9 November 2023
EMA/548651/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

AYVAKYT

International non-proprietary name: avapritinib

Procedure No. EMEA/H/C/005208/II/0023

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AdvSM	Advanced systemic mastocytosis
AE	Adverse event
AESI	Adverse events of special interest
AIM	American Initiative in Mast Cell Diseases
ALP	Alkaline phosphatase
ANCOVA	Analysis of covariance
APTT	Activated partial thromboplastin time
ASM	Aggressive systemic mastocytosis
ATC	Anatomical Therapeutic Chemical
BCRP	Breast cancer resistance protein
BM	Bone marrow
BSC	Best supportive care
CDF	Cumulative density function
CFB	Change from baseline
CI	Confidence interval
CID	Clinically important difference
CIR	Clinically important response
CMQ	Customised MedDRA queries
COA	Clinical Outcome Assessment
COVID-19	Coronavirus disease 2019
CRF	Case report form
CS-AP	Cross sectional analysis population
CSR	Clinical study report
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CXDX	Cycle X Day X
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
DXA	Dual x-ray energy assessment
ECG	Electrocardiogram
ECNM	European Competence Network on Mastocytosis
ECOG PS	Eastern Cooperative Oncology Group Performance Status

eCRF	Electronic case report form
EMA	European Medicines Agency
EOT	End-of-Treatment
EQ	EuroQuol
EQ-5D-5L	EuroQol-5 Dimensions-5 Levels
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GERD	Gastrooesophageal reflux disease
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumor
HLT	High-level Term
ICB	Intracranial bleeding
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISM	Indolent systemic mastocytosis
ISM-SAF	Indolent Systemic Mastocytosis-Symptom Assessment Form
ITT	Intent-to-treat
IWG-MRT-ECNM	International Working Group-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis
KM	Kaplan-Meier
LOCF	last observation carried forward
LPLV	last patient last visit
LS	Least Squares
MAF	Mutant allele fraction
MATE	Mammalian multidrug and toxin extrusion
Max	maximum
MC	mast cell
MCS	Mental Component Score
MCL	mast cell leukemia

MCMC	Markov chain Monte Carlo
MC-QoL	Mastocytosis Quality of Life Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
MRI	Magnetic resonance imaging
MSAF	Mastocytosis Symptom Assessment Form
NCI	National Cancer Institute
NCS	Nerve Conduction Study
NE	Not evaluable
NEC	Not elsewhere classified
PCS	Physical Component Score
PDGFRA	Platelet-derived growth factor alpha
PGIC	Patients' Global Impression of Change
PGIS	Patient's Global Impression of Symptom Severity
PK	Pharmacokinetic(s)
PP	Per-Protocol
PPI	Proton pump inhibitor
PRO	Patient-Reported Outcome
PsAP	Psychometric Analysis Population
PT	Preferred term
PUVA	Psoralen and ultraviolet A
QD	Once daily
QOD	Every Other Day
QoL	Quality of Life
QTc	Corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
RNA	Ribonucleic acid
ROC	Receiver operating characteristic
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Standard error

SF-12	Twelve-item Short Form Health Survey
SM	Systemic mastocytosis
SM-AHN	Systemic mastocytosis with an associated hematologic neoplasm of non-MC lineage
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
SSM	Smouldering systemic mastocytosis
TEAE(s)	Treatment emergent adverse event(s)
TKI	Tyrosine kinase inhibitor
TRT-AP	Test-retest Analysis Population
TSS	Total symptom score
UK	United Kingdom
US	United States
VAS	Visual analogue scale
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Blueprint Medicines (Netherlands) B.V. submitted to the European Medicines Agency on 15 December 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adult patients with indolent systemic mastocytosis (ISM) for avapritinib based on results from the pivotal part of study BLU-285-2203 (PIONEER), this is a 3-part, randomized, double-blind, placebo-controlled, Phase 2 study to evaluate safety and efficacy of avapritinib (BLU-285) in indolent and smoldering systemic mastocytosis with symptoms inadequately controlled with standard therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.0 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

AYVAKYT, was designated as an orphan medicinal product EU/3/18/2074 on 26 October 2018. AYVAKYT was designated as an orphan medicinal product in the following indication: Treatment of mastocytosis.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Ayvakyt as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: http://www.ema.europa.eu/en/medicines/human/EPAR/Ayvakyt

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0083/2020 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol assistance

The MAH received scientific advice from the CHMP on 31 May 2018 (EMEA/H/SA/3738/2/2018/SME/III) regarding non-clinical and clinical aspects of their proposal. After orphan drug designation, follow-up protocol assistance was provided by CHMP on 15 October 2020 (EMEA/H/SA/3738/2/FU/1/2020/PA/SME/II). The advice sought at that time pertained to the following clinical aspects of the dossier.

- Agreement with the dose selection for Part 2 of Study BLU-285-2203.
- Agreement with the proposal to include only patients with moderate-to-severe ISM in Part 2 of Study BLU-285-2203.
- Acceptability of the primary endpoint (proportion of responders, defined as patients experiencing at least a 30% decrease in ISM-SAF Total Symptom Score, from baseline to Cycle 7 Day 1), the statistical hypothesis to analyse the primary endpoint and the selection of and statistical hypotheses for key secondary endpoints.
- Adequacy of the safety database to support an extension of the indication for avapritinib to include the treatment of patients with moderate-to-severe ISM.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Carolina Prieto Fernandez Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	15 December 2022
Start of procedure	27 January 2023
CHMP Rapporteur's preliminary assessment report circulated on	11 April 2023
PRAC Rapporteur's preliminary assessment report circulated on	5 April 2023
PRAC RMP advice and assessment overview adopted by PRAC on	14 April 2023
CHMP Rapporteur's updated assessment report circulated on	22 April 2023
Request for supplementary information adopted by the CHMP on	26 April 2023
MAH's responses submitted to the CHMP on:	12 July 2023
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	18 August 2023
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	18 August 2023
PRAC RMP advice and assessment overview adopted by PRAC on	31 August 2023
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on	10 September 2023
Request for supplementary information adopted by the CHMP on	14 September 2023
MAH's responses submitted to the CHMP on:	6 October 2023
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	17 October 2023

Timetable	Actual dates
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	30 October 2023
PRAC RMP advice and assessment overview adopted by PRAC on	26 October 2023
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on	03 November 2023
CHMP opinion adopted on	9 November 2023
The CHMP adopted a report on similarity of Ayvakyt with Rydapt on	9 November 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

AYVAKYT is indicated for the treatment of adult patients with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment

Epidemiology and risk factors, screening tools/prevention

Systemic mastocytosis (SM) is a rare, clonal mast cells (MC) neoplasm driven by the KIT D816V mutation in ~95% of cases, which results in the abnormal activation of mast cells (Garcia-Montero et al, 2006; Jara-Acevedo et al, 2015; Ungerstedt et al, 2022).

The SM sub-classification based on WHO criteria is provided in the table below:

Table 1. Systemic Mastocytosis Subclassification Based on WHO Criteria

Variant		Diagnostic criteria
Nonadvanced SM	Indolent SM (ISM)	No C-findings; < 2 B-findings
	Smoldering SM (SSM)	No C-findings; ≥ 2 B-findings
Advanced SM (AdvSM)	SM with an associated hematological neoplasm (SM-AHN)	Meets diagnostic criteria for AHN
	Aggressive SM (ASM)	≥ 1 C-finding Does not meet criteria for MCL
	Mast cell leukemia (MCL)	≥ 20% mast cells in BM smear

Abbreviations: AHN = associated hematologic neoplasm; MCL = mast cell leukemia; SM = systemic mastocytosis; WHO = World Health Organization.
Source: Swerdlow et al, 2017; Carter et al, 2014; Metcalfe and Mekori, 2017; Valent 2013.

The prevalence of all types of SM is estimated at ~1 per 10,000, with the prevalence of indolent SM (ISM) accounting for ~0.8 per 10,000 (Cohen et al, 2014). In the Groningen region of the Netherlands, a major referral area for SM patients, the prevalence is estimated at 13 per 100,000.

Systemic mastocytosis preferentially affects Caucasians and there is no sex predominance. Most cases of SM are sporadic and not inherited, occurring in people with no family history of the condition.

Patients with non-advanced SM (90% to 95% of SM patients) primarily have ISM, but a small number of patients have the smouldering SM (SSM) variant, which is associated with increased organ infiltration and MC burden (Swerdlow et al, 2017).

Although organ infiltration by MCs is less extensive in patients with ISM, MC activation leads to severe, even life-threatening, MC mediator-related symptoms and a poor quality of life (Pardanani, 2019; Gilreath et al, 2019). Patients with ISM progress to advanced SM (AdvSM) in approximately 2% of cases. Patients with SSM progress to AdvSM or transform to leukemia in approximately 9% of cases and have a worse survival compared with ISM patients (Trizuljak et al, 2020; Sperr et al, 2019).

An overview of prevalence and incidence of SM in the EU is provided in table 2.

Table 2. Overview of Prevalence and Incidence of Systemic Mastocytosis in the European Union

Disease		Annual Incidence per 10,000	Prevalence per 10,000	References
SM		0.021 to 0.89	0.959 to 5	Cohen et al, 2014; Marton et al, 2016; Orphanet, 2020
Nonadvanced SM	ISM	0.04 to 0.073	0.824 to 1.8	Cohen et al, 2014; Kibsgaard et al, 2020; Marton et al, 2016; Orphanet, 2020
	SSM	–	0.13 (ISM+SSM)	van Doormaal et al, 2013
AdvSM	All subtypes	0.008	0.052	Schwaab et al, 2020
	SM-AHN	0.004	0.031	Cohen et al, 2014
	ASM	0.001	0.009 to 0.09	Cohen et al, 2014; Orphanet, 2020
	MCL	0.001	0.000	Cohen et al, 2014

Abbreviations: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; ISM = indolent systemic mastocytosis; MCL = mast cell leukemia; SM = systemic mastocytosis; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm; SSM = smoldering systemic mastocytosis.

Biologic features, aetiology and pathogenesis

Systemic mastocytosis is a clonal mast cell neoplasm, driven by the KIT D816V mutation, where abnormal activation of MC leads to debilitating life-threatening symptoms. Although heterogeneity characterizes the clinical presentation and prognosis of SM, the pathogenesis is largely shared, with gain of function D816 KIT mutations occurring in 93% of SM cases, regardless of subtype (Garcia-Montero et al, 2006). This shared molecular pathogenesis suggests that a potent, selective, targeted agent against the KIT D816V mutation could be effective across SM subtypes, regardless of the clinicopathological presentation.

Serum tryptase is an important biomarker for mast cell burden and activity and is part of the WHO diagnostic criteria for SM. Although specific criteria of response in objective measures of mast cell burden do not exist for ISM, reduction of 50% or greater from baseline serum tryptase is a criterion for partial remission in the IWG-MRT-ECNM criteria used in AdvSM (Gotlib et al, 2013), and potentially a marker of disease modification in ISM.

Clinical presentation, diagnosis and stage/prognosis

The formal diagnosis of SM is based on pathologic and laboratory criteria established by the WHO (Swerdlow et al, 2017). A diagnosis of SM can be made with the documentation of multifocal dense

infiltrates of neoplastic MCs in bone marrow (BM) and/or other extra cutaneous organs (major criterion) and at least 1 of the following minor criteria:

- Atypical MC morphology in BM and/or extra cutaneous tissue
- Presence of the KIT D816V mutation in BM, blood, or other extracutaneous organ
- Abnormal expression of CD25 with or without CD2 on MCs in BM, blood, or other extracutaneous organ
- Elevated serum tryptase levels

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

SM is broadly divided into advanced SM and non-advanced SM, - based on the degree of organ infiltration (B-findings) and organ damage (C-findings) present, as well as the presence of adverse pathologic features - both of which are characterized by the uncontrolled proliferation and activation of mast cells, often present as aggregates in bone marrow, skin, spleen, liver, GI tract, and other organs (Metcalfe, 2008). (Table 3).

Table 3. B- and C-Findings in Systemic Mastocytosis

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

Abbreviations: ANC = absolute neutrophil count; BM = bone marrow; Hgb = hemoglobin; MC = mast cell.
Source: Swerdlow et al, 2017.

Approximately 10% to 20% of patients meet the WHO diagnostic criteria for advanced SM; the remainder have non-advanced ISM with the exception of a small subset who have non-advanced SSM (Sperr et al, 2019).

Patients with ISM suffer from a broad spectrum of persistent and debilitating symptoms (Jennings et al, 2018; Mesa et al, 2022; Pulfer et al, 2021; van Anrooij et al, 2016). Mutant KIT drives the accumulation and hyperactivity of aberrant mast cells, leading to excessive signaling of vasoactive and inflammatory cytokines, including leukotrienes, prostaglandins, and interleukins (Jackson et al, 2021). Aggregates of activated proliferating mast cells, driven by mutant KIT, result in a constellation of symptoms leading to a significant reduction in quality of life (QoL) caused by recurrent diarrhoea, pruritus, abdominal pain, nausea, headache, flushing, cognitive impairment, fatigue, bone pain, and disfiguring skin lesions that are observed across the spectrum of the disease (Magliacane et al, 2014; Theoharides et al, 2015).

Among patients with SM, 46% (ISM) to 56% (SM) experience anaphylaxis (Brockow et al, 2008; Gülen et al, 2014).

Management

Therapies currently recommended for ISM are considered palliative, administered with the intent of only improving symptoms. Commonly used therapies for treatment of ISM symptoms are presented in the table below.

Table 4. Commonly Used Therapies Directed for Treatment of ISM Symptoms

Symptom	Drug class
Pruritis, flushing	H1 antihistamines, leukotriene inhibitors, NSAIDs
Abdominal pain, cramping, diarrhea, heartburn, nausea, vomiting	H2 antihistamines, PPI, cromolyn, corticosteroids
Headache, cognitive impairment, depression	H1 antihistamines, cromolyn
Hypotension	H1 antihistamines, corticosteroids
Osteoporosis	Bisphosphonate
Anaphylaxis	Corticosteroids, anti-IgE antibody, epinephrine

Abbreviations: IgE = Immunoglobulin E; ISM = indolent systemic mastocytosis; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor. Source: Pardanani 2013.

Globally, there are currently no approved treatments for patients with ISM aiming to reduce their disease burden, treat the underlying driver of ISM, or which impact the ISM disease course.

2.1.2. About the product

Avapritinib (BLU-285) is a small molecule protein tyrosine kinase inhibitor (ATC classification code L01EX18) that targets KIT D816V, PDGFRA and PDGFRA D842 mutants as well as multiple KIT exon 11, 11/17 and 17 mutants. Certain mutations in PDGFRA and KIT can result in the autophosphorylation and constitutive activation of these receptors which can contribute to tumour cell proliferation. Other potential targets for avapritinib include wild type KIT, PDGFRB, and CSFR1.

Avapritinib is currently approved for treatment of unresectable or metastatic gastrointestinal stromal tumour (GIST) - with a recommended starting dose of 300 mg once daily-, and for the treatment of aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL), after at least one systemic therapy – with a recommended starting dose of 200 mg once daily.

The new (initially) claimed indication is:

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

For ISM, the recommended dose of avapritinib is 25 mg orally once daily.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The avapritinib SM clinical development program was initiated in June 2015 and to date consists of the following studies.

Systemic mastocytosis – AdvSM

• 2 clinical studies in patients with AdvSM (BLU-285-2101 and BLU-285-2202, both ongoing)

• An open-label expanded-access program in patients with AdvSM (BLU-285-EAP-02, completed)

• An external control, observational, retrospective study of avapritinib in patients with AdvSM that collected retrospective data on patients treated with BSC in the real-world setting to enable comparative analyses on the efficacy and safety of avapritinib vs BSC (BLU-285-2405, completed)

Systemic mastocytosis – ISM

• A clinical study in patients with ISM (BLU-285-2203, ongoing)

• An open-label expanded-access program in patients with ISM (BLU-EAP-ISM, ongoing)

Systemic mastocytosis – General

• A registry for patients with mastocytosis (Mast Cell Connect Mastocytosis Registry, completed)

• A screening study evaluating the prevalence of KIT D816V mutation in patients with systemic mast cell activation (BLU-SM-1101, ongoing)

As outlined above, scientific advice/protocol assistance was requested in two occasions. The recommendations regarding clinical aspects have overall been followed. However, the same does not apply to suggestions made regarding the non-clinical development; see section 2.2.

2.1.4. General comments on compliance with GCP

The MAH has provided a statement confirming that the clinical studies have been conducted in agreement with GCP compliance.

2.2. Non-clinical aspects

2.2.1. Introduction

New non-clinical information related to the potential genotoxic and carcinogenic effect of avapritinib has been produced from the last line extension of Ayvakit. The new studies submitted in this variation included a new *in vivo* mammalian alkaline Comet assay in rat and the 6-month transgenic mouse carcinogenic assessment study. Also, an exploratory brain analysis from samples of the 3-month repeat-dose toxicology study conducted in dogs was reported.

2.2.2. Pharmacology

No additional pharmacology studies have been conducted with avapritinib for this new indication, which was considered acceptable by CHMP. These studies were provided in the initial MAA.

2.2.3. Toxicology

Repeat dose toxicity

Repeated dose toxicity studies indicated that cases of haemorrhage 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 and 0.8 times the human exposure based on AUC at 25 mg, 200 mg and 300 mg dose once daily, respectively) and choroid plexus oedema in the brain occurred in dogs at doses greater than or equal to 7.5 mg/kg/day (approximately 4.7, 1.0 and 0.4 times the human exposure based on AUC at the clinical dose of 25 mg, 200 mg and 300 mg once daily, respectively). Rats manifested convulsions, which was potentially secondary to inhibition of Nav 1.2 at systemic exposures ≥96, 12 and ≥8-fold higher than the exposure in patients at the clinical dose of 25 mg, 200 mg and 300 mg once daily.

In a 6 month repeat dose toxicology study in rats, rats manifested haemorrhagic and cystic degeneration of the ovarian corpus lutea and vaginal mucification at dose levels greater or equal to 3 mg/kg/day with exposure margins of 15, 3 and 1.3 times the human exposure based on AUC at 25 mg, 200 mg and 300 mg, respectively. In a 9 month repeat dose toxicology study in dogs, hypospermatogenesis (3/4 males) was observed at the highest dose tested, 5 mg/kg/day (5.7, 1.2 and <1 times the human exposure (AUC) at 25 mg, 200 mg and 300 mg dose, respectively).

Genotoxicity

The results of a new *in vivo* mammalian alkaline Comet assay in rat were presented. The previous one was submitted in the (variation EMEA/H/C/5208/X/004/G). Both assays followed a similar protocol. Animals were treated for 2 days by oral gavage and the doses were 37.5, 75, 150 mg/kg/day for males and 25, 50, 100 mg/kg/day for females. The only difference was the batch used, being for this new assay Batch 119200T9009 instead of 0285/02.

It was concluded that avapritinib was negative under the conditions of the study, given that no DNA damage in the liver was induced after oral administration at 0 and 24 hours.

Carcinogenicity

Previous to the definitive 6-month carcinogenicity study, a 5-day and 28-day oral toxicity study was conducted in mice (CByB6F1 wild-type mouse (non-TG mouse)). After 4 weeks of avapritinib treatment on a daily basis (10, 30 or 100 mg/Kg/day), adverse microscopic findings and correlating haematology changes at ≥ 30 mg/kg/day were observed. The NOAEL was established at 10 mg/kg/day, resulting in a mean $AUC_{0\text{-}24hr}$ value of 40,200 hr*ng/mL and a mean C_{max} value of 2790 ng/mL for males and females combined on Day 28.

In the definitive study, avapritinib was administered to transgenic mice (CByB6F1/Tg rasH2 hemizygous) by oral gavage on a daily basis for 26 weeks (3, 10 or 20 mg/Kg/day). The study report indicated no avapritinib-related effects on survival. Clinical observations included skin pallor and discoloration/fur staining (white and/or pale) at ≥ 10 mg/kg/day group males and/or females. Regarding organ weights, lower thymus weights at ≥ 10 mg/kg/day group males and females were reported, microscopically corresponded with lower cellularity of the thymic cortex in both groups.

No significant difference in terms of systemic exposure was found between males and females. No accumulation was observed after comparison exposure on days 1 and 182. The exposure levels quantified at the highest dose evaluated (20 mg/kg/day at day 182) were: mean $AUC_{(0\text{-}24)}$ value of 72,300 ng*hr/mL and mean C_{max} value of 4550 ng/mL.

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

In addition to these studies, a carcinogenic risk assessment based on a weight of evidence (WoE) approach was presented by the MAH, in line with the addendum 'Testing for Carcinogenicity of Pharmaceuticals' (ICH S1B[R1], 2022). A long-term carcinogenicity study with avapritinib is ongoing.

Reproduction toxicity

No new data related to reproduction toxicity have been presented in this variation. Nevertheless, the MAH reconsidered the information included in the SmPC regarding the potential effect of treatment with AYVAKYT on male and female fertility and has amended SmPC sections 4.6 and 5.3 accordingly.

The nonclinical data informing on fertility in humans comprises a dedicated combined male and female fertility and early embryonic development study conducted in rats at oral avapritinib doses of 3, 10, and 30 mg/kg/day for males, and 3, 10, and 20 mg/kg/day for females.

The MAH stated that no direct effects on male or female fertility were noted at the highest dose levels tested in this study (100.8 and 62.6 times the human exposure (AUC) at 25 mg, 20.3 and 9.5 times the human exposure (AUC) at 200 mg and 8.7 and 4.1 times the human exposure (AUC) at 300 mg).

Reduction in sperm production and relative testicular weight were observed in male rats administered avapritinib at exposures of 7 and 30 times, 1 and 5 times, and 0.6 and 3 times the 25 mg, 200 mg, and 300 mg human doses, respectively. Nevertheless, hypospermatogenesis (3/4 males) was observed in the 9 month repeat-dose toxicology study in dogs at the highest dose tested, 5 mg/kg/day (5.7, 1.2 and <1 times the human exposure (AUC) at 25 mg, 200 mg and 300 mg dose, respectively).

Regarding female fertility, the 6 month repeat dose rat toxicity study revealed haemorrhagic and cystic degeneration of the ovarian corpus lutea and vaginal mucification at dose levels greater or equal to 3 mg/kg/day with exposure margins of 15, 3 and 1.3 times the human exposure based on AUC at 25 mg, 200 mg and 300 mg, respectively.

The MAH has included wording in SmPC section 4.6 and section 5.3 to inform on the potential effect of treatment with AYVAKYT on male and female fertility at doses of 200 mg or greater.

Toxicokinetic data

Toxicokinetic data of the 6-month carcinogenicity study are shown in the section above.

2.2.4. Ecotoxicity/environmental risk assessment

The MAH has submitted additional information related to ERA of avapritinib, resulting in the absence of significant increase of PEC surface-water parameter, which is below the trigger value of 0.01 µg/L. Consequently, no phase II would be required.

2.2.5. Discussion on non-clinical aspects

Avapritinib was initially approved for the indication of GIST and then extended to AdvSM. It showed broad inhibitory activity against both primary and secondary KIT and PDGFRA mutants, especially against mutations in exons 17 and 18 including the D816V mutant in KIT (IC_{50} = 0.27 nM) and the D842V mutant in PDGFRA (IC_{50} = 0.24 nM). For this new indication, no additional pharmacological studies have been conducted, which was considered acceptable.

An exploratory brain analysis from samples of the 3-month repeat dose toxicology studies in dogs has been provided with this variation procedure. No effect was reported in animals treated at 30 mg/Kg/day compared to control individuals. It is noted that due to the limited number of animals, no effect of treatment or sex for microglia present in the brain could be concluded. No update of the SmPC was deemed necessary.

In terms of potential genotoxicity of avapritinib, the results reported from a new *in vivo* Comet assay confirmed those obtained in the initial similar study. It is noted that the only difference between both assays is the batch used with no other differences reported. The information obtained is already included in the section 5.3 of the SmPC, and no modification is considered at this point, which was agreed.

With regards to the carcinogenicity profile of avapritinib, the MAH has presented a carcinogenic risk assessment based on a WoE approach. It should be noted that the MAH anticipates that a carcinogenic potential of avapritinib in humans is unlikely. It is noted that a previous scientific advice to conduct the 2-year carcinogenicity study in rats was not followed by the MAH.

As part of the carcinogenic risk assessment, the results of the short-term carcinogenicity study (6-month in CByB6F1/Tg rasH2 Hemizygous Mice) were shown and have been added to the section 5.3 of the SmPC. In this study, clinical observations were noted in the skin and microscopic findings of decreased cortical cellularity with corresponding reduction in thymus weights were reported at ≥ 10 mg/kg/day. It is noted that the selection of dose levels for this study was based on a 28-day study, in which clinical signs were limited to thin fur cover of the forepaw and hind paws (left and right) in females of the 30 and 100 mg/kg/day groups with no changes in body weight or food consumption. Histopathological changes were reported at ≥ 30 mg/Kg/day (sternal bone marrow and thymus). The MAH selected a maximum dose of 20 mg/Kg/day (54.4-fold humans at the dose of 25 mg) for the 6-month study in transgenic mice based on the 50-fold plasma AUC exposure ratio (rodent:human) criterion. However, given that a higher dose level used in the 28-day study (30 mg/Kg/day) had shown a limited toxicity in the previous study, it is anticipated a low (almost negligible) toxic effect in the 6-month study for the 20 mg/Kg/day dose level. Similarly, dose level of 30 mg/Kg QD was described as well-tolerated (not even body weight was affected) in primary pharmacodynamic studies after 27 days of treatment (Pharmacology written summary, initial MAA), also anticipating the absence of a dose-limiting toxicity in the 6-month carcinogenic study. This was confirmed in the 6-month study, in which any change was observed in all tissues analysed. Based on the results of the 6-month transgenic mice study, the MAH concluded no carcinogenic effect of avapritinib.

As for the histopathology data, the MAH mentioned NOAEL values, indicating the absence of hyperplasia or hypertrophy at these NOAEL values in the repeat dose toxicology studies. However, higher doses produced changes in organ weights, bone growth effects in rats and histopathologic findings in dogs

(bone marrow, spleen and testis) even at the recovery euthanasia.

With regards to the hormonal perturbation analysis, the MAH noted that findings were not indicative of direct hormonal changes. However, taking into account that KIT is described to regulate mammalian spermatogenesis along with the effect observed in testis, it should be reconsidered in terms of potential hormonal perturbation. Indeed, effects on adrenal and prostate glands, vagina and ovaries as well as hypospermatogeneis have been reported in repeat dose toxicology studies.

In the assessment of potential for immune modulation, it is noted that immune systems changes were reported in toxicity studies and that dedicated immunotoxicity studies were not conducted with avapritinib.

Finally, additional supportive clinical data were submitted by the MAH but no information related to the treatment duration of the reported cases has been shown.

Taking together these all factors mentioned above, it can be concluded that a 2-year rat study would add value to the assessment of human carcinogenicity risk, given that carcinogenic potential in humans cannot be ruled out. Also, it should be considered that this new indication (ISM) is not an advanced cancer and patients are likely to have a normal life expectancy. The MAH stated that a 2-year carcinogenicity study with avapritinib in rats is currently ongoing. The final report is expected to be available in March 2026 and the information for the long-term carcinogenicity study has been accordingly modified in SmPC section 5.3.

As this is a new therapeutic indication and in line with current ERA guideline (CPMP/SWP/4447/00), environmental risk update was included. As PEC surfacewater was below the action limit, no additional studies are required.

As previously mentioned, new non-clinical data have been produced from the last variation of Ayvakyt submitted by the MAH. Additional estimations of the safety exposure margin based on the clinical dose (25 mg) for the novel indication, in addition to those estimated for previous indication (300/250 mg for GIST/AdvSM, respectively) have been incorporated in the section 5.3 of SmPC. In addition, based on non-clinical finding in animals, male and female fertility may be compromised by treatment with avapritinib. SmPC sections 4.6 and 5.3 have been updated.

Considering that patients with ISM tend to be younger than patients with AdvSM or GIST and may be more likely to want to pursue pregnancy, the MAH proposes to follow a conservative approach and based on CFTG guidance for drugs with suspected human fetotoxicity, proposes that an extension of the use of effective contraception by 2 weeks is recommended for women (i.e. from 1 month to 6 weeks). Based on the half-life of avapritinib, a 2 week washout period is adequate for the drug washout, in line with the proposed recommendation for contraceptive use in men with female partners of childbearing potential after the last dose of avapritinib. The information regarding the need for contraception (in men and women) in section 4.6 of the SmPC was updated accordingly.

2.2.6. Conclusion on the non-clinical aspects

The non-clinical data are sufficient to support the extension of indication to include treatment of adult patients with indolent systemic mastocytosis. Updated information has been reflected in the SmPC sections 4.6 and 5.3.

The updated ERA data submitted show that the use in ISM patients does not lead to a significant increase in environmental exposure. Considering the above data, avapritinib is not expected to pose a risk to the environment.

The following measures are considered necessary to address non-clinical issues:

- The MAH will perform a 2-year carcinogenicity study in rats following the recommendation of the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

- Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects/ Patients	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
Food Effect	BLU-285-0102	5.3.1.1	Food effect, compare PK of avapritinib with or without food (standardized high-fat, high-calorie meal)	Open-label, randomized, single dose, 2-way crossover	Avapritinib; Tablet: 2×100 mg; Oral, fed or fasted	30	Healthy Volunteers	Complete; Clinical Study Report
BA	BLU-285-0101	5.3.1.2	Relative bioavailability, avapritinib tablet versus capsule formulations	Open-label, randomized, single dose, 2-way crossover	Avapritinib; Capsule: 2×100 mg Tablet: 1×200 mg; Oral, fasted	30	Healthy Volunteers	Complete; Clinical Study Report
BE	BLU-285-0105	5.3.1.2	Bioequivalence between 400 mg and 100 mg tablets	Open-label, randomized, single dose, 2-period crossover	Avapritinib; Tablet: 4×100 mg Tablet: 1×400 mg; Oral, fasted	62	Healthy Volunteers	Complete; Clinical Study Report
DDI, PK	BLU-285-0104	5.3.2.2	PK in the presence and absence of itraconazole or rifampin	2-Part, open-label; fixed sequence	Avapritinib single dose: 2 × 100 mg tablet ± itraconazole 200 mg QD (BID on Day 1) Avapritinib single dose: 4 × 100 mg tablet ± rifampin 600 mg QD; Oral, fasted	Part 1: 20 Part 2: 20	Healthy Volunteers	Complete; Clinical Study Report
ADME, Mass Balance	BLU-285-0103	5.3.3.1	ADME and mass balance of avapritinib	Open-label, single dose	Avapritinib; Tablet: 3×100 mg Capsule: 1× ~17 mg [14C]avapritinib O(100 µCi); Oral, fasted	6	Healthy Volunteers	Complete; Clinical Study Report

Hepatic Impair-ment	BLU-285-0107	5.3.3.3	Effect of severe hepatic impairment on the PK of avapritinib	Open-label, single dose	Avapritinib; Tablet: 1 x 100 mg Oral, fasted	16	Healthy Volunteers 8 with severe hepatic impairment 8 matched controls	Complete; Clinical Study Report
Efficacy, Safety, PK	BLU-285-2203	5.3.5.1	Efficacy, Safety, PK, and QOL	A 3-part, randomized, double-blind, placebo-controlled Phase 2 study to evaluate safety and efficacy of avapritinib in ISM and SSM with symptoms inadequately controlled with standard therapy	Part 1: Avapritinib 25, 50, or 100 mg or matching placebo PO, QD in continuous 28-day cycles Part 2: avapritinib 25 mg or matching placebo PO, QD in continuous 28-day cycles Part 3 avapritinib 25 mg PO, QD in continuous 28-day cycles	Part 1: 39 Part 2: 212 Part 3 (rollover from Part 1 and 2): 235	Patients with ISM	Ongoing; Clinical Study Report

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

2.3.2. Pharmacokinetics

Pharmacokinetics in the target population

The clinical pharmacology of avapritinib was further characterized in an efficacy and safety study in patients with ISM (BLU-285-2203).

Table 5. Overview of New Studies Contributing Clinical Pharmacology Data

Study Identifier Status Location of CSR	Study Objective	Study Design	Treatments (Dose, Dosage Form)	Subjects Treated: No. (M/F) Type Age: Mean [Range]	Route	Avapritinib Formulation	Data Included in Current Submission			Location in Module 2.7
							NCA PK	Pop PK	E-R	
Studies in Patients with ISM										
BLU-285-2203 *Part 1*: complete *Part 2*: complete *Part 3*: ongoing CSR BLU-285-2203	*Part 1*: recommended Phase 2 dose, PK, safety, and efficacy of avapritinib *Part 2*: efficacy and safety of avapritinib compared to placebo *Part 3*: long-term safety and efficacy of avapritinib	Double-blind, placebo-controlled, 3-part study	*Part 1*: avapritinib 25, 50, or 100 mg QD + BSC or placebo + BSC *Part 2*: avapritinib 25 mg QD + BSC or placebo + BSC *Part 3*: avapritinib 25 mg QD + BSC	*Part 1*: 39 (9M/30F) patients with ISM 49.2 years, [21-75 years] 25 mg QD: 10 50 mg QD: 10 100 mg QD: 10 Placebo: 9 *Part 2*: 212 patients with ISM 25 mg QD + BSC: 141 (41M/100F) 48.7 years, [18-77 years] Placebo + BSC: 71 (17M/54F) 52.2 years, [26-79 years]	Oral, fasted	25 and 100 mg tablets	Yes	Yes	Yes (E, S)	Module 2.7.2 Section 2.1.1 (NCA PK) Module 2.7.2 Section 2.5.1 (Pop PK) Module 2.7.2 Section 2.5.2 (E-R)

Abbreviations: BSC = best supportive care; CSR = clinical study report; E = efficacy; E-R = exposure-response; F = female; ISM = indolent systemic mastocytosis; M = male; NCA = noncompartmental analysis; No. = number; PK = pharmacokinetic(s); Pop PK = population pharmacokinetics; QD = once daily; S = safety.

The clinical pharmacokinetics (PK) of avapritinib were investigated in patients with Indolent systemic mastocytosis (ISM) to assess:

- Analysis of the PK of avapritinib and the constitutive enantiomers BLU111207 and BLU111208 of its pharmacologically active metabolite M499 (BLU136707) using NCA methods, based on data obtained on C1D1 (single-dose PK) for Part 1 and Part 2 of the study, and on C1D15 (Part 1) or C2D1 (repeat-dose PK) for Part 2 of the study.
- Population analysis of avapritinib PK, including data submitted previously from Study BLU-285-2101 and Study BLU-285-2202 in patients with AdvSM, Study BLU-285-1101 in patients with GIST, and Studies BLU-285-0101, BLU-285-0102, and BLU-285-0105 in healthy subjects, with a covariate analysis to determine whether patient demographics and other factors can be used to explain inter-individual variability in PK parameters.

Study BLU-285-2203

Study BLU-285-2203 is an ongoing, double-blind, placebo-controlled study to investigate the efficacy and safety of avapritinib in combination with BSC administered orally in adult patients with ISM.

The study includes 3 parts:

- In Part 1, the 25 mg QD 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 (Table 5).
- In Part 2, the efficacy of the RP2D (25 mg QD) in combination with BSC was compared with placebo in combination with BSC.
- In the ongoing Part 3 of the study, patients who had completed treatment in Part 1 or Part 2 are participating in a long-term extension, receiving 25 mg QD avapritinib in combination with BSC. As of the data cutoff date for the current submission (23 June 2022), 251 patients were treated with avapritinib or placebo (39 in Part 1, 212 in Part 2, and 235 in Part 3).

The PK parameters for avapritinib and the constitutive enantiomers of the M499 metabolite (BLU111207 and BLU111208) after single (C1D1) and repeat (QD) dosing (C1D15 or C2D1) of avapritinib were estimated using NCA methods. Only samples from Part 1 and Part 2 of the study were analysed. No PK samples were analysed from Part 3.

The sampling schemes for PK analysis are outlined in Table 6.

Table 6: Summary of Pharmacokinetic Sampling Schemes in Study BLU-285-2203

Avapritinib Dose (Formulation)	N (Treated)	Pharmacokinetic Sampling
Part 1 25, 50, 100 mg QD (tablet), or placebo	39	**Part 1 (Intensive)** [a] C1D1: Predose, 0.5, 1, 2, 4, 8, 24, 48, 72 hours postdose C1D15: Predose, 0.5, 1, 2, 4, 8, 24, 48 hours postdose C2D1-C4D1: Predose, 1 time point between 1-8 hours postdose
Part 2 25 mg QD (tablet) or placebo	212	**Part 2 (Intensive)** C1D1: Predose, 1, 4, 6-8 hours postdose C2D1: Predose, 1, 4, 6-8 hours postdose C3D1-C7D1: Predose, 1 time point between 1-8 hours postdose **Part 2 (Sparse)** C1D1-C7D1: Predose, 1 time point between 1-8 hours postdose

Abbreviations: CxDy = Cycle x Day y; CxD1-CyD1 = Day 1 of Cycle x through Cycle y; N = number of patients; QD = once daily.

[a] In Part 1, the C1D2, C1D3, and C1D16 doses were not administered to allow for collection of the 48- and 72-hour postdose samples.

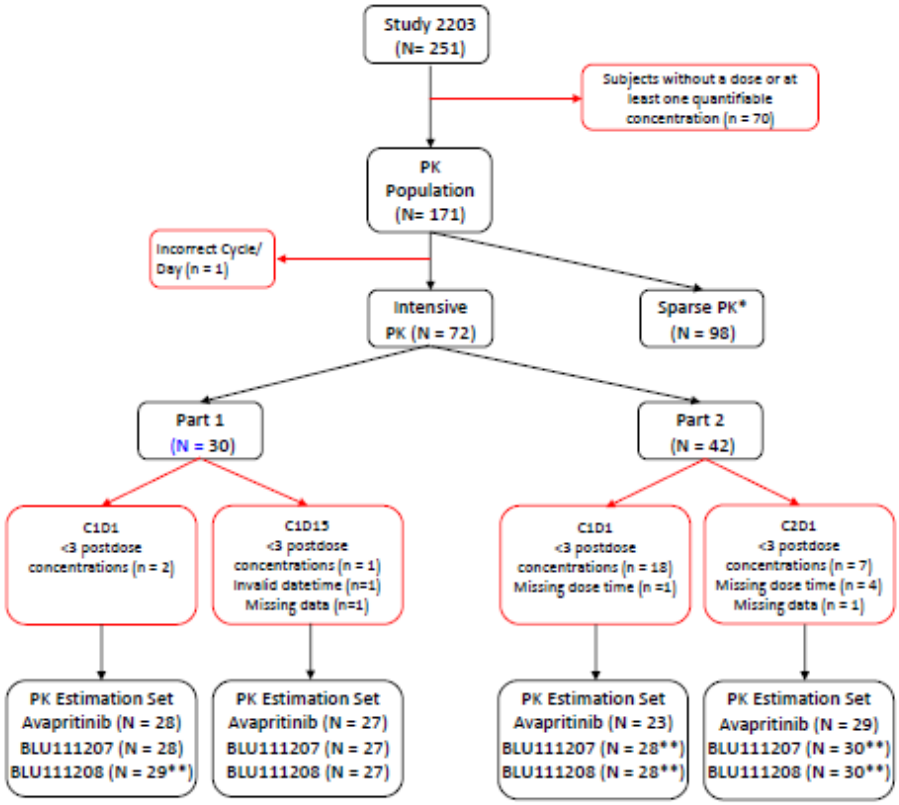
PK Parameter Estimation Set was defined as all patients who received a dose of avapritinib and had at least 3 quantifiable concentrations post-dose. NCA was performed for this group of patients. Patients enrolled in Part 2 with sparse sampling had their exposure metrics derived using population pharmacokinetic methods.

PK Population

PK population was defined as all patients who received at least one dose of avapritinib and had at least one plasma sample collected, and was used for concentration-time listings.

A flowchart detailing the PK Population and PK Estimation Set is shown in Figure 1.

Figure 1. Exclusion of Patients from the Pharmacokinetic Population and Pharmacokinetic Estimation Set



*Patients with sparse PK sampling were not included in the PK Estimation Set, however their concentrations along with nominal times are listed in Appendix 16.9, Tables 69–74.**Patients had metabolite profiles that matched the criteria for the Pharmacokinetic Estimation Set, however their corresponding avapritinib profile did not (i.e. <3 postdose quantifiable concentration).

There were 98 patients in Part 2 with sparse PK sampling, NCA was not performed for these patients. As a result of these exclusions there were 72 patients in the PK Population.

Avapritinib Pharmacokinetics

The summary avapritinib PK parameters by dose and day are displayed in Tables 7 and 8, for Part 1 and in Table 9 and 10 for Part 2.

Table 7. Summary of Avapritinib Pharmacokinetic Parameters on C1D1 by Dose - Part 1

Dose mg	Summary Statistic	C_{max} ng/mL	T_{max} h	T_{last} h	C_{trough} ng/mL	$t_{1/2}$ h	AUC_{0-last} ng.h/mL	AUC_{0-24h} ng.h/mL	$AUC_{0-\infty}$ ng.h/mL	CL/F L/h	V_z/F L
25	N	9	9	9	9	8	9	9	8	8	8
	Mean	26.1	–	–	7.04	37.9	732	398	1130	26.8	1400
	SD	11.5	–	–	2.54	11.0	352	132	449	14.6	829
	CV%	44	–	–	36.1	29	48	33.2	39.8	54.5	59.1
	GeoMean	23.6	–	–	6.64	36.3	639	372	1040	24.1	1260
	GeoMean CV%	55.1	–	–	38.1	33.5	65.2	44.7	49.9	49.9	46.5
	Min	7.67	1.93	24.0	3.46	19.1	237	138	445	13.4	872
	Median	23.8	3.98	71.1	6.20	37.9	816	421	1160	21.5	1140
	Max	48.3	8.00	72.3	11.4	53.7	1210	574	1860	56.2	3370
50	N	9	9	9	9	9	9	9	9	9	9
	Mean	66.5	–	–	14.6	44.9	1630	819	2610	22.9	1420
	SD	31.3	–	–	7.02	12.7	611	328	1140	10.5	649
	CV%	47.1	–	–	48.1	28.3	37.4	40.1	43.8	45.9	45.8
	GeoMean	58.6	–	–	12.9	43.2	1530	753	2390	20.9	1300
	GeoMean CV%	62.4	–	–	60.1	30.7	41	47.6	47.8	47.8	45.5
	Min	19.1	1.00	47.9	5.82	26.5	820	381	1200	11.0	681
	Median	67.5	2.00	71.5	15.2	46.2	1670	824	2680	18.7	1240
	Max	116	4.13	72.0	22.2	64.3	2490	1290	4530	41.6	2620
100	N	10	10	10	10	9	10	10	9	9	9
	Mean	120	–	–	33.7	45.4	3650	1830	5810	19.9	1210
	SD	45.3	–	–	17.6	11.0	1210	534	1970	9.89	329
	CV%	37.8	–	–	52.3	24.2	33.2	29.1	33.8	49.7	27.2
	GeoMean	111	–	–	29.9	44.1	3460	1750	5450	18.3	1170
	GeoMean CV%	46	–	–	57.2	26.5	37	34.3	42.3	42.4	28.7
	Min	42.5	1.98	24.0	10.4	25.5	1920	842	2300	11.1	794
	Median	113	3.92	71.6	31.6	46.9	3570	1840	6030	16.6	1290
	Max	183	7.83	72.5	75.4	65.6	5610	2560	8980	43.5	1700

Parameter exclusions: $t_{1/2}$ was excluded if λ_z was unreliable (defined in Section 8.1.1). $AUC_{0-\infty}$, CL/F, and V_z/F were excluded if λ_z was unreliable or $\%AUC_{ex}$ was >30%.

Table 8. Summary of Avapritinib Pharmacokinetic Parameters on C1D15 by Dose - Part 1

Dose mg	Summary Statistic	$C_{max,ss}$ ng/mL	T_{max} h	T_{last} h	$C_{trough,ss}$ ng/mL	$AUC_{0-last,ss}$ ng.h/mL	$AUC_{0-\tau}$ ng.h/mL	CL_{ss}/F L/h	$R_{ac,AUC0-24h}$	$R_{ac,Cmax}$
25	N	9	9	9	9	9	9	9	9	9
	Mean	80.0	–	–	38.0	2570	1520	21.6	4.06	3.36
	SD	38.2	–	–	24.0	1330	750	12.5	2.20	1.78
	CV%	47.8	–	–	63.2	51.7	49.5	58.1	54.3	52.9
	GeoMean	70.2	–	–	30.0	2220	1330	18.7	3.59	2.98
	GeoMean CV%	62.7	–	–	93.1	65.2	60.7	60.7	56.3	55.5
	Min	29.8	1.95	47.2	7.65	935	608	9.06	1.70	1.48
	Median	85.1	3.97	47.8	40.8	2620	1460	17.1	3.48	3.39
	Max	137	8.00	48.9	76.3	4550	2760	41.1	8.65	7.14
50	N	10	10	10	10	10	9	9	9	9
	Mean	147	–	–	89.6	4890	2820	19.9	3.90	2.97
	SD	40.8	–	–	36.5	1600	904	8.13	2.07	2.37
	CV%	27.7	–	–	40.7	32.8	32	40.8	53	79.8
	GeoMean	141	–	–	83.1	4640	2670	18.7	3.55	2.35
	GeoMean CV%	35.3	–	–	43.3	35.6	37.8	37.9	45.5	84.8
	Min	66.4	1.88	23.0	42.4	2570	1360	12.8	1.90	0.572
	Median	162	4.00	48.0	86.4	4740	3170	15.8	3.33	2.35
	Max	189	8.00	48.8	157	7330	3900	36.9	8.88	8.74
100	N	8	8	8	8	8	8	8	8	8
	Mean	284	–	–	162	9630	5560	20.8	3.25	2.70
	SD	115	–	–	59.9	3850	1880	9.74	0.583	0.688
	CV%	40.5	–	–	36.9	40	33.9	46.9	18	25.5
	GeoMean	260	–	–	151	8620	5220	19.2	3.20	2.61
	GeoMean CV%	49.7	–	–	45.9	61.7	42.7	42.7	19.9	28.6
	Min	119	1.93	24.8	67.7	2660	2580	13.2	2.11	1.50
	Median	310	4.08	47.9	165	10700	6050	16.5	3.26	2.76
	Max	458	8.05	48.6	228	13200	7600	38.8	3.97	3.74

Accumulation ratios were determined by dividing the C1D15 (steady-state) value by the C1D1 value.

Table 9. Summary of Avapritinib Pharmacokinetic Parameters on C1D1 - Part 2

Dose mg	Summary Statistic	C_{max} ng/mL	T_{max} h	T_{last} h	AUC_{0-last} ng.h/mL
25	N	23	23	23	23
	Mean	33.5	–	–	138
	SD	19.5	–	–	104
	CV%	58.3	–	–	75.8
	GeoMean	30.4	–	–	120
	GeoMean CV%	43.5	–	–	49.7
	Min	10.9	0.933	4.98	43.9
	Median	29.1	4.00	5.98	115
	Max	116	6.17	6.17	592

Table 10. Summary of Avapritinib Pharmacokinetic Parameters on C2D1 - Part 2

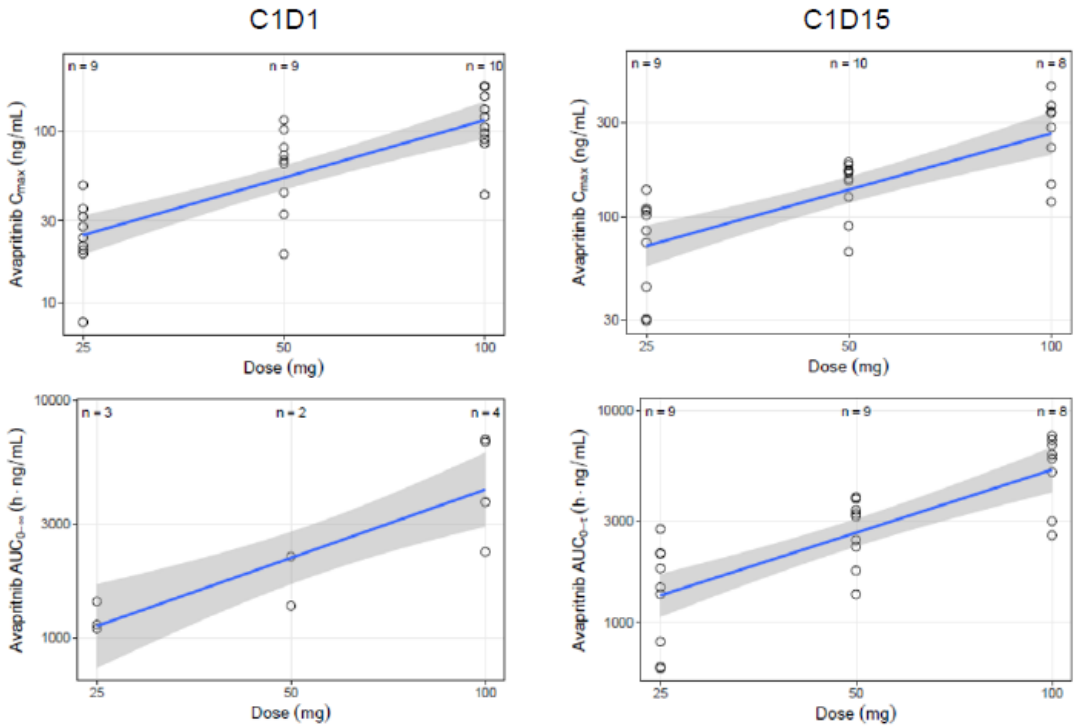
Dose mg	Summary Statistic	$C_{max,ss}$ ng/mL	T_{max} h	T_{last} h	$AUC_{0-last,ss}$ ng.h/mL	$R_{ac,AUC0-last}$	$R_{ac,Cmax}$
25	N	29	29	29	29	17	17
	Mean	80.3	–	–	388	2.90	3.63
	SD	35.3	–	–	160	0.766	1.08
	CV%	44	–	–	41.2	26.4	29.8
	GeoMean	73.5	–	–	357	2.82	3.50
	GeoMean CV%	45.5	–	–	44.4	23.9	27.4
	Min	23.3	3.85	5.83	118	2.03	2.22
	Median	73.2	4.00	6.00	363	2.73	3.36
	Max	205	6.00	6.67	910	5.16	6.55

Accumulation ratios were determined by dividing the C2D1 (steady-state) value by the C1D1 value.

Dose proportionality

In Part 1, a dose-proportional increase in systemic exposure to avapritinib was observed across the dose range of 25 to 100 mg after single-dose administration (C1D1) and at steady state (C1D15) for Cmax and AUC (Figure 2 and Table 7).

Figure 2. Dose Proportionality Analysis of Avapritinib Systemic Exposure After Administration of 25 to 100 mg in Patients with ISM (Study BLU-285-2203, Part 1)



Abbreviations: $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time 0 extrapolated to infinity; $AUC_{0-\tau}$ = area under the plasma concentration-time curve over the dosing interval (τ = 24 hours); C1D1 = Cycle 1 Day 1; C1D15 = Cycle 1 Day 15; CI = confidence interval; C_{max} = maximum plasma concentration; ISM = indolent systemic mastocytosis; n = number of patients in each group.
Note: Both axes are on a log scale. Open circles represent individual values of exposure metric (C1D1: C_{max} or $AUC_{0-\infty}$; C1D15: C_{max} or $AUC_{0-\tau}$), shaded area = 90% CI of the slope, blue line = linear regression.

Table 11. Analysis of Dose Proportionality for Avapritinib Pharmacokinetic Parameters After Administration of 25 to 100 mg in Patients with ISM (Study BLU-285-2203, Part 1)

Cycle	Parameter	β_{est}	90% CI	Critical Interval	Conclusion
C1D1	C_{max}	1.11	0.83, 1.4	0.50-1.50	Proportional
	$AUC_{0-\infty}$	0.96	0.542, 1.37	0.50-1.50	Proportional
C1D15	C_{max}	0.95	0.671, 1.22	0.50-1.50	Proportional
	$AUC_{0-\tau}$	0.98	0.717, 1.25	0.50-1.50	Proportional

Abbreviations: $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time 0 extrapolated to infinity; $AUC_{0-\tau}$ = area under the plasma concentration-time curve over the dosing interval (τ = 24 hours); β_{est} = proportionality constant; C1D1 = Cycle 1 Day 1; C1D15 = Cycle 1 Day 15; CI = confidence interval; C_{max} = maximum plasma concentration; ISM = indolent systemic mastocytosis.
Note: The critical interval is the prespecified acceptable 90% CI of the slope.

BLU111207 Pharmacokinetics

The summary BLU111207 PK parameters by dose and day are displayed in Tables 12 and 13, for Part 1 and in Table 14 and 15 for Part 2.

Table 12. Summary of BLU111207 Pharmacokinetic Parameters on C1D1 by Dose - Part 1

Dose mg	Summary Statistic	C_{max} ng/mL	T_{max} h	T_{last} h	C_{trough} ng/mL	$t_{1/2}$ h	AUC_{0-last} ng.h/mL	AUC_{0-24h} ng.h/mL	$AUC_{0-\infty}$ ng.h/mL
25	N	9	9	9	9	2	9	9	2
	Mean	1.94	–	–	0.984	39.6	73.2	31.8	127
	SD	1.15	–	–	0.445	8.41	41.0	14.2	133
	CV%	59.1	–	–	45.2	21.3	56.1	44.6	104.1
	GeoMean	1.70	–	–	0.822	39.1	62.2	29.2	86.2
	GeoMean CV%	56.9	–	–	88.8	21.7	70.6	47.7	221.2
	Min	0.717	1.93	24.0	0.152	33.6	26.3	12.2	33.6
	Median	1.48	4.02	71.2	1.06	39.6	79.9	28.1	127
	Max	4.36	71.2	72.3	1.44	45.5	146	60.1	221
50	N	9	9	9	9	5	9	9	5
	Mean	4.79	–	–	1.28	44.1	123	51.1	145
	SD	3.66	–	–	0.853	27.1	74.0	26.3	116
	CV%	76.5	–	–	66.5	61.4	60.3	51.5	79.7
	GeoMean	3.65	–	–	0.906	38.5	104	45.7	112
	GeoMean CV%	93	–	–	133.9	61.3	67.6	52.5	93.5
	Min	1.44	1.00	48.0	0.208	20.5	47.9	24.9	56.3
	Median	4.22	4.00	71.7	1.71	33.8	91.2	38.3	76.7
	Max	11.5	71.5	72.0	2.36	88.5	234	95.0	313
100	N	10	10	10	10	5	10	10	5
	Mean	9.44	–	–	4.15	71.0	344	143	787
	SD	5.71	–	–	1.61	13.0	158	70.7	273
	CV%	60.4	–	–	38.8	18.3	46	49.5	34.6
	GeoMean	8.10	–	–	3.78	70.1	307	127	754
	GeoMean CV%	64.5	–	–	52.7	17.2	58.1	56.9	33.3
	Min	2.63	1.98	24.0	1.22	58.7	119	47.4	533
	Median	7.70	3.06	71.6	4.32	66.8	324	129	778
	Max	20.7	71.0	72.5	5.88	93.0	629	273	1230

Parameter exclusions: $t_{1/2}$ was excluded if λ_z was unreliable (defined in Section 8.1.1).

Table 13. Summary of BLU111207 Pharmacokinetic Parameters on C1D15 by Dose - Part 1

Dose mg	Summary Statistic	$C_{max,ss}$ ng/mL	T_{max} h	T_{last} h	$C_{trough,ss}$ ng/mL	$AUC_{0-last,ss}$ ng.h/mL	$AUC_{0-\tau}$ ng.h/mL	$R_{ac,AUC0-24h}$	$R_{ac,Cmax}$
25	N	9	9	9	9	9	9	9	9
	Mean	10.3	–	–	5.56	339	187	5.99	5.51
	SD	6.48	–	–	3.78	211	115	4.08	3.68
	CV%	63.1	–	–	67.9	62.3	61.7	68	66.8
	GeoMean	7.64	–	–	3.84	247	138	4.74	4.49
	GeoMean CV%	117.3	–	–	147.4	126.2	119.9	89.1	77.9
	Min	1.46	0.967	47.2	0.570	51.2	31.1	1.25	1.76
	Median	12.3	3.98	47.8	5.59	466	241	4.99	4.41
	Max	18.1	23.2	48.9	11.5	574	307	13.4	12.3
50	N	10	10	10	10	10	9	9	9
	Mean	17.8	–	–	10.6	584	339	6.81	6.10
	SD	12.9	–	–	9.30	495	273	6.23	6.18
	CV%	72.4	–	–	87.4	84.7	80.6	91.5	101.3
	GeoMean	12.6	–	–	6.39	368	214	4.68	3.36
	GeoMean CV%	129.9	–	–	186.8	162	167.8	120.5	230.5
	Min	2.32	0.500	23.0	0.824	66.7	42.2	1.10	0.202
	Median	18.0	2.00	48.0	9.66	518	376	4.38	2.99
	Max	39.4	23.0	48.8	28.2	1400	771	20.4	19.1
100	N	8	8	8	8	8	8	8	8
	Mean	41.1	–	–	34.7	1700	872	7.85	6.05
	SD	20.8	–	–	17.4	915	436	3.37	3.05
	CV%	50.7	–	–	50.2	53.9	50	42.9	50.5
	GeoMean	37.0	–	–	30.4	1440	779	6.91	5.17
	GeoMean CV%	50.7	–	–	63.2	74.8	54.9	68.5	76
	Min	20.6	2.00	24.8	12.8	424	413	1.73	1.24
	Median	32.8	4.00	47.9	32.6	1480	729	8.12	5.70
	Max	77.4	7.98	48.6	59.3	2950	1520	12.8	11.0

Accumulation ratios were determined by dividing the C1D15 (steady-state) value by the C1D1 value.

Table 14. Summary of BLU111207 Pharmacokinetic Parameters on C1D1 - Part 2

Dose mg	Summary Statistic	C_{max} ng/mL	T_{max} h	T_{last} h	AUC_{0-last} ng.h/mL
25	N	28	28	28	28
	Mean	2.82	–	–	11.4
	SD	1.44	–	–	6.28
	CV%	51.2	–	–	55.2
	GeoMean	2.46	–	–	9.79
	GeoMean CV%	61	–	–	64.7
	Min	0.553	1.08	4.98	1.99
	Median	2.74	4.00	6.00	10.8
	Max	7.51	6.00	6.17	31.4

Table 15. Summary of BLU111207 Pharmacokinetic Parameters on C2D1 - Part 2

Dose mg	Summary Statistic	$C_{max,ss}$ ng/mL	T_{max} h	T_{last} h	$AUC_{0-last,ss}$ ng.h/mL	$R_{ac,AUC0-last}$	$R_{ac,Cmax}$
25	N	30	30	30	30	23	23
	Mean	11.5	–	–	58.0	4.94	6.40
	SD	5.38	–	–	28.3	2.66	3.59
	CV%	46.9	–	–	48.9	53.7	56.1
	GeoMean	9.93	–	–	49.5	4.28	5.45
	GeoMean CV%	67.4	–	–	71	61.5	66.9
	Min	1.50	0.933	5.83	7.25	1.32	1.41
	Median	11.0	4.00	6.00	55.3	4.31	5.90
	Max	22.5	6.67	6.67	108	12.0	15.2

Accumulation ratios were determined by dividing the C2D1 (steady-state) value by the C1D1 value.

The Rmet for BLU111207 (as assessed by AUC) did not appear to be dose dependent but increased slightly between observation periods, the mean ranges were 6.1% – 7.8% and 8.0% – 15% on C1D1 and C1D15, respectively (Table 16).

Table 16. Summary of BLU111207 to Avapritinib Ratio on C1D1 by Dose - Part 1

Visit	Avapritinib Dose (mg)	N	Geometric Mean AUC*		R_{met} (%)
			Avapritinib	BLU111207	BLU111207/Avapritinib
C1D1	25	9	372	29.1	7.82
C1D1	50	9	753	45.7	6.05
C1D1	100	10	1750	127	7.23
C1D15	25	9	1340	138	10.3
C1D15	50	9	2670	214	7.98
C1D15	100	8	5220	779	14.9

*$AUC_{0\text{-}24}$ and AUC_{τ} were reported on C1D1 and C1D15, respectively. Only patients with valid AUCs for both analytes on the same visit were included.

BLU111208 Pharmacokinetics

The summary BLU111208 PK parameters by dose and day are displayed in Tables 17 and 18, for Part 1 and in Table 19 and 20 for Part 2.

Table 17. Summary of BLU111208 Pharmacokinetic Parameters on C1D1 by Dose - Part 1

Dose mg	Summary Statistic	C_{max} ng/mL	T_{max} h	T_{last} h	C_{trough} ng/mL	$t_{1/2}$ h	AUC_{0-last} ng.h/mL	AUC_{0-24h} ng.h/mL	$AUC_{0-\infty}$ ng.h/mL
25	N	9	9	9	9	3	9	9	3
	Mean	2.39	–	–	1.23	57.5	92.6	38.7	252
	SD	1.70	–	–	0.560	13.1	63.4	22.2	190
	CV%	71.1	–	–	45.7	22.7	68.5	57.4	75.3
	GeoMean	1.99	–	–	1.05	56.5	73.0	34.1	176
	GeoMean CV%	67.8	–	–	76.5	24.8	89.2	57	179.4
	Min	0.766	2.00	24.0	0.224	42.7	27.2	13.5	44.8
	Median	1.71	4.02	71.2	1.20	62.6	87.7	32.0	294
	Max	6.08	71.3	72.3	2.08	67.3	215	85.1	417
50	N	10	10	10	10	5	10	9	5
	Mean	5.85	–	–	2.13	116	154	65.7	430
	SD	4.97	–	–	1.37	153	108	33.4	513
	CV%	84.8	–	–	64.3	132.5	69.9	50.7	119.3
	GeoMean	4.47	–	–	1.57	68.1	114	58.5	227
	GeoMean CV%	87.8	–	–	120.2	140.1	113.8	54.8	199.8
	Min	1.53	1.00	7.92	0.379	33.0	16.2	28.5	82.5
	Median	4.69	4.02	71.6	2.25	37.2	130	50.2	108
	Max	18.1	71.5	72.0	4.10	387	313	115	1250
100	N	10	10	10	10	3	10	10	3
	Mean	12.0	–	–	6.64	82.8	509	194	1540
	SD	6.41	–	–	2.12	12.1	213	89.9	497
	CV%	53.4	–	–	32	14.7	41.9	46.4	32.4
	GeoMean	10.7	–	–	6.18	82.2	458	175	1490
	GeoMean CV%	54.6	–	–	47.3	14.7	56.5	52.1	31.1
	Min	4.23	1.98	24.0	1.92	71.3	156	73.7	1220
	Median	9.66	3.06	71.6	6.67	81.6	518	174	1280
	Max	25.4	71.0	72.5	9.32	95.5	861	339	2110

Parameter exclusions: $t_{1/2}$ was excluded if λ_z was unreliable (defined in Section 8.1.1).

Table 18. Summary of BLU111208 Pharmacokinetic Parameters on C1D15 by Dose - Part 1

Dose mg	Summary Statistic	$C_{max,ss}$ ng/mL	T_{max} h	T_{last} h	$C_{trough,ss}$ ng/mL	$AUC_{0-last,ss}$ ng.h/mL	$AUC_{0-\tau}$ ng.h/mL	$R_{ac,AUC0-24h}$	$R_{ac,Cmax}$
25	N	9	9	9	9	9	9	9	9
	Mean	15.8	–	–	9.99	577	312	8.38	7.23
	SD	9.21	–	–	6.49	354	190	4.99	4.13
	CV%	58.1	–	–	65	61.4	60.9	59.5	57.1
	GeoMean	12.4	–	–	6.81	419	234	6.86	6.23
	GeoMean CV%	100.7	–	–	158.1	130.4	117.2	84	64.3
	Min	3.23	2.00	47.2	1.07	72.0	47.0	1.58	2.37
	Median	19.8	4.00	47.8	11.4	801	405	6.16	5.60
	Max	26.6	23.2	48.9	17.9	899	519	15.0	13.8
50	N	10	10	10	10	10	9	9	10
	Mean	26.9	–	–	19.0	954	518	8.22	7.20
	SD	17.5	–	–	14.5	706	387	7.13	6.22
	CV%	65	–	–	76.6	74	74.6	86.8	86.4
	GeoMean	19.7	–	–	12.2	652	348	5.94	4.41
	GeoMean CV%	119.8	–	–	164.2	140.2	147.6	105.7	200.1
	Min	4.24	0.500	23.0	1.96	134	73.4	1.46	0.234
	Median	29.6	1.98	48.0	18.2	920	560	5.04	4.92
	Max	52.8	4.00	48.8	41.5	2020	1080	23.0	19.1
100	N	8	8	8	8	8	8	8	8
	Mean	61.2	–	–	55.1	2610	1330	8.85	6.77
	SD	26.2	–	–	22.8	1210	544	3.59	3.00
	CV%	42.7	–	–	41.3	46.5	40.8	40.6	44.3
	GeoMean	56.7	–	–	50.5	2300	1230	7.88	5.94
	GeoMean CV%	43.4	–	–	49.2	64.2	44.5	64.5	68.8
	Min	33.5	1.97	24.8	25.6	735	709	2.09	1.52
	Median	56.0	4.04	47.9	55.2	2460	1220	9.30	6.90
	Max	106	23.8	48.6	87.6	4190	2120	13.6	11.2

Accumulation ratios were determined by dividing the C1D15 (steady-state) value by the C1D1 value.

Table 19. Summary of BLU111208 Pharmacokinetic Parameters on C1D1 - Part 2

Dose mg	Summary Statistic	C_{max} ng/mL	T_{max} h	T_{last} h	AUC_{0-last} ng.h/mL
25	N	26	26	26	26
	Mean	3.12	–	–	12.8
	SD	1.69	–	–	7.28
	CV%	54.1	–	–	57.1
	GeoMean	2.70	–	–	10.9
	GeoMean CV%	61.6	–	–	65.1
	Min	0.600	1.08	4.98	2.21
	Median	2.98	4.00	5.99	10.9
	Max	8.54	6.00	6.17	35.6

Table 20. Summary of BLU111208 Pharmacokinetic Parameters on C2D1 - Part 2

Dose mg	Summary Statistic	$C_{max,ss}$ ng/mL	T_{max} h	T_{last} h	$AUC_{0-last,ss}$ ng.h/mL	$R_{ac,AUC0-last}$	$R_{ac,Cmax}$
25	N	30	30	30	30	22	22
	Mean	16.4	–	–	83.4	6.56	8.52
	SD	6.99	–	–	37.0	3.53	4.74
	CV%	42.7	–	–	44.4	53.8	55.6
	GeoMean	14.5	–	–	73.2	5.65	7.25
	GeoMean CV%	60.5	–	–	62.9	63.8	67.7
	Min	2.52	0.933	5.83	12.7	1.55	1.78
	Median	15.1	4.05	6.00	76.8	5.93	8.32
	Max	31.4	6.67	6.67	154	14.9	19.2

Accumulation ratios were determined by dividing the C2D1 (steady-state) value by the C1D1 value.

The Rmet for BLU111208 (as assessed by AUC) did not appear to be dose dependent but increased slightly between observation periods, the mean ranges were 7.8% – 10% and 13% – 24% on C1D1 and C1D15, respectively (Table 21).

Table 21. Summary of BLU111208 to Avapritinib Ratio on C1D1 by Dose - Part 1

Visit	Avapritinib Dose (mg)	N	Geometric Mean AUC*		R_{met} (%)
			Avapritinib	BLU111208	BLU111208/Avapritinib
C1D1	25	9	372	34.1	9.14
C1D1	50	9	753	58.5	7.76
C1D1	100	10	1750	175	9.96
C1D15	25	9	1340	234	17.5
C1D15	50	9	2670	348	13.0
C1D15	100	8	5220	1230	23.6

*AUC_{0-24} and AUC_{τ} were reported on C1D1 and C1D15, respectively. Only patients with valid AUCs for both analytes on the same visit were included.

Population Pharmacokinetic Analysis

The overall objective of the analysis was to update the population pharmacokinetic (PK) model to characterize avapritinib exposure as a function of dose, time after dosing, and patient characteristics, including the variability between and within patients with indolent systemic mastocytosis (ISM). To achieve this the following sub-objectives were set:

1. Perform exploratory graphical analysis of the plasma concentration-time profile of avapritinib in study BLU-285-2203.

2. Evaluate and update the previously developed population PK model for avapritinib in healthy volunteers (HVs), patients with gastrointestinal stromal tumours (GIST), and patients with advanced systemic mastocytosis (AdvSM) to describe the plasma concentration-time data from clinical study BLU-285-2203 in patients with ISM.

(a) Quantify population PK parameters, including typical parameter values and random inter-individual and residual variability.

(b) Identify and quantify covariate effects which describe variability in the PK ofavapritinib.

3. Estimate the maximum plasma concentration at steady state (Cmax,ss) and the area under the plasma concentration-time curve from time 0 to 24 hours at steady state (AUC0-24,ss) for patients recruited in study BLU-285-2203 Part 2, on cycle 1 day 15 (C1D15, steady state) where only sparse PK samples were collected.

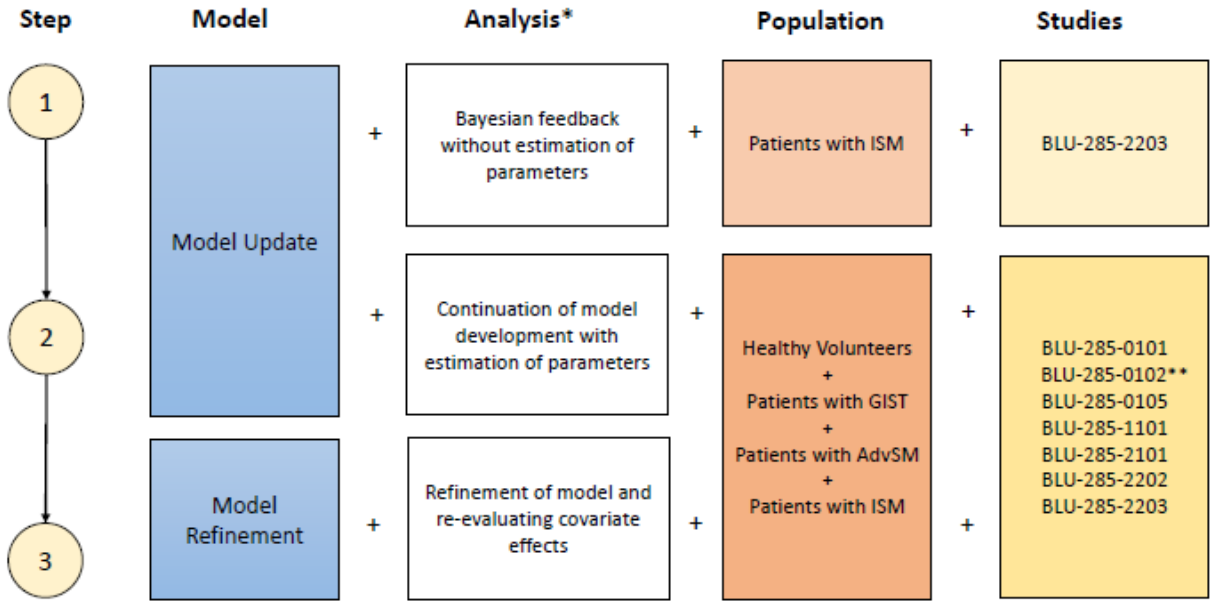
The PK Model was updated in a step-wise manner as follows:

1. Previously developed population PK model was fitted to the data from only study BLU-285-2203 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 in the next step.

2. Data from other studies were included in the model with full parameter estimation.

3. Covariate effects were evaluated through visual inspection of covariate-eta relationships for any obvious trends.

Figure 3. Model Development Flowchart



*The initial model was based on the previously developed population PK model.
** Only fasted observations from study BLU-285-0102 were included in the analysis

A summary of the available studies included in the final analysis dataset is presented in Table 22.

Table 22. Summary of Data Available for the Model Building

Study	Study Description	Dose (Formulation Process)	n	PK Sampling
BLU-285-0101	An open-label, randomized, single-dose, 2-way crossover study to evaluate the relative bioavailability of avapritinib (tablet vs capsule) in healthy adult male subjects	1 x 200 mg (tablet) fasted state: 10h before, & 4h after dosing 2 x 100 mg (capsule) fasted state: 10h before, & 4h after dosing	30	Predose, 0.5, 1, 1.5, 2, 2.5, 3.25, 4, 4.75, 5.5, 6, 8, 10, 12, 24, 48, & 72h
BLU-285-0102	An open-label, randomized, single-dose, 2-way crossover study to evaluate the e ect of food on the pharmacokinetics of avapritinib in healthy adult male subjects	2 x 100 mg (tablet) following an overnight fast 2 x 100 mg (tablet) overnight fast, followed by a high-fat meal 30 min before dosing	30*	Predose, 0.5, 1, 1.5, 2, 2.5, 3.25, 4, 4.75, 5.5, 6, 8, 10, 12, 24, 48, 72, 96, 120, & 168h
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	4 x 100 mg (tablet) following an overnight fast 1 x 400 mg (tablet) following an overnight fast	62	Predose, 0.5, 1, 1.5, 2, 2.5, 3.25, 4, 4.75, 5.5, 6.25, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216 & 240h

Continued on next page.[i] Intensive PK sampling, [s] Sparse PK sampling, Fed subjects from study BLU-285-0102 were not included in the population PK analysis. In study BLU-285-2101, Part 2, and study BLU-285-2202 (intensive sampling), the Cycle 1 Day 2 and Day 16 dose were not administered to allow for collection of the 48-hour postdose sample on Day 3 and Day 17, respectively. Includes patients from Parts 1 & 2. In study BLU-285-2203 (Part 1), the Cycle 1 Day 2, Cycle 1 Day 3, and Cycle 1 Day 16 dose were not administered to allow for collection of the 48 and 72-hour postdose samples. n number of subjects included in the analysis.

Study	Study Description	Dose (Formulation Process)	n	PK Sampling
BLU-285-1101	Phase I, open-label, first-in-human study in patients with GIST & other relapsed refractory solid tumours	**Dose-Escalation (Part 1)** 30, 60, 90, 135, 200, 300, 400, 600 mg (capsule or tablet) once daily fasted 2h before & until 1h after dosing	43	**Dose-Escalation (Part 1)** Lead-in: Predose, 0.5, 1, 2, 4, 8, 10, 24, 48, 72h C1D15: Predose, 0.5, 1, 2, 4, 8h C2-4: Predose
		Dose-Expansion (Part 2: 3 groups) 400, 300 mg (capsule or tablet) once daily fasted 2h before & until 1 hr after dosing Group 1[i] Group 2[i] Group 3[s]	178	**Dose-Expansion (Part 2)** *Intensive Sampling Schedule* C1: Predose, 0.5, 1, 2, 4, 8, 24h C1D15: Predose, 0.5, 1, 2, 4, 8h C2-4: Predose *Sparse Sampling Schedule* C1D15: Predose, 1, 4, 6-8h C2-4: Predose
BLU-285-2101	Phase 1, open-label, first-in-human study in patients with AdvSM and relapsed or refractory myeloid malignancies	**Dose-Escalation (Part 1)** 30, 60, 100, 130, 200, 300, 400 mg (capsule or tablet) once daily fasted 2h before & until 1h after dosing	32	**Dose-Escalation (Part 1)** C1D1: Predose, 0.5, 1, 2, 4, 8, 24h C1D15: Predose, 0.5, 1, 2, 4, 8h C2-4: Predose
		Dose-Expansion (Part 2) 300 or 200 mg (capsule or tablet) once daily fasted 2h before & until 1h after dosing Cohort 1 Cohort 2**	 37 17	**Dose-Expansion (Part 2)** *Cohort 1:* C1D1: Predose, 0.5, 1, 2, 4, 8, 24h C1D15: Predose, 0.5, 1, 2, 4, 8h C2-4: Predose *Cohort 2:* C1D1: Predose, 0.5, 1, 2, 4, 8, 10, 24, 48h C1D15: Predose, 0.5, 1, 2, 4, 8, 10, 24, 48h C2-4: Predose

Continued on next page.[i] Intensive PK sampling, [s] Sparse PK sampling, Fed subjects from study BLU-285-0102 were not included in the population PK analysis. In study BLU-285-2101, Part 2, and study BLU-285-2202 (intensive sampling), the Cycle 1 Day 2 and Day 16 dose were not administered to allow for collection of the 48-hour postdose sample on Day 3 and Day 17, respectively. Includes patients from Parts 1 & 2. In study BLU-285-2203 (Part 1), the Cycle 1 Day 2, Cycle 1 Day 3, and Cycle 1 Day 16 dose were not administered to allow for collection of the 48 and 72-hour postdose samples. n number of subjects included in the analysis.

Study	Study Description	Dose (Formulation Process)	n	PK Sampling
BLU-285-2202	An open-label, single arm, Phase 2 study to evaluate e cacy and safety of avapritinib in patients with AdvSM	200 mg (tablet) once daily fasted 2h before & until 1h after dosing	58	**Intensive Sampling (n 15)**** C1D1: Predose, 0.5, 1, 2, 4, 8, 10, 24, 48h C1D15: Predose, 0.5, 1, 2, 4, 8, 10, 24, 48h C2, C3, C5: Predose, 1 time point between 1-8h **Standard Sampling (all other patients)** C1D1: Predose, 1 time point between 1-8h C1D15: Predose, 1, 4, 6-8h C2, C3, C5: Predose, 1 time point between 1-8h
BLU-285-2203	A 3-part, randomized, double-blind, placebo-controlled Phase 2 study to evaluate e cacy and safety of avapritinib in patients with ISM	**Part 1** 25, 50, 100 mg (tablet) once daily for 16 weeks fasted 2h before & until 1h after dosing	30	**Part 1 (Intensive)** C1D1: Predose, 0.5, 1, 2, 4, 8, 10, 24, 48, 72h C1D15: Predose, 0.5, 1, 2, 4, 8, 10, 24, 48h C2D1, C3D1, C4D1: Predose, 1 time point between 1-8h
		Part 2 25 mg (tablet) once daily for 6 cycles fasted 2h before & until 1h after dosing	139	**Part 2 (Intensive, n 40)** C1D1: Predose, 1, 4, 6-8h C2D1: Predose, 1, 4, 6-8h C3D1-C7D1: Predose, 1 time point between 1-8h **Part 2 (Sparse)** C1D1-C7D1: Predose, 1 time point between 1-8h
		Part 3 (Open-Label Extension) 25 mg (tablet) once daily for up to 5 years fasted 2h before & until 1h after dosing	235	**Part 3** *No PK Samples*

[i] Intensive PK sampling, [s] Sparse PK sampling, Fed subjects from study BLU-285-0102 were not included in the population PK analysis. In study BLU-285-2101, Part 2, and study BLU-285-2202 (intensive sampling), the Cycle 1 Day 2 and Day 16 dose were not administered to allow for collection of the 48-hour postdose sample on Day 3 and Day 17, respectively. Includes patients from Parts 1 & 2. In study BLU-285-2203 (Part 1), the Cycle 1 Day 2, Cycle 1 Day 3, and Cycle 1 Day 16 dose were not administered to allow for collection of the 48 and 72-hour postdose samples. n number of subjects included in the analysis.

The PK analysis population included all subjects and patients that received at least one dose of avapritinib with valid avapritinib concentrations from studies shown in Table 22.

Dataset

A total of 3579 observations in the NONMEM dataset were excluded from the analysis. The majority of these data had dose time related to the samples not known accurately (12.6%), were either BLQ (8.5%) or were associated with the 'fed' treatment arm in BLU-285-0102 (4.1%). A detailed summary of the excluded data is shown in Table 23.

Table 23. Summary of Data in the NONMEM Dataset which were Excluded from Analysis

	BLU-285-0101	BLU-285-0102	BLU-285-0105	BLU-285-1101	BLU-285-2101	BLU-285-2202	BLU-285-2203	Total
Original observations	1020	1200	3100	3264	1433	574	2693	13284
Invalid Datetime	0	0	0	0	0	2 (0.3%)	23 (0.9%)	25 (0.2%)
Duplicate PK measures	0	0	0	0	24 (1.7%)	0	0	24 (0.2%)
Predose BLQ exclusions	30 (2.9%)	30 (2.5%)	62 (2%)	197 (6%)	84 (5.9%)	60 (10.5%)	154 (5.7%)	617 (4.6%)
Missing concentrations	0	1 (0.1%)	0	0	0	0	0	1 (0%)
Postdose BLQ exclusions	57 (5.6%)	64 (5.3%)	70 (2.3%)	122 (3.7%)	51 (3.6%)	9 (1.6%)	145 (5.4%)	518 (3.9%)
Concentrations prior to first dose	0	0	0	3 (0.1%)	1 (0.1%)	0	2 (0.1%)	6 (0%)
Imprecise reference dose time	0	0	0	705 (21.6%)	45 (3.1%)	71 (12.4%)	882 (32.8%)	1703 (12.8%)
Fed treatment arm	0	541 (45.1%)	0	0	0	0	0	541 (4.1%)
Anomalous concentrations*	3 (0.3%)	2 (0.2%)	13 (0.4%)	0	11 (0.8%)	0	1 (0%)	30 (0.2%)
Subjects without usable conc data	0	0	0	36 (1.1%)	0	0	0	36 (0.3%)
Duplicate concentration records	0	0	0	0	0	0	74 (2.7%)	74 (0.6%)
Unresolved date time issues	0	0	0	0	0	0	4 (0.1%)	4 (0%)
Analysis observations	930 (91.2%)	562 (46.8%)	2955 (95.3%)	2201 (67.4%)	1217 (84.9%)	432 (75.3%)	1408 (52.3%)	9705 (73.1%)

BLQ – below the limit of quantitation. Note: the fed treatment arm from study BLU-285-0102 is excluded from the data analysis.
Further explanation for these exclusions is included in Appendix 17.2.1.

A full summary of the demographics for all data are provided in Tables 24 and 25.

Table 24. Categorical Covariates for All Subjects in the Model Build Data

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

Table 25. Continuous Covariates for All Subjects in the Model Build Data

	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.

A full summary of the demographics for patients with ISM are provided in Tables 26 and 27.

Table 26. Categorical Covariates for the Patients with ISM in the Model Build Data

Sex	Race	Form	PPI Use	H2RA Use	CYP3A4 Inhib.	CYP3A4 Ind.
Male: 48 (28.4%) Female: 121 (71.6%)	White: 134 (79.3%) Black: 1 (0.6%) Asian: 1 (0.6%) Other: 4 (2.4%) Unknown: 29 (17.2%)	Tablet: 169 (100%)	Not Used: 123 (72.8%) Used: 46 (27.2%)	Not Used: 53 (31.4%) Used: 116 (68.6%)	Not Used: 162 (95.9%) Used: 7 (4.1%)	Not Used: 154 (91.1%) Used: 15 (8.9%)

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).

Table 27. Continuous Covariates for the Patients with ISM in the Model Build Data

	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	169	169	169	169	169	169	169	169	169	169	169
Mean	48.8	80.6	169	50.9	43.9	83.6	23.6	19.9	7.9	118	88.5
SD	12	17.7	9.79	11.7	3.68	30.8	17.1	14.5	4.5	32.8	18.8
CV%	24.5	22	5.8	23	8.36	36.9	72.6	73.1	57	27.9	21.3
Median	50	79.4	167	47.6	44	77	19	18	6.84	114	88.2
Min	18	45	142	31.4	35	39	7	7	1.71	44.8	36
Max	77	126	196	81	55	219	112	182	29.1	218	143

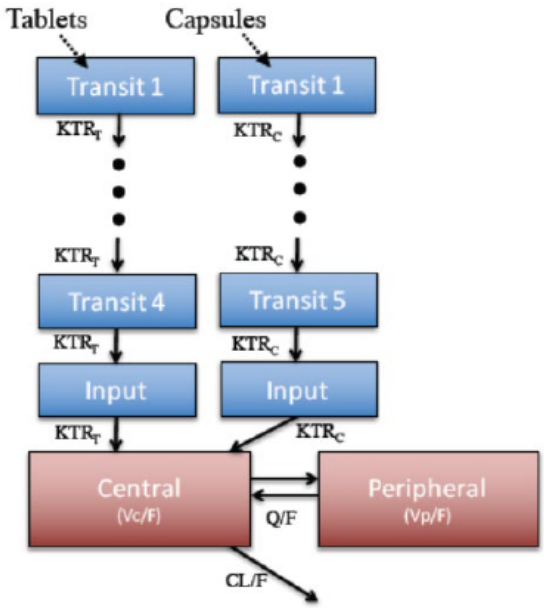
LBW Lean body weight, ALB Albumin, ALP Alkaline phosphatase, ALT Alanine transaminase, AST Aspartate transaminase, CrCL Creatinine clearance, eGFR Estimated glomerular filtration rate.

Previously Developed PK Model for Avapritinib

The analysis was performed by updating the previously developed population PK model in HVs, patients with GIST, and patients with AdvSM, with data from patients with ISM. The PK model was a two-compartment disposition model with absorption modelled via 4 or 5 transit compartments that was dependent on the formulation.

A schematic of the previously developed population PK model for avapritinib is shown in Figure 4, and the parameter estimates of the model are shown in Table 28.

Figure 4. Schematic of the Previously Developed Population PK model for Avapritinib



Abbreviations: CL/F = apparent oral clearance, unadjusted for bioavailability; KTR_C = absorption transit rate constant for capsules; KTR_T = absorption transit rate constant for tablets; Q/F = apparent intercompartmental clearance; V_c/F = apparent volume of distribution for the central compartment; V_p/F = apparent volume of distribution for the peripheral compartment.

Table 28. Parameter Estimates for the Previously Developed Population PK Model

Parameter Name	Estimated Value (95% CI)
Apparent Clearance (CL/F, L/h)	16 (15.3 - 16.8)
Maximum Time-dependent Decrease of CL/F for AdvSM Patients (Fold)	0.386 (0.318 - 0.445)
Time at Half Maximum Decrease of CL/F for AdvSM Patients (h)	200 (120 - 314)
Covariate Effect of AdvSM on CL/F (Fold)	1.32 (1.17 - 1.48)
Apparent Central Volume of Distribution (V_c/F, L)	999 (953 - 1060)
Covariate Effect of LBW on V_c/F	0.336 (0.114 - 0.533)
Apparent Peripheral Volume of Distribution (V_p/F, L)	233 (210 - 256)
Apparent Inter-compartmental Clearance (Q/F, L/h)	13.7 (10.8 - 17.2)
Rate of Transit Absorption for Tablets (KTR_T, 1/h)	3.31 (3.23 - 3.4)
Rate of Transit Absorption for Capsules (KTR_C, 1/h)	3.79 (3.65 - 3.93)
Covariate Effect of AdvSM on KTR (Fold)	1.23 (1.15 - 1.31)
Covariate Effect of PPI Use on KTR (Fold)	0.845 (0.786 - 0.906)
Relative Bioavailability for AdvSM Patients (Fold)	0.65 (0.607 - 0.703)
Relative Bioavailability for GIST Patients (Fold)	0.819 (0.777 - 0.87)
Covariate Effect of PPI Comedication on F (Fold)	0.837 (0.784 - 0.896)
Between Subject Variability for CL/F (%)	43.3 (39.8 - 46.5)
Between Subject Variability for V_c/F (%)	47.8 (44.2 - 52.5)
Correlation between CL/F-V_c/F (–)	0.623 (0.563 - 0.641)
Between Subject Variability for Rate of Transit Absorption (%)	26.7 (20.7 - 31.4)
Between-occasion Variability for Bioavailability (%)	25.1 (23 - 27.4)
Between-occasion Variability for Rate of Transit Absorption (%)	30.8 (26.9 - 34.6)
Residual Unexplained Variability for Study BLU-285-0101/BLU-285-0102 (Proportional) (%)	17.1 (16.3 - 18)
Residual Unexplained Variability for Study BLU-285-0105 (Proportional) (%)	18.4 (17.8 - 19.2)
Residual Unexplained Variability for Study BLU-285-2101/BLU-285-2202 (Proportional) (%)	23 (21.9 - 24.2)
Residual Unexplained Variability for Study BLU-285-1101 (Proportional) (%)	26.2 (25 - 27.4)

Covariate Model Development

The covariates that were considered are presented in Table 29. All covariates that have been identified in the previously developed population PK model were included a priori in the model update.

Table 29. Covariates Assessed in the Population PK Model Update

Covariate	Code	Value	Parameters
Age at baseline (yr)	AGE	Continuous	CL F, V_c F
Total body weight at baseline (kg)	WT	Continuous	CL F, V_c F
[a]Lean body weight at baseline (kg)	LBW	Continuous	CL F, V_c F
[b]Creatinine clearance at baseline (mL min)	CRCL	Continuous	CL F
[c]Estimated glomerular filtration rate at baseline (mL min 1.73 m^2)	EGFR	Continuous	CL F
Alanine aminotransferase at baseline (IU L)	ALT	Continuous	CL F
Aspartate aminotransferase at baseline (IU L)	AST	Continuous	CL F
Bilirubin at baseline (mol L)	BILI	Continuous	CL F
Albumin at baseline (g L)	ALB	Continuous	CL F
Sex	SEX	Categorical	CL F, V_c F
Race	RACE	Categorical	CL F, V_c F
Concomitant CYP3A4 inhibitor	CYPINB	Categorical	CL F, F
Concomitant CYP3A4 inducer	CYPIND	Categorical	CL F, F
Concomitant PPI	PPI	Categorical	CL F, KTR, F
Concomitant H2RA	H2RA	Categorical	CL F, KTR, F
Formulation (capsule, tablet)	FORM	Categorical	CL F, KTR, F
Disease Subpopulation (HV GIST SM)	DSSTAT	Categorical	CL F, V_c F, KTR, F

CL F apparent clearance, V_c F apparent central volume of distribution, KTR absorption transit rate constant, F relative bioavailability

[a]LBW(male)[16] (9270 WT) (6680 (216 BMI))

[a]LBW(female)[16] (9270 WT) (8780 (244 BMI))

[b]CRCL(male)[17] ((140 - AGE) WT) (Serum Creatinine (mol L) 72)

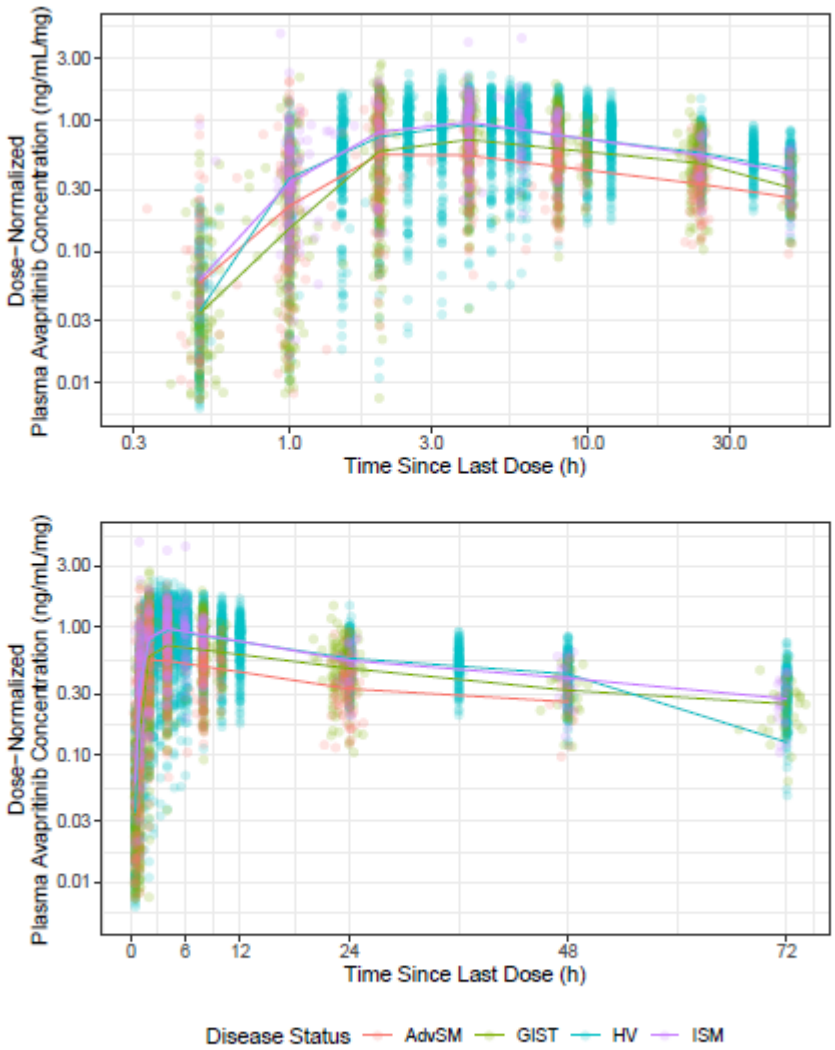
[b]CRCL(female)[17] ((140 - AGE) WT 0.85) (Serum Creatinine (mol L) 72)

[c]eGFR[17] 175 (Serum Creatinine (mg dL)) $^{1.154}$ (AGE) $^{0.203}$ (0.742 if female) (1.212 if African American)

Exploratory Graphical Analysis (Objective 1)

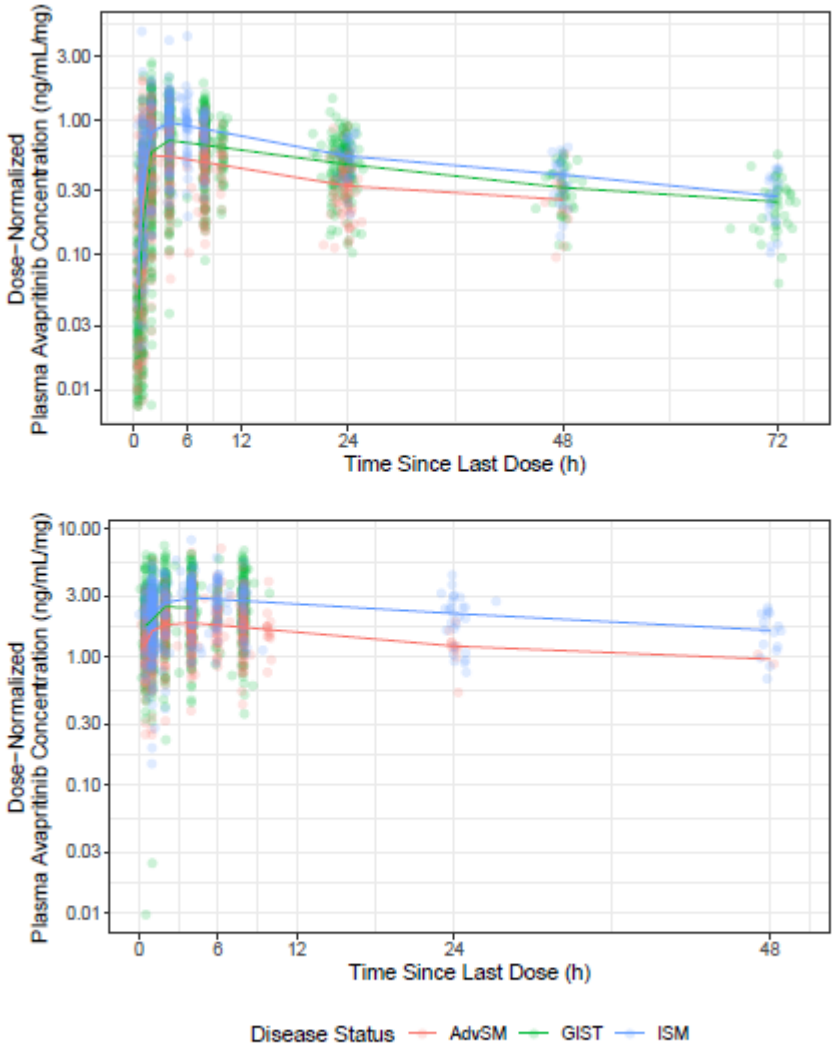
Dose-normalized concentration-time profiles for the HV (studies BLU-285-0101, BLU- 285-0102, and BLU-285-0105), patients with GIST (BLU-285-1101), patients with AdvSM (studies BLU-285-2101 and BLU-285-2202), and patients with ISM (study BLU- 285-2203) at C1D1 and at C1D15 are displayed in Figures 5 and 6.

Figure 5. Dose-Normalized Plasma Concentration-Time Profiles for Avapritinib in Healthy Volunteers and Patients with GIST, AdvSM or ISM (C1D1)



The solid lines show the median, with the filled circles representing the observed data. **Top Panel**: Concentration-time profiles for the first 48 hours postdose. X-axis and Y-axis on log-scale. **Bottom Panel**: Concentration-time profiles for up to 72 hours postdose. Y-axis on log-scale. Data below the LLOQ (2.00 ng mL) were excluded. C1D1 Cycle 1 Day 1.

Figure 6. Dose-Normalized Plasma Concentration-Time Profiles for Avapritinib in Patients with ISM, GIST, or AdvSM (C1D1 & C1D15)



The solid lines show the median, with the filled circles representing the observed data. **Top Panel**: Concentration-time profiles for up to 72 hours postdose (C1D1). **Bottom Panel**: Concentration-time profiles for the first 48 hours postdose (C1D15). Data below the LLOQ (2.00 ng mL) were excluded. Y-axis on log-scale. C1D1 Cycle 1 Day 1, C1D15 Cycle 1 Day 15.

Population Pharmacokinetic Model Development (Objective 2)

The final updated model comprised the same structure and covariate effects as the previous model. No additional covariates were included in the model based on visual inspection of the covariate-eta relationships. Table 30 reports the updated parameter estimates of the model.

Table 30. Parameter Estimates for the Final Population PK Model

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 E ect 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 E ect 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 E ect of AdvSM on KTR (Fold)	1.19 (3.2, 1.11 - 1.26)
Covariate E ect 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 E ect 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.

Evaluation of Covariates in the Final Population PK Model

Impact of Lean Body Weight on Avapritinib PK

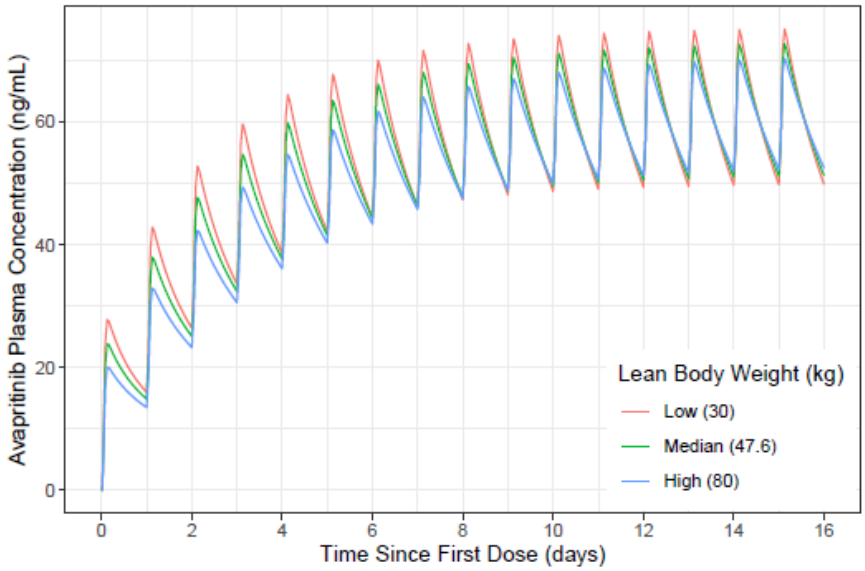
LBW was included a priori as a covariate on Vc/F, which was the same as previously described in the population PK model for HVs, patients with GIST and patients with AdvSM.

The expression in the final population PK model is shown in Equation 7:

$$VcF = 971 * (LBW=47.6)^{0.354} \quad \text{Equation 7}$$

Where 0.354 was the estimated covariate effect of LBW on Vc/F (note that the median LBW of patients with ISM in the analysis population was 47.6 kg). A graphical representation of the relationship between LBW and Vc/F is shown in Figure 7.

Figure 7. Model Predicted Effect of Lean Body Weight



Solid lines represent simulated median concentration-time profiles assuming a patient with ISM with median lean body weight of 47.6 kg receiving 25 mg avapritinib (as tablet formulation) QD.

Impact of Proton Pump Inhibitor (PPI) Use on Avapritinib PK

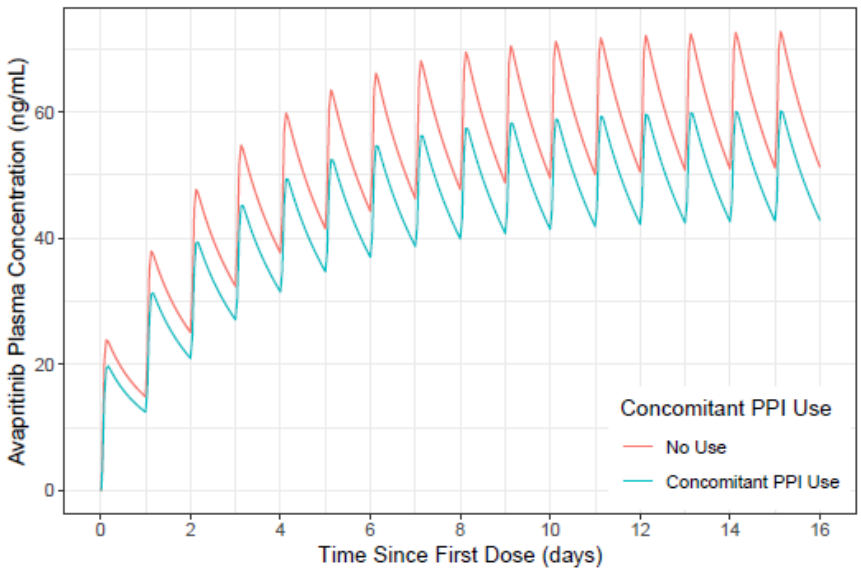
Concomitant PPI use was included a priori as a covariate on bioavailability (F) and KTR. The expressions in the final population PK model is shown in Equation 8 and 9:

F = GISTF * SMF * PPIF Equation 8

KTR = 3.41 (if Tablets) or 3.78 (if Capsules) SMKTR PPIKTR Equation 9

where GISTF and SMF are the covariate effects of being a GIST or AdvSM patient on F, respectively, and PPIF is the estimated covariate effect of concomitant PPI use, where it is 1 if there was no concomitant PPI use (0 to less than 5 consecutive days of PPI use prior to the PK sample), and 0.833 if there was equal or more than 5 consecutive days of PPI use prior to the PK sample. For the effect on KTR (Equation 9, PPIKTR), it is 1 if there was no concomitant PPI use, and 0.869 if there was equal or more than 5 consecutive days of PPI use prior to the PK sample collection.

Figure 8. Model Predicted Effect of Concomitant PPI



Solid lines represent simulated median concentration-time profiles assuming a patient with ISM with median lean body weight of 47.6 kg receiving 25 mg avapritinib (as tablet formulation) QD.

Impact of Patient Population on Avapritinib PK

The covariate effect of patient population on F is shown in Equation 8. Patients with ISM had overall exposure comparable to HVs and the relative F for patients with ISM and HVs were fixed to 1. As previously reported, patients with GIST had a reduced F compared to HVs and GISTF was estimated to be 0.856 (GISTF was fixed to 1 for other patient populations). Similarly patients with AdvSM had the lowest overall exposure compared to the other patient populations and SMF was estimated to be 0.667 (SMF was fixed to 1 for other patient populations).

Patients with AdvSM was also found to have higher KTR previously and this relationship was included in the model a priori. The covariate effect of patient population on KTR is shown in Equation 9, where KTR is dependent on the formulation, and SMKTR was to be 1.19 for patients with AdvSM (SMKTR was fixed to 1 for other patient populations).

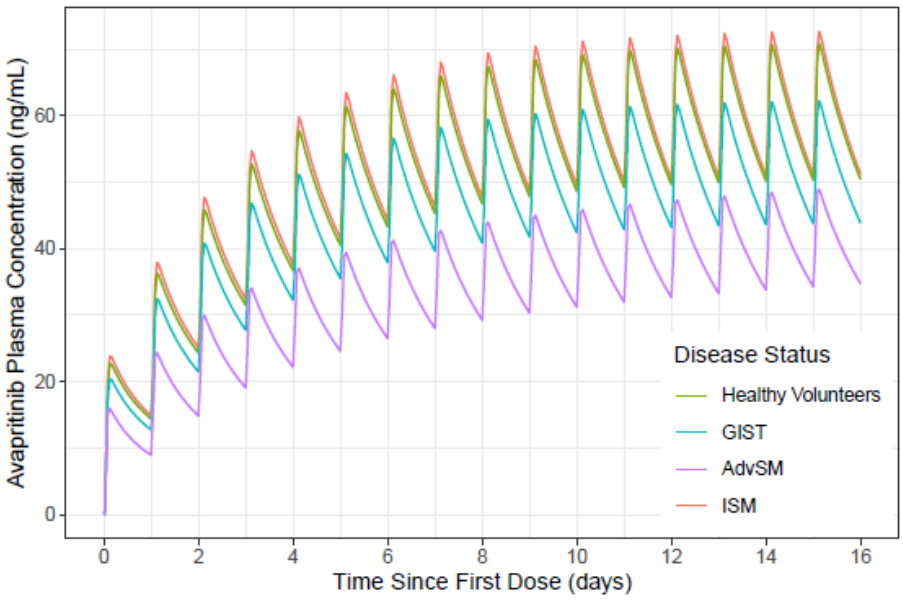
As previously reported, patients with AdvSM exhibited time-dependent reduction in CL/F, which is shown in Equations 10-11

CL F=16.9*SMCL*TIMCL Equation 10

TIMCL=1 (if Healthy or GIST) or 1- (Time (h)*0.394)/(190*Time(h)) (if AdvSM) Equation 11

where SMCL is the covariate effect of AdvSM on CL/F and estimated to be 1.3. TIMCL is a time-dependent decrease in CL/F for patients with AdvSM, where the maximum decrease in CL/F compared to other patient population was 39.4%, and the time at half maximum decrease of CL/F was estimated to be 190 hours since the first dose. A graphical representation of the overall effect of patient population on avapritinib is shown in Figure 9.

Figure 9. Model Predicted Effect of Different Patient Population

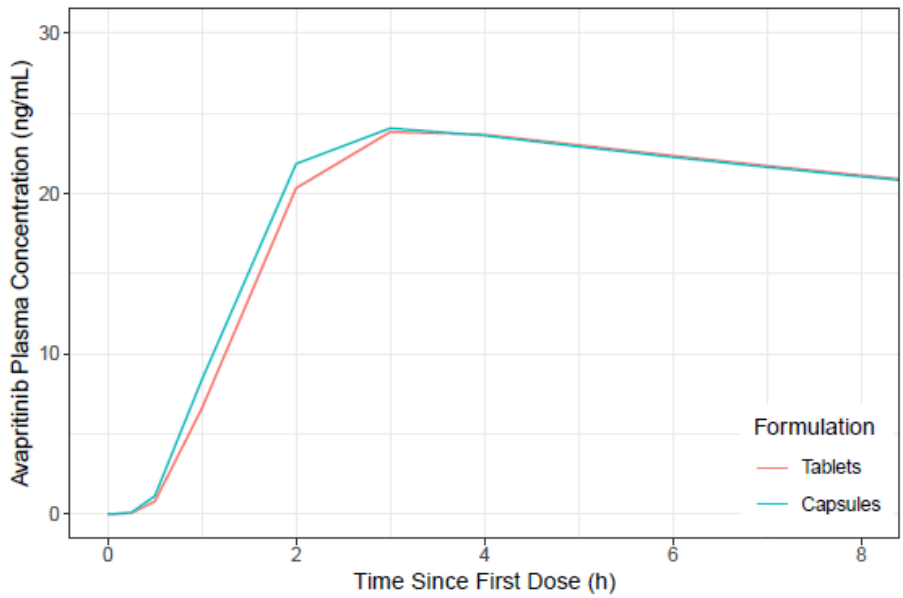


Solid lines represent simulated median concentration-time profiles assuming a patient with ISM with median lean body weight of 47.6 kg receiving 25 mg avapritinib (as tablet formulation) QD.

Impact of Oral Formulation on Avapritinib PK

Formulation of avapritinib was included a priori as a covariate on KTR, as shown in Equation 9, where KTR was dependent upon formulation of the administration i.e. tablets or capsules. A graphical representation of the relationship between formulation and KTR is shown in Figure 10.

Figure 10. Model Predicted Effect of Different Oral Formulation

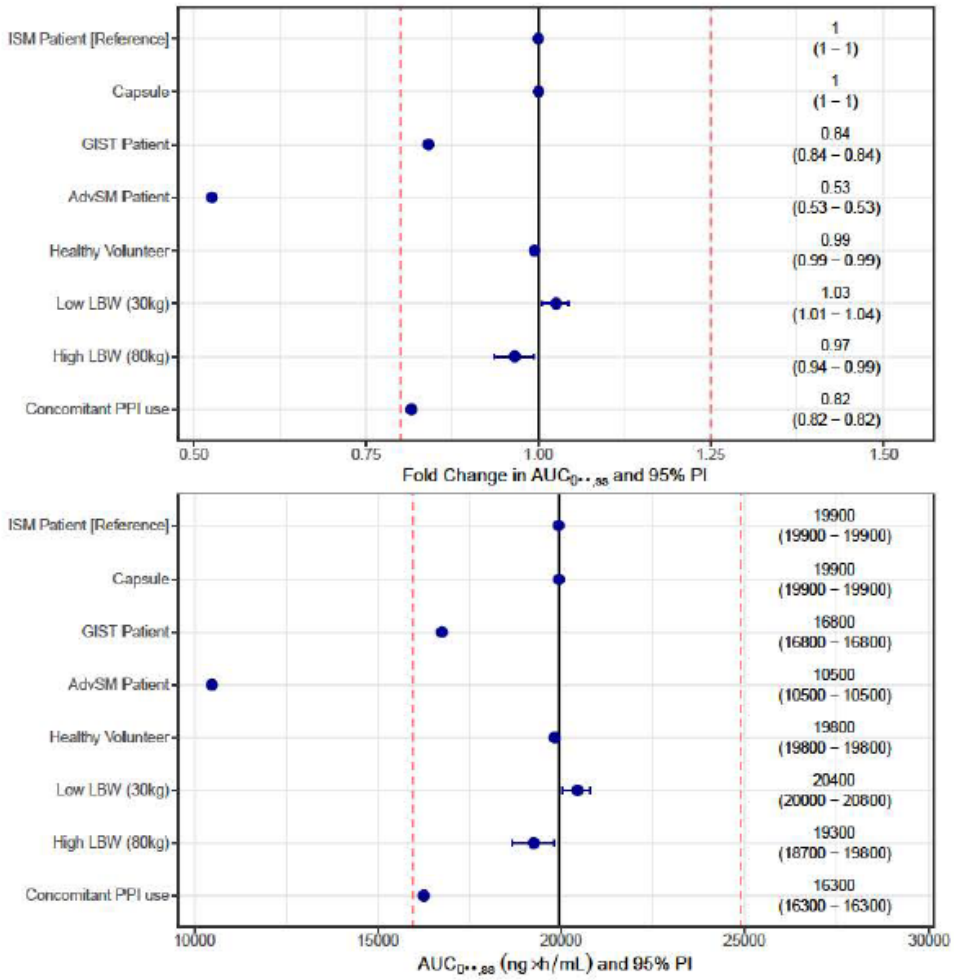


Solid lines represent simulated median concentration-time profiles assuming a patient with ISM with median lean body weight of 47.6 kg receiving 25 mg avapritinib (as tablet formulation) QD.

Forest Plot Investigating the Impact of Covariate Effects on Avapritinib Exposure

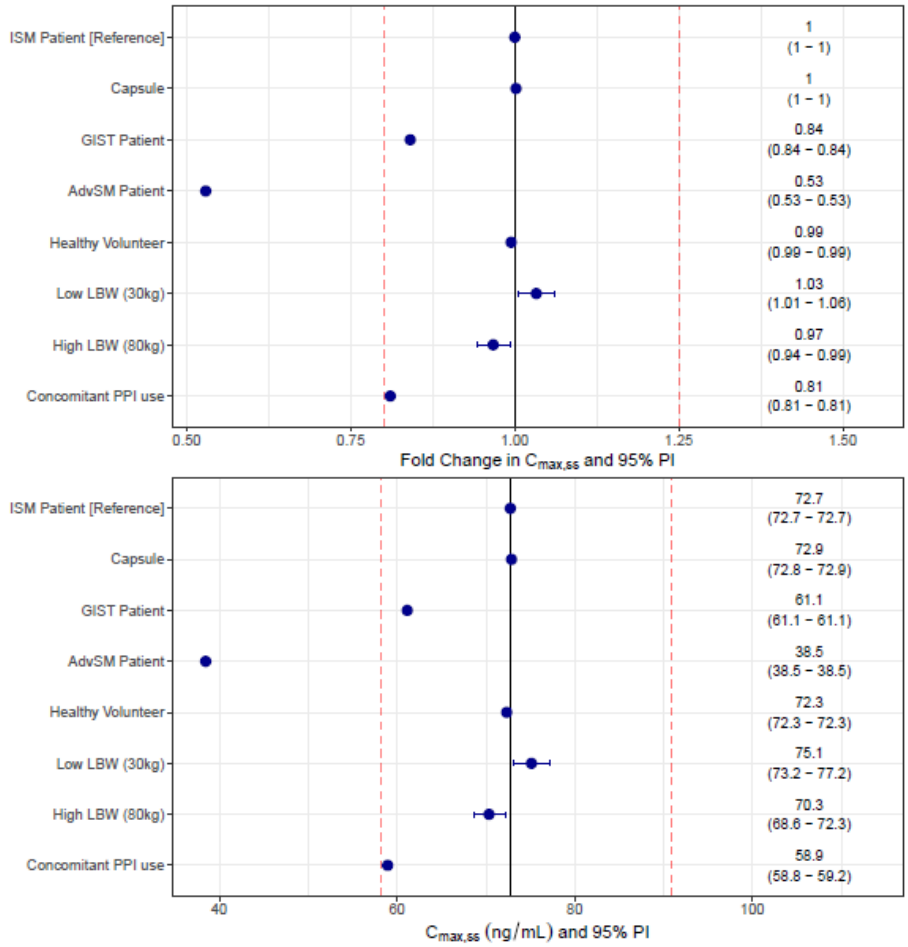
The impact of covariates on the exposure metrics (AUC0T,ss and Cmax,ss) are summarized in Figures 11 and 12.

Figure 11. Model Predicted Effect of Covariates on AUC0-T,ss



The solid black line represents no impact of the covariate with the reference subject referring to a patient 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 80-125% range of the reference subject. The blue dots and error bars represent the median and 95% (2.5^{th} to 97.5^{th} 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.

Figure 12. Model Predicted Effect of Covariates on Cmax,ss

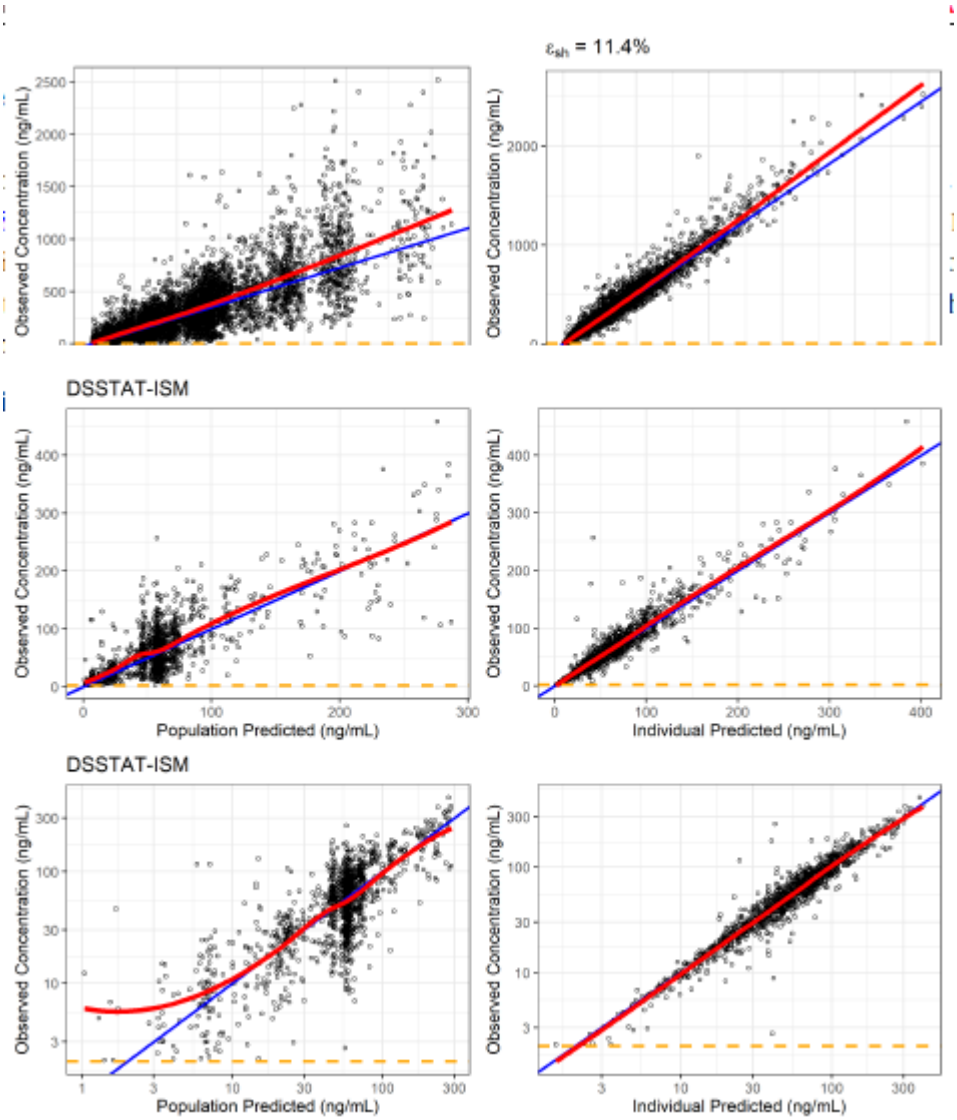


The solid black line represents no impact of the covariate with the reference subject referring to a patient with ISM with median lean body weight of the 47.6 kg receiving 25 mg dose of avapritinib (tablet formulation) QD, sampled every hour on Day 15 (steady state). Dashed red lines represent the 80-125% range of the reference subject. The blue dots and error bars represent the median and 95% (2.5^{th} to 97.5^{th} percentiles of the simulations) prediction intervals (PI) of the covariate e ect based on 1000 simulated subjects within each group including uncertainty on the fixed e ect.

Evaluation of the Final Population PK Model

Plots of observed versus population predicted plasma concentrations and observed versus individual predicted plasma concentrations are presented below in Figure 13.

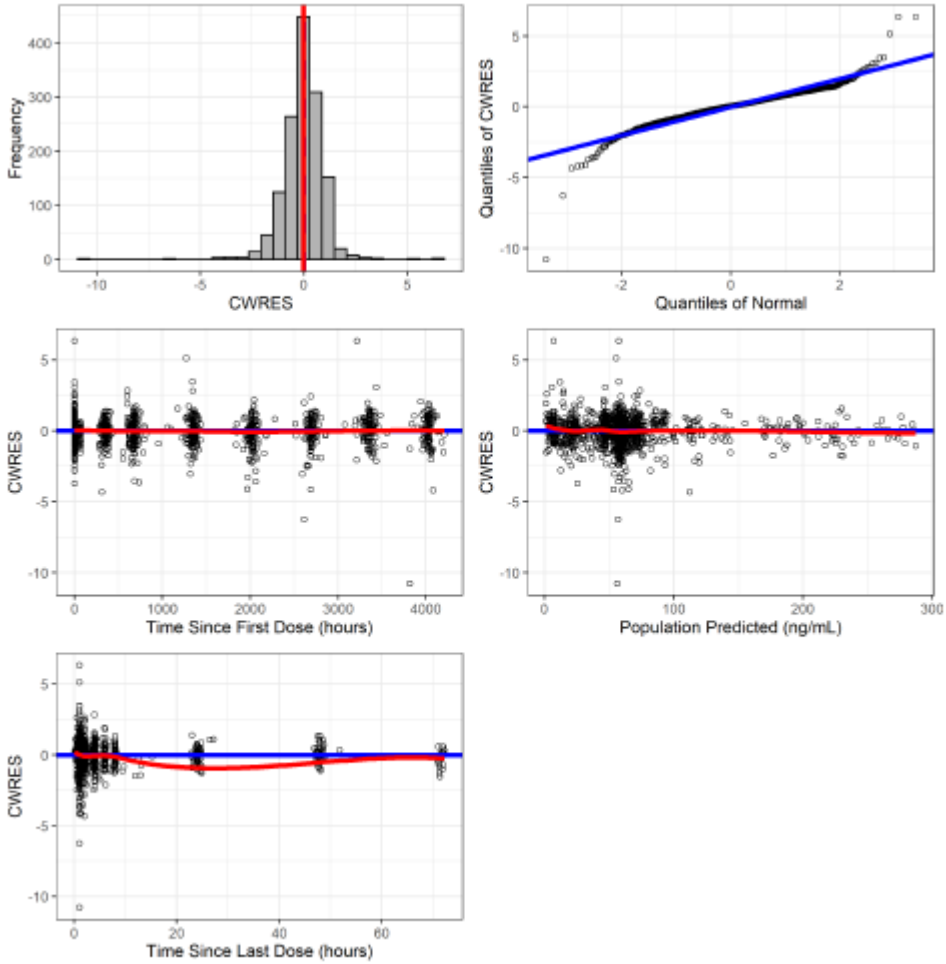
Figure 13. Goodness of Fit Plots for the Final Population PK Model



The solid blue lines represent the line of unity, the solid red lines represent the trend in the data (Loess smooth), the dashed orange line represent the LLOQ (2.00 ng mL), and shrinkage for the residual variability ($_{sh}$) 11.4% . **Top Panel**: all data. **Bottom Panel**: data from patients with ISM only (study BLU-285-2203) .

Additional diagnostic plots of CWRES are shown in Figure 14.

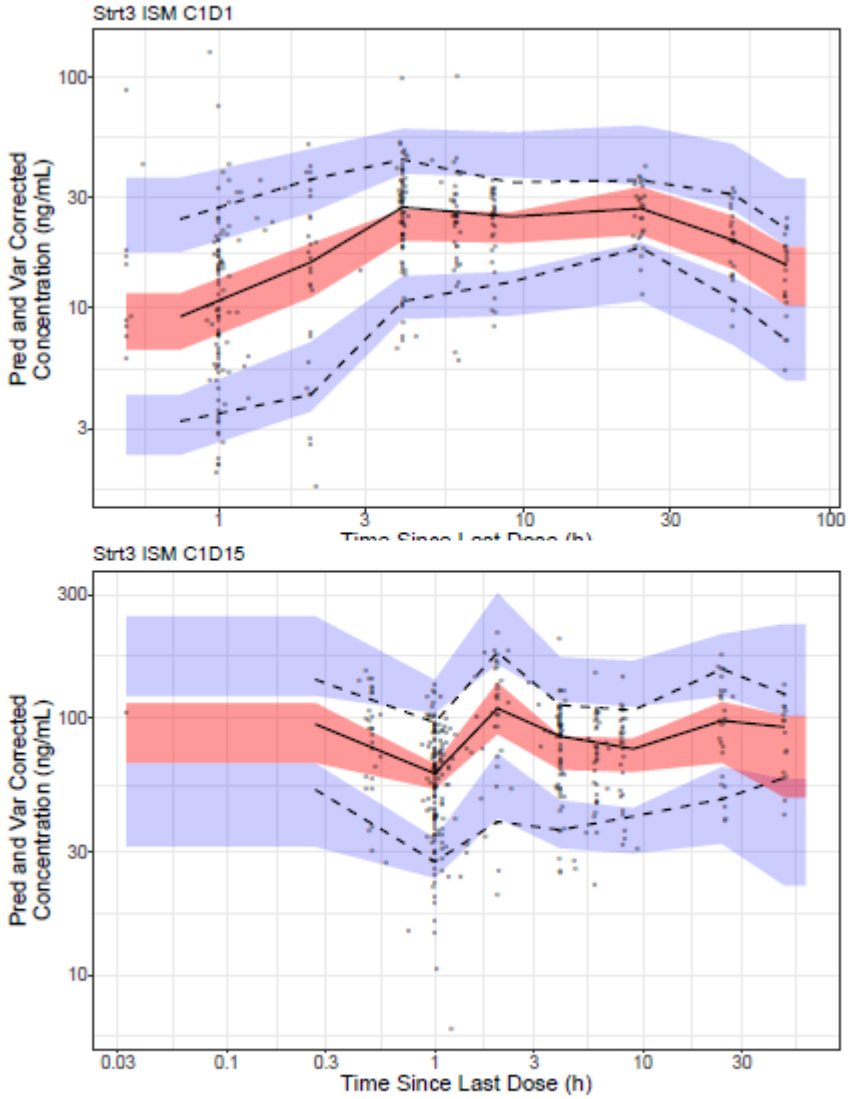
Figure 14. CWRES Plots for the Final Population PK Model



The solid blue lines represents the line of identity or zero, the red lines represents the trend in the data (Loess smooth) or the mean.

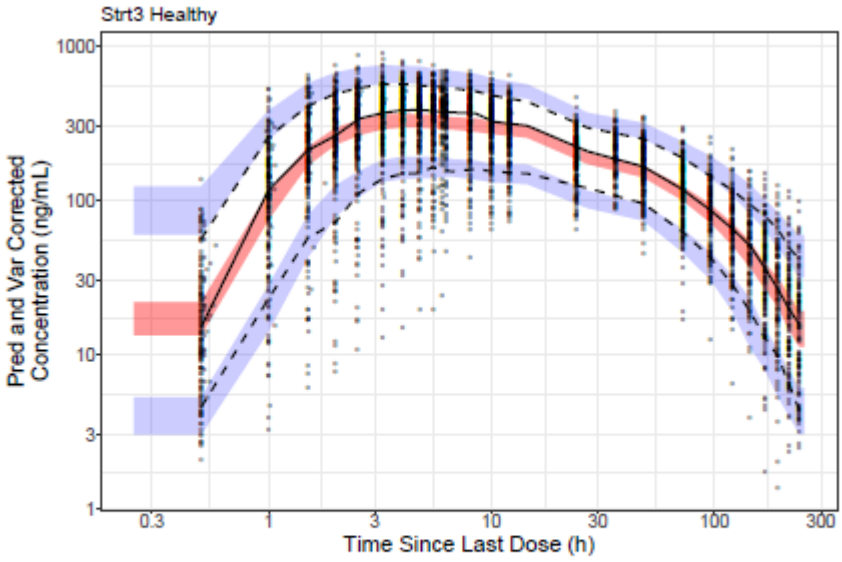
The trend at lower concentrations where the model under-predicts the lower observed concentrations is expected given censoring of data at the LLOQ (2.00 ng/mL). Additionally, the apparent bias at the low population predicted values which occurred during the early absorption phase was evaluated separately using VPCs (Figures 15 – 18).

Figure 15. pvcVPC for the Final Population PK Model: Patients with ISM (C1D1 & C1D15)



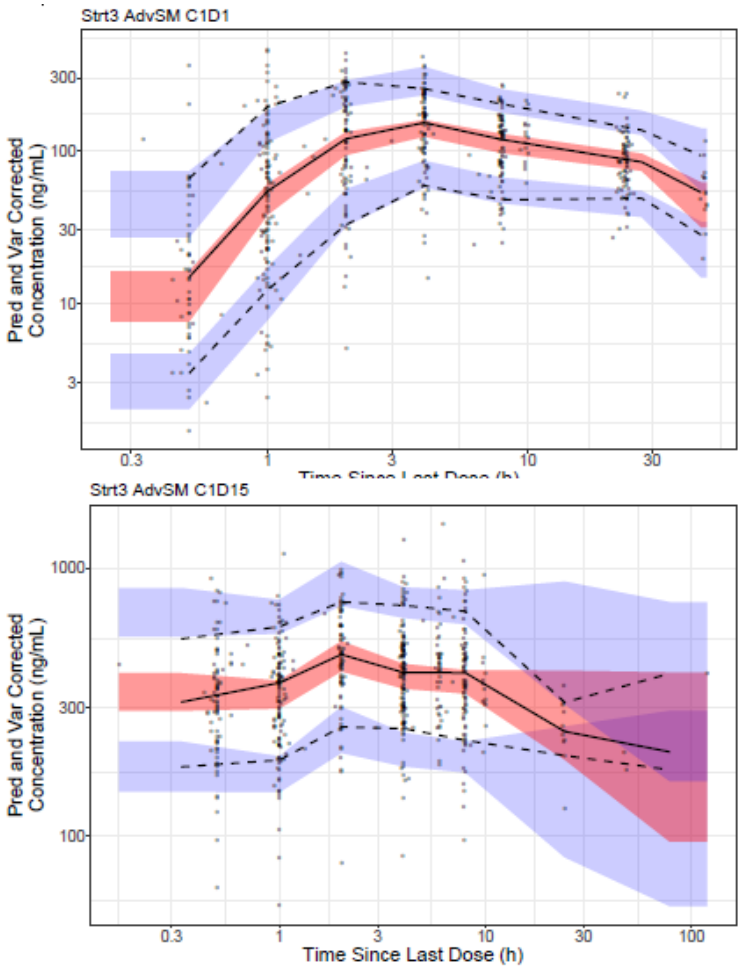
Open circles individual observed, dashed blue lines observed 10th & 90th percentiles of the observed data, solid blue line observed median concentration, shaded areas 95% confidence interval around the model predicted 10th, 50th, & 90th percentiles. **Top Panel**: C1D1. **Bottom Panel**: C1D15: Note: Log-log scale is used. C1D1 Cycle 1 Day 1, C1D15 Cycle 1 Day 15

Figure 16. pvcVPC for the Final Population PK Model: HV



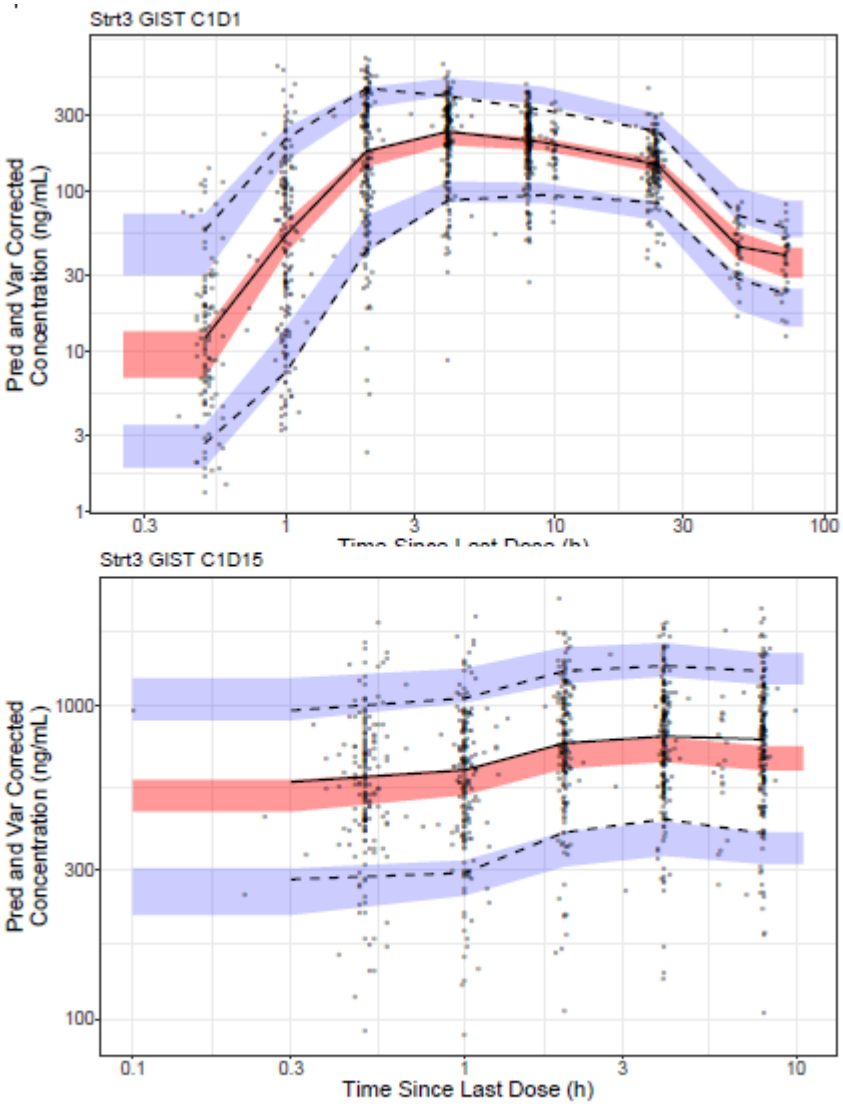
Open circles individual observed, dashed blue lines observed 10th & 90th percentiles of the observed data, solid blue line observed median concentration, shaded areas 95% prediction interval around the model predicted 10th, 50th, & 90th percentiles. Note: Log-log scale is used. C1D1 Cycle 1 Day 1, C1D15 Cycle 1 Day 15

Figure 17. pvcVPC for the Final Population PK Model: Patients with AdvSM (C1D1 & C1D15)



Open circles individual observed, dashed blue lines observed 10th & 90th percentiles of the observed data, solid blue 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

Figure 18. pvcVPC for the Final Population PK Model: Patients with GIST (C1D1 & C1D15)



Open circles individual observed, dashed blue lines observed 10th & 90th percentiles of the observed data, solid blue 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

Predicted Exposure Metric for Patients in Study BLU-285-2203, Part 2 (Objective 3)

The model predicted exposure metrics (AUC0-24,ss, Cmax,ss and trough plasma concentration at steady state (Ctrough,ss)) are summarized in Table 31. The geometric mean of AUC0-24,ss, Cmax,ss and Ctrough,ss were 1320 ng h/mL, 65.3 ng/mL and 45.4 ng/mL, respectively and were consistent with the values reported by non-compartmental analysis (NCA) methods.

Table 31. Summary of Model Predicted Exposure Metrics for Patients in 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

2.3.3. Pharmacodynamics

2.3.4. PK/PD modelling

Given the non-malignant nature of ISM and the difference between the recommended avapritinib dose for patients with ISM (25 mg QD) and the higher recommended doses for patients with AdvSM (200 mg QD) or GIST (300 mg QD), together with the anticipated differences in benefit-risk considerations, the E-R analysis of efficacy and safety outcomes included only data from patients with ISM from Study BLU-285-2203.

The objectives of this analysis were to:

1. Graphically evaluate the effect of avapritinib exposure on selected measures of efficacy and safety in ISM patients from study BLU-285-2203.

2. Present an ER model for the primary efficacy endpoint in ISM patients from study BLU-285-2203.

3. Perform additional descriptive analyses to support dose evaluation.

Analysis Populations

- Efficacy Population

The efficacy analysis was conducted in patients on placebo or active treatment up to at least C7D1.

- Safety population

The safety analysis was conducted in all patients who were enrolled and received at least 1 dose of avapritinib. Additionally, patients on placebo were also included in the safety analyses.

Efficacy Endpoints

The following measures of efficacy were evaluated:

- Activity of avapritinib as measured by change (Δ) in TSS from baseline to C7D1 (or equivalent for patients from Part 1).
- Activity of avapritinib as measured by a ≥30% reduction in TSS from baseline.
- Activity of avapritinib as measured by a ≥50% reduction in TSS from baseline.
- Activity of avapritinib as measured by a ≥50% reduction in serum tryptase from baseline.

Safety Endpoints

The following measures of safety were evaluated:

- All Grade ≥3 adverse events (AEs).
- Grade ≥1 cognitive effects.
- Grade ≥1 edema.
- Grade ≥2 total bilirubin.
- Grade ≥2 hemoglobin.
- Grade ≥1 weight gain/increase.

Each safety endpoint was dichotomized as experiencing zero or ≥ 1 occurrence/event, where only the first onset of an event per patient (and corresponding time to that event) was considered in the analysis (ie, repeat events were not analyzed). If an event occurred either 2 days after the last dose, or after the end of study participation (whichever occurred first), the event was declared as censored.

Exposure Parameters

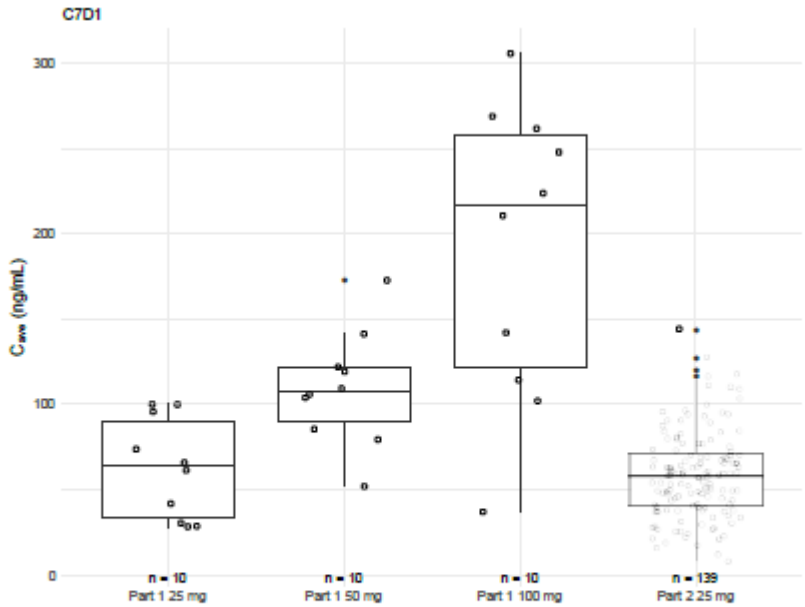
The final, updated population pharmacokinetic (PK) model of avapritinib was used to derive individual estimates of avapritinib exposure.

Cave was derived empirically for each individual using their observed dosing records and empirical Bayes estimates (EBEs) from NON linear Mixed Effects Modelling software (NONMEM). More specifically, for ΔTSS, Cave was computed from the start of treatment until C7D1 (or equivalent for patients in Part 1). For the dichotomous efficacy and safety endpoints, Cave was computed from the start of treatment until the first occurrence of an event or censoring.

Summary of Exposures

Figure 19 displays the distribution of Cave computed up to C7D1 by treatment arm. The PK of avapritinib in ISM patients from study BLU-285-2203 was approximately linear across the dose range of 25 mg to 100 mg.

Figure 19. Cave by Treatment Arm



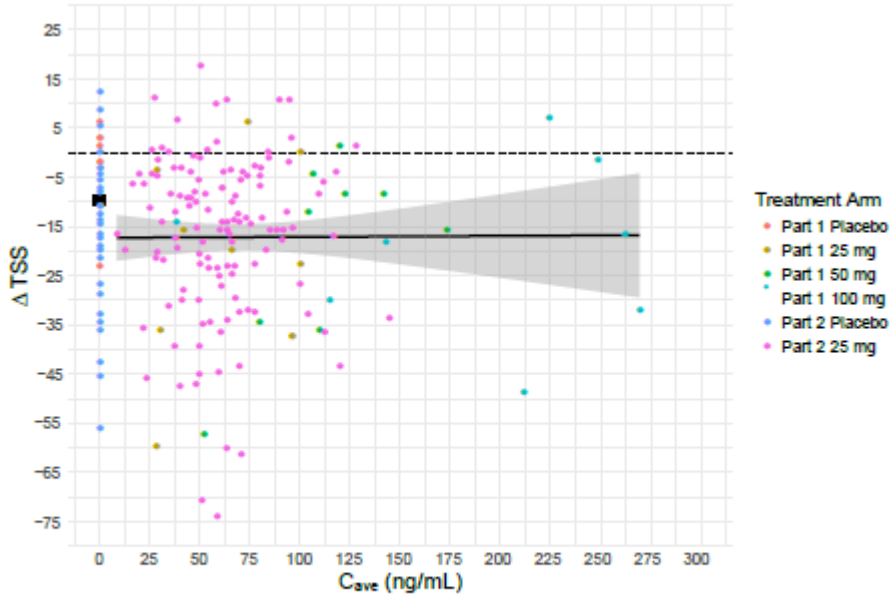
C7D1 = Cycle 7, Day 1. The open circles represent the observed data. The thick solid black lines represent the median of the data, the hinges (top and bottom of the boxes) represent the 25th and 75th percentiles (i.e., the interquartile range, or IQR), the top and bottom whiskers extend to the largest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

Efficacy

A total of 249 patients were included in the efficacy population. Fifteen of these patients had missing values for ΔTSS (i.e., 2 patients from Part 1 and 13 patients from Part 2); therefore, 234 patients were included in analyses of ΔTSS.

Figure 20 displays the relationship between ΔTSS and Cave. The average ΔTSS was approximately -9.65 points in patients on placebo. For patients on active treatment, the average ΔTSS was approximately -17.0 points across the exposure range.

Figure 20. ΔTSS vs. Cave



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 patients on active treatment, and the gray shaded region indicates the 95% confidence interval for the linear model predictions. The dashed black line indicates ΔTSS of 0 (i.e., no change from baseline).

ΔTSS was analyzed in a linear model framework:

$$\Delta TSS_i = \beta_0 + \beta_1 \cdot \text{Placebo}_i + \beta_2 \cdot C_{ave,i} + \beta_3 \cdot (TSS_{baseline,i} - \text{median}(TSS_{baseline})) \quad (1)$$

In Equation 1, Placeboi indicates placebo or active treatment for individual i (i.e., 0 = active treatment, 1 = placebo), and TSSbaseline, i indicates the baseline value of TSS for individual i.

Due to a change in scope of the originally planned ER analyses, covariate modelling and simulation for ΔTSS was not performed.

Table 32 reports the parameter estimates from the model described in Equation 1. After adjustment for baseline TSS, there was no evidence for a Cave effect (p = 0.922), suggesting that the expected average ΔTSS was ≈ -16.7 points across the exposure range in patients on active treatment. There was also evidence that patients on placebo experienced less reduction in TSS at C7D1 from baseline compared to patients on active treatment (p = 0.002).

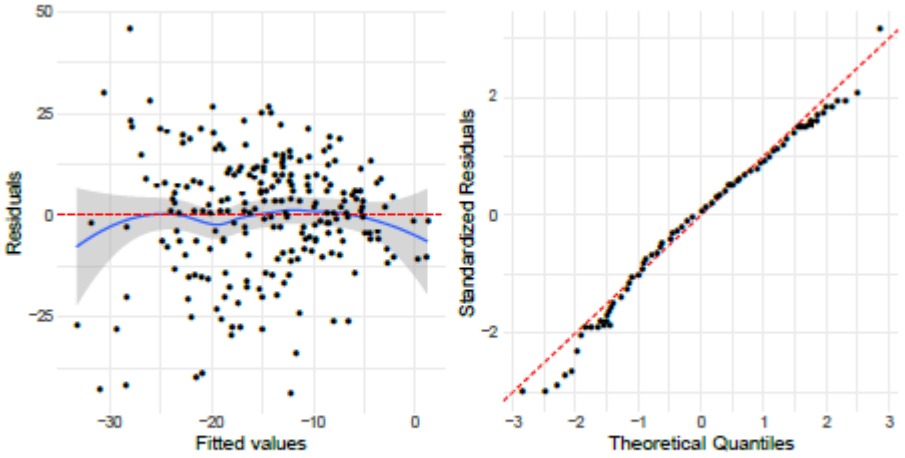
Additionally, there was evidence that patients with higher baseline TSS experienced greater reductions in TSS at C7D1 (p <0.001; median TSS at baseline was 48.6 points).

Table 32: Parameter Estimates from the ΔTSS Model

	Estimate	95% CI	P-value
Intercept	-16.7	(-20.9, -12.5)	<0.001
Placebo (vs. Active)	8.44	(3.1, 13.8)	0.002
Slope for C_{ave}	0.002	(-0.05, 0.05)	0.922
Slope for baseline TSS	-0.31	(-0.41, -0.21)	<0.001

Figure 21 displays key diagnostic plots of the ΔTSS model. The plots suggest that the model provided an acceptable fit to the data.

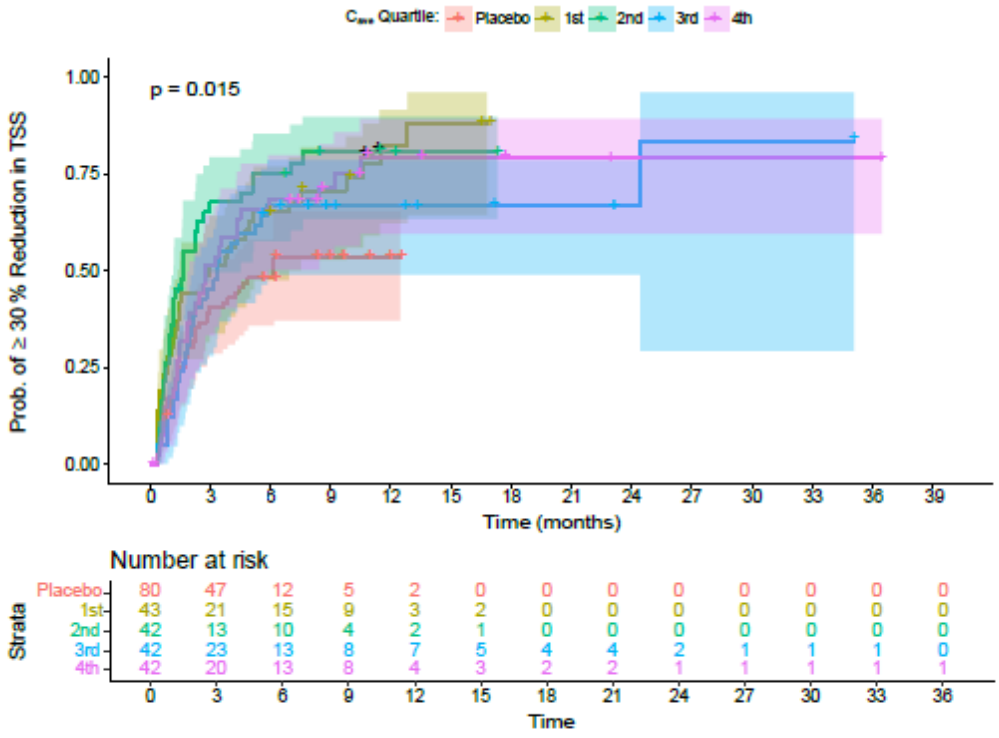
Figure 21. Diagnostic Plots of the ΔTSS Model



The solid circles represent observed data. In the left panel, the solid blue line indicates fits from a nonparametric smoother and the gray shaded region displays the corresponding 95% confidence interval.

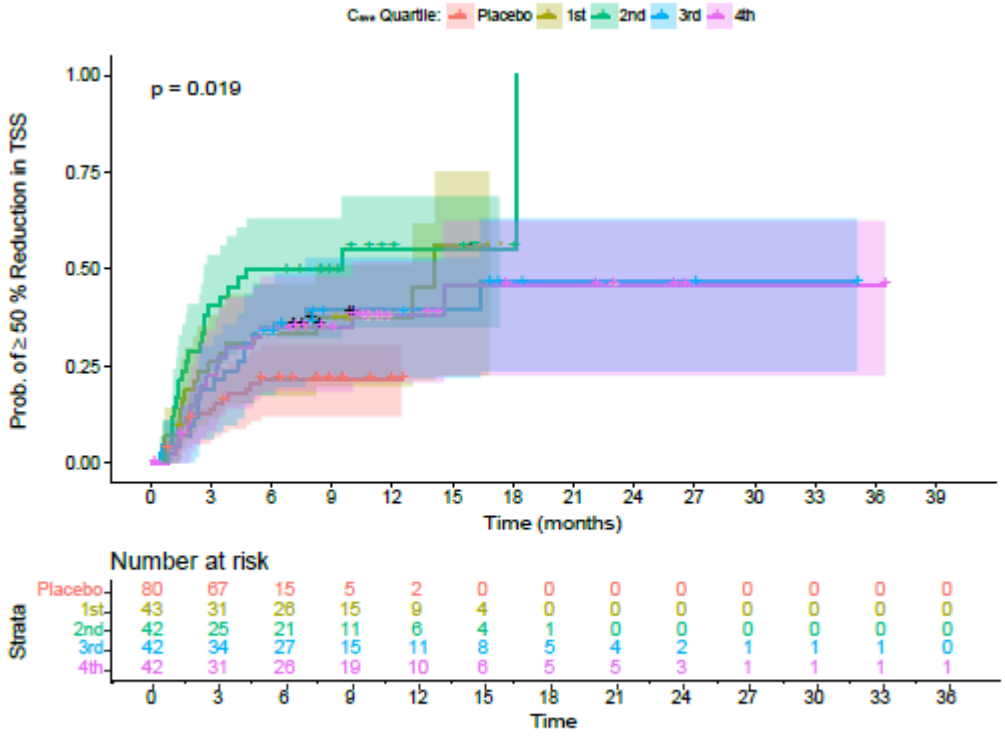
Figures 22 and 23 display KM plots for ≥30% and ≥50% reduction in TSS from baseline (respectively) stratified by Cave quartile. For both endpoints the active treatment groups experienced faster onset of response compared to patients on placebo.

Figure 22. ≥30% Reduction in TSS from Baseline vs. Cave



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

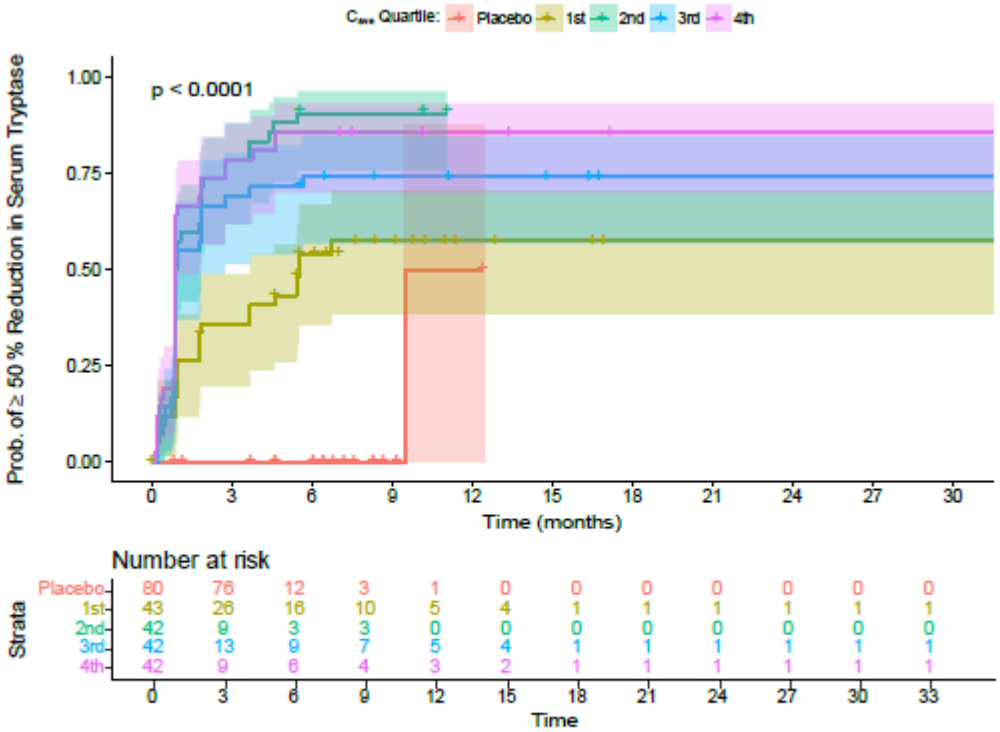
Figure 23. ≥50% Reduction in TSS from Baseline vs. Cave



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

Figure 24 displays a KM plot for a ≥50% reduction in serum tryptase from baseline stratified by Cave quartile. There was evidence that higher levels of exposure were associated with faster onset of ≥50% reduction in serum tryptase.

Figure 24. ≥50% Reduction in Serum Tryptase from Baseline vs. Cave



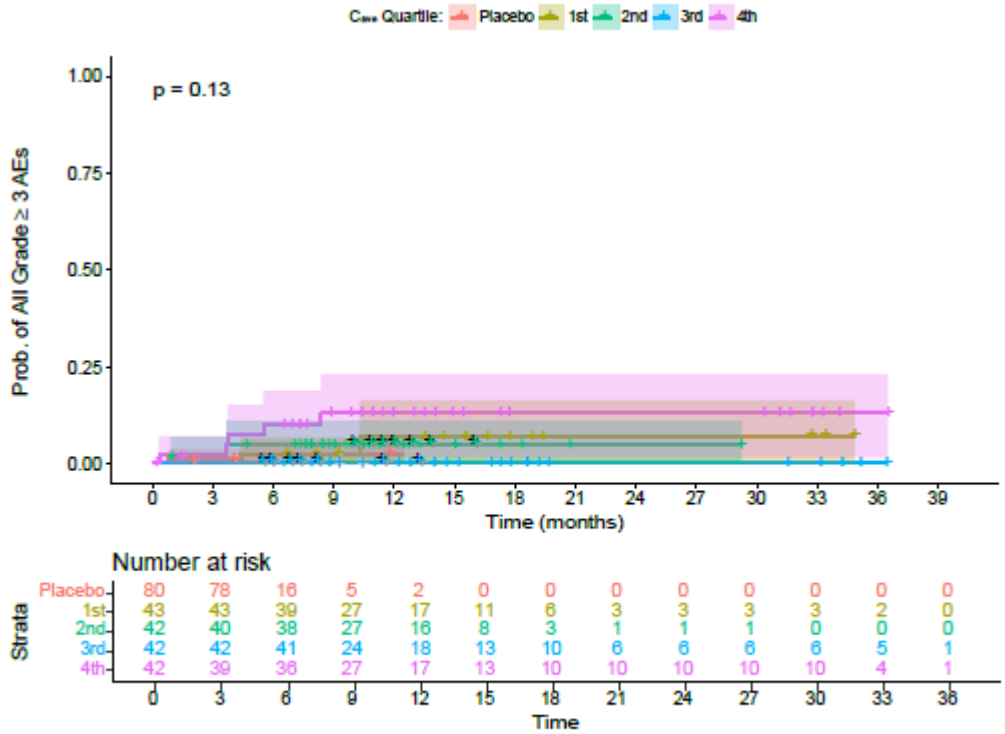
Prob = probability. Solid lines = Kaplan-Meier curves, pluses = observed censoring. The shaded regions represent the 95% CIs for the Kaplan-Meier curves.

Safety

All 249 patients were included in the safety analyses. Figures 25, 26, and 27 show KM plots for all Grade ≥3 AEs, Grade ≥1 cognitive effects, and Grade ≥1 weight gain (respectively) stratified by Cave quartile.

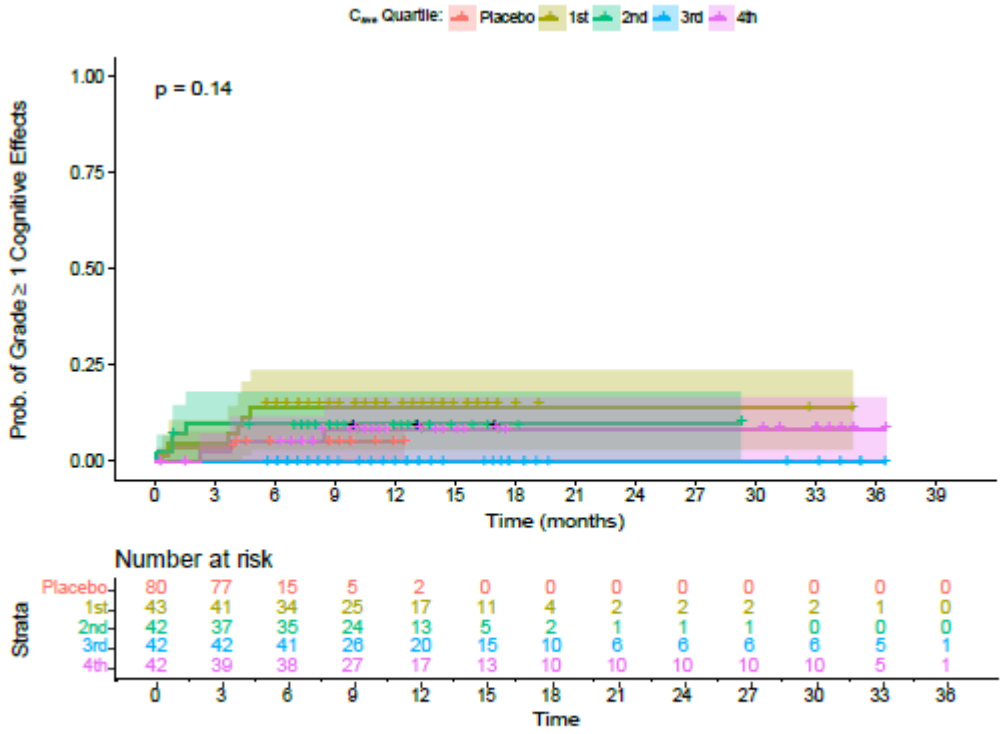
Incidences of all Grade ≥3 AEs, Grade ≥1 cognitive effects, and Grade ≥1 weight gain were very low in patients on active treatment (corresponding percentages of 5.3%, 7.7%, and 2.4%) or placebo (corresponding percentages of 2.5%, 5.0%, and 2.5%).

Figure 25. All Grade ≥3 AEs vs. Cave



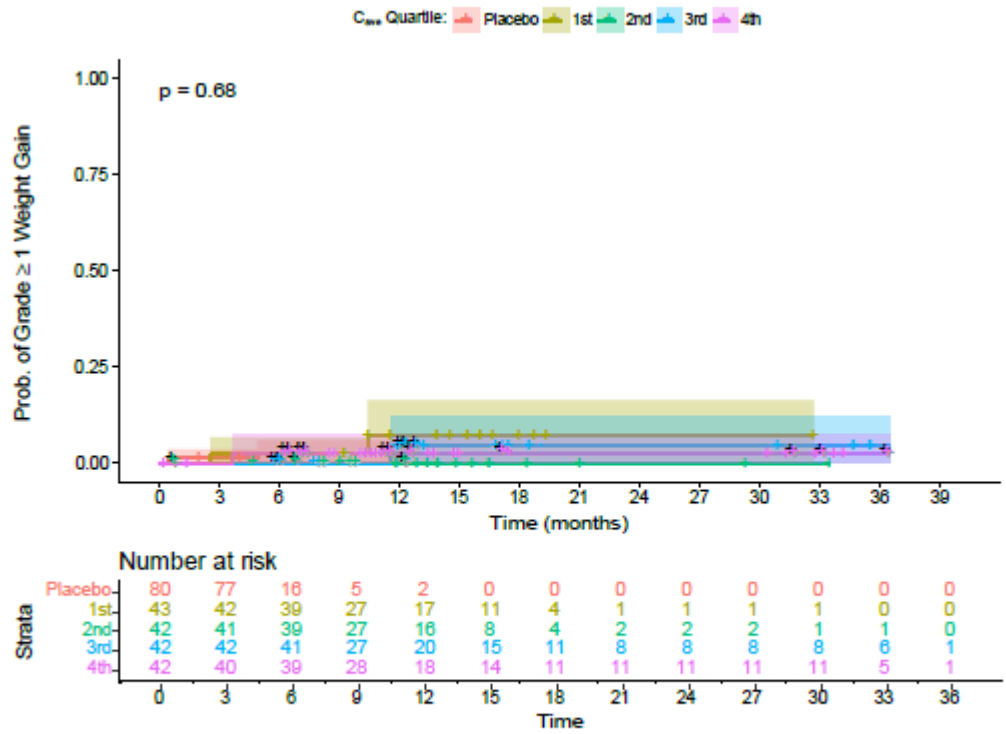
Prob = probability. Solid lines = Kaplan-Meier curves, pluses = observed censoring. The shaded regions represent the 95% CIs for the Kaplan-Meier curves.

Figure 26. Grade ≥1 Cognitive Effects vs. Cave



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

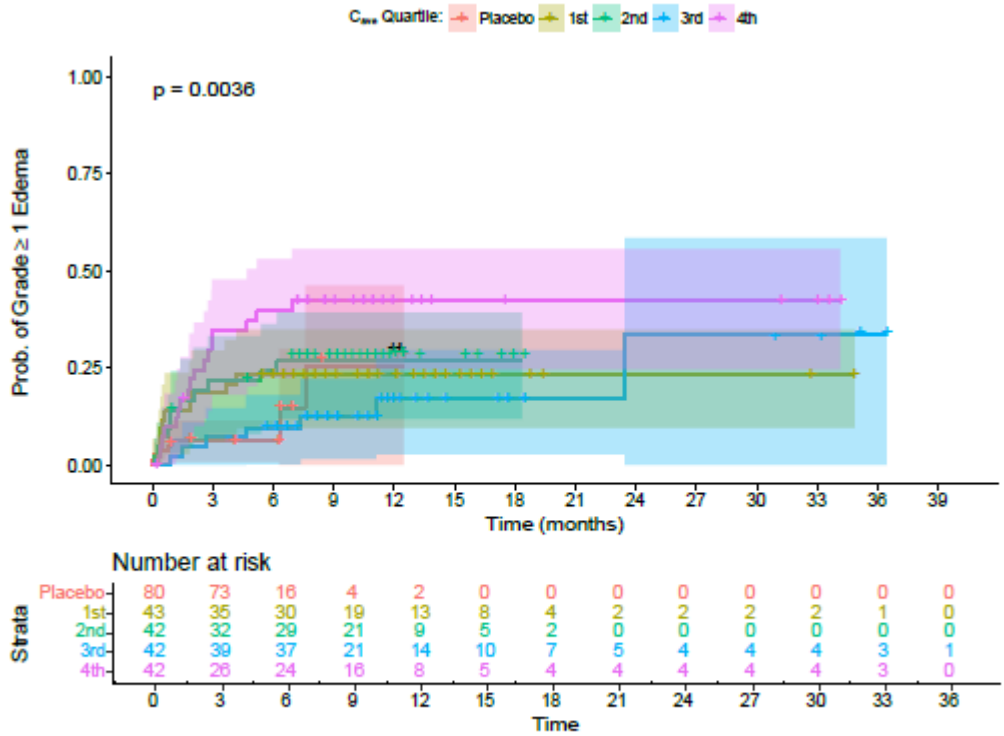
Figure 27. Grade ≥1 Weight Gain vs. Cave



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

Figure 28 displays the KM plot for Grade ≥1 edema stratified by Cave quartile. There was 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%). This trend appeared driven by the 4th quartile of Cave, for which faster onset was observed compared to the other quartiles.

Figure 28. Grade ≥1 Edema vs. Cave



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

Lastly, there were no occurrences of Grade ≥2 hemoglobin or Grade ≥2 total bilirubin, thus graphical evaluations of these endpoints are not shown.

2.3.5. Discussion on clinical pharmacology

Avapritinib for the treatment of indolent systemic mastocytosis (ISM) in adults was evaluated in the placebo-controlled phase 2 study BLU-285-2203.

Non-Compartmental Analysis (NCA) of the data from study BLU-285-2203 reveals dose proportionality between 25 mg and 100 mg in patients with ISM at Day 1 and Day 15 of cycle 1 (C1D15), as the 90% CI ranges within the accepted critical interval of 0.5-1.5 and the graphical representation shows the proportional relationship among dose levels. In addition, the impact of time-dependency processes on the avapritinib PK properties for the 25 mg QD dose between single dose and steady state conditions (C1D15 Part 1) revealed an AUC0-24 accumulation ratio of 3.59 (geometric mean), which is similar across the different indications and doses previously evaluated. Accumulation of BLU111207 and BLU111208 enantiomers was observed after repeated once daily dosing of 25 mg of avapritinib. At steady-state the metabolite to parent ratio of BLU111207 and BLU111208 was 10.3 and 17.5%, respectively, which is slightly lower compared to the ratios observed for patients with AdvSM at Cycle 1 Day 15 (20.5-29.9% and 25.9-34.4%, respectively).

For ISM, the recommended dose of avapritinib is 25 mg orally once daily, on an empty stomach (see Method of administration). This once daily 25 mg dose is also the maximum recommended dose that must not be exceeded in patients with ISM. Treatment of ISM should be continued until disease progression or unacceptable toxicity occurs.

The population PK analysis was based on a pooled dataset from 7 studies, which includes data of avapritinib in healthy volunteers (Study BLU-285-0101, Study BLU-285-0102 and Study BLU-285-0105), in patients

with Gastrointestinal Stromal tumor (GIST) and other relapsed refractory solid tumours (Study BLU-285-1101), in patients with Advanced Systemic Mastocytosis (AdvSM) and relapsed or refractory myeloid malignancies (Study BLU-285-2101, and Study BLU-285-2202) and in patients with ISM.

The final dataset for the current Population PK model development included a total of 9705 observation records from 656 subjects, which includes 1408 records from 169 subjects with ISM. Post-dose PK samples below limit of quantification (BLQ) were low and were excluded from the analysis. M1 method for handling BLQ-data is considered acceptable. The final popPK model was developed using 169 ISM patients, which is accepted, but only 1408 PK observations. The evaluation of the excluded samples was conducted, demonstrating the adequacy of the current population PK model to account for the excluded samples due to imprecise reference dose time. Although the excluded samples are below the corresponding 95% prediction intervals of the 10^{th}, 50^{th} and 90^{th} percentiles at C1D15, it could be partially a consequence of the imprecise reference dose time. Therefore, an adequate predictive capacity of the PK model was demonstrated.

The population PK model development includes the re-use of the previously developed model to characterize the PK of Avapritinib in healthy subjects, patients with GIST and patients with AdvSM. The structural and covariate effects were maintained and no further modification was included.

Avapritinib PK was described using a linear, 2-compartment model with 4 or 5 absorption transit compartments for tablet or capsule formulation respectively. The full PK model contains 7 covariates effects including LBW on Vc/F, concomitant PPI use on KTR and F, lower F in patients with GIST, lower F, lower KTR and time-dependent decrease in CL/F in patients with AdvSM.

A forest plot has been provided to assess the clinical relevance of the covariates selected based on the change on the exposure (AUC,ss and Cmax,ss). The analysis revealed no clinically relevant changes in exposure except for AdvSM patients, which is expected based on the time decrease in clearance and decrease bioavailability of this sub-group of patients. Therefore, no dose adjustment of avapritinib is required based on the covariates included in the population PK model.

An Exposure-Response analysis of efficacy and safety was performed including only data from patients with ISM from Study BLU-285-2203.

Change (Δ) in TSS from baseline to C7D1 was used as the efficacy outcome and Cave was computed until C7D1 or the occurrence of an event and was used as the exposure metric in the exposure efficacy analysis. ΔTSS was analysed in a linear model and the results showed a slight improvement in ΔTSS in patients on active treatment compared to patients in the placebo group but not differences between the different doses where found. No exposure-efficacy relationships was established across the different dose levels evaluated (25-100 mg QD). Therefore, it is not possible to establish the optimal dosing regimen of avapritinib in patients with ISM from the presented exposure-efficacy relationship.

Regarding the safety endpoints, Kaplan-Meier curves stratified by quartiles of Cave were presented. The results showed a statistically difference in the occurrence of grade ≥1 oedema between the active and placebo groups. This result was expected as fluid retention is a frequent adverse effect related to the use of avapritinib. However, no exposure-safety relationship was established across the exposure range of avapritinib. Therefore, it is not possible to establish the optimal dosing regimen of avapritinib in patients with ISM from the presented exposure-safety relationship.

The metabolism of avapritinib is predominantly mediated by CYP3A4/CYP3A5, so the concomitant treatment with drugs that are strong or moderate CYP3A inhibitors or inducers can increase (with inhibitors) or decrease (with inducers) the exposure to avapritinib, as confirmed by a clinical study with concomitant administration of avapritinib with itraconazole (a potent CYP3A inhibitor) or rifampin (a potent CYP3A inducer). The dosing recommendation for avapritinib is therefore to avoid the concomitant use of strong or moderate CYP3A inhibitors or inducers.

The MAH provided the report of the clinical DDI study report (BLU-285-0108) that aims to assess the potential interaction of avapritinib in combination with oral contraceptives and to provide dosing recommendations if required. The combination LNG/EE was selected as this represents a widely used oral contraceptive. The clinical significant bounds of 90% confidence intervals (CIs) selected for this study were 80.00% - 140.00% for AUC0-inf taking into account the doses used in the study and other labelling recommendations and for Cmax an upper clinical significant bound less than 140% as decrease in Cmax is not supposed to affect the clinical efficacy.

Sixteen women were enrolled in the study and 15 of them completed the study and one of them discontinued due to an adverse event (vision blurred).

Following coadministration of 25 mg of avapritinib QD with a single dose of oral contraceptives 0.15 mg LNG/0.03 mg EE, based on GMR, LNG Cmax, AUC0-t and AUC0-inf were 7%, 13% and 16% higher that when LNG was administered as the combination of OC alone. The 90 % CI of LNG Cmax falls below the 140% upper bound and the AUC0-inf falls within the 80-140% clinical significance bounds. On the other hand, based on GMR, EE Cmax, AUC0-t and AUC0-inf were 45.81%, 16.55% and 15.48% higher than when EE was administered as the combination of OC alone. The AUC0-inf falls within the 80-140% clinical significance bounds, however, the 90 % CI of LNG Cmax falls above the 140% upper (CI 17.16%-81.46%).

Despite the slightly higher EE Cmax (45%) , very similar exposures of avapritinib at the proposed dosing regimen at single and steady-state conditions were predicted when a single dose of LNG/EE was coadministered. Therefore, no relevant differences in efficacy/safety are expected since no relevant changes in exposure were predicted.

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology properties of avapritinib in patients with ISM have been adequately characterized based on a totality of population PK model analysis developed in patients with AdvSM and GIST. The exposure-response analyses were not clinically relevant and the proposed dosing regimen seems adequate for the studied population and included accordingly in the SmPC.

2.4. Clinical efficacy

The primary evidence of efficacy and safety of avapritinib in the treatment of ISM comes from Study BLU-285-2203. This study was conducted in patients from North America, countries in the EU, and the UK.

The focus for efficacy analyses in the current procedure is on patients with ISM treated with avapritinib at a dose of 25 mg QD.

Table 33. Overview of Clinical Studies

Study Identifier/ Status	Number of Study Centers/ Countries	Study Objective(s)	Study Design	Disease Population	Dose/Dosing Regimen	Number of Patients
Indolent Systemic Mastocytosis						
BLU-285-2203 (IND number: 124159, EudraCT number: 2018-000588-99, NCT03731260) Part 1: Complete Part 2: Complete Part 3: Ongoing, enrollment complete; data cutoff date of 23 June 2022	42 centers/ 13 countries (Belgium, Canada, Denmark, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, UK, US)	The primary objectives of the study were: **Part 1** To determine the RP2D of avapritinib in patients 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** To assess the long-term safety and efficacy of avapritinib in patients with ISM.	3-part, Phase 2, randomized, double-blind, placebo-controlled study	Male and female patients ≥ 18 years old, with centrally confirmed WHO diagnosis of ISM and moderate to severe symptoms based on the average TSS of ≥ 28 on the ISM-SAF over the 14-day eligibility screening period.	**Part 1:** Avapritinib 25, 50, or 100 mg or matching placebo administered orally QD for at least 12 weeks. **Part 2:** Avapritinib 25 mg or matching placebo administered orally, QD for 6 cycles (24 weeks). **Part 3:** Avapritinib 25 mg administered orally, QD for up to 5 years, inclusive of Part 1 and Part 2.	**Part 1:** 39 patients. **Part 2:** 212 patients. **Part 3:** 235 patients from Part 1 and Part 2 participated in Part 3 of the study.

Abbreviations: C7D1 = Cycle 7 Day 1; ISM = indolent systemic mastocytosis; ISM-SAF = Indolent Systemic Mastocytosis-Symptom Assessment Form; QD = once daily; RP2D = recommended Phase 2 dose; TSS = total symptom score; UK = United Kingdom; US = United States; WHO = World Health Organization.

2.4.1. Dose response studies

Part 1 of the main study BLU 285-2203 had as main objective determining the RP2D of avapritinib in patients with ISM for use in Part 2 and Part 3 of the study.

This Part 1 is presented below under the main study BLU 285-2203 section.

2.4.2. Main study

Study BLU 285-2203 is a 3-part, randomised, double-blind, placebo-controlled Phase 2 study to evaluate safety and efficacy of avapritinib (BLU 285) in patients with indolent and smouldering systemic mastocytosis with symptoms inadequately controlled with standard therapy.

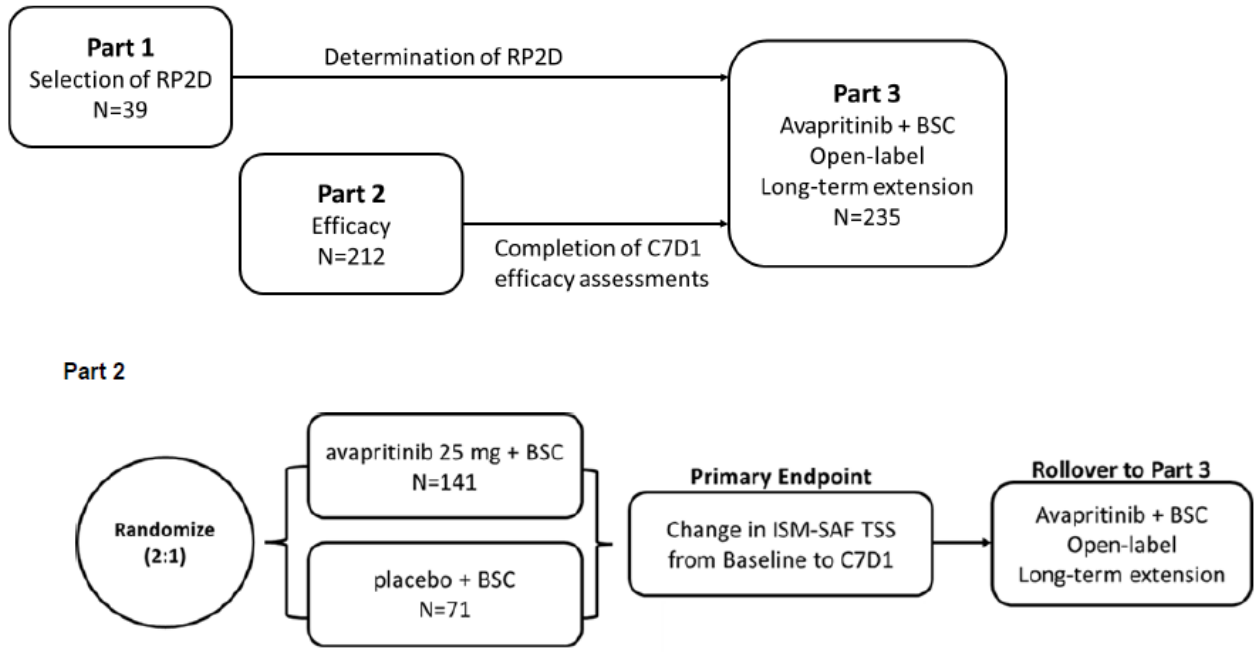
Methods

Study BLU-285-2203 is a 3-part, Phase 2, randomized, double-blind, placebo-controlled study comparing the efficacy and safety of avapritinib in combination with best supportive care (BSC) to placebo in combination with BSC in patients with ISM whose symptoms were not adequately controlled by BSC.

The study was conducted in 3 parts:

- In **Part 1**, the optimal dose of avapritinib (RP2D) was identified in patients with ISM.
- In **Part 2**, patients with ISM were randomly assigned in 2:1 ratio to the avapritinib RP2D identified in Part 1 in combination with BSC, or to placebo in combination with BSC.
- In **Part 3**, patients who complete treatment in Part 1 or Part 2 of the study can participate in a long-term extension, receiving avapritinib at the RP2D in combination with BSC.

Figure 29. Overall study design



Abbreviations: BSC = best supportive care; CXDX = Cycle X Day X; ISM-SAF = Indolent Systemic Mastocytosis-Symptom Assessment Form; RP2D = recommended Phase 2 dose; TSS = total symptom score. Patients who received placebo in Part 2 rolled over to avapritinib treatment in Part 3.

All patients who complete Part 1 or Part 2 were given the opportunity to receive avapritinib at a RP2D to assess long-term efficacy and safety.

Study participants

Main inclusion criteria	**Main exclusion criteria**
1. Patient must be ≥ 18 years of age. 2. Patient must have SM, confirmed by Central Pathology Review of BM biopsy, and central review of B- and C-findings by WHO diagnostic criteria. 3. Patient must have moderate-to-severe symptoms based on minimum mean total symptom score (TSS) over the 14-day eligibility screening period for assessment of TSS. Minimum TSS for eligibility is ≥ 28. 4. Patient must have failed to achieve adequate symptom control for 1 or more baseline symptoms as determined by the Investigator, with at least 2 of the following symptomatic therapies: • H1 blockers. • H2 blockers. • Proton-pump inhibitors. • Leukotriene inhibitors. • Cromolyn sodium.	1. Patient has been diagnosed with any of the following WHO SM sub-classifications: • Cutaneous mastocytosis (CM) only (ie, without documentation of systemic involvement). • SSM • SM-AHN. • ASM. • MCL. • MC sarcoma. 2. Patient has been diagnosed with another myeloproliferative disorder (eg, myelodysplastic syndrome, myeloproliferative neoplasm). 3. Patient has any of the following organ damage C-findings attributable to SM: • Cytopenia. • Hepatomegaly with ascites and impaired liver function.

• Corticosteroids. • Omalizumab. 5. The patient's symptomatic SM therapies (eg, H1 and H2 blockers) must be stable (same dose, no new medications ≥14 days before beginning the 14-day ISM SAF eligibility TSS assessment.). 6. For patients receiving corticosteroids, the dose must be ≤ 20 mg/d prednisone or equivalent, and the dose must be stable for ≥ 14 days before starting the ISM-SAF for the determination of eligibility. 7. Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2. 8. Patient must give written informed consent.	• Palpable splenomegaly with hypersplenism. • Malabsorption with hypoalbuminemia and significant weight loss. • Skeletal lesions: large osteolytic lesions with pathologic fractures. • Life-threatening organ damage in other organ systems that is caused by MC infiltration in tissues. 4. Patient 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 × LLN. • Estimated glomerular filtration rate (eGFR; calculated using the Modification of Diet in Renal Disease equation) < 30 mL/min/1.73 m^2 or creatinine > 1.5 × ULN. • Absolute neutrophil count < 1.5 × 10^9/L. • Hemoglobin < 10 g/dL. • Platelet count < 100 × 10^9/L. 5. Patient has received any of the following medications, therapies, or procedures in the timeframes listed: • Any prior treatment with avapritinib. • Any TKI, including but not limited to masitinib and midostaurin, or investigational agent for < 14 days or 5 half-lives of the drug (whichever is longer) before beginning the 14-day ISM-SAF eligibility TSS assessment. • Any antineoplastic drug therapy (including but not limited to cladribine and interferon alpha, pegylated interferon, or antibody therapy) < 28 days or 5 half-lives of the drug (whichever is longer) before beginning the 14-day ISM-SAF eligibility TSS assessment. • Radiotherapy or psoralen and ultraviolet A (PUVA) therapy < 14 days before beginning the 14-day ISM-SAF eligibility TSS assessment. • Any hematopoietic growth factor < 14 days before starting the ISM-SAF for determination of eligibility. • Any major surgical procedure (minor surgical procedures such as central venous catheter placement, BM biopsy, and feeding tube placement are not considered major surgical

	procedures) < 14 days before starting the ISM-SAF for determination of eligibility. 6. Patient requires therapy with a concomitant medication that is a strong inhibitor or strong inducer of cytochrome P450 3A4 (CYP3A4). 7. Patient has a history of a malignancy that has been diagnosed or required therapy within 3 years before the first dose of study drug. Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational agent may be included after approval by medical monitor. 8. Patient has a QT interval corrected using Fridericia's formula (QTcF) > 480 msec. 9. Patient has a history of a seizure disorder (eg, epilepsy) or requires antiseizure medication. 10. Patient has a history of a cerebrovascular accident or transient ischemic attacks within 12 months before the first dose of study drug. 11. Patient has a known risk or recent history (12 months before the first dose of study drug) of intracranial bleeding (eg, brain aneurysm). 12. Patient has a primary brain malignancy or metastases to the brain. 13. Patient has clinically significant, uncontrolled cardiovascular disease, including Grade III or IV congestive heart failure according to the New York Heart Association classification; myocardial infarction or unstable angina within the previous 6 months; clinically significant, uncontrolled arrhythmias, or uncontrolled hypertension. 14. Patient is unwilling or unable to comply with scheduled visits, drug administration plan, laboratory tests, or other study procedures, including mandatory BM and skin biopsies, and study restrictions.

Treatments

Part 1

Avapritinib (at a dose of 25, 50, or 100 mg QD) or matching placebo was administered orally in 28-day cycles for at least 12 weeks before rolling over to Part 3. Under the original protocol a 200 mg group was also included, however, based on a review of safety and efficacy data from the BLU-285-2101 Phase 1

study, the 200 mg dose group in this study was removed and no patients received the 200 mg dose within this study.

Part 2

Avapritinib RP2D (25 mg) or matching placebo was administered orally, QD in Part 2 in 28-day cycles for 6 cycles. After completion of 6 cycles (24 weeks) of treatment (C7D1) and all post-C7D1 study procedures, patients rolled over to Part 3 of the study where all patients had the opportunity to receive avapritinib 25 mg QD in an open-label fashion.

Part 3

Avapritinib 25 mg was administered orally, QD for up to 5 years, in 28-day cycles, inclusive of Part 1 and Part 2. The study drug was administered at the same dosing frequency as the last cycle in Part 1 or Part 2. The dose administered could be modified under certain circumstances.

In Part 2, dose escalations above 25 mg QD (placebo or avapritinib) were not permitted.

In Part 3 open-label extension, dose escalation from 25 mg QD to 50 mg QD was permitted, if patients met the required criteria as indicated in the protocol.

All patients continued to receive BSC throughout the study.

Objectives

Objectives	Endpoints
Primary	
Part 1	
To determine the RP2D of avapritinib in patients with ISM for use in Part 2 and Part 3 of the study	The RP2D in patients with ISM
Part 2	
To determine mean change in ISM-SAF TSS from baseline to C7D1, compared to placebo	Mean change in ISM-SAF TSS, from baseline to C7D1
Part 3	
To assess the long-term safety and efficacy of avapritinib in ISM patients	The long-term safety and efficacy of avapritinib
Key Secondary (Part 2 Only)	
To determine the proportion of avapritinib-treated patients with ISM with a ≥ 50% reduction in serum tryptase from baseline to C7D1, compared to placebo	Proportion of patients with a ≥ 50% reduction in serum tryptase from baseline to C7D1
To determine 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	Proportion of patients 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
To determine the proportion of avapritinib-treated patients with ISM achieving ≥ 50% reduction in ISM-SAF TSS from baseline to C7D1, compared to placebo.	Proportion of patients with ≥ 50% reduction in ISM-SAF TSS from baseline to C7D1.
To determine the proportion of avapritinib-treated patients with ISM achieving ≥ 30% reduction in ISM-SAF TSS from baseline to C7D1, compared to placebo.	Proportion of patients with ≥ 30% reduction in ISM-SAF TSS from baseline to C7D1.
To determine 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	Proportion of patients with a ≥ 50% reduction in bone marrow mast cells from baseline to C7D1 or no aggregates for patients with aggregates at baseline

Objectives	Endpoints
Additional Secondary	
Parts 1 and 2	
Assess change in the following measures of mast cell burden in each treatment cohort from baseline to C4D1 (Part 1) and C7D1 (Part 2): • Serum tryptase • KIT D816V allele burden in blood • Bone marrow mast cells	Change in measures of mast cell burden from baseline to C4D1 (in Part 1) and to C7D1 (in Part 2): • Serum tryptase • KIT D816V allele burden in blood • Bone marrow mast cells
Assess change in BSC usage for SM symptoms	Change in BSC usage
Assess change in GI and skin domains, neurocognitive symptom cluster (brain fog, headache and dizziness), and individual symptom scores of ISM-SAF	Change in GI and skin domains, neurocognitive symptom cluster (brain fog, headache and dizziness), and individual symptom scores of ISM-SAF
Assess change in "lead (most severe) symptom" and "lead (most severe) domain/symptom cluster" score (ie, individual symptom and domain/symptom cluster with highest mean score at baseline in each patient) of ISM-SAF	Change in "lead (most severe) symptom" and "lead (most severe) domain/symptom cluster" score of ISM-SAF
Assess change in other PROs and QoL measures based on the MC-QoL, PGIS, SF-12, PGIC, and EQ-5D-5L questionnaire	Change in MC-QoL, PGIS, SF-12, PGIC, and EQ-5D-5L
Assess the safety and tolerability of avapritinib, as assessed by AEs, vital signs, ECGs, and laboratory tests	Safety and tolerability of avapritinib, as assessed by AEs, vital signs, ECGs, and laboratory tests
Assess the PK of avapritinib	PK of avapritinib
Correlate avapritinib exposure with safety and efficacy endpoints	Correlations between avapritinib exposure and safety and efficacy endpoints
Additional Secondary	
Part 3	
Assess changes in the following measures of mast cell burden: • Serum tryptase • KIT D816V allele burden in blood • Bone marrow mast cells (optional at approximately 1 year after the biopsy at the end of Parts 1 and 2)	Change in the following measures of mast cell burden: • Serum tryptase • KIT D816V allele burden in blood • Bone marrow mast cells (optional at approximately 1 year after the end of Part 1 and Part 2 biopsy)
Assess change in BSC usage for SM symptoms	Change in BSC concomitant medication usage

Objectives	Endpoints
Assess change in "lead (most severe) symptom" and "lead (most severe) domain/symptom cluster" score (ie, individual symptom and domain/symptom cluster with highest mean score at baseline in each patient) of ISM-SAF	Change in "lead (most severe) symptom" and "lead (most severe) domain/symptom cluster" score of ISM-SAF"
Assess the proportion of avapritinib-treated patients with ISM achieving ≥ 50% reduction in TSS at 1 year after initiation of avapritinib therapy	Proportion of avapritinib-treated patients with ISM achieving ≥ 50% reduction in TSS at 1 year from Part 3 baseline (and Part 1 or Part 2 baseline for patients on same dose of avapritinib in both parts of the study).
Assess the proportion of avapritinib-treated patients with ISM achieving ≥ 30% reduction in TSS at 1 year after initiation of avapritinib therapy	Proportion of avapritinib-treated patients with ISM achieving ≥ 30% reduction in TSS at 1 year from Part 3 baseline (and Part 1 or Part 2 baseline for patients on same dose of avapritinib in both parts of the study).
Assess change in TSS, symptom cluster, domain scores, and individual symptom scores of ISM-SAF from Part 3 baseline (and Part 1 or Part 2 baseline for patients on same dose of avapritinib in both parts of the study) to C4D1, C7D1, C11D1, and C13D1	Change in TSS, symptom cluster, domain scores, and individual symptom scores of ISM-SAF from Part 3 baseline (and from Part 1 and Part 2 baseline for patients receiving same dose of avapritinib in both study parts) to Part 3 C4D1, C7D1, C11D1, and C13D1
Assess change in other PROs and QoL measures based on the MC-QoL, PGIS, SF-12, PGIC, and EQ-5D-5L questionnaires	Change in MC-QoL, PGIS, SF-12, PGIC, and EQ-5D-5L
Assess the safety and tolerability of avapritinib, as assessed by AEs, vital signs, ECGs, and laboratory tests	Safety and tolerability of avapritinib, as assessed by AEs, vital signs, ECGs, and laboratory tests
Exploratory (Parts 1, 2, and 3)	
Explore potential correlations between the ISM-SAF and other PRO and QoL measures and individual measures of mast cell burden	Potential correlations between ISM-SAF, PGIS, other PRO and QoL measures, and individual measures of mast cell burden
Assess correlation of clinical features (eg, demographics, laboratory tests, concomitant medications, AEs, concomitant mutations) with activity against ISM	Correlation of clinical features (eg, demographics, laboratory exams, concomitant medications, AEs, concomitant mutations, etc.) with activity against ISM
Identify potential new biomarkers (DNA, RNA, serum protein) in blood for pharmacodynamic effects and safety of avapritinib	Status of exploratory biomarkers (DNA, RNA, serum protein) in blood with respect to efficacy or safety related endpoints for avapritinib
Assess whether avapritinib can affect platelet aggregation as a possible mechanistic contributor to bleeding events	Platelet aggregation studies at baseline and during treatment, including at the time of bleeding events

Objectives	Endpoints
Assess change in bone density by DXA/bone densitometry scan (optional, performed at the Investigator's discretion)	Change in bone density (optional, performed at the Investigator's discretion)
Assess changes in skin lesions by photography in patients with baseline mastocytosis in skin from baseline to C4D1 (in Part 1) and C7D1 (in Part 2)	Change in percent fractional body surface area involved by mastocytosis in skin, change in lesion number, and change in pigmentation of cutaneous lesions in patients with baseline mastocytosis in skin
Assess changes in skin lesions by photography in patients with new mastocytosis in skin from baseline (Part 3) to C7D1 (Part 3)	Change in percent fractional body surface area involved by mastocytosis in skin, change in lesion number, and change in pigmentation of cutaneous lesions in patients with new mastocytosis in skin at baseline of Part 3.
Assess changes in mast cells in skin biopsies in patients with baseline mastocytosis in skin	Change in skin mast cells in patients with baseline mastocytosis in skin from baseline to C4D1 (in Part 1) and to C7D1 (in Part 2) and at C13D1 (in Part 3, optional).
Assess change in the frequency of anaphylactic episodes based on epinephrine use	Change in number of episodes of anaphylaxis, based on epinephrine use

Abbreviations: AE = adverse event; BSC = best supportive care; CXDX = Cycle X Day X; DNA = deoxyribonucleic acid; DXA = dual x-ray energy assessment; ECG = electrocardiogram; EQ-5D-5L = Fivelevel EuroQuol 5D; GI = gastrointestinal; ISM = indolent systemic mastocytosis; ISM-SAF = Indolent Systemic Mastocytosis-Symptom Assessment Form; MC- QoL= Mastocytosis Quality of Life Questionnaire; PGIC = Patients' Global Impression of Change; PGIS = Patient's Global Impression of Symptom Severity; PK = pharmacokinetic(s); PRO = patient-reported outcome; QoL = Quality of Life; RNA = ribonucleic acid; RP2D = recommended Phase 2 dose; SF-12 = Twelve-item Short Form Health Survey; SM = systemic mastocytosis; TSS = Total symptom score.

ISM-SAF questionnaire

The Indolent Systemic Mastocytosis-Symptom Assessment Form (ISM-SAF) is a 12-item PRO employed for the daily PRO assessment on an eDiary to assess symptoms in patients with ISM. Eleven items (bone pain, abdominal pain, nausea, the spots on the skin, itching, flushing, fatigue, dizziness, brain fog, headache, diarrhoea) that assess the severity of symptoms are graded on an 11-point scale (0 to 10, none to maximum severity), and one item (diarrhoea) assesses the frequency. The ISM-SAF generates scores for each item, for skin domain, GI domain, neurocognitive domain and a TSS. The skin domain includes subscales of the spots on the skin, itching, and flushing, ranging from 0 to 30. The GI domain includes subscales of abdominal pain, nausea, and diarrhoea, ranging from 0 to 30. The neurocognitive domain includes subscales of brain fog, headache, and dizziness, ranging from 0 to 30. The TSS is the sum of the 11 severity items ranged from 0 to 110. For all levels, higher scores represent increased sign and symptom severity. If any item score is missing, the corresponding domain and TSS score will be set as missing on a given day.

The patient will complete the ISM-SAF daily for 4 weeks beginning at the time of informed consent, during which time BSC medications are optimized and stabilized. The ISM-SAF will be completed daily for an additional 2 weeks (14 days) to calculate eligibility TSS score to determine patient eligibility based on the ISM-SAF symptom threshold (≥28 vs. <28). Baseline symptoms will be collected for the 14 days immediately preceding the first dose of study drug or placebo. These data will be used to derive a Baseline TSS. Thereafter the ISM-SAF TSS will be calculated on a daily and bi-weekly basis. A daily TSS is

created by summing the scores for each of the 11 items on a given assessment day, and a bi-weekly TSS (14-day average TSS) is created by averaging the summed daily scores over a pre-specified 14-day period and dividing by the number of non-missing days. A bi-weekly TSS is derived only if the subject completes the ISM-SAF on seven or more of the 14 days, otherwise it will be considered missing for the patient. The average of summed daily scores over a 14-day period, was calculated and used to assess eligibility for inclusion in BLU-285-2203 as well as treatment efficacy at each study timepoint.

The primary efficacy endpoint for Part 2 is the mean change is ISM-SAF TSS from Baseline to Cycle 7 Day 1 (C7D1). Change in TSS from Baseline to C7D1 is defined as (C7D1 TSS - Baseline TSS).

The threshold for baseline ISM moderate vs. severe is 42.

Table 34. Conceptual framework for the ISM-SAF

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

Abbreviations: GI=gastrointestinal

*These reflect non-specific symptoms and intended to be assessed and scored on an item-level basis only (i.e., unlike GI, skin, and neurocognitive symptoms, no domain is hypothesized)

†Though the focus of this dossier is on the ISM-SAF TSS, it is important to note that content validity and psychometric analysis provided herein also support use of the GI Symptom, Skin Symptom, and Neurocognitive Symptom domain scores in the target patient population.

Development of the ISM-SAF PRO questionnaire

The qualitative activities undertaken during the development of the ISM-SAF included a review of empirical literature, advice meetings with therapeutic area experts, qualitative concept elicitation interviews with patients with ISM (n=13) or SSM (n=3), concept selection and questionnaire development, and qualitative cognitive debriefing interviews with patients with ISM.

A translatability assessment was conducted by an independent translation services provider. The following eight languages were selected for the evaluation: Danish (for Denmark), Dutch (for Netherlands and Belgium), Spanish (for Spain), French (for France), German (for Germany), Italian (for Italy), and Swedish (for Sweden).

Qualitative cognitive debriefing interviews were conducted with patients with ISM to evaluate the ISM-SAF for readability, comprehensibility, relevance, and comprehensiveness.

The psychometric performance of ISM-SAF scores was evaluated in an observational study (n=103), during part 1 of study BLU-285-223 (n=38) and in part 1 + part 2 of study BLU-285-223 (n=243).

Identification of severity thresholds in the observational study

As stated above, a prospective, observational study was performed to (1) generate cross-sectional psychometric data for ISM-SAF scores, (2) inform the use of the ISM-SAF as a clinical trial screening tool in BLU-285-2203, and (3) identify TSS cut-off scores capable of distinguishing patients with moderate to severe symptoms from those with mild symptoms.

The observational study utilized an online survey of patients in the US diagnosed with ISM or SSM, who completed clinical outcome assessments using a web-based electronic platform over the course of 15 days. In addition to the ISM-SAF, clinical outcome assessments included the Patient Global Impression of Symptom Severity (PGIS), 12-Item Short Form Survey, Version 2 (SF-12v2®), Mastocytosis Quality of Life Questionnaire (MC-QoL), and Functional Assessment of Cancer Therapy – Cognitive Function (FACT-Cog).

A total of 116 eligible adult patients were screened into the study; 103 were included in the Self-reported Diagnosis Cohort, and 58 were able to provide medical documentation of diagnosis from their physician and were included in the Medically Documented Diagnosis Cohort.

Based on the findings of both the ROC and contingency analyses, using the PGIS as an anchor, a bi-weekly ISM-SAF TSS cut-off value of between 21 and 28 to identify patients with at least moderate symptoms was indicated for screening purposes in the BLU-285-2203 study. The upper value of 28 was selected as a more conservative estimate, and it was assumed that the use of this cut-off would retain a large enough sample to meet clinical study goals. These same analyses based on observational study data were used to establish a TSS cut-off value of 42 to distinguish patients with severe symptoms from those with moderate symptoms.

Results from the observational study and from Part 1 of BLU-285-2203 were shared with the FDA and EMA, and are understood by the MAH to support the conclusion that the ISM-SAF produces reliable and construct valid scores when administered to patients in the target population. To provide further evidence of the reliability and validity of the ISM-SAF, the MAH conducted psychometric analyses based on pooled data from Part 1 and Part 2 of BLU-285-2203. A total of 243 patients from Cohort 1 and Cohort 2 with ISM-SAF data at C1D1 and at C3D1, C4D1, or C7D1 were included in the psychometric analysis population (PsAP) for Part 1 and Part 2. Nearly all patients had bi-weekly scores for all ISM-SAF items throughout the study: 100.0% at Baseline, 98.8% at C3D1, 98.3% at C4D1, 99.2% at C6D1, and 97.9% at C7D1.

Score interpretation and clinical relevance

Researchers are using different nomenclature including the clinically important difference (CID) between groups and clinically important response, most recently referred to as meaningful within-patient change

(MWPC). The CID reflects the difference in scores between two treatment groups that can be considered clinically relevant and distinguishes between-groups change from measurement error. In contrast, the MWPC is the amount of change an individual would have to report to support the conclusion that a treatment benefit has been observed.

To assist in the interpretation of scores of the ISM-SAF, distribution-based methods, anchor-based methods, empirical cumulative distribution function (eCDF) curves, and probability density function (PDF) curves were employed.

Anchor-based analyses from Part 1 Cycle 4 of BLU-285-2203 (based on a PGIS reduction of one or two points from baseline) were used to inform the conclusion that a 30% reduction in the TSS reflects an MWPC, a threshold that aligns with the treatment response criteria of ≥30% proposed by the European Competence Network on Mastocytosis (ECNM) and the American Initiative on Mast Cell Diseases (AIM) Consortium. Score interpretation conclusions from Part 1 were confirmed by the pooled Part 1 and 2 data. Additionally, CID estimates to facilitate the meaning of observed group differences using distribution based methods were proposed by the MAH. The range was generated using two independent distribution-based methods ("1/2 standard deviation at baseline" and the "standard error of measurement") as defined in the psychometric analysis SAP. CID range for the TSS was based on pooled Part 1 and 2 data, and confirmed the difference range previously observed for Part 1.

Sample size

Part 1

The sample size for Part 1 of the study is not determined based on a specific statistical hypothesis; rather, it is chosen to allow analysis of ISM-SAF TSS, PK parameters, safety, and objective measures of MC burden for a range of avapritinib doses in the study population to enable further study of a RP2D in Part 2.

Part 2

Mean change in ISM-SAF TSS from Baseline to C7D1:

With a 1:2 (placebo:avapritinib 25mg) randomization ratio, assuming the null hypothesis is 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 is assumed to be 20, and a 1- sided type I error rate of 0.025, a total of 204 patients will have > 90% power using a 2-sample t-test.

Supportive evidence was from analysis results from Part 1 showing -19.7 mean change (standard deviation 20.2, n=10) in patients treated with avapritinib 25 mg, compared to -3.2 mean change (standard deviation 9.0, n=9) in patients treated with placebo. Further, psychometric evaluation of the ISM-SAF in Part 1 using distribution-based methods identified a 10-point threshold as a conservative approach providing guidance for interpreting substantive results when using ISM-SAF for the comparison of treatment group mean difference. Therefore, in Part 2 the assumption of a mean change of negative 10 in the placebo group was used to take a conservative approach to powering the study, while maintaining a difference of approximately 10 between placebo and avapritinib treatment.

To ensure the study is powered for the primary endpoint and all key secondary endpoints, 204 patients is the proposed sample size for Part 2.

Part 3

Patients rollover to Part 3 from Part 1 and Part 2. The number of patients in Part 3 will be approximately 39+204= 243 patients.

Randomisation

The randomization assignment was implemented by the IRT after screening was completed:

Part 1

Enrolment into Part 1 of the study was randomized in a ratio of 1:1:1:1 to the 3 doses of avapritinib and placebo. Randomization was stratified by presence or absence of mastocytosis in skin at baseline and by baseline serum tryptase level (< 20 vs ≥ 20 ng/mL). All patients received the RP2D when they rolled over to Part 3.

Part 2

Enrolment into Part 2 of the study was randomized in a ratio of 2:1 to 25 mg avapritinib QD and placebo. All patients received 25 mg avapritinib QD (RP2D) when they roll over to Part 3. Randomization in Part 2 was stratified based on baseline serum tryptase level (< 20 ng/mL vs ≥ 20 ng/mL).

Blinding (masking)

The study is double-blinded. Patients, monitors, study centre personnel related to the study, and the Sponsor were blinded to treatment assignment in Part 1 and Part 2 of the study, with the exception of specific unblinded staff involved in safety and pharmacovigilance, and management of the IDMC.

To ensure that the study team members were not unblinded inadvertently, the documentation containing patient treatment assignment information was stored in a pre-identified, secure, limited-access folder or secure network area.

Statistical methods

The final SAP for Part 2 and Part 3 of study dated 07 June 2022 and the interim analysis SAP for Part 1 of the study dated 03 February 2020.

When analysing overall long-term data, information from Parts 1, 2 and 3 were included in the analyses.

Analyses for Part 1 are presented by treatment group. Continuous variables were summarized by reporting the number of observations (n), mean, SD, median, min, and max.

Categorical variables were summarized using frequency tables showing the number and percentage of patients within a particular category, where the denominator was the total number of non-missing values at the applicable time point (unless otherwise specified). Appropriate 95% CIs were also presented as needed.

All analyses for Part 2 are presented by treatment arm, 'placebo' and '25 mg' for patients who initially enrolled into Part 2 of the study. Part 3 analyses that use the Part 3 baseline are presented by patients' initial treatment arm in Part 1 or Part 2 as the following: 'placebo to 25 mg', '25 to 25 mg', '50 to 25 mg', '100 to 25 mg', 'placebo' or '25 to 25 mg', and 'overall'.

The same layout as Part 3 is used for long-term avapritinib summary tables that use avapritinib baseline and data from Part 1, Part 2, and Part 3 (definitions of baseline provided in Section 9.7.1.2).

Summary statistics for continuous variables included n (non-missing observations), mean, SD, minimum, median, and maximum. Summary statistics for categorical variables were presented in terms of frequencies and percentages. Time to event data were summarized using KM method, which included the number of events and censors, the estimated median with 95% CIs, minimum, maximum, and 25th and 75th percentiles.

Analysis populations

- Intent-to-treat (ITT) Population: All randomized patients independent of whether they received the study drug or not. The primary efficacy analysis set is the ITT population.
- Per-Protocol (PP) Population (only for Part 2 and 3)**:** All randomized patients who met the following criteria:
    - Confirmed to have ISM per WHO diagnostic criteria, including Central Pathology Review of bone marrow.
    - Had no major violations of the inclusion criteria (#2, #3, #6) or exclusion criteria (#1, #5, #18):
    - Part 1 or Part 2 baseline TSS score ≥ 28.
    - Had not received wrong study drug at any time during Part 2 of the study (ie, placebo patient received avapritinib by mistake, or vice versa).
    - Had not received concomitant TKI treatment.
- Safety Population: All patients who received at least 1 dose of avapritinib or placebo.

Adjustments for covariates

For the primary analysis, an ANCOVA controlling for randomization stratification factor (serum tryptase <20 ng/mL vs ≥ 20 ng/mL) and baseline ISM status (moderate vs severe) was performed to compare avapritinib and placebo.

Handling of dropouts or missing data

No imputation was made for completely missing date unless otherwise specified.

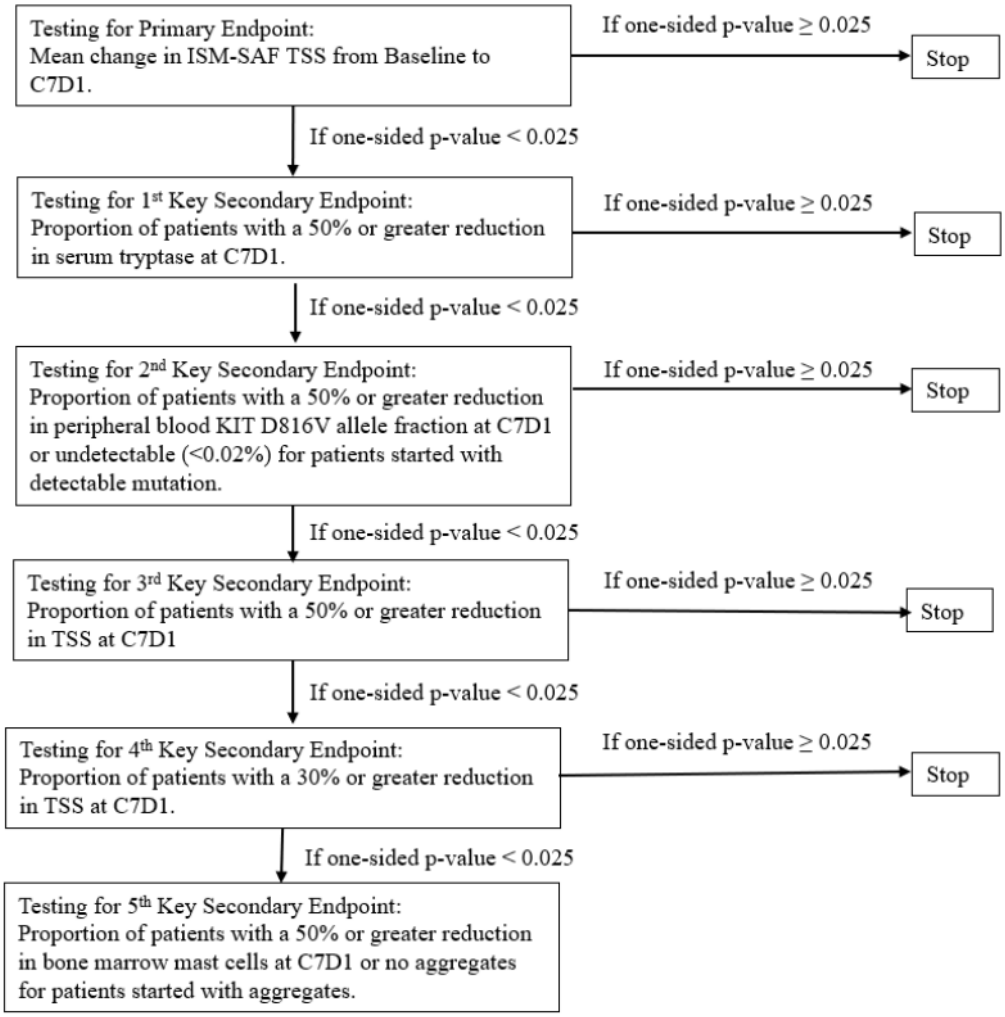
Interim analyses and data monitoring

As per protocol, an interim analysis was performed to determine the RP2D, efficacy, and safety once all Part 1 patients had completed C4D1 assessments. No other interim analysis was planned for the study.

Multiple comparison/multiplicity

The gatekeeping procedure was used to test the primary endpoint and all four key secondary endpoints with the testing order shown in the below Figure 30 to ensure the family-wise type I error is strongly controlled for both the primary endpoint and key secondary endpoints at 1-sided alpha of 0.025.

Figure 30. Gatekeeping Procedure for Primary Endpoint and Key Secondary Endpoints



Results

Study BLU-285-2203 has enrolled 251 patients with ISM, including 246 patients who have received at least 1 dose of avapritinib.

The study is being conducted in 3 parts:

- **Part 1 -** Tested 3 doses of avapritinib in ISM patients (100, 50, and 25 mg vs placebo) and identified 25 mg as the RP2D with the optimized benefit-risk for patients with ISM (39 patients; duration of treatment: at least 12 weeks)
- **Part 2 -** Conducted after the determination of RP2D, in patients with ISM randomly assigned to the avapritinib RP2D identified in Part 1 in combination with BSC (141 patients) or to placebo in combination with BSC (71 patients), to determine the efficacy and safety of avapritinib in combination with BSC compared with placebo in combination with BSC in patients with ISM with moderate to severe symptoms that could not be adequately controlled by BSC (duration of treatment: 24 weeks)
- **Part 3 -** Is ongoing and is intended to further characterize the safety and efficacy of long-term treatment in patients receiving the RP2D in combination with BSC. Patients on placebo in Part 1 or 2 will crossover to receive avapritinib, and patients randomized to receive treatment with avapritinib in

Parts 1 or 2 will continue to receive avapritinib in this open-label extension cohort after completion of Parts 1 or 2. Part 3 duration of treatment: up to 5 years including durations of Parts 1 and 2.

The study included 39 patients (9 patients in placebo, 10 patients in each group of avapritinib 25, 50, and 100 mg) in Part 1 and 212 patients (71 patients in placebo and 141 in the 25 mg Avapritinib Group) in Part 2.

Overall, 235 patients (34 patients from Part 1 and 201 patients from Part 2) rolled over to Part 3 from Part 1 and Part 2 of the study.

Participant flow

Patient disposition

Part 1 of the study completed enrolment with 39 patients. All 39 patients were randomized 1:1:1:1 into 1 of 3 avapritinib dose groups or placebo. Patients received a once-daily dose of either placebo (n=9) or avapritinib (25 mg, 50 mg, 100 mg: n=10 for each group).

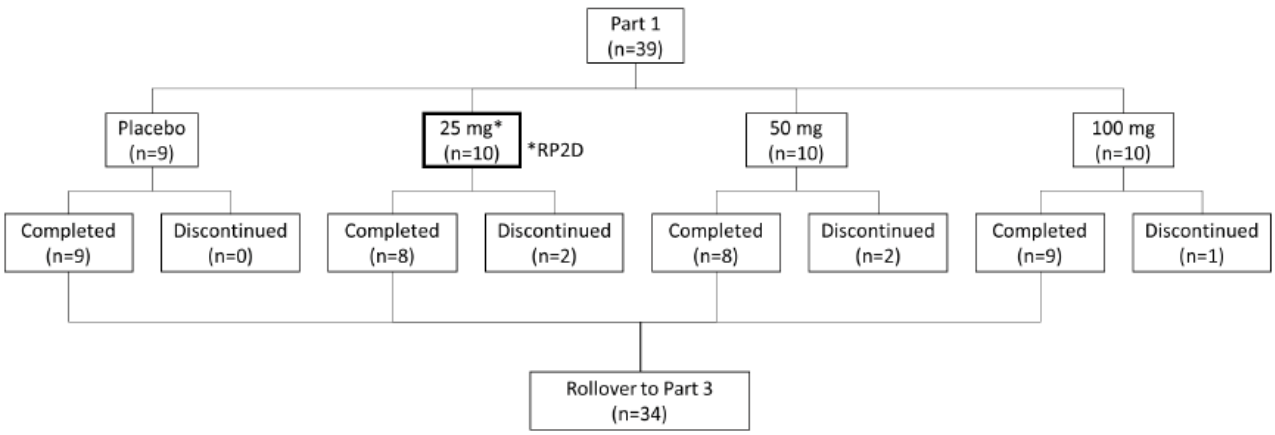
In Part 1, 2 patients from the 25 mg Avapritinib Group discontinued from the study due to non-compliance and AE, respectively.

In the 50 mg Avapritinib Group, 2 patients discontinued due to non-compliance and AE, respectively.

In the 100 mg Avapritinib Group, 1 patient discontinued due to withdrawal by patient.

A total of 34 patients completed Part 1 of the study and rolled over to Part 3.

Figure 31. Disposition of Patients in Part 1 (Including Those Who Rolled Over to Part 3)



Abbreviations: RP2D = recommended Phase 2 dose.

In **Part 2**, both the ITT and Safety Populations included 141 patients in the 25 mg avapritinib group and 71 patients in the placebo group.

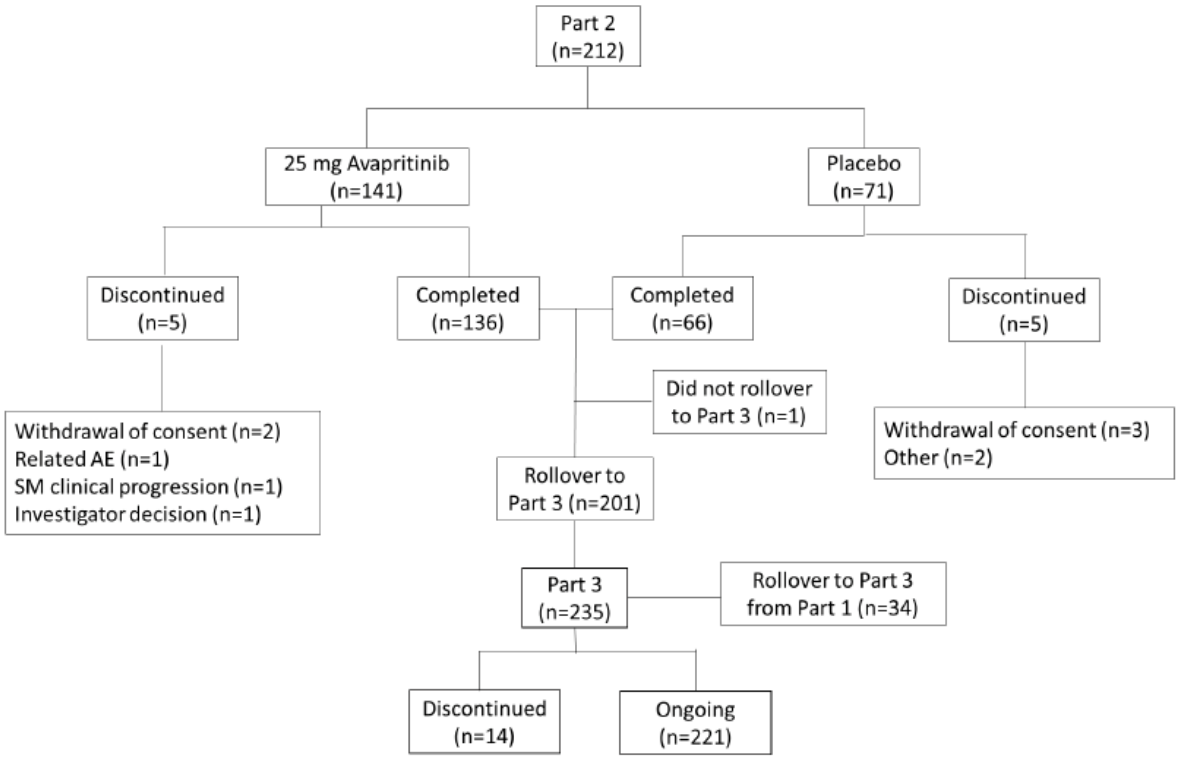
The PP Population in Part 2 included 123 patients in the 25 mg Avapritinib Group and 67 patients in the Placebo Group. In Part 2, patient disposition was similar in the 25 mg Avapritinib Group and Placebo Group. In the 25 mg Avapritinib Group, 5 patients discontinued from the study for the following reasons: withdrawal of consent (n=2), related AE (n=1), SM clinical progression (n=1), and Investigator's decision (n=1).

In the Placebo Group, 5 patients discontinued from the study (3 patients due to withdrawal of consent

and 2 patients due to other reasons).

A total of 136 patients (96.5%) treated with 25 mg avapritinib and 66 patients (93.0%) treated with placebo completed Part 2 of the study. Of these, 1 patient in the 25 mg Avapritinib Group completed Part 2 but did not roll over to Part 3. A total of 201 patients completed Part 2 and rolled over to Part 3.

Figure 32. Disposition of patients in Part 2 of the Study (Including those who rolled over to part 3)



Abbreviations: AE = adverse event; SM = systemic mastocytosis.

Overall, 235 patients rolled over to Part 3 from Part 1 and Part 2 of the study. At the time of the data cut-off (23 June 2022), 14 patients have discontinued from Part 3 of the study and 221 patients were ongoing. Of these, 5 patients discontinued due to AEs, 2 each due to progressive disease and withdrawal of consent, and 1 each due to investigator decision, patient decision, lost to follow-up, and patient withdrew as they requested dose escalation that was not permitted per protocol. Only 1 patient discontinued from the study drug due to lack of effectiveness. Updated data with a data cut-off date of 07 April 2023 (an additional 10 months of follow-up) were provided during the procedure. At the time of this data cut-off, 24 patients have discontinued from Part 3 of the study and 211 patients were ongoing.

Recruitment

- Date first patient enrolled (C1D1): 16 April 2019
- Date last patient enrolled (C1D1): 06 January 2022
- Data cut-off date for the interim analysis: 23 June 2022

Forty-two sites enrolled patients and entered data for this study, including 19 sites in North America, 20 sites in Europe, and 3 sites in the United Kingdom. Two additional sites screened patients but did not enrol any patients.

Conduct of the study

The original Protocol for Study BLU-285-2203 (dated 15 February 2018) was amended 10 times: 5 were global and 5 were country-specific amendments. The study methodology presented for assessment is in accordance with the latest global protocol amendment 9 (dated 07 June 2022).

Table 35. Major Changes of Global Protocol Amendments

Amendment Number	Amendment Date	Summary of Major Changes
1	30 July 2018 First patient screened for the study: 11 January 2019 First patient enrolled in the study: 16 April 2019:	• Part 1 and 2: Primary endpoint changed from mean percent reduction in ISM-SAF TSS to mean change in ISM-SAF TSS from baseline to Week 12. Secondary objectives and endpoints updated to proportion of patients with at least 5-, 10-, and 15-point reductions in TSS and domain scores of ISM-SAF from baseline to Week 12. • Part 3: Secondary objectives and endpoints updated to reflect the time to achieve 5-, 10-, and 15-point reductions in TSS and domain scores

Amendment Number	Amendment Date	Summary of Major Changes
		• Added threshold for eligibility based on ISM-SAF TSS to eligibility criteria • Removed 200 mg dose group from study • Updated duration of patient participation to reflect minimum duration of participation of 26 weeks (Parts 1 and 2) and 8 weeks (Part 3) • Updated dosing guidelines in the event of toxicity or ICB.
2	14 February 2020	• To reduce the risk of ICB, the following changes were made: • Added new dose modifications for moderate thrombocytopenia (< 75,000/μL) • Added precautions around concomitant coagulopathy and use of antithrombotic and anticoagulant therapy • Added an exploratory objective assessing platelet aggregation • Increased monitoring for ICB, including focal neurological history and exam at each visit • Revised informed consent • Other major changes were: • Raised the QTc exclusion threshold from 450 to 480 msec • Added exclusion criteria to exclude patients with known hypersensitivity to the active ingredients or any excipients • Added exclusion criteria to exclude patients who participate in another study • Added precaution to use clothing and sunscreen to avoid direct sun exposure
4	15 June 2020 First patient screened for Part 2 of the study: 23 July 2020 First patient enrolled in Part 2 of the study: 24 September 2020	Major revisions of Part 2 (efficacy) prior to starting Part 2 enrollment included: • Confirmed RP2D to be 25 mg QD based on equivalent efficacy but superior tolerability than 50 and 100 mg QD • Established clinically important response as a ≥ 30% reduction in TSS from baseline based on the psychometric evaluation of the ISM-SAF in Part 1.

Amendment Number	Amendment Date	Summary of Major Changes
		• Changed primary endpoint to the proportion of avapritinib-treated patients with ISM achieving ≥ 30% reduction in TSS from baseline to C7D1, as compared to placebo • Added the following 4 key secondary endpoints: – To determine the proportion of avapritinib-treated patients with a ≥ 50% reduction in serum tryptase from baseline to C7D1, compared to placebo – To determine the proportion of patients with a ≥ 50% reduction in peripheral KIT D816V allele fraction from baseline to C7D1 or undetectable (< 0.02%) for patients with detectable mutation at baseline – To determine mean change in ISM-SAF TSS in patients from baseline to C7D1 – To determine the proportion of patients with a ≥ 50% reduction in bone marrow mast cells from baseline to C7D1 or no aggregates for patients with aggregates at baseline Other major changes included: • Increased sample size in Part 2 to approximately 204 patients, increasing the total number of patients across all parts to approximately 244 patients • Added a stratification to treatment assignment randomization in Part 2 • Instituted blinding to changes in serum tryptase, bone marrow mast cells, and KIT D816V allele fraction during Part 2 • Limited study population to ISM in Part 2 • Clarified exclusion criterion regarding ongoing significant medical conditions that are symptomatically uncontrolled • Increased the number of sites from approximately 20 to approximately 35 sites • Removed dose escalation to > 25 mg QD • Updated the dose-modification guidance to recommend interruption of avapritinib if platelet levels for a patient fall < 100,000/μL

Amendment Number	Amendment Date	Summary of Major Changes
		• Removed the Part 2 and 3 weekly safety visits at C1D8, C1D15, and C1D22 • Added new appendix to provide guidance on study conduct in case of travel restrictions
7	01 November 2021	• Added the option of escalating avapritinib dose to 50 mg in Part 3. Specific criteria for this dose escalation added. • Extended the schedule of ISM-SAF and QoL assessments beyond C13D1 through to EOT. • Clarified use of corticosteroids during the study. If a patient was not on corticosteroids at baseline, corticosteroids were not recommended during the study. Similarly, for patients who were on corticosteroids at baseline, increasing the dosage of these drugs was not recommended during the study.
9	07 June 2022	• Based on FDA feedback received in May 2022, the following changes were made: • The primary objective for Part 2 was changed from 'the proportion of avapritinib treated patients with ISM achieving ≥ 30% reduction in TSS from baseline to C7D1, compared to placebo' to 'mean change in ISM-SAF TSS from baseline to C7D1, compared to placebo'. It enables analyzing symptom reduction as a continuous variable instead of a dichotomous endpoint. • The 'proportion of avapritinib treated patients with ISM achieving ≥ 30% reduction in TSS from baseline to C7D1, compared to placebo' was changed to a key secondary endpoint for Part 2. An additional key secondary endpoint for Part 2, the 'proportion of avapritinib treated patients with ISM achieving ≥ 50% reduction in TSS from baseline to C7D1, compared to placebo' was added. • Analysis method for the 'mean change in ISM-SAF TSS from baseline to C7D1, compared to placebo' was changed from the two-sample t-test to ANCOVA controlling for randomization stratification factor (tryptase) and baseline ISM status (moderate vs severe). • LOCF missing data imputation method was removed.

Abbreviations: ANCOVA = analysis of covariance; CxDx = Cycle X Day X; EOT = End-of-Treatment; FDA = US Food and Drug Administration; ICB = intracranial bleeding; ISM = indolent systemic mastocytosis; ISM-SAF = Indolent Systemic Mastocytosis-Symptom Assessment Form; LOCF = last observation carried forward; QD = once daily; QoL = Quality of Life; RP2D = recommended Phase 2 dose; TSS = Total symptom score.

Protocol deviations

In Part 1, overall, 10 patients had ≥ 1 major protocol deviation.

The most common major protocol deviation was related to informed consent (7 patients overall).

For patients enrolled in Part 2, 41 (29.1%) patients in the 25 mg Avapritinib Group vs. 7 (9.9%) patients in the Placebo Group had ≥ 1 major protocol deviation during Part 2 of the study.

The most common major protocol deviations are outlined in the Table below. All other major protocol deviations occurred in < 2% of patients in either treatment group.

Table 36. Major deviations in > 2% of patients (Part 2)

Deviation Type	Detail	Avapritinib 25 mg n (%)	Placebo n (%)
Missed critical assessment at C7D1[a]	Central tryptase	1 (0.7)	1 (1.4)
	Central Bone marrow biopsy	6 (4.3)	0
	Central skin biopsy	1 (0.7)	0
ISM-SAF Compliance	< 50% completed in a cycle	10 (7.1)	3 (4.2)
ICF compliance	ICF reconsent available but not signed within 2 study visits or administrative error	7 (5.0)	1 (1.4)
Prohibited concomitant medication given [b]	Use of CYP3A4 inhibitor [c]	1 (1.4)	3(2.1)
High dose steroid use	Within 7 days prior to C7D1 or for 14 consecutive days during the study	3 (2.1)	0
Randomized to incorrect tryptase level	Tryptase ≥ 20 ng/mL at Screening and randomized to < 20 ng/mL stratification group	3 (2.1)	1 (1.4)
	Tryptase < 20 ng/mL at Screening and randomized to ≥ 20 ng/mL stratification group	1 (0.7)	0
Dosing compliance	< 75% prescribed dose received in a cycle	5 (3.5)	0

a Two of the 11 patients categorized as having missed critical assessments were determined to be minor deviations after database lock and thus were miscategorized, therefore reasons for only 9 patients are listed in this table.

b Two of the 6 patients categorized as having prohibited concomitant medication given were later determined to be minor deviations as the steroid use did not meet the criteria for major deviation (ie, use within 7 days before C7D1 or for 14 consecutive days during the study). Therefore, only 4 patients are listed in this table.

C Five additional patients who had protocol deviations for CYP 3A4 inhibitor use are not included in Table 99.1.2.1.1, as the start date of use was prior to study entry (see listing 16.2.2.1).

Patients with missing TSS at Part 2 C7D1 were excluded from the primary efficacy analysis using ANCOVA method but was included in the sensitivity analysis using Markov chain Monte Carlo (MCMC) imputation method. Likewise, patients who received high dose steroids within C7D1 were excluded from the primary efficacy analysis using ANCOVA method but were included in the sensitivity analysis using MCMC imputation method.

Baseline data

Part 1 of study BLU 285-2203

Demographic characteristics

In Part 1, the majority of the patients were female (76.9%), < 65 years old (87.2%), White (92.3%), and not Hispanic and Latino (89.7%). Baseline height and weight were similar across treatment groups.

Part 1: Demographics and Baseline Characteristics
Intent-to-Treat Population

	Placebo (N=9)	Avapritinib 25 mg (N=10)	Avapritinib 50 mg (N=10)	Avapritinib 100 mg (N=10)	Overall (N=39)
Age (Years)					
n	9	10	10	10	39
Mean (StdDev)	50.2 (11.57)	51.1 (16.89)	48.0 (8.98)	47.6 (14.49)	49.2 (12.92)
Median	51.0	52.0	50.5	46.0	51.0
Min, Max	29, 68	23, 75	33, 61	21, 72	21, 75
Age, n (%)					
<65	8 (88.9)	7 (70.0)	10 (100)	9 (90.0)	34 (87.2)
>=65	1 (11.1)	3 (30.0)	0	1 (10.0)	5 (12.8)
Sex, n (%)					
Male	2 (22.2)	0	4 (40.0)	3 (30.0)	9 (23.1)
Female	7 (77.8)	10 (100)	6 (60.0)	7 (70.0)	30 (76.9)
Race, n (%)					
White	9 (100)	10 (100)	8 (80.0)	9 (90.0)	36 (92.3)
Black or African American	0	0	1 (10.0)	0	1 (2.6)
Asian	0	0	0	0	0
American Indian or Alaska Native	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Other	0	0	0	0	0
Unknown	0	0	1 (10.0)	1 (10.0)	2 (5.1)

Abbreviations: Min = minimum, Max = maximum, StdDev = standard deviation. TSS = Total Symptom Score, GSS = Gastrointestinal Symptom Score, SSS = Skin Symptom Score, SM = Systemic Mastocytosis, ISM = Indolent Systemic Mastocytosis, SSM = Smoldering Systemic Mastocytosis, BSC = Best Supportive Care
Note: Percentages are based on number of patients in the ITT Population.
[1] Baseline Body Mass Index (BMI) is calculated as weight (kg)/ (height (m))^2.
[2] Baseline anaphylaxis event rate is calculated as number of events between Informed Consent to C1D1/(C1D1 date - Informed Consent date)
Cross References: Listing 16.2.4.1.1a, 16.2.4.1.2a, 16.2.4.1.3a
Program: t-14-01-03-01a.sas Table Generation: 11MAY2020 13:21

Disease characteristics

In Part 1, at baseline, all patients had significant sign and symptom burden as assessed by the ISM-SAF with a mean (SD) TSS of 53.3 (19.34).

Baseline mean (SD) serum tryptase was 83.78 (100.530) ng/mL and 89.7% patients had bone marrow mast cell aggregates.

KIT D816V mutation was detected in peripheral blood in 79.5% of patients at baseline with a mean (SD) allele fraction of 4.274 (8.4802).

Part 2 of study BLU 285-2203

Demographic characteristics

Table 37. Demographic Characteristics (Part 2 ITT Population)

Category	Avapritinib 25 mg N=141	Placebo N=71
Age (years) [a]		
Mean (SD)	48.7 (11.70)	52.2 (12.52)
Median (Min, Max)	50.0 (18, 77)	54.0 (26, 79)
Age group, n (%)		
< 65 years	132 (93.6)	60 (84.5)
≥ 65 years	9 (6.4)	11 (15.5)
Sex, n (%)		
Female	100 (70.9)	54 (76.1)
Male	41 (29.1)	17 (23.9)
Ethnicity, n (%)		
Hispanic or Latino	6 (4.3)	1 (1.4)
Not Hispanic or Latino	99 (70.2)	58 (81.7)
Not reported	22 (15.6)	10 (14.1)
Race, n (%)		
Asian	1 (0.7)	0
White	109 (77.3)	61 (85.9)
Unknown	27 (19.1)	8 (11.3)
Other	4 (2.8)	2 (2.8)
Height (cm)		
n	137	70
Mean (SD)	169.05 (9.726)	166.55 (9.073)
Median (Min, Max)	167.00 (152.4, 194.0)	165.00 (150.2, 195.0)
Weight (kg)		
n	141	71
Mean (SD)	81.12 (17.915)	82.19 (17.796)
Median (Min, Max)	80.20 (45.0, 126.4)	80.70 (44.4, 134.8)
BMI (kg/m^2) [b]		
n	137	70
Mean (SD)	28.31 (5.400)	29.46 (5.276)
Median (Min, Max)	27.84 (17.6, 42.0)	28.99 (19.7, 43.7)

Abbreviations: BMI = body mass index; ITT = Intent-to-Treat; Max = maximum; Min = minimum; SD = standard deviation.

[a] Age at the time of informed consent.

[b] Baseline BMI was calculated as weight (kg)/(height (m))^2.

Part 2 ITT population of the study included more female (100 [70.9%] patients in the 25 mg Avapritinib Group; 54 [76.1%] patients in the Placebo Group) than male (41 [29.1%] patients in the 25 mg Avapritinib Group; 17 [23.9%] patients in the Placebo Group).

Most patients in both groups were < 65 years (93.6% in the 25 mg Avapritinib Group and 84.5% in the Placebo Group), not Hispanic or Latino (70.2% in the 25 mg Avapritinib Group and 81.7% in the Placebo Group), and White (77.3% patients in the 25 mg Avapritinib Group and 85.9% patients in the Placebo Group), and other baseline characteristics (mean height [cm], weight [kg], and body mass index [kg/m2]) were similar in both groups.

Baseline disease characteristics

Table 38. Baseline Disease Characteristics (Part 2 ITT/Safety Population)

Category	Avapritinib 25 mg N=141	Placebo N=71
Baseline ISM-SAF TSS [a] (Range: 0-110)		
n	139	71
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)
Baseline ISM severity based on ISM-SAF TSS [a], n (%)		
≥ 42 (Severe)	87 (61.7)	45 (63.4)
< 42 (Moderate)	52 (36.9)	26 (36.6)
Baseline Serum Tryptase (ng/mL) [b]		
n	141	71
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)
Baseline KIT D816V Mutation Allele Burden as Measured by MAF using ddPCR from Blood (Central Assay) [b]		
n	141	71
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)

Category	Avapritinib 25 mg N=141	Placebo N=71
Baseline Percent Bone Marrow Mast Cells (Central Pathology Review) [b]		
N	141	71
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)
Baseline GI domain score on ISM-SAF [a] (Range: 0-30)		
n	139	71
Mean (SD)	9.71 (6.202)	10.41 (6.847)
Median (Min, Max)	8.43 (0.0, 26.8)	9.79 (0.0, 28.0)
Baseline skin domain score on ISM-SAF [a] (Range: 0-30)		
N	139	71
Mean (SD)	15.50 (7.123)	17.20 (7.612)
Median (Min, Max)	15.15 (0.0, 30.0)	17.85 (0.0, 30.0)
Baseline neurocognitive symptom cluster on ISM-SAF [a] (Range: 0-30)		
N	139	71
Mean (SD)	13.04 (6.779)	12.71 (6.969)
Median (Min, Max)	12.62 (0.0, 29.6)	11.29 (0.4, 29.1)
Baseline lead (most severe) symptom on ISM-SAF [c]		
N	139	71
Mean (SD)	7.66 (1.693)	7.91 (1.679)
Median (Min, Max)	7.69 (3.6, 10.0)	8.00 (4.1, 10.0)
Baseline lead (most severe) domain/neurocognitive symptom cluster score on ISM-SAF [d]		
N	139	71
Mean (SD)	17.51 (6.033)	18.58 (6.397)
Median (Min, Max)	17.21 (5.6, 30.0)	18.64 (4.8, 30.0)
Baseline concomitant BSC use [e]		
n	141	71
Mean (SD)	3.7 (1.94)	3.8 (1.83)
Median (Min, Max)	3.0 (0, 11)	4.0 (1, 8)

Category	Avapritinib 25 mg N=141	Placebo N=71
Mast Cell (counts/mm^2) in Skin by Central Lab (Lesional)		
N	107	60
Mean (SD)	561.2 (399.65)	637.6 (488.71)
Median (Min, Max)	459.0 (89, 2870)	617.5 (83, 2609)
Mast Cell (counts/mm^2) in Skin by Central Lab (Non-lesional)		
n	106	60
Mean (SD)	152.2 (76.28)	165.9 (166.00)
Median (Min, Max)	131.5 (35, 659)	129.0 (59, 1337)

Abbreviations: BSC = best supportive care; CXDX = Cycle X Day X; ddPCR = digital-droplet polymerase chain reaction, GI = gastrointestinal; ISM = indolent systemic mastocytosis; ISM-SAF = Indolent Systemic Mastocytosis-Symptom Assessment Form; ITT = Intent-to-Treat; MAF = mutant allele fraction; Max = maximum; Min = minimum; SD = standard deviation, TSS = Total symptom score.

[a] Baseline TSS score is defined as the 14-day average of TSS from C1D–14 to C1D–1. If a patient is missing more than 7 days of score between C1D-14 and C1D-1, the baseline score is considered as missing for the patient.

[b] Baseline refers to the last assessment value prior to C1D1 dosing in Part 2 of the study.

[c] The "lead symptom" score refers to the individual symptom with highest score at baseline in each patient.

[d] The "lead domain/symptom cluster" score refers to the domain/symptom cluster with highest score at baseline in each patient

[e] Concomitant BSC medications are coded using WHO Drug Global B3 March 2022. Baseline BSC is the number of BSC taken on C1D1.

At Part 2 baseline, patients in both the 25 mg Avapritinib Group and the Placebo Group had significant sign and symptoms burden as assessed by the ISM-SAF with a mean (SD) TSS of 50.17 (19.145) in the 25 mg Avapritinib Group and 52.43 (19.823) in the Placebo Group. The thresholds for moderate symptoms of ISM were a TSS of ≥ 28 to < 42, and for severe symptoms of ISM a TSS of ≥ 42. The percentage of patients with severe symptoms of ISM was balanced between the 25 mg Avapritinib Group (61.7%) and the Placebo Group (63.4%).

Other baseline disease parameters including ISM-SAF domain scores, serum tryptase, KIT D816V MAF, bone marrow mast cells, and concomitant BSC use were similar in the 25 mg Avapritinib Group and the Placebo Group and consistent with characteristics observed in the ISM patient population.

At baseline, 12 of 212 (5.7%) patients tested negative for KIT D816V by both central and local testing (n=2 Placebo Group; n=10 Avapritinib Group).

Medical and surgical history

All patients in Part 2 had ongoing medical history. The majority of medical and surgical history events reported are commonly observed in patients with ISM and were similar in the 25 mg Avapritinib Group and Placebo Group. The most common medical history events by System Organ Class were Gastrointestinal Disorders (80.9% in the 25 mg Avapritinib Group and 77.5% in the Placebo Group) followed by Musculoskeletal and Connective Tissue Disorders (79.4% in the 25 mg Avapritinib Group and 81.7% in the Placebo Group), and Skin and Subcutaneous Tissue Disorders (78.0% in the 25 mg Avapritinib Group and 73.2% in the Placebo Group).

Table 39. Ongoing Medical History with Incidence ≥ 10% in Either Treatment Group (Part 2 Safety Population)

System Organ Class Preferred Term	Avapritinib 25 mg N=141 n (%)	Placebo N=71 n (%)
Patients with Ongoing Medical History	141 (100.0)	71 (100.0)
Gastrointestinal Disorders	114 (80.9)	55 (77.5)
Diarrhoea	85 (60.3)	35 (49.3)
Abdominal pain	45 (31.9)	21 (29.6)
Nausea	39 (27.7)	19 (26.8)
Gastrooesophageal reflux disease	38 (27.0)	10 (14.1)
Abdominal distension	14 (9.9)	8 (11.3)
Constipation	13 (9.2)	10 (14.1)
Musculoskeletal and Connective Tissue Disorders	112 (79.4)	58 (81.7)
Bone pain	53 (37.6)	28 (39.4)
Arthralgia	33 (23.4)	7 (9.9)
Osteopenia	32 (22.7)	9 (12.7)
Osteoporosis	27 (19.1)	22 (31.0)
Myalgia	19 (13.5)	9 (12.7)
Back pain	18 (12.8)	2 (2.8)
Skin and Subcutaneous Tissue Disorders	110 (78.0)	52 (73.2)
Pruritus	61 (43.3)	31 (43.7)
Urticaria pigmentosa	50 (35.5)	26 (36.6)
Urticaria	17 (12.1)	8 (11.3)
Rash maculo-papular	11 (7.8)	11 (15.5)
General Disorders and Administration Site Conditions	96 (68.1)	39 (54.9)
Fatigue	67 (47.5)	30 (42.3)
Feeling abnormal	37 (26.2)	9 (12.7)
Asthenia	16 (11.3)	4 (5.6)
Nervous System Disorders	95 (67.4)	44 (62.0)
Headache	52 (36.9)	26 (36.6)
Dizziness	29 (20.6)	13 (18.3)
Migraine	22 (15.6)	9 (12.7)
Memory impairment	20 (14.2)	8 (11.3)
Disturbance in attention	19 (13.5)	6 (8.5)
Vascular Disorders	85 (60.3)	48 (67.6)
Flushing	62 (44.0)	35 (49.3)
Hypertension	37 (26.2)	15 (21.1)

System Organ Class Preferred Term	Avapritinib 25 mg N=141 n (%)	Placebo N=71 n (%)
Metabolism and Nutrition Disorders	76 (53.9)	35 (49.3)
Obesity	39 (27.7)	20 (28.2)
Psychiatric Disorders	69 (48.9)	30 (42.3)
Depression	38 (27.0)	14 (19.7)
Anxiety	27 (19.1)	6 (8.5)
Insomnia	22 (15.6)	9 (12.7)
Respiratory, Thoracic and Mediastinal Disorders	52 (36.9)	24 (33.8)
Asthma	19 (13.5)	8 (11.3)
Dyspnoea	15 (10.6)	4 (5.6)
Immune System Disorders	46 (32.6)	24 (33.8)
Drug hypersensitivity	16 (11.3)	6 (8.5)
Seasonal allergy	7 (5.0%)	8 (11.3%)
Endocrine Disorders	35 (24.8)	15 (21.1)
Hypothyroidism	26 (18.4)	9 (12.7)
Social Circumstances	26 (18.4)	15 (21.1)
Menopause	18 (12.8)	10 (14.1)

Note: Medical history is classified by SOC and PT using MedDRA version 25.0.

Prior and concomitant medications

All patients in the 25 mg Avapritinib Group and the Placebo Group were treated with at least 2 current or prior BSC medications as per study inclusion criteria. The majority of patients in the Part 2 safety population received concomitant BSC medication/therapy (99.3% in the 25 mg Avapritinib Group and 100.0% in the Placebo Group). The most commonly used BSC medications were antihistamines for systemic use such as H1 antihistamines (97.2% in the 25 mg Avapritinib Group and 100.0% in the Placebo Group) and drugs such as H2 antihistamines and proton pump inhibitors (73.8% in the 25 mg Avapritinib Group and 78.9% in the Placebo Group).

Patients also received concomitant medication/therapy other than BSC (97.9% in the 25 mg Avapritinib Group and 100.0% in the Placebo Group). The most common concomitant medication/therapies other than BSC used were viral vaccine (43.3% in the 25 mg Avapritinib Group and 43.7% in the Placebo Group) and other analgesics and antipyretics (36.2% in the 25 mg Avapritinib Group and 35.2% in the Placebo Group). Antidepressants and anxiolytic medications were also used often (19.1% and 16.3% in the 25 mg Avapritinib Group and 21.1% and 22.5% in the Placebo Groups, respectively). The use of opioids was similar between the 2 groups: 22.0% in the 25 mg Avapritinib Group and 22.5% in the Placebo Group).

Table 40. Prior Mastocytosis therapy - Part 2 Baseline (Safety population)

Overall	Placebo (N=71) n (%)	Avapritinib 25 mg (N=141) n (%)
Therapy, n(%)		
Interferon alpha	8 (11.3)	9 (6.4)
Midostaurin	2 (2.8)	8 (5.7)
Cladribine (2CdA)	2 (2.8)	7 (5.0)
Imatinib	1 (1.4)	7 (5.0)
Hydroxyurea	0	5 (3.5)
Dasatinib	1 (1.4)	3 (2.1)
Other	2 (2.8)	2 (1.4)
PUVA	10 (14.1)	2 (1.4)
Brentuximab vedotin	0	1 (0.7)
Other TKI therapy	0	1 (0.7)
Radiation therapy	0	1 (0.7)
Masitinib	1 (1.4)	0
Nilotinib	1 (1.4)	0
Indication, n(%)		
Cutaneous Mastocytosis	3 (4.2)	4 (2.8)
ISM	16 (22.5)	26 (18.4)
SSM	0	1 (0.7)
Prior lines of therapy		
1	13 (18.3)	27 (19.1)
2	4 (5.6)	8 (5.7)
3	2 (2.8)	3 (2.1)
4	0	2 (1.4)
5	0	1 (0.7)
6	0	1 (0.7)
7	0	1 (0.7)
NA	10 (14.1)	4 (2.8)
Duration of prior mastocytosis therapy (Weeks) [1]		
n	18	30
Mean (StdDev)	185.13 (271.142)	108.04 (129.310)
Median	52.14	52.21
Min, Max	0.1, 791.1	0.1, 523.6
Best response to prior mastocytosis therapy		
Improvement	10 (14.1)	11 (7.8)
Worsening	2 (2.8)	1 (0.7)
Lack of response	4 (5.6)	12 (8.5)
Other	2 (2.8)	6 (4.3)

[1] Duration of Prior Mastocytosis therapy is calculated as the sum of the duration of all mastocytosis therapy excluding overlaps.

Part 3 of study BLU 285-2203 – Long-term study

Demographic characteristics

Table 41. Demographics and Baseline Characteristics Intent-to-Treat Population, Part 3 (Part 3 Baseline)

	Placebo -> 25mg (N=75) n/N (%)	Avapritinib 25 -> 25 mg (N=143) n/N (%)	Pooled Placebo/ Avapritinib 25 -> 25 mg (N=218) n/N (%)	Avapritinib 50 -> 25 mg (N=8) n/N (%)	Avapritinib 100 -> 25 mg (N=9) n/N (%)	Overall (N=235) n/N (%)
Age (Years) [1]						
n	75	143	218	8	9	235
Mean (StdDev)	51.8 (12.58)	48.7 (11.65)	49.8 (12.04)	48.3 (6.88)	46.6 (14.97)	49.6 (12.00)
Median	53.0	50.0	51.0	50.5	45.0	51.0
Min, Max	26, 79	18, 75	18, 79	36, 57	21, 72	18, 79
Age Group, n/N (%)						
< 65 Years	64/75 (85.3)	133/143 (93.0)	197/218 (90.4)	8/8 (100.0)	8/9 (88.9)	213/235 (90.6)
>= 65 Years	11/75 (14.7)	10/143 (7.0)	21/218 (9.6)	0	1/9 (11.1)	22/235 (9.4)
< 65 Years	64/75 (85.3)	133/143 (93.0)	197/218 (90.4)	8/8 (100.0)	8/9 (88.9)	213/235 (90.6)
65 - 74 Years	9/75 (12.0)	9/143 (6.3)	18/218 (8.3)	0	1/9 (11.1)	19/235 (8.1)
75 - 84 Years	2/75 (2.7)	1/143 (0.7)	3/218 (1.4)	0	0	3/235 (1.3)
>= 85 Years	0	0	0	0	0	0
Sex, n/N (%)						
Male	19/75 (25.3)	40/143 (28.0)	59/218 (27.1)	3/8 (37.5)	2/9 (22.2)	64/235 (27.2)
Female	56/75 (74.7)	103/143 (72.0)	159/218 (72.9)	5/8 (62.5)	7/9 (77.8)	171/235 (72.8)

Abbreviations: ddPCR= digital-droplet polymerase chain reaction, SM = Systemic Mastocytosis, ECOG= Eastern Cooperative Oncology Group.
[1] Age at the time of informed consent.
[2] Baseline Body Mass Index (BMI) is calculated as weight (kg)/ (height (m))^2.
Cross References: Listing 16.2.4.1.1, 16.2.4.1.2, 16.2.4.1.3
Program: ../BLU-285/2203_Blinded/CSR/Final/Programs/prod/tables/t-dm-itt-b.sas Date: 10:35/15AUG2022

Baseline disease characteristics

Prior to starting Part 3, patients who were in the Placebo Group during Part 1 or Part 2 had higher symptom burden as assessed by the ISM-SAF than the patients who were in the avapritinib groups in Part 1 or Part 2.

At the Part 3 baseline, the mean (SD) TSS was 33.14 (20.061) for the 25 mg to 25 mg Avapritinib Group and 43.51 (19.761) for the Placebo to 25 mg Avapritinnib Group.

At Part 3 baseline, patients who were in the Placebo Group during Part 1 or Part 2 also had higher mast cell burden than the patients who were in the avapritinib groups as assessed by serum tryptase and KIT D816V MAF levels.

Numbers analysed

Table 42. Analysis Populations (Part 2) in Study BLU-285-2203

Analysis Population	25 mg Avapritinib n (%)[a]	Placebo n (%)[a]
Intent-to-treat population	141 (100.0)	71 (100.0)
Safety population	141 (100.0)	71 (100.0)
Per-protocol population	123 (87.2)	67 (94.4)

a Percentages were based on the number of patients in the intent-to-treat population.

Table 43. Analysis Populations (Part 3) in Study BLU-285-2203

Analysis Population	Placebo to 25 mg n (%)	Avapritinib 25 mg to 25 mg n (%)	Avapritinib 25 mg [a] n (%)	Avapritinib 50 mg to 25 mg n (%)	Avapritinib 100 mg to 25 mg n (%)	All n (%)
Intent-to-Treat Population	75 (100.0)	143 (100.0)	218 (100.0)	8 (100.0)	9 (100.0)	235 (100.0)
Safety Population	75 (100.0)	143 (100.0)	218 (100.0)	8 (100.0)	9 (100.0)	235 (100.0)
Per-Protocol Population	71 (94.7)	125 (87.4)	196 (89.9)	7 (87.5)	8 (88.9)	211 (89.8)

a *This group includes the patients who received placebo or 25 mg avapritinib in Part 1 or Part 2, and does not include the patients who received 50 mg or 100 mg avapritinib in Part 1.*

Table 44. Analysis Populations (Parts 1, 2, and 3 [All Avapritinib Treated])

Analysis Population	Placebo to 25 mg n (%)	Avapritinib 25 mg to 25 mg/NA n (%)	Avapritinib 25 mg [a] n (%)	Avapritinib 50 mg to 25 mg/NA n (%)	Avapritinib 100 mg to 25 mg/NA n (%)	All n (%)
Intent-to-Treat Population	75 (100.0)	151 (100.0)	226 (100.0)	10 (100.0)	10 (100.0)	246 (100.0)
Safety Population	75 (100.0)	151 (100.0)	226 (100.0)	10 (100.0)	10 (100.0)	246 (100.0)
Per-Protocol Population	71 (94.7)	132 (87.4)	203 (89.8)	9 (90.0)	8 (80.0)	220 (89.4)

Abbreviation: NA = not applicable.
Note: Percentages were based on the number of patients in the Intent-to-Treat Population.
Note: NA denotes the patients who did not rollover to Part 3.
a This group includes the patients who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the patients who received 50 mg or 100 mg avapritinib in Part 1.

Outcomes and estimation

The analysis of efficacy for avapritinib was based primarily on Part 2 results of the comparison between placebo and the RP2D of 25 mg avapritinib.

The Part 1 analyses are based on a data cut-off date of 27 December 2019 and the Part 2 and 3 analyses are based on the data cut-off date of 23 June 2022. During the procedure, updated data of Part 3 were provided based on a data cut-off date of 07 April 2023.

Part 1 of study BLU 285-2203

At C4D1 (12 weeks of treatment), the mean (SD) reduction in TSS of the ISM-SAF was greater in all Avapritinib Groups compared with the Placebo Group: –12.54 (13.234) for the 25 mg group, –12.32

(14.194) for the 50 mg group, –21.35 (18.769) for the 100 mg group, and –3.36 (7.998) for the Placebo Group.

The 100 mg dose was associated with the greatest reduction in TSS at C4D1. However, additional analyses showed that the TSS reduction plateaued after C4D1. The 25 mg and 50 mg dose groups achieved a similar mean reduction in TSS to the 100 mg cohort by C7D1.

Table 45. Mean Change in TSS of the ISM-SAF from Baseline to C4D1 and C7D1 (Part 1 ITT Population)

Parameter	Placebo N=9	25 mg QD N=10	50 mg QD N=10	100 mg QD N=10
Baseline				
Mean (SD)	53.78 (19.458)	53.21 (16.924)	56.32 (18.334)	49.79 (24.423)
Median (Min, Max)	51.00 (29.3, 99.9)	56.08 (26.8, 72.7)	54.71 (27.5, 90.1)	51.75 (19.3, 88.1)
C4D1				
Mean (SD)	50.42 (15.360)	40.66 (17.529)	48.54 (18.673)	31.81 (16.791)
Median (Min, Max)	50.71 (33.1, 80.7)	44.00 (5.3, 66.1)	51.61 (23.1, 72.7)	28.14 (12.8, 63.6)
C7D1 (data on file)				
Mean (SD)	50.542 (14.293)	33.546 (19.076)	37.718 (18.773)	34.326 (20.414)
Median (Min, Max)	47.462 (31.214, 76.786)	31.586 (2.786, 62.929)	39.000 (11.000, 70.214)	37.750 (13.077, 67.643)
Change from baseline at C4D1				
Mean (SD)	–3.36 (7.998)	–12.54 (13.234)	–12.32 (14.194)	–21.35 (18.769)
Median (Min, Max)	–0.42 (–19.1, 4.6)	–12.49 (–34.9, 6.1)	–4.59 (–34.8, –0.2)	–15.90 (–54.8, 3.1)
Difference (95% CI) with Placebo		–9.2 (–19.93, 1.56)	–9.0 (–20.68, 2.77)	–18.0 (–32.99, –2.99)
Change from baseline at C7D1 (data on file)				
Mean (SD)	–3.241 (8.960)	–19.659 (20.193)	–19.433 (19.031)	–18.833 (16.575)
Median (Min, Max)	–1.846 (–23.071, 6.500)	–17.934 (–59.614, 6.250)	–12.100 (–57.310, 1.385)	–16.545 (–48.527, 7.214)

Abbreviations: CXDX = Cycle X Day X; CI = confidence interval, ITT = Intent-to-treat; ISM-SAF = Indolent Systemic Mastocytosis-Symptom Assessment Form; Max = maximum; Min = minimum; QD = once daily; SD = standard deviation; TSS = Total symptom score. Note: Baseline score is defined as the 14-day average of TSS from Day –14 to Day –1. C4D1 TSS is defined as the 14-day average of TSS from Day 71 to Day 84. If a patient is missing more than 7 days of score between Day –14 to Day –1, the baseline TSS is considered missing for the patient. If a patient is missing more than 7 days of TSS between Day 71 to Day 84, the C4D1 TSS is considered missing for the patient.

Patients in all Avapritinib Groups showed significant reductions in the key objective measures of disease compared to placebo at C4D1, with additional reductions at C7D1 in avapritinib-treated patients.

Table 46. Change in Objective Measures of Mast Cell Burden from Baseline to C4D1 (Part 1 ITT Population)

Mast cell burden	Placebo N=9	25 mg QD N=10	50 mg QD N=10	100 mg QD N=10
Mean Percentage (SD) change in serum tryptase from baseline to C4D1	–3.28 (14.043)	–55.58 (24.827)	–76.25 (8.877)	–71.82 (28.803)
Mean Percentage (SD) change in bone marrow mast cells from baseline to C4D1	8.3 (45.90)	–24.5 (82.88)	–53.3 (24.21)	–68.3 (22.99)
Mean Percentage (SD) change in blood KIT D816V allele fraction from baseline to C4D1	2.069 (13.3289)	–46.388 (19.7829)	–30.943 (46.6143)	–73.764 (10.8258)

Abbreviations: CXDX = Cycle X Day X, ITT = Intent-to-treat; QD = once daily, SD = standard deviation Note: Baseline score refers to the last assessment value prior to C1D1 dosing.

Based on the results from Part 1 of the study 25 mg avapritinib was chosen as the RP2D for Part 2 and Part 3. The 100 mg dose was associated with the fastest symptom reduction, with a rapid reduction in TSS to C4D1; however, the TSS reduction plateaued after C4D1. The 25 mg and 50 mg dose groups achieved a similar mean reduction in TSS to the 100 mg cohort by C7D1.

Part 2 of study BLU 285-2203

***Primary efficacy endpoint* - Mean change in ISM-SAF TSS, from baseline to C7D1**

At Part 2 Baseline, the mean (SD) ISM-SAF TSS was 50.17 (19.145) points for the 25 mg Avapritinib Group and 52.43 (19.823) for the Placebo Group.

During treatment, there was reduction in the ISM-SAF TSS for both groups: In the Placebo Group, there was a reduction in the ISM-SAF TSS until C3D1, consistent with an early placebo effect, followed by a plateau of the ISM-SAF TSS through C7D1 (24 weeks).

At C7D1, the LS mean (SE) change from baseline in the ISM-SAF TSS was –15.58 (1.536) points for the 25 mg Avapritinib Group and -9.15 (2.013) for the Placebo Group.

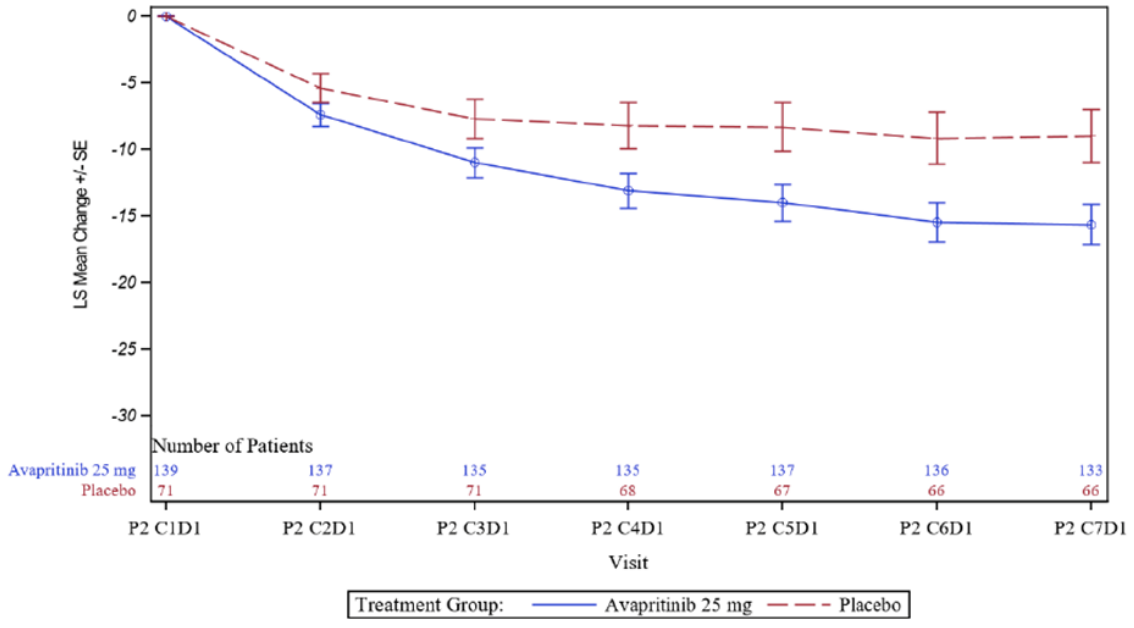
The difference (95% CI) between the groups was -6.43 (–10.90, –1.96) points. This difference was statistically significant (1-sided p-value = 0.003). As pre-specified, with a 1-sided p-value < 0.025, avapritinib is considered superior in reducing SM symptoms as compared to placebo.

Table 47. Mean Change in TSS of ISM-SAF from Baseline to C7D1 (Part 2 ITT Population)

Parameter	Avapritinib 25 mg N=141	Placebo N=71
Baseline		
n	139	71
Mean (SD)	50.17 (19.145)	52.43 (19.823)
Median	47.86	47.79
Min, Max	12.1, 102.7	18.0, 104.4
C7D1		
n	130	65
Mean (SD)	33.48 (20.056)	42.32 (21.027)
Median	31.39	38.21
Min, Max	0.9, 103.5	5.5, 86.1
CFB		
n	128	65
LS Mean (SE) [a]	–15.58 (1.536)	–9.15 (2.013)
95% CI [a]	–18.61, –12.55	–13.12, –5.18
Difference (95% CI) in CFB [a]	–6.43 (–10.90, –1.96)	
p-value [b]	0.003	

Abbreviations: ANCOVA = analysis of covariance; CFB = change from baseline; CI = confidence interval; CXDX = Cycle X Day X; ISM-SAF = Indolent Systemic Mastocytosis-Symptom Assessment Form; ITT = Intentto- treat; LS Mean = least squares mean; Max = maximum; Min = minimum; SD = standard deviation; SE = standard error; TSS = Total symptom score.
a Change from baseline summary and difference of mean change from baseline between 25 mg avapritinib and placebo are from LS mean estimation of the ANCOVA model that controlling for randomization stratification factor (tryptase) and baseline ISM status (moderate vs severe).
b One-sided p-value from ANCOVA model controlling for randomization stratification factor (tryptase) and baseline ISM status (moderate vs severe).

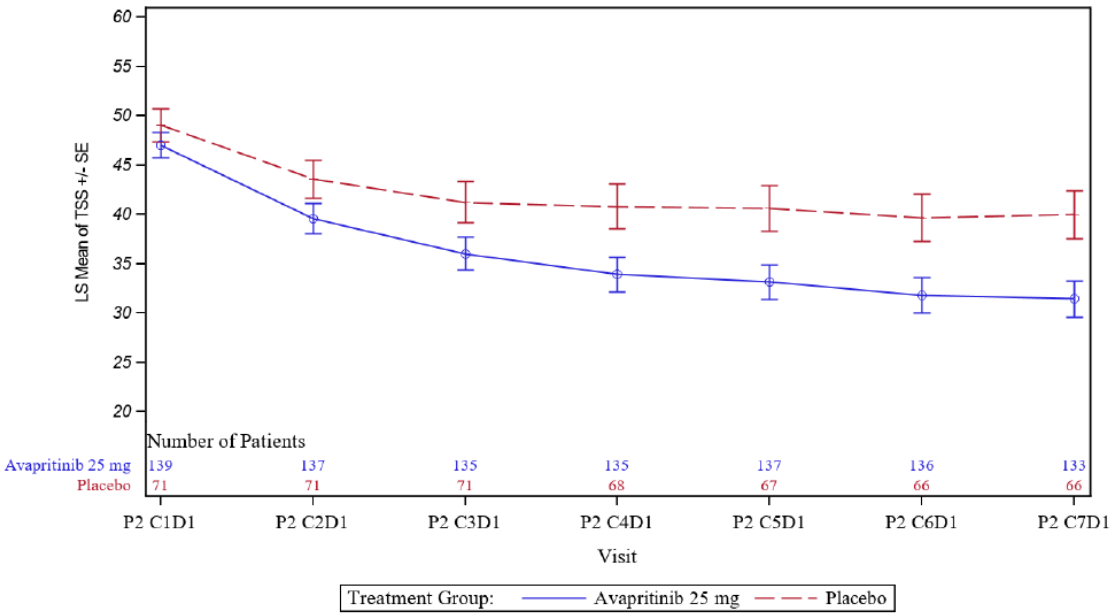
Figure 33. Change from Baseline in ISM-SAF TSS (Part 2 ITT Population)



Abbreviations: CXDX = Cycle X Day X; ISM-SAF = Indolent Systemic Mastocytosis-Symptom Assessment Form; ITT = Intent-to treat; LS Mean = Least Squares Mean; SE = Standard Error; TSS = Total symptom score.

Note: For the 3 patients who received high-dose steroids (defined as prednisone > 20 mg/day or equivalent in the 7 days before C7D1 or greater than 14 consecutive days), the TSS score at C7D1 are set to missing for primary efficacy analysis but are included in the figures of change over time.

Figure 34. LS Mean Plot of TSS of the ISM-SAF from Part 2 Baseline to Part 2 Cycle 7 Day 1



Abbreviations: ISM-SAF = Indolent Systemic Mastocytosis Symptom Assessment Form; TSS = total symptom score

Sensitivity analyses

- *Mean change from baseline in ISM-SAF TSS at C7D1 using Markov chain Monte Carlo (MCMC) imputation*

A sensitivity analysis with MCMC simulation to impute the missing baseline or C7D1 values was performed in the ITT population. The sensitivity analysis was consistent with the primary analysis. At C7D1, the LS mean (SE) change from baseline in the ISM-SAF TSS was −15.33 (1.544) points for the 25 mg Avapritinib Group and −9.64 (2.023) for the Placebo Group. The difference (95% CI) between the groups was −5.69 (−10.16, −1.23) points. This difference was statistically significant (1-sided p-value = 0.006).

- *Mean change from baseline in ISM-SAF TSS at C7D1 in the PP Population*

A sensitivity analysis for the primary analysis was performed in the PP population. The PP population included 123 patients in the 25 mg Avapritinib Group and 67 patients in the Placebo Group.

The sensitivity analysis was consistent with the primary analysis. Over time, there was reduction in the ISM-SAF TSS for both groups. At C7D1, the LS mean (SE) change from baseline in the ISM-SAF TSS was −16.80 (1.722) points for the 25 mg Avapritinib Group and -9.27 (2.198) for the Placebo Group. The difference (95% CI) between the groups was −7.53 (−12.36, −2.70) points. This difference was statistically significant (1-sided p-value = 0.001). The MCMC sensitivity analysis for the mean change in the ISM-SAF TSS in the PP population was consistent with the overall sensitivity analysis in the PP population and the primary analysis.

- *Cumulative density function plots*

CDF plots of ISM-SAF TSS at C4D1 and C7D1 in Part 2 for the ITT were produced. The x-axis of the CDF plot presents TSS change from baseline and the y-axis presents the cumulative proportion of patients with the TSS change from baseline equal or smaller than the value specified in the x-axis. For any given

value of CFB (x-axis), the proportion of patients who had a CFB equal or smaller than that value was consistently greater in the 25 mg Avapritinib Group compared with the Placebo Group at C4D1 which improved at C7D1.

Key secondary efficacy endpoints

- **Proportion of patients with ≥ 50% and ≥ 30% reduction in ISM-SAF TSS in patients from baseline to C7D1**

The proportion of patients with ≥ 50% and ≥ 30% reduction in the ISM-SAF TSS from baseline to C7D1 were evaluated as key secondary endpoints.

Over time, there was a greater increase in the percentage of patients with ≥ 50% and ≥ 30% reduction in the ISM-SAF TSS for the 25 mg Avapritinib Groups compared to the placebo group.

At C7D1, 24.8% of patients in the 25 mg Avapritinib Group (95% CI: 17.9, 32.8) vs 9.9% of patients in the Placebo Group (95% CI: 4.1, 19.3) achieved ≥ 50% reduction in the ISM-SAF TSS.

At C7D1, 45.4% of patients in the 25 mg Avapritinib Group (95% CI: 37.0, 54.0) vs 29.6% of patients in the Placebo Group (95% CI:19.3, 41.6) achieved ≥ 30% reduction in the ISM-SAF TSS.

The odds ratio (95% CI) calculated to compare the 25 mg Avapritinib Group with the Placebo Group was 3.10 (1.24, 8.64) for the ≥ 50% reduction endpoint and 2.07 (1.08, 3.99) for the ≥ 30% reduction endpoint.

Both odds ratios were statistically significant (1-sided p-value = 0.005 for ≥ 50% TSS reduction and 0.009 for ≥ 30% TSS reduction).

Table 48. Proportion of Patients with ≥ 50% and ≥ 30% Reduction in ISM-SAF TSS at C7D1 (Part 2 ITT Population)

	Avapritinib 25 mg N=141 n/N (%) (95% CIs)	Placebo N=71 n/N (%) (95% CIs)	Odds Ratio (95% CIs) [a]	P-Value [b]
Patients with ≥ 50% reduction in TSS [c]	35/141 (24.8) (17.9, 32.8)	7/71 (9.9) (4.1, 19.3)	3.10 (1.24, 8.64)	0.005
Patients with ≥ 30% reduction in TSS [c]	64/141 (45.4) (37.0, 54.0)	21/71 (29.6) (19.3, 41.6)	2.07 (1.08, 3.99)	0.009

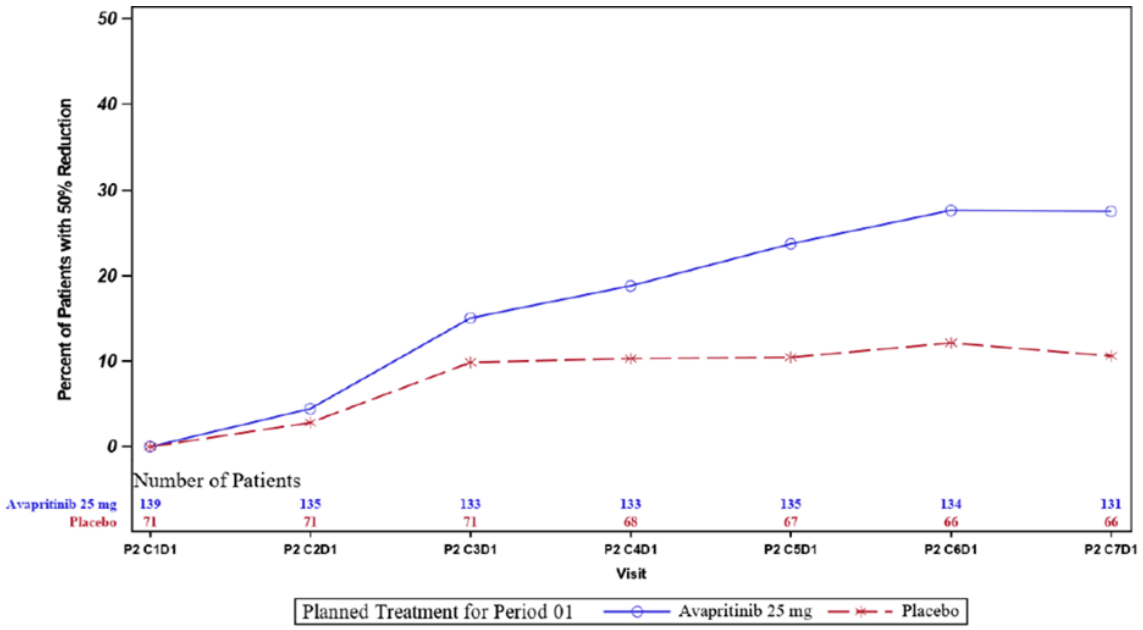
Abbreviations: CI = confidence interval; CXDX = Cycle X Day X; ISM-SAF = Indolent Systemic Mastocytosis-Symptom Assessment Form; ITT = Intent-to treat, TSS = Total symptom score.

a Odds Ratio is to compare 25 mg Avapritinib with Placebo for each subgroup.

b One-sided p-value is from Cochran-Mantel-Haenszel test with controlling for randomization stratification factor (Serum tryptase < 20 ng/mL vs ≥ 20 ng/mL) and baseline ISM status (moderate vs severe).

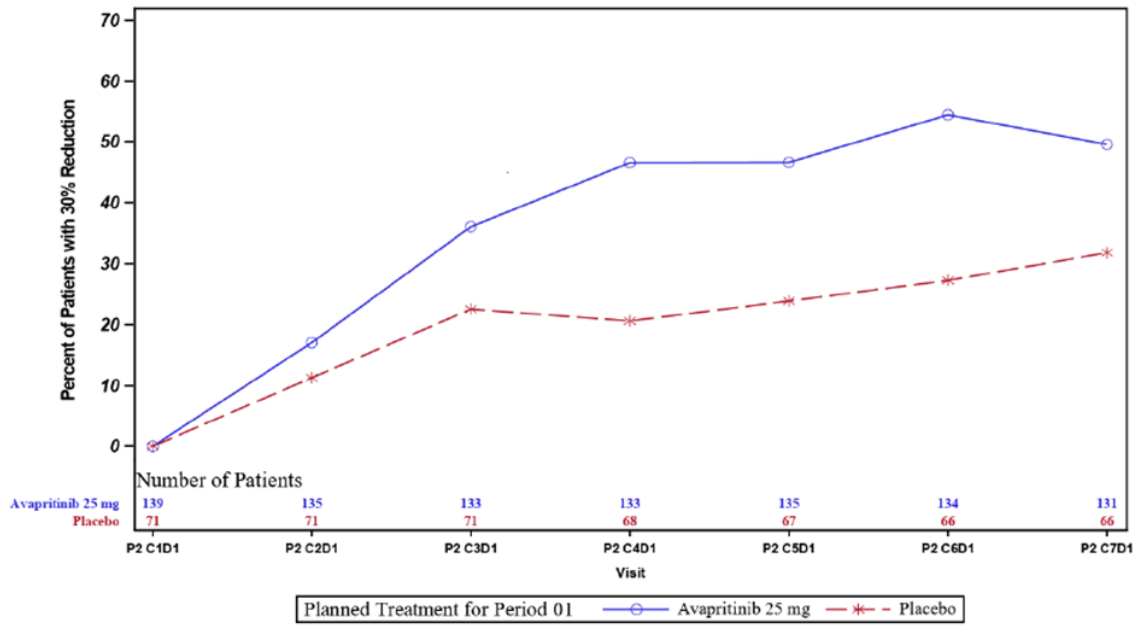
c Patients with high-dose steroid use within 7 days before C7D1, or greater than 14 consecutive days at any point from C1D1 to C7D1 were counted in the denominator but not numerator

Figure 35. Percent of Patients with ≥ 50% Reduction in the ISM-SAF TSS Over Time from Baseline to Part 2 C7D1 (ITT Population, Patients with Baseline TSS Score)



Abbreviations: CXDX = Cycle X Day X; ISM-SAF = Indolent Systemic Mastocytosis-Symptom Assessment Form; ITT = Intent-to treat; TSS = Total Symptom Score.

Figure 36. Percent of Patients with ≥ 30% Reduction in the ISM-SAF TSS Over Time from Baseline to Part 2 C7D1 (ITT Population, Patients with Baseline TSS Score)



Abbreviations: CXDX = Cycle X Day X; ISM-SAF = Indolent Systemic Mastocytosis-Symptom Assessment Form; ITT = Intent-to treat; TSS = Total Symptom Score.

- **Proportion of Patients with ≥ 50% reduction in objective measures of mast cell burden**

The proportion of patients who achieved ≥ 50% reduction in objective measures of mast cell burden from baseline to C7D1 were evaluated as key secondary endpoints. These measures included serum tryptase, KIT D816V MAF, and bone marrow mast cells.

Table 149. Proportion of Patients with a ≥50% Reduction in Objective Measures of Mast Cell Burden from Baseline to C7D1 (Part 2 ITT Population)

Parameter	25 mg Avapritinib N=141 n/N (%) (95% CI)	Placebo N=71 n/N (%) (95% CI)	Odds ratio (95% CIs) [a]	p-Value [b]
Proportion of patients with ≥ 50% reductions in serum tryptase	76/141 (53.9) (45.3, 62.3)	0/71 (0.0) (0.0, 5.1)	NE (30.59, NE)	< 0.0001
Proportion of patients with ≥ 50% reduction in KIT D816V MAF or undetectable (< 0.02%) for patients with detectable mutation at baseline	80/118 (67.8) (58.6, 76.1)	4/63 (6.3) (1.8, 15.5)	39.34 (10.93, 140.56)	< 0.0001
Proportion of patients with ≥ 50% reduction in bone marrow mast cells or no aggregates for patients with aggregates at baseline	56/106 (52.8) (42.9, 62.6)	13/57 (22.8) (12.7, 35.8)	4.74 (2.06, 11.45)	< 0.0001

Abbreviations: C7D1 = Cycle 7 Day 1; CI = confidence interval; EOS = end-of-study; ISM = indolent systemic mastocytosis; ITT = intent-to-treat; KIT = V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; MAF = mutant allele fraction; NE = not evaluable. a Odds ratio is to compare 25 mg avapritinib with placebo for each subgroup. b One-sided p-value is from Cochran-Mantel-Haenszel test with controlling for randomization stratification factor (serum tryptase < 20 ng/mL vs. ≥ 20 ng/mL) and baseline ISM status (moderate vs. severe). Note: Patients who reached C7D1 or EOS prior to C7D1 with missing baseline or C7D1 assessment were counted in the denominator.

The odds ratios between avapritinib and placebo were statistically significant for all 3 endpoints.

Detailed results on the objective measures of mast cell burden are given below.

Serum tryptase

At C7D1, 53.9% of patients in the 25 mg Avapritinib Group (95% CI: 45.3, 62.3) vs. 0.0% of patients in the Placebo Group (95% CI: 0.0, 5.1) achieved ≥ 50% reduction in serum tryptase.

Of note, 58 of 107 (54.2%) patients in the 25 mg Avapritinib Group with baseline serum tryptase ≥ 20 ng/mL achieving a level of < 20 ng/mL (below the SM diagnosis criterion) at C7D1, with half of these patients (29/58) achieving a level of < 11.4 ng/mL (ULN), compared with 1 of the 50 (2.0%) patients in the Placebo Group with baseline serum tryptase ≥ 20 ng/Ml achieving a level of < 20 ng/mL at C7D1.

KIT D816V MAF

At C7D1, 67.8% of patients in the 25 mg Avapritinib Group (95% CI: 58.6, 76.1) vs. 6.3% of patients in the Placebo Group (95% CI: 1.8, 15.5) achieved either ≥ 50% reduction in KIT D816V MAF or became undetectable (< 0.02% LLD). This analysis was limited to patients with detectable mutations at baseline (LLD 0.02%). Of note, among 109 patients in the 25 mg Avapritinib Group with detectable KIT D816V MAF at baseline, 12 (11.0%) had undetectable KIT D816V MAF at C7D1; in the Placebo Group, among 54 patients with detectable KIT D816V MAF at baseline, 3 (5.6%) had undetectable KIT D816V MAF at C7D1.

Additionally, 14/40 (35.0%) patients in the 25 mg Avapritinib Group with KIT D816V MAF ≥ 1% at baseline reduced to KIT D816V MAF < 1% at C7D1; in the Placebo Group, this was 0/22 patients.

Bone marrow mast cells

At C7D1, 52.8% of patients in the 25 mg Avapritinib Group (95% CI: 42.9, 62.6) vs. 22.8% of patients in the Placebo Group (95% CI: 12.7, 35.8) achieved ≥ 50% reduction in bone marrow mast cells or no mast cell aggregates. This analysis was limited to patients with mast cell aggregates at baseline.

Of note, in the 25 mg Avapritinib Group, 33/91 (36.3%) patients with bone marrow aggregates at baseline did not have bone marrow aggregates present at C7D1.

In the Placebo Group, 6/50 (12.0%) patients with bone marrow aggregates at baseline did not have bone marrow aggregates present at C7D1.

Additional secondary efficacy endpoints

- **Change from Baseline to C7D1 objective measures of mast cell burden**

At C7D1, the mean (SD) change from baseline in serum tryptase was –26.02 (35.662) for the 25 mg Avapritinib Group and 9.65 (41.924) for the Placebo Group.

At C7D1, the mean (SD) change from baseline in KIT D816V MAF was –1.178 (2.6978) for the 25 mg Avapritinib Group and 0.139 (0.9700) for the Placebo Group.

At C7D1, the mean (SD) change from baseline in bone marrow mast cells was –3.3 (10.99) for the 25 mg Avapritinib Group and –2.0 (7.32) for the Placebo Group in the ITT population.

- **Change in BSC usage for SM symptoms**

At baseline, 140 (99.3%) patients in the 25 mg Avapritinib Group and 71 (100.0%) patients in the Placebo Group were taking BSC. 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 GERD (73.8% in the 25 mg Avapritinib Group and 78.9% in the Placebo Group). By C7D1, 30 (21.3%) patients in the 25 mg Avapritinib Group and 9 (12.7%) patients in the Placebo Group had a reduction in the dose and/or frequency of BSC medications used. Four (2.8%) patients in the 25 mg Avapritinib Group had complete discontinuation of their BSC medications. None of the patients in the Placebo Group had complete discontinuations of their BSC medications. A total of 11 (7.8%) patients in the Avapritinib Group and 8 (11.3%) patients in the Placebo Group had increases in the dose and/or frequency of BSC medications used.

- **Change in lead (most severe) domain and lead (most severe) symptom**

The "lead" (most severe) domain (GI, skin, and neurocognitive domains) and symptom of the ISM-SAF were identified on a per patient basis using the domain/symptom with the highest score for that patient.

At baseline, the most common lead (most severe) domain in both treatment groups was the skin domain reported in 46/71 (64.8%) patients in the Placebo Group and 76/139 (54.7%) patients in the 25 mg Avapritinib Group and the most common lead (most severe) symptom in both treatment groups was fatigue, reported in 59/139 (42.4%) patients in the 25 mg Avapritinib Group and 28/71 (39.4%) patients in the Placebo Group followed by spots reported in 31/139 (22.3%) patients in the 25 mg Avapritinib Group and 20/71 (28.2%) patients in the Placebo Group.

Both, the most severe domain and the most severe symptom showed a statistically significant improvement in patients with ISM treated with avapritinib compared to patients treated with placebo; see table below.

Table 50. Change from Baseline in Lead (Most Severe) Domain/Symptom Scores of the ISM-SAF at C7D1 (Part 2 ITT Population)

	25 mg Avapritinib N=131		Placebo N=66		Difference (95% CI) p-value [a]
	Mean (SD) Change	Mean (SD) Percent Change	Mean (SD) Change	Mean (SD) Percent Change	
Lead (most severe) domain of the ISM-SAF	–6.52 (6.218)	–35.73 (32.454)	–3.36 (4.490)	–19.12 (26.486)	–3.16 (–4.69, –1.63) < 0.0001
Lead (most severe) symptom of the ISM-SAF	–2.22 (2.302)	–28.97 (28.962)	–1.42 (1.875)	–19.78 (25.318)	–0.80 (–1.45, –0.16) 0.015

Abbreviations: CI = confidence interval; ISM-SAF = Indolent Systemic Mastocytosis-Symptom Assessment Form; SD = standard deviation. a A 2-sample t-test and the difference between treatment and placebo groups with corresponding 95% CIs for mean changes from baseline to C7D1.
Note: The "lead domain" refers to the domain with highest score at baseline in each patient. If patient has a tie with multiple lead domains, the average change from baseline for each domain is used for the summary. The "lead symptom" score refers to the individual symptom with highest score (individual symptoms were scored from 0-10) at baseline in each patient. If patient has a tie with multiple lead (most severe) symptoms, the average of change from baseline is used for the summary.

- ***Analysis of individual domains***

The GI, skin, and neurocognitive domain scores of the ISM-SAF reduced from baseline over time for both treatment groups. Among these domains, the difference between the 25 mg avapritinib group and placebo group was greatest for the skin domain scores.

At C7D1, the mean (SD) change from baseline in the *GI domain* score for the 25 mg Avapritinib Group was –3.74 (4.868) and –3.14 (4.664) for the Placebo Group. The difference (95% CI) between the groups was –0.60 (–2.03, 0.83) with a 2-sample t-test p-value of 0.410.

At C7D1, the mean (SD) change from baseline in the *skin domain* score for the 25 mg Avapritinib Group was –5.87 (6.485) and –2.64 (4.105) for the Placebo Group. The difference (95% CI) between the groups was –3.23 (–4.73, –1.73) with a 2-sample t-test p-value of < 0.0001.

At C7D1, the mean (SD) change from baseline in the *neurocognitive domain* score for the 25 mg Avapritinib Group was –4.03 (5.223) and -2.81 (4.285) for the Placebo Group. The difference (95% CI) between the groups was –1.22 (–2.69, 0.25) with a 2-sample t-test p-value of 0.102.

- **Analysis of individual symptoms**

By C7D1, there were reductions in the mean individual symptom scores of the ISM-SAF for all symptom domains for both treatment groups. The reductions were greater for the 25 mg Avapritinib Group compared to the Placebo Group across all the individual symptoms.

For the individual symptom scores of the ISM-SAF, statistically significant differences in the mean change from baseline between the 25 mg Avapritinib Group and Placebo Group were seen at C7D1 in the following individual symptoms: spots severity, itching severity, and flushing severity.

Table 51. Change from Baseline in Individual Symptom Scores of the ISM-SAF at C7D1 (Part 2 ITT Population)

Individual Score of the ISM-SAF	25 mg Avapritinib N = 131		Placebo N = 66		Difference (95% CI) p-value [a]
	Mean (SD) Change	Mean (SD) Percent Change	Mean (SD) Change	Mean (SD) Percent Change	
Bone pain severity	–1.35 (2.020)	–20.57 (57.851)	–0.82 (1.828)	–14.73 (36.686)	–0.53 (–1.11, 0.05) 0.076
Abdominal pain severity	–1.54 (1.820)	–38.18 (71.684)	–1.20 (1.921)	–14.59 (104.765)	–0.33 (–0.88, 0.22) 0.236
Nausea severity	–1.09 (1.990)	–26.35 (119.754)	–1.05 (1.895)	–14.92 (112.515)	–0.05 (–0.63, 0.54) 0.873
Spots severity	–1.86 (2.238)	–33.11 (46.119)	–0.63 (1.482)	–7.05 (41.915)	–1.23 (–1.76, –0.70) < 0.0001
Itching severity	–2.21 (2.704)	–32.85 (69.982)	–1.06 (1.953)	–11.98 (40.633)	–1.16 (–1.82, –0.49) < 0.001
Flushing severity	–1.80 (2.539)	–30.19 (50.937)	–0.96 (1.862)	–14.80 (41.648)	–0.84 (–1.47, –0.21) 0.009
Fatigue severity	–1.72 (2.230)	–16.97 (92.475)	–1.11 (1.880)	–15.86 (29.589)	–0.60 (–1.23, 0.03) 0.061
Dizziness severity	–1.29 (2.123)	–21.89 (113.088)	–0.93 (2.019)	–25.37 (62.566)	–0.36 (–0.98, 0.26) 0.258
Brain fog severity	–1.40 (1.994)	–21.06 (105.229)	–0.98 (1.694)	–18.85 (37.978)	–0.42 (–0.98, 0.15) 0.146
Headache severity	–1.34 (1.950)	–29.85 (68.575)	–0.89 (1.605)	–7.21 (77.156)	–0.45 (–0.99, 0.10) 0.110
Diarrhea count	–0.55 (1.095)	–31.08 (83.779)	–0.44 (1.088)	–18.12 (73.348)	–0.11 (–0.44, 0.21) 0.503
Diarrhea severity	–1.11 (1.890)	–32.04 (78.509)	–0.89 (1.882)	–21.73 (82.133)	–0.22 (–0.78, 0.34) 0.445

Abbreviations: CI = confidence interval; CXDX = Cycle X Day X; ISM-SAF = Indolent Systemic Mastocytosis-Symptom Assessment Form; ITT = Intent-to-treat; SD = standard deviation.

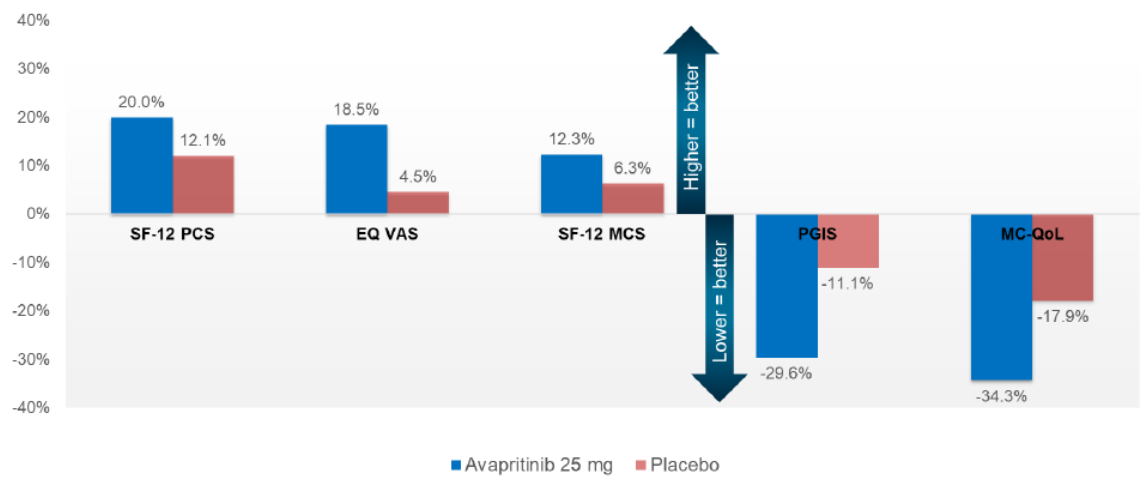
[a] A 2-sample t-test and the difference between treatment and placebo group with corresponding 95% CI for mean changes from baseline to C7D1.

Note: Baseline score is defined as the 14-day average of individual symptom scores from C1D–14 to C1D–1. C7D1 score is defined as the 14-day average of individual symptom scores prior to C7D1 visit. If a patient is missing more than 7 days of score between C1D–14 and C1D–1, the baseline score is considered as missing for the patient. If a patient misses more than 7 days of the score from the 14 days period for calculating C7D1 score, then the C7D1 score is considered as missing.

- **Quality of life measures**

For all QoL measures (MC-QoL, PGIS, SF-12, PGIC, and EQ-5D-5L), a greater improvement was observed at Part 2 C7D1 in the 25 mg Avapritinib Group than the Placebo Group.

Figure 37. Percent Change from Baseline at C7D1 in PRO and QoL Measures (Part 2 ITT Population)



Abbreviations: CXDX = Cycle X Day X; EQ = EuroQuol; ITT = Intent-to-treat; MC-QoL = Mastocytosis Quality of Life Questionnaire; MCS = Mental Component Score; PCS = Physical Component Score; PGIS = Patient's Global Impression of Symptom Severity; PRO = Patient-Reported Outcome; QoL = Quality of Life; SF-12 = Twelve-item Short Form Health Survey; VAS = visual analogue scale.

Exploratory efficacy endpoints

- **Change in anaphylaxis based on epinephrine use**

At baseline, 7 (5.0%) patients in the 25 mg Avapritinib Group and none in the Placebo Group had anaphylaxis that required epinephrine treatment. Postbaseline, 2 (1.4%) patients in the 25 mg Avapritinib Group and 3 (4.2%) patients in the Placebo Group had anaphylaxis that required epinephrine treatment.

- **Change in bone density**

A total of 78 patients in the 25 mg Avapritinib Group and 33 patients in the Placebo Group had bone density scans at baseline. At C7D1, 50 patients in the 25 mg Avapritinib Group and 23 patients in the Placebo Group had bone density scans. No trends were observed in the Z-scores.

Part 3 of study BLU 285-2203

In Part 3 of the study, all patients received 25 mg avapritinib.

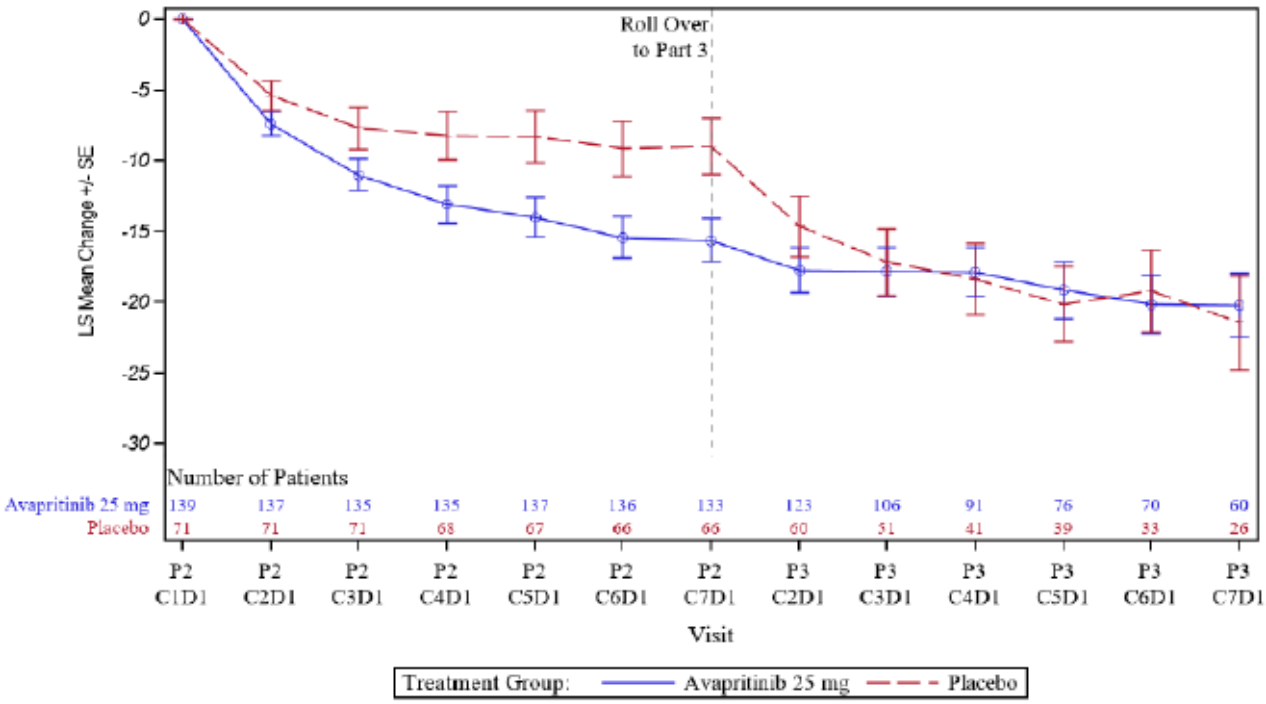
Long-term efficacy was assessed in the overall population (Part 1/2/3) using the avapritinib baseline (the last observation prior to the first dose of avapritinib in any part).

- **Reduction in ISM-SAF TSS over time**

Over time there was a greater reduction in the ISM-SAF TSS in the 25 mg Avapritinib Group as compared to the Placebo Group. An initial reduction in the ISM-SAF TSS was noted for both groups, consistent with regression to the means and placebo effect. In the Placebo Group, there was a reduction in the ISM-SAF TSS until Part 2 C3D1, consistent with an early placebo effect, followed by a plateau of the ISM-SAF TSS through Part 2 C7D1. After rollover to Part 3, for patients who rolled over from 25 mg avapritinib in Part

2, there was further reduction in the ISM-SAF TSS up to Part 3 C2D1 at which point the mean change in ISM-SAF TSS leveled off and remained stable through Part 3 C7D1. For patients who rolled over from placebo in Part 2 to 25 mg avapritinib in Part 3, the ISM-SAF TSS decreased through Part 3 C5D1 and stabilized through Part 3 C7D1.

Figure 38. LS Mean Plot of Change in TSS of the ISM-SAF from Baseline to Part 3 C7D1

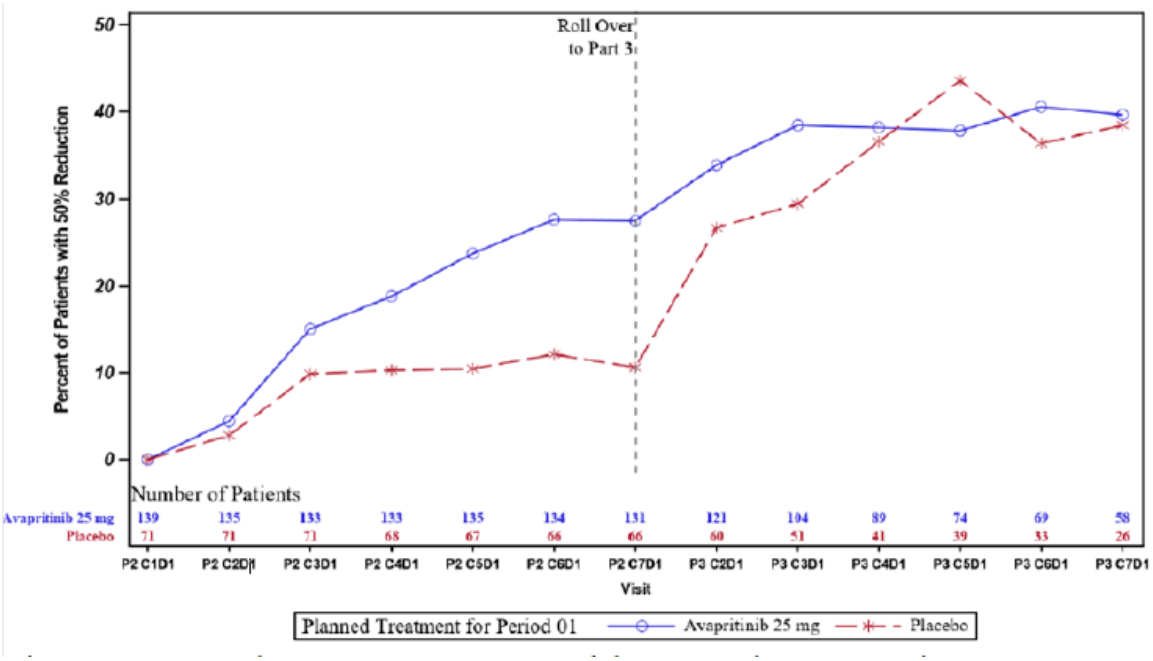


Abbreviations: CXDX = Cycle X Day X, ISM-SAF = Indolent Systemic Mastocytosis-Symptom Assessment Form; LS Mean = Least Squares Mean; SE = Standard Error; TSS = Total symptom score.

The overall Part 1/2/3 analyses, which analyzed efficacy using the avapritinib baseline for each group, showed a greater reduction in the ISM-SAF TSS in patients who had been in the 25 mg Avapritinib Group since Part 1 or Part 2 compared to patients who rolled over to 25 mg avapritinib in Part 3 from placebo in Part 1 or 2 at all time points. At C7D1 (using the avapritinib baseline), the mean (SD) change from baseline in the ISM-SAF TSS was −16.89 (16.744) points for the group of patients who rolled over from 25 mg avapritinib in Part 1 or 2 to 25 mg avapritinib in Part 3 and −10.19 (13.948) for the patients who rolled over from placebo in Part 1 or 2 to 25 mg avapritinib in Part 3. These data show that with longer exposure there are further reductions in the ISM-SAF TSS. Indeed, for patients who had reached C13D1, additional small reductions in ISM-SAF TSS were seen. The mean (SD) change in ISMSAF TSS was −21.22 (−19.018) for patients who rolled over from 25 mg avapritinib and −12.31 (−11.653) for patients who rolled over from placebo.

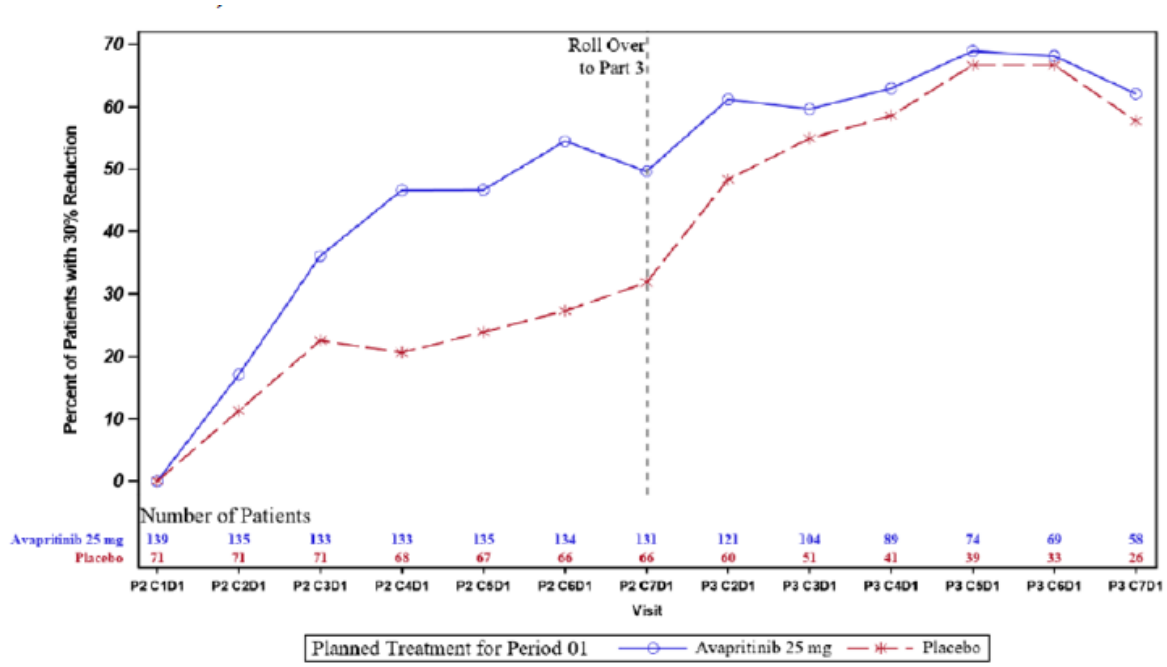
Over time, for patients who rolled over from 25 mg avapritinib in Part 2 to 25 mg avapritinib in Part 3, the proportion of patients with ≥ 50% and ≥ 30% reduction in the ISM-SAF TSS further increased until Part 3 C3D1 (≥ 50%) and C5D1 (≥ 30%) and then stabilized. For patients who rolled over from placebo in Part 2 to 25 mg avapritinib in Part 3, the proportion of patients with ≥ 50% and ≥ 30% reduction in the ISM-SAF TSS increased through Part 3 C7D1. By Part 3 C7D1, a similar proportion of patients from both treatment groups had reached ≥ 50% and ≥ 30% reductions in TSS.

Figure 39. Percent of Patients with ≥ 50% Reduction of TSS of the ISM-SAF Over Time from Baseline to Part 3 C7D1 (ITT Population, Patients with Baseline TSS Score)



Abbreviations: CXDX = Cycle X Day X, ISM-SAF = Indolent Systemic Mastocytosis-Symptom Assessment Form, ITT = Intent-to-Treat; TSS = Total symptom score. Note: Denominator is calculated as patients with baseline TSS score and non-missing TSS score at the time point.

Figure 40. Percent of Patients with ≥ 30% Reduction of TSS of the ISM-SAF Over Time from Baseline to Part 3 C7D1 (ITT Population, Patients with Baseline TSS Score)



Abbreviations: CXDX = Cycle X Day X, ISM-SAF = Indolent Systemic Mastocytosis-Symptom Assessment Form,

ITT = Intent-to-Treat. Note: Denominator is calculated as patients with baseline TSS score and non-missing TSS score at the time point.

At C7D1 (using the avapritinib baseline), among the patients who rolled over from placebo in Part 1 or Part 2 to 25 mg avapritinib in Part 3 7/37 (18.9%) of patients had ≥ 50% reduction in the ISM-SAF TSS which was similar to that reported in the 25 mg Avapritinib Group in Part 2.

Among patients who rolled over from 25 mg avapritinib in Part 1 or Part 2 to 25 mg avapritinib in Part 3, 39/151 (25.8%) had ≥ 50% reduction in the ISM-SAF TSS.

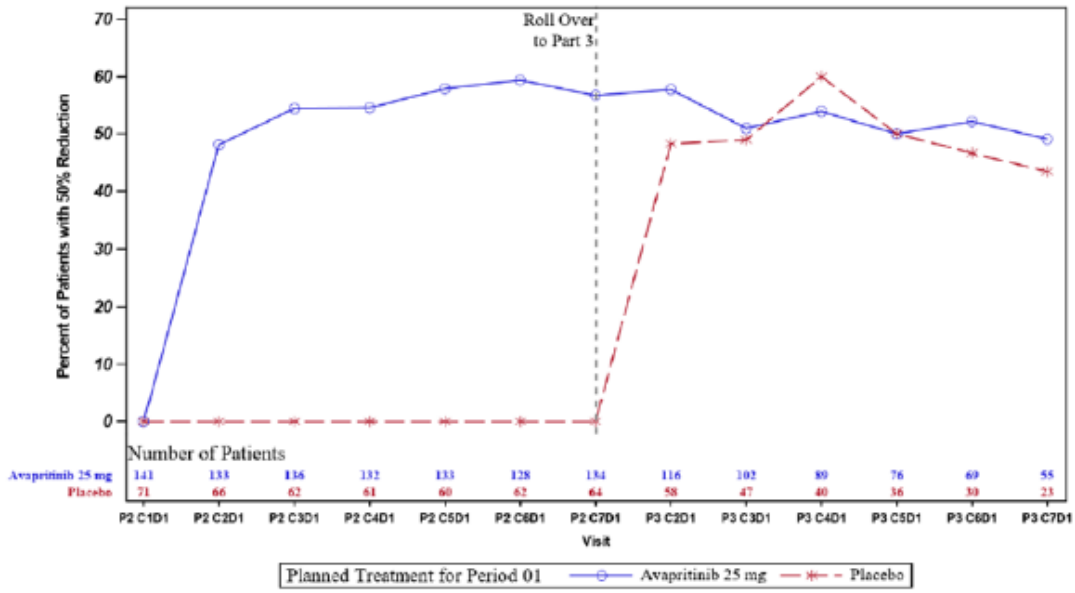
At C7D1 (using the avapritinib baseline), among the patients who rolled over from placebo in Part 1 or Part 2 to 25 mg avapritinib in Part 3, 11/37 (29.7%) of patients had ≥ 30% reduction in the ISM-SAF TSS. Among patients who rolled over from 25 mg avapritinib in Part 1 or Part 2 to 25 mg avapritinib in Part 3, 71/151 (47.0%) had ≥ 30% reduction in the ISM-SAF TSS.

- **Reduction in objective measures of mast cell burden over time**

The reduction in the ISM-SAF TSS score over time in patients who rolled over from placebo in Part 1 or Part 2 to 25 mg avapritinib in Part 3 was supported by reductions over time in the objective measures of mast cell burden (tryptase, D816V MAF, percent bone marrow mast cells).

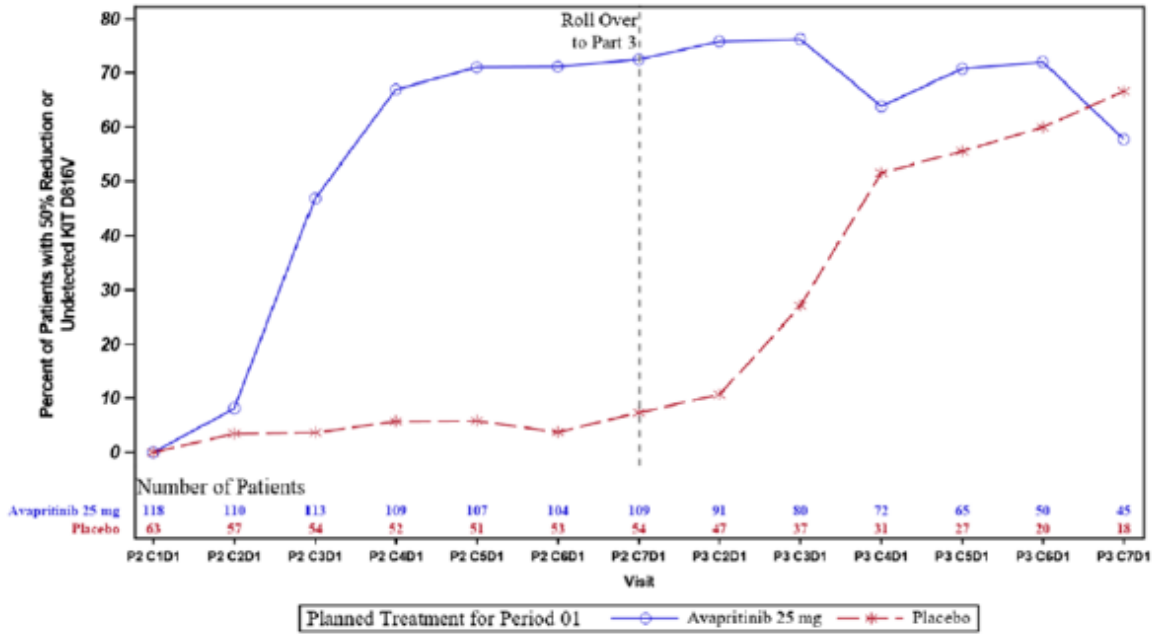
Over time, a greater proportion of patients in the 25 mg Avapritinib Group had ≥ 50% reduction in serum tryptase as compared to the Placebo Group. None of the patients in the Placebo Group had ≥ 50% reduction in serum tryptase in Part 2. After rollover to Part 3, among the patients who rolled over from placebo in Part 2 to 25 mg avapritinib in Part 3, the proportion of patients who had ≥ 50% reduction in serum tryptase increased sharply at Part 3 C2D1 reaching a plateau by Part 3 C4D1 that was maintained through Part 3 C7D1. A similar trend was observed for KIT D816V MAF, with a slower increase in the proportion of patients who reached a 50% reduction which appeared to increase with time through C7D1.

Figure 141. Percent of Patients with ≥ 50% Reduction of Tryptase Over Time from Baseline to Part 3 C7D1 (ITT Population, Patients with Baseline Tryptase)



Abbreviations: CXDX = Cycle X Day X; ITT = Intent-to-Treat. Note: Denominator is calculated as patients with baseline tryptase and non-missing assessment at the time point.

Figure 42. Percent of Patients with ≥ 50% Reduction or Undetected KIT D816V Over Time from Baseline to Part 3 C7D1 (ITT Population, Patients with Detectable Mutation at Baseline)



Abbreviations: CXDX = Cycle X Day X; ITT = Intent-to-Treat.
Note: Denominator is calculated as patients with detectable mutation at baseline and non-missing assessment at the time point.

At C7D1 (using the avapritinib baseline), 13/37 (35.1%) patients in the placebo to 25 mg group and 81/151 (53.6%) patients in the 25 mg to 25 mg Avapritinib Group had ≥ 50% reduction in serum tryptase.

At C7D1 (using the avapritinib baseline), 13/30 (43.3%) patients in the placebo to 25 mg group and 85/127 (66.9%) patients in the 25 mg to 25 mg Avapritinib Group had ≥ 50% reduction in (or undetected) KIT D816V MAF.

At C7D1 (using the avapritinib baseline), 1/30 (3.3%) patients in the placebo to 25 mg group and 55/116 (47.4%) patients in the 25 mg to 25 mg Avapritinib Group had ≥ 50% reduction in (or no aggregates) bone marrow mast cells.

- **PRO and QoL measures over time**

Improvements in QoL measures were observed over time in the patients who rolled over from placebo or 25 mg avapritinib in Part 1 or Part 2 to 25 mg avapritinib in Part 3.

At C7D1 (using the avapritinib baseline), patients treated with 25 mg avapritinib had improvements in all PRO and QoL measures and these improvements had deepened by 48 weeks (C13D1) of avapritinib treatment.

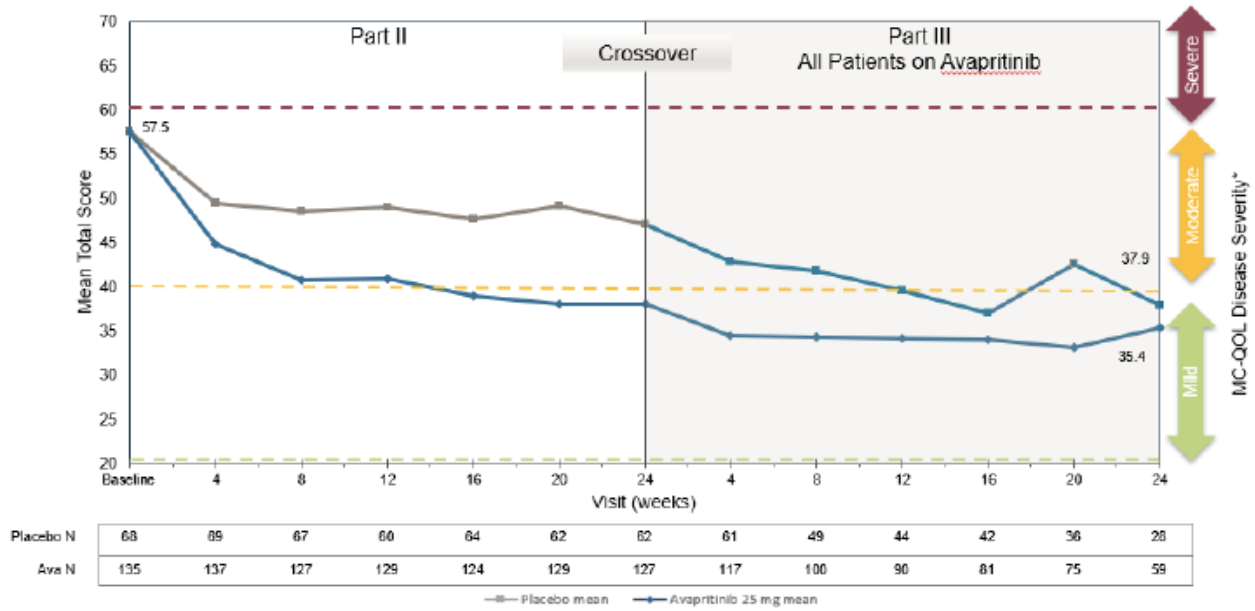
At baseline, patients in both groups reported MC-QoL total scores in the high moderate severity range, on average. In Part 2, for the Placebo group the mean total score remained in the moderate severity range, while for the Avapritinib group there was a steady reduction in the mean total score over time, with C7D1 scores reaching the mild disease severity range. After crossover to active treatment in Part 3, mean total scores for the Placebo group reached the mild disease severity range by C4D1.

Table 52. Mean and Percent Change from Baseline in QoL Measures Over Time (Part 1/2/3 ITT Population)

QoL Endpoint	Avapritinib 25 mg to 25 mg[a] 24 weeks (C7D1)		Avapritinib 25 mg to 25 mg[a] 48 weeks (C13D1)	
	Mean (SD) Change	Mean (SD) Percent Change	Mean (SD) Change	Mean (SD) Percent Change
n (MC-QoL)	130	130	56	56
MC-QoL Range: 0-100	–19.56 (17.895)	–34.84 (30.626)	–23.15 (20.046)	–39.24 (36.456)
n (PGIS)	130		55	
PGIS Range: 0-4	–0.8 (1.06)	NA	–0.9 (1.18)	NA
n (PGIC)	136		58	
PGIC Score at C7D1 Range: 1-7	4.3 (1.72)	NA	4.8 (1.59)	NA
n (SF-12)	129	129	55	55
SF-12-physical component	5.48 (8.346)	19.50 (30.389)	7.18 (8.891)	27.01 (36.043)
SF-12-mental component	4.00 (9.255)	12.72 (26.666)	3.50 (10.190)	11.73 (27.466)
n (EQ-5D-5L VAS)	130	130	56	56
EQ-5D-5L (VAS) Range: 0-100	6.8 (18.67)	19.3 (48.47)	8.4 (19.99)	30.5 (60.70)

Abbreviations: CXDX = Cycle X Day X; EQ-5D-5L = EuroQol-5 Dimensions-5 Levels; ITT = Intent-to-treat; MCQoL = Mastocytosis Quality of Life Questionnaire; PGIC = Patients' Global Impression of Change; PGIS = Patient Global Impression of Symptom Severity; SD = standard deviation; SF-12 = Twelve-item Short Form Health Survey; QoL = quality of life; VAS = visual analogue scale.
aThis group includes the patients who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the patients who received 50 mg or 100 mg avapritinib in Part 1.

Figure 43. MC-QoL Total Score Mean, ITT Patients Part 2 and Part 3



Abbreviations: CXDX = Cycle X Day X; ITT = Intent-to-treat; MC-QoL = Mastocytosis Quality of Life Questionnaire.
Reference: Pulfer et al, 2021

Updated efficacy data (data cutoff date 07 April 2023)

Table 53. Long Term Efficacy (Part 1/2/3) for Avapritinib 25 mg to Avapritinib mg

	All 25 mg Avapritinib[a] N = 226		Avapritinib 25 mg to 25 mg[b] N = 151	
Efficacy parameter	**24 weeks (C7D1)**	**48 weeks (C13D1)**	**24 weeks (C7D1)**	**48 weeks (C13D1)**
Mean change in TSS	n = 213 -14.91 (16.355)	n = 184 -17.80 (19.595)	n = 141 -16.89 (16.744)	n = 128 -20.42 (19.004)
% of patients achieving ≥ 50% reduction in TSS (95% CI)	n = 226 24.3 (18.9, 30.5)	n = 207 33.3 (27.0, 40.2)	n = 151 25.8 (19.1, 33.6)	n = 151 37.1 (29.4, 45.3)
% of patients achieving ≥ 30% reduction in TSS (95% CI)	n = 226 43.8 (37.2, 50.5)	n = 207 45.4 (38.5, 52.5)	n = 151 47.0 (38.9, 55.3)	n = 151 50.3 (42.1, 58.6)

% of patients with a ≥ 50% reduction in serum tryptase (95% CI)	n = 226 50.0 (43.3, 56.7)	n = 207 43.0 (36.2, 50.0)	n = 151 53.6 (45.4, 61.8)	N = 151 42.4 (34.4, 50.7)
% of patients with a ≥ 50% reduction in peripheral blood KIT D816V MAF or undetectable (95% CI)[c]	n = 191 62.3 (55.0, 69.2)	n = 174 51.1 (43.5, 58.8)	n = 127 66.9 (58.0, 75.0)	n = 127 50.4 (41.4, 59.4)

Abbreviations: C7D1 = Cycle 7 Day 1; CI = confidence interval; ISM = indolent systemic mastocytosis; ISM-SAF = Indolent Systemic Mastocytosis-Symptom Assessment Form; ITT = intent-to-treat; MAF = mutant allele fraction; TSS = total symptom score(s).

[a] All 25 mg avapritinib population includes both patients who received avapritinib 25 mg in parts 1 or 2 as well as patients who received placebo in part 2 but then went on to receive 25 mg avapritinib in part 3. For the placebo patients, the 24 and 48 week time points are measured from the time when the patient started avapritinib in part 3.

[b] Avapritinib 25 mg to 25 mg population excludes patients who received placebo in part 2, and only includes patients who received avapritinib 25 mg during part 1 or part 2 of the study.

Source: Updated data tables data cutoff 07 April 2023 Table 14.2.1.2.1c, Table 14.2.1.3.1.1c, Table 14.2.1.3.2.1c, Table 14.2.1.3.4.1c, Table 14.2.1.3.5.1c, Table 14.2.3.3.1c, Table 14.2.4.3.1c, Table 99.2.3.4.1c, and Table 99.2.4.4.1c

Table 54. Mean Change and Percent Change from Baseline in QoL Measures Over Time (Part 1/2/3 ITT Population)

	All 25 mg Avapritinib[a] N = 226				Avapritinib 25 mg to 25 mg[b] N = 151			
	24 weeks (C7D1)		48 weeks (C13D1)		24 weeks (C7D1)		48 weeks (C13D1)	
QoL endpoint	Mean (SD) change	Mean (SD) percent change	Mean (SD) change	Mean (SD) percent change	Mean (SD) change	Mean (SD) percent change	Mean (SD) change	Mean (SD) percent change
n (MC-QoL)	189	189	159	159	132	132	117	117
MC-QoL Range: 0-100	-16.64 (18.390)	-29.84 (33.749)	-18.74 (20.031)	-31.85 (37.743)	-19.31 (17.910)	-34.35 (30.709)	-22.65 (20.116)	-38.85 (35.475)
n (PGIS)	190	NA	159	NA	133	NA	120	NA
PGIS Range: 0-4	-0.7 (1.00)	NA	-0.9 (1.04)	NA	-0.8 (1.05)	NA	-1.0 (1.08)	NA
n (PGIC)	194	NA	162	NA	138	NA	120	NA
PGIC Range: 1-7	4 (1.72)	NA	4.8 (1.75)	NA	4..3 (1.72)	NA	4.7 (1.78)	NA
n (SF-12)	187	187	156	156	131	131	116	116
SF-12 physical component	4.75 (7.952)	16.75 (28.423)	5.23 (8.662)	20.26 (33.758)	5.39 (8.343)	19.24 (30.333)	6.57 (8.683)	24.86 (33.910)
SF-12 mental component	3.72 (9.262)	11.79 (26.301)	3.48 (9.474)	11.89 (29.602)	4.04 (9.192)	12.78 (26.472)	4.43 (9.788)	14.79 (31.615)
n (EQ-5D-5L VAS)	190	190	160	160	133	133	118	118
EQ-5D-5L (VAS) Range: 0-100	6.7 (17.53)	20.3 (52.83)	8.0 (16.69)	22.3 (45.05)	6.4 (18.68)	18.5 (48.23)	8.8 (18.23)	25.3 (50.25)

Abbreviations: CXDX = Cycle X Day X; EQ-5D-5L = EuroQol 5-Dimension 5-Level Questionnaires; ITT = intent-to-treat; MC-QoL = Mastocytosis-Quality of Life Questionnaire; NA = not applicable; PGIC = Patients Global Impression of Change; PGIS = Patients Global Impression of Symptom Severity; QoL = quality of life; SD = standard deviation; SF-12 = 12-Item Short Form Health Survey; VAS = visual analog scale.
[a] All 25 mg avapritinib population includes both patients who received avapritinib 25 mg in parts 1 or 2 as well as patients who received placebo in part 2 but then went on to receive 25 mg avapritinib in part 3. For the placebo patients, the 24 and 48 week time points are measured from the time when the patient started avapritinib in part 3.
[b] Avapritinib 25 mg to 25 mg population excludes patients who received placebo in part 2, and only includes patients who received avapritinib 25 mg during part 1 or part 2 of the study.
Note: A decrease in the MC-QoL and PGIS scores indicate improvement, and an increase in the PGIC, SF-12 and EQ-5D-5L scores indicate improvement.

Ancillary analyses

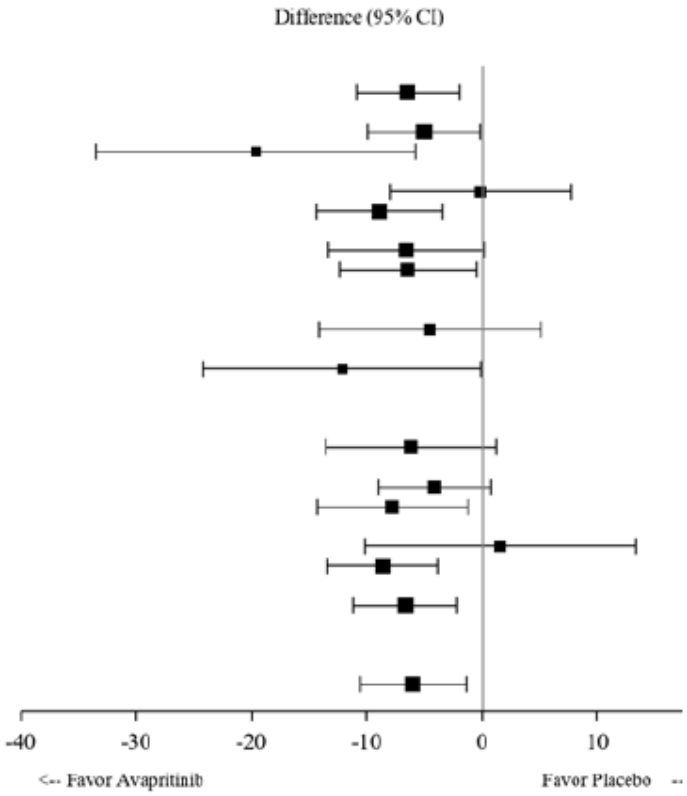
Subgroup analysis

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), ECOG PS (0 or 1, 2+), and prior TKI therapy (yes, no).

Figure 44. Forest Plot of mean change from baseline in ISM-SAF TSS at C7D1 (Part 2 IIT Population)

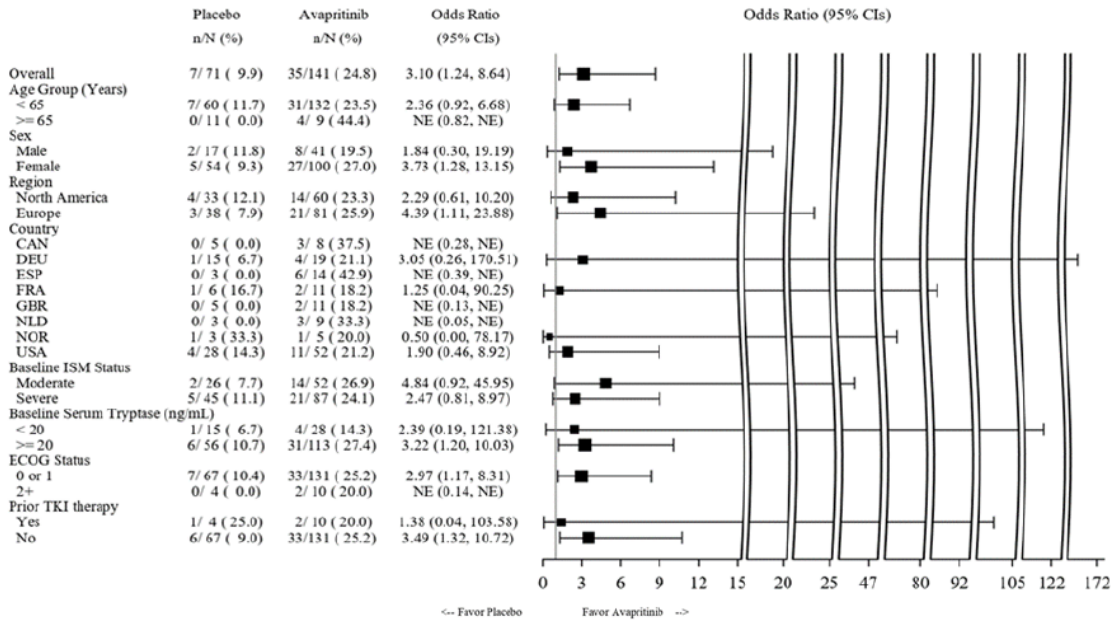
	Placebo			Avapritinib			Difference
	n	LS Mean	SE	n	LS Mean	SE	(95% CI)
Overall	65	-9.15	2.013	128	-15.58	1.536	-6.43 (-10.90, -1.96)
Age Group (Years)							
< 65	55	-10.07	2.191	119	-15.14	1.583	-5.07 (-9.92, -0.21)
>= 65	10	-5.63	6.953	9	-25.24	8.755	-19.62 (-33.50, -5.73)
Gender							
Male	17	-12.17	3.446	39	-12.34	2.383	-0.17 (-8.03, 7.68)
Female	48	-8.21	2.488	89	-17.13	1.989	-8.92 (-14.38, -3.46)
Region							
North America	30	-12.00	2.983	53	-18.58	2.413	-6.58 (-13.33, 0.16)
Europe	35	-7.19	2.697	75	-13.66	1.970	-6.47 (-12.43, -0.52)
Country							
CAN	4	NA	NA	8	NA	NA	NA (NA, NA)
DEU	14	-9.43	3.602	16	-13.96	3.493	-4.53 (-14.17, 5.11)
ESP	3	NA	NA	14	N.A	NA	NA (NA, NA)
FRA	6	-4.34	4.547	9	-16.49	3.554	-12.16 (-24.18, -0.13)
GBR	4	NA	NA	11	NA	NA	NA (NA, NA)
NLD	3	NA	NA	8	NA	NA	NA (NA, NA)
NOR	3	NA	NA	5	NA	NA	NA (NA, NA)
USA	26	-12.79	3.276	45	-18.95	2.685	-6.16 (-13.55, 1.24)
Baseline ISM Status							
Moderate	23	-4.98	2.218	49	-9.15	1.558	-4.17 (-9.09, 0.75)
Severe	42	-13.95	2.849	79	-21.75	2.284	-7.80 (-14.34, -1.27)
Baseline Serum Tryptase (ng/mL)							
< 20	14	-14.60	4.797	27	-13.01	3.358	1.58 (-10.14, 13.30)
>= 20	51	-7.55	1.995	101	-16.18	1.437	-8.63 (-13.41, -3.85)
ECOG Status							
0 or 1	62	-9.27	2.018	118	-15.97	1.552	-6.70 (-11.24, -2.17)
2+	3	NA	NA	10	NA	NA	NA (NA, NA)
Prior TKI therapy							
Yes	4	NA	NA	9	NA	NA	NA (NA, NA)
No	61	-8.63	2.063	119	-14.67	1.571	-6.04 (-10.63, -1.45)



Abbreviations: CXDX = Cycle X Day X; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; ISM-SAF = Indolent Systemic Mastocytosis-Symptom Assessment Form; ITT = Intent-to treat; LS Mean = Least Squares Mean; NA = Not applicable; SE = Standard Error; TKI = tyrosine kinase inhibitor; TSS = Total symptom score.

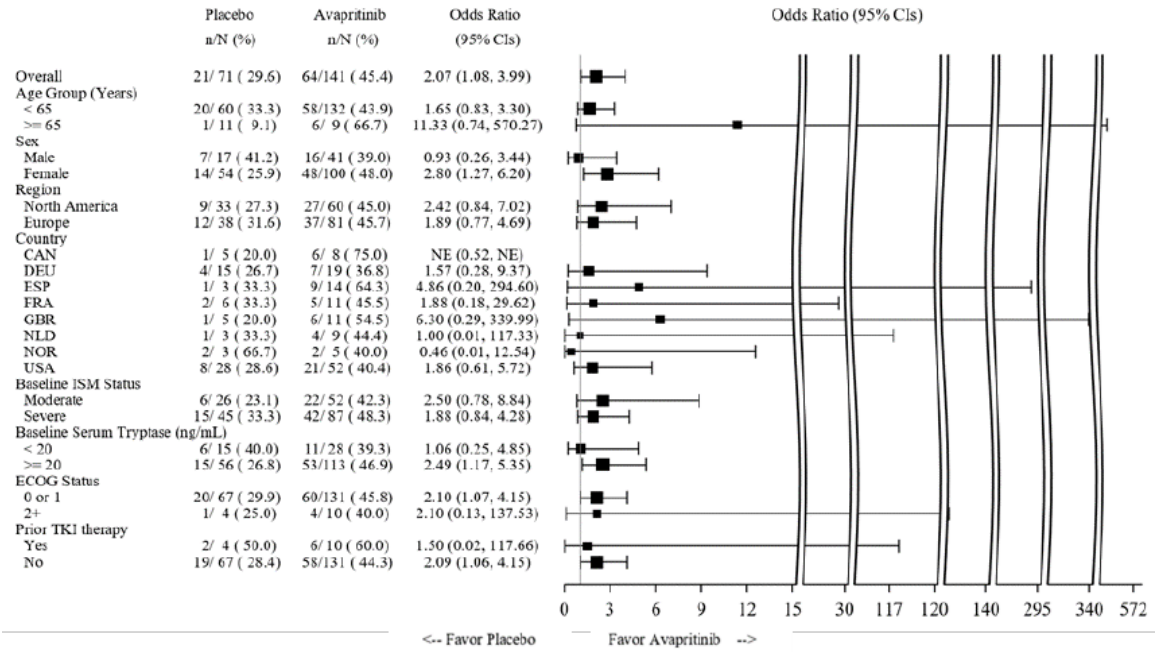
Secondary endpoints

Figure 45. Forest Plot of Patients with ≥ 50% Reduction in ISM-SAF TSS at C7D1 (Part 2 ITT Population)



Abbreviations: C7D1 = Cycle 7 Day 1; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; ISM = Indolent Systemic Mastocytosis; ISM-SAF = Indolent Systemic Mastocytosis-Symptom Assessment Form; ITT = intent-to-treat; NE = not estimated; TKI = tyrosine kinase inhibitor; TSS = total symptom score. Note: An odds ratio of > 1 indicates that treatment with avapritinib is favored.

Figure 46. Forest Plot of Patients with ≥ 30% Reduction in ISM-SAF TSS at C7D1 (Part 2 ITT Population)



Abbreviations: C7D1 = Cycle 7 Day 1; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; ISM = Indolent Systemic Mastocytosis; ISM-SAF = Indolent Systemic Mastocytosis-Symptom Assessment Form; ITT = intent-to-treat; NE = not estimated; TKI = tyrosine kinase inhibitor; TSS = total symptom score. Note: An odds ratio of > 1 indicates that treatment with avapritinib is favored.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well

as the benefit risk assessment (see later sections).

Table 55. Summary of efficacy for study BLU-285-2203

Title: BLU-285-2203 study: 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 smouldering systemic mastocytosis with symptoms inadequately controlled with standard therapy			
Study identifier	BLU-285-2203 EudraCT number: 2018-000588-99 PIONEER		
Design	Study BLU-285-2203 is a 3-part, Phase 2, randomized, double-blind, placebo-controlled study comparing the efficacy and safety of avapritinib in combination with best supportive care (BSC) to placebo in combination with BSC in patients with indolent systemic mastocytosis (ISM) whose symptoms were not adequately controlled by BSC.		
	Duration of Main phase (Part 2): Duration of Run-in phase: Duration of Extension phase (Part 3):		Date first patient enrolled in Part 2 of the study: 24 September 2020 Data cut-off for analyses: 23 June 2022 Not applicable Ongoing, patients will continue to receive avapritinib 25 mg QD in Part 3 of study BLU-285-2203 for up to 5 years, in 28-day cycles, inclusive of Part 1 and Part 2 of study BLU-285-2203.
Hypothesis	Superiority To evaluate efficacy and safety of avapritinib in patients with ISM with symptoms inadequately controlled with standard therapy. The primary analyses were performed for the ITT population and presented by treatment arm.		
Treatments groups	Avapritinib 25 mg + BSC		Oral dose of avapritinib 25 mg QD + BSC n = 141
	Placebo + BSC		Oral dose of placebo QD + BSC n = 71
Endpoints and definitions	Primary endpoint: **Mean change in ISM-SAF TSS** (ISM-Symptom Assessment Form Total Symptom Score)	Mean change in ISM-SAF TSS from Baseline to C7D1	Mean change in ISM-SAF TSS from Baseline to C7D1.

	Key secondary endpoints: **Reduction in mast cell burden**	≥50% reduction in **serum tryptase** from Baseline to C7D1	Proportion of patients with a ≥50% reduction in serum tryptase from Baseline to C7D1.
		≥50% reduction in **peripheral blood KIT D816V allele fraction** from Baseline to C7D1 (%)	Proportion of patients 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.
		≥50% reduction in **bone marrow mast cells** from Baseline to C7D1 (%)	Proportion of patients with a ≥50% reduction in bone marrow mast cells from Baseline to C7D1 or no aggregates for patients with aggregates at Baseline.
	Key secondary endpoints: **Reduction in ISM-SAF TSS**	**≥50% reduction** in ISM-SAF TSS from Baseline to C7D1 (%)	Proportion of patients with ≥50% reduction in ISM-SAF TSS from Baseline to C7D1.
		≥30% reduction in ISM-SAF TSS from Baseline to C7D1 (%)	Proportion of patients with ≥30% reduction in ISM-SAF TSS from Baseline to C7D1.

Database lock	Data cut-off for analyses was 23 June 2022.		
Results and Analysis			
Analysis description	**Primary analysis: Mean change in ISM-SAF TSS**		
Analysis population and time point description	The primary efficacy analysis set is the ITT population, which includes all randomized patients, independent of whether they received the study medication or not. All primary efficacy analyses are based on the ITT population. All patients in the ITT population are analyzed according to the avapritinib dose/placebo they were randomly assigned to receive and not according to what they actually received, if different.		
Descriptive statistics and estimate variability	Treatment group	Avapritinib 25 mg + BSC	Placebo + BSC
	Number of patients	141	71
	Mean change in TSS from baseline to C7D1 (95% confidence interval)	-15.58 (-18.61, -12.55)	-9.15 (-13.12, -5.18)
Effect estimate per comparison	Mean change in TSS from Baseline to C7D1	Comparison groups	Avapritinib 25 mg + BSC versus placebo + BSC
		Difference between groups	-6.43
		95% confidence interval	-10.90, -1.96
		p-value	0.003

Analysis description	**Key secondary analyses: Reduction in mast cell burden**		
Analysis population and time point description	Same as for the primary analysis, ITT population.		
Descriptive statistics and estimate variability	Treatment group	Avapritinib 25 mg + BSC	Placebo + BSC
	Number of patients	141	71
	≥50% reduction in serum tryptase from Baseline to C7D1 (%) (95% confidence interval)	53.9 (45.3, 62.3)	0.0 (0.0, 5.1)
Effect estimate per comparison	≥50% reduction in serum tryptase from Baseline to C7D1 (%)	Comparison groups	Avapritinib 25 mg + BSC versus placebo + BSC
		Odds ratio	NE
		95% confidence interval	30.59, NE
		p-value	<0.0001
Descriptive statistics and estimate variability	Treatment group	Avapritinib 25 mg + BSC	Placebo + BSC
	Number of patients	118	63
	≥50% reduction in peripheral blood KIT D816V allele fraction from Baseline to C7D1 (%) (95% confidence interval)	67.8 (58.6, 76.1)	6.3 (1.8, 15.5)
Effect estimate per comparison	≥50% reduction in peripheral blood KIT D816V allele fraction from Baseline to C7D1 (%)	Comparison groups	Avapritinib 25 mg + BSC versus placebo + BSC
		Odds ratio	39.34
		95% confidence interval	10.93, 140.56
		p-value	<0.0001
Descriptive statistics and estimate variability	Treatment group	Avapritinib 25 mg + BSC	Placebo + BSC
	Number of patients	106	57
	≥50% reduction in bone marrow mast cells from Baseline to C7D1 (%) (95% confidence interval)	52.8 (42.9, 62.6)	22.8 (12.7, 35.8)
Effect estimate per comparison		Comparison groups	Avapritinib 25 mg + BSC versus placebo + BSC
		Odds ratio	4.74

	≥50% reduction in bone marrow mast cells from Baseline to C7D1 (%)	95% confidence interval	2.06, 11.45
		p-value	<0.0001
Analysis description	**Key secondary analyses: reduction in ISM-SAF TSS**		
Analysis population and time point description	Same as for the primary analysis, ITT population.		
Descriptive statistics and estimate variability	Treatment group	Avapritinib 25 mg + BSC	Placebo + BSC
	Number of patients	141	71
	≥50% reduction in ISM-SAF TSS from Baseline to C7D1 (%) (95% confidence interval)	24.8 (17.9, 32.8)	9.9 (4.1, 19.3)
Effect estimate per comparison	≥50% reduction in ISM-SAF TSS from Baseline to C7D1 (%)	Comparison groups	Avapritinib 25 mg + BSC versus placebo + BSC
		Odds ratio	3.10
		95% confidence interval	1.24, 8.64
		p-value	0.005
Descriptive statistics and estimate variability	Treatment group	Avapritinib 25 mg + BSC	Placebo + BSC
	Number of patients	141	71
	≥30% reduction in ISM-SAF TSS from Baseline to C7D1 (%) (95% confidence interval)	45.4 (37.0, 54.0)	29.6 (19.3, 41.6)
Effect estimate per comparison	≥30% reduction in ISM-SAF TSS from Baseline to C7D1 (%)	Comparison groups	Avapritinib 25 mg + BSC versus placebo + BSC
		Odds ratio	2.07
		95% confidence interval	1.08, 3.99
		p-value	0.009

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	20/246	4/246	0
Non-Controlled trials	Not applicable	Not applicable	Not applicable

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

This variation application is primarily supported by the results from part 2 of the pivotal study BLU-285-2203 (PIONEER), a 3-part, randomized, double-blinded, placebo-controlled, phase 2 study to evaluate the efficacy and safety of avapritinib (BLU-285) in patients with ISM with symptoms inadequately controlled with standard therapy.

Initially, patients with both ISM and smouldering systemic mastocytosis (SSM) were planned to be included in study BLU-285-2203. However, no SSM patients were finally enrolled (in Part 2). This was justified by the MAH on the following grounds: that SSM patients have higher disease burden and are at higher risk of progression to advanced systemic mastocytosis (AdvSM). The study protocol for part 2 was updated in this regard with amendment 4, and only ISM patients were included. This approach was considered acceptable.

Forty-two sites in 13 countries enrolled patients and entered data for this study, including 19 sites in North America, 20 sites in Europe, and 3 sites in the United Kingdom. The European population is considered well represented with 119 (n=212; 56%) patients from European countries included in part 2 of study BLU-285-2203.

The focus for efficacy analyses in the current procedure is on patients with ISM treated with avapritinib at a dose of 25 mg QD. The proposal for a lower dose than the one recommended for the already approved indication in the AdvSM scenario seems reasonable in the context of a "non-aggressive/non-advanced" disease with the aim of downgrading toxicity and taking into consideration the (expected) long-term treatment. The RP2D was established based on Part 1 of the BLU 285-2203 study (see below).

Overall, the proposed design of the study is considered adequate. The study is placebo-controlled. This is endorsed as there are no drugs specifically approved in the EU for patients with ISM, and current treatment of the disease is based on supportive care to control symptoms. A period of 24 weeks for the double-blinded placebo comparison can be accepted. Nevertheless, the interpretation of long-term efficacy data, which are considered of particular relevance in this indolent scenario, is hampered by the absence of a control arm in part 3 of the study. Further, the overall sample size of study BLU-285-2203 is limited, although this can be acknowledged taking into account the rarity of this disease.

The primary endpoint for efficacy assessment in Part 2 of the study is defined as the mean change from baseline to cycle 7 day 1 (C7D1; week 24) in the total symptom score (TSS) using the Indolent Systemic Mastocytosis-Symptom Assessment Form (ISM-SAF). The proposal to use a continuous variable for the primary efficacy assessment of symptom reduction is considered adequate.

The ISM-SAF has been (recently) developed as a patient-reported outcome (PRO) questionnaire. It assesses the severity of eleven items (bone pain, abdominal pain, nausea, spots on the skin, itching, flushing, fatigue, dizziness, brain fog, headache and diarrhoea) which are graded on an 11-point numerical scale [from 0=no (sign/symptom) to 10=worst imaginable (sign/symptom)] using a 24-hour recall period. An additional item asks responders to record diarrhoea frequency during the prior 24 hours. The ISM-SAF can be scored at an item level or combined to create the above mentioned 'Total Symptom Score' (TSS) which is the sum of the 11 severity items ranged from 0 to 110. A 'Gastrointestinal

Symptom Score', a 'Skin Symptom Score' and a 'Neurocognitive Symptom Score' can also be derived from data reported, which are scored from 0 to 30 (each of them). These scores can be calculated on a daily or a bi-weekly basis.

The development and content validity as well as the psychometric properties of this PRO were discussed during regulatory interactions at EU level (EMEA/H/SA/3738/2/2018/SME/III; EMEA/H/SA/3738/2/FU/1/2020/PA/SME/II). At that time, the questionnaire was overall regarded as an acceptable tool to quantitate efficacy in ISM.

The proposed inclusion and exclusion criteria are overall considered reflective of a patient population with ISM that fail to achieve control under symptomatic therapies and have remaining moderate to severe symptomatology. An ISM-SAF TSS ≥28 was the pre-specified symptom severity threshold for the inclusion of patients in the study. This threshold was selected based on an observational study in 103 US patients diagnosed with ISM or SSM. Based on the findings of both received operating characteristics (ROC) and contingency analyses, using the Patient Global Impression of Symptom Severity (PGIS) as an anchor, a bi-weekly ISM-SAF TSS cut-off value of between 21 and 28 was defined to identify patients with at least moderate symptoms. The upper value of 28 was selected by the MAH as a more conservative estimate. A similar approach was used to identify patients with severe symptoms for whom a cut-off of ≥42 was selected. The proposed thresholds for inclusion in the study are considered basically acceptable.

The original protocol for study BLU-285-2203 (dated 15 February 2018) was amended 10 times: 5 were global and 5 were country-specific amendments. The study methodology presented for assessment is in accordance with the latest global protocol amendment 9 (dated 07 June 2022).

In the original protocol, the proposed primary endpoint was mean percent reduction in ISM-SAF TSS from baseline to week 12 (C4D1), which was then modified to mean change in ISM-SAF TSS from baseline to week 12 based on the feedback received from the FDA (amendment 1). In amendment 4 (15 June 2020), the primary endpoint was changed to the proportion of avapritinib-treated patients with ISM achieving ≥30% reduction in TSS from baseline to C7D1 (apparently, this change was agreed by the FDA). Later on, with amendment 9 (07 June 2022) the primary endpoint was changed, again, to mean change in ISM-SAF TSS from baseline to C7D1, compared to placebo (as discussed with the FDA).

In addition, the sample size was increased in Part 2 (and consequently in Part 3) as a result of amendment 4 and increased from 72 to 204 patients.

Even if the finally agreed/selected primary endpoint as well as the sample size can be considered overall adequate from a regulatory perspective, changes have been implemented during an ongoing study and therefore the MAH was requested to provide a detailed description on how these major changes should be expected to have not affected the integrity and the internal validity of the study. Overall, the protocol amendment 4 was made before the start of Part 2 of the study and therefore there was no impact on the integrity of the study. Regarding protocol amendment 9 the change in the primary endpoint was made prior to the last patient last visit for Part 2 (21 Jun 2022) while the study was blinded and therefore with no impact on the integrity of the study.

Regarding major protocol deviations (reported in more than 2% of patients in part 2 of the study), there was a higher rate in the avapritinib arm compared with the placebo arm (29.9% vs. 9.9%). None are thought to impact the integrity of the data.

In 2018, the MAH sought advice (EMEA/H/SA/3738/2/2018/SME/III) to ask about the appropriateness of the LOCF method to account for missing data. This method was strongly discouraged. The MAH followed the EMA advice and, in the final protocol, the approach was changed to the exclusion of patients with missing values at baseline or C7D1 TSS from the analysis. As sensitivity analysis, Markov chain Monte Carlo (MCMC) simulations to impute missing values at baseline or C7D1 was proposed. From a regulatory point of view, this is still not the preferred option to assess the agreed primary endpoint since the exclusion of

potential informative data from the primary efficacy analysis, i.e. intercurrent events (ICEs), might hamper the results and, consequently, their interpretation impacting the extrapolation of (the magnitude of) the treatment effect reported in the targeted population. Generally, the treatment policy estimand (where the value of the endpoint is used regardless of the occurrence of ICEs) is the strongly preferred strategy for the handling of these events. However, it is acknowledged that in some instances, the collection of these intercurrent events is not possible. For this reason, the MAH was requested to conduct additional analyses to better contextualise these results. Results of these analyses were consistent with the primary analysis.

Part 1 - Dose response study

The main objective was to identify the optimal dose of avapritinib (RP2D) in patients with ISM.

Baseline height and weight were similar across treatment groups. At baseline, all patients had significant sign and symptom burden as assessed by the ISM-SAF with a mean (SD) TSS of 53.3 (19.34). Baseline mean (SD) serum tryptase was 83.78 (100.530) ng/mL and 89.7% patients had bone marrow mast cell aggregates. KIT D816V mutation was detected in peripheral blood in 79.5% of patients at baseline with a mean (SD) allele fraction of 4.274 (8.4802).

At C4D1, the mean (SD) reduction in TSS of the ISM-SAF was greater in all avapritinib groups compared with the placebo group: –12.54 (13.234) for the 25 mg group, –12.32 (14.194) for the 50 mg group, –21.35 (18.769) for the 100 mg group, and –3.36 (7.998) for the placebo group.

The 100 mg dose was associated with the greatest reduction in TSS at C4D1. However, additional analyses showed that the TSS reduction plateaued after C4D1. The 25 mg and 50 mg dose groups achieved a similar mean reduction in TSS to the 100 mg cohort by C7D1.

Based on the above reported results from Part 1 of the study, 25 mg avapritinib was chosen as the RP2D for Part 2 and Part 3. The 25 mg cohort had a better safety profile in terms of Grade 3 AEs, required no dose modifications and no discontinuations of the study drug, with acceptable and comparable efficacy results and was expected by the MAH to allow long-term treatment.

As stated above, the proposed dose, which is lower than that recommended for the already approved indication in the advanced disease setting (i.e. AdvSM), is considered reasonable in a "non-aggressive" scenario where downgrading toxicity is of importance.

Efficacy data and additional analyses

In Part 2, both the ITT and Safety Populations included 141 patients in the 25 mg avapritinib group and 71 patients in the placebo group. The primary efficacy assessment was based on results reported in the ITT population.

Regarding baseline characteristics, the ITT population included more females than males (70.9% vs. 29.1% in the avapritinib arm and 76.1% vs. 23.9% in the placebo arm, for female and male patients, respectively). Literature is available suggesting a female predominance (Kanamori et al, 2015), which is consistent with the patient population enrolled in the study. Most patients in both groups were < 65 years (93.6% in the 25 mg avapritinib group and 84.5% in the placebo group), not Hispanic or Latino (70.2% in the 25 mg avapritinib group and 81.7% in the placebo group), and White (77.3% patients in the 25 mg avapritinib group and 85.9% patients in the placebo group), and other baseline characteristics (mean height [cm], weight [kg], and body mass index [kg/m2]) were similar in both groups. Of note, the proportion of female and white patients was higher in the placebo group.

The mean ISM-SAF TSS at baseline (SD) was comparable for the placebo and the avapritinib arms, i.e. 50.17 (19.145) points for the 25 mg avapritinib group and 52.43 (19.823) for the placebo group. Of note, while all patients seem to fulfil the eligibility criteria (eligibility TSS is defined as the 14-day average of

TSS starting from the date that investigator deemed BSC medications are optimized and stabilised), there were some patients (14 in the avapritinib arm and 4 in the placebo arm) with a TSS < 28 at baseline. Indeed, the minimum ISM-SAF TSS value at baseline was 12.1 in the avapritinib arm and 18 in the placebo arm. The percentage of patients with severe symptoms of ISM (i.e. defined as an ISM-SAF TSS ≥42) was balanced between the 25 mg avapritinib group (61.7%) and the placebo group (63.4%).

Overall, the 94.3% rate of KIT D816V positivity was consistent with the anticipated ~95% rate of KIT D816V positivity noted in the ISM literature *(Garcia-Montero et al, 2006; Jara-Acevedo et al, 2015; Ungerstedt et al, 2022)*.

The majority of patients who received avapritinib (99.3%) or placebo (100%) received concomitant best supportive care at baseline (median of 3 therapies in the avapritinib group and 4 in the placebo group). The most common therapies in patients treated with avapritinib were H1 antihistamines (97.2%), H2 antihistamines (66%), leukotriene inhibitors (34.8%) and cromolyn sodium (30.5%).

Although cyto-reductive treatment is mainly indicated in advanced mastocytosis, several patients in the current study received treatment with midostaurin, imatinib, dasatinib, etc. In total, there were 19 patients who had received prior therapy with TKIs before enrolment in the study (14 in the avapritinib arm and 4 in the placebo arm). However, according to the MAH limited information is available on the reasons for the previous treatment received but efficacy results for these patients have been provided and appear consistent with those of the overall population.

The analysis of efficacy for avapritinib was based primarily on the results from the comparison between placebo and the RP2D of 25 mg avapritinib in Part 2 of study BLU 285-2203. During treatment, there was reduction in the ISM-SAF TSS for both groups. In the placebo group, a reduction in the ISM-SAF TSS was observed until C3D1 followed by a plateau of the ISM-SAF TSS through C7D1.

At C7D1, the LS mean (SE) change from baseline in the ISM-SAF TSS was –15.58 (1.536) points for the 25 mg avapritinib group and -9.15 (2.013) for the placebo group. Change from baseline to C7D1 in ISM-SAF TSS showed a difference of -6.43 (95% IC: -10.90, -1.96) between treatment arms. This difference was statistically significant ($p<0.003$). It is noticeable that the regression to the mean observed in the placebo group is numerically larger than the estimated improvement seen with the addition of avapritinib.

Results from the analysis of the primary endpoint in relevant subgroups were overall consistent with only two subgroups (male and patients with serum tryptase <20 ng/mL) apparently deriving less benefit from the experimental treatment (based on point estimates of mean change). These two subgroups are of small sample size and therefore results should be interpreted with caution.

The results for the (key) secondary efficacy endpoints showed also statistically significant results. The proportion of patients with ≥ 50% and ≥ 30% reduction in ISM-SAF TSS from baseline to C7D1 was of 24.8% vs. 9.9% and 45.4% vs 29.6% for the avapritinib and placebo groups, respectively. Also, the proportion of patients with ≥ 50% reduction in objective measures of mast cell burden (serum tryptase, KIT D816V MAF and bone marrow mast cells) showed results in favour of avapritinib treatment with all 3 endpoints reported as statistically significant.

The clinically important difference (CID) between groups for the TSS (reported using the recently developed PRO ISM-SAF), derived using distribution-based methods, may range from 6 to 10. This is based on pooled data from Part 1 and 2 of study BLU 285-2203, considered by the MAH as confirmation of the CID range previously observed for Part 1 (i.e. from 7 to 10). However, the MAH was requested to further clarify/discuss the approach followed to inform this CID, including the fact that basically the same data were used for threshold determination as well as for final inference which constitute a limitation. Moreover, considering the data submitted from the mentioned analyses, a CID of 10 would appear a more conservative threshold. The CID range was generated using two independent distribution-based methods,

based on a pooled analysis of Part 1 and Part 2 data at C7D1. The methods used to determine the range of values for a CID were pre-specified in the psychometric analysis SAP and the CID analysis was performed by an independent organisation using blinded data, which is reassuring. The MAH was requested to perform an anchor-based method. However, anchor-based methods were only used to establish thresholds of meaningful within patient change (responder analysis). In this regard, based on the anchor-based method a CID range for the ISM-SAF TSS was considered as clinically relevant. Thus, at a group level, patients receiving avapritinib experienced a change in TSS that can be considered of clinical relevance in contrast to those patients receiving placebo.
Nevertheless, to assess whether between-group differences in ISM-SAF TSS values at C7D1 were clinically meaningful only distribution-based analyses were used. In addition to the above, similar concerns were identified in relation to the suitable threshold for the responder criterion in the primary endpoint, i.e. in terms of interpretation of the clinical relevance of reported statistically significant changes in within-patient score changes in the ISM-SAF TSS. Even if the argumentation that a 30% reduction in the TSS reflects a meaningful within-patient change (MWPC) can be followed, as it aligns with the treatment response criteria of ≥30% proposed by both European and American network/consortium, the relative change strongly depends not only on the absolute improvement but also on the baseline value of the included patients. Indeed, all patients included (albeit a few exceptions) had a baseline TSS above 28, according to the inclusion criteria, with a mean ISM-SAF TSS at baseline around 50. Thus, the MAH was requested to provide the number of patients that achieved a TSS <28 as well as the proportion of patients with ≥30% reduction in ISM-SAF TSS from baseline to C7D1 that achieved a TSS<28. The proportion of patients with TSS<28 at C7D1 (week 24) was higher in the avapritinib arm compared with the placebo arm in the overall population (41.1% avapritinib vs 23.9% placebo) as well as in patients with moderate (60.5% vs 36.4%) and severe (26.4% vs 11.1%) symptoms. Moreover, the proportion of patients who achieved ≥30% reduction in TSS and a TSS<28 was also higher in the avapritinib arm (44/141 [31%] avapritinib vs 11/71 [15.5%] placebo). These results are supportive of the primary endpoint and its clinical relevance.

The reported reduction in the dose and/or frequency of BSC medications used by C7D1 was higher in patients treated with avapritinib than in those receiving placebo, i.e. 30 (21.3%) and 9 (12.7%), respectively. Even though these observed trends to decreases of background therapy compared to placebo may not seem very compelling a further analysis of the primary endpoint with BSC as covariate and the results were consistent with the primary analysis.

Results have also been separately reported for the different 'symptom domain clusters' (GI, skin and neurocognitive) showing that the greatest effect apply to the skin symptoms. Indeed, a statistically significant difference was observed in the reduction of the mean skin domain scores between treatment arms (–5.87 and –2.64, for the avapritinib and placebo arms respectively; difference between the groups of -3.23). In contrast, the mean difference from baseline in the score for the GI and neurocognitive domains (-0.60 and -1.22, respectively) were lower and not statistically significant. Data from the analysis of individual symptoms are difficult to interpret but statistically significant differences in the mean change from baseline between the experimental and the placebo group at C7D1 were only seen in the spots severity, itching severity, and flushing severity domains/symptoms. Avapritinib is acknowledged to have beneficial effects across all ISM symptoms, since decreases in systemic measures of mast cell burden have been observed as well as improvements in all symptoms scores and domains, including improvement in most severe symptoms. Patients treated with avapritinib, to a greater or lesser extent, have shown a (higher) decrease in all individual symptoms and symptoms domains compared with placebo, although the highest effect is clearly observed in skin symptoms. Minor differences were observed in the GI domain but it was in fact the one with lower baseline scores. Besides, as pointed out by the MAH, results in other secondary endpoints of measure of mast cell burden also showed a beneficial effect with avapritinib.

The change in quality of life measures based on different scales/questionnaires (i.e. MC-QoL, PGIS, PGIC, SF-12 and EQ-5D-5L) was assessed as a secondary endpoint in part 2 of study BLU 285-2203. Results seem compatible with an improvement in QoL in avapritinib treated patients.

Anaphylaxis is a common manifestation of disease in ISM. These episodes can be life threatening and are feared by patients who need to carry epinephrine auto-injectors at all times. The inclusion of an (exploratory) endpoint to compare the number of anaphylactic episodes, based on epinephrine use, is therefore welcome. At baseline, 7 (5.0%) patients in the avapritinib group and none in the placebo group had anaphylaxis that required epinephrine treatment. Post baseline, 2 (1.4%) and 3 (4.2%) patients in the avapritinib and placebo group, respectively, had anaphylaxis that required epinephrine treatment. The small sample size and the short duration of part 2 of the study limits the interpretation of this analysis.

Part 3 – Long-term study

Of the 202 patients that completed Part 2 of the study: 1 patient in the 25 mg avapritinib group completed Part 2 but did not roll over to Part 3. Thus, 201 patients completed Part 2 and rolled over to Part 3. Additionally, 34 patients from part 1 rolled over to part 3. In total, 235 patients rolled over to Part 3 from Part 1 and Part 2 of the study. At the time of the initial data cut-off (23 June 2022), 14 patients have discontinued from Part 3 of the study and 221 patients are ongoing.

At the time of the data cut-off (23 June 2022), mean (SD) treatment duration was almost twice as long in the Part 1/2/3 All 25 mg avapritinib group (10.41 months [7.167]) compared with patients in the 25 mg avapritinib group of Part 2.

As expected, patients who were in the placebo group during Part 1 or Part 2 had higher mast cell burden than the patients who were in the avapritinib groups as assessed by serum tryptase and KIT D816V MAF levels at baseline (before starting part 3).

The results from the long-term open-label Part 3 of the study and in the overall population (Part 1/2/3) submitted seemingly show that the efficacy of avapritinib is maintained beyond C7D1, though interpretation of these data is hampered by the open label nature of this part of the study. Of note, the observed improvement in the ISM-SAF TSS and objective measures of mast cell burden, in patients previously treated with avapritinib who rolled over to avapritinib in part 3, are considered supportive.

Updated efficacy data based on a data cut-off (DCO) date of 07 April 2023 were submitted during the procedure. At the time of this DCO, of the 234 patient who rollover to Part 3, 24 had discontinued study and 211 were ongoing. Results at 48 weeks show an improvement in mean change of TSS and in the proportion of patients achieving $\geqslant$50% and $\geqslant$30% reduction in TSS compared with the assessment at 24 weeks. Regarding objective markers of mast cell burden, a decrease in the proportion of patients with a $\geqslant$50% reduction in serum tryptase and the proportion of patients with a $\geqslant$50% reduction in KIT D816V MAF was observed. No updated data on bone marrow mast cells have been provided since bone marrow biopsy was optional at week 48 and few patients have results. QoL was overall maintained at 48 weeks. The number of patients with a decrease in the use of BSC medications was higher at week 48 than at week 24 (47 [31.1%] patients vs. 38 [25.2%] patients, respectively). However, no additional patients discontinued BSC medications (4 patients).

Overall, the efficacy of avapritinib appears to be maintained with a longer follow-up although a decrease in the proportion of patients with response in mast cell burden is observed. Since Part 3 is intended to continue for up to 5 years, a commitment to submit results of Part 3 of the study annually was required. The MAH has committed to submit an annual report of study BLU-285-2203 starting in August 2024 and continuing annually until completion of the study as a Post Authorisation Measure (REC).

Of note, with protocol amendment 7 the possibility to increase the dose from 25 mg QD to 50 mg QD in Part 3 of the study was included. Nevertheless, no patient in Part 3 had escalated to 50 mg at the time at

the initial data cut-off date (i.e. 23 June 2022). Up to the new data cut-off (07 April 2023) 10 patients had dose escalated to 50 mg. Among patients who dose escalated, TSS improved in the majority of patients (in 2 patients TSS was stable or even increased and for 1 patient no information is provided). Trypsase and KITD816V VAF decreased in all patients in which it was assessed (8 and 5, respectively).

2.4.4. Conclusions on the clinical efficacy

Efficacy data show a statistically significant reduction in the mean change from baseline to C7D1 (week 24) in the total symptom score (TSS) using the Indolent Systemic Mastocytosis-Symptom Assessment Form (ISM-SAF). The (key) secondary efficacy endpoints also show statistically significant results. The efficacy of avapritinib appears to be maintained in the long term although the interpretation of the data is hampered by the absence of a control arm in Part 3 of the study.

The following measures are considered necessary to address issues related to efficacy:

- Since the study BLU-285-2203 is intended to continue for up to 5 years, the MAH has committed to submit an annual report until completion of the study following recommendation from the CHMP.

2.5. Clinical safety

Introduction

The safety database to support the proposed extension of indication consists of a single, phase II, placebo-controlled study in patients with ISM (study BLU-285-2203). Study BLU-285-2203 is a 3-part, Phase 2, randomized, double-blind, placebo-controlled study comparing the safety and efficacy of avapritinib in combination with BSC to placebo in combination with BSC in patients with ISM whose symptoms were not adequately controlled by BSC.

Safety data focuses on ISM patients treated with avapritinib 25 mg QD or placebo in Part 2 of Study BLU-285-2203. In addition, overall safety data, assessed across all 3 study parts, including patients who received any dose of avapritinib in any part of the study are included.

The data cut-off date for the submission was 23/06/2022. As part of the responses to the CHMP's D120 LOQ, the MAH submitted a safety update (new data cut-off date 07/04/2023) for part 3 of study BLU-285-2203.

Table 56. Overview of the Phase 2 Study BLU-285-2203 Included in the Clinical Summary of Safety

	Part 1	**Part 2**	**Part 3**
Status	Completed	Completed	Ongoing (most recent data cutoff of 07 April 2023)
Study Design	Multicenter, randomized, double-blind, placebo-controlled		Multicenter, open-label, long-term extension
Study Objectives	Primary: To determine the RP2D of avapritinib in patients with ISM for use in Part 2 and Part 3 of the study	Primary: To determine mean change in ISM SAF TSS from baseline to C7D1, compared to placebo Key secondary: • To determine the proportion of avapritinib-treated patients with ISM with a ≥ 50% reduction in serum tryptase from baseline to C7D1, compared to placebo.	Primary: To assess the long-term safety and efficacy of avapritinib in ISM patients

	Part 1	Part 2	Part 3
		• To determine 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. • To determine the proportion of avapritinib-treated patients with ISM achieving ≥ 50% reduction in ISM-SAF TSS from baseline to C7D1, compared to placebo. • To determine the proportion of avapritinib-treated patients with ISM achieving ≥ 30% reduction in ISM-SAF TSS from baseline to C7D1, compared to placebo. • To determine 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.	
Study Population	Patients with ISM		
Study Drug Doses and Regimens	Avapritinib: 25, 50, or 100 mg PO QD Placebo PO QD	Avapritinib: 25 mg PO QD (RP2D) Placebo PO QD	Avapritinib: 25 mg PO at the same dosing frequency as the last cycle in Part 1 or Part 2
Treatment Duration	At least 12 weeks	24 weeks	Up to 5 years (including duration of Parts 1 and 2)
Number of Countries (Sites) with Centers Enrolling Patients	13 (42)		
Number of Patients	Planned: 40 Dosed: 39 Discontinued treatment: 5 Rollover to Part 3: 34	Planned: 204 Dosed: 212 (25 mg Avapritinib: 141; Placebo: 71) Discontinued treatment: 10 (25 mg Avapritinib: 5; Placebo: 5) Rollover to Part 3: 201; 1 patient did not roll over	Planned: 244 Dosed: 235 Discontinued treatment: 24
Demographics	39 patients 9 M/30 F Age: 21-75 years (median: 51 years) White: 92.3%; Asian: 0%; Black: 2.6%; Other/Unknown: 5.1%	25 mg Avapritinib: 141 patients; 41 M/100 F; median (range) age: 50.0 (18-77) years; White: 77.3%; Asian: 0.7%; Black: 0%; Other/Unknown: 21.9% Placebo: 71 patients; 17 M/54 F; median (range) age:54.0 (26-79) years; White: 85.9%; Asian: 0%; Black: 0%; Other/Unknown: 14.1%	235 patients 64 M/171 F Age: 18-79 years (median: 51.0 years) White: 81.7%; Asian: 0.4%; Black: 0.4%; Other/Unknown: 17.4%

Abbreviations: C7D1 = Cycle 7 Day 1; F = female; ISM = indolent systemic mastocytosis; ISM-SAF = indolent systemic mastocytosis-symptom assessment form; KIT = V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; M = male; PO = per os (by mouth); QD = once daily; RP2D = recommended Phase 2 dose; TSS = total symptom score.

Safety data have been presented separately for Part 2 (placebo-controlled) of study BLU-285-2203 and the overall safety database (all ISM patients included in the study).

Patient exposure

The safety population included 246 patients who have received at least 1 dose of avapritinib ("All Avapritinib" Group):

- **Part 1 (completed)**: Identified the recommended phase 2 dose (RP2D), it included 39 patients (placebo: 9; avapritinib 25mg: 10; avapritinib 50mg: 10; avapritinib 100mg: 10), with a median treatment duration of 15 to 20 weeks.
- **Part 2 (completed)**: ISM patients were randomly assigned to the avapritinib 25mg QD in combination with BSC (141 patients) or to placebo in combination with BSC (71 patients), with a treatment duration of 24 weeks.
- **Part 3 (on-going)**: an open label extension cohort in which patients that participated in Part 1 or 2 could join and receive the avapritinib intended dose (25mg QD) with an overall treatment duration of up to 5 years (including Parts 1 and 2). A total of 235 patients have enrolled, including 34 patients from Part 1 and 201 patients who rolled over from Part 2.

A total of 226 patients who only received the 25 mg dose comprise the "All 25 mg Avapritinib" Group. Of them, 151 patients had received 25 mg avapritinib in Part 1 or Part 2 (and Part 3 if they rolled over), and 75 patients had received placebo in Part 1 or Part 2 and 25 mg avapritinib in Part 3. Additionally, 10 patients each had received avapritinib 50 mg and 100 mg in Part 1 prior to rollover to 25 mg in Part 3.

Table 57. Summary of Analysis Populations (Part 2 and Part 1/2/3)

Analysis Population	Safety Population, n (%)
Part 2	
Placebo N = 71	71 (100.0)
25 mg Avapritinib N = 141	141 (100.0)
Overall Data – Part 1/2/3 (Avapritinib Treated)	
Placebo to 25 mg N = 75	75 (100.0)
Avapritinib 25 mg to 25 mg/NA N = 151	151 (100.0)
All 25 mg Avapritinib N = 226	226 (100.0)
Avapritinib 50 mg to 25 mg/NA N = 10	10 (100.0)
Avapritinib 100 mg to 25 mg/NA N = 10	10 (100.0)
All Avapritinib N = 246	246 (100.0)

Abbreviations: NA = not applicable (patients who did not roll over to Part 3). Percentages were based on the number of patients in the Intent-to-Treat Population.

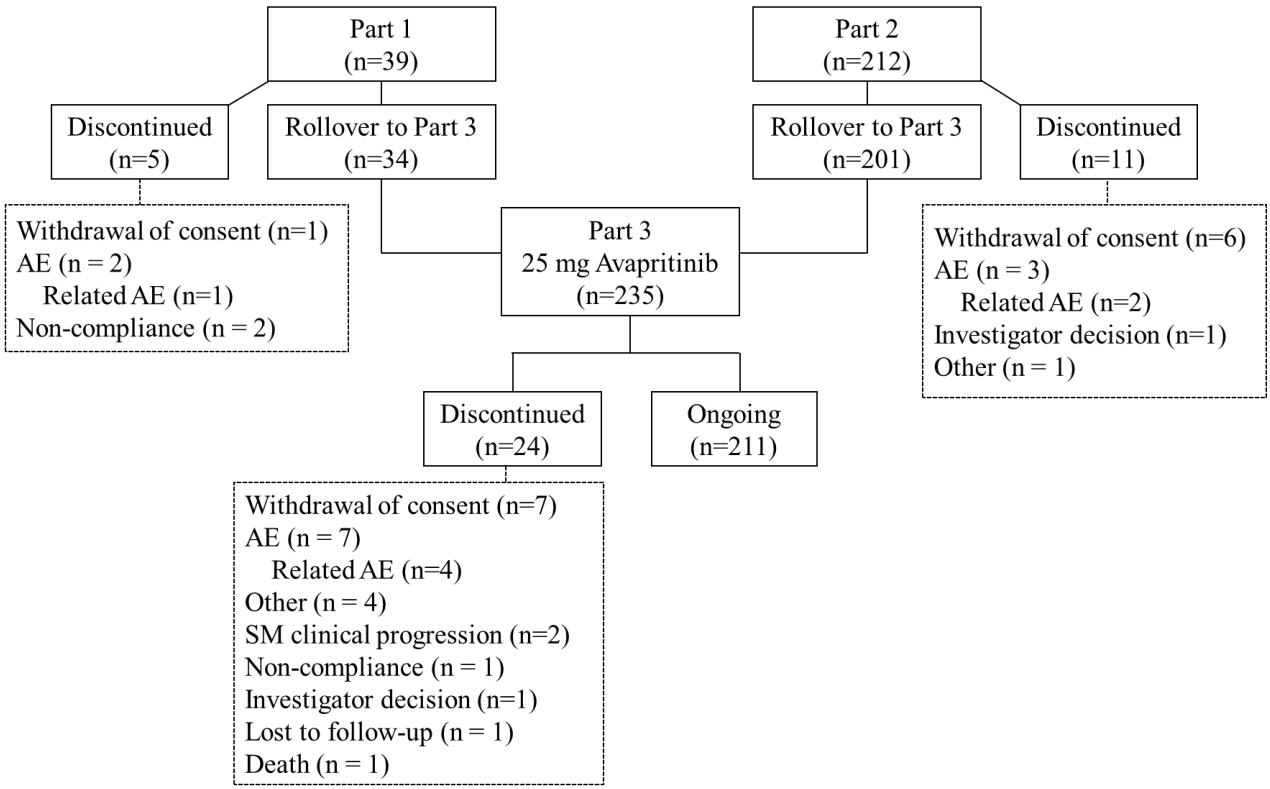
- Disposition

In Part 2 of the study, 5 patients in the 25 mg Avapritinib Group discontinued from the study due to: withdrawal of consent (n=2), AE (n=1), SM clinical progression (n=1), and investigator's decision (n=1). In the Placebo Group, 5 patients discontinued due to: withdrawal of consent (n=3) and other reasons (n=2).

A total of 136 patients (96.5%) treated with 25 mg avapritinib and 66 patients (93.0%) treated with placebo completed Part 2 of the study. Of these, 1 patient in the 25 mg Avapritinib Group completed Part 2 but did not roll over to Part 3.

Overall, 235 patients rolled over to Part 3 from Part 1 and Part 2 of the study. At the time of the data cutoff for the updated data (07 April 2023), 24 patients have discontinued from Part 3 of the study and 211 patients are ongoing (Figure 47).

Figure 47. Disposition of Patients in Part 1/2/3 (07 April 2023)



Abbreviations: AE = adverse event, SM = systemic mastocytosis.

- Study Drug Exposure

Part 2 of study BLU 285 2203:

A total of 141 patients were randomized and exposed to 25 mg avapritinib and 71 patients were randomized and exposed to placebo (see table below).

Table 58. Treatment Exposure (Part 2 Safety Population)

Parameter	**25 mg Avapritinib N = 141**	**Placebo N = 71**
Number of doses administered		
n	141	71
Mean (SD)	163.6 (24.30)	162.4 (26.71)
Median (min, max)	169.0 (20, 195)	168.0 (25, 196)
Duration of treatment (months)[a]		
n	141	71
Mean (SD)	5.46 (0.726)	5.43 (0.806)
Median (min, max)	5.55 (0.7, 6.5)	5.55 (0.8, 6.4)
Relative dose intensity[b]		
n	141	NA
Mean (SD)	99.7 (1.99)	NA

Parameter	25 mg Avapritinib N = 141	Placebo N = 71
Median (min, max)	100.0 (83, 101)	NA

Abbreviations: max = maximum; min = minimum; NA = not applicable; SD = standard deviation. [a]Duration of Treatment is defined as (treatment end date-treatment start date + 1)/30.4375. [b] Relative Dose Intensity: dose intensity/planned dose intensity. Planned dose intensity is based on initial assigned daily dose. Note: One month is considered to be 30.4375 days.

Overall Avapritinib Population

The overall data are based on all 246 patients (All Avapritinib Group) who were treated with at least 1 dose of avapritinib in any part of the study (Table 59).

Table 59. Treatment Exposure (Part 1/2/3 [Avapritinib Treated] Safety Population)

	23 June 2022 Data Cutoff Date		07 April 2023 Data Cutoff Date	
Parameter	All 25 mg Avapritinib[a] N = 226	All Avapritinib N = 246	All 25 mg Avapritinib[a] N = 226	All Avapritinib N = 246
Number of doses administered				
n	226	246	226	246
Mean (SD)	311.4 (216.31)	353.1 (269.02)	565.4 (250.41)	600.8 (297.23)
Median (min, max)	269.5 (11, 1113)	288.0 (4, 1113)	542.0 (20, 1398)	555.5 (4, 1389)
Duration of treatment (Months)[c]				
n	226	246	226	246
Mean (SD)	10.41 (7.167)	11.84 (8.997)	18.91 (8.140)	20.12 (9.770)
Median (min, max)	8.87 (0.5, 36.7)	9.74 (0.2, 36.7)	18.00 (0.7, 46.1)	18.33 (0.2, 46.1)
< 6 months, n (%)	53 (23.5)	55 (22.4)	11 (4.9)	13 (5.3)
≥ 6 months, n (%)	173 (76.5)	191 (77.6)	215 (95.1)	233 (94.7)
≤ 12 months, n (%)	155 (68.6)	158 (64.2)	40 (17.7)	43 (17.5)
> 12 months, n (%)	71 (31.4)	88 (35.8)	186 (82.3)	203 (82.5)
Cumulative dose (total dose taken) (mg)				
n	226	246	226	246
Mean (SD)	7786.4 (5407.69)	9788.5 (9556.05)	14220.2 (6409.23)	16082.6 (10139.62)
Median (min, max)	6750.0 (263, 27825)	7300.0 (263, 56900)	13650.0 (500, 42025)	13962.5 (400, 64000)
Average daily dose (mg)				
n	226	246	226	246
Mean (SD)	25.0 (0.02)	26.6 (7.57)	25.1 (0.63)	26.6 (7.30)
Median (min, max)	25.0 (25, 25)	25.0 (25, 100)	25.0 (25, 30)	25.0 (25, 100)
Dose intensity (mg/day)				
n	226	246	226	246
Mean (SD)	24.6 (1.59)	25.9 (6.49)	24.6 (1.97)	25.8 (6.25)
Median (min, max)	25.0 (12, 25)	25.0 (12, 88)	25.0 (12, 30)	25.0 (12, 88)
Relative dose intensity[c]				
n	226	246	226	246
Mean (SD)	99.7 (1.83)	99.5 (2.54)	100.2 (2.69)	100.0 (3.17)
Median (min, max)	100.0 (75, 100)	100.0 (75, 101)	100.0 (91, 122)	100.0 (84, 122)

Abbreviations: max = maximum; min = minimum; NA = not applicable; SD = standard deviation.

[a] This group includes the patients who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the patients who received 50 mg or 100 mg avapritinib in Part 1.

[b] Duration of Treatment is defined as (treatment end date-treatment start date + 1)/30.4375.
[c] Relative Dose Intensity: dose intensity/planned dose intensity. Planned dose intensity is based on initial assigned daily dose.
Note: One month is considered to be 30.4375 days.

- Demographics and other characteristics of the study population (Safety population)

Demographics and Baseline disease characteristics

Part 2 of study BLU 285 2203:

Table 60. Demographic Characteristics (Part 2 Safety Population)

Category	**25 mg Avapritinib N = 141**	**Placebo N = 71**
Age (years)[a]		
Mean (SD)	48.7 (11.70)	52.2 (12.52)
Median (min, max)	50.0 (18, 77)	54.0 (26, 79)
Age group, n (%)		
< 65 years	132 (93.6)	60 (84.5)
≥ 65 years	9 (6.4)	11 (15.5)
Sex, n (%)		
Female	100 (70.9)	54 (76.1)
Male	41 (29.1)	17 (23.9)
Ethnicity, n (%)		
Hispanic or Latino	6 (4.3)	1 (1.4)
Not Hispanic or Latino	99 (70.2)	58 (81.7)
Not reported	22 (15.6)	10 (14.1)
Unknown	14 (9.9)	2 (2.8)
Race, n (%)		
Asian	1 (0.7)	0
White	109 (77.3)	61 (85.9)
Unknown	27 (19.1)	8 (11.3)
Other	4 (2.8)	2 (2.8)
Height (cm)		
n	137	70
Mean (SD)	169.05 (9.726)	166.55 (9.073)
Median (min, max)	167.00 (152.4, 194.0)	165.00 (150.2, 195.0)
Weight (kg)		
n	141	71
Mean (SD)	81.12 (17.915)	82.19 (17.796)
Median (min, max)	80.20 (45.0, 126.4)	80.70 (44.4, 134.8)
BMI (kg/m^2)[b]		
n	137	70
Mean (SD)	28.31 (5.400)	29.46 (5.276)
Median (min, max)	27.84 (17.6, 42.0)	28.99 (19.7, 43.7)
Baseline ISM-SAF TSS[c] (Range: 0-110)		
n	139	71
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)
Baseline ISM severity based on ISM-SAF TSS, n (%)[d]		
≥ 42 (Severe)	87 (61.7)	45 (63.4)
< 42 (Moderate)	52 (36.9)	26 (36.6)
Baseline Serum Tryptase (ng/mL)		
n	141	71
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)
Baseline Percent Bone Marrow Mast Cells (Central Pathology Review)[e]		
n	141	71
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)
Baseline KIT D816V Mutation Allele Burden as Measured by MAF using ddPCR from Blood (Central Assay)[d]		

Category	25 mg Avapritinib N = 141	Placebo N = 71
n	141	71
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)
Mast Cell (counts/mm^2) in Skin by Central Lab (Lesional)		
n	107	60
Mean (SD)	561.2 (399.65)	637.6 (488.71)
Median (min, max)	459.0 (89, 2870)	617.5 (83, 2609)
Mast Cell (counts/mm^2) in Skin by Central Lab (Non-lesional)		
n	106	60
Mean (SD)	152.2 (76.28)	165.9 (166.00)
Median (min, max)	131.5 (35, 659)	129.0 (59, 1337)

Abbreviations: BMI = body mass index; ddPCR = digital-droplet polymerase chain reaction; ISM = indolent systemic mastocytosis; ISM-SAF = indolent systemic mastocytosis-symptom assessment form; KIT = V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; MAF = minor allele frequency; max = maximum; min = minimum; SD = standard deviation; TSS = total symptom score.

[a]Age at the time of informed consent. [e] BMI was calculated as weight (kg)/(height (m))^2. [c]Baseline TSS score is defined as the 14-day average of TSS from C1D–14 to C1D–1. If a patient is missing more than 7 days of score between C1D-14 and C1D-1, the baseline score is considered as missing for the patient. [d]Baseline refers to the last assessment value prior to C1D1 dosing in Part 2 of the study.

Overall Avapritinib Population

Table 61. Demographic Characteristics (Part 1/2/3 [Avapritinib Treated] Safety Population)

Category	All 25 mg Avapritinib[a] N = 226	All Avapritinib N = 246
Age (years), n[b]		
Mean (SD)	49.8 (12.28)	49.7 (12.23)
Median (min, max)	51.0 (18, 79)	51.0 (18, 79)
Age group, n (%)		
< 65 years	203 (89.8)	222 (90.2)
≥ 65 years	23 (10.2)	24 (9.8)
Sex, n (%)		
Female	166 (73.5)	179 (72.8)
Male	60 (26.5)	67 (27.2)
Ethnicity, n (%)		
Hispanic or Latino	7 (3.1)	8 (3.3)
Not Hispanic or Latino	170 (75.2)	189 (76.8)
Not reported	32 (14.2)	32 (13.0)
Unknown	17 (7.5)	17 (6.9)
Race, n (%)		
Asian	1 (0.4)	1 (0.4)
White	185 (81.9)	202 (82.1)
Unknown	35 (15.5)	37 (15.0)
Other	5 (2.2)	5 (2.0)
Height (cm)		
n	221	241
Mean (SD)	168.25 (9.495)	168.30 (9.626)
Median (min, max)	165.60 (150.2, 195.0)	165.90 (142.2, 195.6)
Weight (kg)		
n	226	246
Mean (SD)	81.31 (18.634)	81.29 (18.375)
Median (min, max)	80.10 (44.1, 148.9)	80.60 (44.1, 148.9)
BMI (kg/m^2)[c]		
n	221	241
Mean (SD)	28.61 (5.644)	28.58 (5.499)
Median (min, max)	28.10 (17.6, 51.4)	28.18 (17.6, 51.4)
Baseline ISM-SAF TSS[d] (Range: 0-110)		
n	224	244
Mean (SD)	48.08 (19.465)	48.48 (19.621)

Category	All 25 mg Avapritinib[a] N = 226	All Avapritinib N = 246
Median (min, max)	45.04 (5.2, 102.7)	45.62 (5.2, 102.7)
Baseline ISM severity based on ISM-SAF TSS, n (%)[d]		
≥ 42 (Severe)	131 (58.0)	145 (58.9)
< 42 (Moderate)	93 (41.2)	99 (40.2)
Baseline Serum Tryptase (ng/mL)		
n	226	246
Mean (SD)	63.38 (70.265)	67.0 (77.548)
Median (min, max)	39.20 (3.6, 590.4)	40.25 (3.6, 590.4)
Baseline Bone Marrow Mast Cells (Central Pathology Review) [e]		
n	226	246
Mean (SD)	11.14 (11.229)	11.58 (11.761)
Median (min, max)	7.00 (1.0, 60.0)	7.00 (1.0, 60.0)
Baseline KIT D816V Mutation Allele Burden as Measured by MAF using ddPCR from Blood (Central Assay)		
n	226	246
Mean (SD)	3.097 (6.9739)	3.154 (7.0658)
Median (min, max)	0.385 (0.00, 41.29)	0.350 (0.00, 41.29)
Mast Cell (counts/mm^2) in Skin by Central Lab (Lesional)		
n	180	197
Mean (SD)	568.3 (439.20)	579.7 (509.79)
Median (min, max)	451.5 (83, 2870)	446.0 (53, 4300)
Mast Cell (counts/mm^2) in Skin by Central Lab (Non-lesional)		
n	179	196
Mean (SD)	166.4 (112.11)	160.5 (109.98)
Median (min, max)	133.0 (35, 837)	130.0 (10,837)

Abbreviations: BMI = body mass index; ddPCR = digital-droplet polymerase chain reaction; ISM = indolent systemic mastocytosis; ISM-SAF = indolent systemic mastocytosis-symptom assessment form; KIT = V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; MAF = minor allele frequency; max = maximum; min = minimum; SD = standard deviation; TSS = total symptom score.

[a]This group includes the patients who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the patients who received 50 mg or 100 mg avapritinib in Part 1. [b] Age at the time of informed consent. [c] BMI was calculated as weight (kg)/(height (m))^2. [d] Baseline TSS score is defined as the 14-day average of TSS from C1D–14 to C1D–1. If a patient is missing more than 7 days of score between C1D-14 and C1D-1, the baseline score is considered as missing for the patient. [e] Baseline refers to the last assessment value prior to C1D1 dosing in the study. Note: Baseline is defined as the day the first avapritinib dose was received. For the 25 mg avapritinib and all groups, this would be either Part 1 C1D1, Part 2 C1D1, or Part 3 C1D1.

Medical history and concomitant medication

Part 2 of study BLU 285 2203:

Table 62. Ongoing Medical History in ≥ 10% of Patients Overall (Part 2 Safety Population)

System Organ Class Preferred Term	25 mg Avapritinib N = 141 n (%)	Placebo N = 71 n (%)
Patients with ongoing medical history	141 (100.0)	71 (100.0)
Gastrointestinal Disorders	114 (80.9)	55 (77.5)
Diarrhoea	85 (60.3)	35 (49.3)
Abdominal pain	45 (31.9)	21 (29.6)
Nausea	39 (27.7)	19 (26.8)
Gastrooesophageal reflux disease	38 (27.0)	10 (14.1)
Abdominal distension	14 (9.9)	8 (11.3)
Constipation	13 (9.2)	10 (14.1)
Musculoskeletal and Connective Tissue Disorders	112 (79.4)	58 (81.7)
Bone pain	53 (37.6)	28 (39.4)
Arthralgia	33 (23.4)	7 (9.9)
Osteopenia	32 (22.7)	9 (12.7)
Osteoporosis	27 (19.1)	22 (31.0)
Myalgia	19 (13.5)	9 (12.7)
Back pain	18 (12.8)	2 (2.8)
Skin and Subcutaneous Tissue Disorders	110 (78.0)	52 (73.2)

System Organ Class Preferred Term	25 mg Avapritinib N = 141 n (%)	Placebo N = 71 n (%)
Pruritus	61 (43.3)	31 (43.7)
Urticaria pigmentosa	50 (35.5)	26 (36.6)
Urticaria	17 (12.1)	8 (11.3)
Rash maculo-papular	11 (7.8)	11 (15.5)
General Disorders and Administration Site Conditions	96 (68.1)	39 (54.9)
Fatigue	67 (47.5)	30 (42.3)
Feeling abnormal	37 (26.2)	9 (12.7)
Asthenia	16 (11.3)	4 (5.6)
Nervous System Disorders	95 (67.4)	44 (62.0)
Headache	52 (36.9)	26 (36.6)
Dizziness	29 (20.6)	13 (18.3)
Migraine	22 (15.6)	9 (12.7)
Memory impairment	20 (14.2)	8 (11.3)
Disturbance in attention	19 (13.5)	6 (8.5)
Vascular Disorders	85 (60.3)	48 (67.6)
Flushing	62 (44.0)	35 (49.3)
Hypertension	37 (26.2)	15 (21.1)
Metabolism and Nutrition Disorders	76 (53.9)	35 (49.3)
Obesity	39 (27.7)	20 (28.2)
Psychiatric Disorders	69 (48.9)	30 (42.3)
Depression	38 (27.0)	14 (19.7)
Anxiety	27 (19.1)	6 (8.5)
Insomnia	22 (15.6)	9 (12.7)
Respiratory, Thoracic and Mediastinal Disorders	52 (36.9)	24 (33.8)
Asthma	19 (13.5)	8 (11.3)
Dyspnoea	15 (10.6)	4 (5.6)
Immune System Disorders	46 (32.6)	24 (33.8)
Drug hypersensitivity	16 (11.3)	6 (8.5)
Endocrine Disorders	35 (24.8)	15 (21.1)
Hypothyroidism	26 (18.4)	9 (12.7)
Social Circumstances	26 (18.4)	15 (21.1)
Menopause	18 (12.8)	10 (14.1)

Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities. Note: Medical history is classified by system organ class and preferred term using MedDRA version 25.0.

Overall Avapritinib Population

Table 63. Ongoing Medical History in ≥ 10% of Patients Overall (Part 1/2/3 [Avapritinib Treated] Safety Population)

System Organ Class Preferred Term	All 25 mg Avapritinib N = 226 n (%)	All Avapritinib N = 246 n (%)
Patients with ongoing medical history	226 (100.0)	246 (100.0)
Gastrointestinal Disorders	183 (81.0)	199 (80.9)
Diarrhoea	129 (57.1)	139 (56.5)
Abdominal pain	66 (29.2)	73 (29.7)
Nausea	64 (28.3)	69 (28.0)
Gastrooesophageal reflux disease	52 (23.0)	59 (24.0)
Constipation	24 (10.6)	26 (10.6)
Musculoskeletal and Connective Tissue Disorders	180 (79.6)	197 (80.1)
Bone pain	85 (37.6)	96 (39.0)
Osteoporosis	53 (23.5)	56 (22.8)
Osteopenia	44 (19.5)	50 (20.3)
Arthralgia	43 (19.0)	48 (19.5)
Myalgia	28 (12.4)	28 (11.4)
Skin and Subcutaneous Tissue Disorders	173 (76.5)	189 (76.8)

System Organ Class Preferred Term	All 25 mg Avapritinib N = 226 n (%)	All Avapritinib N = 246 n (%)
Pruritus	99 (43.8)	107 (43.5)
Urticaria pigmentosa	80 (35.4)	90 (36.6)
Urticaria	25 (11.1)	26 (10.6)
Nervous System Disorders	147 (65.0)	164 (66.7)
Headache	79 (35.0)	92 (37.4)
Dizziness	44 (19.5)	46 (18.7)
Migraine	34 (15.0)	35 (14.2)
Memory impairment	29 (12.8)	34 (13.8)
Disturbance in attention	26 (11.5)	28 (11.4)
General Disorders and Administration Site Conditions	145 (64.2)	155 (63.0)
Fatigue	103 (45.6)	111 (45.1)
Feeling abnormal	48 (21.2)	52 (21.1)
Vascular Disorders	136 (60.2)	147 (59.8)
Flushing	98 (43.4)	107 (43.5)
Hypertension	53 (23.5)	58 (23.6)
Metabolism and Nutrition Disorders	119 (52.7)	126 (51.2)
Obesity	63 (27.9)	64 (26.0)
Psychiatric Disorders	106 (46.9)	118 (48.0)
Depression	57 (25.2)	60 (24.4)
Anxiety	37 (16.4)	43 (17.5)
Insomnia	34 (15.0)	43 (17.5)
Respiratory, Thoracic and Mediastinal Disorders	83 (36.7)	94 (38.2)
Asthma	27 (11.9)	33 (13.4)
Immune System Disorders	72 (31.9)	81 (32.9)
Drug hypersensitivity	23 (10.2)	25 (10.2)
Social Circumstances	47 (20.8)	54 (22.0)
Menopause	31 (13.7)	33 (13.4)
Endocrine Disorders	51 (22.6)	52 (21.1)
Hypothyroidism	35 (15.5)	36 (14.6)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities. [a] This group includes the patients who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the patients who received 50 mg or 100 mg avapritinib in Part 1. Note: Medical history is classified by system organ class and preferred term using MedDRA version 25.0.

Concomitant Medications

Part 2 of study BLU 285 2203:

The majority of patients who had prior treatment with cytoreductive therapies such as tyrosine kinase inhibitors for mastocytosis had 1 prior line of therapy: 19.1% patients in the 25 mg Avapritinib Group and 18.3% patients in the Placebo Group. A few patients in both groups had 2 to 3 prior lines of mastocytosis therapy. The most commonly reported concomitant BSC medication/therapies included medications such as proton pump inhibitors and H2 blockers, antihistamines for systemic use, leukotriene inhibitors and anti-IgE antibodies, intestinal anti-inflammatory agents such as oral cromolyn, and corticosteroids for systemic use. Most commonly reported concomitant BSC medication/therapies included drugs for peptic ulcer and gastrooesophageal reflux disease (12.1% and 12.7%), antihistamines for systemic use (10.6% and 9.9%), intestinal anti-inflammatory agents (10.6% and 7.0%), corticosteroids for systemic use (9.9% and 2.8%), and other systemic drugs for obstructive airway diseases (6.4% and 4.2%).

The majority of patients in the Part 2 safety population received concomitant medication/therapy other than BSC (97.9% in the 25 mg Avapritinib Group and 100% in the Placebo Group). The use of concomitant medications by WHO drug classification ATC class 3 was similar between the treatment groups. The most common concomitant medication/therapies used were viral vaccine (43.3% in the 25 mg Avapritinib Group and 43.7% in the Placebo Group), other analgesics and antipyretics (36.2% in the 25 mg Avapritinib Group

and 35.2% in the Placebo Group). Antidepressants and anxiolytic medications were also used often (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 2 groups: 22.0% in the 25 mg Avapritinib Group and 22.5% in the Placebo Group.

Overall Avapritinib Population

Prior mastocytosis therapy, concomitant BSC medication, and use of concomitant medication other than BSC for the Overall Avapritinib Population (Part 1/2/3) which included patients who rolled over to Part 3 from Parts 1 and 2 were consistent with the use of these medications/therapies in Part 2.

Adverse events

Overall Adverse Events

Part 2 of study BLU 285 2203

Table 64. Summary of Adverse Events (Part 2 Safety Population)

Patients with at Least One Event	25 mg Avapritinib N = 141 n (%)	Placebo N = 71 n (%)
Any AE	128 (90.8)	66 (93.0)
AE related to study drug	77 (54.6)	32 (45.1)
SAE	7 (5.0)	8 (11.3)
SAE related to study drug	0	0
Grade 1 AE	48 (34.0)	15 (21.1)
Grade 1 AE related to study drug	56 (39.7)	20 (28.2)
Grade 2 AE	50 (35.5)	36 (50.7)
Grade 2 AE related to study drug	18 (12.8)	10 (14.1)
Grade ≥ 3 AE	30 (21.3)	15 (21.1)
Grade ≥ 3 AE related to study drug	3 (2.1)	2 (2.8)
AE leading to interruption of study drug	12 (8.5)	9 (12.7)
Related AE leading to interruption of study drug	5 (3.5)	4 (5.6)
AE leading to dose reduction of study drug	2 (1.4)	1 (1.4)
Related AE leading to dose reduction of study drug	1 (0.7)	1 (1.4)
AE leading to permanent discontinuation of study drug	3 (2.1)	1 (1.4)
Related AE leading to permanent discontinuation of study drug	2 (1.4)	1 (1.4)
Death	0	0

Abbreviations: AE = adverse event; SAE = serious adverse event. Notes: All AEs are Treatment Emergent AEs. Treatment Emergent AE was defined as any AE that occurred between the Part 2 Day 1 through a day prior to Part 3 Day 1, or through 30 days after the last dose if patient did not rollover to Part 3. Each patient is counted only once and with the highest severity grade. Relationship to study drug is as per the Investigator assessment.

Overall Avapritinib Population

Table 65. Summary of Adverse Events (Part 1/2/3 [Avapritinib Treated] Safety Population)

	23 June 2022 Data Cutoff Date		07 April 2023 Data Cutoff Date	
Patients with at least one event	All 25 mg Avapritinib N = 226 n (%)	All Avapritinib N = 246 n (%)	All 25 mg Avapritinib N = 226 n (%)	All Avapritinib N = 246 n (%)
Patients with at least 1 AE	202 (89.4)	221 (89.8)	223 (98.7)	242 (98.4)
AE related to study drug	130 (57.5)	147 (59.8)	151 (66.8)	168 (68.3)
SAE	24 (10.6)	30 (12.2)	31 (13.7)	38 (15.4)
SAE related to study drug	1 (0.4)	2 (0.8)	2 (0.9)	3 (1.2)
Grade 1 AE	58 (25.7)	58 (23.6)	38 (16.8)	38 (15.4)
Grade 1 AE related to study drug	82 (36.3)	87 (35.4)	92 (40.7)	97 (39.4)

	23 June 2022 Data Cutoff Date		07 April 2023 Data Cutoff Date	
Patients with at least one event	**All 25 mg Avapritinib N = 226 n (%)**	**All Avapritinib N = 246 n (%)**	**All 25 mg Avapritinib N = 226 n (%)**	**All Avapritinib N = 246 n (%)**
Grade 2 AE	86 (38.1)	91 (37.0)	99 (43.8)	102 (41.5)
Grade 2 AE related to study drug	42 (18.6)	49 (19.9)	48 (21.2)	55 (22.4)
Grade ≥ 3 AE	58 (25.7)	72 (29.3)	86 (38.1)	102 (41.5)
Grade ≥ 3 AE related to study drug	6 (2.7)	11 (4.5)	11 (4.9)	16 (6.5)
AE leading to interruption of study drug	26 (11.5)	37 (15.0)	38 (16.8)	49 (19.9)
Related AE leading to interruption of study drug	13 (5.8)	20 (8.1)	18 (8.0)	25 (10.2)
AE leading to reduction of study drug	7 (3.1)	11 (4.5)	13 (5.8)	17 (6.9)
Related AE leading to reduction of study drug	5 (2.2)	9 (3.7)	11 (4.9)	15 (6.1)
AE leading to permanent discontinuation of study drug	7 (3.1)	8 (3.3)	12 (5.3)	13 (5.3)
Related AE leading to permanent discontinuation of study drug	4 (1.8)	5 (2.0)	6 (2.7)	7 (2.8)
Death	0	0	1 (0.4)	1 (0.4)

Abbreviations: AE = adverse event; SAE = serious adverse event.
a This group includes the patients who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the patients who received 50 mg or 100 mg avapritinib in Part 1.
Notes: All AEs are Treatment Emergent AEs. Treatment Emergent AE was defined as any AE that occurred between the Part 2 Day 1 through a day prior to Part 3 Day 1, or through 30 days after the last dose if patient did not rollover to Part 3. Each patient is counted only once and with the highest severity grade.
Relationship to study drug is as per the Investigator assessment.

Common Adverse Events

Part 2 of study BLU 285 2203

The most commonly reported AEs across both groups (≥ 10%) included headache, nausea, COVID-19, dizziness, and diarrhea. Of these events, COVID-19 and dizziness had a slightly higher incidence in the 25 mg Avapritinib Group compared to the Placebo Group.

Table 66. Adverse Events in ≥ 5% of Patients in Either Treatment Group by Preferred Term (Part 2 Safety Population)

Preferred Term	**25 mg Avapritinib N = 141 n (%)**	**Placebo N = 71 n (%)**
Patients with any AEs	128 (90.8)	66 (93.0)
Headache	27 (19.1)	14 (19.7)
Nausea	18 (12.8)	12 (16.9)
COVID-19	17 (12.1)	8 (11.3)
Dizziness	16 (11.3)	6 (8.5)
Diarrhoea	15 (10.6)	8 (11.3)
Fatigue	14 (9.9)	6 (8.5)
Flushing	13 (9.2)	3 (4.2)
Oedema peripheral	12 (8.5)	3 (4.2)
Arthralgia	11 (7.8)	5 (7.0)
Pruritus	11 (7.8)	5 (7.0)
Face oedema	10 (7.1)	1 (1.4)
Blood alkaline phosphatase increased	9 (6.4)	1 (1.4)
Periorbital oedema	9 (6.4)	2 (2.8)
Abdominal pain	8 (5.7)	4 (5.6)

Preferred Term	25 mg Avapritinib N = 141 n (%)	Placebo N = 71 n (%)
Insomnia	8 (5.7)	2 (2.8)
Alanine aminotransferase increased	7 (5.0)	2 (2.8)
Alopecia	6 (4.3)	4 (5.6)
Hypertension	6 (4.3)	5 (7.0)
Nasopharyngitis	6 (4.3)	5 (7.0)
Vomiting	6 (4.3)	4 (5.6)
Urinary tract infection	5 (3.5)	5 (7.0)

Abbreviations: AE = adverse event; COVID-19 = Coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities. Note: AEs are coded using MedDRA version 25.0. All AEs are Treatment Emergent AEs. A patient is counted only once for multiple events within the same preferred term.

Of all AEs reported, face oedema was the only AE that had a higher incidence in the 25 mg Avapritinib Group compared to the Placebo Group by greater than 5% (7.1% vs 1.4%; Table 67).

Table 67. Summary of Grouped Oedema Events (Part 2 Safety Population)

Adverse Drug Reaction Term	25 mg Avapritinib N = 141 n (%)	Placebo N = 71 n (%)
Eye edema	18 (12.8)	5 (7.0)
Peripheral edema	17 (12.1)	4 (5.6)
Face oedema	10 (7.1)	1 (1.4)
General edema	4 (2.8)	0

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred term.
Notes: AEs are coded using MedDRA version 25.0. All AEs are Treatment Emergent AEs. A patient is counted only once for multiple events within the same group. Pooled terms are as follows: Eye edema: Periorbital oedema, Eyelid oedema, Swelling of eyelid, Eye oedema, Orbital oedema, Eye swelling. General Edema: Fluid retention, Generalised oedema, Oedema. Peripheral Edema: Oedema peripheral, Peripheral swelling. Note: Face oedema is a PT and not a pooled term. Relationship to study drug is as per the Investigator assessment.

Overall Avapritinib Population

The most commonly reported AEs (by PT) occurring in ≥ 10% of the 226 patients in the All 25 mg Avapritinib Group were COVID-19, headache, nausea, diarrhoea, dizziness, pruritus, fatigue, and oedema peripheral, (table 68). The incidence of AEs in the All Avapritinib Group was similar to that of the All 25 mg Avapritinib Group. Data for the overall Avapritinib Group (n= 246) are similar.

Table 68. Adverse Events in ≥ 5% of Patients by Preferred Term (Part 1/2/3 [Avapritinib Treated] Safety Population)

	23 June 2022 Data Cutoff Date		07 April 2023 Data Cutoff Date	
Preferred Term	All 25 mg Avapritinib N = 226 n (%)	All Avapritinib N = 246 n (%)	All 25 mg Avapritinib N = 226 n (%)	All Avapritinib N = 246 n (%)
Patients with any AEs	202 (89.4)	221 (89.8)	223 (98.7)	242 (98.4)
COVID-19	50 (22.1)	57 (23.2)	92 (40.7)	99 (40.2)
Headache	41 (18.1)	50 (20.3)	50 (22.1)	58 (23.6)
Nausea	31 (13.7)	43 (17.5)	39 (17.3)	50 (20.3)
Diarrhoea	26 (11.5)	34 (13.8)	37 (16.4)	45 (18.3)
Dizziness	31 (13.7)	39 (15.9)	33 (14.6)	41 (16.7)
Pruritus	24 (10.6)	29 (11.8)	36 (15.9)	41 (16.7)
Fatigue	24 (10.6)	29 (11.8)	32 (14.2)	37 (15.0)
Oedema peripheral	25 (11.1)	30 (12.2)	32 (14.2)	37 (15.0)
Arthralgia	20 (8.8)	25 (10.2)	29 (12.8)	34 (13.8)
Blood alkaline phosphatase increased	19 (8.4)	20 (8.1)	23 (10.2)	26 (10.6)

	23 June 2022 Data Cutoff Date		07 April 2023 Data Cutoff Date	
Preferred Term	**All 25 mg Avapritinib N = 226 n (%)**	**All Avapritinib N = 246 n (%)**	**All 25 mg Avapritinib N = 226 n (%)**	**All Avapritinib N = 246 n (%)**
Flushing	22 (9.7)	24 (9.8)	24 (10.6)	26 (10.6)
Periorbital oedema	17 (7.5)	22 (8.9)	21 (9.3)	26 (10.6)
Back pain	14 (6.2)	19 (7.7)	20 (8.8)	25 (10.2)
Hypertension	19 (8.4)	20 (8.1)	23 (10.2)	25 (10.2)
Abdominal pain	16 (7.1)	19 (7.7)	21 (9.3)	24 (9.8)
Insomnia	19 (8.4)	21 (8.5)	22 (9.7)	24 (9.8)
Upper respiratory tract infection	10 (4.4)	14 (5.7)	19 (8.4)	23 (9.3)
Vomiting	9 (4.0)	13 (5.3)	19 (8.4)	23 (9.3)
Weight increased	14 (5.7)	14 (5.7)	19 (8.4)	22 (8.9)
Nasopharyngitis	14 (5.7)	14 (5.7)	20 (8.8)	21 (8.5)
Urinary tract infection	11 (4.9)	13 (5.3)	17 (7.5)	20 (8.1)
Constipation	13 (5.8)	16 (6.5)	16 (7.1)	19 (7.7)
Anaphylactic reaction	9 (4.0)	15 (6.1)	12 (5.3)	18 (7.3)
Face oedema	14 (6.2)	19 (7.7)	13 (5.8)	18 (7.3)
Hypersensitivity	6 (2.7)	10 (4.1)	13 (5.8)	17 (6.9)
Rash	11 (4.9)	12 (4.9)	16 (7.1)	17 (6.9)
Sinusitis	10 (4.4)	11 (4.5)	16 (7.1)	17 (6.9)
Abdominal distension	12 (5.3)	13 (5.3)	15 (6.6)	16 (6.5)
Pain in extremity	6 (2.7)	9 (3.7)	13 (5.8)	16 (6.5)
Alopecia	12 (5.3)	13 (5.3)	14 (6.2)	15 (6.1)
Cough	10 (4.4)	10 (4.1)	15 (6.6)	15 (6.1)
Disturbance in attention	9 (4.0)	11 (4.5)	13 (5.8)	15 (6.1)
Fall	6 (2.7)	9 (3.7)	12 (5.3)	15 (6.1)
Palpitations	11 (4.9)	13 (5.3)	13 (5.8)	15 (6.1)
Dyspnoea	9 (4.0)	13 (5.3)	10 (4.4)	14 (5.7)
Peripheral swelling	10 (4.4)	12 (4.9)	12 (5.3)	14 (5.7)
Alanine aminotransferase increased	8 (3.5)	11 (4.5)	10 (4.4)	13 (5.3)
Blood creatinine increased	8 (3.5)	9 (3.7)	12 (5.3)	13 (5.3)
Bone pain	9 (4.0)	10 (4.1)	12 (5.3)	13 (5.3)
Paraesthesia	7 (3.1)	11 (4.5)	9 (4.0)	13 (5.3)
Contusion	11 (4.9)	11 (4.5)	12 (5.3)	12 (4.9)

Abbreviations: AE = adverse event; COVID-19 = Coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities.

a This group includes the patients who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the patients who received 50 mg or 100 mg avapritinib in Part 1.

Note: AEs are coded using MedDRA version 25.0. All AEs are Treatment Emergent AEs. A patient is counted only once for multiple events within the same preferred term.

Adverse Events by Severity

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Most of the patients experienced Grade 1 or 2 AEs in both treatment groups.

In the 25 mg Avapritinib Group, 48 patients (34.0%) experienced Grade 1 AEs, 50 patients (35.5%) had Grade 2 AEs, 28 patients (19.9%) had Grade 3 AEs, and 2 patients (1.4%) had Grade 4 AEs. In the Placebo Group, 15 patients (21.1%) experienced Grade 1 AEs, 36 patients (50.7%) had Grade 2 AEs, 15 patients (21.1%) had Grade 3 AEs, and no patients had Grade 4 AEs.

In the 25 mg Avapritinib Group, 1 patient experienced a Grade 4 event of acute myeloid leukaemia associated with a Grade 4 event of neutrophil count decreased, both were assessed as not related to study drug by the Investigator. The other Grade 4 event was hypokalaemia that occurred in a patient with a medical history of intermittent diarrhoea and was assessed as not related to study drug by the Investigator.

The most commonly reported Grade 3 event was anaphylactic reaction, reported in 4 patients (2.8%); the event was assessed as not related to study drug by the Investigator in all 4 patients. Anaphylactic reaction is a common clinical manifestation of ISM. All other Grade 3 AEs were reported in 1 or 2 patients. Most Grade 3 AEs were assessed as not related by the Investigator. The only related Grade 3 AEs were blood alkaline phosphatase increased, disturbance in attention, and neutrophil count decreased, all reported in 1 patient (0.7%) each.

In the Placebo Group, the most commonly reported Grade 3 event was anaphylactic reaction in 3 patients (4.2%) and was assessed as not related to study drug in all cases. All other Grade 3 AEs were reported in 1 or 2 patients each. Most of the Grade 3 AEs were assessed as not related to study drug by the Investigator. The only related Grade 3 AEs were headache, diarrhea, and anxiety, all reported in 1 patient (1.4%) each.

Overall Avapritinib Population

Of the 226 patients in the 25 mg Avapritinib Group, 86 patients (38.1%) experienced Grade ≥3 AEs. Grade ≥3 anaphylactic reaction AEs were reported in 12 patients (5.3%), in all cases they were assessed as not related to study drug by the Investigator. Grade ≥3 hypertension AEs were reported in 10 patients (4.4%). The types and incidences of AEs by severity grade in the All Avapritinib Group were similar to those in the All 25 mg Avapritinib Group and no trends or concerns were identified.

In the All 25 mg Avapritinib Group, most of the patients experienced Grade 1 or Grade 2 AEs (Table 69). An increase of ≥ 10% compared with the original submission was noted for Grade ≥3 AEs (25.7% vs 38.1%), however the incidence of related Grade ≥3 AEs remained similar to what was reported in the original submission (2.7% vs 4.9%). One new related SAE and one not related death were reported in the update period.

Table 69. Grade ⩾3 Adverse Events Occurring in More than One Patient by Preferred Term (Part 1/2/3 [Avapritinib Treated] Safety Population)

	23 June 2022 Data Cutoff Date		**07 April 2023 Data Cutoff Date**	
Preferred Term	**All 25 mg Avapritinib N = 226 n (%)**	**All Avapritinib N = 246 n (%)**	**All 25 mg Avapritinib N = 226 n (%)**	**All Avapritinib N = 246 n (%)**
Patients with at least one grade 3 or higher AE	58 (25.7)	72 (29.3)	86 (38.1)	102 (41.5)
Anaphylactic reaction	9 (4.0)	14 (5.7)	12 (5.3)	18 (7.3)
Hypertension	5 (2.2)	5 (2.0)	10 (4.4)	10 (4.1)
Diarrhoea	2 (0.9)	4 (1.6)	5 (2.2)	7 (2.8)
Hypersensitivity	1 (0.4)	3 (1.2)	5 (2.2)	7 (2.8)
Arthralgia	1 (0.4)	4 (1.6)	3 (1.3)	6 (2.4)
Abdominal pain	3 (1.3)	3 (1.2)	4 (1.8)	4 (1.6)
Headache	0	2 (0.8)	2 (0.9)	4 (1.6)
Neutrophil count decreased	2 (0.9)	2 (0.8)	4 (1.8)	4 (1.6)
Dizziness	2 (0.9)	2 (0.8)	3 (1.3)	3 (1.2)
Mast cell activation syndrome	2 (0.9)	2 (0.8)	3 (1.3)	3 (1.2)
Mastocytosis	2 (0.9)	2 (0.8)	3 (1.3)	3 (1.2)
Migraine	2 (0.9)	2 (0.8)	3 (1.3)	3 (1.2)
Syncope	3 (1.3)	3 (1.2)	3 (1.3)	3 (1.2)
Weight increased	0	0	3 (1.3)	3 (1.2)
Anaphylactic shock	1 (0.4)	2 (0.8)	1 (0.4)	2 (0.8)

	23 June 2022 Data Cutoff Date		07 April 2023 Data Cutoff Date	
Preferred Term	**All 25 mg Avapritinib N = 226 n (%)**	**All Avapritinib N = 246 n (%)**	**All 25 mg Avapritinib N = 226 n (%)**	**All Avapritinib N = 246 n (%)**
Back pain	1 (0.4)	2 (0.8)	1 (0.4)	2 (0.8)
Bone pain	1 (0.4)	1 (0.4)	1 (0.4)	2 (0.8)
COVID-19	0	1 (0.4)	1 (0.4)	2 (0.8)
COVID-19 pneumonia	2 (0.9)	2 (0.8)	2 (0.9)	2 (0.8)
Disturbance in attention	1 (0.4)	2 (0.8)	1 (0.4)	2 (0.8)
Electrocardiogram QT prolonged	1 (0.4)	1 (0.4)	2 (0.9)	2 (0.8)
Fall	0	1 (0.4)	0	2 (0.8)
Flushing	2 (0.9)	2 (0.8)	2 (0.9)	2 (0.8)
Gastroenteritis	1 (0.4)	1 (0.4)	2 (0.9)	2 (0.8)
Gastrointestinal disorder	1 (0.4)	2 (0.8)	1 (0.4)	2 (0.8)
Hypokalaemia	1 (0.4)	1 (0.4)	2 (0.9)	2 (0.8)
Mastocytic leukaemia	1 (0.4)	1 (0.4)	2 (0.9)	2 (0.8)
Nephrolithiasis	1 (0.4)	1 (0.4)	2 (0.9)	2 (0.8)
Pancreatitis acute	1 (0.4)	1 (0.4)	2 (0.9)	2 (0.8)
Pruritus	2 (0.9)	2 (0.8)	2 (0.9)	2 (0.8)
Rash maculo-papular	2 (0.9)	2 (0.8)	2 (0.9)	2 (0.8)
Tooth abscess	1 (0.4)	2 (0.8)	1 (0.4)	2 (0.8)
Tooth infection	1 (0.4)	1 (0.4)	1 (0.4)	2 (0.8)

Abbreviations: AE = adverse event; COVID-19 = Coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities.

a This group includes the patients who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the patients who received 50 mg or 100 mg avapritinib in Part 1.

Notes: AEs are coded using MedDRA version 25.0. All AEs are Treatment Emergent AEs. A patient is counted only once for multiple events within the same preferred term.

Adverse Events by Relationship to Study Drug

Part 2 of study BLU 285 2203

In Part 2, the incidence of AEs assessed as related to study drug by the Investigator was higher in the 25 mg Avapritinib Group (54.6%) than in the Placebo Group (45.1%).

Table 70. Related Adverse Events in ≥ 2% of Patients in Either Treatment Group by Preferred Term (Part 2 Safety Population)

Preferred Term	**25 mg Avapritinib N = 141 n (%)**	**Placebo N = 71 n (%)**
Patients with any AEs	77 (54.6)	32 (45.1)
Headache	11 (7.8)	7 (9.9)
Nausea	9 (6.4)	6 (8.5)
Oedema peripheral	9 (6.4)	1 (1.4)
Periorbital oedema	9 (6.4)	2 (2.8)
Fatigue	6 (4.3)	2 (2.8)
Flushing	6 (4.3)	0
Alopecia	5 (3.5)	3 (4.2)
Blood alkaline phosphatase increased	5 (3.5)	0
Contusion	5 (3.5)	0
Eyelid oedema	5 (3.5)	1 (1.4)
Face oedema	5 (3.5)	0

Preferred Term	25 mg Avapritinib N = 141 n (%)	Placebo N = 71 n (%)
Aspartate aminotransferase increased	4 (2.8)	1 (1.4)
Diarrhoea	4 (2.8)	2 (2.8)
Dizziness	4 (2.8)	5 (7.0)
Hair colour changes	4 (2.8)	1 (1.4)
Photosensitivity reaction	4 (2.8)	0
Alanine aminotransferase increased	3 (2.1)	1 (1.4)
Blood lactate dehydrogenase increased	3 (2.1)	0
Dry mouth	3 (2.1)	1 (1.4)
Muscle spasms	3 (2.1)	0
Disturbance in attention	2 (1.4)	2 (2.8)
Weight increased	1 (0.7)	2 (2.8)
Eye pain	0	2 (2.8)
Paraesthesia	0	2 (2.8)
Vision blurred	0	2 (2.8)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities. Notes: AEs are coded using MedDRA version 25.0. All AEs are Treatment Emergent AEs. A patient is counted only once for multiple events within the same preferred term. Relationship to study drug is as per the Investigator assessment.

Overall Avapritinib Population

The most common study-drug related AEs (as assessed by the Investigator) reported in ≥ 5% of the 226 patients in the All 25 mg Avapritinib Group, were headache, oedema peripheral, nausea, and periorbital oedema (table 71).

Table 271. Related Adverse Events in ≥ 2% of Patients by Preferred Term (Part 1/2/3 [Avapritinib Treated] Safety Population)

	23 June 2022 Data Cutoff Date		07 April 2023 Data Cutoff Date	
Preferred Term	All 25 mg Avapritinib N = 226 n (%)	All Avapritinib N = 246 n (%)	All 25 mg Avapritinib N = 226 n (%)	All Avapritinib N = 246 n (%)
Patients with any AEs	130 (57.5)	147 (59.8)	151 (66.8)	168 (68.3)
Oedema peripheral	18 (8.0)	23 (9.3)	23 (10.2)	28 (11.4)
Nausea	17 (7.5)	28 (11.4)	17 (7.5)	27 (11.0)
Headache	18 (8.0)	24 (9.8)	20 (8.8)	25 (10.2)
Periorbital oedema	16 (7.1)	21 (8.5)	18 (8.0)	23 (9.3)
Face oedema	8 (3.5)	13 (5.3)	8 (3.5)	13 (5.3)
Fatigue	10 (4.4)	12 (4.9)	11 (4.9)	13 (5.3)
Diarrhoea	7 (3.1)	9 (3.7)	10 (4.4)	12 (4.9)
Dizziness	10 (4.4)	13 (5.3)	9 (4.0)	12 (4.9)
Alopecia	10 (4.4)	10 (4.1)	11 (4.9)	11 (4.5)
Hair colour changes	7 (3.1)	10 (4.1)	7 (3.1)	11 (4.5)
Blood alkaline phosphatase increased	7 (3.1)	8 (3.3)	8 (3.5)	9 (3.7)
Weight increased	5 (2.2)	5 (2.0)	9 (4.0)	9 (3.7)
Eyelid oedema	6 (2.7)	6 (2.4)	8 (3.5)	8 (3.3)
Aspartate aminotransferase increased	4 (1.8)	5 (2.0)	6 (2.7)	7 (2.8)
Blood creatinine increased	4 (1.8)	4 (1.6)	7 (3.1)	7 (2.8)
Contusion	7 (3.1)	7 (2.8)	7 (3.1)	7 (2.8)
Disturbance in attention	4 (1.8)	5 (2.0)	6 (2.7)	7 (2.8)
Flushing	7 (3.1)	7 (2.8)	7 (3.1)	7 (2.8)

	23 June 2022 Data Cutoff Date		07 April 2023 Data Cutoff Date	
Preferred Term	**All 25 mg Avapritinib N = 226 n (%)**	**All Avapritinib N = 246 n (%)**	**All 25 mg Avapritinib N = 226 n (%)**	**All Avapritinib N = 246 n (%)**
Alanine aminotransferase increased	3 (1.3)	4 (1.6)	5 (2.2)	6 (2.4)
Hypophosphataemia	1 (0.4)	1 (0.4)	4 (1.8)	6 (2.4)
Muscle spasms	4 (1.8)	5 (2.0)	5 (2.2)	6 (2.4)
Palpitations	5 (2.2)	6 (2.4)	5 (2.2)	6 (2.4)
Photosensitivity reaction	4 (1.8)	4 (1.6)	6 (2.7)	6 (2.4)
Decreased appetite	3 (1.3)	5 (2.0)	3 (1.3)	5 (2.0)
Hypertension	2 (0.9)	3 (1.2)	4 (1.8)	5 (2.0)
Lacrimation increased	3 (1.3)	3 (1.2)	4 (1.8)	5 (2.0)
Vomiting	1 (0.4)	3 (1.2)	3 (1.3)	5 (2.0)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.
a This group includes the patients who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the patients who received 50 mg or 100 mg avapritinib in Part 1.
Notes: AEs are coded using MedDRA version 25.0. All AEs are Treatment Emergent AEs. A patient is counted only once for multiple events within the same preferred term.
Relationship to study drug is as per the Investigator assessment.

Data for the overall Avapritinib Group (n= 246) were consistent.

Analysis of Adverse Events by Organ System or Syndrome

Part 2 of study BLU 285 2203

In the 25 mg Avapritinib Group, the SOC in which most patients experienced AEs was Nervous System Disorders (54 patients [38.3%]), followed by Gastrointestinal Disorders (52 patients [36.9%]). In the Placebo Group, these were also the most common SOCs (24 patients [33.8%] and 27 [38.0%], respectively). This likely reflects the burden of the underlying disease.

The SOC in which most patients experienced SAEs was Infections and Infestations (2 patients [1.4%]) in the 25 mg Avapritinib Group, and Infections and Infestations (3 patients [4.2%]) and Immune System Disorders (2 patients [2.8%]) in the Placebo Group. In other SOCs, only 1 patient each experienced an SAE. None of the SAEs were assessed as related to study drug by the Investigator.

The SOC in which patients had dose reductions were Gastrointestinal Disorders, General Disorders and Administration Site Conditions, and Nervous System Disorders in the 25 mg Avapritinib Group and Nervous System Disorders in the Placebo Group. All were reported in 1 patient each and the event in the Nervous System Disorders SOC (memory impairment) was assessed as related to study drug by the Investigator in both patients in the 25 mg Avapritinib Group and the Placebo Group.

The SOC in which most patients in the 25 mg Avapritinib Group had AEs leading to permanent study drug discontinuation was Nervous System Disorders (2 patients [1.4%]). The events were assessed as related to study drug by the Investigator in both patients. In other SOCs, AEs leading to study drug discontinuation were assessed as not related to study drug by the Investigator and were reported by 1 patient each. In the Placebo Group, 1 patient (1.4%) experienced AEs leading to discontinuation in 3 SOCs (Gastrointestinal Disorders, General Disorders and Administration Site Conditions, and Nervous System Disorders), that were all assessed as related to study drug by the Investigator.

Table 72. Adverse Events in ≥ 10% of Patients in Either Treatment Group by SOCs (Part 2 Safety Population)

System Organ Class	25 mg Avapritinib N = 141 n (%)	Placebo N = 71 n (%)
Patients with any AE	128 (90.8)	66 (93.0)
Nervous System Disorders	54 (38.3)	24 (33.8)
Gastrointestinal Disorders	52 (36.9)	27 (38.0)
General Disorders and Administration Site Conditions	51 (36.2)	15 (21.1)
Infections and Infestations	49 (34.8)	22 (31.0)
Skin and Subcutaneous Tissue Disorders	43 (30.5)	21 (29.6)
Investigations	33 (23.4)	14 (19.7)
Musculoskeletal and Connective Tissue Disorders	32 (22.7)	19 (26.8)
Eye Disorders	28 (19.9)	10 (14.1)
Vascular Disorders	28 (19.9)	9 (12.7)
Psychiatric Disorders	19 (13.5)	5 (7.0)
Respiratory, Thoracic, and Mediastinal Disorders	18 (12.8)	8 (11.3)
Metabolism and Nutrition Disorders	16 (11.3)	5 (7.0)
Injury, Poisoning, and Procedural Complications	14 (9.9)	10 (14.1)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class.
Note: AEs are coded using MedDRA version 25.0. All AEs are Treatment Emergent AEs. A patient is counted only once for multiple events within the same SOC.

The most common SOCs (in ≥ 10% of patients) with AEs that were assessed as related to study drug by the Investigator were the following:

In the 25 mg Avapritinib Group:

- Nervous System Disorders (23 patients [16.3%]); mainly headache (11 patients [7.8%]) and dizziness (4 patients [2.8%]), all others in 1 or 2 patients each.
- General Disorders and Administration Site Conditions (21 patients [14.9%]); mainly oedema peripheral (9 patients [6.4%]), fatigue (6 patients [4.3%]), and face oedema (5 patients [3.5%]), all others in 1 or 2 patients each. The majority of these events were Grade 1 and there were no SAEs.
- Eye Disorders (19 patients [13.5%]); mainly periorbital oedema (9 patients [6.4%] and eyelid oedema (5 patients [3.5%], all others in 1 or 2 patients each.
- Skin and Subcutaneous Tissue Disorders (19 patients [13.5%]); mainly alopecia (5 patients [3.5%]), hair colour change (4 patients [2.8%]), and photosensitivity reaction (4 patients [2.8%]), all others in 1 or 2 patients each.
- Gastrointestinal Disorders (18 patients [12.8%]); mainly nausea (9 patients [6.4%]), diarrhoea (4 patients [2.8%]), and dry mouth (3 patients [2.1%]), all others in 1 patient each.
- Investigations (16 patients [11.3%]); mainly blood alkaline phosphatase increased (5 patients [3.5%]), aspartate aminotransferase increased (4 patients [2.8%]), alanine aminotransferase increased (3 patients [2.1%]), and blood lactate dehydrogenase increased (3 patients [2.1%]), all others in 1 or 2 patients each. The majority of these events were Grade 1 or 2 and there were no SAEs.

In the Placebo Group:

- Nervous System Disorders (15 patients [21.1%]); mainly headache (7 patients [9.9%]), and dizziness (5 patients [7.0%]), all others in 1 or 2 patients each.
- Eye Disorders (9 patients [12.7%]); mainly periorbital oedema, eye pain, and vision blurred (2 patients [2.8%] each), all others in 1 patient each.

- Gastrointestinal Disorders (8 patients [11.3%]); mainly nausea (6 patients [8.5%]), all others in 1 or 2 patients each.
- Skin and Subcutaneous Tissue Disorders (8 patients [11.3%]); mainly alopecia (3 patients [4.2%]), all others in 1 patient each.

In the 25 mg Avapritinib Group, 3 patients (2.1%) experienced Grade 3 AEs assessed as related to study drug by the Investigator. These were in the SOCs Investigations (blood alkaline phosphatase increased and neutrophil count decrease) and Nervous System Disorders (disturbance in attention). In the Placebo Group, 2 patients (2.8%) experienced a total of 3 Grade 3 AEs assessed as related by the Investigator. These were in the SOCs Gastrointestinal Disorders (diarrhoea), Nervous System Disorders (headache), and Psychiatric Disorders (anxiety). All other AEs assessed as related to study drug by the Investigator were Grade 1 or 2.

Overall Avapritinib Population

In the All 25 mg Avapritinib Group, the SOC in which most patients experienced AEs was Infections and Infestations (155 patients [68.6%]), followed by Gastrointestinal Disorders (117 patients [51.8]). These were similar with the observations in the All Avapritinib Group. Overall, no clinically meaningful differences were observed as compared to Part 2 of the study.

Table 73. Adverse Events with ⩾ 5%Incidence Rate by SOCs (Part 1/2/3 [Avapritinib Treated] Safety Population, 07 April 2023)

System Organ Class/ Preferred Term	**All 25 mg Avapritinib N = 226 n (%)**		**All Avapritinib N = 246 n (%)**	
	All Grades	**Grade ≥3**	**All Grades**	**Grade ≥3**
Patients with at least one AE	223 (98.7)	86 (38.1)	242 (98.4)	102 (41.5)
Blood and lymphatic system disorders	35 (15.5)	9 (4.0)	40 (16.3)	9 (3.7)
Cardiac disorders	31 (13.7)	3 (1.3)	34 (13.8)	3 (1.2)
Palpitations	13 (5.8)	0	15 (6.1)	0
Congenital, familial and genetic disorders	5 (2.2)	1 (0.4)	5 (2.0)	1 (0.4)
Ear and labyrinth disorders	21 (9.3)	0	22 (8.9)	0
Endocrine disorders	6 (2.7)	0	8 (3.3)	0
Eye disorders	70 (31.0)	0	77 (31.3)	0
Periorbital oedema	21 (9.3)	0	26 (10.6)	0
Gastrointestinal disorders	117 (51.8)	18 (8.0)	132 (53.7)	20 (8.1)
Nausea	39 (17.3)	0	50 (20.3)	0
Diarrhoea	37 (16.4)	5 (2.2)	45 (18.3)	7 (2.8)
Abdominal pain	21 (9.3)	4 (1.8)	24 (9.8)	4 (1.6)
Vomiting	19 (8.4)	0	23 (9.3)	0
Constipation	16 (7.1)	0	19 (7.7)	0
Abdominal distension	15 (6.6)	1 (0.4)	16 (6.5)	1 (0.4)
General disorders and administration site conditions	102 (45.1)	6 (2.7)	114 (46.3)	7 (2.8)
Fatigue	32 (14.2)	0	37 (15.0)	1 (0.4)
Oedema peripheral	32 (14.2)	1 (0.4)	37 (15.0)	1 (0.4)
Face oedema	13 (5.8)	0	18 (7.3)	0
Peripheral swelling	12 (5.3)	0	14 (5.7)	0

System Organ Class/ Preferred Term	All 25 mg Avapritinib N = 226 n (%)		All Avapritinib N = 246 n (%)	
	All Grades	**Grade ≥3**	**All Grades**	**Grade ≥3**
Hepatobiliary disorders	11 (4.9)	0	12 (4.9)	0
Immune system disorders	25 (11.1)	16 (7.1)	32 (13.0)	23 (9.3)
Anaphylactic reaction	12 (5.3)	12 (5.3)	18 (7.3)	18 (7.3)
Hypersensitivity	13 (5.8)	5 (2.2)	17 (6.9)	7 (2.8)
Infections and infestations	155 (68.6)	14 (6.2)	170 (69.1)	18 (7.3)
COVID-19	92 (40.7)	1 (0.4)	99 (40.2)	2 (0.8)
Upper respiratory tract infection	19 (8.4)	0	23 (9.3)	0
Nasopharyngitis	20 (8.8)	0	21 (8.5)	0
Urinary tract infection	17 (7.5)	1 (0.4)	20 (8.1)	1 (0.4)
Sinusitis	16 (7.1)	0	17 (6.9)	0
Injury, poisoning and procedural complications	49 (21.7)	2 (0.9)	60 (24.4)	6 (2.4)
Fall	12 (5.3)	0	15 (6.1)	2 (0.8)
Contusion	12 (5.3)	0	12 (4.9)	0
Investigations	88 (38.9)	12 (5.3)	99 (40.2)	13 (5.3)
Blood alkaline phosphatase increased	23 (10.2)	1 (0.4)	26 (10.6)	1 (0.4)
Weight increased	19 (8.4)	3 (1.3)	22 (8.9)	3 (1.2)
Alanine aminotransferase increased	10 (4.4)	1 (0.4)	13 (5.3)	1 (0.4)
Blood creatinine increased	12 (5.3)	0	13 (5.3)	0
Metabolism and nutrition disorders	43 (19.0)	3 (1.3)	51 (20.7)	4 (1.6)
Musculoskeletal and connective tissue disorders	105 (46.5)	10 (4.4)	115 (46.7)	16 (6.5)
Arthralgia	29 (12.8)	3 (1.3)	34 (13.8)	6 (2.4)
Back pain	20 (8.8)	1 (0.4)	25 (10.2)	2 (0.8)
Pain in extremity	13 (5.8)	1 (0.4)	16 (6.5)	1 (0.4)
Bone pain	12 (5.3)	1 (0.4)	13 (5.3)	2 (0.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	17 (7.5)	3 (1.3)	20 (8.1)	3 (1.2)
Nervous system disorders	114 (50.4)	13 (5.8)	128 (52.0)	17 (6.9)
Headache	50 (22.1)	2 (0.9)	58 (23.6)	4 (1.6)
Dizziness	33 (14.6)	3 (1.3)	41 (16.7)	3 (1.2)
Disturbance in attention	13 (5.8)	1 (0.4)	15 (6.1)	2 (0.8)
Paraesthesia	9 (4.0)	0	13 (5.3)	0
Psychiatric disorders	47 (20.8)	1 (0.4)	55 (22.4)	3 (1.2)
Insomnia	22 (9.7)	0	24 (9.8)	0
Renal and urinary disorders	20 (8.8)	3 (1.3)	27 (11.0)	3 (1.2)
Reproductive system and breast disorders	23 (10.2)	0	24 (9.8)	0
Respiratory, thoracic and mediastinal disorders	45 (19.9)	1 (0.4)	50 (20.3)	1 (0.4)

System Organ Class/ Preferred Term	All 25 mg Avapritinib N = 226 n (%)		All Avapritinib N = 246 n (%)	
	All Grades	**Grade ≥3**	**All Grades**	**Grade ≥3**
Cough	15 (6.6)	0	15 (6.1)	0
Dyspnoea	10 (4.4)	0	14 (5.7)	0
Skin and subcutaneous tissue disorders	119 (52.7)	4 (1.8)	131 (53.3)	4 (1.6)
Pruritus	36 (15.9)	2 (0.9)	41 (16.7)	2 (0.8)
Rash	16 (7.1)	0	17 (6.9)	0
Alopecia	14 (6.2)	0	15 (6.1)	0
Hair colour changes	7 (3.1)	0	11 (4.5)	0
Social circumstances	3 (1.3)	0	3 (1.2)	0
Surgical and medical procedures	1 (0.4)	0	1 (0.4)	0
Vascular disorders	64 (28.3)	12 (5.3)	72 (29.3)	12 (4.9)
Flushing	24 (10.6)	10 (4.4)	26 (10.6)	10 (4.1)
Hypertension	23 (10.2)	2 (0.9)	25 (10.2)	2 (0.8)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable; SOC = system organ class.
Note: AEs are coded using MedDRA version 25.0. All AEs are treatment emergent AEs. A patient is counted only once for multiple events within the same SOC.
Note: NA denotes the patients who did not rollover to Part 3.
[a] This group includes the patients who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the patients who received 50 mg or 100 mg avapritinib in Part 1.

Serious adverse event/deaths/other significant events

Deaths

One fatal SAE of multiple organ dysfunction syndrome, assessed as not related by the Investigator, was reported in the update period. The event was assessed to be due to patient's anaphylaxis.

Serious Adverse Events

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Table 74. Serious Adverse Events by Preferred Term (Part 2 Safety Population)

Preferred Term	25 mg Avapritinib N = 141 n (%)	Placebo N = 71 n (%)
Patients with at least 1 SAE	7 (5.0)	8 (11.3)
Abdominal pain	1 (0.7)	0
Acute myeloid leukaemia	1 (0.7)	0
Anaphylactic reaction	1 (0.7)	1 (1.4)
Bacteraemia	1 (0.7)	0
COVID-19 pneumonia	1 (0.7)	1 (1.4)
Chest pain	1 (0.7)	0
Pelvic haematoma	1 (0.7)	0
Adenovirus infection	0	1 (1.4)
Allergy to vaccine	0	1 (1.4)
COVID-19	0	1 (1.4)
Foot deformity	0	1 (1.4)
Hypertension	0	1 (1.4)
Mastocytosis	0	1 (1.4)
Mental status changes	0	1 (1.4)
Tachycardia	0	1 (1.4)

Abbreviations: AE = adverse event; COVID-19 = Coronavirus Disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event. Notes: AEs are coded using MedDRA version 25.0. All AEs are Treatment Emergent AEs. A patient is counted only once for multiple events within the same preferred term.

Overall Avapritinib Population

The most commonly reported SAEs, anaphylactic reaction (1.8%) reported in 4 patients and mastocytosis (0.9%) reported in 3 patients, occur frequently in patients with ISM. All other events were reported in ≤2 patients each and no trends were observed (Table 75). One new SAE, Grade 3 oedema peripheral, assessed by the Investigator as related to study drug was reported in the update period (07 April 2023). The patient later resumed with reduced dose with no further worsening of the edema.

Table 75. Serious Adverse Events by Preferred Term (Part 1/2/3 [Avapritinib Treated] Safety Population)

	23 June 2022 Data Cutoff Date		07 April 2023 Data Cutoff Date	
Preferred Term	**All 25 mg Avapritinib N = 226 n (%)**	**All Avapritinib N = 246 n (%)**	**All 25 mg Avapritinib N = 226 n (%)**	**All Avapritinib N = 246 n (%)**
Patients with at least one serious AE	24 (10.6)	30 (12.2)	31 (13.7)	38 (15.4)
Anaphylactic reaction	1 (0.4)	2 (0.8)	4 (1.8)	5 (2.0)
Hypersensitivity	1 (0.4)	2 (0.8)	2 (0.9)	3 (1.2)
Mastocytosis	2 (0.9)	2 (0.8)	3 (1.3)	3 (1.2)
Abdominal pain	2 (0.9)	2 (0.8)	2 (0.9)	2 (0.8)
COVID-19 pneumonia	2 (0.9)	2 (0.8)	2 (0.9)	2 (0.8)
Gastrointestinal disorder	1 (0.4)	2 (0.8)	1 (0.4)	2 (0.8)
Headache	0	1 (0.4)	1 (0.4)	2 (0.8)
Mast cell activation syndrome	1 (0.4)	1 (0.4)	2 (0.9)	2 (0.8)
Nephrolithiasis	1 (0.4)	1 (0.4)	2 (0.9)	2 (0.8)
Pancreatitis acute	1 (0.4)	1 (0.4)	2 (0.9)	2 (0.8)

Abbreviations: AE = adverse event; COVID-19 = Coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities.
a This group includes the patients who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the patients who received 50 mg or 100 mg avapritinib in Part 1.
Notes: AEs are coded using MedDRA version 25.0. All AEs are Treatment Emergent AEs. A patient is counted only once for multiple events within the same preferred term.

Other Significant Adverse Events

Adverse Events of Special Interest

The AESIs include intracranial bleeding (ICB) and cognitive effects.

Intracranial bleeding

There were no ICB events reported in the study up to the latest cut-off date.

Cognitive Effects

Patients with ISM typically have a higher incidence of neurocognitive symptoms related to underlying disease (Gülen et al, 2016) compared to the general population.

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The incidence of cognitive effect AEs was slightly lower in the 25 mg Avapritinib Group (4 patients [2.8%]) than in the Placebo Group (3 patients [4.2%]). The most commonly reported event was memory impairment, in 2 patients (1.4%) in the 25 mg Avapritinib Group and 1 patient (1.4%) in the Placebo Group. Amnesia and mood altered occurred in 1 patient (0.7%) each in the 25 mg Avapritinib Group, and mental impairment and mental status changes occurred in 1 patient (1.4%)

each in the Placebo Group. Most of the AEs were Grade 1 in the 25 mg Avapritinib Group with only 1 patient experiencing a Grade 2 AE (memory impairment). In the Placebo Group, 1 patient experienced a Grade 3 event, which was reported as serious (mental status changes); all other events were reported as Grade 1 events. None of the events led to study drug discontinuation in either treatment group and 1 patient in each group experienced events leading to dose reduction (These data indicate that treatment with 25 mg avapritinib is not associated with an increased risk of cognitive effects in patients with ISM.

Table 76. Adverse Events of Cognitive Effect by Preferred Term (Part 2 Safety Population)

Preferred Term	25 mg Avapritinib N = 141 n (%)	Placebo N = 71 n (%)
Patients with at least 1 AE of cognitive effect	4 (2.8)	3 (4.2)
Memory impairment	2 (1.4)	1 (1.4)
Amnesia	1 (0.7)	0
Mood altered	1 (0.7)	0
Mental impairment	0	1 (1.4)
Mental status changes	0	1 (1.4)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities. Note: AEs are coded using MedDRA version 25.0. All AEs are Treatment Emergent AEs. A patient is counted only once for multiple events within the same preferred term/category.

Overall Avapritinib Population

In the All 25 mg Avapritinib Group, a total of 15 patients (6.6%) experienced cognitive effect AEs through the update period. These were assessed as related to study drug in 7 patients (3.1%). The most commonly reported event through the update period was memory impairment in 9 patients (4.0%) and cognitive disorders in 3 patients (1.3%) through the update period and all other events were reported in 1 patient each. In the All Avapritinib Group, other than the patients already reported in the All 25 mg Avapritinib Group, there were no additional patients who experienced cognitive effects during the update period.

Table 77. Adverse Events of Cognitive Effect by Preferred Term (Part 1/2/3 [Avapritinib Treated] Safety Population)

	23 June 2022 Data Cutoff Date		07 April 2023 Data Cutoff Date	
Preferred Term	All 25 mg Avapritinib N = 226 n (%)	All Avapritinib N = 246 n (%)	All 25 mg Avapritinib N = 226 n (%)	All Avapritinib N = 246 n (%)
Patients with at least 1 AE of cognitive effect	8 (3.5)	16 (6.5)	15 (6.6)	23 (9.3)
Memory impairment	5 (3.3)	7 (2.8)	9 (4.0)	10 (4.1)
Cognitive disorder	1 (0.7)	4 (1.6)	3 (1.3)	6 (2.4)
Agitation	1 (0.7)	2 (0.8)	1 (0.4)	2 (0.8)
Amnesia	1 (0.7)	2 (0.8)	1 (0.4)	2 (0.8)
Confusional state	0	2 (0.8)	0	2 (0.8)
Delirium	0	1 (0.4)	0	1 (0.4)
Disorientation	0	1 (0.4)	0	1 (0.4)
Mood altered	1 (0.7)	1 (0.4)	1 (0.4)	1 (0.4)
Psychotic disorder	0	0	1 (0.4)	1 (0.4)
Somnolence	0	1 (0.4)	0	1 (0.4)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.
a This group includes the patients who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the patients who received 50 mg or 100 mg avapritinib in Part 1.

Note: AEs are coded using MedDRA version 25.0. All AEs are Treatment Emergent AEs. A patient is counted only once for multiple events within the same preferred term/category.

Laboratory findings

Serum Chemistry

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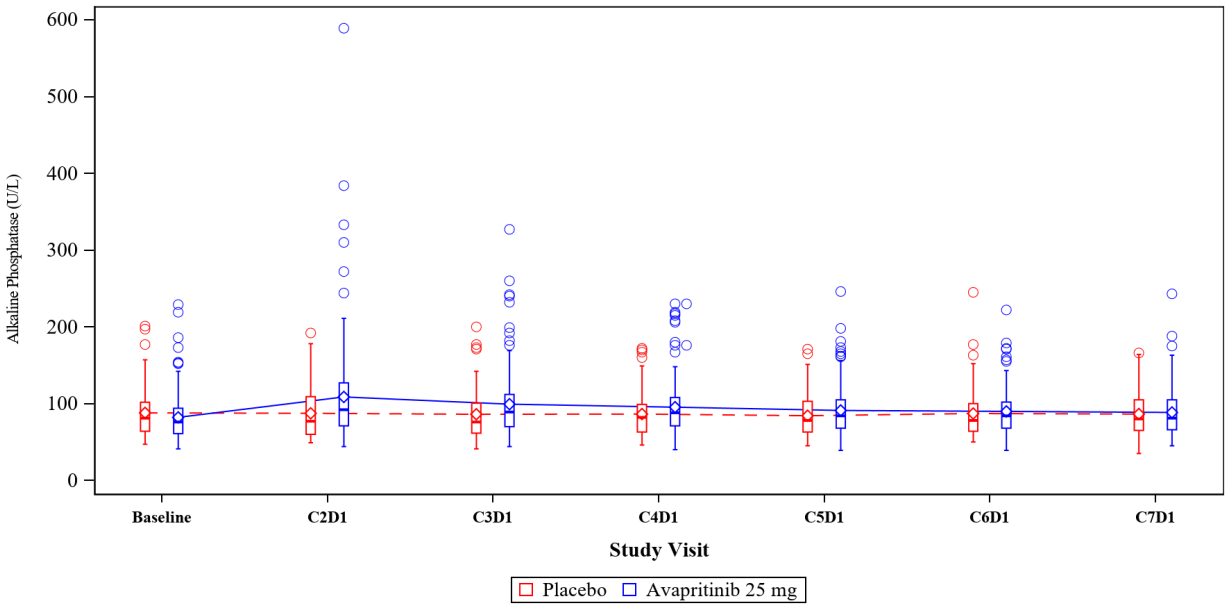
An initial and transient increase in ALP (mean within the normal ranges) was noted in the 25 mg Avapritinib Group. This was observed initially with its peak at C2D1 returning to baseline by C6D1. This transient increase in ALP was possibly due to lysis of mast cells infiltrating the bone and was not considered clinically meaningful.

Figure 48. Box Plot of Alkaline Phosphatase Laboratory Test (Part 2 Safety Population)



A summary of shifts reported in ≥ 5% patients in Part 2 is presented in Table 78.

Table 78. Patients with Shifts in Serum Chemistry Parameters (≥ 5% in Any Group) from Baseline to Worst on-Treatment Value CTCAE Grade (Part 2 Safety Population)

Serum Chemistry Parameters	25 mg Avapritinib N = 141 n/N (%)			Placebo N = 71 n/N (%)		
	Any Shift	Shift to Grade 2	Shift to Grade 3 or 4	Any Shift	Shift to Grade 2	Shift to Grade 3 or 4
Creatinine increase	29/141 (20.6)	0	0	9/71 (12.7)	0	0
ALP increase	29/141 (20.6)	2 (1.4)	0	6/71 (8.5)	0	0
AST increase	18/141 (12.8)	0	0	4/70 (5.7)	0	0
Direct bilirubin increase	17/126 (13.5)	4/126 (3.2)	0	3/63 (4.8)	0	0
ALT increase	13/141 (9.2)	0	1/141 (0.7)	7/71 (9.9)	0	0
Total bilirubin increase	12/141 (8.5)	3/141 (2.1)	1/141 (0.7)	2/71 (2.8)	1/71 (1.4)	0
Potassium increase	9/141 (6.4)	0	1/141 (0.7)	6/71 (8.5)	0	0

Serum Chemistry Parameters	25 mg Avapritinib N = 141 n/N (%)			Placebo N = 71 n/N (%)		
	Any Shift	Shift to Grade 2	Shift to Grade 3 or 4	Any Shift	Shift to Grade 2	Shift to Grade 3 or 4
Potassium decrease	14/141 (9.9)	0	2/141 (1.4)	4/71 (5.6)	0	0
Calcium decrease	12/141 (8.5)	1/141 (0.7)	0	5/69 (7.2)	0	0
Glucose decrease	7/141 (5.0)	0	0	0	0	0
Magnesium decrease	7/137 (5.1)	0	1/137 (0.7)	2/69 (2.9)	0	0

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Event. Note: Percentages are based on patients with baseline and at least one on-treatment CTCAE grade.

Overall Avapritinib Population

Shift analyses from baseline to highest, lowest, and worst value on treatment based on the NCI CTCAE were conducted for selected chemistry parameters. A summary of shifts reported in ≥ 5% patients in the Part 1/2/3 overall analyses is presented in Table 79.

Table 79. Patients with Shifts in Serum Chemistry Parameters (⩾ 5% in Any Group) from Baseline to Worst On-treatment Value CTCAE (Part 1/2/3 Safety Population 07 April 2023)

Serum Chemistry Parameters	All 25 mg Avapritinib N = 226 n/N (%)			All Avapritinib N = 246 n/N (%)		
	Any Shift	Shift to Grade 2	Shift to Grade 3 or 4	Any Shift	Shift to Grade 2	Shift to Grade 3 or 4
Creatinine increase	71/226 (31.0)	1/226 (0.4)	0	80/245 (32.7)	1/245 (0.4)	0
ALP increase	60/226 (26.2)	4/226 (1.8)	0	70/245 (28.6)	6/245 (2.0)	1/245 (0.4)
AST increase	50/226 (22.1)	1/226 (0.4)	0	59/245 (24.1)	2/245 (0.8)	1/245 (0.4)
Direct bilirubin increase	45/203 (22.2)	15/203 (7.4)	1/203 (0.5)	49/221 (22.2)	15/221 (6.8)	1/221 (0.5)
ALT increase	44/226 (19.5)	3/226 (1.3)	1/226 (0.4)	51/245 (20.8)	3/245 (1.2)	1/245 (0.4)
Total bilirubin increase	30/226 (13.3)	9/226 (4.0)	1/226 (0.4)	32/245 (13.1)	10/245 (4.1)	1/245 (0.4)
Potassium increase	21/226 (9.3)	2/226 (0.9)	1/226 (0.4)	23/245 (9.4)	2/245 (0.8)	1/245 (0.4)
Sodium increase	19/226 (8.4)	2/226 (0.9)	0	21/245 (8.6)	2/245 (0.8)	0
Calcium increase	18/226 (8.0)	0	0	20/245 (8.2)	0	0
Potassium decrease	39/226 (17.3)	0	3/225 (1.3)	44/245 (18.0)	0	3/245 (1.2)
Calcium decrease	33/226 (14.6)	2/226 (0.9)	2/226 (0.9)	38/245 (15.5)	2/245 (0.8)	2/245 (0.8)

Glucose decrease	29/226 (12.8)	4/226 (1.8)	0	33/245 (13.5)	4/245 (1.6)	0
Magnesium decrease	16/222 (7.2)	1/222 (0.5)	1/222 (0.5)	18/241 (7.5)	1/241 (0.4)	1/241 (0.4)
Sodium decrease	16/226 (7.1)	2/226 (0.9)	0	18/245 (7.3)	2/245 (0.8)	0

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Event.
a This group includes the patients who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the patients who received 50 mg or 100 mg avapritinib in Part 1.
b This column also includes patients from the 50 mg to 25 mg and 100 mg to 25 mg Avapritinib Groups.
Note: Percentages are based on patients with baseline and at least 1 on-treatment CTCAE grade.

Liver Function Tests

There were no patients that met the criteria for potential Hy's law defined as post-baseline total bilirubin elevation to ≥ 2x upper limit of normal (ULN) occurring on or within 30 days after a post-baseline ALT or AST elevation to ≥ 3x ULN and concurrent ALP is < 2x ULN.

A limited number of patients had bilirubin elevation ≥ 2x ULN. These were generally not associated with ALT/AST increase and ALP values were within normal ranges, which doesn't suggest a clinically meaningful cholestasis. All patients had confounding factors including Gilbert's syndrome, ongoing medical history of increase in bilirubin levels, cholelithiasis or dyslipidemia. Relevant AEs were reported in 3 patients, all assessed as not related to study drug, and resolved while receiving continued treatment with avapritinib.

Haematology

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Shift analyses from baseline to highest, lowest, and worst value on treatment based on the NCI CTCAE were conducted for hematology parameters. A summary of shifts reported in ≥ 5% patients is presented in Table 80.

Table 80. Patients with Shifts in Hematology Parameters from Baseline to Worst on-Treatment CTCAE Grade (Part 2 Safety Population)

Hematology Parameters	**25 mg Avapritinib N = 141 n/N (%)**			**Placebo N = 71 n/N (%)**		
	Any Shift	**Shift to Grade 2**	**Shift to Grade 3 or 4**	**Any Shift**	**Shift to Grade 2**	**Shift to Grade 3 or 4**
Hemoglobin decrease	21/141 (14.9)	2/141 (1.4)	0	9/71 (12.7)	1/71 (1.4%)	0
Leukocytes decrease	22/141 (15.6)	2/141 (1.4)	1/141 (0.7)	4/71 (5.6)	1/71 (1.4)	1/71 (1.4)
Lymphocytes decrease	6/140 (4.3)	2/140 (1.4)	0	3/71 (4.2)	0	0
Neutrophils decrease	11/141 (7.8)	3/141 (2.1)	2/141 (1.4)	7/71 (9.9)	3/71 (4.2)	0
Platelets decrease	5/141 (3.5)	0	0	2/71 (2.8)	0	0

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Event. Note: Percentages are based on patients with baseline and at least one on-treatment CTCAE grade.

Overall Avapritinib Population

Shift analyses from baseline to highest, lowest, and worst value on treatment based on the NCI CTCAE were conducted for hematology parameters. A summary of shifts from baseline reported in ≥ 5% patients in the Part 1/2/3 overall analyses through the update period is presented in Table 81.

Table 81. Patients with Shifts in Hematology Parameters from Baseline to Worst on-Treatment Value CTCAE Grade (Part 1/2/3 Safety Population)

Hematology Parameters	All 25 mg Avapritinib N = 226 n/N (%)			All Avapritinib N = 246 n/N (%)		
	Any Shift	Shift to Grade 2	Shift to Grade 3 or 4	Any Shift	Shift to Grade 2	Shift to Grade 3 or 4
Hemoglobin decrease	52/226 (23.0)	6/226 (2.7)	0	61/245 (24.9)	9/245 (3.7)	0
Leukocytes decrease	56/226 (24.8)	10/226 (4.4)	1/226 (0.4)	59/245 (24.1)	10/245 (4.1)	1/245 (0.4)
Lymphocytes decrease	31/226 (13.7)	12/226 (5.3)	3/226 (1.3)	34/245 (13.9)	14/245 (5.7)	3/245 (1.2)
Neutrophils decrease	43/226 (19.0)	16/226 (7.1)	5/226 (2.2)	46/245 (18.8)	4/245 (1.6)	5/245 (2.0)
Platelets decrease	14/226 (6.2)	0	0	16/245 (6.5)	0	0

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Event.
a This group includes the patients who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the patients who received 50 mg or 100 mg avapritinib in Part 1
b This column also includes patients from the 50 mg to 25 mg and 100 mg to 25 mg Avapritinib Groups.
Note: Percentages are based on patients with baseline and at least 1 on-treatment CTCAE grade.

Coagulation

Part 2 of study BLU 285 2203

AEs associated with coagulation were activated partial thromboplastin time prolonged and blood fibrinogen decreased in 1 (0.7%) patient each in the 25 mg Avapritinib Group; both AEs were nonserious. The AE of activated partial thromboplastin time prolonged was assessed as not related to avapritinib by the Investigator and the AE of blood fibrinogen decreased was assessed as related to avapritinib.

Overall Avapritinib Population

Apart from the AEs associated with coagulation reported in Part 2, a Grade 1 non-serious AE of activated partial thromboplastin time prolonged was reported in one patient in the All 25 mg Avapritinib Group. The event was assessed as related to study drug by the investigator. No additional AEs associated with coagulation were reported in the All Avapritinib Group.

With the most recent data cut-off, there were no clinically meaningful changes from baseline over time observed in coagulation parameters of activated partial thromboplastin time, fibrinogen, and prothrombin international normalized ratio, and prothrombin time across groups through the update period.

Vital sign measurements

Part 2 of study BLU 285 2203

There were few clinically significant abnormalities reported as AEs associated with vital signs parameters, and they were similar between the two treatment groups. In the 25 mg Avapritinib Group the following AEs were reported, hypertension in 6 (4.3%) patients, weight increased in 4 (2.8%) patients, and weight decreased, hypotension, and orthostatic hypotension in 1 (0.7%) patient each. In the Placebo Group, hypertension was reported in 5 (7.0%) patients, weight increased in 3 (4.2%) patients, and weight decreased in 1 (1.4%) patient. All AEs associated with vital signs parameters were nonserious for the patients in the 25 mg Avapritinib Group, and 1 patient reported an SAE of hypertension (unrelated) in the Placebo Group. The AEs of hypertension and weight increased in 1 patient each were assessed as related to avapritinib by the Investigator; and the AEs of weight increased in 2 patients and hypertension in 1 patient were assessed as related in the Placebo Group.

Overall Avapritinib Population (initial submission)

AEs associated with vital signs parameters were hypertension in 19 (8.4%) patients, weight increased in 11 (4.9%) patients, weight decreased in 4 (1.8%) patients, hypotension in 2 (0.9%) patients, and orthostatic hypotension, blood pressure increased, and prehypertension in 1 (0.4%) patient each in the All 25 mg Avapritinib Group. All AEs associated with vital signs parameters were nonserious in the All 25 mg Avapritinib Group. The AEs of weight increased in 5 patients, hypertension in 2 patients, and blood pressure increased, and weight decreased in 1 patient each were assessed as related to avapritinib by the Investigator.

Cardiovascular effects

Part 2 of study BLU 285 2203

One patient each in the 25 mg Avapritinib Group had QTcF > 480 msec and > 500 msec compared to no patients in the Placebo Group. Overall, 10 patients (7.1%) in the 25 mg Avapritinib Group and 5 patients (7.9%) in the Placebo Group had a QTcF increase of > 30 msec from baseline. An increased QTcF > 60 msec from baseline was reported in 3 (2.1%) patients in the 25 mg Avapritinib Group and none in the Placebo Group. It should be noted that a QTcF > 480 msec was an exclusion criterion for the study (as of Amendment 2). All patients with > 60 msec increase from baseline were female. QTcF was > 500 msec in 1 of the patients and was not associated with any relevant AEs. In the remaining 2 patients, QTcF didn't increase beyond 470 msec which is considered to be within the upper normal range in female patients and therefore considered not clinically meaningful.

AEs associated with ECG findings were electrocardiogram QT prolonged in 2 patients and electrocardiogram T wave inversion in 1 patient in the 25 mg Avapritinib Group; electrocardiogram QT prolonged in 1 patient in the Placebo Group. All AEs were nonserious. The AEs of electrocardiogram QT prolonged were of severity Grade 3 (unrelated) and Grade 1 (related), and electrocardiogram T wave inversion was Grade 1 (related), all reported in 1 patient each in the 25 mg Avapritinib Group. The AE of electrocardiogram QT prolonged was Grade 2, and not related to study drug by the Investigator.

A search of the AE dataset was performed using the PTs from the SMQ Torsade de pointes/QT Prolongation. The search revealed 3 patients (2.1%) in the 25 mg Avapritinib Group and 1 patient (1.4%) in the Placebo Group who experienced events within the SMQ. The reported events included electrocardiogram QT prolonged (2 patients in the 25 mg Avapritinib Group and 1 patient in the Placebo Group) and syncope (2 patients in the 25 mg Avapritinib Group). None of the events were serious. One patient with a medical history of intermittent dizziness experienced a Grade 3 syncope assessed as not related to study drug. The event was not associated with QT prolongation at the time of the occurrence. The patient continued treatment with no new episodes reported. Syncope, Grade 1 in severity, was not associated with QT prolongation in the other patient either. It is important to note that patients with ISM frequently suffer from mast cell mediator related symptoms that include syncope. Patients with QT prolongation reported as AEs are described above.

Overall Avapritinib Population (initial submission)

Overall, 2 patients in the All 25 mg Avapritinib Group had QTcF > 480 msec and 1 patient had > 500 msec (described in Part 2). In the All 25 mg Avapritinib Group, 24 patients (10.6%) had a QTcF increase of > 30 msec from baseline. An increased QTcF > 60 msec from baseline was reported in 6 patients (2.7%) in this group.

AEs associated with ECG findings were limited and included electrocardiogram QT prolonged in 4 patients, and electrocardiogram QRS complex prolonged and electrocardiogram T wave inversion in 1 patient each in the All 25 mg Avapritinib Group. Except for 1 AE of Grade 3, nonserious, electrocardiogram QT prolonged (unrelated), all other AEs were nonserious, Grade 1, and assessed as related to avapritinib by the Investigator.

The search using SMQ Torsade de pointes/QT Prolongation revealed 8 patients overall who experienced events in Part 1/2/3. In addition to the 6 patients described above in Part 2 results, 5 patients experienced events in the All Avapritinib Group. 3 of them occurred while on Part 3. Of these, 2 patients had received Placebo prior to 25 mg Avapritinib in Part 3: 1 experienced a Grade 1 loss of consciousness assessed as not related by the Investigator with no ECG abnormalities findings, the other patient experienced a Grade 1 QT prolonged event described above; one patient experienced a Grade 3 syncope assessed as not related by the Investigator and had no QT prolongation findings in the ECG results. None of the events were serious and all resolved with continued treatment. 2 out of 5 patients experienced events within the SMQ during Part 1: one patient experienced a Grade 3 syncope while receiving 25 mg avapritinib, which resolved with continued treatment, was assessed as not related to study drug by the Investigator and patient had QTcF within the normal ranges at the time of reported event; the remaining patient experienced a Grade 1 QT prolonged AE while receiving 100 mg avapritinib, assessed as not related to study drug by the Investigator. None of the events were serious.

ECOG Performance Status

Part 2 of study BLU 285 2203

Most patients (> 90%) had a baseline ECOG performance status of 0 or 1 in both treatment groups; and 10 (7.1%) patients in the 25 mg Avapritinib Group and 4 (5.6%) patients in the Placebo Group had a baseline ECOG performance status of 2. There were no shifts to ECOG performance status of 4 and only 1 shift to an ECOG performance status of 3 in the 25 mg Avapritinib Group during Part 2 of the study.

Overall Avapritinib Population (initial submission)

Overall, most patients (> 90%) had a baseline ECOG performance status of 0 or 1, 17 (7.5%) patients had 2 in the All 25 mg Avapritinib Group. Shifts to an ECOG performance status of 3 or higher were uncommon. Most patients maintained their baseline score, with some patients shifting to a score of 0 or 1.

Brain Imaging Assessment (initial submission)

Brain imaging was performed at screening and patients with baseline abnormalities indicative of risk for intracranial haemorrhage, or prior, recent, or current intracranial haemorrhage, were excluded from the study. One patient in the 25 mg Avapritinib Group had abnormal brain imaging findings at Part 1 C5D1, that was assessed as related to sinusitis.

Safety in special populations

Intrinsic and Extrinsic Factors

Subgroup analyses of AEs were performed for intrinsic factors of age (< 65 years, ≥ 65 years), sex (female, male), baseline ISM status (moderate, severe), baseline serum tryptase (< 20 ng/mL, ≥ 20 ng/mL), and

extrinsic factors of region (North America, Europe), number of baseline BSC therapies (< 4, ≥ 4), prior cytoreductive therapy (yes, no), and baseline opioid use (yes, no).

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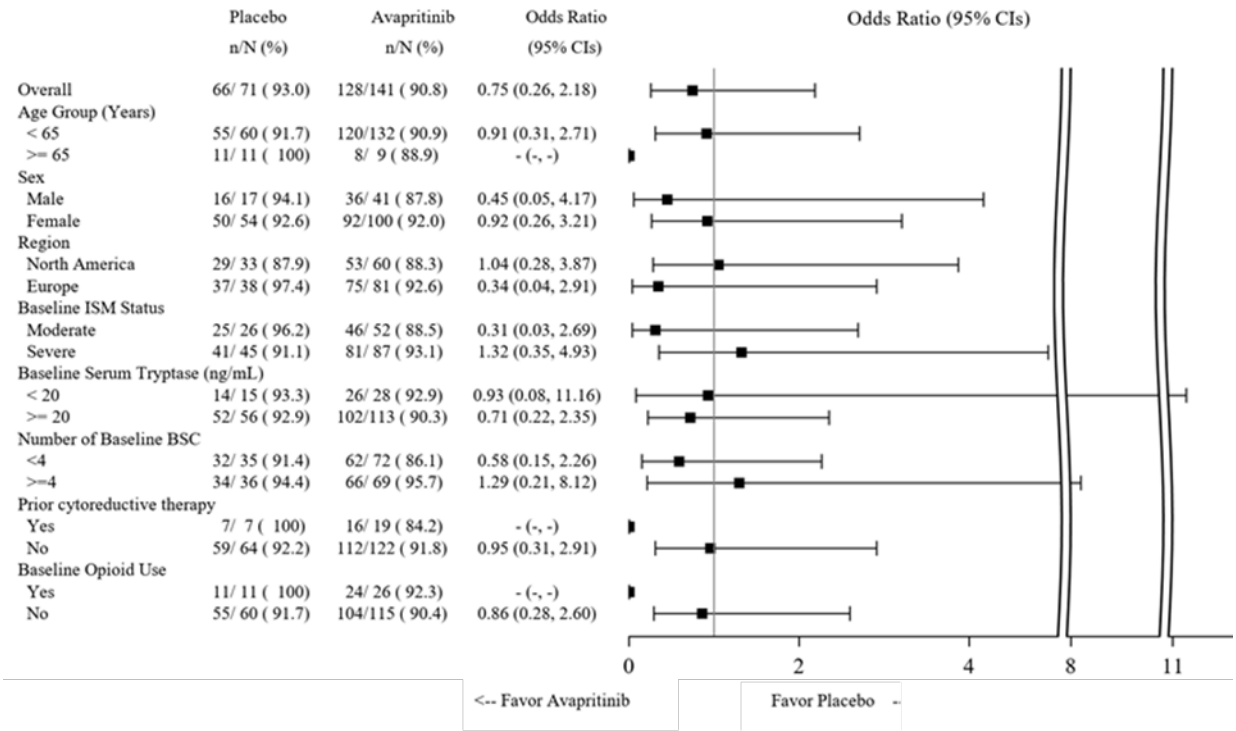
Treatment with avapritinib 25 mg was not associated with an increase in the probability of having an AE in the subgroups of age, sex, baseline serum tryptase, baseline cytoreductive therapy and baseline opioids, as compared with placebo (odds ratio < 1.0) (Figure 49). A higher probability of experiencing AEs occurred with avapritinib treatment for patients with severe baseline ISM status, number of baseline BSC ≥ 4, and in the North America region (odds ratio > 1); however, none of these comparisons were statistically significant. Because the odds ratio for the North America region only just exceeded 1 (odds ratio 1.04), and no relevant trends were seen compared with Europe, this analysis is not considered further.

The majority of the patients were female (76.9%), < 65 years of age (87.2%), White (92.3%), and not Hispanic and Latino (89.7%), therefore analyses of AEs by subgroups based on these factors are not informative. The main differences observed between 25 mg avapritinib and placebo in the subgroup analyses of baseline ISM status and number of baseline BSC therapies are summarized below.

Figure 49. Forest Plot of Adverse Events (Part 2 Safety Population)



Abbreviations: BSC = best supportive care; CI = confidence interval; ISM = indolent systemic mastocytosis; N = total number of subjects in the subgroup; n = number of subjects with events. Note: Odds ratio and p-value obtained using logistic regression with placebo as the reference category. – represents odds ratios and p-values that were not estimable due to quasi-complete separation. An odds ratio of > 1 indicates that treatment with avapritinib is favored.

Baseline ISM Status

Compared with placebo, an increase in the probability of having an AE with 25 mg avapritinib was observed in patients with severe ISM (odds ratio = 1.32). In patients with severe ISM, this difference in favor of placebo was accounted for mainly by higher incidences of AEs with 25 mg avapritinib in the SOCs of:

Nervous System Disorders (placebo 35.6%, 25 mg avapritinib 41.4%, not on account of any specific types of AEs)

Gastrointestinal Disorders (placebo 31.1%, 25 mg avapritinib 40.2%, mostly on account of diarrhoea and constipation)

Eye Disorders (placebo 15.6%, 25 mg avapritinib 24.1%, mostly on account of periorbital oedema and eyelid oedema)

Investigations (placebo 20.0%, 25 mg avapritinib 27.6%, mostly on account of liver transaminases)

Metabolism and Nutrition Disorders (placebo 6.7%, 25 mg avapritinib 17.2%, mostly on account of hypokalaemia, decreased appetite, iron deficiency, fluid retention, and hypophosphataemia)

Psychiatric Disorders (placebo 4.4%, 25 mg avapritinib 13.8%, mostly on account of anxiety and insomnia)

Conversely, in the following SOCs, higher incidences of AEs occurred with 25 mg avapritinib in patients with moderate ISM, but not in patients with severe ISM:

Infections and Infestations (placebo 15.4%, 25 mg avapritinib 34.6%, mostly on account of COVID-19, sinusitis, and upper respiratory tract infection)

Number of Baseline BSC Therapies

Compared with placebo, an increase in the probability of having an AE with 25 mg avapritinib was observed in patients with ≥ 4 BSC medications at baseline (odds ratio = 1.29). In patients with ≥ 4 BSC at baseline, this difference in favor of placebo was accounted for mainly by higher incidences of AEs with 25 mg avapritinib in the SOCs of:

Nervous System Disorders (placebo 33.3%, 25 mg avapritinib 43.5%, mostly on account of dizziness and disturbance in attention)

Skin and Subcutaneous Tissue Disorders (placebo 27.8%, 25 mg avapritinib 34.8%, mostly on account of pruritus)

Eye Disorders (placebo 16.7%, 25 mg avapritinib 24.6%, mostly on account of periorbital oedema, eyelid edema, and lacrimation increased)

Psychiatric Disorders (placebo 5.6%, 25 mg avapritinib 15.9%, mostly on account of anxiety and insomnia)

Reproductive System and Breast Disorders (placebo 0%, 25 mg avapritinib 7.2%, not on account of any specific types of AEs)

Conversely, in the following SOCs, higher incidences of AEs occurred with 25 mg avapritinib in patients with < 4 BSC at baseline, but not in patients with ≥ 4 BSC at baseline:

Investigations (placebo 20.0%, 25 mg avapritinib 25.0%, mostly on account of aspartate aminotransferase increased)

Metabolism and Nutrition Disorders (placebo 5.7%, 25 mg avapritinib 11.1%, not on account of any specific types of AEs)

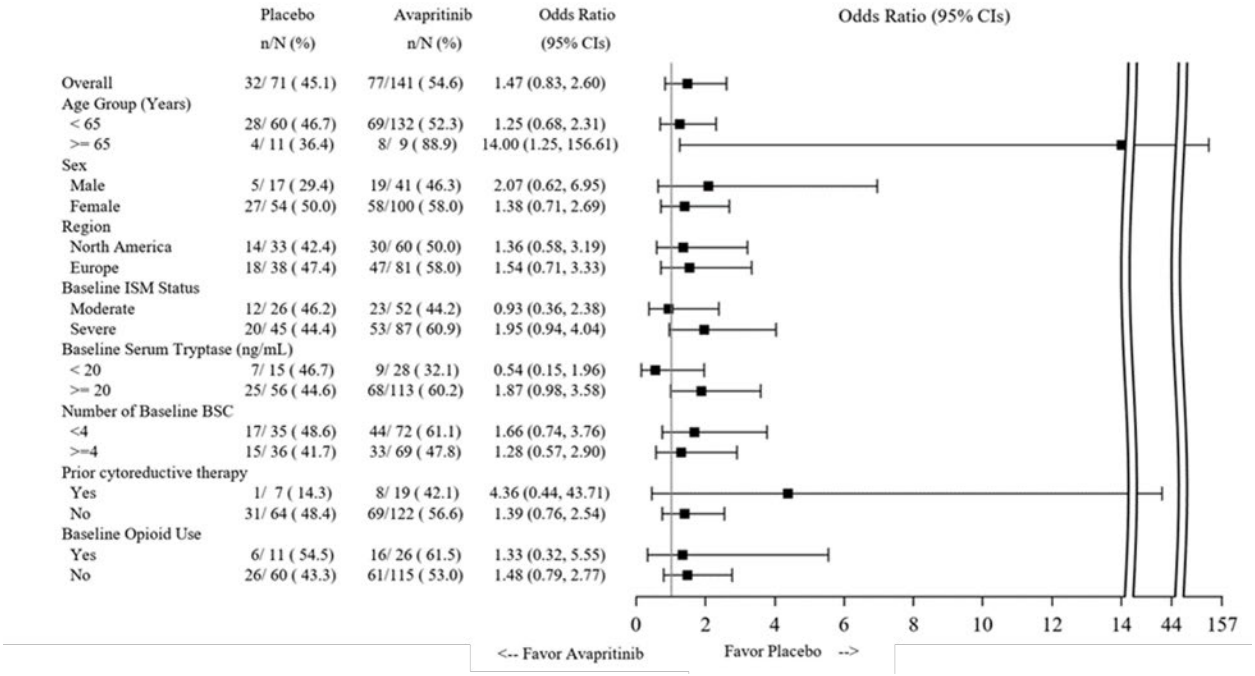
Renal and Urinary Disorders (placebo 0%, 25 mg avapritinib 5.6%, not on account of any specific types of AEs)

Related Adverse Events (Investigator Assessment)

Subgroup analyses of study drug-related AEs, as assessed by the Investigator generally indicated an increase in the probability of having a related AE with avapritinib 25 mg, compared with placebo, in all

subgroup categories, with the highest probability being for the age group ≥ 65 years old (Table 21); however the number of patients in this category is small and hence the analysis is not informative.

Figure 250. Forest Plot of Related Adverse Events (Part 2 Safety Population)



Abbreviations: AE = adverse event; BSC = best supportive care; CI = confidence interval; ISM = indolent systemic mastocytosis; N = total number of subjects in the subgroup; n = number of subjects with events. Notes: Odds ratio and p-value obtained using logistic regression with placebo as the reference category.
- represents odds ratios and p-values that were not estimable due to quasi-complete separation. An odds ratio of > 1 indicates that treatment with avapritinib is favored. Relationship of AE to treatment was defined as AE that is considered to be related to the study drug by the Investigator according to the predefined criteria.

Overall Avapritinib Population

The subgroup analyses for the overall population (Part 1/2/3) of Study BLU-285-2203 did not reveal any new concerns pertaining to any of the subgroup categories with longer exposure to 25 mg avapritinib beyond Part 2 of the study. Among the subgroups of baseline ISM status and number of baseline BSC medications used (as summarized for Part 2 in Section 5.1.1.1), none of the SOCs and PTs with a higher incidence in the 25 mg Avapritinib Group than in the Placebo Group in Part 2 showed any relevant change in incidence in the overall population.

Age

As part of the responses to CHMP's D120 LOQ, additional safety data in elderly patients was provided.

Part 2: The number of patients in the 65-74 years of age subgroup is limited (8 and 9 patients in the 25 mg Avapritinib Group and the Placebo Group respectively) and very few patients were in the 75-84 years of age subgroup (1 and 2 patients in the 25 mg Avapritinib Group and the Placebo Group respectively). There were no patients ≥85 years old (this column has been removed from the table 82).

Table 82. Summary of Selected Safety Data by Age Subgroups (Part 2, Safety Population, 23 June 2022)

	Avapritinib 25 mg N=141			**Placebo N=71**		
MedDRA Terms	**Age <65 N =132 n (%)**	**Age 65-74 N = 8 n (%)**	**Age 75-84 N =1 n (%)**	**Age <65 N = 60 n (%)**	**Age 65-74 N = 9 n (%)**	**Age 75-84 N =2 n (%)**
Total AEs	120 (90.9)	7 (87.5)	1 (100)	55 (91.7)	9 (100)	2 (100)
Serious AEs – Total	6 (4.5)	0	1 (100)	6 (10.0)	2 (22.2)	0
- Fatal	0	0	0	0	0	0
- Hospitalization New	6 (4.5)	0	0	3 (5.0)	2 (22.2)	0
- Prolonged existing hospitalization	1 (<1)	0	0	1 (1.7)	0	0
- Life-threatening	0	0	0	0	0	0
- Disability/incapacity	0	0	0	0	0	0
- Other (medically significant)	1 (<1)	0	1 (100)	1 (1.7)	0	0
AE leading to drop-out	2 (1.5)	0	1 (100)	1 (1.7)	0	0
Psychiatric disorders	18 (13.6)	1 (12.5)	0	4 (6.7)	1 (11.1)	0
Nervous system disorders	53 (40.2)	1 (12.5)	0	20 (33.3)	3 (33.3)	1 (50.0)
Accidents and injuries	10 (7.6)	0	1 (100)	4 (6.7)	0	0
Cardiac disorders	10 (7.6)	0	1 (100)	5 (8.3)	0	0
Vascular disorders	27 (20.5)	0	1 (100)	8 (13.3)	1 (11.1)	0
Cerebrovascular disorders	0	0	0	0	0	0
Infections and infestations	47 (35.6)	2 (25.0)	0	18 (30.0)	3 (33.3)	1 (50.0)
Anticholinergic syndrome	0	0	0	0	0	0
Quality of life decreased	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	21 (15.9)	0	0	7 (11.7)	2 (22.2)	0

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.

Overall Data (Part 1/2/3): there is a small number of patients in the 65-74 years of age subgroup (19 and 20 patients in the All 25 mg Avapritinib Group and All Avapritinib Group respectively) and very few patients were in the 75-84 years of age subgroup (4 patients in each, All 25 mg Avapritinib Group and All Avapritinib Group). There were no patients ≥85 years old (this column has been removed from the table 83).

Table 83. Summary of Selected Safety Data by Age Subgroups (Part 1/2/3, Safety Population, 07 April 2023)

	All 25 mg Avapritiniba N = 226 n (%)			All Avapritinib N = 246 n (%)		
MedDRA Terms	**Age <65 N = 203 n (%)**	**Age 65-74 N = 19 n (%)**	**Age 75-84 N = 4 n (%)**	**Age <65 N = 222 n (%)**	**Age 65-74 N = 20 n (%)**	**Age 75-84 N = 4 n (%)**
Total AEs	200 (98.5)	19 (100)	4 (100)	218 (98.2)	20 (100)	4 (100)
Serious AEs – Total	27 (13.3)	3 (15.8)	1 (25.0)	33 (14.9)	4 (20.0)	1 (25.0)
- Fatal	0	1 (5.3)	0	0	1 (5.0)	0
- Hospitalization New	26 (12.8)	2 (10.5)	0	32 (14.4)	3 (15.0)	0
- Prolonged existing hospitalization	1 (<1)	1 (5.3)	0	1 (<1)	1 (5.0)	0
- Life-threatening	1 (<1)	1 (5.3)	0	1 (<1)	1 (5.0)	0
- Disability/incapacity	0	1 (5.3)	0	0	1 (5.0)	0
- Other (medically significant)	1 (<1)	0	1 (25.0)	1 (<1)	0	1 (25.0)
AE leading to drop-out	10 (4.9)	1 (5.3)	1 (25.0)	11 (5.0)	1 (5.0)	1 (25.0)
Psychiatric disorders	43 (21.2)	3 (15.8)	1 (25.0)	50 (22.5)	4 (20.0)	1 (25.0)
Nervous system disorders	107 (52.7)	6 (31.6)	1 (25.0)	120 (54.1)	7 (35.0)	1 (25.0)
Accidents and injuries	21 (10.3)	3 (15.8)	1 (25.0)	25 (11.3)	3 (15.0)	1 (25.0)
Cardiac disorders	30 (14.8)	0	1 (25.0)	33 (14.9)	0	1 (25.0)
Vascular disorders	57 (28.1)	4 (21.1)	3 (75.0)	64 (28.8)	5 (25.0)	3 (75.0)
Cerebrovascular disorders	1 (<1)	0	0	2 (<1)	0	0
Infections and infestations	140 (69.0)	12 (63.2)	3 (75.0)	154 (69.4)	13 (65.0)	3 (75.0)
Anticholinergic syndrome	0	0	0	0	0	0
Quality of life decreased	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	52 (25.6)	3 (15.8)	2 (0.0)	62 (27.9)	4 (20.0)	2 (50.0)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.
a This group includes the patients who received placebo or 25 mg avapritinib in Part 1 or Part 2 and does not include the patients who received 50 mg or 100 mg avapritinib in Part 1.

MAH provided safety data broken down by age groups (e.g. < 65 years, ≥ 65 years) as part of the responses to CHMP's D120 LOQ.

The majority of the patients were < 65 years of age, 203/226 and 222/246 in the All 25 mg Avapritinib Group and All Avapritinib Group respectively.

The proportion of patients ≥ 65 years old experiencing any AE in the All 25 MG Avapritinib Group was very similar to that of patients < 65 years old (98.5% and 100% respectively).

Compared with patients < 65 years old, in the All 25 mg Avapritinib Group, a higher incidence of events in the following SOCs was observed in patients ≥ 65 years of age. These were similar in the All Avapritinib Group.

- Eye Disorders [29.6% (60/203 patients) and 43.5% (10/23 patients)], driven by periorbital edema which is a known event to occur with avapritinib and was frequently reported in patients < 65 years of age as well;

- Skin and subcutaneous tissue disorders [51.7% (105/203 patients) and 60.9% (14/23 patients)], driven by pruritus, which was reported frequently in patients < 65 years of age as well.

Compared with patients < 65 years old, a higher incidence of the following events was observed in patients ≥ 65 years of age in the All 25 mg Avapritinib Group: oedema peripheral (12.3% and 30.4%), face oedema (4.4% and 17.4%), nausea (16.3% and 26.1%), arthralgia (11.8% and 21.7%) and cough (5.4% and 17.4%), however these were not considered clinically meaningful. No additional observations were noted in the All Avapritinib Group.

Overall, the number of SAEs was limited in patients ≥ 65 years and no trends were observed. Similarly, no trends were observed regarding Grade ≥3 AEs and cognitive AEs in patients ≥ 65 years old compared to patients < 65 years old.

Overall, the data does not suggest that elderlies are at higher risk for developing AEs, SAEs, Grade ≥ 3 AEs or cognitive AEs when compared to younger population, however the number of patients in this category is significantly smaller.

Exposure-Response Analysis

The exposure-response analysis of the safety endpoints from Study BLU-285-2203, in which the time to event for AEs of interest and avapritinib C_{ave} categorized by quartiles was evaluated, revealed no clear relationships between avapritinib exposure and the very low incidences of all Grade ≥ 3 AEs, Grade ≥ 1 cognitive effect AEs, and Grade ≥ 1 weight gain. There was evidence for an association between avapritinib exposure and oedema AEs. In the 25 mg group, most of the oedema AEs were Grade 1 or 2 in severity (majority Grade 1) and none were Grade ≥ 3. None of the oedema AEs were reported as serious or led to discontinuation of avapritinib.

Safety related to drug-drug interactions and other interactions

Drug Interactions

Information in this section was submitted previously and is available in Module 2.7.4, Section 5.3, Original Application (GIST) and in Module 2.7.4, Section 5.3 for the AdvSM indication.

Use in Pregnancy and Lactation

There are no data in pregnant women exposed to avapritinib, the secretion of avapritinib in human milk or its effects on the breastfed infant, or on milk production to assess the risks. Further discussion was submitted previously and is available in Module 2.7.4, Section 5.4, AdvSM indication.

Overdose

No cases of overdose have been reported. The highest dose of avapritinib studied clinically is 600 mg PO Overdose includes any dose higher than the intended dose as per the protocol. There is limited experience with cases of overdose reported in humans. There were 7 cases of overdose (due to additional 25 mg doses administered) reported in 5 patients treated with avapritinib 25 mg QD, none of them were associated with

AEs (CSR BLU-285-2203, Listing 16.2.5.1). It should be noted that higher doses of avapritinib (200 mg and 300 mg) are approved and the safety profile at these doses is well known.

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

Drug Abuse

There have been no reports of patient abuse of or dependence on avapritinib. Because avapritinib is not pharmacologically or structurally related to drugs known to have abuse potential, drug abuse with avapritinib is unlikely.

Withdrawal and Rebound

No formal studies of withdrawal or rebound effects associated with avapritinib treatment have been conducted. There have been no AEs of "drug withdrawal syndrome" (MedDRA PT) reported to date.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No formal studies on the effects of avapritinib on the ability to drive or operate machinery have been performed.

Supportive Data

Clinical Pharmacology Studies in Healthy Subjects

In addition to earlier clinical studies, the clinical pharmacology of avapritinib was further characterized in the Phase 2 (BLU-285-2203) efficacy and safety study in patients with ISM (Module 2.7.2), and in the Phase 1 study (BLU-285-0107) investigating the effect of severe HI on the PK of avapritinib. Study BLU-285-0107 demonstrated that severe HI was associated with a 20% increase in AUC0-∞ and a 20% decrease in Cmax for total plasma avapritinib, together with a 61% increase in AUC0-∞ and an 8% increase in Cmax for unbound plasma avapritinib. Further details are available in CSR BLU 285-0107.

Compassionate Use Program

One patient with ISM has been treated in the avapritinib compassionate use program. As of the data cutoff date (23 June 2022), this patient was still ongoing, and no SAEs had been reported.

Expanded Access Program

No patients with ISM were treated with avapritinib as part of the Expanded Access Program as of the data cutoff date of 23 June 2022.

Discontinuation due to adverse events

- Adverse Events Leading to Study Drug Discontinuation

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Three (3) patients (2.1%) in the 25 mg Avapritinib Group experienced AEs leading to study drug discontinuation, including palpitation, non-cardiac chest pain, acute myeloid leukaemia, disturbance in attention (related), dizziness (related), dyskinesia (related), dyspnoea, and hypertension. In the Placebo Group, 1 patient (1.4%) experienced AEs leading to discontinuation (diarrhoea, general physical health deterioration, and headache, all related). In the 25 mg Avapritinib Group, 1 AE of Grade 4 acute myeloid leukaemia (unrelated) leading to study drug discontinuation in 1 patient was reported as serious.

Overall Avapritinib Population (original submission)

Of the 226 patients in the All 25 mg Avapritinib Group, 7 patients (3.1%) experienced AEs leading to study drug discontinuation during 25 mg avapritinib treatment. Dyspnoea was reported in 2 patients (0.9%), all others were reported in 1 patient each (acute myeloid leukaemia, disturbance in attention [related], dizziness [related], dyskinesia [related], hypertension, mastocytotic leukaemia, migraine [related], non-cardiac chest pain, pain in extremity [related], palpitations, peripheral swelling, and weight decreased [related]). Of these, 2 AEs that were assessed as not related to study drug by the Investigator, Grade 4 acute myeloid leukaemia and Grade 3 mastocytotic leukaemia in 1 patient each, were reported as serious in the All 25 mg Avapritinib Group. No new concerns were observed from the patients in the All Avapritinib Group regarding the AEs that led to discontinuation. In this group, there was 1 additional patient, who experienced a Grade 2 delirium (related) that led to discontinuation while on 50 mg avapritinib during Part 1 of the study.

- Adverse Events Leading to Dose Modification

Dose-modification guidelines for toxicities assessed as related to avapritinib by the Investigator were followed as per BLU-285-2203, Protocol, and included a change in dosing regimen from QD to QOD in patients who received 25 mg and reduction to a lower dose for patients who received 50 mg and 100 mg.

Part 2 of study BLU 285 2203

Low proportion of patients experienced **AEs leading to dose reduction** in both treatment groups. These included 2 patients (1.4%) in the 25 mg Avapritinib Group (1 patient with diarrhoea [unrelated], nausea [unrelated], face oedema [unrelated] and 1 patient with memory impairment [related]), and 1 patient in the Placebo Group (memory impairment; related). Out of these, 1 patient each rolled over to Part 3 at QOD (avapritinib-treated patient) and QD (placebo treated patient) regimens. The remaining patient in the 25 mg Avapritinib Group, later withdrew consent and did not roll over to Part 3. None of the events leading to dose reduction were serious.

AEs leading to dose interruptions occurred in 12 patients (8.5%; related in 5 patients [3.5%]) in the 25 mg Avapritinib Group compared to 9 patients (12.7%; related in 4 patients [5.6%]) in the Placebo Group.
In the 25 mg Avapritinib Group, dizziness (all related) was the only AE leading to dose interruption in 2 patients (1.4%), and all other AEs were reported in 1 patient each. In the Placebo Group, 3 patients (4.2%) reported headache [2 related], 2 patients (2.8%) reported vision blurred [1 related], and all other AEs leading to dose interruption were reported in 1 patient each. In the 25 mg Avapritinib Group, 2 patients had SAEs leading to dose interruption (Grade 3 COVID-19 pneumonia in 1 patient and Grade 2 pelvic haematoma in 1 patient; both unrelated) and in the Placebo Group, 2 patients had SAEs leading to dose interruptions (COVID-19 pneumonia in 1 patient and COVID-19 in 1 patient; both Grade 3 unrelated).

Overall Avapritinib Population (original submission)

Of the 226 patients in the All 25 mg Avapritinib Group, 7 patients (3.1%) experienced **AEs leading to dose reduction** (neutropenia [related], diarrhoea [unrelated], nausea [unrelated], face oedema [related], non-cardiac chest pain [related], liver function test increased [unrelated], neutrophil count decreased [related], and pain in extremity [related]) reported in 1 patient each. None of these events were serious. No new concerns were observed in the All Avapritinib Group regarding AEs leading to dose reduction. There were 4 additional patients who experienced AEs leading to dose reduction, and all occurred while being on a higher dose of avapritinib in Part 1, including 1 SAE of Grade 3 gastrointestinal disorder that was assessed as related to study drug in a patient who received 50 mg avapritinib.

Of the 226 patients in the All 25 mg Avapritinib Group, 26 patients (11.5%) experienced **AEs leading to dose interruption** during 25 mg avapritinib treatment; of whom 13 patients (5.8%) had AEs assessed as related to study drug by the Investigator. Dizziness was reported in 3 patients (1.3%; all related), headache (all related), nausea (1 related), COVID-19 (all unrelated), COVID 19 pneumonia (all unrelated), migraine

(all related), neutrophil count decreased (1 related), and non-cardiac chest pain (1 related) were reported in 2 patients (0.9%) each, all others were reported in 1 patient each. Additional to the events reported above, 3 AEs (Grade 3 pancreatitis, Grade 3 nephrolithiasis, and Grade 3 COVID 19 pneumonia in 1 patient each; all unrelated) leading to dose interruption in 1 patient each were reported as serious in the All 25 mg Avapritinib Group. No new concerns were observed in the All Avapritinib Group regarding the AEs that led to dose interruption. There were 3 additional patients with SAEs leading to dose interruption (delirium in Part 1 in a patient with 50 mg avapritinib, fall in Part 1 in a patient with 100 mg avapritinib, and arthralgia in Part 3 in a patient who had rolled over from 100 mg avapritinib).

Post marketing experience

Avapritinib has not been yet approved in any country or region for the treatment of patients with ISM; therefore, no postmarketing data are available regarding the use of avapritinib in patients with ISM.

Since the initial marketing authorization of avapritinib for GIST and the extension to include AdvSM, postmarketing reported events are consistent with the known safety profile of avapritinib in these indications; no new risks have been identified. Cumulatively, since the International Birth Date until 08 July 2022 (Data Lock Point of the avapritinib PBRER 4), the overall estimated post-marketing exposure to avapritinib is 1223 patient-years, and this exposure is aligned with the higher doses of avapritinib given for GIST and AdvSM, 300 mg and 200 mg daily, respectively.

Late breaking safety data

After the data cutoff date (23 June 2022 for Study BLU-285-2203) through the late breaking data cutoff date (within 30 days after the last dose of avapritinib) (23 August 2022), one SAE of hypersensitivity, assessed as unrelated by the Investigator, was received. No deaths or related SAEs, as assessed by the Investigator, have been reported since the data cutoff date through the late breaking data cutoff date.

Adverse drug reaction as reported in the SmPC

Indolent systemic mastocytosis

System Organ Class / frequency category	Adverse reactions	Avapritinib (25 mg once daily) + Best Supportive Care All grades%	Grades ≥3 %
Psychiatric disorders			
Common	Insomnia	5.7	-
Vascular disorders			
Common	Flushing	9.2	1.4
Skin and subcutaneous tissue disorders			
Common	Photosensitivity reaction	2.8	-
General disorders and administration site conditions			
Very common	Peripheral oedema[1]	12.1	-
Common	Face oedema	7.1	-
Investigations			
Common	Blood alkaline phosphatase increased	6.4	0.7

[1]Peripheral oedema (including oedema peripheral and peripheral swelling)
-: no adverse reactions reported

No intracranial haemorrhages were reported in 141 patients with ISM receiving 25 mg of avapritinib during the 24-week duration of Part 2 of the PIONEER study.

2.5.1. Discussion on clinical safety

The MAH has provided safety data from a single, phase II, 3-part study in patients with ISM (study BLU-285-2203). Safety data have been presented separately for the 24-week, placebo-controlled part of the study (Part 2) and the overall study population. For the present assessment, the subset of ISM patients included in Part 2 (n=141) is the most relevant patient subset to characterise safety in the intended target population, as it provides short-term comparative safety, while the rest of patient subsets are mainly supportive.

At the time of the most recent data cut-off (07/04/2023), parts 1 and 2 of study BLU-285-2203 had been completed, while part 3 was still ongoing (planned overall study follow-up: up to 5 years). Safety data from the avapritinib 25mg Safety Population, which include 226 patients treated with avapritinib 25mg across Part 1/2/3 of study BLU-285-2203, is the key subset for long-term data.

Patient exposure

In Part 2 of study BLU-285-2203, which consisted of a 24-week, double-blind period, the median (SD) treatment duration was limited (5.46 months (0.726) for patients in 25 mg Avapritinib Group and 5.43 months (0.806) for patients in the Placebo Group). Longer exposure was reported for the Overall Avapritinib Population, where the median (range) treatment duration was 25.0 (12, 25) months in the All 25 mg Avapritinib Group, with 76.5% patients received ≥ 6 months of avapritinib treatment and 31.4% patients received > 12 months of avapritinib treatment.

In general, treatment discontinuations were low in part 2 of the study, and similar in number in both treatment groups (5 patients each). At the time of the data cut-off, 14 additional patients had discontinued treatment in part 3 of the study (main reason AE). Likewise, the number of ISM patients who had dose modifications was also low in part 2 and the overall safety population. Overall, avapritinib 25 mg QD appears to be reasonably tolerated, and toxicities seem manageable with dose modifications.

Regarding the population included, although some small differences are observed between both treatment groups on part 2 (e.g., higher % of patients in the placebo group are 65 or older, have higher baseline serum tryptase median levels, higher KIT D816V mutation burden), overall it appears to be representative of the intended target population.

Regarding the avapritinib 25mg Safety Population, as of the most recent data cut-off (07/04/2023), treatment exposure also increased, had a median duration of 18.00 months (range: 0.7-46.1) for the avapritinib 25mg treatment group, 211 patients were still ongoing in part 3 of the study and 24 had discontinued. The most frequent reasons for study discontinuation were withdrawal of consent and AE (n=7, each). These 2 reasons account for 2/3 of all discontinuations, although the number of discontinuations is low, which is reassuring.

Adverse events

Common AEs

In part 2, the most commonly reported AEs across both groups (≥ 10%) were headache, nausea, COVID-19, dizziness, and diarrhoea. The frequency of G≥3 AEs (overall and related) was similar in both groups.

Incidence of AEs and SAEs increased over time with the increased treatment duration, as seen in the overall avapritinib population (25mg and all-doses avapritinib populations).

No deaths were reported in part 2 of the study.
In the placebo-controlled part of the study, SAEs were more frequently reported in the placebo group than in the avapritinib group (11.3% vs. 5.0%, respectively). No SAEs related to treatment were reported on either group in this part of the study.

Related AEs were reported by 77 (54.6%) and 32 (45.1%) avapritinib and placebo patients respectively, in the placebo-controlled part of the study. Frequency increased slightly with the increased treatment duration, which is not unexpected, and could also be affected by the open-label nature of part 3.

Regarding AE Severity in part 2, similar % of patients in the avapritinib and placebo groups experienced Grade ≥3 AEs . Proportion of patients with Grade ≥3 AEs increased slightly with treatment exposure. The most common Grade ≥3 AEs reported during any part of the study was anaphylactic reaction, which is also seen in ISM. Due to its potential severity and outcomes, the SmPC has been amended to adequately reflect this.

The proportion of patients with any AEs leading to dose modifications or permanent treatment discontinuations were generally low across the different parts of the study. In the placebo-controlled part, 3 (2.1%) in avapritinib 25mg group and 1 (1.4%) in placebo group permanently discontinued treatment due to AEs, while 12 and 9 patients required dose interruptions and 2 and 1 patients required dose adjustments. In the overall avapritinib population the discontinuations and dose modifications remained low. These findings suggest an acceptable tolerability, manageable by dose adjustments.

Regarding the avapritinib 25mg Safety Population (data cut-off date 07/04/2023), overall, no concerning/worrisome differences in the type of AEs, their incidence, seriousness or severity emerged with treatment over a longer period of time. An increase of ≥ 10% compared with the original data was noted for Grade ≥3 AEs, however the incidence of related Grade ≥3 AEs remained low. One new related SAE and one not related death were reported in the update period.
One single death was reported in the study up to the most recent cut-off date. It occurred in part 3 of the study, in the context of a SAE of multiple organ dysfunction syndrome, and it was assessed as not related by the Investigator.

Intracranial bleeding and cognitive effects are important identified risk for avapritinib in GIST and AdvSM and have been included as important potential risks for ISM. No intracranial bleeding AEs were reported in study BLU-285-2203 up to the most recent cut-off date. (see SmPC section 4.4). Regarding cognitive effects in the All 25 mg avapritinib Group, a total of 15 patients (6.6%) experienced cognitive effect AEs. These were assessed as related to study drug in 7 patients (3.1%). The most commonly reported event was memory impairment in 9 patients (4.0%) and cognitive disorders in 3 patients (1.3%) and all other events were reported in 1 patient each. In Part 2 of the PIONEER study, cognitive effects occurred in 2.8% of patients with ISM who received 25 mg of avapritinib (see section 4.4); all cognitive effects were Grade 1 or 2. Overall, none of the patients who received avapritinib in Part 2 of PIONEER required permanent treatment discontinuation for cognitive effects. Overall, cognitive effects were reported at lower frequencies than those previously reported for GIST and AdvSM indications, the reasons for these differences are not entirely clear since the mechanism of occurrence is not well-known and CNS involvement isn't unusual in SM. However, the non-severe (G<3) nature of most of the events is reassuring.

Although oedema AEs were not predefined as AESIs, these AEs were reported in the previous GIST and AdvSM submissions and "fluid retention (pleural effusion)" was defined as identified risks.
The MAH provided data on these AEs separately for the part 2 population and the overall avapritinib population. Oedema AEs were frequent in the placebo-controlled part of the study and the overall avapritinib population. Most of these AEs were considered related by the investigators and were mostly grade <3 in intensity. In addition, longer treatment exposure did not appear to increase their occurrence. Localised (peripheral, facial) oedemas in patients with ISM, have been included in the PI with a frequency category of at least common (see SmPC sections 4.4 and 4.8).

In patients with ISM, QT interval assessments by ECG should be considered, in particular in patients with concurrent factors that could prolong QT (e.g. age, pre-existing heart rhythm disorders, etc.)- see SmPC section 4.4.

The number of and elderly patients (≥65 years old) included in the study is rather small (9 patients in part 2, and 23 patients treated with avapritinib 25mg in all 3 parts of the study), while no patients over the age of 85 were included. SAEs, in the 25mg avapritinib groups, AEs leading to drop-out, accident/injuries AEs and vascular disorders occurred slightly more frequently in patients age ≥ 65 than those <65 years of age. Overall, no meaningful differences in safety were observed between patients ≥65 years and those <65 years.

The small size of the safety database in patients with ISM (226 patients treated with avapritinib 25mg QD; 246 patients treated with any dose) is a limitation in this assessment, however prior knowledge on the safety of avapritinib in the GIST and AdvSM indications sufficiently alleviate this concern. The recommended dose of avapritinib is 25 mg once daily (QD), with the possibility to perform dose adjustment based on tolerability. This selected dose for patients with ISM, Avapritinib 25mg QD, is almost ten times lower than that for AdvSM, and more than ten times lower than the GIST dose appears to have an acceptable tolerability, manageable by dose modifications. Further, annual updates from study BLU-285-2203 and submission of the final CSR will provide additional data in this context.

2.5.2. Conclusions on clinical safety

Avapritinib 25mg was well tolerated based on the low frequency of AEs leading to dose interruptions/reductions. The recommendations for dose adjustments appear to mitigate these toxicities over time. Overall, the safety profile appears consistent to that known in previous indications, no new safety concerns have been identified. Safety data have been reflected in the product information.

The following measures are considered necessary to address issues related to efficacy:

- The MAH will provide updated safety results of the study BLU-285-2203 annually until completion of the study. The final CSR should also be submitted when available following recommendation from the CHMP.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version 4.0 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.4 is acceptable.

The CHMP endorsed the Risk Management Plan version 4.4 with the following content:

Safety concerns

Summary of Safety Concerns	
Important identified risks	Intracranial haemorrhage (GIST and AdvSM) Cognitive effects (GIST and AdvSM) Drug-drug interactions with moderate or strong CYP3A inhibitors or inducers (all indications)

Important potential risks	Intracranial haemorrhage (ISM) Cognitive effects (ISM) Cardiac toxicity, including QT prolongation (all indications) Embryofoetal toxicity (all indications)
Missing information	Use in patients with severe hepatic impairment (all indications) Drug-drug interactions with CYP3A substrates (all indications)

Abbreviations: AdvSM = advanced systemic mastocytosis; GIST = gastrointestinal stromal tumour; ISM = indolent systemic mastocytosis.

Pharmacovigilance plan

No amendment to the current pharmacovigilance plan is proposed, which is accepted.

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 2 – imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Study BLU-285-1406 "Observational study evaluating the long-term safety and efficacy of avapritinib in the first-line treatment of patients with platelet-derived growth factor alpha D842V mutated gastrointestinal stromal tumour" Ongoing	The overall objective is to collect long-term safety and efficacy data for avapritinib in first-line patients with PDGFRA D842V-mutated GIST. Primary objective: – To describe types, severity, and rates of adverse events, serious adverse events, adverse events leading to discontinuation or decreased dosing of avapritinib, adverse events of special interest, and deaths. Secondary objective: – To evaluate efficacy in terms of disease response to treatment, progression-free survival, and overall survival, as well as duration of treatment and duration of response.	– Intracranial haemorrhage – Cognitive effects – Drug-drug interactions with moderate or strong CYP3A inhibitors or inducers – Cardiac toxicity, including QT prolongation – Embryofoetal toxicity – Use in patients with severe hepatic impairment – Drug-drug interactions with CYP3A substrates	– Annual progress reports	– Annually starting from August 2022 until August 2025
			– Interim report	– February 2025
			– Final clinical study report	– Q1 2027

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 – required additional pharmacovigilance activities				
Study BLU-285-1107 "Clinical drug-drug interaction study of avapritinib with a CYP3A substrate" Ongoing	– To investigate net effect of CYP3A inhibition and induction by avapritinib on midazolam pharmacokinetics in patients	– Drug-drug interactions with CYP3A substrates	– Study completion	– December 2024
			– Final clinical study report	– May 2025

Abbreviations: CYP3A = cytochrome P450 isozyme 3A; GIST = gastrointestinal stromal tumour; PDGFRA = platelet-derived growth factor receptor alpha; Q = quarter.

Risk minimisation measures

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Intracranial haemorrhage (GIST and AdvSM)	Routine risk minimisation measures: – SmPC sections 4.2, 4.4 and 4.8 – PL sections 2 and 4 SmPC section 4.2 contains recommendation on dose interruptions, permanent discontinuation, and platelet support. SmPC section 4.4 provides guidance on MRI/CT, platelet count monitoring, and recommendation on permanent drug discontinuation. PL section 2 gives recommendation on treatment interruption. PL section 4 provides guidance on MRI/CT. Restricted prescription medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting: – Follow-up questionnaire Additional pharmacovigilance activities: – Study BLU-285-1406 (final study report: Q1 2027)
Cognitive effects (GIST and AdvSM)	Routine risk minimisation measures: – SmPC sections 4.2, 4.4, 4.7 and 4.8 – PL sections 2 and 4 SmPC section 4.2 contains recommendations on dose modifications and permanent discontinuation of therapy. Restricted prescription medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting: – Follow-up questionnaire Additional pharmacovigilance activities: – Study BLU-285-1406 (final study report: Q1 2027)
Drug-drug interactions with moderate or strong	Routine risk minimisation measures:	Additional pharmacovigilance activities:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
CYP3A inhibitors or inducers (all indications)	– SmPC sections 4.2, 4.4, 4.5, and 5.2 – PL section 2 SmPC section 4.2 contains recommendation on concomitant use of avapritinib with moderate or strong CYP3A inhibitors. Restricted prescription medicine Additional risk minimisation measures: None	– Study BLU-285-1406 (final study report Q1 2027)
Intracranial haemorrhage (ISM)	Routine risk minimisation measures: – SmPC sections 4.2, 4.4 and 4.8 – PL section 2 SmPC section 4.4 provides guidance on MRI/CT and permanent drug discontinuation. PL section 2 gives recommendation on treatment interruption. Restricted prescription medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting: – Follow-up questionnaire Additional pharmacovigilance activities: None
Cognitive effects (ISM)	Routine risk minimisation measures: – SmPC sections 4.2, 4.4, 4.7 and 4.8 – PL section 2 Restricted prescription medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting: – Follow-up questionnaire Additional pharmacovigilance activities: None
Cardiac toxicity, including QT prolongation (all indications)	Routine risk minimisation measures: – SmPC sections 4.4, 4.8 and 5.1 – PL sections 2 and 4 SmPC section 4.4 includes recommendation for interval assessment of QT interval. Restricted prescription medicine Additional risk minimisation measures: None	Additional pharmacovigilance activities: – Study BLU-285-1406 (final study report: Q1 2027)
Embryofoetal toxicity (all indications)	Routine risk minimisation measures: – SmPC sections 4.6 and 5.3 – PL section 2 SmPC section 4.6 and PL section 2 includes recommendation on the use of effective contraception during therapy. Restricted prescription medicine Additional risk minimisation measures: None	Additional pharmacovigilance activities: – Study BLU-285-1406 (final study report Q1 2027)
Use in patients with severe hepatic	Routine risk minimisation measures: – SmPC sections 4.2 and 5.2	Additional pharmacovigilance activities:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
impairment (all indications)	– PL section 3 SmPC section 4.2 includes dosing recommendations in patients with severe hepatic impairment. Restricted prescription medicine Additional risk minimisation measures: None	– Study BLU-285-1406 (final study report Q1 2027)
Drug-drug interaction with CYP3A substrates (all indications)	Routine risk minimisation measures: – SmPC sections 4.5 and 5.2 – PL section 2 Restricted prescription medicine Additional risk minimisation measures: None	Additional pharmacovigilance activities: – Study BLU-285-1406 (final study report: Q1 2027) – Study BLU-285-1107 (final study report: May 2025)

Abbreviations: AdvSM = advanced systemic mastocytosis; CT = computed tomography; CYP3A = cytochrome P450 isozyme 3A; GIST = gastrointestinal stromal tumour; ISM = indolent systemic mastocytosis; MRI = magnetic resonance imaging; PL = package leaflet; Q = quarter; QD = once daily; SmPC = summary of product characteristics

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1, 5.2 and 5.3of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Please refer to Attachment 1, which includes all agreed changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The Package Leaflet changes included in this Type II variation are not significant for its readability, as there are no new critical safety issues and no new key messages for the safe use of Ayvakyt. In addition, the MAH noted that the format, design, layout and writing style of the Package Leaflet remain the same as in the Package Leaflets that went through consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The approved indication is:

AYVAKYT is indicated for the treatment of adult patients with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment (see section 5.1).

3.1.2. Available therapies and unmet medical need

There are currently no approved treatments for patients with ISM to reduce their disease burden, treat the underlying driver of ISM, or which impact the ISM disease course.

Therapies currently recommended for ISM are considered palliative, administered with the intent of only improving symptoms.

3.1.3. Main clinical studies

This application is based on the results from the ongoing 3-part, randomized, double-blind, placebo-controlled phase-2 Study BLU-285-2203 (PIONEER) in patients with ISM with moderate or severe symptoms that failed to achieve control under symptomatic therapies.

The study was conducted in 3 parts:

- In **Part 1**, the optimal dose of avapritinib (RP2D) was identified in patients with ISM.
- In **Part 2**, patients with ISM were randomly assigned in 2:1 ratio to the avapritinib RP2D (25 mg QD) identified in Part 1 in combination with BSC, or to placebo in combination with BSC.
- In **Part 3**, patients who complete treatment in Part 1 or Part 2 of the study can participate in a long-term extension, receiving avapritinib at the RP2D in combination with BSC.

The main efficacy data come from Part 2 of the study in which 212 patients were enrolled (141 in the avapritinib arm and 71 in the placebo arm). Overall, 235 patients (34 patients from Part 1 and 201 patients from Part 2) rolled over to Part 3 from Part 1 and Part 2 of the study.

The primary endpoint in Part 2 of the study was defined as the mean change from baseline to cycle 7 day 1 (C7D1; week 24) in the total symptom score (TSS) using the Indolent Systemic Mastocytosis-Symptom Assessment Form (ISM-SAF) compared to placebo.

The results of Part 2 are based on a data cut-off date of 23 June 2022. Updated efficacy and safety data from Part 3 were provided during the procedure with a data cut-off date of 7 April 2023. At the time of this last DCO, Part 3 was ongoing.

3.2. Favourable effects

Primary endpoint

At C7D1, the LS mean (SE) change from baseline in the ISM-SAF TSS was –15.58 (1.536) points for the 25 mg avapritinib group and –9.15 (2.013) for the placebo group. The difference (95% CI) between the groups was –6.43 (–10.90, –1.96) points. This difference was statistically significant (1-sided p-value = 0.003).

Key secondary endpoints

The results of the key secondary endpoints at C7D1 supported the primary efficacy analysis.

- 24.8% (95% CI: 17.9, 32.8) of patients in the avapritinib group vs 9.9% (95% CI: 4.1, 19.3) of patients in the placebo group achieved ≥ 50% reduction in the ISM-SAF TSS. The odds ratio (OR) was 3.10 (95% CI: 1.24, 8.64); 1-sided p-value = 0.005.
- 45.4% (95% CI: 37.0, 54.0) of patients in the Avapritinib group vs 29.6% (95% CI: 19.3, 41.6) of patients in the placebo group achieved ≥ 30% reduction in the ISM-SAF TSS. The OR was 2.07 (95% CI: 1.08, 3.99); 1-sided p-value = 0.009.

- 53.9% (95% CI: 45.3, 62.3) of patients in the avapritinib group vs 0.0% (95% CI: 0.0, 5.1) of patients in the placebo group achieved ≥50% reduction in serum tryptase. The OR was not evaluable (95% CI: 30.59, not evaluable); 1-sided p-value < 0.0001.
- 67.8% (95% CI: 58.6, 76.1) of patients in the avapritinib group vs 6.3% (95% CI: 1.8, 15.5) of patients in the placebo group achieved either ≥50% reduction in KIT D816V MAF or became undetectable (< 0.02%). The OR was 39.34 (95% CI: 10.93, 140.56); 1-sided p-value < 0.0001.
- 52.8% (95% CI: 42.9, 62.6) of patients in the avapritinib group vs 22.8% (95% CI: 12.7, 35.8) of patients in the placebo group achieved either ≥ 50% reduction in bone marrow mast cells or no mast cell aggregates. The OR 4.74 (95% CI: 2.06, 11.45); 1-sided p-value < 0.0001.

3.3. Uncertainties and limitations about favourable effects

While a period of 24 weeks for the double-blinded placebo comparison can be accepted, the interpretation of long-term efficacy data, which are considered of particular relevance in this indolent scenario, is hampered by the absence of a control arm in Part 3 of the study. The MAH will provide updated efficacy results of the study BLU-285-2203 annually until completion of the study. The final CSR will be submitted when available.

3.4. Unfavourable effects

Placebo-controlled part of study BLU 285 2203 (Part 2)

Overall, 128 patients (90.8%) in the 25 mg Avapritinib Group and 66 patients (93.0%) in the Placebo Group experienced at least 1 AE. Of them, 77 patients (54.6%) in the 25 mg Avapritinib Group and 32 patients (45.1%) in the Placebo Group experienced related AEs. Grade ≥ 3 AEs were reported in 21.3% and 21.1% patients, respectively. Related Grade ≥ 3 AEs were reported in 3 patients (2.1%) in the 25 mg Avapritinib Group and 2 patients (2.8%) in the Placebo Group.

The most common AEs in ISM patients (≥ 10% of patients) on either group were headache (19.1% avapritinib vs. 19.7% placebo), nausea (12.8% vs. 16.9%), COVID-19 (12.1% vs. 11.3%), dizziness (11.3% vs. 8.5%), and diarrhea (10.6% vs. 11.3%).

SAEs were reported in 5.0% and 11.3% patients in the 25 mg Avapritinib Group compared to the Placebo Group, respectively. No SAEs were assessed as related to study drug by the Investigator in either group.

There were **no deaths** in Part 2 of the study.

AEs led to interruption of study treatment in 8.5% and 12.7% of patients in the 25 mg Avapritinib Group and Placebo Group, respectively; Related AEs leading to treatment interruptions occurred in 3.5% of patients in the 25 mg Avapritinib Group and 5.6% of patients in the Placebo Group.

AEs led to dose reduction in 2 patients (1.4%) in the 25 mg Avapritinib Group (related in 1 patient [0.7%]) and 1 patient (1.4%) in the Placebo Group (related). AEs led to **permanent study treatment discontinuation** in 3 patients (2.1%) in the 25 mg Avapritinib Group (related in 2 patients [1.4%]) and 1 patient (1.4%) in the Placebo Group (related).

By **SOC,** in the avapritinib 25mg group, nervous system disorders were the most commonly reported (38.3%), followed by GI disorders (36.9%), general disorders and administration site conditions (36.2%), infections and infestations (34.8%) and skin/subcutaneous tissue disorders (30.5%). In the placebo group, GI disorders were the most commonly reported (38.0%), followed by nervous system disorders (33.8%), and infections and infestations (31.0%).

Cognitive effects and intracranial bleedings were considered AESI in the study. Cognitive effects were reported by 2.8% and 4.2%, in avapritinib 25mg and placebo groups, respectively, a majority of the cases were considered treatment related.

No intracranial bleedings AESIs were reported.

Overall avapritinib 25 mg population (data cut-off date 07 April 2023)

Of the 226 patients in the All 25 mg Avapritinib Group, 223 (98.7%) patients experienced AEs and 151 (66.8%) patients experienced AEs that were assessed as related to study drug by the Investigator. A total of 86 (38.1%) patients experienced Grade ≥ 3 AEs. Among these patients, AEs were assessed as related to study drug by the Investigator in 11 (4.9%) patients. The most common AEs in ISM patients treated with 25 mg QD (≥ 10% of patients) were COVID-19 (22.1%) headache (18.1%), nausea (13.7%), dizziness (13.7%), diarrhoea (11.5%), oedema peripheral (11.1%), fatigue and pruritus (10.6%, each).

A total of 31 (13.7%) patients had **SAEs** and 1 patient (0.4%) experienced an SAE that was assessed as related to the study drug by the Investigator. One single deaths was reported during part 3 of the study, in the context of a multiple organ dysfunction syndrome (SAE, non-related).

AEs led to interruption of study treatment in 38 (16.8) of patients (assessed as related in 18 (8.0%) patients). Overall, 13 (5.8%) patients experienced **AEs leading to dose reduction** (related in 11 (4.9%)) and 12 (5.3%) of patients had **AEs leading to permanent treatment discontinuation** (related in 6 (2.7%)).

By **SOC**, infections and infestations were the most commonly reported disorders (n=170, 69.1%), followed by GI disorders (n=132; 53.7%).

Of the 226 patients, 15 (6 .6%) experienced **cognitive effects** (most common: memory impairment, 9 [4%]). No **intracranial bleedings AESIs** were reported up to the most recent cut-off date.

3.5. Uncertainties and limitations about unfavourable effects

The main limitations for the characterization of the safety profile of avapritinib in the ISM indication, in particular with regards to long-term safety and less common ADRs, are related to the small size of the safety database (246 ISM patients, 226 received 25mg QD) and limited long-term follow-up, with all evidence deriving from a single on-going study. The MAH will provide updated safety results of the study BLU-285-2203 annually until completion of the study. The final CSR will be submitted when available.

Moreover, there is uncertainty regarding the potential effect on the course of the disease after avapritinib treatment discontinuation.

The uncertainties regarding the carcinogenic potential of avapritinib is also considered of concern. To address this, a 2-year study in rats will be submitted by the MAH following the recommendation of the CHMP.

3.6. Effects Table

Table 84. Effects Table for Patients with ISM in Study BLU-285-2203 (PIONEER) at C7D1- (Part 2 ITT Population) - DCO 23 June 2022

Effect	Short description	Unit	Avapritinib 25 mg + BSC (N= 141)	Control Placebo + BSC (N=71)	Uncertainties / Strength of evidence	References
Favourable Effects-Part 2 study BLU-285-2203						
Primary endpoint						

Effect	Short description	Unit	Avapritinib 25 mg + BSC (N= 141)	Control Placebo + BSC (N=71)	Uncertainties / Strength of evidence	References
Mean change in ISM-SAF TSS	Mean change in ISM-SAF TSS from Baseline to C7D1	Mean (95% CI)	-15.58 (-18.61, -12.55)	-9.15 (-13.12, -5.18)	Difference (95% CI): −6.43 (−10.90, −1.96); 1-sided P-value = 0.003	CSR
Key secondary endpoints						
% of patients achieving ≥ 50% reduction in ISM-SAF TSS	% of patients achieving ≥ 50% reduction in ISM-SAF TSS at C7D1	% (95% CI)	24.8 (17.9, 32.8)	9.9 (4.1, 19.3)	OR (95% CI): 3.10 (1.24, 8.64); 1-sided P-value = 0.005	CSR
% of patients achieving ≥ 30% reduction in ISM-SAF TSS	% of patients achieving ≥ 30% reduction in ISM-SAF TSS at C7D1	% (95% CI)	45.4 (37.0, 54.0)	29.6 (19.3, 41.6)	OR (95% CI): 2.07 (1.08, 3.99); 1-sided P-value = 0.009	CSR
% of patients with a ≥ 50% reduction in serum tryptase	% of patients with a ≥ 50% reduction in serum tryptase at C7D1	% (95% CI)	53.9 (45.3, 62.3)	0 (0.0, 5.1)	OR (95% CI): NE (30.59, NE); 1-sided P-value < 0.0001	CSR
% of patients with a ≥ 50% reduction in peripheral blood KIT D816V MAF or undetectable	% of patients with a ≥ 50% reduction in peripheral blood KIT D816V MAF or undetectable at C7D1	N % 95% IC	N=118 67.8 (58.6, 76.1)	N=63 6.3 (1.8, 15.5)	OR (95% CI): 39.34 (10.93, 140.56); 1-sided P-value < 0.0001	CSR
% of patients with a ≥ 50% reduction in bone marrow mast cells or no aggregates	% of patients with a ≥ 50% reduction in bone marrow mast cells or no aggregates at C7D1	N % 95% IC	N=106 52.8 (42.9, 62.6)	N=57 22.8 (12.7, 35.8)	OR (95% CI): 4.74 (2.06, 11.45); 1-sided P-value < 0.0001	CSR
Unfavourable Effects						

Effect	Short description	Unit	Avapritinib 25 mg + BSC (N= 141)	Control Placebo + BSC (N=71)	Uncertainties / Strength of evidence	References
Part 2*	AE overall	%	90.8	93.0		
	≥G3 AEs		21.3	21.1		
	SAEs		5.0	11.3		
	AEs leading to death		0.0	0.0		
	AE leading to treatment discontinuation		2.1	1.4		
	AE leading to dose reductions		1.4	1.4		
	AE leading to dose interruptions		8.5	12.7		
Avapritinib 25mg QD population**	AE overall	n (%)	223 (98.7)	N/A		
	≥G3 AEs		86 (38.1)			
	SAEs		31 (13.7)			
	AEs leading to death		1 (0.4)			
	AE leading to treatment discontinuation		12 (5.3)			
	AE leading to dose reductions		13 (5.8)			
	AE leading to dose interruptions		38 (16.8)			

Abbreviations: C7D1 = Cycle 7 Day 1; CI = confidence interval; ISM = indolent systemic mastocytosis; ISM-SAF = Indolent Systemic Mastocytosis-Symptom Assessment Form; ITT = intent-to-treat; NE = not evaluable; TSS = total symptom score(s). MAF = mutant allele fraction.

Notes: * *Data cut-off date 23 June 2022;* ** *Data cut-off date 07 April 2023.*

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The efficacy and safety of avapritinib in the indication for the treatment of ISM is based on a 3-part, placebo-controlled, Phase 2 study (BLU-285- 2203). In part 2 of the study a statistically significant reduction in the mean change from baseline to week 24 (C7D1) in the TSS using the ISM-SAF has been reported. The results for the (key) secondary efficacy endpoints also show statistically significant results in favour of the avapritinib arm.

The positive results observed in the primary endpoint are supported by a clear benefit of avapritinib over placebo in the secondary endpoints, including a decrease in systemic measures of mast cell burden, which is reasuring. Besides, while the effect of avapritinib was higher in skin symptoms, a decrease in all individual symptoms is observed to a greater or lesser extent. Thus, the effect of avapritinib in patients with ISM can be considered of clinical relevance.

Efficacy data in the long-term showed that the efficacy appears to be maintained in the long term, but additional data would be required. The MAH will submit an annual report of study BLU-285-2203 and continuing annually until completion of the study as per the recommendation of the CHMP (REC).

Regarding safety issues, the overall safety database for avapritinib in patients with ISM is small and the long-term exposure is limited, which raises concerns regarding the characterisation of long-term safety profile and less frequent adverse events. However, prior knowledge on the GIST and AdvSM indications could alleviate to some extent the concern, and longer-term data provided during the current variation further substantiate the safety of avapritinib in the intended indication.

The overall incidence of adverse events, including serious and severe AEs is lower in ISM patients than those previously reported for the higher doses used in the GIST/AdvSM indications. Avapritinib 25mg was acceptably tolerated based on the low frequency of AEs leading to dose interruptions/reductions. The recommendations for dose adjustments appear to mitigate these toxicities over time.

It is encouraging to note a low number of adverse events, as well as no intracranial haemorrhage events in view of the reported safety profile of avapritinib. However, it is recognized that a lower dose of avapritinib has been used in the current study and ISM patients with known risk factors for ICB were excluded. In addition, it needs to be taken into account that it is expected to treat patients over an extended period of time. Overall, the safety profile appears consistent to that known in previous indications, no new safety concerns have been identified. Annual updates and the final CSR data for study (BLU-285- 2203) will complement the current knowledge.

3.7.2. Balance of benefits and risks

Avapritinib has shown benefit in terms of the primary and key secondary endpoints in patients with moderate to severe ISM inadequately controlled with standard symptomatic therapy.

The overall safety profile of avapritinib appears consistent with that seen in the GIST/AdvSM indications. Avapritinib 25mg QD was acceptably tolerated and toxicity was overall manageable in the proposed treatment setting.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Ayvakyt is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include for avapritinib treatment of adult patients with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment based on results from the pivotal part of study BLU-285-2203 (PIONEER), this is a 3-part, randomized, double-blind, placebo-controlled, Phase 2 study to evaluate safety and efficacy of avapritinib (BLU-285) in indolent and smoldering systemic mastocytosis with symptoms inadequately controlled with standard therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.4 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Ayvakyt is not similar to Rydapt within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Ayvakyt-H-C-5208-II-0023’