevance of the ISM-SAF). However, there were some content validity issues identified with the construction of these instruments:

- Potential incomprehension of concepts (brain fog, spots on skin, bone pain). While the qualitative study results showed that the majority of the participants (n $\geq$8 of 10, 80%) interpreted the items as intended, there were some items in which participants requested further clarification of the symptoms (e.g., suggested adding definitions and/or revising item wording).
- Item relevancy questionable for select items (nausea, headaches, dizziness, diarrhea frequency). The qualitative study results showed that majority (>50%) of the participants reported that they did not experience these symptom(s) in the referenced timeframe (i.e., "past 24 hours").

Concerns regarding item relevancy for select items were consistent with the quantitative results observed from the Applicant's noninterventional, observational study which are described in the Other Measurement Properties section. However, they were mitigated to a certain extent due to the baseline data from Part 2 of Study BLU-285-2203 (see Other Measurement Properties section).

**Other Measurement Properties**

The Applicant evaluated the other measurement properties of the ISM-SAF using data from the following sources:

- Observational study (n=103): a prospective, noninterventional, observational survey study to conduct an exploratory psychometric evaluation of the ISM-SAF scores in U.S. participants diagnosed with ISM or SSM. Participants completed PRO assessments using a web-based electronic platform (SurveyMonkey) over the course of 15 days.
- Study BLU-285-2203 (n=243): a multicenter, randomized, double-blind, placebo-controlled Phase 2 study to evaluate the safety and efficacy of avapritinib in subjects with ISM. Study BLU-285-2203 consisted of Part 1 (n=39) and Part 2 (n=212), which were combined for the psychometric analyses of ISM-SAF.

The findings from the psychometric analyses conducted in the observational study and Part 1 of Study BLU-285-2203 should be cautiously interpreted due to the small sample sizes. The analysis population in the observational study was predominantly white (n=101 of 103, 98.1%), female (n=84 of 103, 81.6%) with a mean age of 50.2 years (SD =12.6 years), which was consistent with the enrolled population in Parts 1 and 2 of Study BLU-285-2203 [white (n=200 of 243, 82.3%), female (n=179 of 243, 73.7%) with a mean age of 50 years (SD =12 years)].

Based on the review team's assessment, the results from the construct validity (convergent validity, divergent validity, and known groups validity) and responsiveness analyses were generally within acceptable and reasonable range. However, the following issues were identified with the other measurement properties:

- Item relevancy. Based on item-level distributional data from the observational study, >40% (n >42 of 103) of participants endorsed the least severe response category (i.e., "no symptom") at baseline (e.g., nausea, dizziness, headache). While these results are consistent with the qualitative study findings, it is inconsistent with the baseline data from Part 2 of Study BLU-285-2203 where few participants (n ≤24 of 206, 12%) endorsed the least severe response category for all symptom items at baseline. These inconsistent findings may be a result of the heterogeneity of ISM.
- Potential inadequate scoring algorithm. There is a lack of sufficient evidence to adequately support the scoring algorithm for the TSS including the use of a total score and biweekly average score.
  - While the Applicant conducted interitem correlations and multitrait multi-item analyses, they did not conduct a confirmatory factor analysis to support the unidimensionality of the ISM-SAF (i.e., the instrument items can adequately be summed to generate a total score). However, on face the items included in the total score are of similar concepts (i.e., sign and symptom severity).
  - The Applicant's justification for using a 14-day average was based on the unpredictability of patients' symptom experience and unknown triggers of symptom flare-ups (i.e., variability in ISM symptom severity). To further support this justification, the FDA requested the Applicant to conduct sensitivity analyses for the primary and 3rd and 4th ranked key secondary efficacy endpoints using a weekly average score. The results from these sensitivity analyses were similar to the results with the use of a biweekly average score.

*COA reviewer's comment: the Applicant evaluated the reliability (i.e., internal consistency reliability) of the 14-day average score using data from the observational study. The results from these analyses were within acceptable and reasonable range.*

- There was concern regarding data missingness within the 14-day timeframe of the biweekly average score. However, the Applicant provided frequency distributions of participants who missed one to seven consecutive days and/or nonconsecutive days in Part 2 of Study BLU-285-2203 which demonstrated that the majority of the participants (n >202 of 243, 95%) had one day or less missing TSS data. Few participants (n ≤3 of 243, 1.2%) had six or seven consecutive days missing during Part 2 of Study BLU-285-2203.

  *COA reviewer's comment: In the PRO evidence dossier, the Applicant indicated that the 50% rule of thumb (requiring at least 7 of the 14 days; with one to seven missed days, consecutive or nonconsecutive allowed) was a balance between including data that are available, but still having sufficient data to have confidence in the scores produced.*

  For more details regarding the Applicant's justification of the scoring algorithm, refer to the Applicant's response to FDA Information Request dated March 24, 2023 (SDN207, eCTD SN0130).

For more details on the analysis population, methodology and results of the psychometric analyses, refer to the Applicant's PRO evidence dossier.

**Conclusion**

The review team concurs that the Applicant reasonably established content validity and the other measurement properties for the ISM-SAF. The instrument may be optimized by further defining some of the concepts (e.g., brain fog, spots on skin) to avoid potential patient incomprehension. The scoring algorithm (i.e., dimensionality of the instrument) for the ISM-SAF TSS may need to be further explored and confirmed.

### 32.3.3. Clinical Meaningfulness of ISM-SAF TSS for the Primary and Key Secondary Efficacy Endpoints

**Issue**

The clinical meaningfulness of the ISM-SAF TSS-based primary and key secondary efficacy endpoint results was challenging to interpret due to the following:

- *Sub-Issue 1*: The evaluation of clinically meaningful within-subject change in the primary endpoint of absolute change in the ISM-SAF TSS from baseline to C7D1 was challenging due to limitations of the anchor scales and the absence of supportive qualitative data.
- *Sub-Issue 2*: There was insufficient evidence to support that the prespecified ≥50% reduction in the ISM-SAF TSS responder endpoint was located above the threshold(s) representing a clinically meaningful within-subject improvement prior to the initiation of the phase 3 study.
- *Sub-Issue 3*: The prespecified ≥30% reduction in the ISM-SAF TSS responder threshold was based on Part 1 data (i.e., C4D1) of Study BLU-285-2203 and did not represent a clinically meaningful within-subject improvement based on Part 2 data (i.e., C7D1) of Study BLU-285-2203.

**Background**

**Sub-Issue 1**

During the IND phase, FDA recommended the Applicant to evaluate and justify the clinical relevance of any observed treatment effect in the primary endpoint by conducting anchor-based analyses supplemented with empirical cumulative distribution function (eCDF) and probability density function (PDF) curves using pooled data (across study arms) to evaluate the meaningfulness of different within-subject changes.

In the final written response dated April 18, 2018, the FDA expressed concerns regarding the Applicant's anchor scales (i.e., Patient Global Impression of Severity [PGIS] and Patient Global Impression of Change [PGIC] scales; refer to Section 42.1 for copies of the instruments):

- Regarding the PGIS scale, the concern was that participants may not be able to distinguish between some of the response categories (e.g., severe versus very severe). FDA recommended the Applicant to use a PGIS scale with a 4-point verbal rating scale.
- Regarding the PGIC scale, the concern was that some of the response category descriptions in item 1 were unclear and only assessed improvement and not worsening. FDA recommended including a PGIC scale that included a balanced response scale assessing both improvement and worsening.

Further, in the Meeting Preliminary Comments dated March 25, 2022, the FDA reiterated the limitations of the anchors. Specifically, the PGIC scale did not appear to be adequate due to several limitations (e.g., misaligned measurement concepts, misaligned recall period, potential recall error, unbalanced and illogical response options, high number of response options). Additionally, the PGIS scale had its own limitations (e.g., misaligned recall period, potential incomprehension of response categories). Given these concerns, the Applicant indicated in the PRO evidence dossier that only PGIS was being used as an anchor to inform the interpretation of the ISM-SAF TSS.

Due to the limitations of the anchor scales, the FDA recommended the Applicant to collect qualitative exit interview data to help facilitate the interpretation of the quantitative anchor-based analysis results. Despite this advice, the Applicant did not collect and submit any qualitative data to aid in the interpretation of the ISM-SAF TSS-based endpoints in Study BLU-285-2203.

**Sub-Issue 2**

The Applicant included the proportion of subjects with a 50% or greater reduction in the ISM-SAF TSS at C7D1 as a key secondary efficacy endpoint in the final version of the SAP submitted on June 08, 2022. This key secondary endpoint was not agreed upon by FDA prior to the pre-sNDA meeting held on September 19, 2022 (Meeting Minutes dated on October 5, 2022). FDA cautioned the Applicant that there was insufficient evidence to support the proposed responder threshold.

**Sub-Issue 3**

The ≥30% reduction in the ISM-SAF TSS responder endpoint was prespecified by the Applicant based on Part 1 data (i.e., C4D1) of Study BLU-285-2203. During the IND phase, FDA cautioned the Applicant that further evidence would be needed to support that ≥30% the ISM-

SAF TSS responder threshold as clinically meaningful using Part 2 data (Meeting Preliminary Comments dated May 19, 2020; Postmeeting FDA Comments via email communication dated June 10, 2020; Meeting Minutes dated May 24, 2022; FDA Comments via email communication dated June 2, 2022 and July 22, 2022). FDA's concern with the ≥30% the ISM-SAF TSS responder threshold established using Part 1 data were further confirmed by the Applicant's own analyses. According to the Applicant's written response dated March 24, 2023 to FDA's information request dated March 09, 2023, the Applicant's anchor-based analyses suggested a meaningful within-subject change responder threshold of 39.8% reduction in the ISM-SAF TSS using Part 2 data with the PGIS scale.

**Assessment**

**Sub-Issues 1, 2 and 3**

Of note, for development programs utilizing COA-based endpoints, it is important to evaluate how well results of a COA-based endpoint correspond to a treatment benefit that is meaningful to patients. Based on the FDA Guidance for Industry *Patient-Reported Outcome Measures*: Use in Medical Product Development to Support Labeling Claims, sponsors should use anchor-based methods[1] to directly incorporate patients' perspectives to help interpret the clinical meaningfulness of COA-based endpoint results. Anchor-based analyses should be conducted based on pooled data across arms and the clinically meaningful within-subject change threshold(s) identified should not be derived based on maximizing the between group difference.

According to the Applicant's PRO evidence dossier, the Applicant conducted anchor-based analyses based on Part 1 data from BLU-285-2203. All analyses were then replicated based on pooled data from Part 1 and Part 2 to confirm the clinically meaningful within-subject change thresholds derived using Part 1 data. Table 14 summarizes the anchors utilized by the Applicant. While the PGIS scale does have limitations, the review team considered it to still be informative. As such the PGIS scale was used as the primary anchor to support the quantitative anchor-based analyses.

[1] Anchor scale(s) are used as external criteria to define patients who have or have not experienced a meaningful change in their condition, with the change in PRO score observed in these sets of patients referenced in the interpretation of within-subject change scores.

**Table 14. Summary of Proposed Anchor Scales for ISM-SAF**

| COA Attribute | Anchor (Concept) | Anchor Response Scale | Recall Period (Target/Anchor) | Timing of Endpoint (Target/Anchor) |
|---|---|---|---|---|
| ISM-SAF (Symptom severity) | PGIS scale (symptom severity) | 5-point NRS: Absent, Minimal, Moderate, Severe, Very Severe | 24 hours/ Momentary ("right now") | C7D1/C7D1 |
| | PGIC scale item 1 (SM status: activity limitations, symptoms, emotions, and overall quality of life) | 7-point VRS: No Change, Almost the Same, A Little Better, Somewhat Better, Moderately Better, Better, A Great Deal Better | 24 hours/ comparison of current state to earlier period ("since beginning treatment at this clinic") | C7D1/C7D1 |
| | PGIC scale item 2 (SM status) | 11-point NRS: Much Better, No Change, Much Worse | 24 hours/ comparison of current state to earlier period ("since beginning care at this clinic") | C7D1/C7D1 |

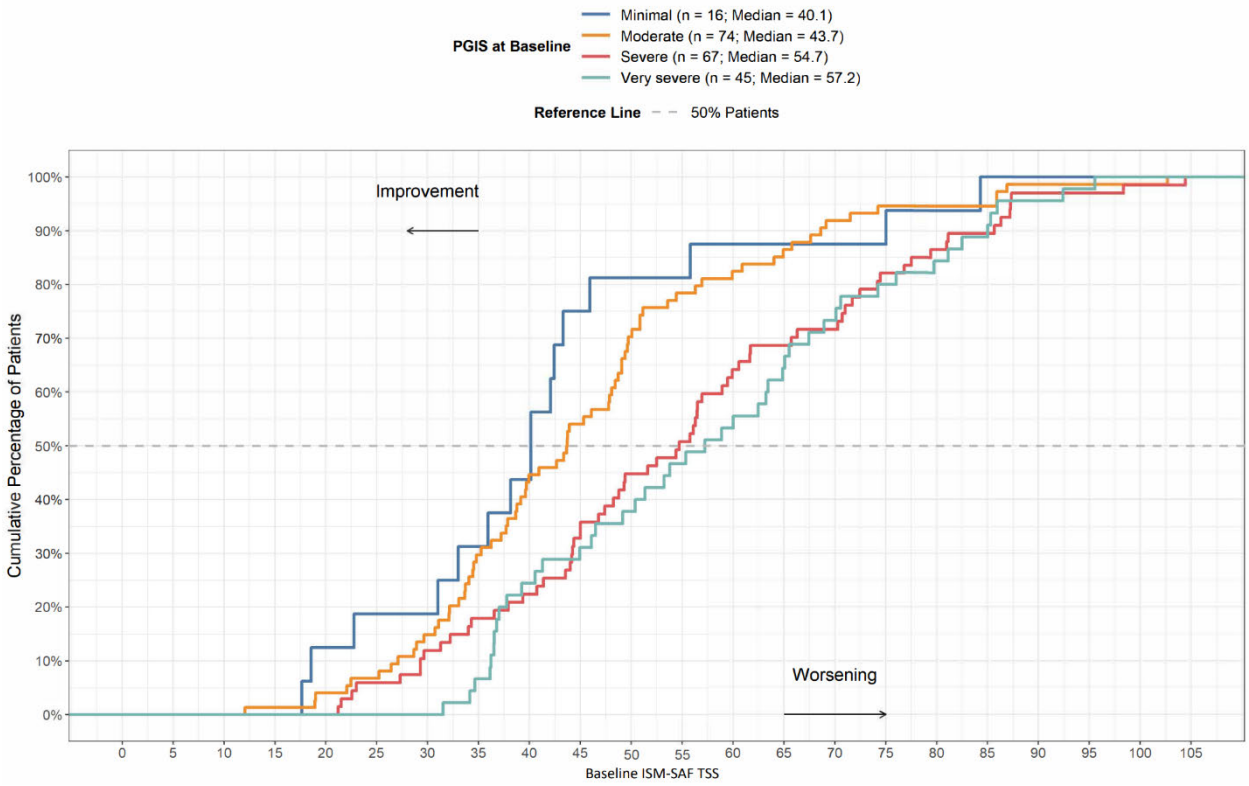
Source: Reviewer's table.
Abbreviations: C7D1, cycle 7 day 1; COA, clinical outcome assessment; NRS, numeric rating scale; PGIS, Patient Global Impression of Severity; PGIC, Patient Global Impression of Change.

The Applicant's anchor-based analyses included in the PRO evidence dossier did not propose a threshold, or a range of thresholds for the absolute change in the ISM-SAF TSS as meaningful improvement to patients. For the percent change in the ISM-SAF TSS, the Applicant proposed a single responder threshold of a 30% improvement in the ISM-SAF TSS as a meaningful improvement to patients. FDA issued an IR on March 09, 2023 to request additional anchor-based analyses based on absolute change and percent change from baseline to C7D1 using Part 2 data only. The Applicant provided a written response to the IR on March 24, 2023 and reported "the absolute change in TSS at C3D1, C4D1, and C7D1 was -13.5, -15.1, and -20.9 points, respectively, with corresponding percent change ranging from -26.9% to -39.8% [-26.9%, -29.4%, and -39.8%, respectively]." Furthermore, despite the higher threshold estimated based on C7D1 data (i.e., -39.8%) the Applicant concluded that the results were consistent with the prespecified responder threshold of ≥30% reduction in the ISM-SAF TSS and that this threshold is considered a clinically meaningful improvement to patients. The Applicant did not provide additional evidence to support the proposed responder threshold of ≥50% reduction in the ISM-SAF TSS is clinically meaningful to patients.

FDA reviewed the Applicant's anchor-based analyses using Part 2 data and conducted independent analyses based on absolute change and percent change in the ISM-SAF TSS at C7D1. FDA's anchor-based analyses, that took into consideration of both subjects' baseline symptom severity and the limitations of the PGIS scale, suggested a meaningful within-subject improvement range should be 18.8 to 21.2-points and 43.5% to 50.2% in absolute change and percent change from baseline to C7D1, respectively (more detailed discussion below).

The Applicant relied on a collapsed 1- to 2-category improvement on the PGIS scale from baseline to C7D1 to conduct their anchor-based analyses with the justification that "given overlapping 95% [confidence intervals] CIs in percent change TSS (i.e., patients with a two-category PGIS change could not be distinguished from those with a one-category PGIS change), use of a collapsed one- to two-category change in PGIS would constitute meaningful benefit in ISM patients." This justification appeared incomplete and required further investigation. As part of the review team's assessment of the appropriateness of the PGIS scale, the PGIS response category at baseline was evaluated. As can be seen in the eCDF plot of baseline ISM-SAF TSS by PGIS category at baseline below (Figure 9), the "Severe" and "Very severe" curves overlapped, and the "Minimal" and "Moderate" curves also had notable overlaps, indicating that the issue noted by the Applicant likely arose from subjects with comparable baseline severity as assessed by the ISM-SAF TSS choosing among overlapping response levels such that a 1- or 2-category change on the PGIS scale reflected similar change on the underlying symptom severity.

**Figure 9. eCDF, Baseline ISM-SAF TSS by PGIS Category at Baseline, Study BLU-285-2203 Part 2**




Source: Reviewer's figure
Abbreviations: eCDF, empirical cumulative distribution function; PGIS, patient global impression of severity

The review team made the decision to first consider the overlapping PGIS response categories together then leverage both a 1-category and a 2-category improvement on the PGIS scale to derive a range of clinically meaningful within-subject change thresholds.

On the PGIS scale, a 1-category and 2-category improvement could occur in the following ways (Table 15):

**Table 15. 1-Category and 2-Category Improvement on the PGIS Scale**

| | PGIS at C7D1 | |
|---|---|---|
| **PGIS Scale at Baseline** | **1-Category Improvement** | **2-Category Improvement** |
| Very severe | Severe | Moderate |
| Severe | Moderate | Minimal |
| Moderate | Minimal | Absent |
| Minimal | Absent | NA |

Source: Reviewer's table.
Abbreviations: C7D1, cycle 7 day 1; PGIS, patient global impression of severity; NA, not applicable.

What subjects consider to be a clinically meaningful improvement may be impacted by their baseline symptom severity. Subjects' baseline symptom severity should be considered when determining a range of clinically meaningful within-subject change thresholds. Table 16 shows the distribution of change patterns in PGIS scale between baseline and C7D1 using data pooled across arms. The majority of subjects reported "Moderate" to "Very severe" symptoms at baseline. For subjects who reported "Moderate" symptoms, 38.2% reported a 1-category improvement. For subjects who reported "Severe" symptoms at baseline, 33.3% reported a 1-category of improvement, followed by 25.0% reporting a 2-category improvement. For subjects who reported "Very severe" symptoms at baseline, 23.7% reported a 1-category of improvement and 47.4% reported a 2-category improvement.

**Table 16. Category Change (n [%]) in the PGIS Scale From Baseline to C7D1 by Baseline PGIS Category, Study BLU-285-2203 Part 2**

| | Change From Baseline to C7D1 in the PGIS Scale | | | | | | |
|---|---|---|---|---|---|---|---|
| **Baseline PGIS Category** | **Improved 4 Categories (N=1)** | **Improved 3 Categories (N=6)** | **Improved 2 Categories (N=33)** | **Improved 1 Category (N=56)** | **No Change (N=64)** | **Worsen 1 Category (N=19)** | **Worsen 2 Categories (N=2)** |
| Minimal (n=16) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (6.7%) | 12 (80.0%) | 1 (6.7%) | 1 (6.6%) |
| Moderate (n=74) | 0 (0%) | 0 (0%) | 0 (0%) | 26 (38.2%) | 27 (39.7%) | 14 (20.6%) | 1 (1.5%) |
| Severe (n=68) | 0 (0%) | 1 (1.7%) | 15 (25.0%) | 20 (33.3%) | 20 (33.3%) | 4 (6.7%) | 0 (0%) |
| Very severe (n=45) | 1 (2.6%) | 5 (13.2%) | 18 (47.4%) | 9 (23.7%) | 5 (13.1%) | 0 (0%) | 0 (0%) |

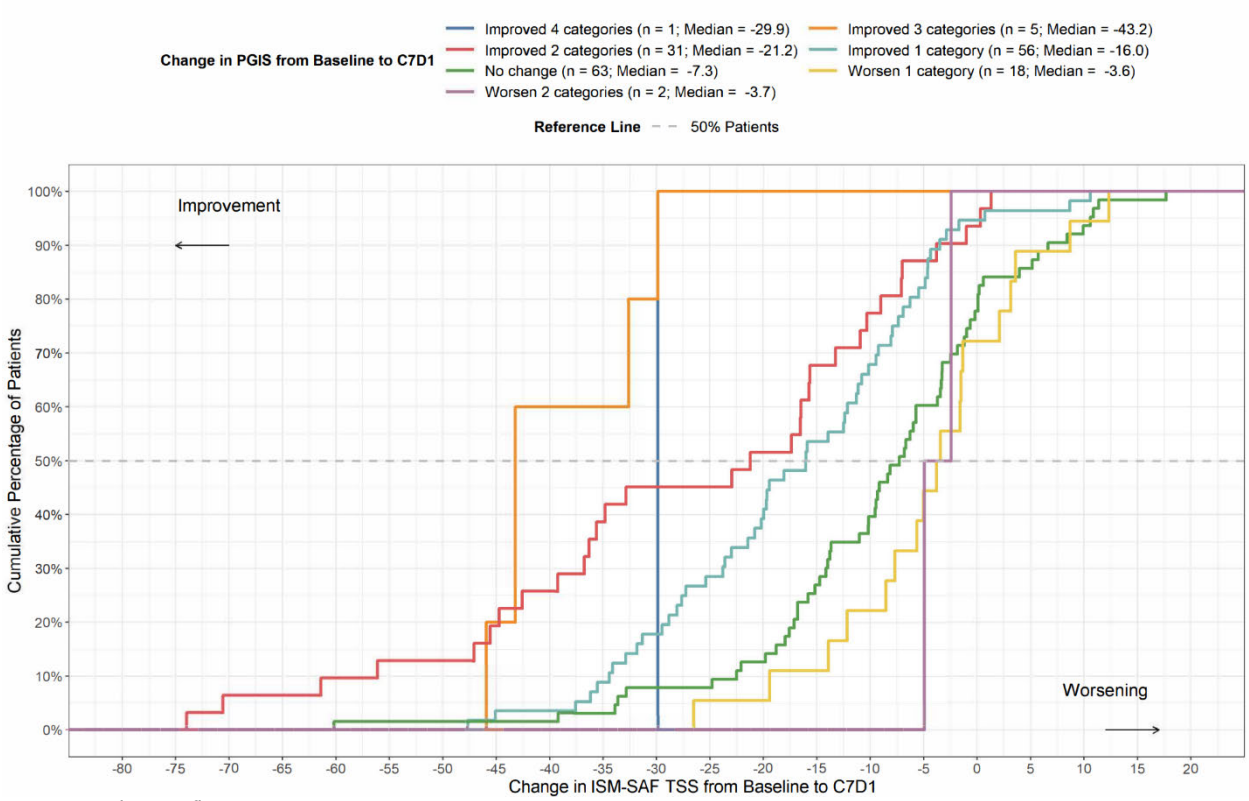
Source: Reviewer's table
Abbreviations: C7D1, cycle 7 day 1; PGIS, patient global impression of severity

Absolute Change From Baseline to C7D1 in the ISM-SAF TSS

Figure 10 below shows the eCDF plot of absolute change in the ISM-SAF TSS from baseline to C7D1 by the PGIS scale. Based on visual inspection, while a large separation was not consistently observed between the "1-category improvement" and "2-category improvement" curves, the two curves had notable large separation in the region where the absolute change in the ISM-SAF TSS is larger (i.e., lower end of the x-axis). Using a 2-category improvement and 1-category improvement on the PGIS scale as the respective lower and upper bounds, a meaningful within-subject improvement threshold range could be between -21.2- to -16.0-points. In order to minimize misclassifying subjects who did not experience a meaningful improvement

(i.e., no change and worsening in the PGIS scale) as experiencing a meaningful improvement, a threshold of at least -17-point should be considered.

**Figure 10. eCDF, Absolute Change From Baseline to C7D1 in the ISM-SAF TSS by PGIS Category of Change From Baseline, Study BLU-285-2203 Part 2**




Source: Reviewer's figure
Abbreviations: C7D1, cycle 7 day 1; eCDF, empirical cumulative distribution function; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; PGIS, patient global impression of severity; TSS, Total symptom score

When subjects' baseline PGIS score was taken into account, the median change from baseline to C7D1 in the ISM-SAF TSS for different baseline symptom severity varied (see Table 17 and Table 18 below). An 18.8-point improvement would ensure that at least 50% of subjects who were moderate at baseline experienced a meaningful change of 1-category improvement on the PGIS scale; and a 21.2-point improvement (considering "Severe" and "Very severe" together) would ensure that at least 50% of subjects who were severe to very severe at baseline experienced a meaningful change of 2-category improvement on the PGIS scale. Therefore, given the limitation of the PGIS scale and in the absence of supportive qualitative data, it is reasonable to conclude that a meaningful within-subject improvement threshold may be between 18.8-point and 21.2-point improvement in the absolute change from baseline to C7D1 in the ISM-SAF TSS.

**Table 17. Absolute Change From Baseline to C7D1 in the ISM-SAF TSS by Baseline PGIS for Subjects Who Achieved a 1-Category Improvement on PGIS, Study BLU-285-2203 Part 2**

| | | PGIS Category at Baseline | | | | |
|---|---|---|---|---|---|---|
| **Description** | **Statistics** | **Minimal (N=1)** | **Moderate (N=26)** | **Severe (N=20)** | **Very Severe (N=9)** | **Total** |
| Absolute Change from baseline to C7D1 in the ISM-SAF TSS | 10th Percentile | -27.6 | -37.5 | -29.1 | -31.8 | -34.4 |
| | 25th Percentile | -27.6 | -32.9 | -20.4 | -23.6 | -27.4 |
| | 50th Percentile | -27.6 | -18.8 | -9.7 | -19.7 | -16.0 |
| | 75th Percentile | -27.6 | -10.8 | -4.6 | -12.1 | -7.6 |
| | 90th Percentile | -27.6 | -4.6 | -1.09 | 8.6 | -3.5 |

Source: Reviewer's table
Abbreviations: C7D1, cycle 7 day 1; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; PGIS, patient global impression of severity; TSS, Total symptom score

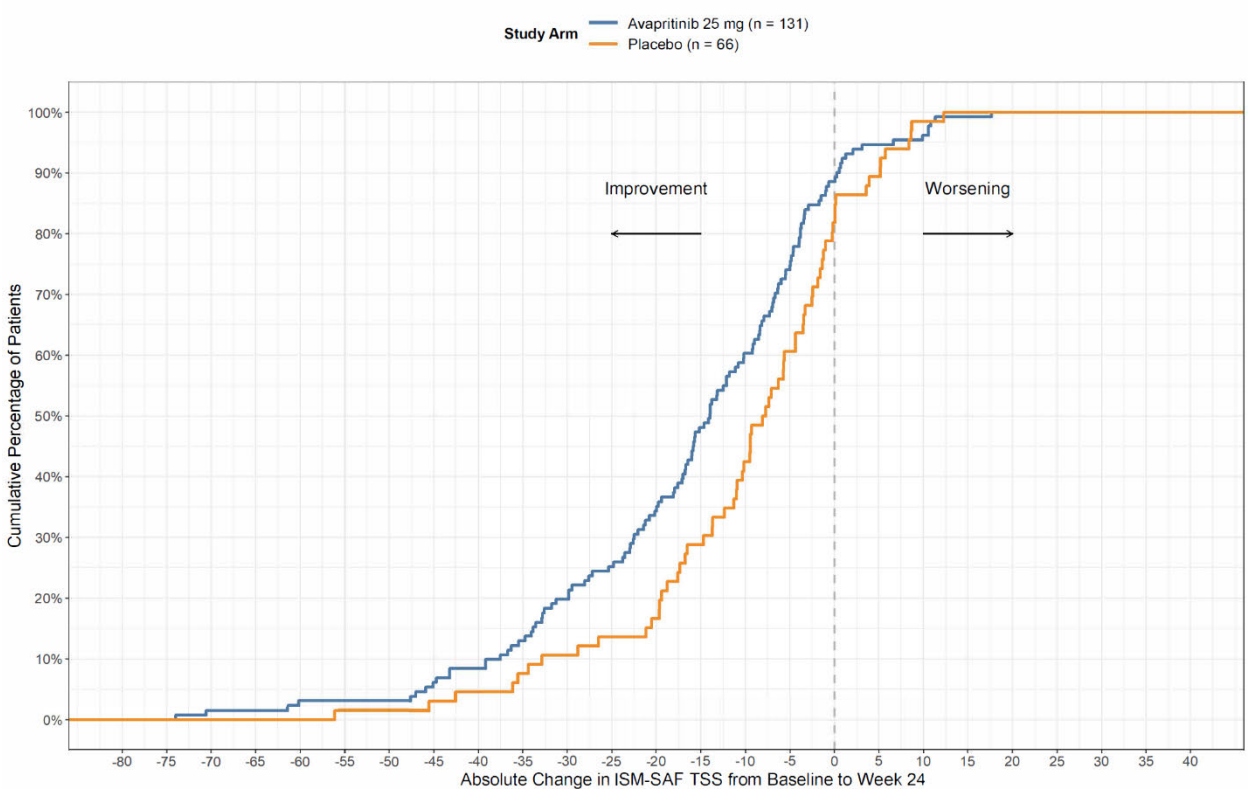
**Table 18. Absolute Change From Baseline to C7D1 in the ISM-SAF TSS by Baseline PGIS for Subjects Who Achieved a 2-Category Improvement on PGIS Scale, Study BLU-285-2203 Part 2**

| | | PGIS Category at Baseline | | |
|---|---|---|---|---|
| **Description** | **Statistics** | **Severe (N=14)** | **Very Severe (N=17)** | **Total** |
| Change from baseline to C7D1 in the ISM-SAF TSS | 10th Percentile | -56.1 | -61.4 | -56.1 |
| | 25th Percentile | -45.6 | -36.3 | -42.6 |
| | 50th Percentile | -35.2 | -16.5 | -21.2 |
| | 75th Percentile | -15.7 | -7.0 | -10.3 |
| | 90th Percentile | -10.9 | 0.3 | -3.8 |

Source: Reviewer's table
Abbreviations: C7D1, cycle 7 day 1; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; PGIS, patient global impression of severity; TSS, Total symptom score

Figure 11 below shows a supportive graph (i.e., eCDF) of within-subject changes in the ISM-SAF TSS from baseline to C7D1 with separate curves for each treatment arm. Visual inspection of the graph shows separation between the two curves in the FDA-estimated meaningful change range of 18.8-point to 21.2-point improvement). A greater proportion of subjects treated with avapritinib experienced a meaningful improvement compared to those treated with placebo.

**Figure 11. eCDF, Change in the ISM-SAF TSS From Baseline to C7D1 by Treatment Arm, Study BLU-285-2203 Part 2**

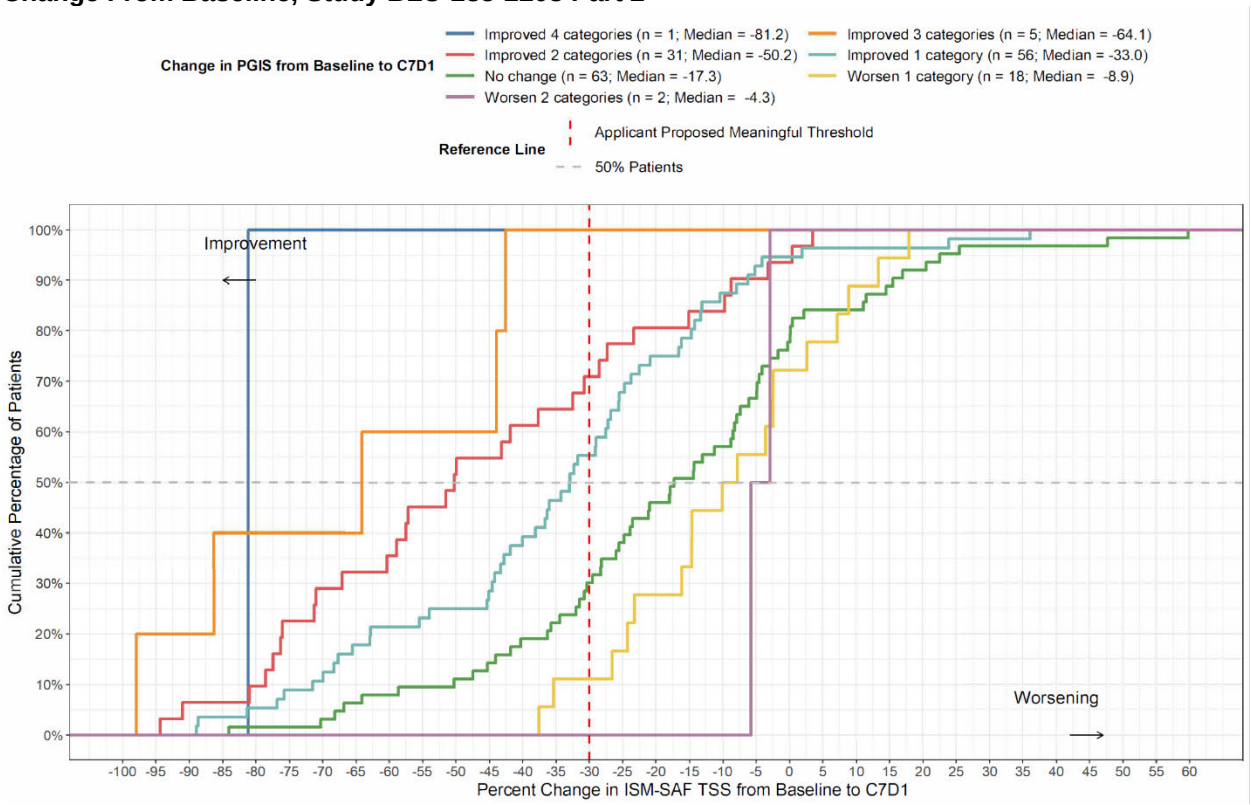



Source: Reviewer's figure
Abbreviations: C7D1, cycle 7 day 1; eCDF, empirical cumulative distribution function; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; PGIS, patient global impression of severity; TSS, total symptom score

Percent Change From Baseline to C7D1 in the ISM-SAF TSS

Figure 12 below shows the eCDF plot of percent change in the ISM-SAF TSS from baseline to C7D1 by the PGIS category of change from baseline. Similar to the observations made with the absolute change in the ISM-SAF TSS, the "1-category improvement" and "2-category improvement" curves had notable large separation in the region where the percent change in the ISM-SAF TSS is larger. Using a 2-category improvement and 1-category improvement on the PGIS scale as the respective lower and upper bounds, a meaningful within-subject improvement threshold range could be between -50.2% to -33.0.%. To minimize misclassifying subjects who did not experience a meaningful improvement (i.e., no change and worsening in the PGIS scale) as experiencing a meaningful improvement, a threshold of at least -40% should be considered.

**Figure 12. eCDF, Percent Change From Baseline to C7D1 in the ISM-SAF TSS by PGIS Category of Change From Baseline, Study BLU-285-2203 Part 2**




Source: Reviewer's figure
Abbreviations: C7D1, cycle 7 day 1; eCDF, empirical cumulative distribution function; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; PGIS, patient global impression of severity; TSS, Total symptom score; PGIS, patient global impression of severity

When subjects' baseline PGIS score was taken into account, the median change from baseline to C7D1 in the ISM-SAF TSS for different baseline symptom severity varied (see Table 19 and Table 20 below). A 43.5% improvement would ensure that at least 50% of subjects who were moderate at baseline experienced a meaningful change of 1-category improvement on the PGIS scale; and a 50.2% improvement (considering "Severe" and "Very severe" together) would ensure that at least 50% of subjects who were "Severe" to "Very severe" at baseline experienced a meaningful change of 2-category improvement on the PGIS scale. Therefore, the review team determined that a meaningful within-subject improvement threshold should be between 43.5% to 50.2% improvement in the percent change from baseline to C7D1 in the ISM-SAF TSS. These analysis results indicated that a 50% reduction in the ISM-SAF TSS could be viewed as meaningful improvement to subjects.

**Table 19. Percent Change From Baseline to C7D1 in the ISM-SAF TSS by Baseline PGIS for Subjects Who Achieved a 1-Category Improvement on the PGIS Scale, Study BLU-285-2203 Part 2**

| | | PGIS Category at Baseline | | | | |
|---|---|---|---|---|---|---|
| Description | Statistics | Minimal (N=1) | Moderate (N=26) | Severe (N=20) | Very Severe (N=9) | Total |
| Absolute Change from baseline to C7D1 in the | 10 [h] Percentile | -76.9 | -81.3 | -49.5 | -43.3 | -71.5 |
| | 25 [h] Percentile | -76.9 | -68.3 | -33.0 | -40.1 | -49.7 |

| | | PGIS Category at Baseline | | | | |
|---|---|---|---|---|---|---|
| Description | Statistics | Minimal (N=1) | Moderate (N=26) | Severe (N=20) | Very Severe (N=9) | Total |
| ISM-SAF TSS | 50 [h] Percentile | -76.9 | -43.5 | -25.3 | -32.3 | -33.0 |
| | 75 [h] Percentile | -76.9 | -27.2 | -8.3 | -24.7 | -18.7 |
| | 90 [h] Percentile | -76.9 | -13.3 | -1.1 | 23.9 | -6.2 |

Source: Reviewer's table
Abbreviations: C7D1, cycle 7 day 1; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; PGIS, patient global impression of severity; TSS, Total symptom score

**Table 20. Percent Change From Baseline to C7D1 in the ISM-SAF TSS by Baseline PGIS for Subjects Who Achieved a 2-Category Improvement on the PGIS Scale, Study BLU-285-2203 Part 2**

| | | PGIS Category at Baseline | | |
|---|---|---|---|---|
| Description | Statistics | Severe (N=14) | Very Severe (N=17) | Total |
| Change from baseline to C7D1 in the ISM-SAF TSS | 10th Percentile | -81.0 | -77.4 | -78.5 |
| | 25th Percentile | -76.0 | -49.9 | -71.3 |
| | 50th Percentile | -63.7 | -30.7 | -50.2 |
| | 75th Percentile | -51.5 | -9.7 | -27.3 |
| | 90th Percentile | -41.9 | 0.5 | -8.7 |

Source: Reviewer's table
Abbreviations: C7D1, cycle 7 day 1; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; PGIS, patient global impression of severity; TSS, Total symptom score

### Conclusion

The results of the anchor-based analyses that incorporated the subjects' perspectives taken as a whole and with due consideration to the limitations of the available anchors indicated that the observed improvement in ISM-related signs and symptoms from Part 2 of Study BLU-285-2203 in subjects treated with avapritinib, as assessed by the primary endpoint of absolute change from baseline to C7D1 in the ISM-SAF TSS, are representative of a clinically meaningful within-subject improvement. For future studies in this indication, when possible, we recommend including multiple anchors and additional qualitative evidence to facilitate the interpretation of COA-based endpoint results.

While the prespecified ≥50% reduction in the ISM-SAF TSS responder threshold appeared to represent a meaningful improvement to patients, there was a lack of clinical meaningfulness of the prespecified ≥30% reduction in the ISM-SAF TSS responder threshold.

# 33. Safety (Risk and Risk Management)

## 33.1. Potential Risks or Safety Concerns Based on Nonclinical Data

No new safety concerns for avapritinib were identified based on the nonclinical review of NDA 212608 Supplement 013 for the ISM indication.

## 33.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

The avapritinib product label approved under NDA 212608 on March 9, 2023, states in the Warnings and Precautions section that there is a potential increased risk of intracranial hemorrhage (ICH), photosensitivity, and a broad spectrum of cognitive adverse reactions can occur in patients receiving avapritinib. The label recommends discontinuing avapritinib for any occurrence of ICH. There is a Limitation of Use (LoU) for the treatment of patients with AdvSM with platelet counts of less than 50 X $10^9$/L. The product label also recommends that depending on the severity of cognitive effects that avapritinib may be continued at the same dose, withheld, and then resumed at the same or reduced dose upon improvement, or permanently discontinued. Most recently, the product label recommends that patients with photosensitivity to avapritinib should limit direct ultraviolet exposure. The most common adverse reactions in patients with AdvSM (incidence ≥20% of subjects exposed to avapritinib in clinical trials) are edema, diarrhea, nausea, and fatigue/asthenia.

*Reviewer comment: Patients with thrombocytopenia were excluded from the clinical trial including patients with ISM (Study 2203). Although no ICH events were reported among patients in trial 2203 there is still a potential risk of ICH for patients with ISM who develop thrombocytopenia with platelet counts below 50 x $10^9$/L. Therefore, the LOU for thrombocytopenia (below platelet count 50 x $10^9$/L) should also apply to patients with ISM as it does for patients with AdvSM.*

## 33.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

### 33.3.1. Adverse Events Identified in Postmarket Experiences

In NDA 212608 supporting document 158 letter date March 7, 2023 (received March 7, 2023), the Applicant submitted an Annual Report covering the reporting period from January 9, 2021, through January 8, 2022. In NDA 212608 supporting document 160 letter date March 15, 2023 (received March 15, 2023), the Applicant submitted a Periodic Benefit-Risk Evaluation Report (PBRER) covering the reporting period from July 9, 2021, to January 8, 2023. In this PBRER the Applicant states that since January 9, 2020, the overall estimated postmarketing exposure to avapritinib is (b) (4) patient-years. During the reporting interval, the estimated overall postmarketing exposure to avapritinib was (b) (4) patient-years. In addition, the Applicant reported four new cases of ICH in the overall avapritinib postmarketing safety database, of which three cases were reported to have systemic mastocytosis (SM) (disease subtype not specified in reports) and one case was reported to have AdvSM. Two of the four cases had, “platelet count reduced” noted (specific platelet counts not reported by the Applicant) and two cases had no details regarding platelet count. However, all four cases were reported to be related to avapritinib. In three of the four cases the dose of avapritinib was reported to be 100 mg administered once daily (all three cases with SM). The fourth case with AdvSM had avapritinib dose reported as unknown. All four cases had avapritinib dosing discontinued.

*Clinical reviewer comment: No new safety signals were identified in the review of the Annual Report letter date March 7, 2023, or the PBRER letter date March 15, 2021. The risk of serious and life-threatening bleeding remains a risk of avapritinib.*

### 33.3.2. Expectations on Safety

Broadly, similar safety concerns for avapritinib for the treatment of ISM can be expected as for avapritinib for the treatment of AdvSM. ISM is similar to AdvSM in that mastocytosis results from a clonal proliferation of morphologically and immunophenotypically abnormal mast cells due to mutation of the KIT D816 V allele. ISM and SSM usually have median survival measured in decades while ASM, SM-AHN and MCL have a shorter median survival measured in months to years (Horny et al. 2008). Although no ICH events were reported among subjects in trial 2203, there is still a potential risk of ICH for patients with ISM who have thrombocytopenia with platelet counts below 50 x 109/L for other reasons. Therefore, the LoU for thrombocytopenia (platelet count below 50 x 109/L) should also apply to patients with ISM as it does for patients with AdvSM receiving avapritinib therapy.

### 33.3.3. Additional Safety Issues From Other Disciplines

No new or additional safety concerns were identified from other disciplines.

## 33.4. FDA Approach to the Safety Review

In Study 2203, there were 226 subjects with ISM who were treated with avapritinib 25 mg orally once daily in Part 1 (dose finding portion of the study), Part 2 (randomized controlled portion of the study) and Part 3 (extension portion of the study). There were 246 subjects with ISM who received placebo or 25 mg avapritinib in Part 1 or Part 2, as well as the subjects who received 50 mg or 100 mg avapritinib in Part 1.

In total, 39 subjects were enrolled in Part 1 (placebo [n =9] or avapritinib [25 mg, 50 mg, 100 mg n=10 for each group]). The safety analysis primarily focused on the Part 2 (randomized, double-blind, placebo-controlled part) safety population which included 141 subjects in the 25 mg avapritinib group and 71 subjects in the placebo group. In Part 3, 235 subjects were treated with 25 mg avapritinib, of these, 75 subjects were in the placebo to 25 mg avapritinib group (received placebo in Part 1 or Part 2 and rolled over to 25 mg avapritinib in Part 3), 143 subjects were in the 25 mg to 25 mg avapritinib group (received 25 mg avapritinib in Part 1 or Part 2 and rolled over to 25 mg avapritinib in Part 3), 8 subjects were in the 50 mg to 25 mg avapritinib group (received 50 mg avapritinib in Part 1 and rolled over to 25 mg avapritinib in Part 3), and 9 subjects were in the 100 mg to 25 mg avapritinib Group (received 100 mg avapritinib in Part 1 and rolled over to 25 mg avapritinib in Part 3).

The clinical safety review focuses on part 2 of the trial which was the randomized placebo-controlled portion of the trial and the entire study consisting of all 3 parts. The review of safety was based upon:

- Clinical study report (CSR) for studies
- Protocol for studies
- Data sets for the populations described above
- Summary of clinical safety
- Patient narratives
- Case report forms

Case report forms and narratives were provided and reviewed for AEs of interest, serious adverse events (SAEs), and deaths (no deaths were reported in the trial).

No major issues were identified with the respect to recoding, coding, and categorizing AEs. The analysis dataset for adverse events data file was reviewed for accuracy of translation of the verbatim to preferred term by manual review.

## 33.5. Adequacy of the Clinical Safety Database

In Study 2203, the median duration of therapy for subjects who received 25-mg avapritinib once daily was 38.6 weeks (range 2.0, 159.4 weeks). Approximately 30% of the subjects treated with avapritinib 25 mg were treated for ≥50 weeks of therapy. The table below shows the overall duration of therapy for subjects treated with avapritinib 25 mg

**Table 21. Duration of Exposure, Safety Population, Study BLU-285-2203 Overall (Parts 1/2/3)**

| Parameter | Avapritinib 25 mg* N=226 n (%) | All N=246 n (%) |
|---|---|---|
| Duration of treatment, weeks | | |
| Mean (SD) | 45.3 (31.2) | 51.5 (39.1) |
| Median (Q1, Q3) | 38.6 (26.7, 57.4) | 42.4 (27.3, 63.4) |
| Min, max | 2, 159.4 | 0.9, 159.4 |
| Total exposure (person years) | 196 | 243 |
| Subjects treated, by duration, n (%) | | |
| <12 weeks | 28 (12.4) | 30 (12.2) |
| ≥12 to <26 weeks | 25 (11.1) | 25 (10.2) |
| ≥26 to <50 weeks | 91 (40.3) | 92 (37.4) |
| ≥50 to <100 weeks | 69 (30.5) | 70 (28.5) |
| ≥100 weeks | 13 (5.8) | 29 (11.8) |

Source: adex.xpt and adsl.xpt; Software: R
Duration is at least 12 weeks (Part 1), 24 weeks (Part 2), and up to 5 years (Part 3).
Analysis duration median (min, max) is 42.4 (0.9, 159.4) weeks.
*This group includes the subjects who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the subjects who received 50 mg or 100 mg avapritinib in Part 1.
The “All” study arm includes the subjects who received placebo or 25 mg avapritinib in Part 1 or Part 2, as well as the subjects who received 50 mg or 100 mg avapritinib in Part 1.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

In Part 2 of the study (randomized, double-blind, placebo-controlled part), subjects were exposed to avapritinib 25 mg QD in combination with BSC or placebo in combination with BSC for 24 weeks. Exposure of Part 2 of the study is described in the table below.

**Table 22. Duration of Exposure, Safety Population, Study BLU-285-2203 Part 2**

| Parameter | Avapritinib 25 mg N=141 n (%) | Placebo N=71 n (%) |
|---|---|---|
| Duration of treatment, weeks | | |
| Mean (SD) | 23.7 (3.2) | 23.6 (3.5) |
| Median (Q1, Q3) | 24.1 (24, 24.3) | 24.1 (24, 24.3) |
| Min, max | 2.9, 28.3 | 3.6, 28 |
| Total exposure (person years) | 64 | 32 |
| Subjects treated, by duration, n (%) | | |
| <12 weeks | 3 (2.1) | 2 (2.8) |
| ≥12 to <18 weeks | 0 | 2 (2.8) |
| ≥18 to <24 weeks | 31 (22.0) | 13 (18.3) |
| ≥24 weeks | 107 (75.9) | 54 (76.1) |

Source: adsl.xpt; Software: R
Duration is 24 weeks.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

*Reviewer Comment: the duration of avapritinib therapy in Study 2203 is adequate to evaluate the safety of avapritinib for the treatment of ISM.*

# 33.6. Safety Results

## 33.6.1. Safety Results, Study 2203

### 33.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Pooled Analyses

**Part 2 of Study 2203**

An overview of adverse events in Part 2 of the study is described in Table 23 below.

**Table 23. Overview of Adverse Events, Safety Population, Study BLU-285-2203 Part 2**

| Event Category | Avapritinib 25 mg N=141 n (%) | Placebo N=71 n (%) |
|---|---|---|
| SAE | 7 (5.0) | 8 (11.3) |
| SAEs with fatal outcome | 0 | 0 |
| Life-threatening SAEs | 1 (0.7) | 0 |
| AE leading to permanent discontinuation of study drug | 3 (2.1) | 1 (1.4) |
| AE leading to dose modification of study drug | 12 (8.5) | 9 (12.7) |
| AE leading to interruption of study drug | 12 (8.5) | 9 (12.7) |
| AE leading to reduction of study drug | 2 (1.4) | 1 (1.4) |
| AE leading to dose delay of study drug | 0 | 0 |

| Event Category | Avapritinib 25 mg N=141 n (%) | Placebo N=71 n (%) |
|---|---|---|
| Any AE | 128 (90.8) | 66 (93.0) |
| Severe and worse | 30 (21.3) | 15 (21.1) |
| Moderate | 50 (35.5) | 36 (50.7) |
| Mild | 48 (34.0) | 15 (21.1) |

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that occurred between the Part 2 D1 through a day prior to Part 3 D1 if patient rolled over to Part 3; through 30 days after the last dose if patient did not rollover to Part 3.
Duration is 24 weeks.
Severity as assessed by the investigator.
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; D, day; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

*Clinical reviewer comment: overall, avapritinib in combination with BSC appears well tolerated compared to placebo in combination with BSC, with a lower proportion of patients in the avapritinib arm experiencing SAEs and AEs leading to dose modification. After considering drug-relatedness of the described AEs, the clinical reviewer determined 5% of patients experienced adverse reactions (AR) leading to avapritinib dose interruption. See additional safety analysis in Section 43 of the review.*

## Pooled Analysis of Study 2203 (Parts 1/2/3)

See Table 24 below for an overview of adverse events in Parts 1, 2, and 3 of the trial. Overall, 10.6% of subjects were reported to have a serious adverse event (SAE). There were few additional, e.g., approximately 2% additional SAEs reported, among subjects who were treated with higher doses of avapritinib, i.e., 50 mg or 100 mg administered once daily in part 1 of the study. This trend of minor increase in AEs in the 50 mg and 100 mg dose is consistent in terms of any AEs that were reported as well as severity of AEs reported.

**Table 24. Overview of Adverse Events, Safety Population, Study BLU-285-2203 Overall (Parts 1/2/3)**

| Event Category | Avapritinib 25 mg* N=226 n (%) | All N=246 n (%) |
|---|---|---|
| SAE | 24 (10.6) | 30 (12.2) |
| SAEs with fatal outcome | 0 | 0 |
| Life-threatening SAEs | 1 (0.4) | 1 (0.4) |
| AE leading to permanent discontinuation of study drug | 7 (3.1) | 8 (3.3) |
| AE leading to dose modification of study drug | 27 (11.9) | 38 (15.4) |
| AE leading to interruption of study drug | 26 (11.5) | 37 (15.0) |
| AE leading to reduction of study drug | 7 (3.1) | 11 (4.5) |
| AE leading to dose delay of study drug | 0 | 0 |
| Other | 0 | 0 |

| Event Category | Avapritinib 25 mg* N=226 n (%) | All N=246 n (%) |
|---|---|---|
| Any AE | 202 (89.4) | 221 (89.8) |
| Severe and worse | 58 (25.7) | 72 (29.3) |
| Moderate | 86 (38.1) | 91 (37.0) |
| Mild | 58 (25.7) | 58 (23.6) |

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that occurred between the first dose of avapritinib in the study through 30 days after the last dose.
Duration is at least 12 weeks (Part 1), 24 weeks (Part 2), and up to 5 years (Part 3).
Analysis duration median (min, max) is 42.4 (0.9, 159.4) weeks.
Severity as assessed by the investigator.
*This group includes the subjects who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the subjects who received 50 mg or 100 mg avapritinib in Part 1.
The "All" study arm includes the subjects who received placebo or 25 mg avapritinib in Part 1 or Part 2, as well as the subjects who received 50 mg or 100 mg avapritinib in Part 1.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

*Clinical reviewer comment: overall, the adverse event profile in all three parts of the study was consistent with the safety results from the randomized, placebo-controlled part (Part 2) of the study.*

#### 33.6.1.2. Deaths, Study 2203

No deaths were reported in any part of Study 2203.

#### 33.6.1.3. Serious Treatment-Emergent Adverse Events, Study 2203

**Part 2 of Study 2203**

Serious adverse events (SAEs) were reported infrequently in part 2 of Study 2203. Overall, a lower proportion of subjects in the avapritinib group had SAEs compared to placebo, 5% versus 11%, respectively. There were no SAEs reported with a frequency of at least 2% among subjects treated with avapritinib as shown in the table below.

**Table 25. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Study BLU-285-2203 Part 2**

| System Organ Class<br>Preferred Term | Avapritinib 25 mg N=141 n (%) | Placebo N=71 n (%) | Avapritinib 25 mg vs. Placebo Risk Difference (%) (95% CI) |
|---|---|---|---|
| Any SAE | 7 (5.0) | 8 (11.3) | -6.3 (-14.5, 1.9) |
| Blood and lymphatic system disorders (SOC) | 0 | 1 (1.4) | -1.4 (-4.1, 1.3) |
| Mastocytosis | 0 | 1 (1.4) | -1.4 (-4.1, 1.3) |
| Cardiac disorders (SOC) | 0 | 1 (1.4) | -1.4 (-4.1, 1.3) |
| Tachycardia | 0 | 1 (1.4) | -1.4 (-4.1, 1.3) |
| Gastrointestinal disorders (SOC) | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Abdominal pain | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| General disorders and administration site conditions (SOC) | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Chest pain | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |

| System Organ Class<br>Preferred Term | Avapritinib 25 mg N=141 n (%) | Placebo N=71 n (%) | Avapritinib 25 mg vs. Placebo Risk Difference (%) (95% CI) |
|---|---|---|---|
| Immune system disorders (SOC) | 1 (0.7) | 2 (2.8) | -2.1 (-6.2, 2.0) |
| Anaphylactic reaction | 1 (0.7) | 1 (1.4) | -0.7 (-3.8, 2.4) |
| Allergy to vaccine | 0 | 1 (1.4) | -1.4 (-4.1, 1.3) |
| Infections and infestations (SOC) | 2 (1.4) | 3 (4.2) | -2.8 (-7.9, 2.3) |
| Bacteremia | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| COVID-19 pneumonia | 1 (0.7) | 1 (1.4) | -0.7 (-3.8, 2.4) |
| Adenovirus infection | 0 | 1 (1.4) | -1.4 (-4.1, 1.3) |
| COVID-19 | 0 | 2 (2.8) | -2.8 (-6.7, 1.0) |
| Musculoskeletal and connective tissue disorders (SOC) | 0 | 1 (1.4) | -1.4 (-4.1, 1.3) |
| Foot deformity | 0 | 1 (1.4) | -1.4 (-4.1, 1.3) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC) | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Acute myeloid leukemia | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Reproductive system and breast disorders (SOC) | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Pelvic hematoma | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Vascular disorders (SOC) | 0 | 1 (1.4) | -1.4 (-4.1, 1.3) |
| Hypertension | 0 | 1 (1.4) | -1.4 (-4.1, 1.3) |

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that occurred between the Part 2 D1 through a day prior to Part 3 D1 if subject rolled over to Part 3; through 30 days after the last dose if subject did not rollover to Part 3.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
COVID-19 replaces: Mental status changes
Abbreviations: AE, adverse event; CI, confidence interval; D, day; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SOC, system organ class

*Clinical reviewer comment: serious adverse reactions occurred 0.7% of patients in the avapritinib group and included pelvic hematoma in one patient. SAEs of bacteremia, COVID-19 pneumonia, abdominal pain, chest pain and acute myeloid leukemia (AML) were not considered related to avapritinib after review of the patient narratives in which alternative etiologies were identified. The patient with abdominal pain was likely due to endometriosis per the patient narrative. COVID-19 pneumonia was not considered related to avapritinib due to the ongoing pandemic and viral infections have not been a previously described AR in other indications. The event of bacteremia occurred following with an infection of a patient's device (port). One patient experienced acute myeloid leukemia on day 169 of therapy. This was most likely related to the patient's underlying disorder of myelofibrosis, or less likely ISM. Lastly, chest pain occurred acutely following spraying pesticide in a patient with a pacemaker. At the time of the chest pain event the patient became acutely hypertensive, the clinical reviewer agrees with the investigator that the event was most likely secondary to an arrhythmia.*

**Pooled Analysis of Study 2203 (Parts 1/2/3)**

In Parts 1/2/3 of Study 2203 there were no serious adverse events (SAEs) reported in ≥1% of subjects other than mastocytosis (1.3%). All SAEs reported in the clinical trial are described in Table 26 below.

**Table 26. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Study BLU-285-2203 Overall (Parts 1/2/3)**

| System Organ Class<br>Preferred Term | Avapritinib 25 mg*<br>N=226<br>n (%) | All<br>N=246<br>n (%) |
|---|---|---|
| Any SAE | 24 (10.6) | 30 (12.2) |
| Blood and lymphatic system disorders (SOC) | 3 (1.3) | 3 (1.2) |
| Mastocytosis | 3 (1.3) | 3 (1.2) |
| Cardiac disorders (SOC) | 1 (0.4) | 1 (0.4) |
| Acute myocardial infarction | 1 (0.4) | 1 (0.4) |
| Gastrointestinal disorders (SOC) | 6 (2.7) | 8 (3.3) |
| Abdominal pain | 2 (0.9) | 2 (0.8) |
| Gastrointestinal disorder | 1 (0.4) | 2 (0.8) |
| Gastric hemorrhage | 1 (0.4) | 1 (0.4) |
| Nausea | 0 | 1 (0.4) |
| Pancreatitis | 1 (0.4) | 1 (0.4) |
| Pancreatitis acute | 1 (0.4) | 1 (0.4) |
| General disorders and administration site conditions (SOC) | 4 (1.8) | 4 (1.6) |
| Pyrexia | 2 (0.9) | 2 (0.8) |
| Chest pain | 1 (0.4) | 1 (0.4) |
| Pain | 1 (0.4) | 1 (0.4) |
| Immune system disorders (SOC) | 3 (1.3) | 5 (2.0) |
| Anaphylactic reaction | 1 (0.4) | 2 (0.8) |
| Hypersensitivity | 1 (0.4) | 2 (0.8) |
| Anaphylactic shock | 1 (0.4) | 1 (0.4) |
| Infections and infestations (SOC) | 3 (1.3) | 6 (2.4) |
| COVID-19 pneumonia | 2 (0.9) | 2 (0.8) |
| Bacteremia | 1 (0.4) | 1 (0.4) |
| COVID-19 | 0 | 1 (0.4) |
| Postoperative wound infection | 0 | 1 (0.4) |
| Viral infection | 0 | 1 (0.4) |
| Injury, poisoning and procedural complications (SOC) | 2 (0.9) | 4 (1.6) |
| Fall | 0 | 1 (0.4) |
| Procedural pain | 1 (0.4) | 1 (0.4) |
| Tendon rupture | 0 | 1 (0.4) |
| Vaccination complication | 1 (0.4) | 1 (0.4) |
| Investigations (SOC) | 2 (0.9) | 2 (0.8) |
| Blood creatinine increased | 1 (0.4) | 1 (0.4) |
| Fibrin D dimer increased | 1 (0.4) | 1 (0.4) |
| Musculoskeletal and connective tissue disorders (SOC) | 1 (0.4) | 2 (0.8) |
| Arthralgia | 0 | 1 (0.4) |
| Bone pain | 1 (0.4) | 1 (0.4) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC) | 3 (1.3) | 3 (1.2) |
| Acute myeloid leukemia | 1 (0.4) | 1 (0.4) |
| Mastocytic leukemia | 1 (0.4) | 1 (0.4) |
| Systemic mastocytosis | 1 (0.4) | 1 (0.4) |
| Nervous system disorders (SOC) | 1 (0.4) | 2 (0.8) |
| Headache | 0 | 1 (0.4) |
| Migraine | 1 (0.4) | 1 (0.4) |
| Psychiatric disorders (SOC) | 0 | 1 (0.4) |
| Delirium | 0 | 1 (0.4) |
| Renal and urinary disorders (SOC) | 1 (0.4) | 1 (0.4) |
| Nephrolithiasis | 1 (0.4) | 1 (0.4) |

| System Organ Class<br>Preferred Term | Avapritinib 25 mg*<br>N=226<br>n (%) | All<br>N=246<br>n (%) |
|---|---|---|
| Reproductive system and breast disorders (SOC) | 1 (0.4) | 1 (0.4) |
| Pelvic hematoma | 1 (0.4) | 1 (0.4) |

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that occurred between the first dose of avapritinib in the study through 30 days after the last dose.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is at least 12 weeks (Part 1), 24 weeks (Part 2), and up to 5 years (Part 3).
Analysis duration median (min, max) is 42.4 (0.9, 159.4) weeks.
*This group includes the subjects who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the subjects who received 50 mg or 100 mg avapritinib in Part 1.
The "All" study arm includes the subjects who received placebo or 25 mg avapritinib in Part 1 or Part 2, as well as the subjects who received 50 mg or 100 mg avapritinib in Part 1.
Mastocytosis replaces: Mast cell activation syndrome
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SOC, system organ class

In Study 2203 there were two subjects with SAEs of pancreatitis identified, i.e., one acute pancreatitis and one chronic pancreatitis SAE, respectively. Pancreatitis was not previously identified as a potential SAE for avapritinib in the GIST or AdvSM indications. The two cases with SAEs of pancreatitis are discussed below.

- Subject ID (b) (6) (chronic pancreatitis): This subject was a female age 51 years who was initially enrolled in the placebo group of part 2 of Study 2203. The subject's past medical history consisted of ISM, type 2diabetes mellitus, hypertension, Covid-19 infection, and pancreatitis associated with the glucagon-like peptide-1 (GLP-1) agonist semaglutide for diabetes management. The subject was enrolled in part 2 of the study for approximately 6 months then crossed over to the open-label extension part 3 of the study. The subject was treated with avapritinib 25 mg orally once daily for 161 days. At that time avapritinib therapy was interrupted for Grade 3 pancreatitis. The subject's laboratory results included serum lipase 948.4 U/L, white blood cell 13.570 x 109/L, serum blood glucose 352 mg/dL. Hepatic enzymes were reported to be within normal limits. The subject was reported to have recently started therapy with the GLP-1 agonist dulaglutide (administered once weekly although the specific start date for this drug was not specified) for diabetes management. Dulaglutide was discontinued and avapritinib therapy was interrupted for 3 days with decrease in serum lipase to 298.4 U/L at which time avapritinib drug therapy was restarted without recurrence of elevated serum pancreatic enzymes. The subject remained on avapritinib therapy for an additional 129 days until the end of the study. This event was assessed by the investigator to be unrelated to study drug.
- Subject ID (b) (6) (acute pancreatitis): This subject was female age 40 years who was initially enrolled in the placebo group of part 2 of Study 2203. The subject's past medical history consisted of ISM, hepatic steatosis, hypertriglyceridemia, and cholecystitis. The subject was enrolled in part 2 of the study for approximately 6 months then crossed over to the open-label extension part 3 of the study. The subject was treated with avapritinib 25 mg orally once daily for 428 days. At that time avapritinib therapy was discontinued due to Grade 3 acute pancreatitis. The subject's laboratory results included serum lipase 2322 U/L, mildly elevated serum low-density lipoprotein 236 mg/dL and total cholesterol 392 mg/dl. Hepatic enzymes and complete blood count were reported to be within normal limits.

Avapritinib therapy was interrupted for five days. Avapritinib therapy was restarted after complete resolution of the pancreatitis event on day 433 with no recurrence of elevated pancreatic enzymes. The subject remained on avapritinib therapy for an additional nine days until the end of the study. This event was assessed by the investigator to be unrelated to study drug.

*Reviewer comment: the clinical reviewer agrees with the investigator assessments that the chronic and acute pancreatitis AEs were unrelated to study drug. The case of chronic pancreatitis appears to be temporally related to concomitant therapy with the GLP-1 agonist dulaglutide. The patient previously had pancreatitis related to the GLP-1 agonist semaglutide. The patient did not have a recurrence of the event after restarting avapritinib therapy. The case of the acute pancreatitis AE appears to be related to underlying hepatic steatosis and hypertriglyceridemia. The patient had been on avapritinib therapy for 428 days prior to the event. The patient did not have a recurrence of the event after restarting avapritinib therapy.*

When using FDA Medical Dictionary for Regulatory Activities queries (FMQs), only the SAE of hypersensitivity reaction was reported in ≥2.0% (i.e., 2.0%) of subjects.

**Table 27. Subjects With Serious Adverse Events by System Organ Class, FDA Medical Query (Narrow), and Preferred Term, Occurring in at Least 2% of Subjects in Any Arm, Safety Population, Study BLU-285-2203 Overall (Parts 1/2/3)**

| System Organ Class<br>FMQ (Narrow)<br>Preferred Term | Avapritinib 25 mg*<br>N=226<br>n (%) | All<br>N=246<br>n (%) |
|---|---|---|
| Immune system disorders (SOC) | | |
| Hypersensitivity (FMQ) | 3 (1.3) | 5 (2.0) |

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that occurred between the first dose of avapritinib in the study through 30 days after the last dose.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is at least 12 weeks (Part 1), 24 weeks (Part 2), and up to 5 years (Part 3).
Analysis duration median (min, max) is 42.4 (0.9, 159.4) weeks.
*This group includes the subjects who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the subjects who received 50 mg or 100 mg avapritinib in Part 1.
The “All” study arm includes the subjects who received placebo or 25 mg avapritinib in Part 1 or Part 2, as well as the subjects who received 50 mg or 100 mg avapritinib in Part 1.
Abbreviations: AE, adverse event; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

*Clinical reviewer comment: the rate of SAEs continued to be low in all three parts of the trial. Most SAEs were related to the underlying disease, i.e., hypersensitivity, mastocytosis and mastocytic leukemia. Of note, mast cell leukemia and AML transformation is rare in patients with ISM but can occur.*

### 33.6.1.4. Adverse Events Leading to Treatment Discontinuation, Study 2203

**Part 2 of Study 2203**

Overall, there was low rate of drug discontinuations in both study arms. Aes leading to drug discontinuation are described in Table 28 and Table 29.

**Table 28. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Study BLU-285-2203 Part 2**

| System Organ Class<br>Preferred Term | Avapritinib 25 mg N=141 n (%) | Placebo N=71 n (%) | Avapritinib 25 mg vs. Placebo Risk Difference (%) (95% CI) |
|---|---|---|---|
| Any AE leading to Discontinuation | 3 (2.1) | 1 (1.4) | 0.7 (-2.9, 4.4) |
| Cardiac disorders (SOC) | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Palpitations | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| General disorders and administration site conditions (SOC) | 1 (0.7) | 1 (1.4) | -0.7 (-3.8, 2.4) |
| Noncardiac chest pain | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| General physical health deterioration | 0 | 1 (1.4) | -1.4 (-4.1, 1.3) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC) | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Acute myeloid leukemia | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Nervous system disorders (SOC) | 2 (1.4) | 0 | 1.4 (-0.5, 3.4) |
| Disturbance in attention | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Dizziness | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Dyskinesia | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Respiratory, thoracic and mediastinal disorders (SOC) | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Dyspnea | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Vascular disorders (SOC) | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Hypertension | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that occurred between the Part 2 D1 through a day prior to Part 3 D1 if patient rolled over to Part 3; through 30 days after the last dose if patient did not rollover to Part 3.
Duration is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; D, day; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

**Table 29. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class, FDA Medical Query (Narrow), and Preferred Term, Safety Population, Study BLU-285-2203 Part 2**

| System Organ Class<br>FMQ (Narrow)<br>Preferred Term | Avapritinib 25 mg N=141 n (%) | Placebo N=71 n (%) | Avapritinib 25 mg vs. Placebo Risk Difference (%) (95% CI) |
|---|---|---|---|
| Cardiac disorders (SOC) | | | |
| Palpitations (FMQ) | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Palpitations | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Systemic Hypertension (FMQ) | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Hypertension | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| General disorders and administration site conditions (SOC) | | | |
| Dizziness (FMQ) | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Dizziness | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC) | | | |
| Malignancy (FMQ) | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Acute myeloid leukemia | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |

| System Organ Class<br>FMQ (Narrow)<br>Preferred Term | Avapritinib 25 mg N=141 n (%) | Placebo N=71 n (%) | Avapritinib 25 mg vs. Placebo Risk Difference (%) (95% CI) |
|---|---|---|---|
| Respiratory, thoracic and mediastinal disorders (SOC) | | | |
| Dyspnea (FMQ) | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Dyspnea | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that occurred between the Part 2 D1 through a day prior to Part 3 D1 if subject rolled over to Part 3; through 30 days after the last dose if subject did not rollover to Part 3.
Duration is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.
Abbreviations: AE, adverse event; CI, confidence interval; D, day; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

*Clinical reviewer comment: Adverse reactions leading to drug discontinuation occurred in 0.7% of patients in the avapritinib group, this included dyspnea, dizziness, noncardiac chest pain, palpitations, hypertension all in one patient. There was one patient with disturbance in attention and dyskinesia in another patient which the investigator noted as related to study drug, but after further review of the patient narrative it appears this was present at baseline. As noted in Section 33.6.1.3 the event of AML is not considered related to avapritinib.*

**Pooled Analysis of Study 2203 (Part ½/3)**

There were no Aes leading to discontinuations reported in ≥2% of subjects using preferred term (PT) or FMQ narrow terms. The most common Aes reported was dyspnea and malignancy (0.9%) as shown in the tables below.

**Table 30. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Study BLU-285-2203 Overall (Parts 1/2/3)**

| System Organ Class<br>Preferred Term | Avapritinib 25 mg* N=226 n (%) | All N=246 n (%) |
|---|---|---|
| Any AE leading to Discontinuation | 7 (3.1) | 8 (3.3) |
| Cardiac disorders (SOC) | 1 (0.4) | 1 (0.4) |
| Palpitations | 1 (0.4) | 1 (0.4) |
| General disorders and administration site conditions (SOC) | 2 (0.9) | 2 (0.8) |
| Noncardiac chest pain | 1 (0.4) | 1 (0.4) |
| Peripheral swelling | 1 (0.4) | 1 (0.4) |
| Investigations (SOC) | 1 (0.4) | 1 (0.4) |
| Weight decreased | 1 (0.4) | 1 (0.4) |
| Musculoskeletal and connective tissue disorders (SOC) | 1 (0.4) | 1 (0.4) |
| Pain in extremity | 1 (0.4) | 1 (0.4) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC) | 2 (0.9) | 2 (0.8) |
| Acute myeloid leukemia | 1 (0.4) | 1 (0.4) |
| Mastocytic leukemia | 1 (0.4) | 1 (0.4) |
| Nervous system disorders (SOC) | 3 (1.3) | 3 (1.2) |
| Disturbance in attention | 1 (0.4) | 1 (0.4) |
| Dizziness | 1 (0.4) | 1 (0.4) |
| Dyskinesia | 1 (0.4) | 1 (0.4) |
| Migraine | 1 (0.4) | 1 (0.4) |

| System Organ Class<br>Preferred Term | Avapritinib 25 mg*<br>N=226<br>n (%) | All<br>N=246<br>n (%) |
|---|---|---|
| Psychiatric disorders (SOC) | 0 | 1 (0.4) |
| Delirium | 0 | 1 (0.4) |
| Respiratory, thoracic and mediastinal disorders (SOC) | 2 (0.9) | 2 (0.8) |
| Dyspnea | 2 (0.9) | 2 (0.8) |
| Vascular disorders (SOC) | 1 (0.4) | 1 (0.4) |
| Hypertension | 1 (0.4) | 1 (0.4) |

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that occurred between the first dose of avapritinib in the study through 30 days after the last dose.
Duration is at least 12 weeks (Part 1), 24 weeks (Part 2), and up to 5 years (Part 3).
Analysis duration median (min, max) is 42.4 (0.9, 159.4) weeks.
*This group includes the subjects who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the subjects who received 50 mg or 100 mg avapritinib in Part 1.
The "All" study arm includes the subjects who received placebo or 25 mg avapritinib in Part 1 or Part 2, as well as the subjects who received 50 mg or 100 mg avapritinib in Part 1.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

**Table 31. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class, FDA Medical Query (Narrow), and Preferred Term, Safety Population, Study BLU-285-2203 Overall (Parts 1/2/3)**

| System Organ Class<br>FMQ (Narrow)<br>Preferred Term | Avapritinib 25 mg*<br>N=226<br>n (%) | All<br>N=246<br>n (%) |
|---|---|---|
| Cardiac disorders (SOC) | | |
| Palpitations (FMQ) | 1 (0.4) | 1 (0.4) |
| Palpitations | 1 (0.4) | 1 (0.4) |
| Systemic Hypertension (FMQ) | 1 (0.4) | 1 (0.4) |
| Hypertension | 1 (0.4) | 1 (0.4) |
| General disorders and administration site conditions (SOC) | | |
| Dizziness (FMQ) | 1 (0.4) | 1 (0.4) |
| Dizziness | 1 (0.4) | 1 (0.4) |
| Peripheral Edema (FMQ) | 1 (0.4) | 1 (0.4) |
| Peripheral swelling | 1 (0.4) | 1 (0.4) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC) | | |
| Malignancy (FMQ) | 2 (0.9) | 2 (0.8) |
| Acute myeloid leukemia | 1 (0.4) | 1 (0.4) |
| Mastocytic leukemia | 1 (0.4) | 1 (0.4) |
| Nervous system disorders (SOC) | | |
| Confusional State (FMQ) | 0 | 1 (0.4) |
| Delirium | 0 | 1 (0.4) |
| Headache (FMQ) | 1 (0.4) | 1 (0.4) |
| Migraine | 1 (0.4) | 1 (0.4) |

| System Organ Class<br>FMQ (Narrow)<br>Preferred Term | Avapritinib 25 mg*<br>N=226<br>n (%) | All<br>N=246<br>n (%) |
|---|---|---|
| Respiratory, thoracic and mediastinal disorders (SOC) | | |
| Dyspnea (FMQ) | 2 (0.9) | 2 (0.8) |
| Dyspnea | 2 (0.9) | 2 (0.8) |

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that occurred between the first dose of avapritinib in the study through 30 days after the last dose.
Duration is at least 12 weeks (Part 1), 24 weeks (Part 2), and up to 5 years (Part 3).
Analysis duration median (min, max) is 42.4 (0.9, 159.4) weeks.
Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.
*This group includes the subjects who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the subjects who received 50 mg or 100 mg avapritinib in Part 1.
The "All" study arm includes the subjects who received placebo or 25 mg avapritinib in Part 1 or Part 2, as well as the subjects who received 50 mg or 100 mg avapritinib in Part 1.
Abbreviations: AE, adverse event; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

### 33.6.1.5. Treatment-Emergent Adverse Events, Study 2203

**Part 2 of Study 2203**

AEs that were reported in at least 5% of subjects treated with avapritinib and at least 2% greater than placebo were viral infection (17.7%), peripheral edema (17%), fatigue (14.9%), eye edema (13.5%), dizziness (12.8%), hemorrhage (10.6%), erythema (9.9%), flushing (9.2%), respiratory tract infection (7.8%), face edema (7.1%), hepatic injury (7.1%), serum blood alkaline phosphatase elevated (6.4%), insomnia (5.7%), serum alanine amino transferase increased (5.0%). The tables below show the common adverse events occurring at ≥2% frequency in Study 2203 by preferred term (Table 32), FMQ (Table 33) and grouped queries (Table 34).

**Table 32. Subjects With Common Adverse Events Occurring at ≥2% Frequency, Safety Population, Study BLU-285-2203 Part 2**

| Preferred Term | Avapritinib 25 mg<br>N=141<br>n (%) | Placebo<br>N=71<br>n (%) | Avapritinib 25 mg<br>vs. Placebo<br>Risk Difference<br>(%) (95% CI) |
|---|---|---|---|
| Any AE | 128 (90.8) | 66 (93.0) | -2.2 (-9.8, 5.5) |
| Face edema | 10 (7.1) | 1 (1.4) | 5.7 (0.6, 10.7) * |
| Flushing | 13 (9.2) | 3 (4.2) | 5.0 (-1.7, 11.7) |
| Blood alkaline phosphatase increased | 9 (6.4) | 1 (1.4) | 5.0 (0.1, 9.9) * |
| Edema peripheral | 12 (8.5) | 3 (4.2) | 4.3 (-2.3, 10.9) |
| Contusion | 6 (4.3) | 0 | 4.3 (0.9, 7.6) * |
| Periorbital edema | 9 (6.4) | 2 (2.8) | 3.6 (-2.0, 9.1) |
| Sinusitis | 5 (3.5) | 0 | 3.5 (0.5, 6.6) * |
| Upper respiratory tract infection | 5 (3.5) | 0 | 3.5 (0.5, 6.6) * |
| Dizziness | 16 (11.3) | 6 (8.5) | 2.9 (-5.4, 11.2) |
| Insomnia | 8 (5.7) | 2 (2.8) | 2.9 (-2.6, 8.3) |
| Aspartate aminotransferase increased | 6 (4.3) | 1 (1.4) | 2.8 (-1.5, 7.2) |
| Blood lactate dehydrogenase increased | 4 (2.8) | 0 | 2.8 (0.1, 5.6) * |
| Bone pain | 4 (2.8) | 0 | 2.8 (0.1, 5.6) * |
| Photosensitivity reaction | 4 (2.8) | 0 | 2.8 (0.1, 5.6) * |
| Skin lesion | 4 (2.8) | 0 | 2.8 (0.1, 5.6) * |
| Alanine aminotransferase increased | 7 (5.0) | 2 (2.8) | 2.1 (-3.1, 7.4) |

| Preferred Term | Avapritinib 25 mg N=141 n (%) | Placebo N=71 n (%) | Avapritinib 25 mg vs. Placebo Risk Difference (%) (95% CI) |
|---|---|---|---|
| Abdominal distension | 5 (3.5) | 1 (1.4) | 2.1 (-2.0, 6.2) |
| Anxiety | 5 (3.5) | 1 (1.4) | 2.1 (-2.0, 6.2) |
| Asthenia | 5 (3.5) | 1 (1.4) | 2.1 (-2.0, 6.2) |
| Dry eye | 5 (3.5) | 1 (1.4) | 2.1 (-2.0, 6.2) |
| Dry mouth | 5 (3.5) | 1 (1.4) | 2.1 (-2.0, 6.2) |
| Eyelid edema | 5 (3.5) | 1 (1.4) | 2.1 (-2.0, 6.2) |
| Lacrimation increased | 5 (3.5) | 1 (1.4) | 2.1 (-2.0, 6.2) |
| Peripheral swelling | 5 (3.5) | 1 (1.4) | 2.1 (-2.0, 6.2) |
| Decreased appetite | 3 (2.1) | 0 | 2.1 (-0.3, 4.5) |
| Influenza like illness | 3 (2.1) | 0 | 2.1 (-0.3, 4.5) |
| Iron deficiency | 3 (2.1) | 0 | 2.1 (-0.3, 4.5) |
| Respiratory tract infection | 3 (2.1) | 0 | 2.1 (-0.3, 4.5) |
| SARS-CoV-2 test positive | 3 (2.1) | 0 | 2.1 (-0.3, 4.5) |
| Taste disorder | 3 (2.1) | 0 | 2.1 (-0.3, 4.5) |
| Tooth infection | 3 (2.1) | 0 | 2.1 (-0.3, 4.5) |
| Fatigue | 14 (9.9) | 6 (8.5) | 1.5 (-6.7, 9.6) |
| Back pain | 4 (2.8) | 1 (1.4) | 1.4 (-2.4, 5.3) |
| Dyspepsia | 4 (2.8) | 1 (1.4) | 1.4 (-2.4, 5.3) |
| Epistaxis | 4 (2.8) | 1 (1.4) | 1.4 (-2.4, 5.3) |
| Feeling abnormal | 4 (2.8) | 1 (1.4) | 1.4 (-2.4, 5.3) |
| Gastroesophageal reflux disease | 4 (2.8) | 1 (1.4) | 1.4 (-2.4, 5.3) |
| Hypokalemia | 4 (2.8) | 1 (1.4) | 1.4 (-2.4, 5.3) |
| Muscle spasms | 4 (2.8) | 1 (1.4) | 1.4 (-2.4, 5.3) |
| Rash maculo-papular | 4 (2.8) | 1 (1.4) | 1.4 (-2.4, 5.3) |
| Tinnitus | 4 (2.8) | 1 (1.4) | 1.4 (-2.4, 5.3) |
| COVID-19 | 17 (12.1) | 8 (11.3) | 0.8 (-8.3, 9.9) |
| Arthralgia | 11 (7.8) | 5 (7.0) | 0.8 (-6.7, 8.2) |
| Pruritus | 11 (7.8) | 5 (7.0) | 0.8 (-6.7, 8.2) |
| Disturbance in attention | 5 (3.5) | 2 (2.8) | 0.7 (-4.2, 5.6) |
| Blood uric acid increased | 3 (2.1) | 1 (1.4) | 0.7 (-2.9, 4.4) |
| Hot flush | 3 (2.1) | 1 (1.4) | 0.7 (-2.9, 4.4) |
| Hypersensitivity | 3 (2.1) | 1 (1.4) | 0.7 (-2.9, 4.4) |
| Muscle twitching | 3 (2.1) | 1 (1.4) | 0.7 (-2.9, 4.4) |
| Noncardiac chest pain | 3 (2.1) | 1 (1.4) | 0.7 (-2.9, 4.4) |
| Abdominal pain | 8 (5.7) | 4 (5.6) | 0.0 (-6.5, 6.6) |
| Constipation | 6 (4.3) | 3 (4.2) | 0.0 (-5.7, 5.8) |
| Hair color changes | 4 (2.8) | 2 (2.8) | 0.0 (-4.7, 4.7) |
| Rash | 4 (2.8) | 2 (2.8) | 0.0 (-4.7, 4.7) |
| Headache | 27 (19.1) | 14 (19.7) | -0.6 (-11.9, 10.7) |
| Diarrhea | 15 (10.6) | 8 (11.3) | -0.6 (-9.6, 8.3) |
| Dry skin | 3 (2.1) | 2 (2.8) | -0.7 (-5.2, 3.8) |
| Paresthesia | 3 (2.1) | 2 (2.8) | -0.7 (-5.2, 3.8) |
| Alopecia | 6 (4.3) | 4 (5.6) | -1.4 (-7.7, 4.9) |
| Vomiting | 6 (4.3) | 4 (5.6) | -1.4 (-7.7, 4.9) |
| Anaphylactic reaction | 4 (2.8) | 3 (4.2) | -1.4 (-6.8, 4.0) |
| Palpitations | 4 (2.8) | 3 (4.2) | -1.4 (-6.8, 4.0) |
| Weight increased | 4 (2.8) | 3 (4.2) | -1.4 (-6.8, 4.0) |
| Blood creatinine increased | 2 (1.4) | 2 (2.8) | -1.4 (-5.7, 2.9) |
| Pain | 2 (1.4) | 2 (2.8) | -1.4 (-5.7, 2.9) |
| Cough | 3 (2.1) | 3 (4.2) | -2.1 (-7.3, 3.2) |
| Eye pain | 1 (0.7) | 2 (2.8) | -2.1 (-6.2, 2.0) |
| Hyperhidrosis | 1 (0.7) | 2 (2.8) | -2.1 (-6.2, 2.0) |

| Preferred Term | Avapritinib 25 mg N=141 n (%) | Placebo N=71 n (%) | Avapritinib 25 mg vs. Placebo Risk Difference (%) (95% CI) |
|---|---|---|---|
| Hypertension | 6 (4.3) | 5 (7.0) | -2.8 (-9.6, 4.0) |
| Nasopharyngitis | 6 (4.3) | 5 (7.0) | -2.8 (-9.6, 4.0) |
| Hyperuricemia | 2 (1.4) | 3 (4.2) | -2.8 (-7.9, 2.3) |
| Cystitis | 0 | 2 (2.8) | -2.8 (-6.7, 1.0) |
| Eosinophilia | 0 | 2 (2.8) | -2.8 (-6.7, 1.0) |
| Gastritis | 0 | 2 (2.8) | -2.8 (-6.7, 1.0) |
| Hand fracture | 0 | 2 (2.8) | -2.8 (-6.7, 1.0) |
| Ligament sprain | 0 | 2 (2.8) | -2.8 (-6.7, 1.0) |
| Musculoskeletal chest pain | 0 | 2 (2.8) | -2.8 (-6.7, 1.0) |
| Urticaria pigmentosa | 0 | 2 (2.8) | -2.8 (-6.7, 1.0) |
| Urinary tract infection | 5 (3.5) | 5 (7.0) | -3.5 (-10.2, 3.2) |
| Pain in extremity | 1 (0.7) | 3 (4.2) | -3.5 (-8.4, 1.4) |
| Vision blurred | 1 (0.7) | 3 (4.2) | -3.5 (-8.4, 1.4) |
| Nausea | 18 (12.8) | 12 (16.9) | -4.1 (-14.4, 6.2) |
| Erythema | 0 | 3 (4.2) | -4.2 (-8.9, 0.5) |
| Osteoarthritis | 0 | 3 (4.2) | -4.2 (-8.9, 0.5) |

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that occurred between the Part 2 D1 through a day prior to Part 3 D1 if subject rolled over to Part 3; through 30 days after the last dose if subject did not rollover to Part 3.
Duration is 24 weeks.
Coded as MedDRA preferred terms.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Constipation replaces: Abdominal mass
COVID-19 replaces: Acute kidney injury, Mental status changes, Dyspnea
Abbreviations: AE, adverse event; CI, confidence interval; D, day; N, number of subjects in treatment arm; n, number of subjects with adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

**Table 33. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Study BLU-285-2203 Part 2**

| System Organ Class FMQ (Narrow) | Avapritinib 25 mg N=141 n (%) | Placebo N=71 n (%) | Avapritinib 25 mg vs. Placebo Risk Difference (%) (95% CI) |
|---|---|---|---|
| Blood and lymphatic system disorders (SOC) | | | |
| Anemia | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Thrombocytopenia | 1 (0.7) | 1 (1.4) | -0.7 (-3.8, 2.4) |
| Cardiac disorders (SOC) | | | |
| Cardiac conduction disturbance | 3 (2.1) | 1 (1.4) | 0.7 (-2.9, 4.4) |
| Myocardial Ischemia | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Arrhythmia | 4 (2.8) | 3 (4.2) | -1.4 (-6.8, 4.0) |
| Palpitations | 4 (2.8) | 3 (4.2) | -1.4 (-6.8, 4.0) |
| Tachycardia | 2 (1.4) | 2 (2.8) | -1.4 (-5.7, 2.9) |
| Systemic hypertension | 6 (4.3) | 5 (7.0) | -2.8 (-9.6, 4.0) |
| Ear and labyrinth disorders (SOC) | | | |
| Vertigo | 2 (1.4) | 0 | 1.4 (-0.5, 3.4) |

| System Organ Class<br>FMQ (Narrow) | Avapritinib 25 mg N=141 n (%) | Placebo N=71 n (%) | Avapritinib 25 mg vs. Placebo Risk Difference (%) (95% CI) |
|---|---|---|---|
| Gastrointestinal disorders (SOC) | | | |
| Dry Mouth | 5 (3.5) | 1 (1.4) | 2.1 (-2.0, 6.2) |
| Dyspepsia | 5 (3.5) | 2 (2.8) | 0.7 (-4.2, 5.6) |
| Constipation | 6 (4.3) | 3 (4.2) | 0.0 (-5.7, 5.8) |
| Diarrhea | 15 (10.6) | 8 (11.3) | -0.6 (-9.6, 8.3) |
| Abdominal pain | 11 (7.8) | 6 (8.5) | -0.6 (-8.5, 7.2) |
| Vomiting | 6 (4.3) | 4 (5.6) | -1.4 (-7.7, 4.9) |
| Pancreatitis | 0 | 1 (1.4) | -1.4 (-4.1, 1.3) |
| Nausea | 18 (12.8) | 12 (16.9) | -4.1 (-14.4, 6.2) |
| General disorders and administration site conditions (SOC) | | | |
| Peripheral edema | 17 (12.1) | 4 (5.6) | 6.4 (-1.2, 14.0) |
| Dizziness | 18 (12.8) | 7 (9.9) | 2.9 (-5.9, 11.8) |
| Fatigue | 20 (14.2) | 9 (12.7) | 2.2 (-7.5, 11.9) |
| Decreased appetite | 3 (2.1) | 0 | 2.1 (-0.3, 4.5) |
| Fall | 2 (1.4) | 1 (1.4) | 0.0 (-3.4, 3.4) |
| Pyrexia | 1 (0.7) | 1 (1.4) | -0.7 (-3.8, 2.4) |
| Hepatobiliary disorders (SOC) | | | |
| Hepatic injury | 10 (7.1) | 2 (2.8) | 4.3 (-1.4, 10.0) |
| Immune system disorders (SOC) | | | |
| Angioedema | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Hypersensitivity | 10 (7.1) | 5 (7.0) | 0.0 (-7.3, 7.4) |
| Anaphylactic reaction | 4 (2.8) | 3 (4.2) | -1.4 (-6.8, 4.0) |
| Infections and infestations (SOC) | | | |
| Viral infection | 25 (17.7) | 11 (15.5) | 2.2 (-8.3, 12.8) |
| Nasopharyngitis | 13 (9.2) | 6 (8.5) | 0.8 (-7.3, 8.8) |
| Pneumonia | 1 (0.7) | 1 (1.4) | -0.7 (-3.8, 2.4) |
| Purulent material | 0 | 1 (1.4) | -1.4 (-4.1, 1.3) |
| Bacterial infection | 12 (8.5) | 9 (12.7) | -4.2 (-13.2, 4.8) |
| Metabolism and nutrition disorders (SOC) | | | |
| Lipid disorder | 1 (0.7) | 1 (1.4) | -0.7 (-3.8, 2.4) |
| Musculoskeletal and connective tissue disorders (SOC) | | | |
| Arthralgia | 11 (7.8) | 5 (7.0) | 0.8 (-6.7, 8.2) |
| Back pain | 5 (3.5) | 2 (2.8) | 0.7 (-4.2, 5.6) |
| Tendinopathy | 3 (2.1) | 1 (1.4) | 0.7 (-2.9, 4.4) |
| Myalgia | 1 (0.7) | 1 (1.4) | -0.7 (-3.8, 2.4) |
| Gout | 0 | 1 (1.4) | -1.4 (-4.1, 1.3) |
| Fracture | 1 (0.7) | 3 (4.2) | -3.5 (-8.4, 1.4) |
| Arthritis | 1 (0.7) | 4 (5.6) | -4.9 (-10.5, 0.6) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC) | | | |
| Malignancy | 2 (1.4) | 1 (1.4) | 0.0 (-3.4, 3.4) |
| Nervous system disorders (SOC) | | | |
| Syncope | 2 (1.4) | 0 | 1.4 (-0.5, 3.4) |
| Tremor | 2 (1.4) | 0 | 1.4 (-0.5, 3.4) |
| Dysgeusia | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Seizure | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Headache | 28 (19.9) | 14 (19.7) | 0.1 (-11.2, 11.5) |
| Somnolence | 2 (1.4) | 1 (1.4) | 0.0 (-3.4, 3.4) |
| Paresthesia | 5 (3.5) | 4 (5.6) | -2.1 (-8.3, 4.1) |

| System Organ Class<br>FMQ (Narrow) | Avapritinib 25 mg N=141 n (%) | Placebo N=71 n (%) | Avapritinib 25 mg vs. Placebo Risk Difference (%) (95% CI) |
|---|---|---|---|
| Psychiatric disorders (SOC) | | | |
| Insomnia | 8 (5.7) | 2 (2.8) | 2.9 (-2.6, 8.3) |
| Anxiety | 5 (3.5) | 1 (1.4) | 2.1 (-2.0, 6.2) |
| Depression | 3 (2.1) | 0 | 2.1 (-0.3, 4.5) |
| Irritability | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Psychosis | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Renal and urinary disorders (SOC) | | | |
| Renal & urinary tract infection | 5 (3.5) | 8 (11.3) | -7.7 (-15.7, 0.2) |
| Reproductive system and breast disorders (SOC) | | | |
| Abnormal uterine bleeding | 3 (2.1) | 1 (1.4) | 0.7 (-2.9, 4.4) |
| Excessive menstrual bleeding | 2 (1.4) | 1 (1.4) | 0.0 (-3.4, 3.4) |
| Sexual dysfunction | 2 (1.4) | 1 (1.4) | 0.0 (-3.4, 3.4) |
| Erectile dysfunction | 0 | 1 (1.4) | -1.4 (-4.1, 1.3) |
| Respiratory, thoracic and mediastinal disorders (SOC) | | | |
| Dyspnea | 4 (2.8) | 1 (1.4) | 1.4 (-2.4, 5.3) |
| Respiratory failure | 2 (1.4) | 0 | 1.4 (-0.5, 3.4) |
| Bronchospasm | 0 | 1 (1.4) | -1.4 (-4.1, 1.3) |
| Cough | 3 (2.1) | 3 (4.2) | -2.1 (-7.3, 3.2) |
| Skin and subcutaneous tissue disorders (SOC) | | | |
| Erythema | 14 (9.9) | 5 (7.0) | 2.9 (-4.8, 10.6) |
| Pruritus | 12 (8.5) | 6 (8.5) | 0.1 (-7.9, 8.0) |
| Urticaria | 2 (1.4) | 1 (1.4) | 0.0 (-3.4, 3.4) |
| Rash | 11 (7.8) | 6 (8.5) | -0.6 (-8.5, 7.2) |
| Alopecia | 6 (4.3) | 4 (5.6) | -1.4 (-7.7, 4.9) |
| Vascular disorders (SOC) | | | |
| Hemorrhage | 15 (10.6) | 3 (4.2) | 6.4 (-0.5, 13.3) |
| Hypotension | 2 (1.4) | 0 | 1.4 (-0.5, 3.4) |

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that occurred between the Part 2 D1 through a day prior to Part 3 D1 if subject rolled over to Part 3; through 30 days after the last dose if subject did not rollover to Part 3.
Duration is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
For specific preferred terms under each FMQ, see the table “Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term…”
Abbreviations: AE, adverse event; CI, confidence interval; D, day; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

**Table 34. Grouped Queries, Safety Population, Study BLU-285-2203 Part 2**

| Grouped Query | Avapritinib 25 mg N=141 n (%) | Placebo N=71 n (%) | Avapritinib 25 mg vs. Placebo Risk Difference (%) (95% CI) |
|---|---|---|---|
| Any GQ | 112 (79.4) | 52 (73.2) | 6.2 (-6.1, 18.5) |
| Flushing | 16 (11.3) | 3 (4.2) | 7.1 (0.1, 14.1) * |
| Eye edema | 19 (13.5) | 5 (7.0) | 6.4 (-1.8, 14.6) |
| Peripheral edema | 17 (12.1) | 4 (5.6) | 6.4 (-1.2, 14.0) |
| Respiratory tract infection | 11 (7.8) | 1 (1.4) | 6.4 (1.2, 11.6) * |
| Orbital edema | 12 (8.5) | 2 (2.8) | 5.7 (-0.3, 11.7) |
| COVID-19 | 21 (14.9) | 8 (11.3) | 3.6 (-5.8, 13.0) |
| Sleep disorder | 8 (5.7) | 2 (2.8) | 2.9 (-2.6, 8.3) |
| Depression | 4 (2.8) | 0 | 2.8 (0.1, 5.6) * |
| Dysgeusia | 4 (2.8) | 0 | 2.8 (0.1, 5.6) * |

| Grouped Query | Avapritinib 25 mg N=141 n (%) | Placebo N=71 n (%) | Avapritinib 25 mg vs. Placebo Risk Difference (%) (95% CI) |
|---|---|---|---|
| Edema | 4 (2.8) | 0 | 2.8 (0.1, 5.6) * |
| Photosensitivity disorder | 4 (2.8) | 0 | 2.8 (0.1, 5.6) * |
| SARS-CoV-2 test positive | 4 (2.8) | 0 | 2.8 (0.1, 5.6) * |
| Rash | 9 (6.4) | 3 (4.2) | 2.2 (-4.0, 8.3) |
| Tooth infection | 3 (2.1) | 0 | 2.1 (-0.3, 4.5) |
| Dizziness | 16 (11.3) | 7 (9.9) | 1.5 (-7.2, 10.2) |
| Cognitive disorder | 10 (7.1) | 4 (5.6) | 1.5 (-5.4, 8.3) |
| Dysesthesia | 4 (2.8) | 1 (1.4) | 1.4 (-2.4, 5.3) |
| Dyspnea | 4 (2.8) | 1 (1.4) | 1.4 (-2.4, 5.3) |
| Mental status changes | 4 (2.8) | 1 (1.4) | 1.4 (-2.4, 5.3) |
| Bladder pain | 2 (1.4) | 0 | 1.4 (-0.5, 3.4) |
| Chest pain | 2 (1.4) | 0 | 1.4 (-0.5, 3.4) |
| Esophageal stenosis | 2 (1.4) | 0 | 1.4 (-0.5, 3.4) |
| Gastrointestinal bleeding | 2 (1.4) | 0 | 1.4 (-0.5, 3.4) |
| Hypoesthesia | 2 (1.4) | 0 | 1.4 (-0.5, 3.4) |
| Joint swelling | 2 (1.4) | 0 | 1.4 (-0.5, 3.4) |
| Polyuria | 2 (1.4) | 0 | 1.4 (-0.5, 3.4) |
| Skin wound | 2 (1.4) | 0 | 1.4 (-0.5, 3.4) |
| Tonsilitis | 2 (1.4) | 0 | 1.4 (-0.5, 3.4) |
| Tremor | 2 (1.4) | 0 | 1.4 (-0.5, 3.4) |
| Arthralgia | 11 (7.8) | 5 (7.0) | 0.8 (-6.7, 8.2) |
| Hair disorder | 5 (3.5) | 2 (2.8) | 0.7 (-4.2, 5.6) |
| Paresthesia | 5 (3.5) | 2 (2.8) | 0.7 (-4.2, 5.6) |
| Agitation | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Calculus urinary | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Gastrointestinal infection | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Mood altered | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Muscle injury | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Nail disorder | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Neutropenia | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Pharyngitis | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Skin infection | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Anaphylactic reaction | 8 (5.7) | 4 (5.6) | 0.0 (-6.5, 6.6) |
| Allergy to chemicals | 2 (1.4) | 1 (1.4) | 0.0 (-3.4, 3.4) |
| Arrhythmia | 2 (1.4) | 1 (1.4) | 0.0 (-3.4, 3.4) |
| Oropharyngeal pain | 2 (1.4) | 1 (1.4) | 0.0 (-3.4, 3.4) |
| Headache | 29 (20.6) | 15 (21.1) | -0.6 (-12.2, 11.0) |
| Abdominal pain | 11 (7.8) | 6 (8.5) | -0.6 (-8.5, 7.2) |
| Menstrual disorder | 3 (2.1) | 2 (2.8) | -0.7 (-5.2, 3.8) |
| Laryngeal edema | 1 (0.7) | 1 (1.4) | -0.7 (-3.8, 2.4) |
| Laryngeal inflammation | 1 (0.7) | 1 (1.4) | -0.7 (-3.8, 2.4) |
| Menstruation irregular | 1 (0.7) | 1 (1.4) | -0.7 (-3.8, 2.4) |
| Nasal congestion | 1 (0.7) | 1 (1.4) | -0.7 (-3.8, 2.4) |
| Pain of skin | 1 (0.7) | 1 (1.4) | -0.7 (-3.8, 2.4) |
| Pain of skin | 2 (1.4) | 2 (2.8) | -1.4 (-5.7, 2.9) |
| Allergy to arthropod sting | 0 | 1 (1.4) | -1.4 (-4.1, 1.3) |
| Animal bite | 0 | 1 (1.4) | -1.4 (-4.1, 1.3) |
| Immunization reaction | 0 | 1 (1.4) | -1.4 (-4.1, 1.3) |
| Pancreatitis | 0 | 1 (1.4) | -1.4 (-4.1, 1.3) |
| Trichoglossia | 0 | 1 (1.4) | -1.4 (-4.1, 1.3) |
| Hypertension | 7 (5.0) | 5 (7.0) | -2.1 (-9.0, 4.9) |
| Eye pain | 1 (0.7) | 2 (2.8) | -2.1 (-6.2, 2.0) |
| Urticaria | 2 (1.4) | 3 (4.2) | -2.8 (-7.9, 2.3) |

| Grouped Query | Avapritinib 25 mg N=141 n (%) | Placebo N=71 n (%) | Avapritinib 25 mg vs. Placebo Risk Difference (%) (95% CI) |
|---|---|---|---|
| Gastritis | 0 | 2 (2.8) | -2.8 (-6.7, 1.0) |
| Fracture | 1 (0.7) | 3 (4.2) | -3.5 (-8.4, 1.4) |
| Joint injury | 1 (0.7) | 3 (4.2) | -3.5 (-8.4, 1.4) |
| Visual acuity reduced | 2 (1.4) | 4 (5.6) | -4.2 (-9.9, 1.5) |
| Musculoskeletal pain | 9 (6.4) | 13 (18.3) | -11.9 (-21.8, -2.1) * |

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that occurred between the Part 2 D1 through a day prior to Part 3 D1 if subject rolled over to Part 3; through 30 days after the last dose if subject did not rollover to Part 3.
Duration is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

*Clinical reviewer comment: The treatment-emergent adverse event (TEAE) tables were further analyzed to determine relatedness to avapritinib.*

*The most common TEAE identified was viral infections, which occurred in a higher proportion of patients in the avapritinib arm compared to the placebo arm, 17.7% versus 15.5%, respectively. The grouped term of viral infections included COVID-19, SARS-CoV-2 test positive, norovirus test positive, adenovirus infection, papilloma viral infection, COVID-19 pneumonia, oral herpes, influenza, viral infection, post viral fatigue syndrome, and gastroenteritis viral. The clinical reviewer agreed with the Applicant that COVID-19 was likely not related to avapritinib as it occurred in a similar proportion of patients in each treatment arm (12.1% and 11.3% in avapritinib and placebo groups, respectively) and it was during the COVID-19 pandemic. Further, viral infections are not described as an AR for other avapritinib approved indications. When removing terms related to COVID-19 from the grouped term viral infections, the proportion of patients with viral infections (without COVID-19) was approximately 4% of patients in each treatment arm. Therefore, the clinical reviewer determined not to include viral infections as an AR.*

*The Applicant proposed to split the FMQ grouped term hemorrhage into hematoma and hemorrhage. The clinical reviewer agreed with this proposal as the majority of cases were due to bruising. Therefore, the grouped term hematoma included contusion, hematoma and pelvic hematoma. In addition, the grouped term hemorrhage included; epistaxis, gingival bleeding, rectal hemorrhage, retinal hemorrhage, and hematochezia. Grouped terms, hemorrhage and hematoma, occurred in 6% and 5% of patients in the avapritinib arm, respectively and will be described in the avapritinib USPI in Section 6.*

*The FMQ hepatic injury, included a TEAE of hepatomegaly in one patient. Patient* (b) (6) *is a 72-year-old male, who experienced Grade 1 hepatomegaly on study day 1. While the patient had no history of hepatomegaly, it was unlikely related to avapritinib as it occurred on the first day of the study. Therefore, to better characterize this grouped term it was renamed liver transaminases increased, which includes PTs of alanine aminotransferase increased and aspartate aminotransferase increased. Liver transaminases increased occurred in 6% of patients in the avapritinib arm and 3% in the placebo arm. This risk will be described in the avapritinib USPI Section 6.*

*After considering relatedness of TEAE to avapritinib and appropriate terms to describe TEAEs, the clinical reviewer derived the table below. The most common (>10%) ARs in the avapritinib arm were eye edema, dizziness, peripheral edema and flushing.*

**Table 35. Adverse Reactions Occurring in Avapritinib-Treated Subjects With Indolent Systemic Mastocytosis During PIONEER Study**

| | Avapritinib (25 mg Once Daily) + BSC N=141 | Placebo + BSC N=71 |
|---|---|---|
| **Adverse Reactions[a, b]** | **%** | **%** |
| Eye edema | 13 | 7 |
| Dizziness | 13 | 10 |
| Peripheral edema | 12 | 6 |
| Hemorrhage | 5 | 3 |
| Flushing | 11 | 4 |
| Respiratory tract infection | 8 | 1 |
| Face edema | 7 | 1 |
| Insomnia | 6 | 3 |
| Liver transaminase increased | 6 | 3 |
| Hematoma | 6 | 1 |
| Blood alkaline phosphatase increased | 6 | 1 |
| Rash | 6 | 4 |

Source: Clinical reviewer
[a]Adverse reactions that occurred in ≥5% of Avapritin b-treated subjects and at least 2 times greater than placebo-treated subjects.
[b]Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0
Abbreviations: BSC, best supportive care

*Photosensitivity occurred in 2.8% of patients in the avapritinib arm compared to none in the placebo arm. Given this is a newly identified warning in the approved avapritinib label it will be described as a clinically relevant AR.*

*Overall, the safety profile of avapritinib in Study BLU-285-2203 Part 2, appears to be similar to that in the safety profile of avapritinib described in the approved product label for the AdvSM indication.*

**Pooled Analysis of Study 2203 (Parts 1/2/3)**

Overall, the most common treatment-emergent adverse events reported in ≥10% of subjects in Study 2203 among subjects treated with 25 mg of avapritinib are viral infection (28.3%), headache (18.1%), dizziness (16.8%), fatigue (15.5%), peripheral edema (15.5%), nausea (13.7%), bacterial infection (13.3%), nasopharyngitis (13.3%), rash (12.8%), hemorrhage (11.9%), pruritus (11.9%), diarrhea (11.5%), abdominal pain (11.5%), fatigue (10.6%), and erythema (10.6%).

**Table 36. Subjects With Common Adverse Events Occurring at ≥2% Frequency, Safety Population, Study BLU-285-2203 Overall (Parts 1/2/3)**

| Preferred Term | Avapritinib 25 mg* N=226 n (%) | All N=246 n (%) |
|---|---|---|
| Any AE | 202 (89.4) | 221 (89.8) |
| COVID-19 | 50 (22.1) | 57 (23.2) |
| Headache | 41 (18.1) | 50 (20.3) |
| Nausea | 31 (13.7) | 43 (17.5) |
| Dizziness | 30 (13.3) | 38 (15.4) |
| Diarrhea | 26 (11.5) | 34 (13.8) |
| Edema peripheral | 25 (11.1) | 30 (12.2) |
| Fatigue | 24 (10.6) | 29 (11.8) |
| Pruritus | 24 (10.6) | 29 (11.8) |
| Arthralgia | 20 (8.8) | 25 (10.2) |
| Flushing | 22 (9.7) | 24 (9.8) |
| Periorbital edema | 17 (7.5) | 22 (8.9) |
| Insomnia | 19 (8.4) | 21 (8.5) |
| Blood alkaline phosphatase increased | 19 (8.4) | 20 (8.1) |
| Hypertension | 19 (8.4) | 20 (8.1) |
| Abdominal pain | 16 (7.1) | 19 (7.7) |
| Back pain | 14 (6.2) | 19 (7.7) |
| Face edema | 14 (6.2) | 19 (7.7) |
| Constipation | 13 (5.8) | 16 (6.5) |
| Anaphylactic reaction | 9 (4.0) | 15 (6.1) |
| Nasopharyngitis | 13 (5.8) | 14 (5.7) |
| Upper respiratory tract infection | 10 (4.4) | 14 (5.7) |
| Weight increased | 11 (4.9) | 14 (5.7) |
| Abdominal distension | 12 (5.3) | 13 (5.3) |
| Alopecia | 12 (5.3) | 13 (5.3) |
| Palpitations | 11 (4.9) | 13 (5.3) |
| Urinary tract infection | 11 (4.9) | 13 (5.3) |
| Vomiting | 9 (4.0) | 13 (5.3) |
| Dyspnea | 8 (3.5) | 12 (4.9) |
| Peripheral swelling | 10 (4.4) | 12 (4.9) |
| Rash | 11 (4.9) | 12 (4.9) |
| Alanine aminotransferase increased | 8 (3.5) | 11 (4.5) |
| Contusion | 11 (4.9) | 11 (4.5) |
| Disturbance in attention | 9 (4.0) | 11 (4.5) |
| Paresthesia | 7 (3.1) | 11 (4.5) |
| Sinusitis | 10 (4.4) | 11 (4.5) |
| Bone pain | 9 (4.0) | 10 (4.1) |
| Cough | 10 (4.4) | 10 (4.1) |
| Hair color changes | 7 (3.1) | 10 (4.1) |
| Hypersensitivity | 6 (2.7) | 10 (4.1) |
| Anxiety | 8 (3.5) | 9 (3.7) |
| Aspartate aminotransferase increased | 7 (3.1) | 9 (3.7) |
| Blood creatinine increased | 8 (3.5) | 9 (3.7) |
| Fall | 6 (2.7) | 9 (3.7) |
| Lacrimation increased | 8 (3.5) | 9 (3.7) |
| Myalgia | 7 (3.1) | 9 (3.7) |
| Pain in extremity | 6 (2.7) | 9 (3.7) |
| Feeling abnormal | 7 (3.1) | 8 (3.3) |
| Gastroesophageal reflux disease | 6 (2.7) | 8 (3.3) |
| Hot flush | 6 (2.7) | 8 (3.3) |
| Influenza like illness | 6 (2.7) | 8 (3.3) |

| Preferred Term | Avapritinib 25 mg* N=226 n (%) | All N=246 n (%) |
|---|---|---|
| Noncardiac chest pain | 5 (2.2) | 8 (3.3) |
| Asthenia | 7 (3.1) | 7 (2.8) |
| Decreased appetite | 4 (1.8) | 7 (2.8) |
| Dry eye | 7 (3.1) | 7 (2.8) |
| Dry mouth | 5 (2.2) | 7 (2.8) |
| Dyspepsia | 6 (2.7) | 7 (2.8) |
| Epistaxis | 7 (3.1) | 7 (2.8) |
| Memory impairment | 5 (2.2) | 7 (2.8) |
| Muscle spasms | 6 (2.7) | 7 (2.8) |
| Pyrexia | 5 (2.2) | 7 (2.8) |
| Rash maculo-papular | 6 (2.7) | 7 (2.8) |
| Skin lesion | 7 (3.1) | 7 (2.8) |
| Tooth infection | 6 (2.7) | 7 (2.8) |
| Urticaria | 7 (3.1) | 7 (2.8) |
| Vertigo | 7 (3.1) | 7 (2.8) |
| Abdominal pain upper | 6 (2.7) | 6 (2.4) |
| Depression | 4 (1.8) | 6 (2.4) |
| Eyelid edema | 6 (2.7) | 6 (2.4) |
| Gastrointestinal disorder | 4 (1.8) | 6 (2.4) |
| Hemorrhoids | 4 (1.8) | 6 (2.4) |
| Hyperuricemia | 5 (2.2) | 6 (2.4) |
| Hypoesthesia | 3 (1.3) | 6 (2.4) |
| Hypophosphatemia | 4 (1.8) | 6 (2.4) |
| Pain | 4 (1.8) | 6 (2.4) |
| Tremor | 4 (1.8) | 6 (2.4) |
| Vision blurred | 4 (1.8) | 6 (2.4) |
| Abdominal discomfort | 5 (2.2) | 5 (2.0) |
| Anemia | 4 (1.8) | 5 (2.0) |
| Blood uric acid increased | 4 (1.8) | 5 (2.0) |
| Dry skin | 4 (1.8) | 5 (2.0) |
| Electrocardiogram QT prolonged | 4 (1.8) | 5 (2.0) |
| Hematoma | 4 (1.8) | 5 (2.0) |
| Hyperhidrosis | 3 (1.3) | 5 (2.0) |
| Hypokalemia | 5 (2.2) | 5 (2.0) |
| Joint swelling | 4 (1.8) | 5 (2.0) |
| Lymphadenopathy | 3 (1.3) | 5 (2.0) |
| Mastocytosis | 5 (2.2) | 5 (2.0) |
| Migraine | 5 (2.2) | 5 (2.0) |
| Procedural pain | 4 (1.8) | 5 (2.0) |
| Rhinitis | 5 (2.2) | 5 (2.0) |
| Tinnitus | 5 (2.2) | 5 (2.0) |
| Vaccination complication | 4 (1.8) | 5 (2.0) |

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that occurred between the first dose of avapritinib in the study through 30 days after the last dose.
Duration is at least 12 weeks (Part 1), 24 weeks (Part 2), and up to 5 years (Part 3).
Analysis duration median (min, max) is 42.4 (0.9, 159.4) weeks.
Coded as MedDRA preferred terms.
*This group includes the subjects who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the subjects who received 50 mg or 100 mg avapritinib in Part 1.
The “All” study arm includes the subjects who received placebo or 25 mg avapritinib in Part 1 or Part 2, as well as the subjects who received 50 mg or 100 mg avapritinib in Part 1.
COVID-19 replaces: Dyspnea, Dizziness, Hypogeusia, Hyposmia
Mastocytosis replaces: Mast cell activation syndrome
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event

**Table 37. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Study BLU-285-2203 Overall (Parts 1/2/3)**

| System Organ Class<br>FMQ (Narrow) | Avapritinib 25 mg*<br>N=226<br>n (%) | All<br>N=246<br>n (%) |
|---|---|---|
| Blood and lymphatic system disorders (SOC) | | |
| Anemia | 4 (1.8) | 5 (2.0) |
| Thrombocytopenia | 3 (1.3) | 3 (1.2) |
| Leukopenia | 2 (0.9) | 2 (0.8) |
| Cardiac disorders (SOC) | | |
| Systemic hypertension | 20 (8.8) | 21 (8.5) |
| Palpitations | 11 (4.9) | 13 (5.3) |
| Arrhythmia | 6 (2.7) | 7 (2.8) |
| Cardiac conduction disturbance | 5 (2.2) | 6 (2.4) |
| Tachycardia | 2 (0.9) | 3 (1.2) |
| Myocardial ischemia | 2 (0.9) | 2 (0.8) |
| Acute coronary syndrome | 1 (0.4) | 1 (0.4) |
| Myocardial infarction | 1 (0.4) | 1 (0.4) |
| Ear and labyrinth disorders (SOC) | | |
| Vertigo | 7 (3.1) | 7 (2.8) |
| Endocrine disorders (SOC) | | |
| Hyperglycemia | 4 (1.8) | 7 (2.8) |
| Gastrointestinal disorders (SOC) | | |
| Nausea | 31 (13.7) | 43 (17.5) |
| Diarrhea | 26 (11.5) | 34 (13.8) |
| Abdominal pain | 26 (11.5) | 29 (11.8) |
| Constipation | 13 (5.8) | 16 (6.5) |
| Dyspepsia | 13 (5.8) | 14 (5.7) |
| Vomiting | 9 (4.0) | 13 (5.3) |
| Dry mouth | 5 (2.2) | 7 (2.8) |
| Pancreatitis | 3 (1.3) | 3 (1.2) |
| General disorders and administration site conditions (SOC) | | |
| Dizziness | 38 (16.8) | 46 (18.7) |
| Fatigue | 35 (15.5) | 40 (16.3) |
| Peripheral edema | 34 (15.0) | 40 (16.3) |
| Fall | 6 (2.7) | 9 (3.7) |
| Decreased Appetite | 4 (1.8) | 7 (2.8) |
| Pyrexia | 5 (2.2) | 7 (2.8) |
| Hepatobiliary disorders (SOC) | | |
| Hepatic injury | 12 (5.3) | 15 (6.1) |
| Immune system disorders (SOC) | | |
| Hypersensitivity | 18 (8.0) | 25 (10.2) |
| Anaphylactic reaction | 10 (4.4) | 16 (6.5) |
| Angioedema | 5 (2.2) | 7 (2.8) |
| Infections and infestations (SOC) | | |
| Viral infection | 64 (28.3) | 74 (30.1) |
| Bacterial infection | 30 (13.3) | 39 (15.9) |
| Nasopharyngitis | 30 (13.3) | 35 (14.2) |
| Fungal infection | 5 (2.2) | 7 (2.8) |
| Purulent material | 3 (1.3) | 4 (1.6) |
| Pneumonia | 1 (0.4) | 1 (0.4) |
| Metabolism and nutrition disorders (SOC) | | |
| Lipid disorder | 3 (1.3) | 4 (1.6) |

| System Organ Class<br>FMQ (Narrow) | Avapritinib 25 mg*<br>N=226<br>n (%) | All<br>N=246<br>n (%) |
|---|---|---|
| Musculoskeletal and connective tissue disorders (SOC) | | |
| Arthralgia | 20 (8.8) | 25 (10.2) |
| Back Pain | 16 (7.1) | 21 (8.5) |
| Fracture | 6 (2.7) | 10 (4.1) |
| Myalgia | 7 (3.1) | 9 (3.7) |
| Tendinopathy | 6 (2.7) | 8 (3.3) |
| Arthritis | 3 (1.3) | 5 (2.0) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC) | | |
| Malignancy | 6 (2.7) | 7 (2.8) |
| Nervous system disorders (SOC) | | |
| Headache | 46 (20.4) | 55 (22.4) |
| Paresthesia | 11 (4.9) | 17 (6.9) |
| Tremor | 4 (1.8) | 6 (2.4) |
| Syncope | 4 (1.8) | 4 (1.6) |
| Confusional state | 0 | 3 (1.2) |
| Dysgeusia | 2 (0.9) | 3 (1.2) |
| Somnolence | 2 (0.9) | 3 (1.2) |
| Seizure | 1 (0.4) | 1 (0.4) |
| Psychiatric disorders (SOC) | | |
| Insomnia | 19 (8.4) | 21 (8.5) |
| Depression | 7 (3.1) | 10 (4.1) |
| Anxiety | 8 (3.5) | 9 (3.7) |
| Irritability | 2 (0.9) | 4 (1.6) |
| Parasomnia | 2 (0.9) | 2 (0.8) |
| Psychosis | 1 (0.4) | 1 (0.4) |
| Self-Harm | 1 (0.4) | 1 (0.4) |
| Study agent abuse potential | 0 | 1 (0.4) |
| Renal and urinary disorders (SOC) | | |
| Renal & urinary tract infection | 13 (5.8) | 16 (6.5) |
| Acute kidney injury | 1 (0.4) | 1 (0.4) |
| Reproductive system and breast disorders (SOC) | | |
| Abnormal uterine bleeding | 5 (2.2) | 6 (2.4) |
| Excessive menstrual bleeding | 4 (1.8) | 4 (1.6) |
| Sexual dysfunction | 4 (1.8) | 4 (1.6) |
| Respiratory, thoracic and mediastinal disorders (SOC) | | |
| Dyspnea | 11 (4.9) | 15 (6.1) |
| Cough | 10 (4.4) | 10 (4.1) |
| Bronchospasm | 2 (0.9) | 3 (1.2) |
| Respiratory failure | 2 (0.9) | 2 (0.8) |
| Skin and subcutaneous tissue disorders (SOC) | | |
| Rash | 29 (12.8) | 33 (13.4) |
| Pruritus | 27 (11.9) | 32 (13.0) |
| Erythema | 24 (10.6) | 27 (11.0) |
| Alopecia | 13 (5.8) | 14 (5.7) |
| Urticaria | 7 (3.1) | 7 (2.8) |

| System Organ Class<br>FMQ (Narrow) | Avapritinib 25 mg*<br>N=226<br>n (%) | All<br>N=246<br>n (%) |
|---|---|---|
| Vascular disorders (SOC) | | |
| Hemorrhage | 27 (11.9) | 31 (12.6) |
| Hypotension | 3 (1.3) | 3 (1.2) |
| Thrombosis | 1 (0.4) | 1 (0.4) |
| Thrombosis Arterial | 1 (0.4) | 1 (0.4) |

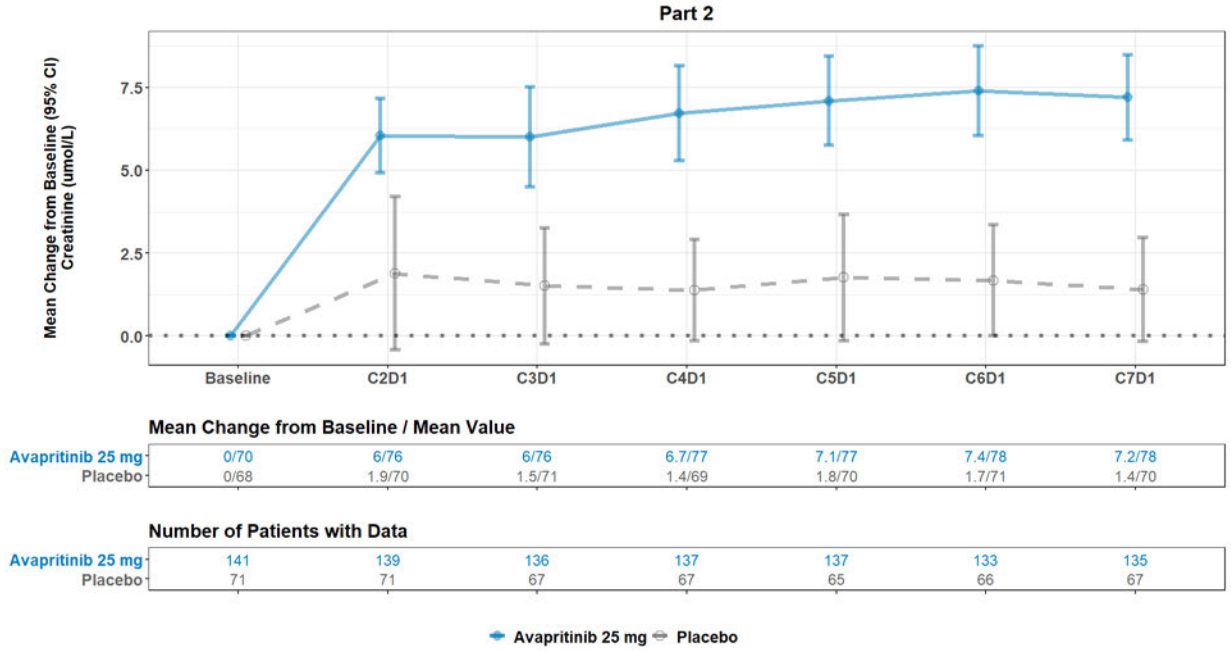
Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that occurred between the first dose of avapritinib in the study through 30 days after the last dose.
Duration is at least 12 weeks (Part 1), 24 weeks (Part 2), and up to 5 years (Part 3).
Analysis duration median (min, max) is 42.4 (0.9, 159.4) weeks.
Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.
*This group includes the subjects who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the subjects who received 50 mg or 100 mg avapritinib in Part 1.
The “All” study arm includes the subjects who received placebo or 25 mg avapritinib in Part 1 or Part 2, as well as the subjects who received 50 mg or 100 mg avapritinib in Part 1.
Abbreviations: AE, adverse event; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

*Clinical reviewer comment: TEAEs observed in all three parts of the trials combined was generally consistent with the randomized, placebo-controlled portion (Part 2).*

#### 33.6.1.6. Laboratory Findings

In the randomized Part 2 portion of the study there were no clinically relevant differences over time (baseline to cycle 7 day 1) in clinical laboratory parameters (serum chemistries or hepatic enzymes) in the avapritinib group compared to the placebo group other than serum creatinine; in which a baseline mean increase of approximately 7 µmol/L was among subjects in the avapritinib 25 mg group compared to approximately 1.5 µmol/L among subjects in the placebo group. The figure below shows the mean serum creatinine change from baseline over time. A similar change in serum creatinine over time was observed in the pooled analysis of parts 1/2/3 of Study 2203.

**Figure 13. Mean Laboratory (Kidney Function) Data Change From Baseline Over Time, Safety Population, Study BLU-285-2203 Part 2**

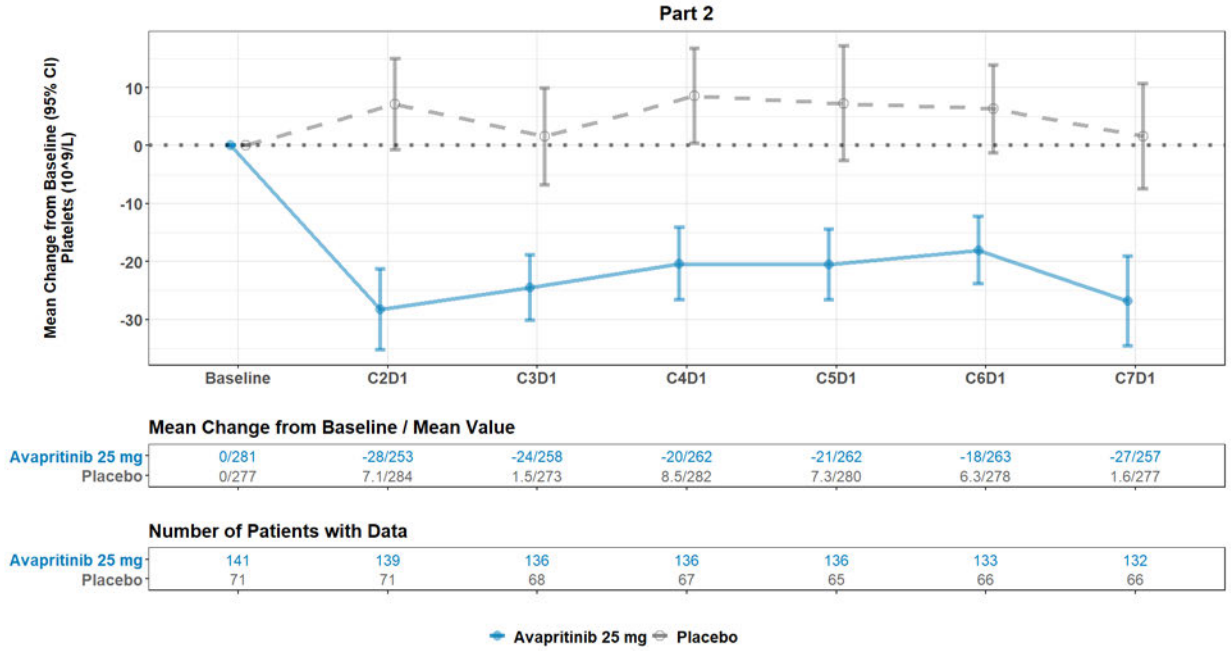



Source: ad b.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.
Data are presented in 28-day cycles and time points are labeled as CXDX (e.g., C2D1 is cycle 2, day 1).
Abbreviations: C, cycle; CI, confidence interval; D, day

*Reviewer comment: there appears to be an increase in the mean serum creatinine among patients treated with avapritinib compared to placebo over time from baseline to cycle 7 day 1. However, an approximate 5.5 µmol/L relative mean serum creatinine increase is not clinically significant.*

In the randomized Part 2 portion of the study there were no clinically relevant differences in hematologic laboratory parameters (white blood cell counts or hemoglobin) in the avapritinib group compared to the placebo group other than platelet count, in which a baseline mean decrease of approximately 20-30 x 109/L was observed among subjects in the avapritinib 25 mg group compared subjects in the placebo group. The figure below shows the mean platelet count change from baseline over time. A similar change in platelet count over time was observed in the pooled analysis of parts 1/2/3 of Study 2203.

**Figure 14. Mean Laboratory (Hematology) Data Change From Baseline Over Time, Safety Population, Study BLU-285-2203 Part 2**




Source: ad b.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.
Data are presented in 28-day cycles and time points are labeled as CXDX (e.g., C2D1 is cycle 2, day 1).
Abbreviations: C, cycle; CI, confidence interval; D, day

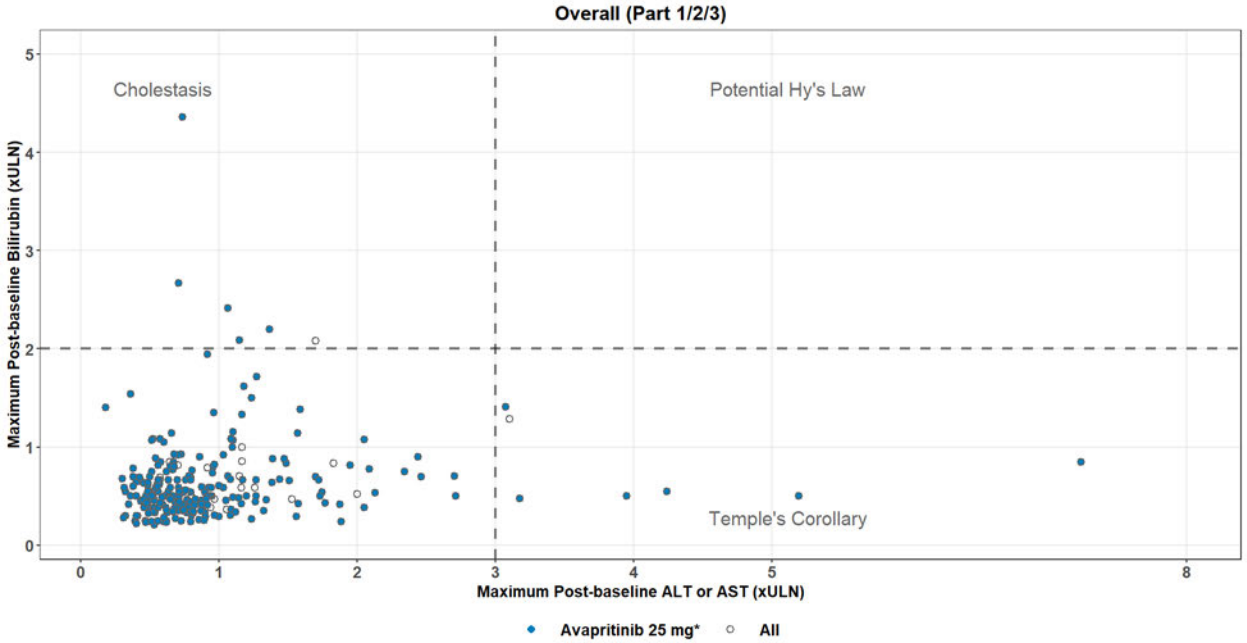
*Reviewer comment: Thrombocytopenia is a potentially clinically relevant TEAE among patients treated with avapritinib with ISM due to the potential increased risk of bleeding. One patient in each treatment arm in Part 2 had an AE of thrombocytopenia. Two patients in the avapritinib arm were noted to have a platelet count <100x109/L, none were below 50x109/L. It should also be noted that platelets are acute phase reactants. Likely, the difference in platelet count between the avapritinib group and placebo group is not clinically significant.*

*In Part 2 of Study 2203, 10.6% of in the avapritinib arm experienced an TEAE of hemorrhage compared to 4.2% of patients in the placebo arm. In all three parts of Study 2203, 11.9% of patients who took at least one dose of avapritinib 25 mg experienced a TEAE of hemorrhage (see reviewer comment for detailed discussions of bleeding and TEAEs and intracranial hemorrhage risk in Section 33.6.1.5. Treatment-Emergent Adverse Events, Study 2203 and Section 33.7. Key Safety Review Issues, respectively). However, no patient had a platelet count below 50 X 109/L in any part of Study 2203 and the Applicant did not report low platelets or drop in platelets as occurring with bleeding events.*

### 33.6.1.7. Assessment of Drug-Induced Liver Injury, Study 2203

There were no cases reported in Study 2203 Parts 1/2/3 with elevated serum liver enzymes (aspartate amino transferase (AST) and alanine amino transferase (ALT) and serum total bilirubin consistent with Hy's Law, see figure below.

**Figure 15. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Study BLU-285-2203 Overall (Parts 1/2/3)**



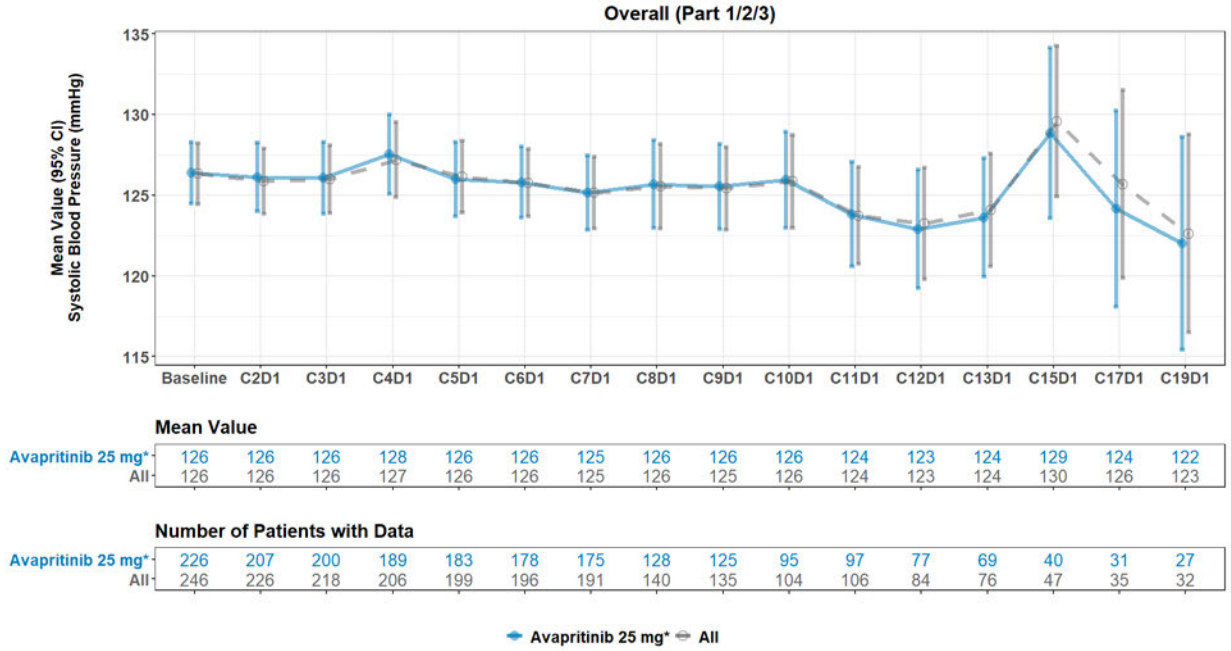

Source: ad b.xpt; Software: R
Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.
A potential Hy's Law case (red circle) was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN within 30 days after a postbaseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN (note ALP values are not circled).
All subjects with at least one postbaseline ALT or AST and bilirubin are plotted.
*This group includes the subjects who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the subjects who received 50 mg or 100 mg avapritinib in Part 1.
The “All” study arm includes the subjects who received placebo or 25 mg avapritinib in Part 1 or Part 2, as well as the subjects who received 50 mg or 100 mg avapritinib in Part 1.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; ULN, upper limit of normal

### 33.6.1.8. Vital Signs Analyses, Study 2203

**Pooled Analysis of Study 2203 (Parts 1/2/3)**

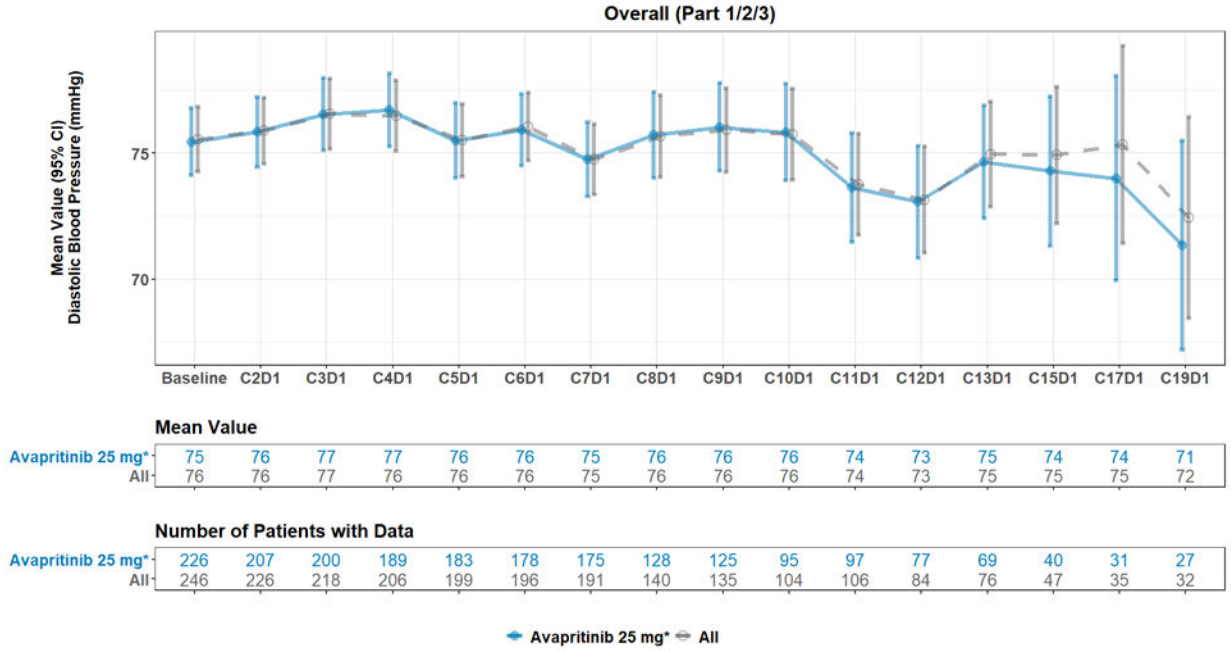
Overall, no clinically significant changes in vital signs were reported between the avapritinib arm and the placebo arm in all three parts of Study 2203. Mean systolic blood pressure, diastolic blood pressure, and pulse rate are shown in the figures below.

**Figure 16. Mean and 95% Confidence Interval of Systolic Blood Pressure Over Time by Treatment Arm, Safety Population, Study BLU-285-2203 Overall (Parts 1/2/3)**



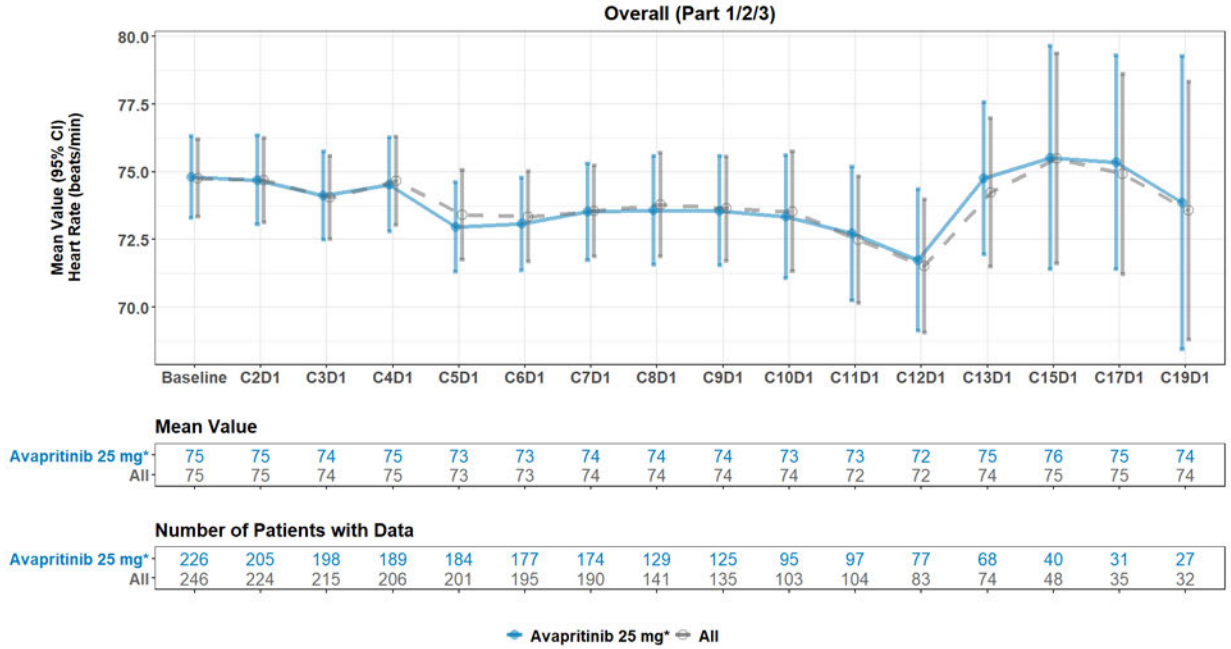

Source: advs.xpt; Software: R
Vertical bars show 95% confidence intervals.
*This group includes the subjects who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the subjects who received 50 mg or 100 mg avapritinib in Part 1.
The “All” study arm includes the subjects who received placebo or 25 mg avapritinib in Part 1 or Part 2, as well as the subjects who received 50 mg or 100 mg avapritinib in Part 1.
Data are presented in 28-day cycles and time points are labeled as CXDX (e.g., C2D1 is cycle 2, day 1).
Abbreviations: C, cycle; CI, confidence interval; D, day

**Figure 17. Mean and 95% Confidence Interval of Diastolic Blood Pressure Over Time by Treatment Arm, Safety Population, Study BLU-285-2203 Overall (Parts 1/2/3)**




Source: advs.xpt; Software: R
Vertical bars show 95% confidence intervals.
*This group includes the subjects who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the subjects who received 50 mg or 100 mg avapritinib in Part 1.
The “All” study arm includes the subjects who received placebo or 25 mg avapritinib in Part 1 or Part 2, as well as the subjects who received 50 mg or 100 mg avapritinib in Part 1.
Data are presented in 28-day cycles and time points are labeled as CXDX (e.g., C2D1 is cycle 2, day 1).
Abbreviations: C, cycle; CI, confidence interval; D, day

**Figure 18. Mean and 95% Confidence Interval of Pulse Rate Over Time by Treatment Arm, Safety Population, Study BLU-285-2203 Overall (Parts 1/2/3)**




Source: advs.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.
*This group includes the subjects who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the subjects who received 50 mg or 100 mg avapritinib in Part 1.
The "All" study arm includes the subjects who received placebo or 25 mg avapritinib in Part 1 or Part 2, as well as the subjects who received 50 mg or 100 mg avapritinib in Part 1.
Data are presented in 28-day cycles and time points are labeled as CXDX (e.g., C2D1 is cycle 2, day 1).
Abbreviations: C, cycle; CI, confidence interval; D, day

### 33.6.1.9. Subgroup Analyses, Study2203

**Part 2 of Study 2203**

In Part 2 of Study 4311, there were no clinically relevant proportional differences between treatment groups reporting adverse events by sex, age, race ethnicity or study site as shown in the table below.

**Table 38. Overview of Adverse Events by Demographic Subgroup, Safety Population, Study BLU-285-2203 Part 2**

| Characteristic | Avapritinib 25 mg N=141 $n/N_s$ (%) | Placebo N=71 $n/N_s$ (%) | Avapritinib 25 mg vs. Placebo Risk Difference (%) (95% CI) |
|---|---|---|---|
| Sex, n (%) | | | |
| Female | 92/100 (92.0) | 50/54 (92.6) | -0.6 (-9.4, 8.2) |
| Male | 36/41 (87.8) | 16/17 (94.1) | -6.3 (-21.3, 8.7) |
| Age group, years, n (%) | | | |
| <65 | 120/132 (90.9) | 55/60 (91.7) | -0.8 (-9.3, 7.8) |
| ≥65 | 8/9 (88.9) | 11/11 (100) | -11.1 (-31.6, 9.4) |
| Age group ≥75, years, n (%) | | | |
| ≥75 | 1/1 (100) | 2/2 (100) | 0 (0, 0) |

| Characteristic | Avapritinib 25 mg N=141 n/$N_s$ (%) | Placebo N=71 n/$N_s$ (%) | Avapritinib 25 mg vs. Placebo Risk Difference (%) (95% CI) |
|---|---|---|---|
| Race, n (%) | | | |
| Asian | 1/1 (100) | 0/0 (NA) | NA |
| White | 100/109 (91.7) | 56/61 (91.8) | -0.1 (-8.7, 8.5) |
| Other | 3/4 (75.0) | 2/2 (100) | -25.0 (-67.4, 17.4) |
| Unknown | 24/27 (88.9) | 8/8 (100) | -11.1 (-23.0, 0.7) |
| Ethnicity, n (%) | | | |
| Hispanic or Latino | 4/6 (66.7) | 1/1 (100) | -33.3 (-71.1, 4.4) |
| Not Hispanic or Latino | 93/99 (93.9) | 53/58 (91.4) | 2.6 (-6.1, 11.2) |
| Not Reported | 20/22 (90.9) | 10/10 (100) | -9.1 (-21.1, 2.9) |
| Unknown | 11/14 (78.6) | 2/2 (100) | -21.4 (-42.9, 0.1) |
| Is in United States, n (%) | | | |
| United States | 45/52 (86.5) | 24/28 (85.7) | 0.8 (-15.1, 16.8) |
| Non-United States | 83/89 (93.3) | 42/43 (97.7) | -4.4 (-11.3, 2.5) |

Source: adae.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; $N_s$, total number of subjects for each specific subgroup and were assigned to that specific arm

# 33.7. Key Safety Review Issues

## 33.7.1. Risk of Intracranial Hemorrhage

**Issue**

The avapritinib product label states in the Warnings and Precautions section that there is a potential increased risk of intracranial hemorrhage (ICH). The clinical reviewer assessed if this risk also applies to patients with ISM.

**Background**

Intracranial hemorrhage is a known adverse reaction for patients exposed to avapritinib. As stated in the approved product label, ICH (e.g., subdural hematoma, intracranial hemorrhage, and cerebral hemorrhage) occurred in 2.9% of the 749 subjects with GIST or AdvSM who received avapritinib in clinical trials. Less than 1% of ICH events have been fatal. In patients with AdvSM who received avapritinib 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. Given the risk of ICH in the presence of thrombocytopenia, the product label contains a Limitation of Use (LoU) for avapritinib for the treatment of patients with AdvSM with platelet counts of less than 50 X $10^9$/L.

In this sNDA, the Applicant (b) (4) In addition, patients with thrombocytopenia (<100 × 109/L) were excluded from the clinical trial as this would not be consistent with the diagnosis of ISM based on WHO criteria (see Section 41, Table 59 for WHO criteria).

**Assessment**

No cases of ICH were reported among subjects with ISM in Study 2203. Although, events of hemorrhage did occur.

In Part 2 of Study 2203 (randomized, placebo-controlled part), 10.6% of in the avapritinib arm experienced an TEAE of hemorrhage (grouped narrow FMQ) compared to 4.2% of subjects in the placebo arm. Preferred terms captured in this grouped term from the avapritinib group included hematoma, rectal hemorrhage, contusion, pelvic hematoma, retinal hemorrhage, epistaxis, gingival bleeding, and hematochezia. All events were grade 1 or 2 in severity. There was one SAE of pelvic hematoma, although this event was complicated by a recent bone marrow biopsy procedure.

In all three parts of Study 2203, 11.9% of subjects who took at least one dose of avapritinib 25 mg experienced a TEAE of hemorrhage (grouped narrow FMQ).

No subject had a platelet count below 50 X $10^9$/L in any part of Study 2203.

**Conclusion**

Avapritinib at the 25 mg dose daily causes bleeding as demonstrated by a higher proportion of subjects in the avapritinib arm experienced a TEAE of bleeding compared to the placebo arm. The risk of ICH is unclear in this population as the sample size in Study 2203 was small and patients with thrombocytopenia were excluded from the study. Although no ICH events were reported among subjects in Study 2203, there is still a potential risk of ICH for patients with ISM who have thrombocytopenia with platelet counts below 50 x $10^9$/L for other etiologies (i.e., immune thrombocytopenia purpura, concomitant medications, infections, or concurrent illness such as systemic lupus erythematosus or malignancy). Therefore, the LoU for thrombocytopenia (platelet count below 50 x $10^9$/L) should also apply to patients with ISM as it does for patients with AdvSM receiving avapritinib therapy.

# 34. Therapeutic Individualization

## 34.1. Intrinsic Factors

**Renal Impairment**

No clinically significant differences in the PK of avapritinib were observed based on mild to moderate ($CL_{cr}$ 30 to 89 mL/min estimated by Cockcroft-Gault) renal impairment. The effect of severe renal impairment ($CL_{cr}$ 15 to 29 mL/min) and end-stage renal disease ($CL_{cr}$ <15 mL/min) on the pharmacokinetics of avapritinib is unknown.

**Hepatic Impairment**

During the approval of avapritinib dated February 14, 2020, PMR 7781-3 was issued to complete a pharmacokinetic trial to determine an appropriate dose of avapritinib to minimize toxicity in patients with severe hepatic impairment in accordance with the FDA Guidance for Industry entitled *"Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."* The Applicant submitted the study report for

Study BLU-285-0107: Effect of Severe Hepatic Impairment on Avapritinib Pharmacokinetics, as a part of the efficacy supplement.

In this study, eight subjects with severe hepatic impairment (Child-Pugh Class C) and eight matched healthy control subjects each received a single 100 mg oral dose of avapritinib under fasting conditions. Severe hepatic impairment increased unbound avapritinib exposures, as compared with the control subjects. Based on geometric mean ratios, unbound maximum plasma concentration ($C_{max}$) and unbound area under the concentration-time curve ($AUC_{0-\infty}$) increased by 8% and 61%, respectively, in the subjects with severe hepatic impairment. PBPK model was used to predict the repeat-dose PK of avapritinib in subjects with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), or severe (Child-Pugh Class C) hepatic impairment. The PBPK model predictions indicated that mild and moderate hepatic impairment would have minimal impact on systemic exposures to total and unbound avapritinib. The PBPK model predicted that severe hepatic impairment would result in 1.6- and 1.7-fold increases in the $C_{max}$ and $AUC_{0-\tau}$ of unbound plasma avapritinib at steady state, respectively, compared with subjects with normal hepatic function. Since avapritinib is a low extraction ratio drug, little change in $C_{max}$ following single dose is expected as severe hepatic impairment had minimal impact on hepatic/gut first pass bioavailability. At steady state, change in $C_{max}$ is driven by the decrease in clearance due to severe hepatic impairment, and in similar magnitude to AUC change.

No dose modification is recommended for patients with mild or moderate hepatic impairment. For patients with severe hepatic impairment, modifications of the avapritinib starting dose are recommended i.e., from 25 mg QD to 25 mg every other day (QOD) in ISM, from 200 mg QD to 100 mg QD in AdvSM, and from 300 mg QD to 200 mg QD in GIST. The proposed dose modifications considered the increased exposure but at the same time adjusted to the nearest dose strength available. We considered the $C_{max}$ and AUC ratios at the steady state for the dose adjustment of avapritinib, like the approach taken for dose adjustment with moderate CYP3A inhibitors. For ISM, because 25 mg is the lowest available strength, a less frequent regimen is chosen to account for the increased exposure. Overall, the review team agrees with the proposed dose modifications. The review team also agrees that PMR 7781-3 has been fulfilled.

## 34.2. Extrinsic Factors

No new information on extrinsic factors has been submitted. The existing information from the USPI related to these factors is applicable.

## 34.3. Plans for Pediatric Drug Development

There are no plans for pediatric drug development at this for avapritinib for the ISM indication. Avapritinib received Orphan Drug Designation for the treatment of mastocytosis on January 21, 2016.

# 34.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

## Animal Data

The following nonclinical data are used to support the label. Additional detailed information is available in Part III, Additional Analyses and Information (Section 39) for nonclinical data.

**Table 39. Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation**

| Labeling Section | Nonclinical Data |
|---|---|
| 8.1 Pregnancy | In a reproductive toxicity study, administration of avapritinib to rats during the period of organogenesis resulted in decreased fetal body weights, postimplantation 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 31.4, 6.3 and 2.7 times the human exposure based on AUC at the 25 mg, 200 mg and 300 mg dose, respectively). |
| 8.2 Lactation | 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. |
| 8.3 Females and Males of Reproductive Potential | Based on findings from animal studies, AYVAKIT may impair female and male fertility. The effect was not reversible within a two-month recovery period [see Nonclinical Toxicology (13.1)]. |
| 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility | Avapritinib was not mutagenic in a 6-month transgenic mouse study up to the highest dose evaluated at 20 mg/kg/day. 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 nongenotoxic.<br>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 8.7 times and 0.5 time the 300 mg human dose, respectively. There were no direct effects on fertility in rats of either sex in a dedicated fertility and early embryonic development study. Avapritinib partitioned into seminal fluids up to 0.2 times the concentration found in human plasma at 300 mg. In female rats there was an increase in pre-implantation loss 300 mg and in early resorptions at exposure of 2.7 times the human exposure at 300 mg with an overall decrease in viable embryos. Cystic degeneration of corpora lutea and vaginal mucification was also observed in female rats administered avapritinib for up to 6 months at exposure of 1.3 times the human exposure based on AUC at the 300 mg dose). |

Source: FDA Reviewer
Abbreviations: MRHD, maximum recommended human dose; BSA, body surface area

Details of above information and dose multiples shown are based on body surface area compared between animals.

# 35. Product Quality

**Approval**

The Office of Pharmaceutical Quality (OPQ) review team has assessed NDA 212608 with respect to chemistry, manufacturing, and controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such OPQ recommends approval of this NDA from a quality perspective.

## 35.1. Device or Combination Product Considerations

There are no combination product considerations, avapritinib is administered orally.

# 36. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

A signed written informed consent form was required in order to enroll in Study 2203. An Institutional Review Board (IRB) and Institutional Ethics Committee (IEC) reviewed the study. The study will be conducted according to Good Clinical Practices and Declaration of Helsinki Guidelines.

# 37. Advisory Committee Summary

An Advisory Committee meeting was not convened to discuss this application. No issues were identified that might have benefitted from a public discussion.

# III. Additional Analyses and Information

# 38. Summary of Regulatory History

The investigational new drug application (IND) 124159 was submitted on August 6, 2015, to study BLU-285 (also referred to as avapritinib) for the treatment of patients with advanced systemic mastocytosis (AdvSM) including aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematologic neoplasm (SM-AHN) and mast cell leukemia (MCL) and indolent systemic mastocytosis (ISM). BLU-285 was also investigated for the treatment of unresectable gastrointestinal stromal tumors (GISTs) under a separate IND (IND 125379).

Avapritinib was granted orphan drug designation (#15-5065) for the treatment of mastocytosis on January 21, 2016, and Breakthrough Therapy designation for treatment of moderate to severe ISM on December 23, 2020.

A carcinogenicity special protocol assessment request was submitted on July 8, 2022, and agreement communication was issued July 14, 2022.

The Applicant submitted various meeting requests to obtain feedback and guidance in preparation for submission of a supplemental NDA (sNDA) for treatment of ISM. On May 20, 2020, the End-of-Phase 2 meeting was held. A pre-sNDA meeting was held on September 19, 2022.

NDA 212608 for AYVAKIT® (avapritinib) tablets was approved on January 9, 2020, for the treatment of adult patients with unresectable or metastatic (GISTs harboring platelet derived growth factor receptor alpha (PDGFRA) exon 18 mutations including the PDGFRA D842V mutation. On June 16, 2021, S-006 was approved, which provided for the treatment of adult patients with AdvSM, including patients with aggressive systemic mastocytosis (ASM), SM-AHN, and S-007 was approved, which provided for treatment of adult patients with mast cell leukemia.

On November 22, 2023, the Applicant submitted S-013, which proposes addition of the indication of treatment of ISM.

# 39. Pharmacology Toxicology

## 39.1. Summary Review of Studies Submitted With the Investigational New Drug Application

No new nonclinical studies were submitted under IND 124159. All avapritinib nonclinical studies, except for Section 39.2, were previously reviewed and can be found in the integrated multidisciplinary review of the original NDA application.

## 39.2. Individual Reviews of Studies Submitted With the New Drug Application

**Carcinogenicity Study**

**Study Title: BLU-285: A 26-Week (Once Daily) Oral (Gavage) Carcinogenicity Study in CByB6F1/Tg rasH2 Hemizygous Mice**

**Table 40. Study Summary of 26-Week Oral Carcinogenicity Study in CByB6F1/Tg rasH2 Hemizygous Mice**

| Study Parameter | Information |
|---|---|
| Study no. | 01499039 |
| Study report location | eCTD 4.2 |
| Conducting laboratory and location | (b) (4) |

| Study Parameter | Information |
|---|---|
| | (b) (4) |
| Date of study initiation | February 11, 2021 |
| GLP compliance | Yes |
| QA statement | Yes |
| Drug, lot #, and % purity | Avapritinib (BLU-285), 0285/02 and 19600T9009 |
| CAC concurrence | Pending |
| Key study findings | • There were no avapritinib-related effects on survival<br>• No avapritinib-related effects were observed on incidence of neoplasm or on mortality for either sex<br>• No non-neoplastic findings related to avapritinib were observed |
| Adequacy of carcinogenicity study | The ECAC concurrence was not sought prior to initiation of the carcinogenicity for the adequacy of the carcinogenicity study design. The dose selection criteria are not known |
| Appropriateness of test models | Yes |
| Evaluation of tumor findings | There were no avapritinib-related tumors found in RasH2 transgenic mice after 26-week dosing |

Source: Reviewer's analysis
Abbreviations: CAC, Carcinogenicity Assessment Committee; ECAC, executive carcinogenicity assessment committee; GLP, good laboratory practices; QA, quality assurance

**Table 41. Study Methods of 26-Week Oral Carcinogenicity Study in CByB6F1/Tg rasH2 Hemizygous Mice**

| Method | Information |
|---|---|
| Doses | 0, 3 (Low dose: LD), 10 (Mid dose: MD), or 20 (High dose: HD) mg/kg/day of BLU-285,<br>75 mg/kg/day of NMU (positive control) |
| Frequency of dosing | Once daily for avapritinib,<br>Single dose on Day 1 for NMU |
| Dose volume | 10 mL/kg |
| Route of administration | Oral gavage for avapritinib,<br>Intraperitoneal (IP) injection for N-Nitrosomethylurea (NMU) |
| Formulation/Vehicle | 0.5% Carboxymethylcellulose (CMC; medium viscosity)-Na (w/v): 1% Tween® 80 (v/v) in deionized water (pH 2–3) for avapritinib, citrate-buffered saline (pH 4.5) |
| Basis of dose selection | None |
| Species/Strain | Mouse/CByB6F1/Tg rasH2 hemizygous transgenic mice |
| Number/Sex/Group | 25/sex/avapritinib groups, 10/sex/NMU group |
| Age | Approximately 8weeks old |
| Paradigm for dietary restriction | None |
| Dual control employed | None |
| Interim sacrifice | None |
| Satellite groups | Toxicokinetic groups (6/sex/group of avapritinib): CByB6F1-Tg(HRAS)2Jic Wild type (Non-Tg) animals were used for the Toxicokinetic Study |
| Deviation from study protocol | None of the deviations were considered to have impacted the overall integrity of the study of the interpretation of the study results and conclusions. |

Source: Reviewer's analysis
Abbreviations: CMC, carboxymethylcellulose; HD, high dose; IP, intraperitoneal; LD, low dose; MD, mid dose; NMU, nitrosomethylurea; pH, potential hydrogen

## Observations and Results

### Mortality

There were no avapritinib-related effects on mortality. The statistical analysis provided by the Applicant showed that avapritinib did not impact on the survival rate through Week 26. The Agency Statistical Reviewer's Report showed no statistically significant dose response relationship in the mortality in both sexes. The pairwise comparisons also showed that AYVAKIT had no statistically significant effects on mortality between the treated groups in both sexes.

**Table 42. Survival Rate (%) After 26-Week Dosing of AYVAKIT in Main Study**

| Variable | BLU-285 (mg/kg/day) | | | | NMU (mg/kg/day) |
|---|---|---|---|---|---|
| Sex | 0 | 3 | 10 | 20 | 75 |
| Male % (n/N) | 96 (24/25) | 88 (22/25) | 96 (24/25) | 92 (23/25) | 50 (5/10) |
| Female % (n/N) | 100 (25/25) | 96 (24/25) | 100 (25/25) | 92 (23/25) | 40 (2/10) |

Source: Reviewer's analysis
Abbreviations: N, number of subjects; n, numbers of subjects of given variable; NMU, N-Nitrosomethylurea

**Table 43. Summary of Unscheduled Deaths of Main Study**

| | Males | | | | | Females | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Group** | **1** | **2** | **3** | **4** | **5** | **1** | **2** | **3** | **4** | **5** |
| **Dose (mg/kg/day)** | **0** | **3** | **10** | **20** | **75** | **0** | **3** | **10** | **20** | **75** |
| **No. of animals per group** | **25** | **25** | **25** | **25** | **10** | **25** | **25** | **25** | **25** | **10** |
| Unscheduled euthanasia | 0 | 1 | 0 | 0 | 5 | 0 | 1 | 0 | 0 | 3 |
| Found dead | 1 | 2 | 1 | 2 | 0 | 0 | 0 | 0 | 2 | 3 |
| Terminal euthanasia | 24 | 22 | 24 | 23 | 5 | 25 | 24 | 25 | 23 | 4 |

Source: Applicant's submission

This carcinogenicity study using CByB6F1-Tg(HRAS)2Jic Hemizygous (Tg) mouse was considered valid based on higher incidence of neoplasms of all types in the 75 mg/kg/day positive control group (males and females) than in the control or any avapritinib-treated groups.

**Table 44. Cause of Death and Notable Clinical Findings in Early Decedents**

| Animal No./Sex | Dose Level (mg/kg/day) | Fate/Animal Disposition | Fate Day | Notable Clinical Findings/Body Weight Changes | Cause of Unscheduled Death/Related Macro/Microscopic Findings |
|---|---|---|---|---|---|
| 1015/M | 0 | FD | 122 | - | Spleen; sarcoma |
| 2020/M | 3 | UE | 27 | Labored breathing, shallow breathing, hunched posture, cold to touch, and decreased activity. Approximate 22% body weight loss from Day 22–27. | Undetermined |
| 2509/F | 3 | UE | 76 | Shallow breathing, hunched posture, thin, decreased activity, and red eyeball. Approximate 17% body weight loss from Days 71–76. | Lymphoma, malignant: aorta, cervix, gut-associated lymphoid tissue, adrenal gland, heart, kidney, liver, lung, lymph nodes (mandibular and mesenteric), skeletal muscle, ovary, skin, duodenum, spleen, stomach, urinary bladder, uterus, and vagina |
| 2007/M | 3 | FD | 127 | - | Undetermined |
| 2003/M | 3 | FD | 133 | - | Undetermined |
| 3008/M | 10 | FD | 162 | Labored breathing | Undetermined |
| 4025/M | 20 | FD | 102 | - | Prostate: adenocarcinoma |
| 4015/M | 20 | FD | 123 | - | Lymphoma, malignant: spleen and liver |
| 4513/F | 20 | FD | 172 | - | Undetermined |
| 4515/F | 20 | FD | 181 | Increased respiratory rate, hunched posture, and decreased activity. | Lung: bronchioloalveolar carcinoma |

M = male, F = female; - = not applicable; UE = unscheduled euthanasia; FD = found dead.
Source: Applicant's submission

### Clinical Signs

Avapritinib-related clinical observations were limited to the skin and fur including skin pallor, discoloration/fur staining in multiple areas (abdominal, axillary, inguinal, muzzle, urogenital, dorsal and/or ventral cervical/thoracic/generalized, forelimb, hind paw, scapular, and/or cranium) at MD and/or HD animals. Black skin discoloration of the urogenital region was noted in HD females between Days 155 to 184.

Positive control group presented increased respiratory rate, abnormal breathing, hunched posture, cold to touch, low carriage, decreased activity, erected fur, thin, suspected dehydration, enlarged eyeball, and/or prominent backbone.

### Body Weights and Feed Consumption

No avapritinib-related effects were observed.

### Gross Pathology

No avapritinib-related palpable masses or macroscopic findings were noted. Palpable masses were observed in one control, two MD, and one HD animal. These findings corresponded with

masses in the skin (sarcoma, adenocarcinoma, or papilloma noted microscopically). The masses were considered incidental and of the nature commonly observed findings of the strain and age of mice.

Positive control group presented expected results of palpable masses from NMU dosing, which support the validity of the carcinogenicity study in RasH2 transgenic mice.

### Organ Weights

Avapritinib-related effect was observed in thymus with lower organ weights at MD and HD, which corresponded to microscopical findings of decreased cellularity in thymic cortex.

**Table 45. Organ Weight Changes (% Difference Compared to Controls) After 26-Week Dosing of Avapritinib**

| | Males | | | | | Females | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Group** | **1** | **2** | **3** | **4** | **5** | **1** | **2** | **3** | **4** | **5** |
| **Dose (mg/kg/day)** | **0** | **3** | **10** | **20** | **75** | **0** | **3** | **10** | **20** | **75** |
| **No. Animals per Group** | **24** | **22** | **24** | **23** | **5** | **25** | **24** | **25** | **23** | **4** |
| **Thymus (No. Weighed)**[b] | (24) | (22) | (24) | (23) | (5) | (25) | (24) | (25) | (23) | (4) |
| Absolute value | 0.03 | -9.2 | **-39.5**** | **-56.9**** | +449.6 | 0.03 | -8.9 | **-35.56** | **-39.21*** | +357.4 |
| % of body weight | 0.11 | -10.6 | **-42.4**** | **-57.3**** | +648.2 | 0.15 | -11.6 | **-37.8*** | **-41.8**** | +411.0 |
| % of brain weight | 6.72 | -9.2 | **-40.6**** | **-57.7**** | +497.9 | 7.02 | -9.6 | **-35.12** | **-39.76*** | +353.4 |

Source: Applicant's submission
[b] Control group expressed as mean values; all other values expressed as percent difference from the control group means.
* = Statistically significantly different from the control group at ≤0.05 using Dunnett's test.
** = Statistically significantly different from the control group at ≤0.01 using Dunnett's test.
Bold = Values considered to be BLU-285-related.

### Histopathology

Peer Review

Pathology peer review was conducted by [redacted] (b) (4) from the same clinical research organization, [redacted] (b) (4).

Neoplastic

All neoplastic microscopic findings in unscheduled death or terminal euthanasia animals were considered not avapritinib-related, but incidental or commonly observed in this strain and age of mice. There were no statistically significant findings reported by the Applicant.

- The Agency Statistical Reviewer's analysis also showed that there were no tumors with a statistically significant dose response relationship in tumor incidences. The pairwise comparisons also did not show any statistically significant. increase/decrease between dosing groups except the positive control groups. Positive control groups when compared to vehicle control group showed statistically significant increases of malignant lymphoma in hematolymphoid system, bronchioloalveolar adenoma in the lung, papilloma in the skin and in the stomach, which provides the validity of the carcinogenicity study.

**Table 46. Tumor Types With Statistically Significant (P<0.05) Dose Response Relationships or Pairwise Comparisons of Treated Groups and Controls in Male Mice**

Male Mice Using Poly-3 test

| Organ Name | Tumor Name | 0 mg Vehicle Cont (N=25) P - Trend | 3 mg Low (N=25) P - C vs. L | 10 mg Med (N=25) P - VC vs. M | 20 mg High (N=25) P - VC vs. H | 75 mg Positive Cont (N=10) P - VC vs. PC |
|---|---|---|---|---|---|---|
| Epididymis | Fibroma | 0/25 (24)<br>0.5053 | 0/25 (23)<br>NC | 1/25 (25)<br>0.5102 | 0/25 (23)<br>NC | 0/10 (6)<br>NC |
| Gland, Pituitary | Hemangioma | 0/25 (24)<br>0.7447 | 1/25 (24)<br>0.5000 | 0/24 (24)<br>NC | 0/24 (22)<br>NC | 0/10 (6)<br>NC |
| Gland, Prostate | Adenocarcinoma | 0/25 (24)<br>0.2500 | 0/25 (23)<br>NC | 0/25 (25)<br>NC | 1/25 (24)<br>0.5000 | 0/10 (6)<br>NC |
| Gland, Seminal Vesicle | Adenocarcinoma | 0/25 (24)<br>NC | 0/25 (23)<br>NC | 0/25 (25)<br>NC | 0/25 (23)<br>NC | 1/10 (7)<br>0.2258 |
| Hemolymphoreticular Tissue | Lymphoma, Malignant | 0/25 (24)<br>0.2500 | 0/25 (23)<br>NC | 0/25 (25)<br>NC | 1/25 (24)<br>0.5000 | 3/10 (8)<br>0.0113* |
| Lung | Bronchioloalveolar Adenoma | 0/25 (24)<br>0.6235 | 1/25 (23)<br>0.4894 | 1/25 (25)<br>0.5102 | 0/25 (23)<br>NC | 2/10 (7)<br>0.0452* |
| | Hemangioma | 0/25 (24)<br>0.5053 | 0/25 (23)<br>NC | 1/25 (25)<br>0.5102 | 0/25 (23)<br>NC | 0/10 (6)<br>NC |
| Muscle, Skeletal | Rhabdomyosarcoma | 0/25 (24)<br>NC | 0/25 (23)<br>NC | 0/25 (25)<br>NC | 0/25 (23)<br>NC | 1/10 (7)<br>0.2258 |
| Skin | Papilloma | 0/25 (24)<br>NC | 0/25 (23)<br>NC | 0/25 (25)<br>NC | 0/25 (23)<br>NC | 3/10 (7)<br>0.0078* |
| | Sarcoma | 0/25 (24)<br>0.5053 | 0/25 (23)<br>NC | 1/25 (25)<br>0.5102 | 0/25 (23)<br>NC | 0/10 (6)<br>NC |
| Small Intestine, Duodenum | Sarcoma | 0/25 (24)<br>0.2421 | 0/25 (23)<br>NC | 0/25 (25)<br>NC | 1/25 (23)<br>0.4894 | 0/10 (6)<br>NC |
| Spleen | Hemangiosarcoma | 0/25 (24)<br>NC | 0/25 (23)<br>NC | 0/24 (24)<br>NC | 0/25 (23)<br>NC | 1/10 (7)<br>0.2258 |
| | Sarcoma | 1/25 (25)<br>1.0000 | 0/25 (23)<br>1.0000 | 0/24 (24)<br>1.0000 | 0/25 (23)<br>1.0000 | 0/10 (6)<br>1.0000 |
| Stomach | Papilloma | 0/25 (24)<br>NC | 0/25 (23)<br>NC | 0/25 (25)<br>NC | 0/25 (23)<br>NC | 5/10 (9)<br>0.0005* |
| | Squamous Cell Carcinoma | 0/25 (24)<br>NC | 0/25 (23)<br>NC | 0/25 (25)<br>NC | 0/25 (23)<br>NC | 1/10 (6)<br>0.2000 |

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = not calculable
*: Statistically significant at 0.05 for common and rare tumors, respectively in pairwise comparisons.

Source: FDA Statistical Analysis Report

**Table 47. Tumor Types With Statistically Significant (P<0.05) Dose Response Relationships or Pairwise Comparisons of Treated Groups and Controls in Female Mice**

Female Mice Using Poly-3 test

| Organ Name | Tumor Name | 0 mg Vrhicle Cont (N=25) P - Trend | 3 mg Low (N=25) P - C vs. L | 10 mg Med(N=25) P - VC vs.M | 20 mg High (N=25) P - VC vs. H | 75 mg Positive Cont (N=10) P - VC vs. PC |
|---|---|---|---|---|---|---|
| Gland, Harderian | Adenoma | 0/25 (25)<br>NC | 0/25 (24)<br>NC | 0/25 (25)<br>NC | 0/25 (25)<br>NC | 2/10 (6)<br>0.0323* |
| Hemolymphoreticular Tissue | Histiocytic Sarcoma | 0/25 (25)<br>NC | 0/25 (24)<br>NC | 0/25 (25)<br>NC | 0/25 (25)<br>NC | 1/10 (6)<br>0.1935 |
| | Lymphoma, Malignant | 1/25 (25)<br>0.9394 | 1/25 (25)<br>0.7551 | 0/25 (25)<br>1.0000 | 0/25 (25)<br>1.0000 | 6/10 (9)<br>0.0004* |
| Large Intestine, Colon | Squamous Cell Carcinoma | 1/25 (25)<br>1.0000 | 0/25 (24)<br>1.0000 | 0/25 (25)<br>1.0000 | 0/25 (25)<br>1.0000 | 0/10 (6)<br>1.0000 |
| Lung | Bronchioloalveolar Carcinoma | 0/25 (25)<br>0.2525 | 0/25 (24)<br>NC | 0/25 (25)<br>NC | 1/25 (25)<br>0.5000 | 0/10 (6)<br>NC |
| Skin | Papilloma | 0/25 (25)<br>0.5051 | 0/25 (24)<br>NC | 1/25 (25)<br>0.5000 | 0/25 (25)<br>NC | 2/10 (6)<br>0.0323* |
| Spleen | Hemangiosarcoma | 1/25 (25)<br>1.0000 | 0/25 (24)<br>1.0000 | 0/25 (25)<br>1.0000 | 0/25 (25)<br>1.0000 | 0/10 (6)<br>1.0000 |
| Stomach | Papilloma | 0/25 (25)<br>NC | 0/25 (24)<br>NC | 0/25 (25)<br>NC | 0/25 (25)<br>NC | 4/9 (7)<br>0.0010* |
| | Squamous Cell Carcinoma | 0/25 (25)<br>NC | 0/25 (24)<br>NC | 0/25 (25)<br>NC | 0/25 (25)<br>NC | 1/9 (6)<br>0.1935 |
| Thymus | Thymoma, Benign | 1/25 (25)<br>1.0000 | 0/25 (24)<br>1.0000 | 0/25 (25)<br>1.0000 | 0/22 (22)<br>1.0000 | 0/10 (6)<br>1.0000 |
| Uterus | Adenoma | 0/25 (25)<br>NC | 0/25 (24)<br>NC | 0/25 (25)<br>NC | 0/25 (25)<br>NC | 1/10 (6)<br>0.1935 |

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = not calculable
*: Statistically significant at 0.05 for common and rare tumors, respectively in pairwise comparisons.

Source: FDA Statistical Analysis Report

Non-Neoplastic

Higher incidences of lower cortical cellularity were noted in thymus microscopically at the MD and HD. There was lack of correlation between the microscopic findings in thymus and survival rate.

**Table 48. Microscopic Findings After 26-Week Dosing of Avapritinib**

| | Males | | | | | Females | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Group** | **1** | **2** | **3** | **4** | **5[a]** | **1** | **2** | **3** | **4** | **5[a]** |
| **Dose (mg/kg/day)** | **0** | **3** | **10** | **20** | **75** | **0** | **3** | **10** | **20** | **75** |
| **No. Animals per Group** | **24** | **22** | **24** | **23** | **5** | **25** | **24** | **25** | **23** | **4** |
| **Thymus (No. Examined)** | (24) | (22) | (24) | (22) | (5) | (25) | (24) | (25) | (21) | (4) |
| Cellularity, decreased; cortical | 1 | 0 | 8 | 18 | 2 | 3 | 5 | 7 | 15 | 2 |
| Mild | 0 | - | 6 | 5 | 0 | 0 | 4 | 5 | 9 | 1 |
| Moderate | 0 | - | 0 | 7 | 1 | 0 | 0 | 1 | 4 | 1 |
| Marked | 1 | - | 2 | 6 | 1 | 2 | 1 | 1 | 2 | 0 |
| Severe | 0 | - | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |

Source: Applicant's submission
(Excerpted from submission)
[a] Group 5 was a positive control group administered 75 mg/kg/day NMU rather than BLU-285.
- = No noteworthy findings.

There were no other notable or statistically significant non-neoplastic findings observed, but common findings seen in this strain and age of mice.

### Toxicokinetics

The systemic exposure to avapritinib increased with dose increment in an approximately dose proportional manner. The accumulation of avapritinib was not noted after repeated dosing. Sex differences in systemic exposure to avapritinib were not evident.

**Table 49. Toxicokinetics Parameters After AYVAKIT Dosing on Days 1 and 182**

| Dose | $AUC_{(0-24)}$ (ng•hr/mL) | | $C_{max}$ (ng/mL) | | $t_{max}$ (hr) | |
|---|---|---|---|---|---|---|
| | Day 1 | Day 182 | Day 1 | Day 182 | Day 1 | Day 182 |
| **Males** | | | | | | |
| 3 mg/kg/day | 9320 | 11,300 | 668 | 696 | 2 | 4 |
| 10 mg/kg/day | 32,800 | 38,200 | 2390 | 2190 | 2 | 4 |
| 20 mg/kg/day | 67,000 | 77,000 | 4270 | 4630 | 2 | 8 |
| | | | | | | |
| **Females** | | | | | | |
| 3 mg/kg/day | 9210 | 7540 | 702 | 475 | 4 | 1 |
| 10 mg/kg/day | 30,400 | 29,000 | 2140 | 1930 | 4 | 4 |
| 20 mg/kg/day | 68,600 | 66,500 | 4790 | 4620 | 1 | 4 |
| | | | | | | |
| **Sex Combined** | | | | | | |
| 3 mg/kg/day | 9270 | 9410 | 667 | 566 | 2 | 4 |
| 10 mg/kg/day | 31,600 | 33,600 | 2190 | 2060 | 2 | 4 |
| 20 mg/kg/day | 67,800 | 72,300 | 4300 | 4550 | 2 | 4 |

Source: Applicant's submission
Abbreviations: $AUC_{(0-24)}$, area under the concentration-time curve from time 0 to time 24 hours; $C_{max}$, maximum plasma concentration; $t_{max}$, time to maximum plasma concentration

### Dosing Solution Analysis

The dosing formulations were within the protocol-specified range of target concentrations for suspensions and were homogeneous. No avapritinib was detected in vehicle control samples.

### Summary of Applicant's Rationale for Not Conducting 2-Year Carcinogenicity Study in Rats

Blueprint Medicine is seeking a waiver for conducting a 2-year rat carcinogenicity study for avapritinib based on a weight-of-evidence (WOE) approach derived from available biologic, pharmacologic, and toxicologic information indicating that a 2-year rat carcinogenicity study would not add value to the carcinogenic risk assessment of avapritinib. The Applicant conducted a 26-week carcinogenicity study in transgenic RasH2 mouse to support the expansion of indication with ISM under NDA 212608.

Avapritinib is a tyrosine kinase inhibitor that targets platelet-derived growth factor receptor alpha (PDGFRα), PDGFRα D842 mutants, and other exon 18 mutants, as well as KIT and multiple KIT exon 11, 11/17, and 17 mutants with half maximal inhibitory concentrations ($IC_{50}$) within nanomolar range. The mechanism of action of avapritinib for the indication of ISM remains the

same as for the originally approved indication of advanced systemic mastocytosis (AdSM) in 2020.

The request provided a carcinogenicity risk assessment which considered:

- The 26-week carcinogenicity study in RasH2 transgenic mice did not produce any avapritinib-related neoplastic findings.
- No evidence of carcinogenic potential is identified based on drug target biology and mechanism of action of avapritinib.
- No potential carcinogenicity was identified from off-target potential of avapritinib in secondary pharmacology.
- No avapritinib-related preneoplastic microscopic/macroscopic findings or perturbation of endocrine and reproductive organs were observed in chronic toxicology studies in rats and dogs.
- There was no evidence of genotoxicity of avapritinib.
- The available human data from clinical trials did not suggest any association of secondary malignancies with avapritinib treated population with GIST, AdvSM, or ISM.

Based on this WOE, Blueprint Medicines would like to request that the requirement for a 2-year Sprague Dawley rat carcinogenicity study of avapritinib be waived.

Division Conclusion Regarding Human Carcinogenic Potential:

Unlikely, therefore a 2-year rat carcinogenicity study would not add value.

ECAC+ Recommendations:

Pending review and final decision.

# 40. Clinical Pharmacology

## 40.1. In Vitro Studies

None.

## 40.2. In Vivo Studies

**Study BLU-285-0107: Effect of Severe Hepatic Impairment on Avapritinib Pharmacokinetics**

Study Design

This was an open-label, single-dose study to investigate the effect of severe hepatic impairment on the pharmacokinetics (PK) of avapritinib following a single oral dose of 100 mg. Additionally, the study evaluated safety and tolerability together with the PK of unbound avapritinib in subjects with severe hepatic impairment compared with matched control subjects

with normal hepatic function. Eight subjects with severe hepatic impairment (Child-Pugh Class C) and eight control subjects each received a single 100 mg oral dose of avapritinib under fasting conditions. Blood samples for analysis of avapritinib in plasma were taken at prespecified time points, predose and for up to 576 hours after avapritinib administration in subjects with severe hepatic impairment and for up to 240 hours in the control subjects. Blood samples were also collected for the assessment of avapritinib protein binding.

Results

Severe hepatic impairment increased unbound avapritinib exposures, as compared with the control subjects. Based on geometric mean ratios, unbound maximum plasma concentration ($C_{max}$), area under the concentration-time curve ($AUC_{0-240}$), and $AUC_{0-\infty}$ were increased by 8%, 45%, and 61%, respectively, in subjects with severe hepatic impairment (Table 50).

**Table 50. Summary of Plasma Unbound Avapritinib Pharmacokinetic Parameters Following a Single Oral Dose of Avapritinib 100 mg in Subjects With Severe Hepatic Impairment and in Matched Control Subjects With Normal Hepatic Function, Study BLU-285-0107**

| | GeoMean | | | 90% Confidence |
|---|---|---|---|---|
| Parameter | Severe | Control | GeoMean Ratio (%) | Interval |
| $Cu_{max}$ (ng/mL) | 1.29 | 1.20 | 108 | 58.1 - 200.8 |
| $AUCu_{0-240}$ (h•ng/mL) | 87.1 | 59.8 | 145.5 | 108.6 - 194.8 |
| $AUCu_{0-\infty}$ (h•ng/mL) | 105.2 | 65.2 | 161.3 | 121.4 - 214.4 |

Source: Blu-285-0107 Clinical Study Report Table 11-6
Abbreviations: AUCu, area under the concentration-time curve of unbound drug; $Cu_{max}$, maximum plasma concentration of unbound drug

Conclusions

No dose modification is required for patients with mild or moderate hepatic impairment. In subjects with severe hepatic impairment (Child-Pugh Class C), an increase in unbound avapritinib of 61% was observed. Therefore, a dose reduction to 200 mg once daily (QD) in GIST, 100 mg QD in AdvSM, and modification of the dosing regimen to 25 mg QOD in ISM is recommended.

## 40.3. Bioanalytical Method Validation and Performance

Method [(b) (4)]-1963-R1 is a LC-MS/MS method developed for the determination of BLU-285 in K2EDTA human plasma using BLU-285-d8 [(b) (4)] as the internal standard (IS). As reported in the validation addendum report, 805-R4448R2A2, BLU-285 in K2EDTA human plasma was determined to be stable for 1774 days at -70°C. The longest span for a study sample from collection date (March 30, 2021) to last analysis date (November 7, 2022) is 587 days at -70°C. The established stability sufficiently covered the storage of the study samples from date of collection until last day of analysis.

The validation characteristics for the avapritinib assay are summarized in below Table 51.

**Table 51. Validation Summary for Determination of Avapritinib in Human Plasma, Study (b) (4)-1963**

| | | | |
|---|---|---|---|
| Method | | LC/MS-MS | |
| Biological matrix and anticoagulant | | Human plasma, K2EDTA | |
| Analyte | | Avapritinib | |
| Internal standard | | Avapritinib-d8 | |
| Extraction procedure | | Protein precipitation | |
| Analysis | | Reversed-phase HPLC separation with a Waters X-bridge Shield RP18 column (50 × 2.1 mm, 5.0µm). MS-MS detection was set at mass transitions of m/z 499.3 to 482.4 for avapritinib and m/z 507.3 to 490.4 for avapritinib-d8 in turbo ion spray positive mode. | |
| Sample extraction volume | | 25 µL | |
| Regression, weighting factor | | Linear regression; 1/x2 | |
| Dynamic range | | 2.00-3000 ng/mL | |
| QC concentrations | | 6.00, 300, 2250, and 22500 (AQL) ng/mL | |
| Linearity | | R2≥0.98 | |
| Lower limit of quantitation | | 2.00 ng/mL | |
| Average recovery of analyte (%) | | 96.2 | |
| Average recovery of internal standard (%) | | Per standard operating procedure at analytical laboratory, if a stable isotope-labeled internal standard was used, the recovery established for the unlabeled analyte will suffice and the recovery for the stable isotope-labeled internal standard is not required. | |
| QC level | | LLOQ | QC (Mid, Low, High) |
| QC intrarun accuracy range (%CV) | Run 1 | 7.0 | 2.0 to 5.2 |
| | Run 2 | 7.4 | 1.3 to 3.8 |
| | Run 3 | 2.1 | 1.1 to 4.6 |
| QC intrarun accuracy range (%Bias) | Run 1 | 8.5 | -5.8 to -2.2 |
| | Run 2 | 6.0 | -4.9 to 0.7 |
| | Run 3 | -6.0 | -6.2 to -1.8 |
| QC sample bench-top stability | | 42 hours at room temperature | |
| Stock and spike solution stability | | 6 hours at room temperature 433 days at -20°C | |
| Processed sample stability | | 171 hours at room temperature | |
| Re-injection reproducibility | | 179.5 hours at room temperature | |
| QC sample freeze/thaw stability | | 3 freeze (-70ºC)/(-20ºC)/thaw cycles | |
| QC sample long-term sample storage stability | | 437 days at -20°C and -70°C | |
| Dilution integrity | | 22500 ng/mL diluted 10-fold | |
| Matrix effect | | Internal standard-normalized matrix factor =1.04±0.03 at 6.00 ng/mL with %CV =2.9%<br>Internal standard-normalized matrix factor =1.07±0.02 at 2250 ng/mL with %CV =1.9% | |
| 5% hemolyzed QC precision range (%CV) | | 2.9 to 5.3 | |
| 5% hemolyzed QC accuracy range (%Bias) | | -2.8 to -0.9 | |

| | |
|---|---|
| Blank selectivity | Blank selectivity samples were within acceptance criteria (at least 5 of 6 blank samples at retention time of the analyte were within ≤20% of mean peak area of the analyte of the 6 LLOQ samples, and at least 5 of 6 blank samples at retention time of the IS were within ≤5% of mean peak area of the IS of the 6 LLOQ samples). |
| Interference | No interference detected from avapritinib to avapritinib-d8 |
| Batch size | 130 samples |
| Carryover evaluation | No observed carryover in Runs 1 to 4 and 6 |

Source: BLU-R4448R2 and BLU-R4448A1

Abbreviations: CV, coefficient of variance; HPLC, high performance liquid chromatography; LC/MS-MS, Liquid chromatography–mass spectrometry; LLOQ, lower limit of quantification; QC, quality control

## 40.4. Immunogenicity Assessment—Impact of Pharmacokinetic/Pharmacodynamic, Efficacy, and Safety

Not applicable.

## 40.5. Pharmacometrics Assessment

**Applicant's Analysis**

### Population PK Analysis

The Applicant updated the population PK (PopPK) model to characterize avapritinib exposure as a function of dose, time after dosing, and subject characteristics, including the variability between and within patients with ISM. Briefly, a dataset of 9705 evaluable plasma concentrations from 656 subjects who received avapritinib was utilized to build the PopPK model. A nonlinear mixed effects modeling approach with the first-order conditional estimation with interaction (FOCEI) method in NONMEM, version 7.4.4 (ICON, Maryland) was used for the PopPK analysis. The body weights of the PopPK modeling population ranged from 39.5 kg to 156 kg and ages ranged from 18 to 90 years. Most of the subjects were white (78.5%) and male (56.6%).

**Table 52. Summary of Studies Included in the Population PK Analysis**

| Study | Title | Subject Population | No. of Subjects | Dose |
|---|---|---|---|---|
| BLU-285-0101 | An open-label, randomized, SD, 2-way crossover study to evaluate the relative bioavailability of avapritinib in healthy adult male subjects | Healthy volunteers | 30 | 1 x 200 mg (tablet); 2 x 100 mg (capsule) |
| BLU-285-0102 | An open-label, randomized, single dose, 2-way crossover study to evaluate the effect of food on the PK of avapritinib in healthy adult male subjects | Healthy volunteers | 30 | 200 mg with overnight fast; 200 mg overnight fast with high-fat meal |
| BLU-285-0105 | An open-label, randomized, single dose, 2-period crossover, bioequivalence study comparing one 400 mg tablet with four 100 mg tablets of avapritinib in healthy adult subjects | Healthy volunteers | 62 | 4 x 100 mg (tablet); 1 x 400 mg (tablet) |
| BLU-285-1101 | Phase I, open-label, first-in-human study in subjects with GIST & other relapsed refractory solid tumors | Subjects with gastrointestinal stromal tumors (GIST), & other relapsed refractory solid tumors | 221 | Part 1: 30, 60, 90, 135, 200, 300, 400, 600 mg QD; Part 2: 400, 300 mg QD |
| BLU-285-2101 | Phase 1, open-label, first-in-human study in subjects with AdvSM and relapsed or refractory myeloid malignancies | Subjects with advanced systemic mastocytosis (AdvSM) and relapsed or refractory myeloid malignancies | 86 | Part 1: 30, 60, 100, 130, 200, 300, 400 mg QD; Part 2: 300, 200 mg QD |
| BLU-285-2202 | An open-label, single arm, Phase 2 study to evaluate efficacy and safety of avapritinib in subjects with AdvSM | AdvSM | 58 | 200 mg QD |
| BLU-285-2203 | A 3-part, randomized, double-blind, placebo-controlled Phase 2 study to evaluate efficacy and safety of avapritinib in subjects with ISM | Subjects with indolent systemic mastocytosis (ISM) | Part 1, 30; Part 2, 139; Part 3, 235 (includes subjects from Part 1 & Part 2) | Part 1: 25, 50, 100 mg QD; Part 2: 25 mg QD; Part 3: 25 mg QD (open-label extension) |

Source: Adapted from Applicant's PopPK report, Page 22-24
Abbreviations: PK, pharmacokinetics; QD, once daily

Listings of the baseline demographics for these subjects are given in Table 53 and Table 54, respectively.

**Table 53. Categorical Covariates for All Subjects in the Population PK Development Dataset**

| Sex | Race | Form | Patient Population | PPI Use | H2RA Use | CYP3A4 Inhib. | CYP3A4 Ind. |
|---|---|---|---|---|---|---|---|
| Male: 371 (56.6%)<br>Female: 285 (43.4%) | White: 515 (78.5%)<br>Black: 27 (4.1%)<br>Asian: 26 (4%)<br>Other: 59 (9%)<br>Unknown: 29 (4.4%) | Tablet: 487 (74.2%)<br>Capsule: 169 (25.8%) | Healthy: 122 (18.6%)<br>GIST: 221 (33.7%)<br>AdvSM: 144 (22%)<br>ISM: 169 (25.8%) | Not Used: 464 (70.7%)<br>Used: 192 (29.3%) | Not Used: 434 (66.2%)<br>Used: 222 (33.8%) | Not Used: 616 (93.9%)<br>Used: 40 (6.1%) | Not Used: 567 (86.4%)<br>Used: 89 (13.6%) |

PPI proton pump inhibitor, H2RA $H_2$-receptor antagonist, Inhib. inhibitor use, Ind. inducer use, Form formulation. Note: 'Not Used' is defined as 0 to 5 days of consecutive use (See Section 9.3).

Source: Applicant's PopPK report, Page 34, Table 3
Abbreviations: PK, pharmacokinetics

**Table 54. Continuous Demographic Covariates for All Subjects in the Population PK Development Dataset**

| | Age (years) | Weight (kg) | Height (cm) | LBW (kg) | ALB (g L) | ALP (IU L) | ALT (IU L) | AST (IU L) | Bilirubin ( mol L) | CrCl (mL min) | eGFR (mL min 1 73m$^2$) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| N | 656 | 656 | 656 | 656 | 656 | 656 | 656 | 656 | 656 | 656 | 656 |
| Mean | 54 | 78 | 171 | 53.3 | 40.9 | 131 | 24.6 | 23.6 | 10.3 | 107 | 89.3 |
| SD | 14.4 | 18 | 9.47 | 11.9 | 5.89 | 147 | 17.9 | 14.4 | 6.2 | 37.4 | 24.4 |
| CV% | 26.6 | 23.1 | 5.55 | 22.4 | 14.4 | 112 | 73 | 61.1 | 60.2 | 35 | 27.3 |
| Median | 54 | 76.8 | 170 | 54 | 42 | 86 | 20 | 21 | 8.55 | 104 | 88.2 |
| Min | 18 | 39.5 | 142 | 28 | 12.7 | 27 | 3 | 5 | 1.71 | 27.6 | 33.2 |
| Max | 90 | 156 | 207 | 85.5 | 55 | 1750 | 215 | 182 | 52 | 329 | 273 |

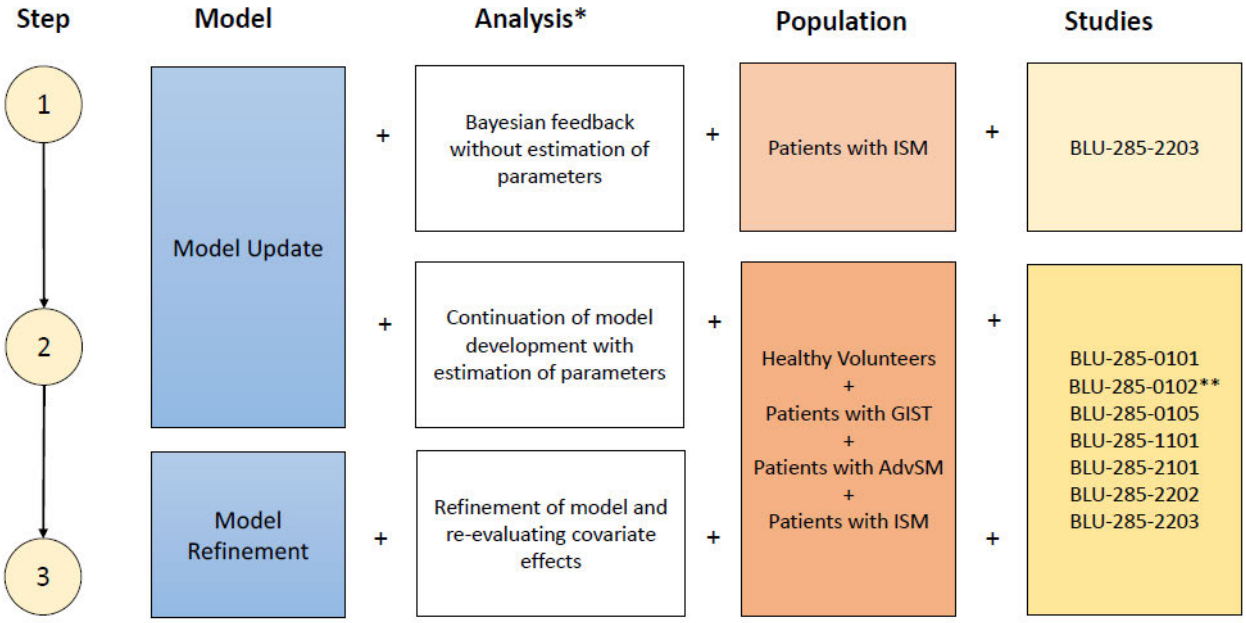
LBW – Lean body weight, ALB Albumin, ALP Alkaline phosphatase, ALT Alanine transaminase, AST Aspartate transaminase, CrCL Creatinine clearance, eGFR Estimated glomerular filtration rate.

Source: Applicant's PopPK report, Page 34, Table 4
Abbreviations: PK, pharmacokinetics

## Population PK Model

To describe the plasma concentration-time data from clinical study BLU-285-2203 in subjects with ISM, the Applicant evaluated and updated the previously developed population PK model for avapritinib in healthy volunteers, subjects with GISTs, and subjects with AdvSM. Briefly, as shown in Figure 19, the previously developed population PK model was firstly fitted to the data from study BLU-285-2203 only without parameter estimation, in a process known as Bayesian feedback. Any biases or changes specific to the ISM population were then compared to the previous analysis populations to inform the model update. Next, data from other studies were included in the model to fully quantify population PK parameters, including typical parameter values and random interindividual and residual variability. Then the covariate effects were evaluated through visual inspection of covariate-eta relationships for any obvious trends. Lastly, the final PopPK model was utilized to estimate the exposure metrics $C_{max,ss}$ and $AUC_{0-24,ss}$ for avapritinib on Cycle 1 Day 15 (C1D15) (steady state) for subjects in study BLU-285-2203 Part 2, where only sparse PK samples were collected.

**Figure 19. Model Development Flowchart**

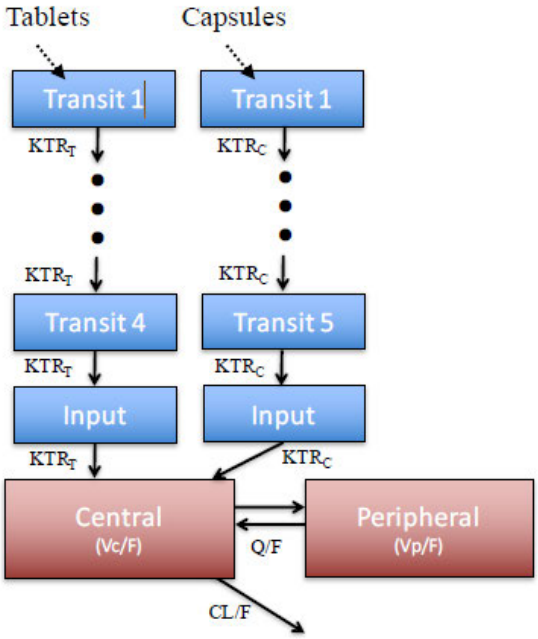



* The initial model was based on the previously developed population PK model as described in Report BLUE201701.[15]
** Only fasted observations from study BLU-285-0102 were included in the analysis.

Source: Applicant's PopPK report, Page 50, Figure 12
Abbreviations: GIST, gastrointestinal stromal tumors; ISM, indolent systemic mastocytosis

As illustrated in Figure 20, the avapritinib PK was described by a two-compartment disposition model with absorption modelled via 4 or 5 transit compartments that was dependent on the formulation. The model was parameterized in terms of CL/F, apparent central volume of distribution after oral dosing (Vc/F), apparent peripheral volume of distribution after oral dosing (Vp/F), apparent (oral) intercompartmental clearance after oral dosing (Q/F) and absorption transit rate constants for tablets and capsules respectively. Interindividual variability was estimated for the elimination clearance, central volume of distribution, transit absorption rate and correlation between clearance and central volume of distribution. Between-occasion variability was estimated for bioavailability and rate of transit absorption. The residual random effect was described with a proportional error model.

**Figure 20. Schematic of the Developed Population PK Model for Avapritinib**

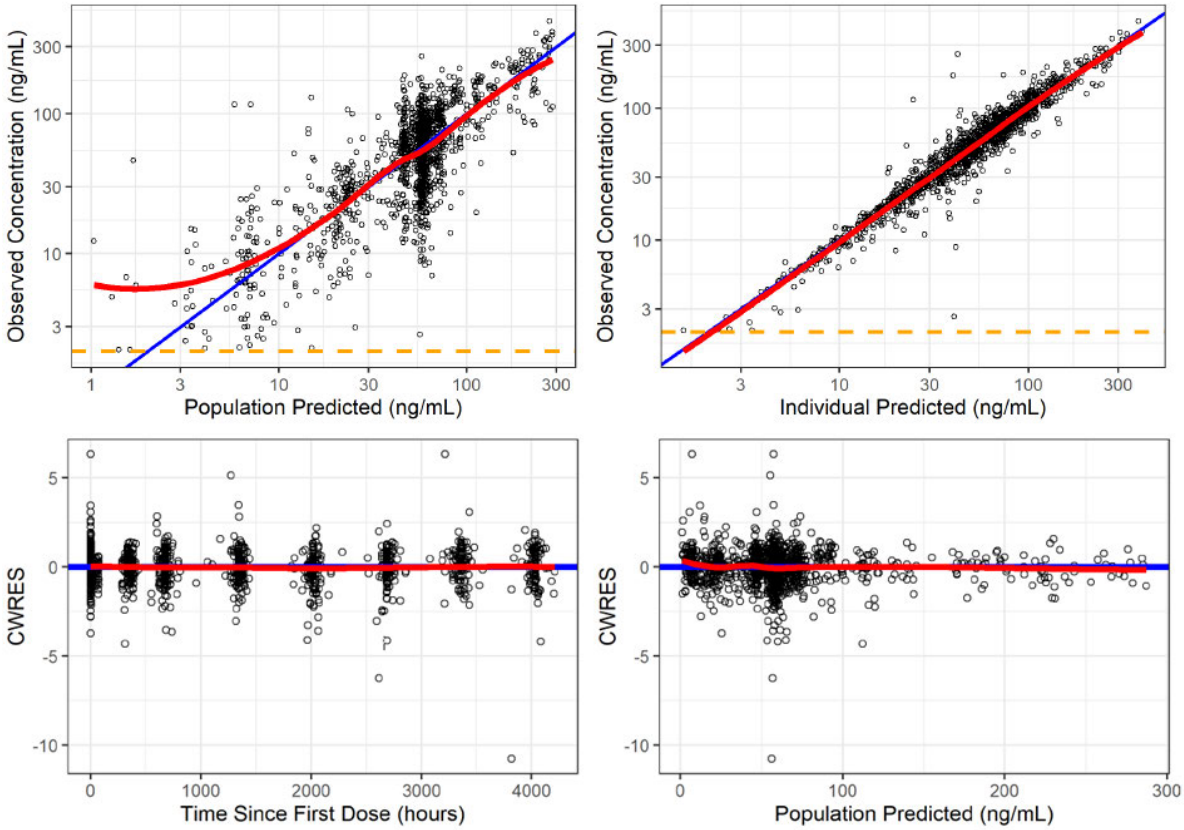



KTR$_T$ = absorption transit rate constant for tablets; KTR$_C$ = absorption transit rate constant for capsules; $V_c/F$ = apparent volume of distribution for the central compartment; Q/F = apparent inter-compartmental clearance; CL/F = apparent clearance; $V_p/F$ = apparent volume of distribution for the peripheral compartment.

Source: Applicant's PopPK report, Page 51, Figure 13
Abbreviations: PK, pharmacokinetics

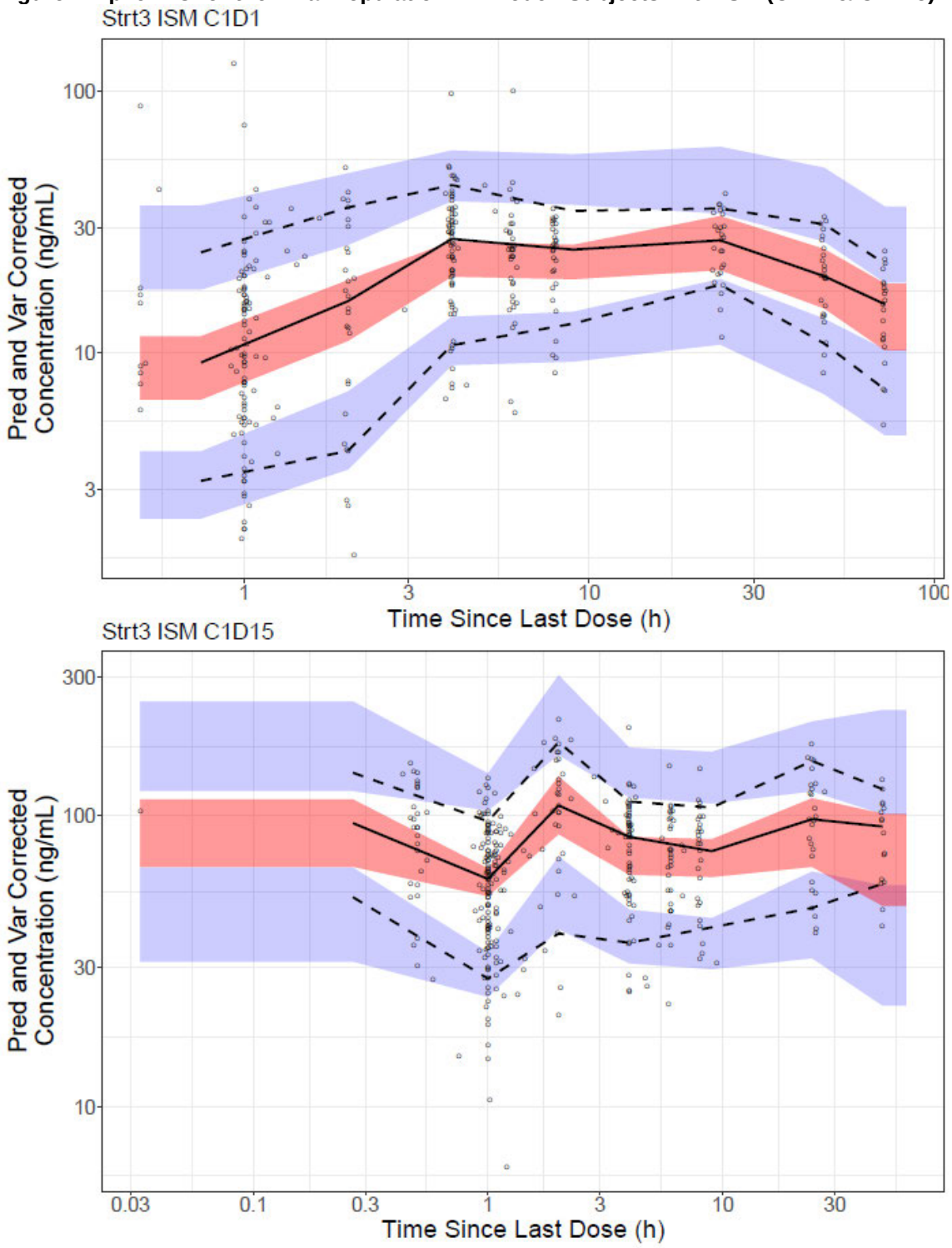
The final PopPK model for avapritinib was assessed with diagnostics plots including goodness-of-fit (Figure 21) and pvcVPC (Figure 22).

**Figure 21. Goodness-of-Fit Plots and CWRES Plots for Final Population PK Model**




Source: Adapted from Applicant's PopPK report, Page 68-69, Figure 17, Figure 18.
Values are indicated by points. Top Panel: the solid blue lines represent the line of unity, the solid red lines represent the trend in the data (Loess smooth), the dashed orange lines represent the LLOQ (2.00 ng/mL). Bottom Panel: the solid blue lines represent the line of identity or zero, the red lines represent the trend in the data (Loess smooth) or the mean.
Abbreviations: CWRES, conditional weighted residuals; PK, pharmacokinetics

**Figure 22. pvcVPC for the Final Population PK Model: Subjects With ISM (C1D1 & C1D15)**




Source: Applicant's PopPK report, Page 73, Figure 22
Open circles = individual observed, dashed black lines =10th & 90th percentiles of the observed data, solid black line = observed median concentration, shaded areas =95% confidence interval around the model predicted 10th, 50th, & 90th percentiles. Top Panel: C1D1. Bottom Panel: C1D15: Note: Log-log scale is used. C1D1 = Cycle 1 Day 1, C1D15 = Cycle 1 Day 15
Abbreviations: ISM, indolent systemic mastocytosis; PK, pharmacokinetics; pvcVPC, prediction and variability corrected visual predictive check

Parameter estimates from the updated population PK model are presented in Table 55. For a typical subject with body weight of 70 kg, the estimated CL/F was 16.9 L/hr, Vc/F was 971 L, Vp/F was 228 L, Q/F was 15.8 L/hr, rate of transit absorption for tablets was 3.41 1/h, rate of transit absorption for capsules was 3.78 1/h, F1 for subjects with AdvSM was 0.667 and F1 for GIST subjects was 0.856. Interindividual variability on CL/F, Vc/F, correlation between CL/F-Vc/F and rate of transit absorption were 44.4%, 50.1%, 0.634 and 24.6%, respectively. Between-occasion variability on bioavailability and rate of transit absorption were 25.3% and 32.9%, respectively. The proportional residual variance estimates for Study BLU-285-0101/BLU-285-0102, Study BLU-285-0105, Study BLU-285-2101/BLU-285-2202, Study BLU-285-1101 and Study BLU-285-2203 were 17.2%, 18.3%, 23.3%, 26.6% and 27%, respectively. This suggests that the updated PopPK model can adequately characterize IIV of those parameters.

**Table 55. Schematic of the Developed Population PK Model for Avapritinib**

| Parameter Name | Estimated Value (%RSE, 95% CI) |
|---|---|
| Apparent Clearance (CL/F, L/h) | 16.9 (2.2, 16.1 - 17.6) |
| Maximum Time-dependent Decrease of CL/F for AdvSM Patients (Fold) | 0.394 (9.7, 0.319 - 0.469) |
| Time at Half Maximum Decrease of CL/F for AdvSM Patients (h) | 190 (26.9, 90 - 291) |
| Covariate Effect of AdvSM on CL/F (Fold) | 1.3 (5.5, 1.16 - 1.44) |
| Apparent Central Volume of Distribution ($V_c$/F, L) | 971 (2.7, 920 - 1020) |
| Covariate Effect of LBW on $V_c$/F | 0.354 (39.9, 0.077 - 0.631) |
| Apparent Peripheral Volume of Distribution ($V_p$/F, L) | 228 (8.9, 188 - 268) |
| Apparent Inter-compartmental Clearance (Q/F, L/h) | 15.8 (17.4, 10.4 - 21.2) |
| Rate of Transit Absorption for Tablets ($KTR_T$, 1/h) | 3.41 (1.3, 3.33 - 3.5) |
| Rate of Transit Absorption for Capsules ($KTR_C$, 1/h) | 3.78 (2.0, 3.63 - 3.93) |
| Covariate Effect of AdvSM on KTR (Fold) | 1.19 (3.2, 1.11 - 1.26) |
| Covariate Effect of PPI Use on KTR (Fold) | 0.869 (3.4, 0.81 - 0.928) |
| Relative Bioavailability for AdvSM Patients (Fold) | 0.667 (4.1, 0.614 - 0.721) |
| Relative Bioavailability for GIST Patients (Fold) | 0.856 (3.1, 0.804 - 0.908) |
| Covariate Effect of PPI Comedication on F (Fold) | 0.833 (3.4, 0.777 - 0.889) |
| Between Subject Variability for CL/F (%) | 44.4 (4.0, 40.5 - 48.1) |
| Between Subject Variability for $V_c$/F (%) | 50.1 (4.6, 44.9 - 55) |
| Correlation between CL/F-$V_c$/F (–) | 0.634 (5.8, 0.589 - 0.666) |
| Between Subject Variability for Rate of Transit Absorption (%) | 24.6 (14.4, 16.1 - 31) |
| Between-occasion Variability for Bioavailability (%) | 25.3 (4.6, 22.8 - 27.5) |
| Between-occasion Variability for Rate of Transit Absorption (%) | 32.9 (7.7, 27.3 - 37.8) |
| Residual Unexplained Variability for Study BLU-285-0101/BLU-285-0102 (Proportional) (%) | 17.2 (6.5, 14.9 - 19.3) |
| Residual Unexplained Variability for Study BLU-285-0105 (Proportional) (%) | 18.3 (4.6, 16.6 - 19.9) |
| Residual Unexplained Variability for Study BLU-285-2101/BLU-285-2202 (Proportional) (%) | 23.3 (23, 21.2 - 25.3) |
| Residual Unexplained Variability for Study BLU-285-1101 (Proportional) (%) | 26.6 (4.0, 24.4 - 28.7) |
| Residual Unexplained Variability for Study BLU-285-2203 (Proportional) (%) | 27 (12.6, 19.1 - 33.3) |

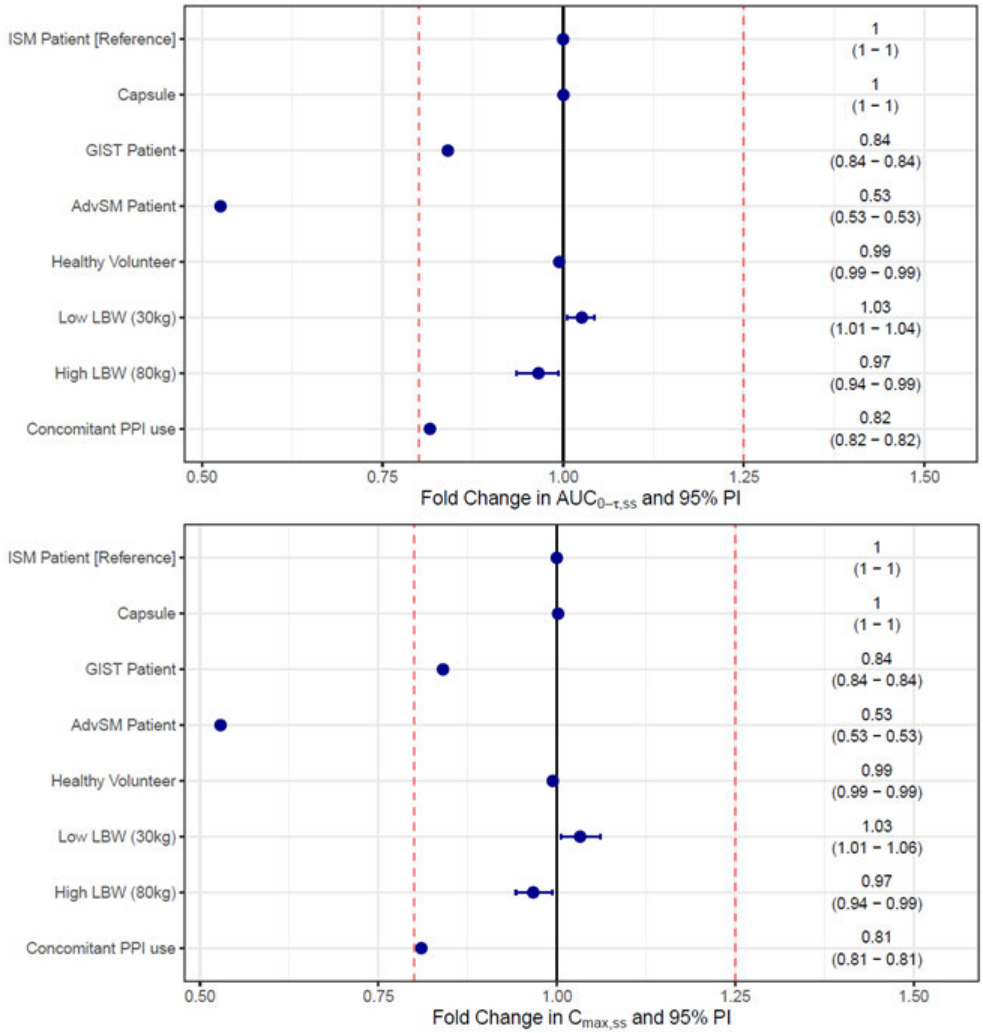
%RSE = relative standard error, CI = confidence interval. Covariate relationships are described in detail in Section 12.2.3.

Source: Applicant's PopPK report, Page 66, Table 15
Abbreviations: PK, pharmacokinetics

As illustrated in Figure 23, there were no impacts on $AUC_{0\text{-}tau,ss}$ or $C_{max,ss}$ whether avapritinib was taken as tablet or capsule and negligible difference in $AUC_{0\text{-}tau,ss}$ or $C_{max,ss}$ between a typical subject with ISM and a typical HV. Small differences (~0.03-fold change) in avapritinib exposure between subjects with low LBW of 30 kg and high LBW of 80 kg were identified. Concomitant proton pump inhibitor (PPI) use with avapritinib reduced $AUC_{0\text{-}tau,ss}$ and $C_{max,ss}$ by approximately 0.19-fold and subjects with GIST had lower (~0.16-fold reduction) $AUC_{0\text{-}tau,ss}$ and $C_{max,ss}$ compared to subjects with ISM. Moreover, subjects with AdvSM had the lowest $AUC_{0\text{-}tau,ss}$ and $C_{max,ss}$ (~0.47-fold reduction) compared to subjects with ISM. Furthermore, additional covariate effects of age, WT, CRCL, eGFR, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, albumin, sex, race, concomitant CYP3A4 inhibitor and

inducers use, and concomitant H2RA use were investigated in this population PK model update and were found to have no statistically significant impact on the PK of avapritinib.

**Figure 23. Model Predicted Effect of Covariates on $AUC_{0\text{-}tau,ss}$ and $C_{max,ss}$**




Source: Adapted from the Applicant's PopPK report, Page 83, Figure 30, Figure 31.
The solid black line represents no impact of the covariate with the reference subject referring to a subject with ISM with median lean body weight of the 47.6 kg receiving 25 mg dose of avapritinib (tablet formulation) QD, sampled every hour on Day 15 (steady state). Dashed red lines represent the 80 to 125% range of the reference subject. The blue dots and error bars represent the median and 95% ($2.5^{th}$ to 97.5th percentiles of the simulations) prediction intervals (PI) of the covariate effect based on 1000 simulated subjects within each group including uncertainty on the fixed effect.
Abbreviations: AUC, area under the concentration-time curve; $C_{max}$, maximum plasma concentration; GIST, gastrointestinal stromal tumors; ISM, indolent systemic mastocytosis; LBW, lean body weight; PPI, proton pump inhibitor

The Applicant applied the final PopPK model to predict exposure metrics ($AUC_{0\text{-}24,ss}$, $C_{max,ss}$ and trough plasma concentration at steady state ($C_{trough,ss}$)), which were summarized in Table 56. The simulated geometric mean of $AUC_{0\text{-}24,ss}$, $C_{max,ss}$ and $C_{trough,ss}$ were 1320 ng·h/mL, 65.3 ng/mL, and 45.4 ng/mL, respectively, which were consistent with the values reported by noncompartmental analysis (NCA) methods.

**Table 56. Summary of Model Predicted Exposure Metrics for Subjects, Study BLU-285-2203 Part 2 C1D15**

| | $AUC_{0\text{-}24,ss}$ (ng.h/mL) | $C_{max,ss}$ (ng/mL) | $C_{trough,ss}$ (ng/mL) |
|---|---|---|---|
| N | 139.00 | 139.00 | 139.00 |
| Mean | 1460.00 | 71.70 | 50.70 |
| Geometric Mean | 1320.00 | 65.30 | 45.40 |
| CV% for geometric mean | 0.50 | 0.48 | 0.53 |
| Minimum | 283.00 | 14.80 | 8.99 |
| Median | 1450.00 | 70.40 | 49.90 |
| Maximum | 3440.00 | 161.00 | 127.00 |
| Lower 95% CI | 420.00 | 22.70 | 13.70 |
| Upper 95% CI | 2880.00 | 137.00 | 104.00 |

Source: Applicant's PopPK report, Page 85, Table 16.
Abbreviations: AUC, area under the concentration-time curve; C, plasma concentration; CV, coefficient of variance

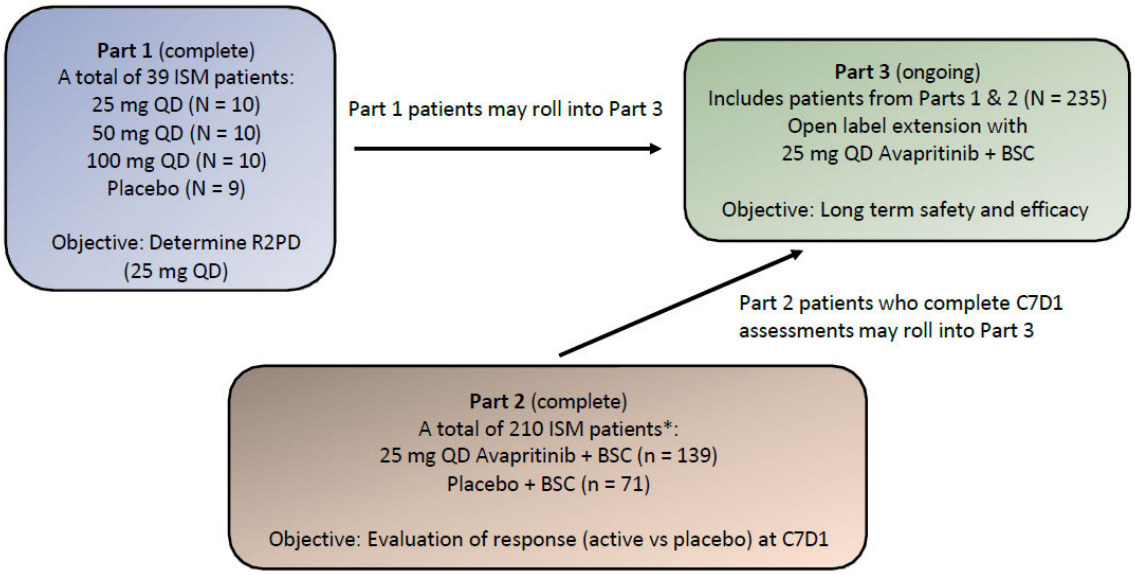
*Reviewer's Comments: The goodness of fit plots indicate that the Applicant's updated population PK model appears adequate to describe avapritinib PK profiles in ISM patients following oral administration. And this model is considered acceptable for PK simulation to support the avapritinib dosing recommendation.*

## Exposure-Response Relationship

The Applicant submitted a separate exposure-response (ER) analysis report entitled "*Exposure Response Analysis for Avapritinib in Patients with Indolent Systemic Mastocytosis*" with applicant Project No. BLUE273410 based on data from study BLU-285-2203. The objectives of the exposure-response analyses were to evaluate the effect of avapritinib exposure on selected measures of efficacy and safety in subjects with ISM from study BLU-285-2203 with descriptive and ER modeling analyses.

As shown in Figure 24, study BLU-285-2203 is a 3-part, Phase 2, randomized, double-blind, placebo-controlled study comparing the efficacy and safety of avapritinib plus best supportive care (BSC) and placebo plus BSC in subjects with ISM whose symptoms are not adequately controlled by BSC. Briefly, the study is being conducted in 3 parts. In Part 1, the recommended Phase 2 dose (RP2D) for subjects with ISM was determined to be 25 mg QD. In Part 2, subjects with ISM were randomly assigned to 25 mg QD avapritinib plus BSC, or to placebo plus BSC. The primary objective was to evaluate the mean change in total symptom score (TSS) from baseline to Cycle 7 Day 1 (C7D1) between the avapritinib and placebo arms. In Part 3, subjects who completed treatment in Part 1 or Part 2 were eligible to participate in an open-label extension, receiving 25 mg QD avapritinib plus BSC. The objective of Part 3 is to evaluate long-term safety and efficacy of avapritinib.

**Figure 24. Study Design for BLU-285-2203**




ISM = indolent systemic mastocytosis, QD = once daily, RP2D = recommended Phase 2 dose, BSC = best supportive care, C7D1 = Cycle 7 Day 1. *Patients from Part 2 included in the current ER analysis (i.e., 2 patients were excluded due to no model predicted exposures).

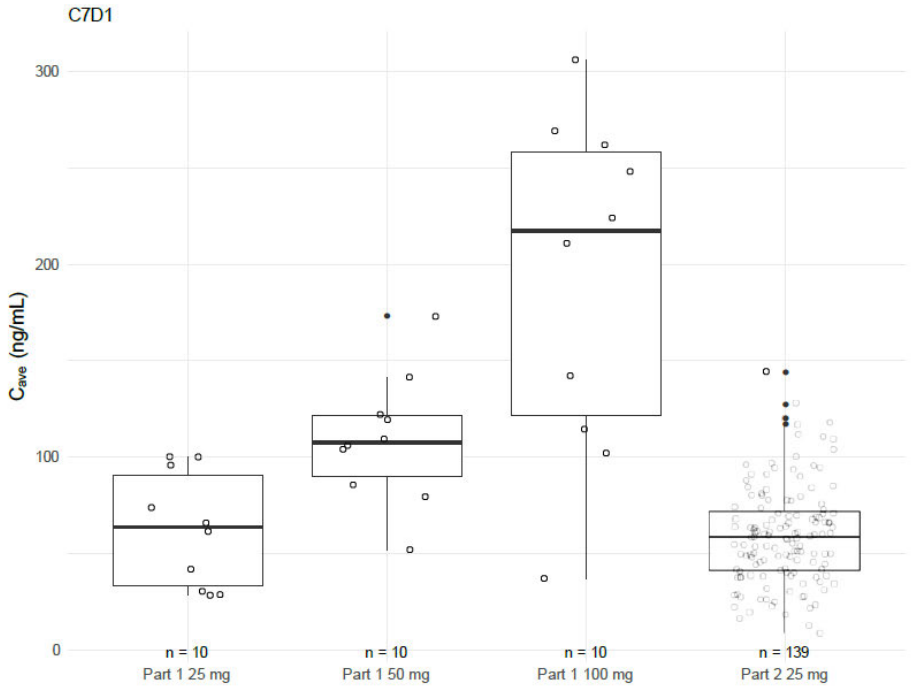
Source: Applicant's ER analyses report, Page 9, Figure 1.

The efficacy analysis was conducted in subjects on placebo or active treatment up to at least C7D1 with TSS recorded at baseline and C7D1. The efficacy endpoints include change in TSS from baseline to C7D1, a ≥30% reduction in TSS from baseline, a ≥50% reduction in TSS from baseline and a ≥50% reduction in serum tryptase from baseline. The safety analysis was conducted in all subjects who were enrolled and received at least one dose of avapritinib. Additionally, subjects on placebo were also included in the safety analyses, where their follow-up time was defined as the duration they received placebo. The safety endpoints include all Grade ≥3 adverse events (AEs), Grade ≥1 cognitive effects, Grade ≥1 edema, Grade ≥2 total bilirubin, Grade ≥2 hemoglobin and Grade ≥1 weight gain/increase. Individual exposure parameters were derived from the updated PopPK model of avapritinib as described above.

Initial graphical investigations of the data by the Applicant indicated that ΔTSS was similar across the exposure range in subjects on active treatment. Moreover, it was apparent that subjects on active treatment yielded improved ΔTSS compared to subjects on placebo. Therefore, the lack of relationship between exposure and ΔTSS together with the clear difference relative to placebo supported selection of the 25 mg QD dose and indicated that further exposure-efficacy modeling and simulation as originally planned would not provide additional information. Regarding the safety endpoints, as most of the subjects included in the current analyses received 25 mg QD, which was the RP2D and the lowest of the candidate doses, and initial graphical evaluations supported 25 mg QD as being well tolerated in subjects with ISM. Therefore, it was decided by the Applicant that the originally planned exposure-safety modeling and simulation activities would not provide additional value to support the 25 mg QD dose. Instead, the ER analyses focused on graphical evaluations and subjects on placebo were included in the analyses. As for ΔTSS, a base model was derived, but covariate modeling and simulations were not performed.

Figure 25 demonstrates the distribution of $C_{ave}$ computed up to C7D1 by treatment arm. The PK of avapritinib in subjects with ISM from study BLU-285-2203 was approximately linear across the dose range of 25 mg to 100 mg.

**Figure 25. $C_{ave}$ by Treatment Arm**

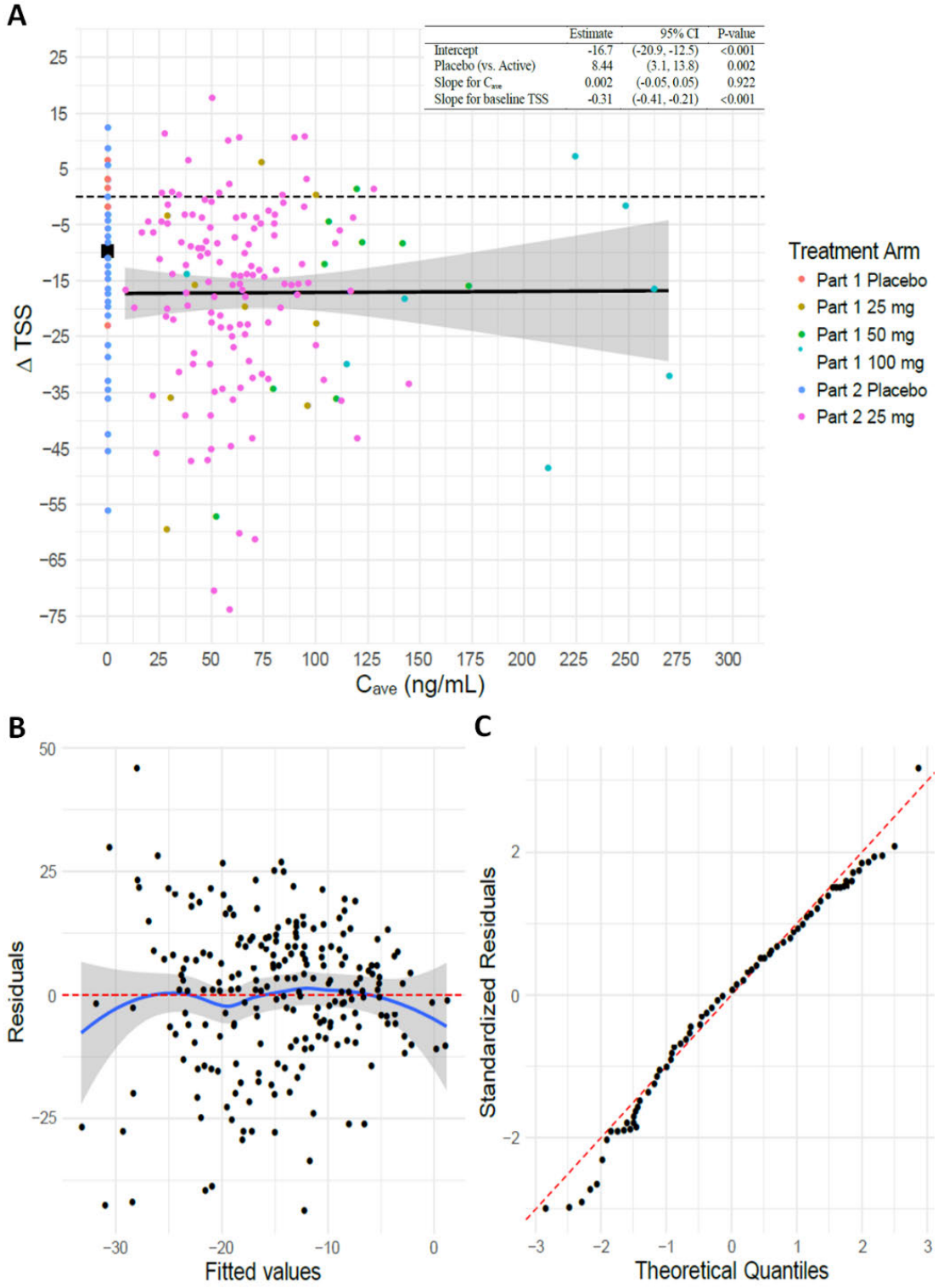



C7D1 = Cycle 7, Day 1. The open circles represent the observed data. The thick solid black lines represent the median of the data, the hinges (top and bottom of the boxes) represent the 25th and 75th percentiles (i.e., the interquartile range, or IQR), the top and bottom whiskers extend to the largest and smallest values that are within 1.5 * IQR of the hinges respectively, and values outside the whiskers are represented with dots.

Source: Applicant's ER analyses report, Page 17, Figure 4.
Abbreviations: $C_{ave}$, average plasma concentration

A total of 234 subjects were included in analyses of ΔTSS. As exhibited in Figure 26 panel A, the average ΔTSS was approximately -9.65 points in subjects on placebo and was around -17.0 in subjects on active treatment. Moreover, based on the parameter estimates table (table-insert in Figure 26 panel A), there was no evidence for a $C_{ave}$ effect (p =0.922), suggesting that the expected average ΔTSS was ≈ -16.7 points across the exposure range in subjects on active treatment (flat ER relationship). Nevertheless, it was evident that subjects on placebo experienced less reduction in TSS at C7D1 from baseline compared to subjects on active treatment (p =0.002). Key diagnostic plots of the ΔTSS model in Figure 26 panel B and panel C suggest that the model provided an acceptable fit to the data.

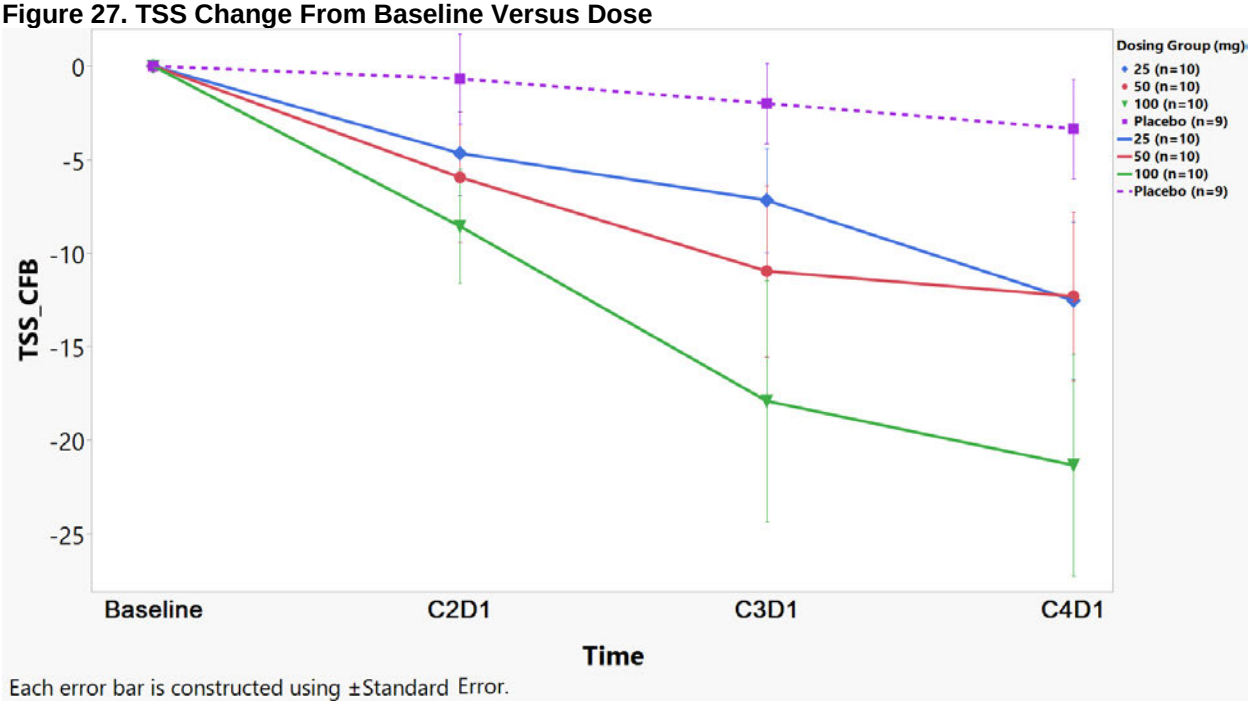
**Figure 26. ΔTSS vs. $C_{ave}$ and Model Diagnostic Plots**




Source: Adapted from the Applicant's ER analyses report, Page 18-19, Figure 5, Table 1, and Figure 6.
The circles represent observed values, the solid black square indicates the average ΔTSS for the placebo groups, the solid black line represents the predictions from a linear model fitted to subjects on active treatment, the dashed black line indicates ΔTSS of 0, the solid blue line indicates fits from a nonparametric smoother and the dashed red lines represent the line of unity or zero, the gray shaded regions display the corresponding 95% confidence interval.
Abbreviations: $C_{ave}$, average plasma concentration; TSS, total symptom score

In addition, the reviewer graphically evaluated dose-response relationship with study BLU-285-2203 Part 1 data, as shown in Figure 27. Given the high standard deviation associated with ΔTSS within each dosing group at different treatment cycles, no clear dose-response trend can be concluded, which is consistent with the above ΔTSS modeling analysis.

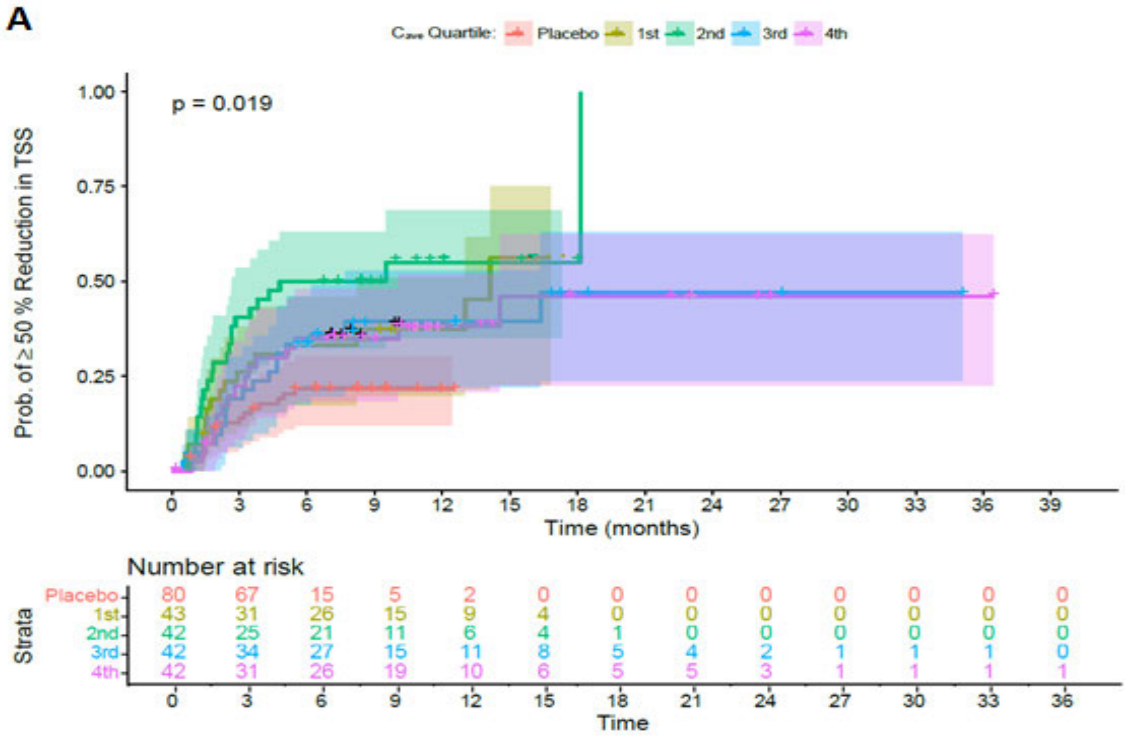
**Figure 27. TSS Change From Baseline Versus Dose**



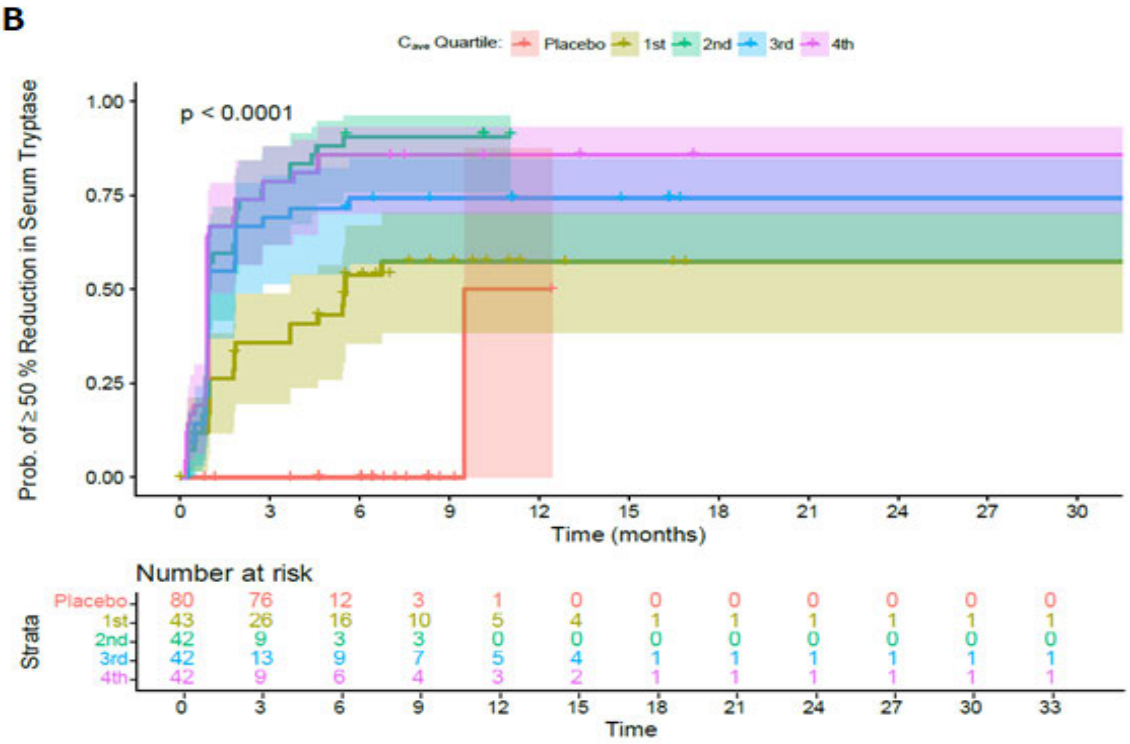

Source: Reviewer's analysis, BLU-285-2203 report, Table 14.2.5.1a, page 1-3.
Abbreviations: TSS, total symptom score; TSS_CFB, TSS change from baseline

Although there was a flat ER relationship for TSS (primary endpoint), the Applicant also generated the KM plots for ≥30% and ≥50% (Figure 28 panel A) reduction in TSS from baseline, and ≥50% reduction in serum tryptase from baseline (Figure 28 panel B) respectively stratified by $C_{ave}$ quartile. Results indicated that active treatment groups experienced faster onset of response compared to subjects on placebo for all three endpoints.

**Figure 28. ≥50% Reduction in TSS and Serum Tryptase From Baseline Versus $C_{ave}$**




Prob = probability. Solid lines = Kaplan-Meier curves, pluses = observed censoring. The shaded regions represent the 95% CIs for the Kaplan-Meier curves.

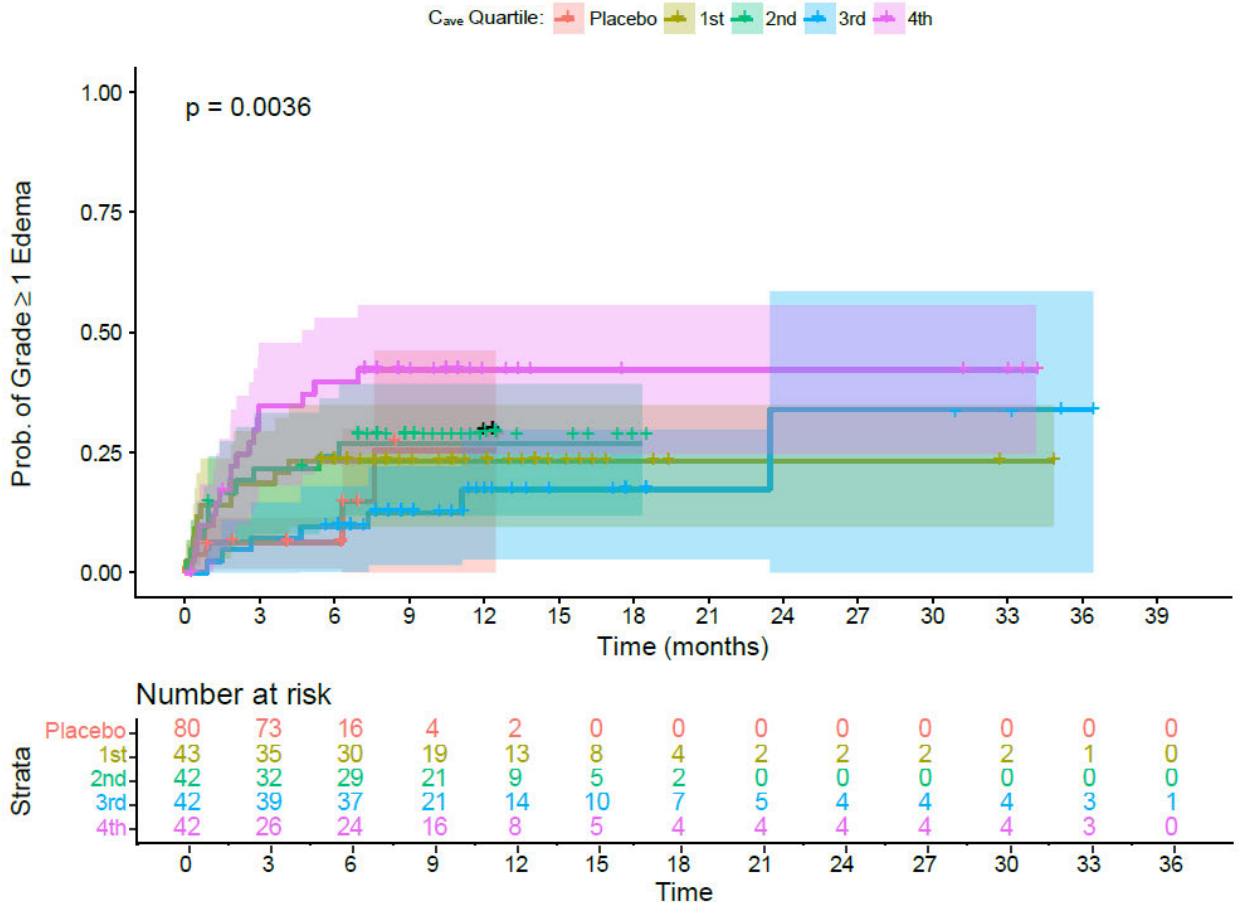



Prob = probability. Solid lines = Kaplan-Meier curves, pluses = observed censoring. The shaded regions represent the 95% CIs for the Kaplan-Meier curves.

Source: Adapted from the Applicant's ER analyses report, Page 21-22, Figure 8, and Figure 9
Abbreviations: $C_{ave}$, average plasma concentration; TSS, total symptom score

A total of 249 subjects were included in the safety analyses. As shown by KM plots in Figure 29, statistical evidence for a trend, with 45 and 7 occurrences in the active and placebo groups, respectively (corresponding percentages of 26.6% and 8.8%) were identified for Grade ≥1 edema. However, this trend did not lead to discontinuations according to the Applicant. No trends were apparent for all Grade ≥3 AEs, Grade ≥1 cognitive effects, and Grade ≥1 weight gain. Moreover, incidences of all Grade ≥3 AEs, Grade ≥1 cognitive effects, and Grade ≥1 weight gain were very low in subjects on active treatment or placebo. In addition, there were no occurrences of Grade ≥2 hemoglobin or Grade ≥2 total bilirubin, thus graphical evaluations of these endpoints are not shown by the Applicant.

**Figure 29. Grade ≥1 Edema Versus $C_{ave}$**




Prob = probability. Solid lines = Kaplan-Meier curves, pluses = observed censoring. The shaded regions represent the 95% CIs for the Kaplan-Meier curves.
Source: Applicant's ER analyses report, Page 26, Figure 13.
Abbreviations: $C_{ave}$, average plasma concentration

*Reviewer's Comments: the Applicant's graphical evaluations and modeling analysis of the ER data from study BLU-285-2203 appear adequate to support selection of the 25 mg QD dose as efficacious, with no clear additional benefit from higher doses. Moreover, incidences of AEs were very low, and no discontinuations occurred, supporting the safety of the 25 mg QD dose.*

**Conclusion**

- Population PK results are consistent with the previous findings and the PK profile in ISM is similar to GIST and healthy volunteers.
- Exposure response for efficacy: There was a flat ER relationship for TSS (primary endpoint). However, faster onset and larger response rates (i.e., ≥50% reduction in serum tryptase, ≥30% and ≥50% reductions in TSS) were identified for the treatment group compared to placebo.
- Exposure response for safety: Higher exposure was associated with higher Grade ≥1 edema, however, this trend did not lead to discontinuations. No clear trends for other AEs (e.g., Grade ≥3 AEs, Grade ≥1 cognitive effects, and Grade ≥1 weight gain) were found.

### 40.6. Pharmacogenetics

Not applicable.

## 41. Study Design

The design of Study 2203 was discussed in detail in Section 32.2. Reproduced below are the study schedule and diagnostic criteria.

**Table 57. Study Schedule, Study 2203 Part 1**

| STUDY ACTIVITIES: | Screening [a] | | | | Part 1 | | | | | | | | Part 3 | | | | | EOT [z] | Safety FU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DURATION IN WKS: | 10-14 Wks Predose | 8-10 Wks Predose | 2-8 Wks Predose | 0-2 Wks Predose | Wk1 | Wk2 | Wk3 | Wk 4 | Wk 8 | Wk 12 assessments will be done between Wk 12-14 | | q 4 Wks starting with Wk 12 D1 and Last visit in Part 1 [y] | Day 1 | Weekly | q 4 Wks | q 12 Wks | q 24 Wks | 14 Days post last dose | 30 days post last dose |
| STUDY DAY: | Day -98 to D -71 | Day -70 to D -57 | Day -56 to D -15 [b] | Day -14 to D -1 | C1D1 pre-dose | C1D8 | C1D15 | C1D22 | C2D1 | C3D1 | C3D8 | | C1D1 | C1D8 to C2D1 | C3D1 to C6D1 | C7D1 to C25D1 | After C25D1 | | |
| WINDOW: | | | | | + 3 days | + 3 days | + 3 days | + 3 days | + 3 days | No site Visit | + 7 days | + 7 days | Pre-dose | + 3 days | + 7 days | + 7 days | + 14 days | + 7 days | + 7 days |
| Informed consent | X [c] | | | | | | | | | | | | | | | | | | |
| ISM-SAF | X [d] | | | | Symptoms will be assessed using the ISM-SAF starting, no later than 5 days after ICF signature through Wk 52 of Part 3 | | | | | | | | | | | | | | |
| Demographics & Medical history [e] | | | x [f] | | | | | | | | | | | | | | | | |
| Physical examination [g] | | | x [f] | | x | x | x | x | x | | x | x | x | x | x | x | x | x | |
| Optimization and stabilization of best supportive care | x [h] | | | | | | | | | | | | | | | | | | |
| Height | | | x | | | | | | | | | | | | | | | | |
| Weight | | | x | | x | x | x | x | x | | x | x | x | x | x | x | x | x | |
| Vital signs [i] | | | x | | x | x | x | x | x | | x | x | x | x | x | x | x | x | |
| ECOG PS | | | x | | x | x | x | x | x | | x | x | x | x | x | x | x | x | |
| 12-lead ECG [j] | | | x | | x | | | | x | | x | x | | x | x | x | x | x | |
| Urine or serum (β-hCG) pregnancy test [l] | | | x [k] | | x | | | | x | | x | x | x | x | x | x | x | x [k] | |
| Hematology | | | x [f] | | x | x | x | x | x | | x | x | x | x | x | x | x | x | |
| Serum chemistry | | | x | | x | x | x | x | x | | x | x | x | x | x | x | x | x | |

| STUDY ACTIVITIES: | Screening [a] | | | | Part 1 | | | | | | | | Part 3 | | | | | EOT [z] | Safety FU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DURATION IN WKS: | 10-14 Wks Predose | 8-10 Wks Predose | 2-8 Wks Predose | 0-2 Wks Predose | Wk1 | Wk2 | Wk3 | Wk 4 | Wk 8 | Wk 12 assessments will be done between Wk 12-14 | | q 4 Wks starting with Wk 12 D1 and Last visit in Part 1 [y] | Day 1 | Weekly | q 4 Wks | q 12 Wks | q 24 Wks | 14 Days post last dose | 30 days post last dose |
| STUDY DAY: | Day -98 to D -71 | Day -70 to D -57 | Day -56 to D -15[b] | Day -14 to D -1 | C1D1 pre-dose | C1D8 | C1D15 | C1D22 | C2D1 | C3D1 | C3D8 | | C1D1 | C1D8 to C2D1 | C3D1 to C6D1 | C7D1 to C25D1 | After C25D1 | | |
| WINDOW: | | | | | ± 3 days | ± 3 days | ± 3 days | ± 3 days | ± 3 days | No site Visit | ± 7 days | ± 7 days | Pre-dose | ± 3 days | ± 7 days | ± 7 days | ± 14 days | ± 7 days | ± 7 days |
| Coagulation | | | x | | | | | | | | | | x | | | | | x | |
| Urinalysis | | | x | | | | | | | | | | x | | | | | x | |
| Blood sample for serum tryptase[m] | | | x [f] | | x | x | x | x | x | | x | | x | x | x | x | x | | |
| Blood sample for *KIT* D816V mutant allele burden (or archival sample) & other mutations[m, n, o] | | | x [f] | | x [o] | | x | | x | | x | x | x [0] | | x | x | x | | |
| Blood sample for exploratory biomarkers[m] | | | | | x | | | | | | x | | x | | x C3 D1 only | | | | |
| BM biopsy, aspirate, and PB smear collection[p] | | | X [f] | | | | | | | | x | | | | | x optional at Wk 52 | | | |
| Archival BM biopsy, aspirate, and PB [q] | | | X [f] | | | | | | | | | | | | | | | | |
| Skin photography [r] | | | x | | | | | | | | x | x | | | x | x through Wk 52 | | | |
| Skin biopsies of lesional and non-lesional skin [s] | | | x | | | | | | | | x | | | | | x optional at Wk 52 | | | |
| DXA scan [t] | | | x | | | | | | | | | x | x | | | x at Wk 52 | x q 12 cycles | | |
| Brain imaging by MRI (preferred) or CT scan with contrast | | | x | | | | | | | | | | | | | | | | |
| Randomization [u] | | | | x | | | | | | | | | | | | | | | |
| Study drug administration | | | | | x daily dosing with either 25mg, 50mg, 100mg or Pbo | | | | | | | | x daily dosing with apavritinib [v] | | | | | | |

| STUDY ACTIVITIES: | Screening [a] | | | | Part 1 | | | | | | | | Part 3 | | | | | EOT [z] | Safety FU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DURATION IN WKS: | 10-14 Wks Predose | 8-10 Wks Predose | 2-8 Wks Predose | 0-2 Wks Predose | Wk1 | Wk2 | Wk3 | Wk 4 | Wk 8 | Wk 12 assessments will be done between Wk 12-14 | | q 4 Wks starting with Wk 12 D1 and Last visit in Part 1 [y] | Day 1 | Weekly | q 4 Wks | q 12 Wks | q 24 Wks | 14 Days post last dose | 30 days post last dose |
| STUDY DAY: | Day -98 to D -71 | Day -70 to D -57 | Day -56 to D -15 [b] | Day -14 to D -1 | C1D1 pre-dose | C1D8 | C1D15 | C1D22 | C2D1 | C3D1 | C3D8 | | C1D1 | C1D8 to C2D1 | C3D1 to C6D1 | C7D1 to C25D1 | After C25D1 | | |
| WINDOW: | | | | | +3 days | +3 days | +3 days | +3 days | +3 days | No site Visit | +7 days | +7 days | Pre-dose | +3 days | +7 days | +7 days | +14 days | +7 days | +7 days |
| PGIS, SF-12, MC-QOL, PGIC, EQ-5D-5L [w] | | | | | x | x | x | x | x | | x | x | x | x | x | x | x | X (EQ-5D-5L) | |
| Blood sampling for PK [m] | | | | | See Appendix 3 for PK sampling schedule | | | | | | | | | | | | | | |
| Best supportive care | x Collected from time of ICF through the Safety FU | | | | | | | | | | | | | | | | | | |
| Documentation of anaphylactic episodes | x All anaphylactic episodes treated with epinephrine will be collected from time of ICF through the EOT | | | | | | | | | | | | | | | | | | |
| AE Monitoring [x] | x | | | | | | | | | | | | | | | | | | |
| Concomitant Medications | x | | | | | | | | | | | | | | | | | | |

[a] Screening assessments must be completed by C1 Day -15
[b] Screening duration may be shortened if screening assessments can be completed sooner
[c] Informed consent must be signed within 14 weeks of Dosing and prior to any screening procedures being performed
[d] ISM-SAF data from C1 Day -70 through C1 Day -57 will be used to determine eligibility based on symptoms severity threshold. ISM-SAF data collected from C1 Day -14 through C1 Day -1 will be used as baseline. The ISM-SAF will be completed through Week 52 of Part 3.
[e] A complete medical history will be obtained at Screening, including demographics, detailed history of SM, any prior CM and prior treatments
[f] Assessments must be completed by Day -28 and results entered in EDC, to allow time for Central Pathology to evaluate ISM diagnosis.
[g] A complete physical exam will be performed at screening, including measurement of liver and spleen by palpation. Following screening, a targeted physical exam may be done but should include measurement of liver and spleen by palpation.
[h] Medications for management of MC-mediated symptoms (best supportive care) will be optimized and stabilized for ≥28 days prior to initiation of the ISM-SAF questionnaire for eligibility (by Day -71)
[i] Vital signs include temperature, pulse and systolic/diastolic BP. BP and pulse should be done while the patient is seated or supine.
[j] A 12-Lead ECG will be conducted after 5 minutes in a recumbent or semi-recumbent position. ECG will be done at screening and on Day 1 of C1, C2, on C3 Day 8, between C3D8 through D15 after completion of the ISM-SAF questionnaire, and on Day 1 of every subsequent cycle in Part 1). In Part 3, ECG will be done on day 1 of every site visit.
[k] A Serum pregnancy test must be performed in women of child-bearing potential within 20 days prior to first dose of study drug and at EOT.
[l] A serum or urine pregnancy test will be performed in women of child-bearing potential on Day 1 of every cycle in Part 1 (other than at C3 at which time it will be done on Day 8). In Part 3, a serum or urine pregnancy test will be done on Day 1 predose and every 4 weeks. In Part 3, when study visits are less frequent than every 4 weeks, a local serum or urine pregnancy test may be done every 4 weeks. Pregnancy test results will be entered in EDC.
[m] Samples must be shipped to a Central Laboratory.

n At Screening, a *KIT* D816V blood sample will be collected and analyzed locally by C1 Day -28 or archival sample may be used. Results must be entered in EDC to allow time for Central Pathology to evaluate the ISM diagnosis. In Part 1, D816V will be done on C1D1, C1D15, C2D1, C3D8 and every 4 weeks until rollover into Part 3. In Part 3, D816V will be done on C1D1 predose, C3D1, every 12 weeks during cycles 6-25 and every 24 weeks during cycles 26 through the end of the 5-year study.

o Testing for other mutations will be done predose and postdose in Part 1 and Part 3.

p Bone marrow biopsy and aspirate samples will be sent to the Central Pathology Laboratory for confirmation of SM diagnosis and quantification of BM MCs. Bone marrow biopsy, aspirate and PB will also be collected in Part 1 during the Week 12 assessment window, after completion of the ISM-SAF (between C3D8 and D15). Optional Bone Marrow Biopsy, aspirate and PB samples will be collected at Week 52.

q Archival BM biopsy, aspirate & PB smear may be used in place of a screening BM biopsy in patients with a diagnosis of ISM, only if the procedure was performed within 24 weeks of C1D1, and so long as no cytoreductive therapy was given between the procedure and C1D1. If archival samples are used, they must be sent to the Central Pathology Laboratory for confirmation of SM diagnosis and quantification of BM MCs. If inadequate for confirmation of diagnosis or quantification of MCs, a fresh BM biopsy, aspirate and PB smear will be requested prior to enrollment.

r Patients with CM at screening will have standardized skin photography taken during Screening, as well as during the Week 12 assessment window (between C3D8 and D15 after completion of the ISM-SAF) and every 12 weeks until Week 52 in Part 3. Skin photography will be taken prior to skin biopsy.

s Patients with CM at Screening will have a 5mm punch biopsy of lesional and non-lesional skin performed at Screening and sent to the Central Pathology Lab for processing and quantification of MC infiltrates. Processing will be done according to the lab manual. The procedure will be repeated during the Week 12 assessment window (between C3D8 through D15 after completion of the ISM-SAF questionnaire). Skin biopsy should be performed after skin photography is taken. An optional lesional and non-lesional skin biopsy will be performed at Week 52.

t DXA Scan for evaluation of bone density of lumbar spine and hip will be performed at Screening, in Part 1 at Cycle 12 (prior to rollover to Part 3,) in Part 3 predose (if not done within the last 6 months) and Week 52 and every 12 cycles thereafter

u Patients will be randomly assigned to avapritinib dose of 25 mg, 50 mg, or 100 mg, or placebo on C1 Day -1.

v All patients rolling over into Part 3 will receive avapritinib at the RP2D determined in Part 1.

w QOLs will be done at each study visit until Part 3, Week 52. PGIC will not be collected at baseline. The EQ-5D-5L will be completed at EOT.

x Serious adverse events are collected from screening through the safety follow up (30 days post last dose). An SAE that occurs >30 days after the last dose of study drug and assessed by the PI to be related to study drug, should be reported. Adverse events are only collected while on study starting at C1D1.

y Once the RP2D is identified, patients will have their last scheduled cycle visit in Part 1 prior to rollover into Part 3. Assessments on the last cycle of Part 1 will form the baseline for Part 3. Dosing in Part 3 Day 1 may be on the same day as the last cycle visit in Part 1; if this is the case, all assessments listed under the last visit in Part 1 in addition to those listed in C1D1 of Part 3, must be completed prior to dosing in Part 3. If the last visit in Part 1 is separate from the 1st dosing day in Part 3, a subset of assessments (listed under C1D1 Part 3) must be completed prior to dosing.

z EOT visit will be done when treatment is discontinued, regardless of which Part of the study this takes place.

Source: Applicant's protocol pages 97-104

**Table 58. Study Schedule, Study 2203 Part 2**

| STUDY ACTIVITIES: | Screening [a] | | | | Part 2 | | | | | | | Part 3 | | | | | EOT [z] | Safety FU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DURATION IN WKS: | 10-14 Wks Predose | 8-10 Wks Predose | 2-8 Wks Predose | 0-2 Wks Predose | Wk1 | Wk2 | Wk3 | Wk 4 | Wk 8 | Wk 12 assessments will be done between Wk 12-14 | | Day 1 | Weekly | q 4 Wks | q 12 Wks | q 24 Wks | 14 Days post last dose | 30 days post last dose |
| STUDY DAY: | Day -98 to D -71 | Day -70 to D -57 | Day -56 to D -15 [b] | Day -14 to D -1 | C1D1 pre-dose | C1D8 | C1D15 | C1D22 | C2D1 | C3D1 | C3D8 [y] Last Part 1 visit | C1D1 | C1D8 to C2D1 | C3D1 to C6D1 | C7D1 to C25D1 | After C25D1 | | |
| WINDOW: | | | | | +3 days | +3 days | +3 days | +3 days | +3 days | No site Visit | +7 days | Pre-dose | +3 days | +7 days | +7 days | +14 days | +7 days | +7 days |
| Informed consent | X [c] | | | | | | | | | | | | | | | | | |
| ISM-SAF | X [d] Symptoms will be assessed using the ISM-SAF starting, no later than 5 days after ICF signature through Week 52 of Part 3 | | | | | | | | | | | | | | | | | |
| Demographics & Medical history [e] | | | x [f] | | | | | | | | | | | | | | | |
| Physical examination [g] | | | x [f] | | x | x | x | x | x | | x | x | x | x | x | x | x | |
| Optimization and stabilization of best supportive care | x [h] | | | | | | | | | | | | | | | | | |
| Height | | | x | | | | | | | | | | | | | | | |
| Weight | | | x | | x | x | x | x | x | | x | x | x | x | x | x | x | |
| Vital signs [i] | | | x | | x | x | x | x | x | | x | x | x | x | x | x | x | |
| ECOG PS | | | x | | x | x | x | x | x | | x | x | x | x | x | x | x | |
| 12-lead ECG [j] | | | x | | x | | | | x | | x | | x | x | x | x | x | |
| Urine or serum (β-hCG) pregnancy test [l] | | | x [k] | | x | | | | x | | x | x | x | x | x | x | x [k] | |
| Hematology | | | x [f] | | x | x | x | x | x | | x | x | x | x | x | x | x | |
| Serum chemistry | | | x | | x | x | x | x | x | | x | x | x | x | x | x | x | |
| Coagulation | | | x | | | | | | | | | x | | | | | x | |
| Urinalysis | | | x | | | | | | | | | x | | | | | x | |

| STUDY ACTIVITIES: | Screening [a] | | | | Part 2 | | | | | | | Part 3 | | | | | EOT [z] | Safety FU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DURATION IN WKS: | 10-14 Wks Predose | 8-10 Wks Predose | 2-8 Wks Predose | 0-2 Wks Predose | Wk1 | Wk2 | Wk3 | Wk 4 | Wk 8 | Wk 12 assessments will be done between Wk 12-14 | | Day 1 | Weekly | q 4 Wks | q 12 Wks | q 24 Wks | 14 Days post last dose | 30 days post last dose |
| STUDY DAY: | Day -98 to D -71 | Day -70 to D -57 | Day -56 to D -15 [b] | Day -14 to D -1 | C1D1 pre-dose | C1D8 | C1D15 | C1D22 | C2D1 | C3D1 | C3D8 [y] Last Part 1 visit | C1D1 | C1D8 to C2D1 | C3D1 to C6D1 | C7D1 to C25D1 | After C25D1 | | |
| WINDOW: | | | | | + 3 days | + 3 days | + 3 days | + 3 days | + 3 days | No site Visit | + 7 days | Pre-dose | + 3 days | + 7 days | + 7 days | + 14 days | + 7 days | + 7 days |
| Blood sample for serum tryptase [m] | | | x [f] | | x | x | x | x | x | | x | x | x | x | x | x | | |
| Blood sample for *KIT* D816V mutant allele burden (or archival sample) & other mutations [m, n, o] | | | x [f] | | x [o] | | x | | x | | x | x [o] | | x | x | x | | |
| Blood sample for exploratory biomarkers [m] | | | | | x | | | | | | x | x | | x C3 D1 only | | | | |
| BM biopsy, aspirate, and PB smear collection [p] | | | x [f] | | | | | | | | x | | | | x optional at Wk 52 | | | |
| Archival BM biopsy, aspirate, and PB [q] | | | x [f] | | | | | | | | | | | | | | | |
| Skin photography [r] | | | x | | | | | | | | x | | | x | x through Wk 52 | | | |
| Skin biopsies of lesional and non-lesional skin [s] | | | x | | | | | | | | x | | | | x optional at Wk 52 | | | |
| DXA scan [t] | | | x | | | | | | | | | | | | x at Wk 52 | x q 12 cycles | | |
| Brain imaging by MRI (preferred) or CT scan with contrast | | | x | | | | | | | | | | | | | | | |
| Randomization [u] | | | | x | | | | | | | | | | | | | | |
| Study drug administration | | | | | x daily dosing at RP2D or Pbo | | | | | | | x daily dosing of avapritinib [v] | | | | | | |
| PGIS, SF-12, MC-QOL, PGIC, EQ-5D-5L [w] | | | | | x | x | x | x | x | | x | x | x | x | x | x | X (EQ-5D-5L) | |
| Blood sampling for PK [m] | | | | | See Appendix 4 for PK sampling schedule | | | | | | | | | | | | | |

| STUDY ACTIVITIES: | Screening [a] | | | | Part 2 | | | | | | | Part 3 | | | | | EOT [z] | Safety FU |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DURATION IN WKS: | 10-14 Wks Predose | 8-10 Wks Predose | 2-8 Wks Predose | 0-2 Wks Predose | Wk1 | Wk2 | Wk3 | Wk 4 | Wk 8 | Wk 12 assessments will be done between Wk 12-14 | | Day 1 | Weekly | q 4 Wks | q 12 Wks | q 24 Wks | 14 Days post last dose | 30 days post last dose |
| STUDY DAY: | Day -98 to D -71 | Day -70 to D -57 | Day -56 to D -15 [b] | Day -14 to D -1 | C1D1 pre-dose | C1D8 | C1D15 | C1D22 | C2D1 | C3D1 | C3D8 [y] Last Part 1 visit | C1D1 | C1D8 to C2D1 | C3D1 to C6D1 | C7D1 to C25D1 | After C25D1 | | |
| WINDOW: | | | | | +3 days | +3 days | +3 days | +3 days | +3 days | No site Visit | +7 days | Pre-dose | +3 days | +7 days | +7 days | +14 days | +7 days | +7 days |
| Best supportive care | x Collected from time of ICF through the Safety FU | | | | | | | | | | | | | | | | | |
| Documentation of anaphylactic episodes | x All anaphylactic episodes treated with epinephrine will be collected from time of ICF through the EOT | | | | | | | | | | | | | | | | | |
| AE Monitoring [x] | x | | | | | | | | | | | | | | | | | |
| Concomitant Medications | x | | | | | | | | | | | | | | | | | |

[a] Screening assessments must be completed by C1 Day -15
[b] Screening duration may be shortened if screening assessments can be completed sooner
[c] Informed consent must be signed within 14 weeks of Dosing and prior to any screening procedures being performed
[d] ISM-SAF data from C1 Day -70 through C1 Day -57 will be used to determine eligibility based on symptoms severity threshold. ISM-SAF data collected from C1 Day -14 through C1 Day -1 will be used as baseline. The ISM-SAF will be completed through Week 52 of Part 3.
[e] A complete medical history will be obtained at Screening, including demographics, detailed history of SM, any prior CM and prior treatments
[f] Assessments must be completed by Day -28 and results and entered in EDC, to allow time for Central Pathology to evaluate ISM diagnosis.
[g] A complete physical exam will be performed at screening, including measurement of liver and spleen by palpation. Following screening, a targeted physical exam may be done but should include measurement of liver and spleen by palpation.
[h] Medications for management of MC -mediated symptoms (best supportive care) will be optimized and stabilized for ≥28 days prior to initiation of the ISM-SAF questionnaire for eligibility (by Day -71)
[i] Vital signs include temperature, pulse and systolic/diastolic BP. BP and pulse should be done while the patient is seated or supine.
[j] A 12-Lead ECG will be conducted after 5 minutes in a recumbent or semi-recumbent position. ECG will be done at screening and on Day 1 of every cycle in Part 2 (other than at C3 at which time it will be done on Day 8). In Part 3, ECG will be done on Day 1 of at every site visit.
[k] A Serum pregnancy test must be performed in women of child-bearing potential within 20 days prior to first dose of study drug and at EOT.
[l] A serum or urine pregnancy test will be performed in women of child-bearing potential on Day 1 of every cycle in Part 2 (other than at C3 at which time it will be done on Day 8). In Part 3, a serum or urine pregnancy test will be done on Day 1 predose and every 4 weeks. When study visits are less frequent than every 4 weeks, a local serum or urine pregnancy test may be done every 4 weeks. Pregnancy test results will be entered in EDC.
[m] Samples must be shipped to a Central Laboratory.
[n] At Screening, *KIT* D816V blood sample will be collected and analyzed locally by C1 Day -28 or archival sample may be used. Results must be entered in EDC to allow time for Central Pathology to evaluate ISM diagnosis. In part 2 D816V will be done on C1D1, C1D15, C2D1, C3D8. In Part 3, D816V will be done on C1D1 predose, C3D1, every 12 weeks during cycles 6-25 and every 24 weeks during cycles 26 through the end of the 5-year study.
[o] Testing for other mutations will be done predose and postdose in Part 2 and Part 3.
[p] Bone marrow biopsy, aspirate and PB will be sent to the Central Pathology Laboratory for confirmation of SM diagnosis and quantification of BM MCs. Bone marrow biopsy, aspirate and PB will also be collected in Part 2 during the Week 12 assessment window, after completion of the ISM-SAF (between C3D8 and D15). Optional Bone Marrow Biopsy, aspirate and PB samples will be collected at Week 52.
[q] Archival BM biopsy, aspirate & PB smear may be used in place of a screening BM biopsy in patients with a diagnosis of ISM/SSM, only if the procedure was performed within 24 weeks of C1D1, and so long as no cytoreductive therapy was given between the procedure and C1D1. If archival samples are used, they must be sent to the Central Pathology Laboratory for confirmation of SM diagnosis and quantification of BM MCs. If inadequate for confirmation of diagnosis or quantification of MCs, a fresh BM biopsy, aspirate and PB smear will be requested prior to enrollment.
[r] Patients with CM at screening will have standardized skin photography taken during Screening, as well as during the Week 12 assessment window (between C3D8 and D15 after completion of the ISM-SAF) and every 12 weeks until Week 52 in Part 3. Skin photography will be taken prior to skin biopsy.
[s] Patients with CM at Screening will have a 5mm punch biopsy of lesional and non-lesional skin performed at Screening and sent to the Central Pathology Lab for processing and quantification of MC infiltrates. Processing will be done according to the lab manual. The procedure will be repeated during the Week 12 assessment window (between C3D8 through D15 after completion of the ISM-SAF questionnaire). Skin biopsy should be performed after skin photography is taken. An optional lesional and non-lesional skin biopsy will be performed at Week 52.
[t] DXA Scan for evaluation of bone density of lumbar spine and hip will be performed at Screening, in Part 3 Week 52, and every 12 cycles thereafter
[u] Patients will be randomly assigned on C1 Day -1 to avapritinib at the RP2D selected in Part 1, or placebo.
[v] All patients rolling over into Part 3 will receive avapritinib at the RP2D determined in Part 1
[w] QOLs will be done at each study visit until Part 3, Week 52. PGIC will not be collected at baseline. The EQ-5D-5L will be completed at EOT.
[x] Serious adverse events are collected from screening through the safety follow up (30 days post last dose). An SAE that occurs >30 days after the last dose of study drug and assessed by the PI to be related to study drug, should be reported. Adverse events are only collected while on study starting at C1D1.
[y] Assessments on the last cycle of Part 2 will form the baseline for Part 3. Dosing in Part 3 Day 1 may be on the same day as the last cycle visit in Part 2; if this is the case, all assessments listed under the last visit in Part 2 in addition to those listed in C1D1 of Part 3, must be completed prior to dosing in Part 3. If the last visit in Part 1 is separate from the 1st dosing day in Part 3, a subset of assessments (listed under C1D1 Part 3) must be done prior to dosing in Part 3.
[z] EOT visit will be done when treatment is discontinued, regardless of which Part of the study this takes place.

Source: Applicant's protocol pages 97-104

**Table 59. WHO SM Criteria**

| **Diagnosis of SM: requires 1 major + 1 minor criterion OR 3 minor criteria** | |
|---|---|
| **Major Criteria** | **Minor Criteria** |
| Multifocal dense infiltrates of MCs (> 15 MCs in aggregates) in sections of BM and/or other extracutaneous organ(s) | • > 25% of all MCs are atypical cells (type I or type II) on BM smears or are spindle-shaped in MC infiltrates detected in BM biopsy or sections of visceral organs<br>• *KIT* point mutation at codon 816 in the BM or another extracutaneous organ<br>• MCs in BM or blood or other extracutaneous organ express CD25 with or without CD2 in addition to normal MC markers<br>• Baseline serum tryptase concentration > 20 ng/mL |
| **Classification of SM: Definition of B- and C-Findings** | |
| **B-Findings** | **C-Findings** |
| • MC infiltration in BM > 30% by histology *and* basal serum tryptase > 200 ng/mL<br>• Hypercellular BM with loss of fat cells, discrete signs of dysmyelopoiesis *without* substantial cytopenias or WHO criteria for an MDS or MPN<br>• Organomegaly[a]: hepatomegaly, splenomegaly, or palpable lymphadenopathy (on CT or ultrasound: > 2 cm) *without* impaired organ function | • Cytopenia(s):<br>○ ANC < $1.0 \times 10^9$/L or<br>○ Hgb <10g/dL or<br>○ Platelet count < $100 \times 10^9$/L<br>• Hepatomegaly with ascites and impaired liver function<br>• Splenomegaly with hypersplenism (eg, as documented by thrombocytopenia, [ie, platelet count < $100 \times 10^9$/L])<br>• Malabsorption with hypoalbuminemia and/or significant weight loss defined as > 10% weight loss over the last 6 months<br>• Skeletal involvement with large osteolytic lesions with pathologic fractures<br>• Life-threatening organ damage in other organ systems that is caused by MC infiltration in tissues |

Abbreviations: ANC = absolute neutrophil count; BM = bone marrow; CD2 = cluster of differentiation 2; CD25 = cluster of differentiation 25; CT = computed tomography; Hgb = hemoglobin; *KIT* = V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; MC = mast cell; MDS = myelodysplastic syndrome; MPN = myeloproliferative neoplasm; SM = systemic mastocytosis; WHO = World Health Organization.

[a] Organomegaly may be documented by palpation or imaging.

Source: (Horny et al, 2008; Swerdlow et al, 2017).

Source: Applicant's protocol page 107

# 42. Efficacy

Efficacy results were discussed in Section 32.2.1.3 Statistical Analysis Plan and focused on the efficacy results obtained from part 2 (randomized controlled portion) of study BLU-285-2203.

The section below shows the conceptual framework for indolent systemic mastocytosis-symptom assessment form used in study BVLU-285-2203.

# 42.1. Patient-Reported Outcome Instruments for Primary and Key Secondary Efficacy Endpoints

## 42.1.1. ISM-SAF

**Table 60. Conceptual Framework for ISM-SAF**

| Domain | Concept | Items |
|---|---|---|
| GI symptom severity* | Abdominal pain | 2. Over the past 24 hours, how severe was your worst abdominal pain? |
| | Nausea | 3. Over the past 24 hours, how severe was your worst nausea? |
| | Diarrhea | 12. Over the past 24 hours, how severe was your worst diarrhea? |
| Skin symptom severity* | Spots | 4. Over the past 24 hours, how severe were the spots on your skin at their worst? |
| | Itching | 5. Over the past 24 hours, how severe was your worst itching? |
| | Flushing | 6. Over the past 24 hours, how severe was your worst flushing? |
| Neurocognitive symptom severity* | Dizziness | 8. Over the past 24 hours, how severe was your worst dizziness? |
| | Brain fog | 9. Over the past 24 hours, how severe was your worst brain fog? |
| | Headache | 10. Over the past 24 hours, how severe was your worst headache? |
| N/A | Bone pain | 1. Over the past 24 hours, how severe was your worst bone pain? |
| | Fatigue | 7. Over the past 24 hours, how severe was your worst fatigue? |
| Diarrhea frequency | Diarrhea | 11. Over the past 24 hours, how many times did you have diarrhea? |

Abbreviations: GI=Gastrointestinal
*Though the focus of this report is on the TSS, it is important to note that psychometric analysis provided herein also evaluated use of the GI Symptom, Skin Symptom, and Neurocognitive Symptom domain scores in terms of distribution, reliability, construct-related validity including sensitivity to change, and clinical interpretability in the target patient population.
Source: PRO Evidence Dossier
Abbreviations: ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form

**Figure 30. Copy of ISM-SAF**

**Indolent Systemic Mastocytosis Symptom Assessment Form (ISM-SAF)**

The following questions are about your systemic mastocytosis. Please select only one answer that best describes your symptoms over the past 24 hours.

Please answer all of the questions and do not skip any. There are no right or wrong answers to any of the questions.

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Over the past 24 hours, how severe was your worst bone pain? | 0 ☐ No bone pain | 1 ☐ | 2 ☐ | 3 ☐ | 4 ☐ | 5 ☐ | 6 ☐ | 7 ☐ | 8 ☐ | 9 ☐ | 10 ☐ Worst imaginable bone pain |
| 2. Over the past 24 hours, how severe was your worst abdominal pain? | 0 ☐ No abdominal pain | 1 ☐ | 2 ☐ | 3 ☐ | 4 ☐ | 5 ☐ | 6 ☐ | 7 ☐ | 8 ☐ | 9 ☐ | 10 ☐ Worst imaginable abdominal pain |
| 3. Over the past 24 hours, how severe was your worst nausea? | 0 ☐ No nausea | 1 ☐ | 2 ☐ | 3 ☐ | 4 ☐ | 5 ☐ | 6 ☐ | 7 ☐ | 8 ☐ | 9 ☐ | 10 ☐ Worst imaginable nausea |
| 4. Over the past 24 hours, how severe were the spots on your skin at their worst? | 0 ☐ No spots | 1 ☐ | 2 ☐ | 3 ☐ | 4 ☐ | 5 ☐ | 6 ☐ | 7 ☐ | 8 ☐ | 9 ☐ | 10 ☐ Worst imaginable spots |

**Indolent Systemic Mastocytosis Symptom Assessment Form (ISM-SAF)**

The following questions are about your systemic mastocytosis. Please select only one answer that best describes your symptoms over the past 24 hours.

Please answer all of the questions and do not skip any. There are no right or wrong answers to any of the questions.

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 5. Over the past 24 hours, how severe was your worst itching? | 0 ☐ No itching | 1 ☐ | 2 ☐ | 3 ☐ | 4 ☐ | 5 ☐ | 6 ☐ | 7 ☐ | 8 ☐ | 9 ☐ | 10 ☐ Worst imaginable itching |
| 6. Over the past 24 hours, how severe was your worst flushing? | 0 ☐ No flushing | 1 ☐ | 2 ☐ | 3 ☐ | 4 ☐ | 5 ☐ | 6 ☐ | 7 ☐ | 8 ☐ | 9 ☐ | 10 ☐ Worst imaginable flushing |
| 7. Over the past 24 hours, how severe was your worst fatigue? | 0 ☐ No fatigue | 1 ☐ | 2 ☐ | 3 ☐ | 4 ☐ | 5 ☐ | 6 ☐ | 7 ☐ | 8 ☐ | 9 ☐ | 10 ☐ Worst imaginable fatigue |
| 8. Over the past 24 hours, how severe was your worst dizziness? | 0 ☐ No dizziness | 1 ☐ | 2 ☐ | 3 ☐ | 4 ☐ | 5 ☐ | 6 ☐ | 7 ☐ | 8 ☐ | 9 ☐ | 10 ☐ Worst imaginable dizziness |

**Indolent Systemic Mastocytosis Symptom Assessment Form (ISM-SAF)**

The following questions are about your systemic mastocytosis. Please select only one answer that best describes your symptoms over the past 24 hours.

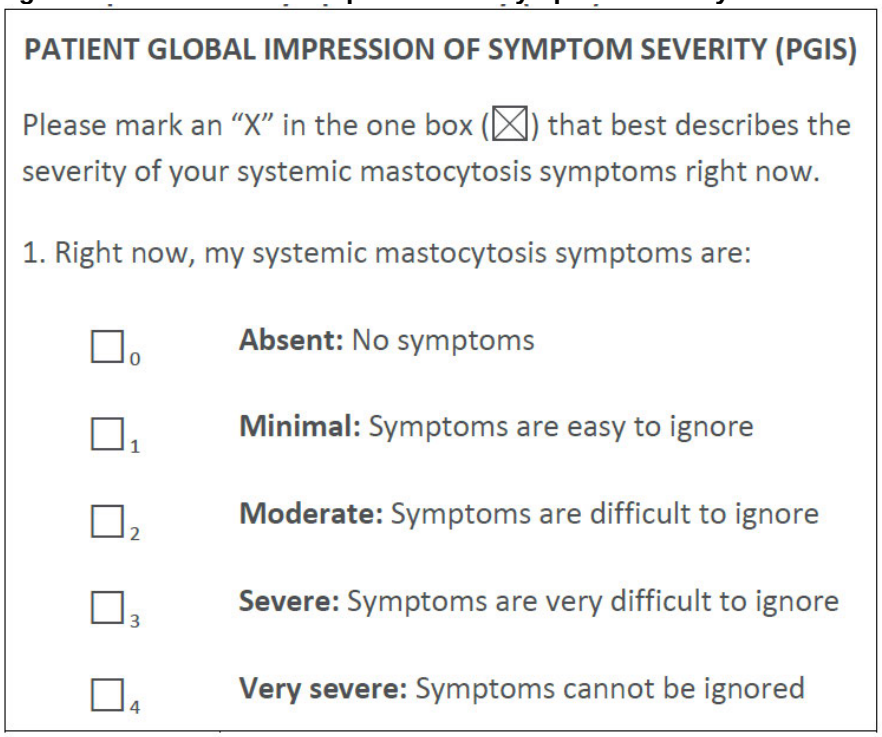
Please answer all of the questions and do not skip any. There are no right or wrong answers to any of the questions.

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 9. Over the past 24 hours, how severe was your worst brain fog? | 0 ☐ No brain fog | 1 ☐ | 2 ☐ | 3 ☐ | 4 ☐ | 5 ☐ | 6 ☐ | 7 ☐ | 8 ☐ | 9 ☐ | 10 ☐ Worst imaginable brain fog |
| 10. Over the past 24 hours, how severe was your worst headache? | 0 ☐ No headache | 1 ☐ | 2 ☐ | 3 ☐ | 4 ☐ | 5 ☐ | 6 ☐ | 7 ☐ | 8 ☐ | 9 ☐ | 10 ☐ Worst imaginable headache |
| 11. Over the past 24 hours, how many times did you have diarrhea? | _____ *(study participant to enter number)* | | | | | | | | | | |
| | *(If study participant selects "0" for Q11, please skip to questionnaire completion screen)* | | | | | | | | | | |
| 12. Over the past 24 hours, how severe was your worst diarrhea? | 0 ☐ No diarrhea | 1 ☐ | 2 ☐ | 3 ☐ | 4 ☐ | 5 ☐ | 6 ☐ | 7 ☐ | 8 ☐ | 9 ☐ | 10 ☐ Worst imaginable diarrhea |

Source: PRO Evidence Dossier

## 42.1.2. Anchor Scales Used for Evaluation of Meaningful Within-Subject Score Change

**Figure 31. Patient Global Impression of Symptom Severity**



**PATIENT GLOBAL IMPRESSION OF SYMPTOM SEVERITY (PGIS)**

Please mark an "X" in the one box (☒) that best describes the severity of your systemic mastocytosis symptoms right now.

1. Right now, my systemic mastocytosis symptoms are:

☐ 0 **Absent:** No symptoms

☐ 1 **Minimal:** Symptoms are easy to ignore

☐ 2 **Moderate:** Symptoms are difficult to ignore

☐ 3 **Severe:** Symptoms are very difficult to ignore

☐ 4 **Very severe:** Symptoms cannot be ignored

Source: PRO Evidence Dossier

**Figure 32. Patient Global Impression of Change**

**PATIENTS' GLOBAL IMPRESSION OF CHANGE (PGIC)**

Please mark an "X" in the one box (☒) that best describes the change in the state of your systemic mastocytosis right now.

**1. Since beginning treatment at this clinic, how would you describe the change (if any) in activity limitations, symptoms, emotions, and overall quality of life, related to your painful condition?**

| | |
|---|---|
| No change (or condition has got worse) | ☐ 1 |
| Almost the same, but hardly a change at all | ☐ 2 |
| A little better, but not noticeable change | ☐ 3 |
| Somewhat better, but the change has not made any real difference | ☐ 4 |
| Moderately better, but the change has not made any real difference | ☐ 5 |
| Better, and a definite improvement that has made a real and worthwhile difference | ☐ 6 |
| A great deal better, and a considerable improvement that has made all the difference | ☐ 7 |

**2. In a similar way, please circle the number below that matches your degree of change since beginning care at this clinic:**

Much Better — No Change — Much Worse

0 1 2 3 4 5 6 7 8 9 10

Source: PRO Evidence Dossier

# 43. Clinical Safety

## Safety Assessment

### Common Terminology Criteria for Adverse Events

Standard toxicity grading according to the Common Terminology Criteria for Adverse Events (CTCAE; Version 5.0) were used to grade AEs. Subjects were monitored according to the study schedule discussed in the Design Section (see above) of this review and which are shown in Table 58 of this review.

Additional safety analyses are shown below.

## Adverse Events by System Organ Class in Part 2 of Study 2203

**Table 61. Subjects With Adverse Events by System Organ Class, Safety Population, Study BLU-285-2203 Part 2**

| System Organ Class | Avapritinib 25 mg N=141 n (%) | Placebo N=71 n (%) | Avapritinib 25 mg vs. Placebo Risk Difference (%) (95% CI) |
|---|---|---|---|
| General disorders and administration site conditions | 51 (36.2) | 15 (21.1) | 15.0 (2.7, 27.4) * |
| Psychiatric disorders | 19 (13.5) | 4 (5.6) | 7.8 (0.1, 15.6) * |
| Vascular disorders | 28 (19.9) | 9 (12.7) | 7.2 (-3.0, 17.3) |
| Eye disorders | 28 (19.9) | 10 (14.1) | 5.8 (-4.7, 16.2) |
| Nervous system disorders | 54 (38.3) | 24 (33.8) | 4.5 (-9.1, 18.1) |
| Metabolism and nutrition disorders | 16 (11.3) | 5 (7.0) | 4.3 (-3.6, 12.2) |
| Renal and urinary disorders | 6 (4.3) | 0 | 4.3 (0.9, 7.6) * |
| Infections and infestations | 49 (34.8) | 22 (31.0) | 3.8 (-9.6, 17.1) |
| Investigations | 33 (23.4) | 14 (19.7) | 3.7 (-7.9, 15.3) |
| Ear and labyrinth disorders | 7 (5.0) | 1 (1.4) | 3.6 (-1.0, 8.1) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 4 (2.8) | 1 (1.4) | 1.4 (-2.4, 5.3) |
| Hepatobiliary disorders | 2 (1.4) | 0 | 1.4 (-0.5, 3.4) |
| Social circumstances | 2 (1.4) | 0 | 1.4 (-0.5, 3.4) |
| Skin and subcutaneous tissue disorders | 43 (30.5) | 21 (29.6) | 0.9 (-12.1, 14.0) |
| Respiratory, thoracic and mediastinal disorders | 17 (12.1) | 8 (11.3) | 0.8 (-8.3, 9.9) |
| Cardiac disorders | 11 (7.8) | 5 (7.0) | 0.8 (-6.7, 8.2) |
| Endocrine disorders | 1 (0.7) | 0 | 0.7 (-0.7, 2.1) |
| Reproductive system and breast disorders | 7 (5.0) | 4 (5.6) | -0.7 (-7.1, 5.8) |
| Congenital, familial and genetic disorders | 1 (0.7) | 1 (1.4) | -0.7 (-3.8, 2.4) |
| Gastrointestinal disorders | 52 (36.9) | 27 (38.0) | -1.1 (-15.0, 12.7) |
| Blood and lymphatic system disorders | 6 (4.3) | 4 (5.6) | -1.4 (-7.7, 4.9) |
| Immune system disorders | 10 (7.1) | 7 (9.9) | -2.8 (-10.9, 5.4) |
| Musculoskeletal and connective tissue disorders | 32 (22.7) | 19 (26.8) | -4.1 (-16.5, 8.3) |
| Injury, poisoning and procedural complications | 14 (9.9) | 10 (14.1) | -4.2 (-13.6, 5.3) |

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that occurred between the Part 2 D1 through a day prior to Part 3 D1 if subject rolled over to Part 3; through 30 days after the last dose if subject did not rollover to Part 3.
Duration is 24 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
For specific preferred terms, see the table “Subjects With Adverse Events by System Organ Class and Preferred Term…”
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; D, day; N, number of subjects in treatment arm; n, number of subjects with adverse event

## Adverse Events Leading to Drug Discontinuation in Part 2 of Study 2203

**Table 62. Listing of Subjects With Adverse Events Leading to Treatment Discontinuation From Study Drug, Safety Population, Study BLU-285-2203 Part 2**

| Study Arm | Subject ID | Dosage | MedDRA Preferred Term | Verbatim Term | SAE | AE Study Day of Onset/Stop | Study Day of Last Dose of Study Drug | Study Day of Discontinuation | Investigator's Assessment of Relatedness |
|---|---|---|---|---|---|---|---|---|---|
| Avapritinib 25 mg | (b) (6) | 25 mg | Disturbance in attention | Concentration impairment | N | 133, NA | 166 | 166 | Related |
| Avapritinib 25 mg | (b) (6) | 25 mg | Dyskinesia | Movements involuntary | N | 152, NA | 166 | 166 | Related |
| Avapritinib 25 mg | (b) (6) | 25 mg | Dizziness | Dizziness | N | 21, NA | 21 | 21 | Related |
| Avapritinib 25 mg | (b) (6) | 25 mg | Dyspnea | Dyspnea | N | 21, 21 | 21 | 21 | Not related |
| Avapritinib 25 mg | (b) (6) | 25 mg | Hypertension | Hypertension | N | 21, 29 | 21 | 21 | Not related |
| Avapritinib 25 mg | (b) (6) | 25 mg | Noncardiac chest pain | Non cardiac chest pain | N | 21, 21 | 21 | 21 | Not related |
| Avapritinib 25 mg | (b) (6) | 25 mg | Palpitations | Palpitations | N | 21, NA | 21 | 21 | Not related |
| Avapritinib 25 mg | (b) (6) | 25 mg | Acute myeloid leukemia | Acute myeloid leukemia | Y | 169, NA | 141 | 141 | Not related |
| Placebo | (b) (6) | NA | General physical health deterioration | Deterioration in general condition | N | 136, NA | 136 | 136 | Related |

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE that occurred between the Part 2 D1 through a day prior to Part 3 D1 if subject rolled over to Part 3; through 30 days after the last dose if subject did not rollover to Part 3.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is 24 weeks.
Relatedness is determined by investigator.
Abbreviations: AE, adverse event; D, day; ID, identifier; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event

### Adverse Events Leading to Drug Modification in Part 2 of Study 2203

In Part 2 of Study 2203, a lower proportion of subjects in the avapritinib arm had a dose modification compared to the placebo arm, 8.5% versus 12.7%, respectively. TEAEs leading to avapritinib dosing interruption or reduction are described below.

**Table 63. Treatment-Emergent Adverse Events Leading to Drug Modification**

| Adverse Event | Avapritinib Arm N=141 n (%) | Placebo Arm N=71 n (%) |
|---|---|---|
| Headache | 1 (0.7%) | 3 (4.2%) |
| COVID-19 | 1 (0.7%) | 1 (1.4%) |
| COVID-19 pneumonia | 1 (0.7%) | 1 (1.4%) |
| Diarrhea | 1 (0.7%) | 1 (1.4%) |
| Hypertension | 1 (0.7%) | 1 (1.4%) |
| Acute myeloid leukemia | 1 (0.7%) | 0 |
| Alanine aminotransferase increased | 1 (0.7%) | 0 |
| Anemia | 1 (0.7%) | 0 |
| Aspartate aminotransferase increased | 1 (0.7%) | 0 |
| Blood alkaline phosphatase increased | 1 (0.7%) | 0 |
| Disturbance in attention | 1 (0.7%) | 0 |
| Dizziness | 1 (0.7%) | 0 |
| Dyskinesia | 1 (0.7%) | 0 |
| Dyspnea | 1 (0.7%) | 0 |
| Electrocardiogram QT prolonged | 1 (0.7%) | 0 |
| Face edema | 1 (0.7%) | 0 |
| Hypokalemia | 1 (0.7%) | 0 |
| Memory impairment | 1 (0.7%) | 0 |
| Nausea | 1 (0.7%) | 0 |
| Neutrophil count decreased | 1 (0.7%) | 0 |
| Noncardiac chest pain | 1 (0.7%) | 0 |
| Norovirus test positive | 1 (0.7%) | 0 |
| Palpitations | 1 (0.7%) | 0 |
| Pelvic hematoma | 1 (0.7%) | 0 |
| Pneumonia | 1 (0.7%) | 0 |
| Vision blurred | 0 | 2 (2.8%) |
| Abdominal pain upper | 0 | 1 (1.4%) |
| Arthralgia | 0 | 1 (1.4%) |
| Eye pain | 0 | 1 (1.4%) |
| General physical health deterioration | 0 | 1 (1.4%) |
| Gingival bleeding | 0 | 1 (1.4%) |
| Hypertriglyceridemia | 0 | 1 (1.4%) |
| Muscular weakness | 0 | 1 (1.4%) |
| Pain in extremity | 0 | 1 (1.4%) |
| Procedural pain | 0 | 1 (1.4%) |

Source: Clinical reviewer

*Clinical reviewer comment: Adverse events leading to dose interruption considered related to avapritinib occurred in 5% of patients. ARs leading to dose interruption included pneumonia, pelvic hematoma, blood alkaline phosphatase increase, alanine aminotransferase increase,*

*aspartate aminotransferase increase, and face edema. All adverse reactions occurred in one patient each.*

*Headache was not considered drug-related as it occurred in a higher rate in the placebo group. In addition, avapritinib does not have a known risk of prolonged QT and the patient was on other medications (i.e., antihistamines). The events of neutropenia and anemia were also not related to avapritinib as the patient developed AML shortly after diagnosis. The event of hypokalemia was likely related to an event of diarrhea.*

**Analysis of Cognitive Disorder Adverse Events in Part 2 Study 2203**

Cognitive disorder is a grouped query term that contains disturbance in attention, mental impairment, memory impairment, depressed level of consciousness, coordination abnormal, and amnesia. Previously, with the approval of avapritinib for the GIST and AdvSM indications cognitive disorders were reported in 39% of the 749 subjects who received avapritinib. Cognitive TEAEs occurred in 28% of 148 subjects with AdvSM who received avapritinib. As noted in Section 33.6, Study 2203 there was a small proportional imbalance disfavoring avapritinib treated subjects compared to subjects who received placebo in terms of reported cognitive disorder adverse events, i.e., 7.1% subjects in the avapritinib treatment group compared to 5.6% subjects in the placebo group. In NDA 212608 supporting document 209 letter date May 4, 2023 (received May 4, 2023), in response to FDA proposed labeling changes regarding the ISM indication for avapritinib, the Applicant states that the preferred terms (PTs) selected for the Applicant's analysis of cognitive TEAEs in Study 2203 were based on the terms proposed by FDA noted above. As a result, the Applicant's search strategy was expanded and includes the following 20 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, encephalopathy, mental impairment, coordination abnormal, depressed level of consciousness, disturbance in attention. Consequentially, this updated the incidence rates of cognitive adverse reactions in the proposed label according to the Applicant to 7.8% for the avapritinib treatment group compared to 7.0% among with subjects in the placebo group.

*Reviewer comment: The clinical reviewer agrees with the Applicant's additional cognitive disorder query terms and analysis. Although the proportions of patients in either treatment group with cognitive disorder adverse reactions increased with additional query terms added to the analysis, overall, there is minimal difference in cognitive disorder adverse reactions among patients treated with avapritinib compared to patients who received placebo in Study 2203. However, given cognitive effects are a well described toxicity of avapritinib across indications, it is reasonably likely that cognitive effects will also occur in the ISM population.*

*The Applicant provided additional data during labeling negotiations in which the clinical reviewer confirmed the median time to onset of the first cognitive adverse reaction was 2.3 months (range: 0 to 5.4 months). Median time to improvement to grade 1 or complete resolution was 2.1 months.*

# 44. Clinical Virology

Not applicable.

# 45. Clinical Microbiology

Not applicable.

# 46. Mechanism of Action/Drug Resistance

Avapritinib is an orally administered inhibitor of the KIT exon 17 D816V Mutation. There is no apparent drug resistance.

# 47. Other Drug Development Considerations

None.

# 48. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

A Clinical Inspection Summary was completed by Dr. Anthony Orencia in the Division of Clinical Compliance Evaluation (Office of Scientific Investigations, (OSI)) final signature date May 15, 2023. Two clinical investigators, Jason Gotlib, M.D. (Stanford Hospital Clinics) and Cem Akin, M.D. (University of Michigan) were inspected because these study sites enrolled the largest proportion of subjects in the United States. The Summary states that a total of 14 subjects were screened and 12 subjects enrolled at Dr. Gotlib's and 25 subjects were screened and 14 subjects enrolled at Dr. Akin's study site. The Summary review states that the study sites entered all the adverse events directly from source records; there was no evidence of under-reporting of adverse events; the primary efficacy endpoint accuracy was not verified during the inspections; and no discrepancies were noted for data entered. The Summary review states no significant objectionable findings were found during the inspection; and a list of inspectional observations (Form FDA 483) was not issued by FDA at the close-out of the inspection for Dr. Gotlib's site. For Dr. Akin's site an FDA Form 483 was issued at the close-out of the site inspection, for not conducting the investigation according to plan. Specifically, for not obtain pregnancy tests for women of childbearing potential every 4 weeks as required by protocol in three subjects.

Dr. Orencia states in the Summary review that no known harms to subject's safety outcomes were found for study participants of childbearing age and that despite the above inspectional deficiency, data are considered reliable for this inspected site, and not considered significant. The final inspection report is currently pending, and an addendum of this summary will be filed by OSI reviewers if there are substantial and significant changes in the final Establishment Inspection Report.

*Reviewer comment: The clinical reviewer agrees with Dr. Orencia's recommendations and Clinical Inspection Summary review (final signature date May 15, 2023). The primary efficacy endpoint was not able to be verified during inspections because the subject completed a questionnaire that was sent directly to the Contract Research Organization in order to maintain*

*blinding. It should be noted that the clinical team had no concerns with the reporting of the primary endpoint (ISM-SAF TSS).*

# 49. Labeling: Key Changes and Considerations

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the currently approved PI. The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

**Table 64. Key Labeling Changes and Considerations**

| **Full PI Sections[1]** | **Rationale for Major Changes to Finalized PI[2] Compared to (FOR NDAs/BLAs: Applicant's Draft PI / FOR EFFICACY SUPPLEMENTS: Currently Approved PI and Applicant's Draft PI)** |
|---|---|
| BOXED WARNING | N/A |
| 1 INDICATIONS AND USAGE | New indication added for Indolent Systemic Mastocytosis.<br>A limitation of use was added "not recommended for the treatment of patients with ISM with platelet counts of less than 50 x $10^9$/L" |
| 2 DOSAGE AND ADMINISTRATION | "Child-Pugh C" added to define patients with severe hepatic impairment. |
| 4 CONTRAINDICATIONS | No change. |
| 5 WARNINGS AND PRECAUTIONS | New Warning added from previously approved supplement for "Photosensitivity".<br>Updated all warnings with data from ISM trial. |
| 6 ADVERSE REACTIONS | Added text to describe serious ARs, permanent discontinuations due to ARs, dosage interruptions due to ARs, most common ARs. Adverse reactions table modified to reflect ARs that occurred in at least 5% of patients and at least 2% more in the treatment arm (over placebo). Used FDA MedDRA Queries to avoid splitting similar clinical concepts and per current FDA policy. |
| 7 DRUG INTERACTIONS | (b) (4) |
| 8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment) | 8.3 Revised to reflect impact on infertility (irreversible) in males and females based on animal studies. |
| 9 DRUG ABUSE AND DEPENDENCE | n/a |
| 10 OVERDOSAGE | n/a |
| 12 CLINICAL PHARMACOLOGY | n/a |
| 13 NONCLINICAL TOXICOLOGY | The Applicant proposed (b) (4) The Division rejected most of the changes and revised for clarity and brevity. |

| Full PI Sections[1] | Rationale for Major Changes to Finalized PI[2] Compared to (FOR NDAs/BLAs: Applicant's Draft PI / FOR EFFICACY SUPPLEMENTS: Currently Approved PI and Applicant's Draft PI) |
|---|---|
| 14 CLINICAL STUDIES | The Agency recommended the Applicant (b) (4) to follow a format consistent with other labels.<br><br>The Agency recommended the Applicant not include (b) (4)<br><br>The Agency recommended the Applicant use the result based on the MCMC with the MAR (a prespecified sensitivity analysis method) for the primary endpoint in the label because this method uses the ITT population. The prespecified primary analysis method for the primary endpoint was based on observed cases, i.e., a mITT population.<br><br>The Agency recommended the Applicant remove (b) (4) |
| 17 PATIENT COUNSELING INFORMATION | Text added to describe photosensitivity. |
| Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) | n/a |

Source: Comparison of Applicant proposed labeling and final labeling.
[1] Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.
Abbreviation(s): ITT, intent-to-treat; ISM SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form MAR, missing at random; MCMC, Markov chain Monte Carlo; PI, Prescribing Information; TSS, total symptom score

# 49.1. Approved Labeling Types

Upon approval of this efficacy supplement, the following labeling documents will be FDA-approved:

- United States Prescribing Information
- Patient Information (Patient Package Insert)

# 50. Postmarketing Requirements and Commitments

No postmarketing requirements (PMRs) or postmarketing commitments (PMCs) are recommended based on this review.

# 51. Financial Disclosure

**Table 65. Covered Clinical Studies: Study BLU-285-2203**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 49 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6 | | |
| 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)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0<br>Significant payments of other sorts: *6 Reviewer comment: All six Investigators reported payments of other sorts made on or after February 2, 1999, from the Applicant of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria. The payments for the 6 investigators ranged from $26,895.67 up to $34,568.46. The Applicant notes that consensus review of study data by random assignment of 3 investigators was required from members of the Study Steering Committee (SSC) and/or Skin Assessment Committee (SAC) members. Also, Study 2203 was a double-blind study design where Investigators are not aware of treatment randomization in Parts1 and 2 of the study. Based on the totality of this information it is reasonably unlikely that data obtained from the 6 investigator sites for whom significant payments were reported would significantly influence the outcomes of the study.*<br>Proprietary interest in the product tested held by investigator: 0<br>Significant equity interest held by investigator: 0<br>Sponsor of covered study: 0 | | |
| 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): 49 | | |
| Is an attachment provided with the reason: | Yes ☒ | No ☐ (Request explanation from Applicant) |

Abbreviation: FDA, Food and Drug Administration

# 52. References

Al-Share, B, A Alloghbi, MN Al Hallak, H Uddin, A Azmi, RM Mohammad, SH Kim, AF Shields, and PA Philip, 2021, Gastrointestinal stromal tumor: a review of current and emerging therapies, Cancer Metastasis Rev, 40(2):625-641.

Alvarez-Twose, I, A Matito, JM Morgado, L Sánchez-Muñoz, M Jara-Acevedo, A García-Montero, A Mayado, C Caldas, C Teodósio, JI Muñoz-González, M Mollejo, L Escribano, and A Orfao, 2017, Imatinib in systemic mastocytosis: a phase IV clinical trial in patients lacking exon 17 KIT mutations and review of the literature, Oncotarget, 8(40):68950-68963.

Bista, A, D Uprety, Y Vallatharasu, L Arjyal, S Ghimire, M Giri, and L Rosenstein, 2018, Systemic Mastocytosis in United States: A Population Based Study, Blood, 132:1830.

Horny, HP, K Sotlar, P Valent, and K Hartmann, 2008, Mastocytosis: a disease of the hematopoietic stem cell, Dtsch Arztebl Int, 105(40):686-692.

Mikkelsen, CS, A Nybo, KB Arvesen, and J Holk-Poulsen, 2014, Delayed diagnosis of adult indolent systemic mastocytosis, Dermatol Reports, 6(1):5199.

Padilla, B, AL Shields, F Taylor, X Li, J McDonald, T Green, AL Boral, HM Lin, C Akin, F Siebenhaar, and B Mar, 2021, Psychometric evaluation of the Indolent Systemic Mastocytosis Symptom Assessment Form (ISM-SAF) in a phase 2 clinical study, Orphanet J Rare Dis, 16(1):434.

Pardanani, A, 2013, How I treat patients with indolent and smoldering mastocytosis (rare conditions but difficult to manage), Blood, 121(16):3085-3094.

Pardanani, A, 2019, Systemic mastocytosis in adults: 2019 update on diagnosis, risk stratification and management, Am J Hematol, 94(3):363-377.

van Anrooij, B, JNG Oude Elberink, LFR Span, JGR de Monchy, S Rosati, AB Mulder, and JC Kluin-Nelemans, 2018, Midostaurin in patients with indolent systemic mastocytosis: An open-label phase 2 trial, J Allergy Clin Immunol, 142(3):1006-1008.e1007.

# 53. Review Team

**Table 66. Reviewers of Integrated Assessment**

| Role | Name(s) |
|---|---|
| Regulatory project manager | Bijal Patel |
| Nonclinical reviewer | Bo Lee |
| Nonclinical team leader | Pedro DelValle |
| OCP reviewer(s) | Anusha Ande, Guansheng Lui |
| OCP team leader(s) | Sudharshan Hariharan, Jiang Liu |
| Clinical reviewer | Andrew Dmytrijuk |
| Clinical team leader | Carrie Diamond |
| Biometrics reviewer | Huan Wang |
| Biometrics team leader | Lola Luo |
| Cross-disciplinary team leader | Carrie Diamond |
| Division director (pharm/tox) | Todd Bourcier |
| Division director (OCP) | Shirley Seo |
| Division director (OB) | Yeh-Fong Chen |
| Division director (clinical) | Ann Farrell |
| Office director (or designated signatory authority) | Ann Farrell |

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

**Table 67. Additional Reviewers of Application**

| Office or Discipline | Name(s) |
|---|---|
| OPQ | Qi Charles Liu, Ramesh Raghavachari |
| Associate Director for Labeling | Virginia Kwitkowski |
| DCOA | Qing Xie, Selena Daniels |
| PFSS | Lili Garrard, Weimeng Wang |
| Microbiology | N/A |
| OPDP | Rebecca Falter |
| OSI | Anthony Orencia, Min Lu |
| OSE/DEPI | N/A |
| OSE/DMEPA | Sue Black, Sali Mahmoud, Hina Mehta |
| OSE/DRISK | N/A |
| Other | Susan Redwood, Barbara Fuller |

Abbreviations: OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management

## 53.1. Reviewer Signatures

Please see next page.

# 53.2. Reviewer Signatures

**Table 53-68 Signatures of Reviewers**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Clinical Pharmacology Discipline<br>Secondary Reviewer | Sudharshan Hariharan<br>OCP<br>DCEP | Sections: 5.2, 6.1, 8.1, 8.2, 14 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature:** **Sudharshan Hariharan**

**Digitally signed by Sudharshan Hariharan**

**Date: 5/19/2023 2:57 PM EDT**
**GUID: 2023519185725**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Clinical Discipline<br>Secondary Reviewer | Carrie Diamond<br>OCHEN<br>DNH | Sections: 1-4, 6, 7, 8-12, 15-16, 17-19, 20-21, 23-36 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature:** **Carrie Diamond**

**Digitally signed by Carrie Diamond**

**Date: 5/19/2023 2:58 PM EDT**
**GUID: 2023519185826**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Regulatory Project Manager Discipline<br>Secondary Reviewer | Julie Van Der Waag<br>ORO<br>DROCHEN | Sections: 12 | Based on my assessment of the application:<br>☐ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☒ Not applicable. | |

**Signature: Julie Van Der Waag**

**Digitally signed by Julie Van Der Waag**

**Date: 5/19/2023 2:59 PM EDT**
**GUID: 202351918597**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Regulatory Project Manager Discipline<br>Primary Reviewer | Bijal Patel<br>ORO<br>DROCHEN | Sections: Regulatory History | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Bijal Patel**

**Digitally signed by Bijal Patel**

**Date: 5/19/2023 3:00 PM EDT**
**GUID: 202351919017**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Consultant Discipline<br>Primary Reviewer | Weimeng Wang<br>OB<br>DBIII | Sections: 6.3.3 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Weimeng Wang**

**Digitally signed by Weimeng Wang**

**Date: 5/19/2023 3:09 PM EDT**
**GUID: 202351919939**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Clinical Outcomes Assessment Reviewer Discipline<br>Secondary Reviewer | Selena Daniels<br>ODES<br>DCOA | Sections: 4, 6.2.1.2, 6.3.2, 6.3.3, 16 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Selena Daniels**

**Digitally signed by Selena Daniels**

**Date: 5/19/2023 3:12 PM EDT**
**GUID: 2023519191253**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Biostatistics Discipline<br>Primary Reviewer | Huan Wang<br>OB<br>DBIX | Sections: 6, 23 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Huan Wang**

**Digitally signed by Huan Wang**

**Date: 5/19/2023 3:18 PM EDT**
**GUID: 2023519191828**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Biostatistics Discipline<br>Secondary Reviewer | Yeh Fong Chen<br>OB<br>DBIX | Sections: 6, 23 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Yeh Fong Chen**

**Digitally signed by Yeh Fong Chen**

**Date: 5/19/2023 3:19 PM EDT**
**GUID: 2023519191926**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Clinical Outcomes Assessment Reviewer Discipline<br>Primary Reviewer | Qing Xie<br>ODES<br>DCOA | Sections: 6.2.1.2, 6.3.2, 6.3.3, 16.1 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Qing Xie**

**Digitally signed by Qing Xie**

**Date: 5/19/2023 4:00 PM EDT**
**GUID: 20235192002**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Pharm-tox/Non-clinical Discipline<br>Primary Reviewer | Bo Yeon Lee<br>OCHEN<br>DPTCHEN | Sections: 5.1, 7.1, 8.4, 13 | Based on my assessment of the application:<br>☐ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☒ Not applicable. | |

**Signature: Bo Yeon Lee**

**Digitally signed by Bo Yeon Lee**

**Date: 5/19/2023 5:26 PM EDT**
**GUID: 2023519212652**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Clinical Pharmacology Discipline<br>Primary Reviewer | Anusha Ande<br>OCP<br>DCEP | Sections: 5,6,8,14 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Anusha Ande**

**Digitally signed by Anusha Ande**

**Date: 5/20/2023 12:24 AM EDT**
**GUID: 202352042434**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Clinical Outcomes Assessment Reviewer Discipline<br>Division Signatory | David Reasner<br>ODES<br>DCOA | Sections: 6.2.1.2, 6.3.2, 6.3.3, 16.1 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: David Reasner**

**Digitally signed by David Reasner**

**Date: 5/21/2023 10:17 AM EDT**
**GUID: 2023521141718**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Associate Director for Labeling Discipline<br>Primary Reviewer | Virginia Kwitkowski<br>OCHEN<br>DNH | Sections: 23 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Virginia Kwitkowski**

**Digitally signed by Virginia Kwitkowski**

**Date: 5/22/2023 8:50 AM EDT**
**GUID: 2023522125032**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Associate Director for Labeling Discipline<br>Secondary Reviewer | Virginia Kwitkowski<br>OCHEN<br>DNH | Sections: 23 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Virginia Kwitkowski**

**Digitally signed by Virginia Kwitkowski**

**Date: 5/22/2023 8:51 AM EDT**
**GUID: 202352212510**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Consultant Discipline<br>Secondary Reviewer | Lili Garrard<br>OB<br>DBIII | Sections: 6.3.3 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Lili Garrard**

**Digitally signed by Lili Garrard**

**Date: 5/22/2023 9:10 AM EDT**
**GUID: 2023522131052**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Pharm-tox/Non-clinical Discipline<br>Secondary Reviewer | Todd Bourcier<br>OCHEN<br>DPTCHEN | Sections: 5.1, 13 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Todd Bourcier**

**Digitally signed by Todd Bourcier**

**Date: 5/22/2023 9:54 AM EDT**
**GUID: 2023522135434**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Clinical Discipline<br>Primary Reviewer | Andrew Dmytrijuk<br>OCHEN<br>DNH | Sections: 1-4, 6, 7, 8-12, 15-16, 17-19, 20-21, 23-36 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Andrew Dmytrijuk**

**Digitally signed by Andrew Dmytrijuk**

**Date: 5/22/2023 10:38 AM EDT**
**GUID: 2023522143841**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Biostatistics Discipline<br>Division Signatory | Yuan Shen<br>OB<br>DBIX | Sections: 6,23 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Yuan Shen**

**Digitally signed by Yuan Shen**

**Date: 5/22/2023 10:53 AM EDT**
**GUID: 202352214538**

| Discipline and Role | Reviewer Name, Office/Center, and Division | Sections Authored in Full or in Part | Recommendation to Signatory | Comments on Recommendation to Signatory |
|---|---|---|---|---|
| Biostatistics Discipline<br>Division Signatory | Yuan Shen<br>OB<br>DBIX | Sections: 6,23 | Based on my assessment of the application:<br>☒ No deficiencies preclude approval.<br>☐ Deficiencies preclude approval.<br>☐ Not applicable. | |

**Signature: Yuan Shen**

**Digitally signed by Yuan Shen**

**Date: 5/22/2023 11:02 AM EDT**
**GUID: 202352215231**

---

**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/

---

CARRIE E DIAMOND
05/22/2023 11:02:45 AM

ANN T FARRELL
05/22/2023 12:26:09 PM

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 212608Orig1s013

# CHEMISTRY REVIEW(S)

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

1. **NDA Supplement Number:** NDA-212608-SUPPL-013
   **sNDA Recommendation:** Approval
   **sNDA Managed by:** OND

2. **Submission(s) Being Reviewed**:

| Submission | Type | Submission Date | CDER Stamp Date | Assigned Date | PDUFA Goal Date | Review Date |
|---|---|---|---|---|---|---|
| Original Supplement | PA | 11/22/2022 | 11/22/2022 | 01/03/2023 | 05/22/2023 | 01/09/2023 |

3. **Provides For:**
   The efficacy supplement is proposing to expand the indication to include the treatment of patients with ISM at the recommended dose of 25 mg QD based on the efficacy and safety data from Part 2 of Study BLU-285-2203 (PIONEER).

4. **Review #**: 01

5. **Clinical Review Division**: OOD/DO3

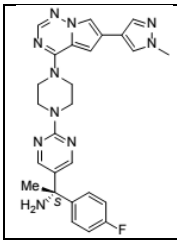
6. **Name and Address of Applicant**:
   Blueprint Medicines Corporation
   45 Sidney Street
   Cambridge, MA, USA 02139

   Contact: Elisabeth Garrison, Pharm.D, MS, Associate Director, Global Regulatory Sciences
   Phone: (b) (6)
   Email: egarrison@blueprintmedicines.com

7. **Drug Product**:

| Drug Name | Dosage Form | Strength | Route of Administration | Rx or OTC | Special Product | Orphan Designation |
|---|---|---|---|---|---|---|
| AYVAKIT™ (avapritinib) | Tablets | 25 mg | Oral | Rx | Yes | 15-5065 |

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

| | |
|---|---|
|  | **USAN:** Avapritinib<br>**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<br>**Molecular formula:** $C_{26}H_{27}FN_{10}$<br>**MW:** 498.57 g/mol |

9. **Indication**:

- Indolent Systemic Mastocytosis (ISM).

**10. Supporting/Related Documents**: none

**11. Disciplines/Consults**: none

**12. Executive Summary**:

This efficacy supplement is proposing to expand the indication to include the treatment of patients with ISM at the recommended dose of 25 mg QD based on the efficacy and safety data from Part 2 of Study BLU-285-2203 (PIONEER).

The applicant has claimed categorical exclusion from the determination of an environmental assessment under 21 CFR Part 25.31 (b). Following approval, the use of the active moiety will increase, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. Based upon peak year (2023) production forecast of (b) (4) avapritinib, the EIC (aquatic) = (b) (4) (or (b) (4) ppb), which is significantly less than 1 ppb. To the applicant's knowledge, no extraordinary circumstances exist by which the proposed use of avapritinib may significantly affect the quality of the human environment. Therefore, the request for categorical exclusion may be granted.

The supplement provides updated PI and carton and container labels for 25 mg strength.
There are no proposed changes to the CMC section 3, 11 and 16.
From a CMC perspective the changes proposed in S013 are acceptable.

**13. Conclusions & Recommendations**:

This supplement is recommended for approval.

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

**15. Primary Reviewer**:

Qi Liu, Ph.D., CMC reviewer, Branch 1, DPMAI, OLDP, OPQ

**16. Secondary Reviewer**:

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

Qi Charles Liu

Digitally signed by Qi Charles Liu
Date: 1/09/2023 03:37:17PM
GUID: 53b4299e000120abe375af2240eda3f5

Ramesh Raghavachari

Digitally signed by Ramesh Raghavachari
Date: 1/10/2023 03:27:27PM
GUID: 502d0913000029f375128b0de8c50020

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 212608Orig1s013

# OTHER REVIEW(S)

# CLINICAL INSPECTION SUMMARY

| | |
|---|---|
| **Date** | May 15, 2023 |
| **From** | Anthony Orencia, M.D., Ph.D., F.A.C.P., Medical Officer<br>Min Lu, M.D., M.P.H., Team Leader<br>Jenn Sellers, M.D., Ph.D., F.A.A.P., Branch Chief<br>Good Clinical Practice Assessment Branch<br>Division of Clinical Compliance Evaluation<br>Office of Scientific Investigations |
| **To** | Andrew Dmytrijuk, M.D., Medical Officer<br>Carrie Diamond, M.D., Medical Team Leader<br>Ann Farrell, M.D., Division Director<br>Bijal Patel, Pharm.D., Regulatory Health Project Manager<br>Division of Nonmalignant Hematology (DNH)<br>Office of Cardiovascular, Hematology, Endocrinology and Nephrology Drugs (OCHEN) |
| **NDA** | NDA 212608 S-013 |
| **Applicant** | Blueprint Medicines Corp. |
| **Drug** | Ayvakit® (avapritinib) |
| **NME** | No |
| **Division Classification** | Kinase inhibitor that targets KIT D816V and other KIT exon17 mutations. |
| **Proposed Indications** | Treatment of patients with indolent systemic mastocytosis |
| **Review Type** | Priority Review |
| **Consultation Request Date** | January 23, 2023 |
| **Summary Goal Date** | May 18, 2023 |
| **Action Goal Date** | May 19, 2023 |
| **PDUFA Date** | May 22, 2023 |

## I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study BLU-285-2203 were submitted to the Agency in support of a New Drug Application (NDA) supplement for avapritinib, proposed for the treatment of patients with indolent systemic mastocytosis. Two clinical investigators, Jason Gotlib, M.D. and Cem Akin, M.D., were inspected.

Based on the inspection results, the study appears to have been conducted adequately and the study data derived from these clinical investigator sites are considered reliable. The data from Study BLU285-2203 submitted to the Agency for assessment appear acceptable in support of the proposed indication.

# I. BACKGROUND

Systemic mastocytosis (SM) is a clonal disorder of neoplastic mast cells (MCs). The disease composite, (a) aggressive systemic mastocytosis (ASM), (b) systemic mastocytosis (SM) with associated hematologic neoplasm (SM-AHN), and (c) mast cell leukemia (MCL), together are referred to as advanced systemic mastocytosis (advanced SM). Systemic mastocytosis is a rare, clonal mast cell neoplasm driven by the KIT D816V mutation, which occurs in 93% of patients with systemic mastocytosis.

A less common subset, indolent systemic mastocytosis (ISM) with a single B finding (refers to organ involvement without organ failure) remains indolent systemic mastocytosis. However, if two or more B findings are detected, the diagnosis changes to smoldering systemic mastocytosis.

Avapritinib as a kinase inhibitor targets KIT D816V and other KIT exon17 mutations.

AYVAKIT® was approved in January 2020 for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) indication, and marketed as 100 mg, 200 mg and 300 mg film-coated tablets for oral administration. Treatment of advanced systemic mastocytosis and smoldering systemic mastocytosis received FDA approval in June 2021. Unlike the recommended daily dose of 300 mg for the GIST indication, the recommended avapritinib recommended daily dose for advanced systemic mastocytosis is 200 mg.

Avapritinib received Breakthrough Therapy Designation on December 23. 2020 for the treatment of patients with indolent systemic mastocytosis and Orphan Drug Designation (ODD #15-5065) for the treatment of mastocytosis. In this sNDA, Blueprint (applicant) proposes avapritinib for the treatment of patients with indolent systemic mastocytosis at the recommended dose of 25 mg QD based on the efficacy and safety data from Part 2 of Study BLU-285-2203 (PIONEER).

**Study BLU-285-2203**

Study BLU-285-2203 was a three-part, Phase 2, randomized, double-blind, placebo-controlled study comparing the efficacy and safety of avapritinib in combination with best supportive to placebo in combination with best supportive care in subjects with indolent systemic mastocytosis whose symptoms were not adequately controlled by best supportive care. The study was conducted in 3 parts. In Part 1, the optimal dose of avapritinib was identified in subjects with indolent systemic mastocytosis. In Part 2, subjects with indolent systemic mastocytosis were randomly assigned in 2:1 ratio to the avapritinib recommended Phase 2 dose identified in Part 1 in combination with best supportive care, or to placebo in combination with best supportive care. In Part 3, subjects who completed treatment in Part 1 or Part 2 of the study participated in a long-term extension, receiving avapritinib at the recommended Phase 2 dose in combination with best supportive care.

The primary study objectives were the following (a) Part 1 to determine the recommended Phase 2 dose of avapritinib in subjects with indolent systemic mastocytosis for use in Part 2 and Part 3 in Study BLU-285-2203. Part 2 was to determine mean change in Indolent Systemic Mastocytosis-Symptom Assessment Form (ISM-SAF) total symptom score (TSS) from baseline to Cycle 7, treatment day 1 (C7D1), compared to placebo, and Part 3 was to assess the long-term safety and efficacy of avapritinib in indolent systemic mastocytosis subjects.

Treatment duration involved the following schedule: For Part 1 of the study: avapritinib (25, 50, or 100 mg) or placebo was administered in 28-day cycles for at least 12 weeks before rolling over to Part 3. For Part 2 of the study: avapritinib recommended phase II dose (25 mg) or placebo was administered in 28-day cycles for six cycles (24 weeks). After completion of six cycles of treatment (C7D1) and all post-C7D1 study procedures, subjects rolled over to Part 3 of the study where all subjects had the opportunity to receive 25 mg avapritinib QD in an open-label fashion. For Part 3 of the study: avapritinib 25 mg is administered for up to five years, in 28-day cycles, inclusive of Part 1 and Part 2.

Forty-two sites enrolled subjects and entered data for this study, including 19 sites in North America, 20 sites in Europe, and 3 sites in the United Kingdom. The first subject enrolled (C1D1) on April 16, 2019, and the last subject enrolled (C1D1) on January 6, 2022. The data cut-off date for the interim analysis was on June 23, 2022.

The study comprised 39 subjects (9 subjects in placebo, 10 subjects in each group of avapritinib 25 mg, 50 mg and 100 mg) in Part 1 and 212 subjects (71 subjects in placebo and 141 in 25 mg avapritinib group) in Part 2.

The primary efficacy endpoint was the change in Indolent Systemic Mastocytosis-Symptom Assessment Form (ISM-SAF) total symptom score (TSS) from baseline to Cycle 7, treatment day 1 (C7D1), compared to placebo.

For purposes of site inspections, per the review division, data verification focused on the Part 2 of the study safety profile of avapritinib as assessed by the type, frequency, severity, timing, and relationship to study drug of any adverse events, serious adverse events, and overall subject safety status. Primary efficacy endpoint raw data was not generated nor directly collected by the clinical study site; thus, precluding clinical site verification of site-level efficacy data for this application supplement.

## II. RESULTS (by site)

**1. Jason Gotlib, M.D./ Site 20-06**
Stanford Hospital Clinics – Stanford Cancer Institute
875 Blake Wilbur Drive
Stanford, CA 94305

Inspection dates: February 13 to 17, 2023

For Part 2 of the study, a total of 14 subjects were screened and 12 subjects enrolled. Three subjects discontinued while on study (two study subjects due to non-compliance and one subject withdrew further participation).

Regulatory and source documents were reviewed. The audit involved a review of records and procedures related to the clinical trial protocol and its amendments; subject selection criteria and consenting; test article controls, including accountability; source data evaluation, adverse event reporting, including assessment of under-reporting of serious adverse events, and laboratory testing.

Source records generally included original records or certified copies of original records. There was adequate documentation to ensure that all subjects were alive and available for the duration of their stated participation in the study. Source records for all enrolled study subjects were examined and verifiable. Records were noted to be complete, legible, and organized. Study activities were conducted in compliance with the protocol.
The study site entered all the adverse events directly from source records. Serious adverse events were reported within 24 hours.

There was no evidence of under-reporting of adverse events. No discrepancies were noted.

The primary efficacy endpoint was not verified during the inspection. The site did not provide the scores because they were blinded to the subject data. The site ensured that the subject completed the questionnaires, but the data were sent directly to the Contract Research Organization and processed. The site was not involved in providing the change in baseline to Cycle 7 Day 1 or the total symptom score (TSS) as calculated by the Contract Research Organization. The subject line listings contained individual Symptom Assessment Form (ISM-SAF) scores; however, the site did not have access to this information, which was reported directly to the CRO/sponsor.

No significant objectionable findings were found during the inspection. A list of inspectional observations (Form FDA 483) was not issued by FDA at the close-out of the inspection.

**2. Cem Akin, M.D./Site 20-09**
University of Michigan
300 River Place, Suite 5900
Detroit, MI 48207

Inspection dates: May 3 to 10, 2023

Of the 25 subjects screened, 14 enrolled and 12 are currently active in Part 3 of the study. There were two participants who discontinued from the study: one subject was discontinued due to adverse events, and one subject was withdrew from the study.

Institutional Review Board approvals, study correspondence, drug accountability, facility adequacy, staff qualifications, and monitoring procedures were reviewed. This inspection covered the safety of study subjects all study participants' adverse event records, along with serious adverse event reporting, protocol deviations, subject eligibility, overall protocol compliance, and the verification of source documentation related to study endpoint criteria.

Adverse event and serious adverse reporting appeared adequate and consistent with the study protocol requirement and the case report form reports. The site added multiple adverse events to the electronic data capture database after the initial cut-off date for analyses, but there was no evidence of underreporting.

The primary efficacy endpoint accuracy was not verified during the inspection. The efficacy data were collected via multiple questionnaires completed on hand-held devices. The data collected was not seen by the clinical investigator and site staff; these data were directly accessed by the sponsor.

An FDA Form 483 was issued at the close-out of the site inspection, for not conducting the investigation according to plan. Specifically, for not obtain pregnancy tests for women of childbearing potential every 4 weeks as required by protocol in three subjects:

a) 8 of 16 pregnancy tests for Subject # (b) (6) were performed late. For example, 3 tests were delayed by 22 weeks, 13 weeks, and 10 weeks.

b) 7 of 19 pregnancy tests for Subject # (b) (6) were performed late. For example, 3 tests were delayed by 13 weeks, and 12 weeks and 2 weeks.

c) 9 of 19 pregnancy tests for subject (b) (6) were performed late. For example, 3 tests were delayed by 12 weeks, 11 weeks, and 11 weeks.

*Reviewer's Comments:*
*No known harms to subject's safety outcomes were found for study participants of child-bearing age. The above inspectional findings were discussed with DHP, in their ongoing reviews.*

Despite the above inspectional deficiency, data are considered reliable for this inspected site, and not considered significant. The final inspection report is currently pending, and an addendum of this summary will be filed if there are substantial and significant changes in the final Establishment Inspection Report.

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

CONCURRENCE:

*{See appended electronic signature page}*
Min Lu, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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

---

**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/

---

ANTHONY J ORENCIA
05/15/2023 04:13:37 PM

MIN LU
05/15/2023 04:15:42 PM

JENN W SELLERS
05/15/2023 04:18:44 PM

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

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

# Memorandum

**Date:** April 18, 2023

**To:** Bijal Patel, MS, Regulatory Project Manager,
Non-malignant Hematology (DNH)

Virginia Kwitkowski, MS, ACNP-BC, Associate Director for Labeling, DNH

**From:** Rebecca Falter, PharmD, BCACP, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

**CC:** Emily Dvorsky, PharmD, RAC, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for AYVAKIT® (avapritinib) tablets, for oral use

**NDA**: 212608, S-013

---

**Background:** In response to DNH's consult request dated December 13, 2022, OPDP has reviewed the proposed Prescribing Information (PI) and Patient Package Insert (PPI) for supplement-013 for for AYVAKIT® (avapritinib) tablets, for oral use (Ayvakit). This supplement proposes a new indication for the treatment of adult patients with indolent systemic mastocytosis.

**PI/PPI:** OPDP's review of the proposed PI is based on the draft labeling accessed from DNH's SharePoint on April 12, 2023, and our comments are provided below.

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

Thank you for your consult. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

33 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

---

/s/

---

REBECCA A FALTER
04/18/2023 01:19:44 PM

**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 18, 2023 |
| To: | Bijal Patel, MS<br>Regulatory Project Manager<br>**Division of Non-Malignant Hematology (DNH)** |
| Through: | LaShawn Griffiths, MSHS-PH, BSN, RN<br>Associate Director for Patient Labeling<br>**Division of Medical Policy Programs (DMPP)**<br><br>Ruth Mayrosh, PharmD<br>Senior Patient Labeling Reviewer<br>**Division of Medical Policy Programs (DMPP)** |
| From: | Susan Redwood, MPH, BSN, RN<br>Patient Labeling Reviewer<br>**Division of Medical Policy Programs (DMPP)**<br><br>Rebecca Falter, PharmD<br>Regulatory Review Officer<br>**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-013 |
| Applicant: | Blueprint Medicines Corporation |

# 1 INTRODUCTION

On November 22, 2022, Blueprint Medicines Corporation submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy to their approved New Drug Application (NDA) 212608/S-013 for AYVAKIT (avapritinib) tablets. With this supplement, the Applicant proposes a new indication for the treatment of adult patients with indolent systemic mastocytosis (ISM).

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 (DNH) on December 13, 2022 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for AYVAKIT (avapritinib) tablets.

# 2 MATERIAL REVIEWED

- Draft AYVAKIT (avapritinib) tablets PPI received on November 22, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 11, 2023.
- Draft AYVAKIT (avapritinib) tablets Prescribing Information (PI) received on November 22, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 11, 2023.

# 3 REVIEW METHODS

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

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.

6 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

---

/s/

---

SUSAN W REDWOOD
04/18/2023 01:34:37 PM

REBECCA A FALTER
04/18/2023 01:38:38 PM

RUTH I MAYROSH
04/18/2023 01:47:51 PM

LASHAWN M GRIFFITHS
04/18/2023 01:57:39 PM

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

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

| | |
|---|---|
| Date of This Review: | March 8, 2023 |
| Requesting Office or Division: | Division of Non-Malignant Hematology (DNH) |
| Application Type and Number: | NDA 212608/S-013 |
| Product Name, Dosage Form, and Strength: | Ayvakit (avapritinib) tablet, 25 mg, 50 mg, 100 mg, 200 mg and 300 mg |
| Product Type: | Single Ingredient Product |
| Rx or OTC: | Prescription (Rx) |
| Applicant/Sponsor Name: | Blueprint Medicines Corporation (Blueprint) |
| FDA Received Date: | 11/22/2022 |
| TTT ID #: | 2022-2924 |
| DMEPA 2 Safety Evaluator: | Sue Black, PharmD |
| DMEPA 2 Team Leader: | Hina Mehta, PharmD |

# 1 REASON FOR REVIEW

Blueprint Medicines Corporation (Blueprint) submitted a supplemental New Drug Application (sNDA) for Ayvakit (avapritinib) tablet proposing to expand the indication to include the treatment of patients with indolent systemic mastocytosis (ISM) at the recommended dose of 25 mg daily based on the efficacy and safety data from Part 2 of Study BLU-285-2203 (PIONEER). In addition, as part of a postmarketing requirement (PMR), Blueprint submitted a clinical study report for Study BLU-285-0107 which evaluated the effect of severe hepatic impairment on the pharmacokinetics (PK) of avapritinib. We reviewed the proposed Ayvakit prescribing information (PI), container label and carton labeling for the 25 mg tablet for areas of vulnerability that may lead to medication errors.

## 1.1 BACKGROUND INFORMATION

Ayvakit (avapritinib) tablets was approved on January 9, 2020 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. In addition, on June 16, 2021, Ayvakit (avapritinib) tablets was approved for the treatment of adult patients with advanced systemic mastocytosis (AdvSM), including patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL). Ayvakit (avapritinib) is currently marketed as 25 mg, 50 mg, 100 mg, 200 mg and 300 mg film-coated tablets for oral administration.

# 2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Review

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

N/A=not applicable for this review

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

# 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Blueprint is proposing to expand the indication to include the treatment of patients with indolent systemic mastocytosis (ISM) at the recommended dose of 25 mg daily based on the efficacy and safety data from Part 2 of Study BLU-285-2203 (PIONEER). In addition, as part of a postmarketing requirement (PMR), Blueprint submitted a clinical study report for Study BLU-285-0107 which evaluated the effect of severe hepatic impairment on the pharmacokinetics (PK) of avapritinib. We note the 25 mg strength tablet is currently marketed as the recommended third dose reduction for adverse reactions in patients with AdvSM. We performed a risk assessment of the proposed PI, container label and carton labeling for the 25 mg tablet to identify deficiencies that may lead to medication errors and other areas of improvement.

We note that the Dosage and Administration section for Ayvakit PI was revised to add dosage information for new indication of ISM (including information regarding concomitant use of CYP3A inhibitors) and dosage modifications for severe hepatic impairment in patients with GIST, AdvSM and ISM. In addition, (b) (4)

We reviewed the proposed edits and identified areas that could be revised to improve clarity. We provide our recommendations in Section 4.1 for the Division to include a description of severe hepatic impairment, (b) (4) and to revise the word "dose" to read "dosage."

We noted that there are no edits to Section 3 Dosage Forms and Strengths and Section 16 How Supplied/Storage and Handling.

We note Section 17 Patient Counseling Information was revised to update information for (b) (4) infertility. We find the proposed edits acceptable from a medication error perspective.

Our review of the container label and carton labeling for the 25 mg tablet identified they were the same as compared to the currently approved container labels and carton labeling for the 25 mg tablet and are acceptable from a medication error perspective.

## 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 submitted container label and carton labeling for the 25 mg tablets are acceptable from a medication error perspective, and have no recommendations at this time.

### 4.1 RECOMMENDATIONS FOR DIVISION OF NON-MALIGNANT HEMATOLOGY (DNH)

A. Highlights of Prescribing Information

1. Dosage and Administration

a. We recommend including a description of severe hepatic impairment. Consider revising to "Patients with Severe Hepatic Impairment (Child-Pugh Class C): Reduce the dosage of AYVAKIT.".

B. Prescribing Information

1. Section 2: Dosage and Administration

a. We recommend [redacted] (similar to currently approved). For example, consider the following revisions:

i. [redacted]

ii. [redacted]

i. Retitle Section 2.5 from [redacted] to "Section 2.5 Dosage Modifications for Adverse Reactions" and include the following:

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

Table 1: Recommended Dosage Reductions for AYVAKIT for Adverse Reactions

| Dose Reduction Level | Dosage in patients with GIST* | Dosage in patients with AdvSM† |
|---|---|---|
| First dose reduction | 200 mg once daily | 100 mg once daily |
| Second dose reduction | 100 mg once daily | 50 mg once daily |
| Third dose reduction | - | 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 × $10^9$/L | Interrupt AYVAKIT until platelet count is ≥ 50 × $10^9$/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

ii. Re-number and revise sections 2.6 and 2.7 to "2.6 Concomitant Use of Strong and Moderate CYP3A Inhibitors" and "2.7 Dosage Modifications for Severe Hepatic Impairment" respectively.
iii. In section 2.7, revise the first statement under the header to "A modified starting dosage of AYVAKIT is recommended for patients with severe hepatic impairment (Child-Pugh Class C) [see Use in Specific Populations (8.7)]:".

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ayvakit received on November 22, 2022 from Blueprint Medicines Corporation (Blueprint).

| Table 2. Relevant Product Information for Ayvakit | |
|---|---|
| Initial Approval Date | 1/9/2020 |
| Active Ingredient | avapritinib |
| Indication | AYVAKIT is a kinase inhibitor indicated for:<br>Gastrointestinal Stromal Tumor (GIST)<br>• 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.<br>Advanced Systemic Mastocytosis (AdvSM)<br>• the treatment of adult patients with AdvSM. AdvSM includes patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SMAHN), and mast cell leukemia (MCL).<br>• 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<br>(b) (4) |
| Route of Administration | oral |
| Dosage Form | tablet |
| Strength | 25 mg, 50 mg, 100 mg, 200 mg and 300 mg |
| Dose and Frequency | • GIST: Select patients for treatment with AYVAKIT based on the presence of a PDGFRA exon 18 mutation.<br>• GIST: The recommended dosage is 300 mg orally once daily.<br>• AdvSM: The recommended dosage is 200 mg orally once daily.<br>• *PROPOSED - ISM: The recommended dosage is 25 mg orally once daily.*<br>• *PROPOSED - Patients with severe hepatic impairment: reduce dose of AYVAKIT.* |
| How Supplied | AYVAKIT (avapritinib) tablets are supplied as follows:<br>• 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).<br>• 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).<br>• 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).<br>• 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). |
| Storage | 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]. |

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 29, 2022, we searched for previous DMEPA reviews relevant to this current review using the term, 212608. Our search identified 4 previous reviews, and we considered our previous recommendations to see if they are applicable for this current review.

| Reviewer | Document Title | Application | Date | RCM No. |
|---|---|---|---|---|
| Stewart, J. | Label and Labeling Review for Ayvakit (avapritinib) Tablets | NDA 212608 | October 29, 2019 | 2019-1281 |
| Stewart, J. | Revised Label and Labeling Memo for Ayvakit (avapritinib) Tablets | NDA 212608 | December 10, 2019 | 2019-1281-1 |
| Stewart, J. | Revised Label and Labeling Memo for Ayvakit (avapritinib) Tablets | NDA 212608 | December 31, 2019 | 2019-1281-2 |
| DeGraw, S. | Label and Labeling Review for Ayvakit (avapritinib) Tablets | NDA 212608/S-006 and S-007 | March 23, 2021 | 2021-2744 and 2021-193 |

APPENDIX G. LABELS AND LABELING

## G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Ayvakit labels and labeling submitted by Blueprint Medicines Corporation (Blueprint).

- Container label received on November 22, 2022
- Carton labeling received on November 22, 2022
- Prescribing Information (Image not shown) received on November 22, 2022, available from:
    - Redline: \\CDSESUB1\EVSPROD\nda212608\0112\m1\us\ayvakit-final-labeling-text-gist-advsm-ism-redline.pdf
    - Annotated: \\CDSESUB1\EVSPROD\nda212608\0112\m1\us\ayvakit-final-labeling-text-gist-advsm-ism-annotated.pdf
    - Clean: \\CDSESUB1\EVSPROD\nda212608\0112\m1\us\ayvakit-final-labeling-text-gist-advsm-ism.pdf

## G.2 Label and Labeling Images

Container Label:


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

Carton Labeling:

---

**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/

---

SUE L BLACK
03/08/2023 03:43:40 PM

HINA S MEHTA
03/10/2023 02:18:20 PM