27 January 2022
EMA/CHMP/135619/2022
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report on group of an extension of marketing authorisation and an extension of indication variation

AYVAKYT

International non-proprietary name: avapritinib

Procedure No. EMEA/H/C/005208/X/0004/G

Note

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

Table of contents

List of abbreviations

Abbreviation	Explanation
%CV	Percent interindividual variability (percent coefficient of variation)
(m)IWG-MRT-ECNM (modified)	International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis.
AdvSM	Advanced Systemic Mastocytosis
AdvSM-SAF	Advanced systemic mastocytosis-Symptom Assessment Form
AE	Adverse event
AESI	Adverse event of special interest
AHN	Associated hematological neoplasm
ALK	Anaplastic lymphoma kinase
AML	Acute myeloid leukemia
ASM	Aggressive systemic mastocytosis
AUC	Area under the plasma concentration-time curve
AUC0-last	Area under the plasma concentration-time curve from time 0 to the last measurable concentration above the lower limit of quantitation
BCRP	Breast cancer resistance protein
BM	Bone marrow
BSEP	Bile salt export pump
Cave	Average plasma concentration
CD	Cluster of differentiation
CEL	Chronic eosinophilic leukemia
CHMP	Committee for Medicinal Products for Human Use
CI	Clinical improvement
CL/F	Apparent oral clearance, unadjusted for bioavailability
Cmax	Maximum plasma concentration
CMML	Chronic myelomonocytic leukemia
CR	Complete remission
CRh	Complete remission with partial recovery of peripheral blood counts
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CxDx	Cycle x Day x
CYP	Cytochrome P450
DoE	Design of Experiment
DOR	Duration of response
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
E-R	Exposure-response
EU	Europe Union
FDA	Food and Drug Administration
FLT3	FMS-related tyrosine kinase 3
GIST	Gastrointestinal stromal tumor

GMP	Good Manufacturing Practice
HDPE	High-Density Polyethylene
HPLC	High Pressure Liquid Chromatography
IA	Interim analysis
IC50	Half-maximal inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICR	Incomplete response
ISE	Integrated Summary of Efficacy
ISM	Indolent systemic mastocytosis
JP	Japanese Pharmacopoeia
LDPE	Low Density Polyethylene
MAF	Mutant allele fraction
MATE	Multidrug and toxin extrusion protein
MC	Mast cell
MCL	Mast cell leukemia
mCR	Morphologic complete remission
mCRh	Morphologic complete remission with partial recovery of peripheral blood counts
MDD	Maximum Daily Dose
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MPN	Myeloproliferative neoplasm
mPR	Morphologic partial remission
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ND	Non Detected
NF	National Formulary
NLT	Not Less Than
NTRK	Neurotrophic tyrosine kinase
OAT	Organic anion transporter
OATP1B	Organic anion transporting polypeptide 1B
OCT	Organic cation transporter
ORR	Overall response rate
OS	Overall survival
PAR	Proven Acceptable Range
PD	Progressive disease
PDGFRA	Platelet-derived growth factor receptor alpha (referring to both gene and protein)
PFS	Progression-free survival
PGIS	Patient’s Global Impression of Symptom Severity
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)

PPR	Pure pathologic response
PPRE	Pure Pathologic Response-Evaluable
PR	Partial remission
PRO	Patient-reported outcome
PT	Preferred term
QD	Once daily
RAC	Response Assessment Committee
RAC-RE	Response Assessment Committee Response-Evaluable
SA	Scientific advice
SAE	Serious adverse event
SD	Stable disease
SM	Systemic mastocytosis
SM-AHN	Systemic mastocytosis with an associated hematologic neoplasm
SmPC	Summary of Product Characteristics
SSC	Study Steering Committee
SSM	Smoldering systemic mastocytosis
StdDev	Standard deviation
t1/2	Apparent terminal elimination half-life
TKI	Tyrosine kinase inhibitor
Tmax	Time of maximum plasma concentration
TTE	Time to event
UGT	Uridine diphosphate-glucuronosyltransferase
US	United States
USP	United States Pharmacopeia
USPI	United States Prescribing Information
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

Blueprint Medicines (Netherlands) B.V. submitted on 4 February 2021 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
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	II

Extension application to add two new strengths of film-coated tablets (25 mg and 50 mg), grouped with a type II variation (C.I.6.a) to introduce a new therapeutic indication for AYVAKYT. Extension of indication to include monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), after at least one systemic therapy based on the results of the BLU-285-2101 and BLU-285-2202 studies. The new indication is applicable to the new and existing presentations (25 mg, 50 mg, 100 mg and 200 mg film-coated tablets). As a consequence, sections 1, 2, 3, 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.2, 5.3, 6.1 and 8 of the SmPC are updated. The Labelling and Package Leaflet are updated in accordance. Version 1.1 of the RMP has also been submitted.

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: https://www.ema.europa.eu/en/medicines/human/EPAR/Ayvakyt

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (c) - Extensions of marketing authorisations and

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Ayvakyt was designated as an orphan medicinal product EU/3/17/1889 granted on 17 July 2017 in the following condition: Treatment of gastrointestinal stromal tumours.

The new indication, which is the subject of this application, falls within a separate orphan designation EU/3/18/2074 granted on 26 October 2018 in the following condition: 'treatment of mastocytosis'.

1.3. 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.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Additional Marketing protection

The MAH requested consideration of one year marketing protection in regards of its application for a new indication in accordance with Article 14(11) of Regulation (EC) 726/2004.

1.6. Protocol assistance

The MAH received Protocol assistance from the CHMP on 31 May 2018 (EMEA/H/SA/3738/2/2018/SME/III). The Protocol assistance pertained to non-clinical and clinical aspects. See also section 2.3

1.7. Steps taken for the assessment of the product

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

Rapporteur: Blanca Garcia-Ochoa Co-Rapporteur: Ingrid Wang

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Menno van der Elst

The application was received by the EMA on	4 February 2021
The procedure started on	25 February 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	31 May 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 May 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	26 May 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 June 2021
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	24 June 2021
The MAH submitted the responses to the CHMP consolidated List of	09 September 2021

Questions on	
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	16 October 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 October 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	11 November
The MAH submitted the responses to the CHMP List of Outstanding Issues on	21 December 2021
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	14 January 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to AYVAKYT on	27 January 2022
The CHMP adopted a report on similarity of Ayvakyt with Rydapt on (see Appendix on similarity)	27 January 2022
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for AYVAKYT in comparison with existing therapies. (see Appendix on Article 14(11))	27 January 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM AHN) or mast cell leukaemia (MCL).

The claimed therapeutic indication reads as follows:

- AYVAKYT is indicated as monotherapy for the treatment of adult patients with advanced systemic mastocytosis (AdvSM), including aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN), and mast cell leukaemia (MCL), after at least one systemic therapy.

Systemic mastocytosis (SM) is a rare clonal mast cell (MC) neoplasm, primarily driven by MCs carrying the KIT D816V mutation that results in constitutive, ligand-independent activation of the receptor tyrosine

kinase. This causes the proliferation, infiltration, and abnormal activation of MCs, leading to debilitating MC-mediator symptoms and, in a subset of patients, organ damage and poor survival (Gilreath et al, 2019; Pardanani 2019).

2.1.2. Epidemiology and risk factors, screening tools/prevention

The SM subclassification 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.

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

Patients with nonadvanced SM (90% to 95% of SM patients) primarily have ISM, but a small number of patients have the 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 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).

Patients with both nonadvanced and advanced SM suffer from a wide variety of severe and unpredictable symptoms and reduced quality of life. Patients have limited treatment options, and the low awareness of SM can result in diagnosis being delayed for several years (Jennings et al, 2018), suboptimal patient care, and exacerbation of the high unmet medical need in this population.

SM with the copresence of an AHN (SM-AHN) comprises 75% of AdvSM cases (Lim et al, 2009). The AHN component is typically myeloid, including CMML, MDS, MPN, CEL, and AML (Pardanani 2019). SM-AHN commonly presents with C-findings and has a median OS of 24 to 35 months (Lim et al, 2009; Sperr et al, 2019).

SM with C-findings, but without additional adverse pathologic features, is rare and known as ASM, which has a median OS of 41 to 68 months (Lim et al, 2009; Sperr et al, 2019).

The presence of excess (≥ 20%) MCs in the BM aspirate smear is characteristic of a rare, highly aggressive SM variant known as MCL. MCL commonly presents with C-findings and can co-occur with AHN. MCL has the worst prognosis of all SM variants, with a median survival of 2 to 23 months (Lim et al, 2009; Sperr et al, 2019).

An overview of prevalence and incidence of SM in the EU is provided in the following table:

Table 2 Overview of Prevalence and Incidence of Systemic Mastocytosis

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.

2.1.3. 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.

2.1.4. 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 BM and/or other extracutaneous organs (major criterion) and at least 1 of the following minor criteria:

- Atypical MC morphology in BM and/or extracutaneous tissues
- 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 can be broadly divided into advanced and nonadvanced disease, based on the degree of organ infiltration (B-findings) and organ damage (C-findings) present, as well as the presence of adverse pathologic features (Table 1).

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.

The advanced forms of SM have features of aggressive leukemias. Patients with AdvSM (comprising 5% to 10% of patients with SM) have adverse clinicopathologic features and poor OS, even with available therapies; see below. These adverse features include organ damage due to MC infiltration (C-findings), copresence of an AHN, and/or excess MCs in the marrow aspirate (Cohen et al, 2014). C-findings are heterogeneous and may occur throughout the body.

There are three subtypes within AdvSM: ASM, SM-AHN and MCL. A diagnosis of ASM requires the presence of WHO C-findings in the absence of adverse pathological features. It is characterized by findings such as low blood cell count, enlarged spleen and decreased bone density, leading to fractures. Median overall survival is 41–68 months. SM-AHN and MCL are often, but not always, associated with WHO C-findings and do not require this for diagnosis. The MCL diagnosis requires the presence of > 20% MCs in the bone marrow

aspirate smear. MCL is further characterized by findings such as infiltration of the abnormal mast cells in bone marrow, blood, and other organs. MCL may occur *de novo* or secondary to previous mastocytosis. The rapid accumulation of mast cells in the bone marrow ultimately results in multi-organ failure. Median overall survival is 2-23 months. A diagnosis of SM-AHN requires the copresence of AHN. This is the most common subtype of AdvSM, with approximately 70% of cases. The AHN component is often underdiagnosed resulting in frequent reclassification whenever patients are referred to centers of excellence. Median overall survival is 24-35 months for SM-AHN.

As indicated above, the prognosis for patients with systemic mastocytosis varies between subtypes. Features that may be associated with a poorer prognosis may include: elevated lactate dehydrogenase levels, anemia, thrombocytopenia, hypoalbuminemia, excess bone marrow blasts, high alkaline phosphatase, hepatosplenomegaly and ascites.

2.1.5. Management

Patients with AdvSM have limited treatment options. In AdvSM, current recommended therapies include midostaurin (approved in US and EU for all subtypes of AdvSM), cladribine, interferon-alfa (both used off-label), and imatinib (approved in US only for a subset of ASM patients). Despite the approval of midostaurin for treatment of AdvSM in 2017, cladribine is still recommended for patients who need rapid debulking or for patients who have to discontinue midostaurin due to toxicity, and interferon is recommended for patients with slow PD without the need for rapid cytoreduction (NCCN 2020; Pardanani 2019; Sperr et al, 2019). In addition, a number of medicines are used for symptom management. Antihistamines are commonly used. Cromolyn sodium, ketotifen and leukotriene-modifying agents are additional medications which may provide benefit.

2.2. About the product

Avapritinib (BLU-285) is a small molecule protein kinase inhibitor (ATC classification code L01EX18). It is a potent and selective inhibitor of mutated KIT kinase (including mutations of the D816 codon) and of the structurally related PDGFRA, targeting the active conformation of the kinase.

Avapritinib shows broad inhibitory activity against both primary and secondary KIT and PDGFRA mutants with most potent activity against activation loop mutants.

The KIT D816V activation loop mutation targeted by avapritinib is present in >95% of patients with SM (Garcia-Montero et al, 2006).

Avapritinib is currently approved for treatment of GIST. The recommended starting dose is 300 mg.

The claimed new indication is: "*AYVAKYT is indicated as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL), after at least one systemic therapy.*"

Posology for AdvSM

For AdvSM, the recommended starting dose of avapritinib is 200 mg orally once daily, on an empty stomach (see Method of administration). This once daily 200 mg dose is also the maximum recommended dose that must not be exceeded by patients with AdvSM. Treatment should be continued until disease progression or unacceptable toxicity occurs.

Treatment with avapritinib is not recommended in patients with platelet count < 50 x 10^9/L (see Table 2 and section 4.4).

Concomitant use of avapritinib with strong or moderate CYP3A inhibitors should be avoided. If concomitant use with a moderate CYP3A inhibitor cannot be avoided, the starting dose of avapritinib must be reduced from 200 mg to 50 mg orally once daily (see section 4.5).

Dose modifications for adverse reactions

Interruption of treatment with or without dose reduction may be considered to manage adverse reactions based on severity and clinical presentation.

The dose should be adjusted based on safety and tolerability.

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

Table 4: Recommended dose reductions for AYVAKYT for adverse reactions

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

Table 5:. Recommended dose modifications for AYVAKYT for adverse reactions

Adverse reaction	Severity*	Dose modification
Patients with GIST or AdvSM		
Intracranial haemorrhage (see section 4.4)	All Grades	Permanently discontinue AYVAKYT.
Cognitive effects** (see section 4.4)	Grade 1	Continue at the same dose, reduce dose or interrupt until improvement to baseline or resolution. Resume at the same dose or at a reduced dose.
	Grade 2 or Grade 3	Interrupt therapy until improved to baseline, Grade 1, or resolution. Resume at the same dose or at a reduced dose.
	Grade 4	Permanently discontinue AYVAKYT.
Other (also see section 4.4 and section 4.8)	Grade 3 or Grade 4	Interrupt therapy until less than or equal to Grade 2. Resume at the same dose or at a reduced dose, if warranted.
Patients with AdvSM		
Thrombocytopenia (see section 4.4)	Less than 50 x 10^9/L	Interrupt dosing until platelet count is ≥ 50 x 10^9/L, then resume at reduced dose (see Table 1). If platelet count does not recover above 50 x 10^9/L, consider platelet support.

* The severity of adverse reactions graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and 5.0
** Adverse reactions with impact on Activities of Daily Living (ADLs) for Grade 2 or higher adverse reactions

2.3. Type of Application and aspects on development

Studies comprising the clinical development program for AdvSM are shown in the table below.

Table 6 Studies comprising the clinical development program for AdvSM

Study Identifier/ Status	**Number of Study Centers/ Countries**	**Study Objective(s)**	**Study Design**	**Disease Population**	**Dose/Dosing Regimen**	**Number of Patients**
Advanced Systemic Mastocytosis						
BLU-285-2101 (NCT02561988, EudraCT number: 2015-001661-12) Part 1: Complete Part 2: Ongoing, enrollment complete; data cut-off date of 20 April 2021	11 centers/ 2 countries (UK, US)	Primary objectives: - MTD and RP2D - Safety and tolerability Secondary objectives: - PK - Changes in serum tryptase concentration and KIT D816V MAF - Changes in PROs and QoL - Reduction in spleen and liver volumes - Preliminary antineoplastic activity (efficacy)	Phase 1, open-label, dose escalation with expansion at the MTD/RP2D	Male or female patients ≥ 18 years old; Part 1: AdvSM, histologically or cytologically-confirmed myeloid malignancy that is relapsed or refractory to standard treatments, or other relapsed or refractory, potentially avapritinib-responsive neoplasms, based on WHO diagnostic criteria Part 2: - Patients with AdvSM based on WHO diagnostic criteria	Part 1: 3 + 3 dose-escalation 30 to 400 mg QD Part 2: Initially avapritinib 300 mg QD (RP2D), changed to 200 mg QD [a]	Part 1: 32 patients Part 2: 54 patients

Study Identifier/ Status	Number of Study Centers/ Countries	Study Objective(s)	Study Design	Disease Population	Dose/Dosing Regimen	Number of Patients
BLU-285-2202 (NCT03580655, EudraCT number: 2017-004836-13) Ongoing; data cutoff date of 20 April 2021	33 centers/ 11 countries (Canada, Denmark, France, Germany, Italy, Netherlands, Norway, Poland, Spain, UK, US)	<u>Primary objective:</u> - Adjudicated ORR (CR/CRh + PR + CI) based on mIWG-MRT-ECNM criteria <u>Secondary objectives:</u> - Change in AdvSM-SAF TSS - Investigator-assessed ORR - Time to event outcomes (TTR, DOR, PFS, OS) - Morphologic response (CR/CRh + PR) based on PPR criteria - ORR, DOR, PFS, and OS by prior therapy and genotype - Changes in measures of MC burden - Changes in PROs and QoL - Assess safety and PK - Correlate exposure with safety and efficacy endpoints	Phase 2, open-label, single-arm, 2-cohort	Male or female patients ≥ 18 years old with AdvSM as confirmed by WHO diagnostic criteria and by the SSC - *Cohort 1:* ≥ 1 measurable C-finding per mIWG-MRT-ECNM, attributed to SM unless diagnosis was MCL (C-findings not required) - *Cohort 2:* ASM, SM-AHN, or MCL and no measurable C-findings per mIWG-MRT-ECNM	Cohort 1 and 2: 200 mg QD [b]	Cohort 1: 85 patients Cohort 2: 22 patients

Abbreviations: AdvSM = advanced systemic mastocytosis; AdvSM-SAF = Advanced Systemic Mastocytosis-Symptom Assessment Form; ASM = aggressive systemic mastocytosis; CI = clinical improvement; CR = complete remission; CRh = complete remission with partial recovery of peripheral blood counts; DOR = duration of response; EudraCT = European Clinical Trials Database; MAF = mutant allele fraction; MCL = mast cell leukemia; mIWG-MRT-ECNM = modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; MTD = maximum tolerated dose; NCT = a unique identification code given to each clinical study record registered on ClinicalTrials.gov; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK= pharmacokinetic; PPR = pure pathologic response; PR = partial remission; PRO = patient-reported outcome; QD = once daily; QoL = quality of life; RP2D = recommended Phase 2 dose; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm; SSC = Study Steering Committee; TSS = total symptom score; TTR = time to response; WHO = World Health Organization; UK = United Kingdom; US = United States. a A dose of 300 mg QD was initially determined as RP2D based on data from Part 1 of Study BLU-285-2101 and later reduced to 200 mg QD based on new data demonstrating efficacy and improved tolerability at this dose level. b Patients were treated at a starting dose of 200 mg QD, with the exception of patients with platelet counts

ranging from 25,000 to 50,000/µL at baseline who were treated at a starting dose of 100 mg QD. With Protocol Amendment 5, patient with platelet counts < 50,000/µL were excluded from enrollment.

Initial scientific advice (SA) from the CHMP, SAWP, regarding the SM program for avapritinib was received on 31 May 2018 (procedure EMEA/H/SA/3738/2/2018/SME/III). This SA procedure addressed the nonclinical and clinical development of avapritinib as well as the development of PRO questionnaires for the AdvSM and ISM/SSM indications in the EU. The SA procedure also included advice on the planned efficacy and safety data to be submitted in support of an indication for treatment of AdvSM.

During the SA the proposed design of the single-arm open-label study BLU-285-2202 was questioned particularly with regards to the inclusion of both midostaurin-naïve patients and experienced patients under the same protocol: "*While investigating patients with prior exposure in a single arm trial might be considered acceptable, and whilst authorisation based on a single-arm trial cannot be precluded, a single arm trial for midostaurin-naïve patients is not supported and a randomised study versus midostaurin, appropriately designed to ensure blinding, is strongly recommended. To comply with this recommendation, whilst still investigating the benefit /risk of avapritinib in the proposed broad population, an acceptable protocol design could include a comparison of midostaurin-naïve patients randomized to midostaurin or avapritinib, along with an uncontrolled cohort investigating avapritinib in midostaurin pre-treated patients, analysed separately.*"

Additionally, the CHMP expressed concerns regarding the proposed sample size: "*In a study including only 60 patients, divided by three different disease entities with very different prognosis, one cannot expect to obtain reliable and interpretable efficacy and safety results. Acknowledging the difficulty in recruiting patients, the Applicant is recommended to increase the study size.*"

Upon consideration of the CHMP scientific advice, the MAH continued with the initial study design and size."

On 18 September 2020, a request for Simultaneous National Scientific Advice was submitted to the Spanish Agency of Medicines and Medical Products and to the Norwegian Medicines Agency for a planned external-control, observational, retrospective study (BLU-285-2405). The objective is to generate real-world data on the best available therapy used to treat patients with AdvSM and to conduct comparative analyses of clinical outcomes between patients treated with avapritinib vs. best available therapy. A meeting was held on 17 November 2020.

2.4. Quality aspects

2.4.1. Introduction

The scope of this extension application is the addition of two strengths, i.e. 25 mg film-coated tablets and 50 mg film-coated tablets, indicated for in adult patients to reduce and adjust the dose in the event of adverse reactions following a starting dose of 200 mg once daily.

The finished product is presented as film-coated tablets containing 25 mg or 50 mg of avapritinib as active substance, respectively.

Other ingredients are:

Tablet core: microcrystalline cellulose, copovidone, croscarmellose sodium, and magnesium stearate

Tablet coat: talc, macrogol 3350, poly(vinyl alcohol), titanium dioxide (E171)

The product is available in high-density polyethylene (HDPE) bottle with child-resistant cap (polypropylene) with foiled induction seal liner (pulp backed heat induction foil) and a desiccant in canister as described in section 6.5 of the SmPC.

2.4.2. Active Substance

The active substance documentation is identical to that of the previously approved authorised strengths and is acceptable.

Physico-chemical properties of the active substance that are relevant for the new strengths have been adequately addressed in the pharmaceutical development of the finished product.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as white round tablet with debossed text. One side reads 'BLU' and other side reads '25' or '50'; they measure approximately 5 mm and 6.35 mm in diameter respectively. All tablet strengths are manufactured using a common blend and are therefore proportional in active substance and excipients. All strengths of the proposed commercial tablets are the same colour but they have different size and marking. The different tablet strengths are distinguishable at a level sufficient to avoid mistakes among the different strengths by the final user.

The goal of the pharmaceutical development was to develop two new strengths, i.e. 25 mg film-coated tablets and 50 mg film-coated tablets.

The quality target product profile product (QTPP) and development targets for the 25 mg and 50 mg tablets are the same as those of the approved tablets (see initial EPAR).

The critical quality attributes (CQAs) for the new strengths are the same as those of the approved ones. The physical and chemical properties of the active substance that were measured to facilitate the identification of possible active substance CQAs and material attributes, that could influence the performance or manufacturability of the new strengths are the same as for the approved tablets. All finished product CQAs are monitored by means of a comprehensive control strategy that includes process design and validated methods for process inputs, in-process controls and final product release tests. The control strategy of the new strengths is the same as the control strategy of the approved strengths.

All the excipients used for the new strengths are the same as those of the approved tablets, with the exception of Opacode blue printing ink, which is not used for the 25 mg and 50 mg strength tablets as they are debossed. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report.

Details of formulation development have been previously provided for the already approved strengths and are applicable to the new strengths, with the exception of the omission of the printing ink.

The dissolution method used in the 25 mg and 50 mg strength tablets is the same as the approved commercial dissolution method. The data provided confirm that the method is able to discriminate between batches showing differences in those parameters/attributes.

Since the tablet is manufactured from a common blend, the 50 mg tablet was considered bracketed in this study and the current commercial dissolution method was determined to be acceptable for the additional dosage strengths.

A biowaiver was requested for 25 mg and 50 mg strength based on *f2* equivalence to the 100 mg tablet. This was accepted due to similarity of the formulations, linear pharmacokinetics are established, and have comparable dissolution profiles.

The finished product used in the bioequivalence studies (25 mg and 100 mg) is coated but the tablets do not have any marking: they are neither printed nor debossed; the clinical material was manufactured at a different site from the proposed manufacturing site of the finished product. When the manufacturing process was transferred to the commercial site, the manufacturing process flow remained unchanged and the equipment was similar with some exceptions, not expected to impact the CQAs of the finished product. Data from in-process testing and release testing confirmed the comparability of the commercial finished product with the product used in the bioequivalence study. Characterisation and optimisation studies were performed to ensure that the process was suitably robust and well-controlled prior to validation.

Historical manufacturing data were reviewed, a risk assessment conducted, and additional processing ranging (DoE) studies were conducted along with other studies. This work has resulted in a thorough understanding of the manufacturing process and appropriate points of control. Critical process parameters have been defined and appropriate ranges have been established for all process parameters. The applicant references to design spaces in the manufacturing process development have been amended as the information submitted of these DoEs is not sufficient to establish design spaces and only NORs and PARs are established. Therefore, the applicant does not claim a design space and the relevant sections of the Module 3 have been updated accordingly.

The primary packaging is high-density polyethylene (HDPE) bottle with child-resistant cap (polypropylene) with foiled induction seal liner (pulp backed heat induction foil) and a desiccant. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The new proposed strengths of finished product are manufactured by one manufacturing site which is different from the currently approved manufacturing site for the 100 mg, 200 mg and 300 mg strengths.

The manufacturing process of the 25 mg 50 mg is the same as that for the approved 100 mg, 200 mg and 300 mg strengths, with the exception of imprinting, as the Patheon 25 mg and 50 mg tablets are debossed.

The manufacturing process consists of 5 main steps considered to be a standard manufacturing process.

A satisfactory validation scheme to support the manufacture of the 25 mg and 50 mg tablets has been provided, this is acceptable for a standard manufacturing process. The results of in-process controls and the

analysis of the samples performed at each step demonstrate that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this pharmaceutical form.

Product specification

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: appearance (visual), identity (UV, HPLC), assay (HPLC), degradation products (HPLC), content uniformity (Ph. Eur .), dissolution (Ph. Eur.), water content (KF), and microbial enumeration (Ph. Eur.).

The potential presence of elemental impurities for the 25 and 50 mg tablets has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The Reference Standards used for the analysis of the finished product is the same as for the active substance and they have considered satisfactory.

Batch analysis results are provided for batches of 50 mg confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the approved specifications, through traditional final product release testing.

Stability of the product

Stability data from primary (registration) pilot scale batches of the strength 25 mg and 100 mg batches of finished product stored for up to 12 months under long term conditions (25 ºC / 60% RH) and accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay (HPLC), degradants, dissolution, water content, solid form and microbial enumeration. The analytical procedures used are stability indicating.

No significant changes have been observed under long term and accelerated conditions.

A temperature cycling study was initiated for the 25 mg and 50 mg tablets to study the effect of exposure to extreme temperatures on product quality when stored in the commercial container closure system.

The data showed that exposure to these extreme temperatures has little to no impact to product quality or tablet performance. In addition, the finished product was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products The photostability data showed that the finished product is not sensitive to light; no changes were observed .

A degradation study exposing tablets to extreme temperature and humidity conditions (80°C/75%RH) was performed on bulk tablet manufactured with the intended commercial manufacturing process. The results show a lower amount of degradation than the authorised strengths.

A simulated in-use study was initiated to study the effect of use of the product in practice via opening and closing the bottle daily at 15.0 – 25.0°C over 97 days. Complete study data were provided; the results for appearance, assay, degradation, dissolution, and water content were presented. No degradant growth was observed during the study.

Bulk tablet hold time studies for the 25 mg and 50 mg strengths, stored in the proposed commercial packaging components have been initiated, and the available data were submitted. The current available data are within the acceptance criteria with negligible changes in any finished product test attribute.

Based on available stability data, the proposed shelf-life of 2 years, without special storage conditions, as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the finished product.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation(s) for future quality development

No applicable

2.5. Non-clinical aspects

2.5.1. Introduction

No new non-clinical studies related to primary and secondary pharmacodynamic, safety pharmacology, pharmacodynamic drug interactions, distribution, excretion or environmental risk assessment with avapritinib have been provided. These investigations were submitted in the original application (Gastrointestinal Stromal Tumour indication).

New studies submitted with this application pertain to:

- absorption and pharmacokinetic drug interactions of avapritinib.
- repeated dose toxicity studies, genotoxicity study and fertility.

All analytical methods used were already validated in the original application of avapritinib, with no additional information in terms of matrix effect, selectivity, accuracy, precision, linearity, recovery dilution integrity, range, or limit of qualification.

2.5.2. Pharmacology

For the new indication (Systemic Mastocytosis), the MAH previously showed the pharmacological activity of avapritinib by inhibiting PDGFRa and KIT. In the case of KIT mutations (D816V), they have been identified with the pathogenesis of this new indication.

In cellular assays, avapritinib inhibited the autophosphorylation of KIT D816V and PDGFRA D842V with IC50 of 4 nM and 30 nM, respectively. In cellular assays, avapritinib inhibited the proliferation in KIT mutant cell lines, including a murine mastocytoma cell line and a human mast cell leukaemia cell line. Avapritinib also showed growth inhibitory activity in a xenograft model of murine mastocytoma with KIT exon 17 mutation.

Reference is made to the published EPAR.

2.5.3. Pharmacokinetics

New data related to absorption and pharmacokinetic drug interactions of avapritinib have been submitted in this procedure. No new data on distribution, metabolism or excretion were produced or incorporated.

2.5.3.1. Absorption

Plasma determinations from rat fertility study (study 0124844), and chronic administration studies both in rats (study 00124815) and dogs (study 00124816) are summarized.

In the fertility study, plasma levels (males only) of avapritinib were analysed on a daily basis for 9 weeks. Data reported on day 64 showed C_{max} values of 644, 2620, and 8120 ng/mL for 3, 10 and 30 mg/kg/day, respectively; and $AUC_{(0-24)}$ values of 9170, 49500, and 134000 ng.h/mL for 3, 10 and 30 mg/kg/day, respectively. Peak concentrations were reported at 6, 12 and 3 hours, respectively for increasing dose levels. Half-life parameter could not be calculated due to limited data in the terminal phase.

The chronic repeat dose toxicity study in rats was conducted in male and female rats. They were daily dosed (oral gavage) for 6 months with avapritinib at 1, 3, or 10 mg/Kg/day. Data revealed accumulation after daily administration (day 1 vs. day 182), and higher levels in females than in males.

In the 9-month repeat toxicity study, male and female dogs were administered with avapritinib at dose levels of 0.5, 1.5, or 5 mg/Kg/day. No accumulation was observed after chronic administration in dogs, with no sex differences in terms of exposure.

2.5.3.2. Pharmacokinetic drug interactions

Avapritinib metabolism in pooled and single donor human liver microsomes, Identification of the UGT enzymes involved in the metabolism of avapritinib hydroxylamine and Drug transporter substrate identification.

These *in vitro* studies related to metabolism of avapritinib complemented the previous information, and further characterised metabolic aspects. These studies showed that BLU-285 is catalysed in the presence of CYP3A5 (with no relation to the different genotypes *1*1, *1*3, *3*3). Also, in such studies it was found that avapritinib is metabolized to its hydroxylamine M514 first and subsequently M514 was metabolized either to the glucuronide conjugate M690 or to the oxidative deaminated product M499. Both metabolites had been previously identified in the original dossier as the major metabolites. The formation of these metabolites was found to be mediated by UGT1A3 and CYP3A4 (mainly), respectively. Finally, avapritinib did not appear to be a substrate for human transporters OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, BCRP, P-gp, or BSEP

2.5.4. Toxicology

Two additional GLP repeated dose toxicity studies, one genotoxicity study and one fertility study have been submitted. These studies encompassed chronic assessment in rats (6-month) and in dogs (9-months), a Comet assay in rats, while the reprotoxicity study was carried out in rats (fertility and early-embryonic development).

2.5.4.1. Single dose toxicity

N/A

2.5.4.2. Repeat dose toxicity

26-week (once daily) oral (gavage) toxicity study in sprague dawley rats with an 8-week recovery period: In this study, male and female rats were orally dosed with avapritinib (1, 3, or 10 mg/Kg/day) for 26 weeks on a daily basis, followed by an 8-week recovery period. In addition to the standard endpoints (body weight, food consumption, ophthalmology, clinical pathology, necropsy findings, organ weights and histopathology), TK parameters were also analysed (as described in TK section). Microscopic changes at terminal necropsy were reported at different tissues and organs (adrenal gland, bone (femur), bone marrow (sternum), thymus, spleen, ovary, vagina, and prostate, most of them observed at 3 and 10mg/Kg/day dose levels). After considering all the findings reported, the MAH established the NOAEL value at 3 mg/Kg/day, corresponding to mean $AUC_{0\text{-}t}$ values of 9710 and 19,900 h•ng/mL and mean Cmax values of 622 and 1260 ng/mL for males and females, respectively, on Day 182 (Week 26).

39-week (once daily) oral (gavage) toxicity study in beagle dogs with an 8-week recovery period: For this study, Beagle dogs were administered with avapritinib (oral gavage) at 0.5, 1.5, or 5 mg/Kg/day for 39 weeks, followed by an 8-week recovery period. As in the case of rat study, TK parameters were also analysed (as described in TK section). Based on clinical observations, changes in serum chemistry and histopathologic findings at terminal necropsy the NOAEL value of the study was found to be 5 mg/Kg/day, corresponding to mean (sexes combined) AUC_{0-t} of 7590 h•ng/mL on Day 273.

2.5.4.3. Genotoxicity

In vivo alkaline Comet assay in rat: The doses tested were 37.5, 75, 150 mg/kg/day for males and 25, 50, 100 mg/kg/day for females. There was no mortality in this study, and no DNA damage was observed in the liver in the in vivo comet assay.

2.5.4.4. Carcinogenicity

N/A

2.5.4.5. Reproductive and developmental toxicity

An oral (gavage) study of the effects of avapritinib on fertility and early embryonic development to implantation in rats: In this study, male (3, 10 or 30 mg/Kg/day) and female (3, 10 or 20 mg/Kg/day) rats were treated (oral gavage) with avapritinib on a daily basis. Males received the test item for 28 days before mating until a minimum of 9 weeks, while females were dosed for 14 days before mating until gestation day 7. Based on the results from the study, it was concluded that the NOAEL for male reproductive toxicity was 30 mg/kg/day and the NOAEL for female reproductive toxicity 20 mg/kg/day. Based on effects on embryonic survival at 10 and 20 mg/kg/day, the NOAEL for early embryonic toxicity was considered to be 3 mg/kg/day.

Avapritinib partitioned into seminal fluids up to 0.5 times the concentration found in human plasma at 200 mg. In female rats there was an increase in pre-implantation loss at the dose of 20 mg/kg/day (12.6 times the human exposure at 200 mg) and in early resorptions at doses $\geq$ 10 mg/kg (6.3 times the human exposure at 200 mg) with an overall decrease in viable embryos at doses $\geq$ 10 mg/kg. Cystic degeneration of corpora lutea and vaginal mucification was also observed in female rats administered avapritinib for up to 6 months at doses greater than or equal to 3 mg/kg/day (approximately 3.0 times the human exposure based on AUC at the 200 mg dose).”

2.5.4.6. Toxicokinetic data

N/A

Local tolerance

N/A

2.5.4.7. Other toxicity studies

N/A

2.5.5. Ecotoxicity/environmental risk assessment

No new data regarding environmental risk assessment of avapritinib have been submitted.

In the initial application, the MAH estimated 14,200 patients to cover the targeted populations of '*adult patients with unresectable or metastatic GIST harbouring the PDGFRα D842V mutation, regardless of prior therapy'*, and '*adult patients with unresectable or metastatic GIST who have been treated with at least 3 prior lines of therapy*'. A GIST prevalence of 2.8 in 10,000 people in the EU was considered for the calculations. The total number of GIST patients in the EEA (i.e. 145,600) was then reduced to approximately 9,000 patients considering that patients with unresectable or metastatic gastrointestinal stromal tumours harbouring the PDGFRα D842V mutation are approximately 5-6% of all GIST patients. In addition, since no prevalence data on fourth line GIST is available, the MAH, based on the argumentation that treatment with regorafenib (third line) is less effective with few responders (less than 10%), proposed that the third-line GIST prevalence was suitable for the purpose of environmental risk analysis. This was estimated as 1 in 100,000 in the UK, which in the EEA represents 5,200 patients. This proposed approach and related data/results were already assessed in the initial application.

In the current line extension, the prevalence for AdvSM has been estimated as 0.1 in 10,000 people (conservative prevalence, based on Cohen et al 2014 and Schwaab et al 2020), resulting in 5,200 patients in the EU, considering population of 520 million people. As for the authorized GIST indication, the MAH used the prior calculation of 9,000 patients (see above). The total number of patients is therefore set at 14,200 patients (5,200+9,000), which is the same number considered in the initial application.

In essence, the PECsw value remained unchanged and below the action limit. The conclusion is that avapritinib does not to pose a risk to the environment following approval of the new proposed indication.

2.5.6. Discussion on non-clinical aspects

Avapritinib is already used in existing marketed products and no significant increase in environmental exposure is anticipated. In the current line extension, the prevalence for AdvSM has been estimated as 0.1 in 10,000 people (conservative prevalence, based on Cohen et al 2014 and Schwaab et al 2020), resulting in 5,200 patients in the EU, considering population of 520 million people. As for the authorized GIST indication, the MAH used the prior calculation of 9,000 patients (see above). The total number of patients is therefore set at 14,200 patients (5,200+9,000), which is the same number considered in the initial application. Therefore, Avapritinib is not expected to pose a risk to the environment.

The MAH has presented a new set of nonclinical data. This update included toxicokinetic analysis of chronic nonclinical studies, metabolic assays (drug interactions and transporters), an additional genotoxicity study, fertility assessment in male and female rats, and the results of the chronic administration of avapritinib in nonclinical species (rat and dog).

Toxicokinetic analysis was done by using analytical methods already validated in the original application of avapritinib, with no additional information in terms of matrix effect, selectivity, accuracy, precision, linearity, recovery dilution integrity, range, or limit of qualification.

The *in vitro* studies related to metabolism of avapritinib complemented the previous information, and further characterised metabolic aspects.

In the original application, avapritinib was tested in the standard battery for genotoxicity testing. It resulted negative in bacterial test and in non-mutagenic or clastogenic *in vivo,* although a positive result was observed in the *in vitro* chromosomal aberration assay. Overall, it was considered as non-genotoxic. In the study submitted in the current procedure (*in vivo* alkaline assay), avapritinib resulted in no DNA damage in the liver in male and female animals administered.

Given the adverse histopathological changes in the reproductive organ in rats and dogs, and pointing to the potential effects on male and female fertility, a fertility and early embryonic development study was conducted. No effects on fertility (reproductive performance, sperm parameters, oestrous cyclicity, or precoital intervals) were noted at the highest dose level tested (30 and 20 mg/Kg/day for males and rats, respectively). However, effects on implantation were reported at medium and highest dose levels, identifying the NOAEL value for early embryonic toxicity as 3 mg/Kg/day.

In the case of the effects observed after chronic administration of avapritinib (6- and 9-month in rats and dogs, respectively), it is noted that they are not considered necessary for oncology indication, in accordance with ICH S9. The MAH conducted such studies for potential nononcology indications, which is not the case of the intended new indication (Systemic Mastocytosis). However, the results can be evaluated in view of any other potential new indications. Appropriate information has been included in section 5.3 of the SmPC.

2.5.7. Conclusion on the non-clinical aspects

From a nonclinical point of view, the new data do not modify the benefit risk assessment previously established in the original application of avapritinib. The new data cover some aspects that were not completely investigated, such as potential drug interactions or fertility. Also, an additional genotoxicity study was conducted. As for chronic administration of avapritinib, the MAH presented two chronic studies. They should be carefully considered in the case of non-oncologic indications.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 7 **Overview of Studies Contributing Clinical Pharmacology Data**

Study Identifier Status Location of CSR	Study Objective	Study Design	Patients (No. (M/F) Type Age: Mean [Range])	Treatments (Dose, Dosage Form) [Product ID]	Route	Avapritinib Formulation	Data Included in Current Submission			Location in Module 2.7
							NCA PK	Pop PK	E-R	
Studies in Patients with AdvSM										
BLU-285-2101 *Part 1*: complete *Part 2*: ongoing CSR BLU-285-2101	*Part 1 (dose-escalation)*: MTD, recommended Phase 2 dose, PK, and safety of avapritinib *Part 2 (expansion)*: Efficacy, PK, PD, and safety of avapritinib	Phase 1, open-label, 2-part study	86 patients with AdvSM (46M/40F) 62.6 years, [34-83 years]	*Part 1*: Escalation from 30 to 400 mg QD *Part 2*: Initially 300 mg QD, reduced to 200 mg QD	Oral, fasted	*Part 1*: 5, 10, 30, or 100 mg drug-in-capsules *Part 1*: 25 and 100 mg tablets	Yes	Yes	Yes (E,S)	Module 2.7.2, Section 2.1 (NCA PK) Module 2.7.2, Section 2.5.1 (PopPK) Module 2.7.2, Section 2.5.3 (E-R)
BLU-285-2202 Ongoing CSR BLU-285-2202	Efficacy and safety of avapritinib	Phase 2, open-label study	62 patients with AdvSM (34M/28F) 67.5 years, [31-88 years]	200 mg QD	Oral, fasted	25 and 100 mg tablets	Yes	Yes	Yes (E,S)	Module 2.7.2, Section 2.2 (NCA PK) Module 2.7.2, Section 2.5.1 (PopPK) Module 2.7.2, Section 2.5.3 (E-R)

Study Identifier Status Location of CSR	Study Objective	Study Design	Patients (No. (M/F) Type Age: Mean [Range])	Treatments (Dose, Dosage Form) [Product ID]	Route	Avapritinib Formulation	Data Included in Current Submission			Location in Module 2.7
							NCA PK	Pop PK	E-R	
Studies in Patients with GIST										
BLU-285-1101 *Part 1*: complete *Part 2*: ongoing CSR BLU-285-1101	*Part 1 (dose-escalation)*: MTD, recommended Phase 2 dose, PK, and safety of avapritinib *Part 2 (expansion)*: Efficacy, PK, PD, and safety of avapritinib	Phase 1, open-label, 2-part first-in-human study	237 patients with GIST and other relapsed and refractory solid tumors (145M/92F) 59.5 years, [25-90 years]	*Part 1*: Escalation from 30 to 600 mg QD *Part 2*: Initially 400 mg QD, reduced to 300 mg QD	Oral, fasted	*Part 1*: 5, 10, 30, or 100 mg drug-in-capsules *Part 2*: Drug-in-capsules, later switched to 100 mg tablets	No	Yes	Yes (S)	Module 2.7.2, Section 2.5.1 (PopPK) Module 2.7.2, Section 2.5.3 (E-R)

Study Identifier Status Location of CSR	Study Objective	Study Design	Patients (No. (M/F) Type Age: Mean [Range])	Treatments (Dose, Dosage Form) [Product ID]	Route	Avapritinib Formulation	Data Included in Current Submission			Location in Module 2.7
							NCA PK	Pop PK	E-R	
BLU-285-1303 Ongoing, enrollment complete No CSR in current submission (study details in Module 2.7.4 and Module 2.7.4, Table 18.3.1.3)	Efficacy and safety of avapritinib vs regorafenib	Phase 3, open-label, randomized study	239 patients with locally advanced unresectable or metastatic GIST (advanced GIST), treated with avapritinib (162M/77F) 61.1 years, [31-91 years]	*Avapritinib*: 300 mg QD *Regorafenib*: 160 mg QD (3 weeks on/ 1 week off)	Oral, fasted	25 and 100 mg tablets	No	No	Yes (S)	Module 2.7.2, Section 2.5.3 (E-R)

Abbreviations: AdvSM = advanced systemic mastocytosis; CSR = clinical study report; E = efficacy; E-R = exposure-response; F = female; GIST = gastrointestinal stromal tumor; ID = identification; M = male; MTD = maximum tolerated dose; NCA = noncompartmental analysis; No. = number; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PopPK = population pharmacokinetics; QD = once daily; S = safety.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Analytical Methods

The analytical methods used in all three studies were previously assessed and found acceptable in a previous application (EMEA/H/C/005208). An addenda to the validation reports were provided to include new stability data, interference and concomitant medications and lipemic effect experiments. Both in-study validations show acceptable calibration standards and QCs. The reasons for the samples re-assayed are considered acceptable. Incurred Sample Reproducibility was performed and the reanalysis confirms the validity and performance of the Analytical Method Procedure for all analytes.

All samples were analysed within the known stability period for BLU-285 (1774 days at -70 °C). The bioanalytical addendum containing additional stability data was submitted during the procedure. New information was provided by the MAH during the procedure, i.e. in the Validation addendum Report where the long term stability data of BLU111207 and BLU111208 were investigated. Data provided still do not cover the maximum storage time for the enantiomers in study BLU-285-2101 and BLU-285-2202. Additional long term stability tests will be performed in first quarter (Q1) of 2023 to cover the maximum storage time for both studies (see also discussion section below).

The bioanalytical report for the study BLU-285-2203 was submitted during the procedure. This was required as those study samples were used to support the application of the strength-based biowaiver. The in-study validation shows acceptable calibration standards and QCs. The reasons for the samples re-assayed are considered acceptable. Incurred Sample Reproducibility was performed and the reanalysis confirms the validity and performance of the Analytical Method Procedure for all analytes.

Non-compartmental PK analysis

Non-compartmental analyses were applied to report pharmacokinetic parameters of avapritinib and the metabolites BLU111207 and BLU111208 in study BLU-285-2101, using the pharmacokinetic R package maNCA. The package and associated code were run in R version 3.3. The following PK parameters were derived using NCA: C_{max}, $C_{max,ss}$, T_{max}, T_{24}, AUC_{last}, AUC_{0-24}, $AUC_{last,ss}$, $AUC_{0-24,ss}$, C_{24}, $t_{1/2}$, CL/F, CL/F_{ss}, Vz/F. Actual time points were used in the analysis. The AUC values were estimated using the linear trapezoidal rule (linear up-linear down). The terminal-phase disposition rate constant (λz) was estimated by linear regression of the terminal log-linear phase of the log-transformed concentration vs. time data, and t½ was estimated as ln(2)/λz. Apparent oral CL was estimated as dose/$AUC_{0-\infty}$, and Vz/F was estimated as dose/($AUC_{0-\infty}$* λz).

In study BLU-285-2203 Part 1, the PK parameters were calculated by non-compartmental analyses using Phoenix 32 Build 8.1.0.

Bioavailability of capsules and tablets

Two different formulations, drug-in-capsule not marketed and marketed tablets were used in the Phase 1 study BLU-285-2101 where PK analysis was performed, merging the data irrespective of the formulation used. In a relative bioavailability study comparing the PK of avapritinib after single-dose administration of either 1 × 200 mg (commercial) tablet or 2 × 100 mg capsules in healthy subjects (Study BLU-285-0101), the 90% CIs of the geometric mean ratio (GMR) values for Cmax and AUC parameters were contained within the equivalence limits of 80.00% to 125.00%, except for the lower bound for Cmax (78.5%). The 200 mg tablet and 2 × 100 mg capsule formulations of avapritinib were therefore considered to have similar bioavailability, and no dose adjustment was needed when switching from the capsule to the tablet formulation. It was concluded that no differences in exposure are expected between both formulations that would require any covariate effect in the population PK model.

Absorption

No new bioavailability studies were submitted. From the refined model, the bioavailability (F) in patients with AdvSM is estimated at 79.3% of the population estimated F in patients with GIST (i.e., ~20% lower).

Distribution

No new clinical distribution studies were submitted. Volume of distribution was estimated using the population PK approach. From the refined model, the population estimated apparent central volume of distribution (Vc/F) is 999 L. Population estimated mean volume of distribution of avapritinib at steady-state (Vss/F) is 1232 L at median lean body weight of 56.8 kg.

Metabolism

Incubations of avapritinib with NADPH-fortified HLM, recombinant human CYP3A4, or human hepatocytes led to the formation of its hydroxylamine metabolite M514, which was subsequently metabolized to either the glucuronide conjugate M690 or the oxidative deaminated product M499. The formation of these metabolites was found to be mediated by UGT1A3 and CYP3A4 (mainly), respectively.

Elimination

No new clinical elimination studies were submitted. Apparent clearance (CL/F) was estimated using the population PK approach. From the refined model, the population estimated mean apparent clearance (CL/F) of avapritinib is 16 L/h in GIST. Population estimated CL/F of avapritinib in AdvSM is 21.1 L/h at treatment

initiation, followed by a time-dependent decline towards 15.9 L/h after 15 days. This prediction is consistent with a time-dependent effect on CL/F in patients with AdvSM which is expected to reach a maximum at Day 15, and that the steady-state CL/F of avapritinib in patients with AdvSM will be close to that in patients with GIST. Following single doses of AYVAKYT in patients with GIST and in patients with AdvSM, the mean plasma elimination half-life of avapritinib was 32 to 57 hours and 20 to 39 hours, respectively.

Dose proportionality and time dependencies

In the initial MAA, dose proportionality was investigated and established over the range of 30 mg to 400 mg in patients with GIST.

In the current application, two separate dose proportionality analyses have been conducted: (i) In patients with AdvSM using data from **Study BLU-285-2101** (30 mg – 400 mg), and (ii) In patients with indolent systemic mastocytosis (ISM) or smoldering systemic mastocytosis (SSM) using data from **Study BLU-285-2203 Part 1** (25 mg – 100 mg). The second analysis was used as a basis to support the biowaiver for the new tablet strengths 25 mg and 50 mg.

Dose proportionality was assessed using the confidence interval criteria (power model).

The steady state geometric mean (CV%) C_{max} and AUC_{0-24} of avapritinib at 200 mg once daily was 377 ng/mL (62%) and 6600 h•ng/mL (54%), respectively. The geometric mean accumulation ratio after repeat dosing (30-400 mg) was 2.6 to 5.8.

Study BLU-285-2101 (AdvSM patients) - (30-400 mg): This open label, 2-part study, included a dose escalation (Part 1, n=32) and an expansion (Part 2, n=54). Patients in Part 1 received daily oral avapritinib starting doses of 30 mg (n=3), 60 mg (n=6), 100 mg (n=3), 130 mg (n=3), 200 mg (n=4), 300 mg (n=6), and 400 mg (n=7). Of the 54 patients receiving at least 1 dose of avapritinib in Part 2, 17 had a starting dose of 200 mg and 37 had a starting dose of 300 mg.

Avapritinib C_{max} and AUC_{0-24} at C1D1 and at steady state (C1D15) are summarised in **Table 8**

The slope of the linear model for C_{max} was 0.78 (90% CI 0.561 – 0.996) on C1D1 and 0.88 (90% CI 0.711 – 1.05) on C1D15. Similarly, for AUC_{last} the slope of the linear model was 0.78 (90% CI 0.563 – 0.989) on C1D1 and 0.90 (90% CI 0.723 – 1.08) for $AUC_{last,ss}$ on C1D15 (results not shown). The 90% CI for the slope were not within the abbreviated critical interval (0.732 – 1.27) except for $C_{max,ss}$ and $AUC_{last,ss}$ on C1D15.

Table 8 Summary of avapritinib PK parameters on C1D1 and C1D15 in study BLU-285-2101.

Avapritinib Dose (mg)	Summary Statistics	C_{max} (ng/mL)	AUC_{0-last} (h*ng/mL)	$C_{max,ss}$ (ng/mL)	$AUC_{0-last,ss}$ (h*ng/mL)
		C1D1		C1D15	
30	n	3	3	3	3
	Mean	27	396	81.3	1680
	95% CI	17.3-36.7	137-655	35.0–128	732–2620
60	n	5	5	5	5
	Mean	58.8	853	153	2960
	95% CI	26.2-91.4	394–1310	93.5–213	1230–4680
100	n	3	3	3	3
	Mean	111	1560	186	3960
	95% CI	27.4–194	-64.4–3180	89.2–283	1230–6680
130	n	3	2	3	3

	Mean	119	1360	222	4820
	95% CI	-43.7–281	-	40.2–403	866–8770
200	n	21	8	18	7
	Mean	143	1680	433	8990
	95% CI	97.8–188	819–2550	319–547	2530–15500
300	n	43	33	41	40
	Mean	233	2900	609	12100
	95% CI	195–272	2430–3370	544–673	10700–13600
400	n	7	6	7	7
	Mean	229	3280	742	15800
	95% CI	47.8–410	558–6010	442–1040	10300–21300

Given the small number of subjects in the dose groups 30 mg – 130 mg (n=3-5) and the high variability, it was not possible to conclude dose proportionality. Subsequently, dose proportionality was conducted over the range 200 mg – 400 mg. A dose-proportional increase in systemic exposure to avapritinib was observed across the dose range after single-dose administration (C1D1) and at steady state (C1D15) for C_{max} and AUC_{last}.

Study BLU-285-2203 Part 1 (25-100 mg) in support of biowaiver claim: Approximately 40 patients, diagnosed with ISM or SSM, were randomly assigned to 1 of 3 doses of avapritinib (25, 50, and 100 mg) or to placebo. Plasma samples for pharmacokinetics (PK) of avapritinib were collected at the following time points at Day 1 (C1D1) and Day 15 (C1D15): Predose, 0.5, 1, 2, 4, 8, and 24 h.

Avapritinib C_{max} and AUC_{0-24} at C1D1 and at steady state (C1D15) are summarised in Table 9.

For C_{max}, the linear model had a slope of 1.15 (90% CI 0.854 – 1.44) on C1D1 and 0.95 (90% CI 0.665 – 1.23) for $C_{max,ss}$ on C1D15. Similarly, for AUC0-24 the linear model had a slope of 1.14 (90% CI 0.901–1.38) on C1D1 and 0.98 (90% CI 0.704 – 1.26) for AUC0-24,ss on C1D15. The 90% CI for the slope of both PK parameters on both observation periods were within the pre-specified critical interval of 0.5 – 1.5, and dose proportionality of avapritinib was concluded over the dose rage 25 – 100 mg.

Table 9 Summary of avapritinib PK parameters on C1D1 and C1D15 in study BLU-285-2203.

Avapritinib Dose (mg)	Summary Statistics	C_{max} (ng/mL)	AUC_{0-24} (h*ng/mL)	$C_{max,ss}$ (ng/mL)	$AUC_{0-24,ss}$ (h*ng/mL)
		C1D1		**C1D15**	
25	n	8	8	8	8
	Mean	25.0	397.3	80.7	1547.6
	SD	11.7	143.3	40.8	806.0
50	n	11	11	11	11
	Mean	54.9	805.9	140.6	2795.6
	SD	27.2	336.1	44.5	983.1
100	n	10	10	8	8
	Mean	119.9	1858.1	238.9	5587.7
	SD	45.3	544.5	115.0	1906.1

Time dependency: In the popPK model a time-dependent covariate effect was included on CL/F in AdvSM patients only. The maximum decrease in CL/F compared to healthy volunteers or patients with GIST was 38.1%, and the time at half maximum decrease of CL/F was estimated to be 211 hours (9 days) since the first dose.

Pharmacokinetics of metabolites: After single- and repeat-dose administration of avapritinib at doses of 30 to 400 mg in patients with AdvSM in study BLU-285-2101, the interindividual variability for PK parameters generally ranged between 15% and 121% for Cmax, AUC_{0-24}, and C_{24}. In the popPK analysis, intra-individual variability on F (i.e. between-occasion variability) was estimated to a coefficient of variation (CV) of 25.1% and inter-individual variability in CL/F was estimated to a CV of 42.1%. Inter-individual variability in Vc and Vp was combined and estimated to a CV of 48%.

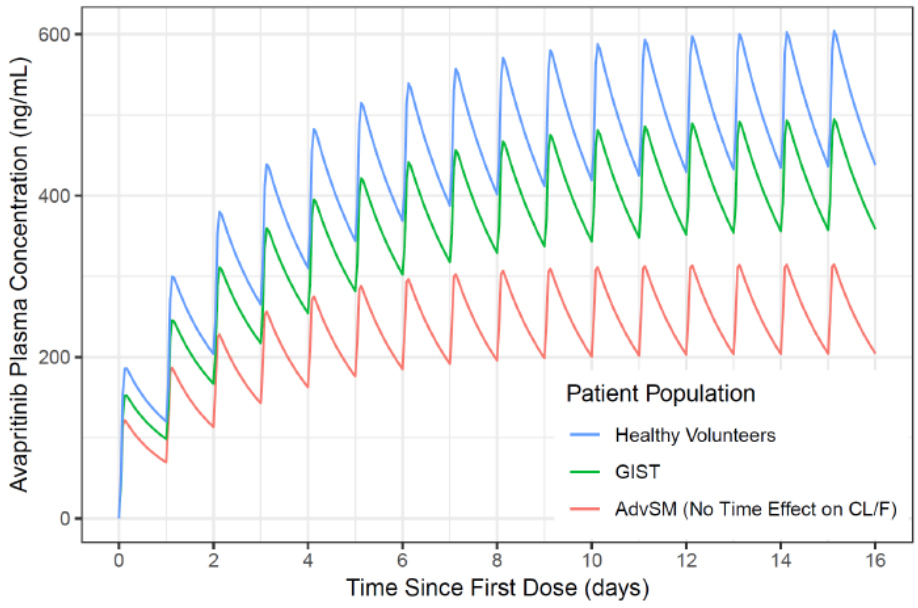
Pharmacokinetics in the target population:

Pharmacokinetic Analysis (NCA) of avapritinib (BLU-285) and its Metabolites, BLU111207 and BLU111208 in Study BLU-285-2101 was performed. A popPK model was provided in the initial application but was refined upon request from the CHMP.

In the final model, compared with healthy subjects, patients with AdvSM have a lower overall exposure. In addition, patients with AdvSM appeared to have a time dependent decrease in CL/F. The additional covariate included in the final model were concomitant PPI use decreased KTR. The covariates that were identified in the previous model in patients with GIST (lean body weight on Vc/F and concomitant PPI use on F) were retained in the updated model, but with updated estimated values. PvcVPCs were generated across subgroups (gender, race, PPI use) and indicated adequate predictive performance (not shown here).

The model-predicted impact of patient population on the concentration-time profile is shown in the figure below.

Figure 11: Simulated PK profiles without time-dependent effects



Abbreviations: AdvSM = advanced systemic mastocytosis, GIST = gastrointestinal stromal tumor, CL/F = apparent oral clearance, PK = pharmacokinetics

Figure 1. Representation of the model predicted effect of Patient Population

The updated popPK model did only identify two covariates significantly impacting on avapritinib exposure: lean body weight on Vc/F and concomitant PPI use on F. Sex and race were no longer significant. The forest plots provided show that the range of lean body weights (30 kg to 80 kg) have modest impact on Cmax,ss (+/ 5%), while concomitant use of PPIs led to ~17% reduction in AUC and Cmax. The combination of high lean body weight and use of PPIs was predicted to reduce Cmax,ss by 19% and is thus of no increased concern than the use of PPIs alone.

The updated popPK modelling data set included 323 males (66%) and 164 females (34%), and the updated modelling did not identify sex as a significant covariate on CL/F. The popPK dataset included mostly White subjects, with a low number of black (n=26) and Asian (n=25) subjects. Caution is advised when interpreting findings for these subgroups.

Population pharmacokinetic analyses indicate that age (18-90 years), body weight (40-156 kg), and albumin concentration have no clinically meaningful effect on the pharmacokinetics of avapritinib.

Pharmacokinetic interaction studies

No clinical drug-drug interaction studies have been conducted. Based on both population and noncompartmental pharmacokinetic analyses for patients with GIST and AdvSM taking gastric acid reducing agents, the effect of gastric acid reducing agents on the bioavailability of avapritinib is not clinically relevant.

2.6.2.2. Pharmacodynamics

Mechanism of action

Primary and Secondary pharmacology

Exposure-efficacy

The E-R efficacy analysis dataset included patients with AdvSM from Studies BLU 285 2101 and BLU-285-2202 who had at least 1 prior systemic therapy.

Best overall response: No clear relationship was evident between avapritinib exposure and BOR in the RAC-RE population, while patients with stable disease in the PPRE tended to have lower C_{ave}.

Progression-free survival and duration of response: No clear relationship with avapritinib exposure were evident in the RAC-RE or PPRE population.

Time to response: Higher C_{ave} was significantly associated with faster response in the RAC-RE population. The probability of a confirmed response by 6 months in patients who responded was 0.33 in the 1st quartile of Cave (95% CI 0 to 0.70). Approximately ≥70% of patients in the 3rd and 4th quartiles of C_{ave} with a confirmed response had responded by 2 months (first measure of efficacy).

Exposure-safety

The E-R safety analysis dataset included 144 patients with AdvSM from Studies BLU-285-2101 and BLU-285-2202, and 383 patients with GIST from BLU-285-1101 and BLU-285-1303, who had safety data and matching

avapritinib exposures. All E-R analyses for safety outcomes were conducted using the E-R safety analysis dataset, which constituted the E-R Safety Population.

Grade 3+ adverse events: Approximately 56% of patients (n=296) experienced at least one Grade 3+ related AE throughout the studies. A statistically significant relationship was evident between Cave and Grade 3+ related AEs, with patients who experienced an event having marginally greater Cave than patients who did not have an event.

Cognitive effects: A total of 199 patients (37.9%) experienced a cognitive effect (pooled; all Grades). Avapritinib Cave was significantly greater in patients with a cognitive effect.

2.6.3. Discussion on clinical pharmacology

The analytical methods used in both studies were previously assessed and found acceptable in a previous application (EMEA/H/C/005208), and both in-study validations show acceptable calibration standards and QCs. However, concerns are raised regarding LTS experiments to cover at least the maximum sample storage period for both metabolites. The MAH agreed that additional long term stability tests will be performed in first quarter (Q1) of 2023 to cover the maximum storage time for both studies BLU-285-2101 and BLU-285-2202.

This grouped variation procedure includes an application for an extension of indication and also a line extension application to include two additional strengths 25 and 50mg. In order to demonstrate that the new strengths are bioequivalent to the currently approved strengths, the MAH has not submitted clinical bioequivalence studies, but instead presented a rationale for a strength-based waiver for the 25 mg and 50 mg tablets. The CHMP Guideline on investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) lists general criteria that must be met for a strength-based biowaiver to be approvable. The MAH has demonstrated that these are met: i.e.: same manufacturing process, identical qualitative composition of the different strengths, quantitatively proportional compositions between the previously approved strengths and the two new strengths, and appropriate *in vitro* dissolution data. The MAH also showed that a dose-proportional increase in systemic exposure (AUC and C_{max}) of avapritinib was observed across the dose range of 25 to 100 mg (**Study BLU-285-2203**). Hence, a strength based biowaiver for the additional strengths of 25 and 50 mg is acceptable.

Dose proportionality data originally provided in the SmPC is following a single dose administration, while in AdvSM a more relevant exposure metrics would be steady-state exposure (avapritinib steady-state Cmax and area under the curve AUC, at C1D15) due to chronic administration. As seen in the results presented by the MAH (**Table 8**), steady-state Cmax and AUC of avapritinib increased proportionally over the dose range of 30 mg to 400 mg. It was agreed that the steady state measures will be more informative for the AdvSM population. It was agreed to include the latter updated knowledge in the SmPC under Pharmacokinetics in the target population (Section 5.2).

The pharmacokinetic characteristics in the target population have been characterized by assuming a similar population PK model as developed for GIST patients, showing minor concerns on the role of clearance values considered. The following patient characteristics were found to significantly influence avapritinib PK across indications: lean body weight on volume of distribution and use of PPIs on bioavailability. The SmPC was updated to reflect this information. The updated popPK modelling did not identify age as a significant covariate after investigation of a broad range of ages, which is in line with previous findings for avapritinib.

The exposure-response relationships for efficacy and safety have not been reliably characterised for avapritinib in AdvSM due to shortcomings in the clinical data set in terms of sample size, exposure ranges represented and clinical dose adaptations that limit the information that can be inferred from the presented analyses. Therefore, the uncertainties regarding the optimal avapritinib dose from the initial application in the GIST population remain. It is unknown whether a lower avapritinib starting dose could have resulted in similar efficacy in AdvSM, but it is likely that the risk of AEs would be reduced.

2.6.4. Conclusions on clinical pharmacology

The CHMP considers the following measures necessary to address the issues related to pharmacology:

- Additional long term stability tests will be performed in first quarter (Q1) of 2023 to cover the maximum storage time for both studies BLU-285-2101 and BLU-285-2202

2.6.5. Clinical efficacy

The claimed indication in the current Marketing Authorization Application (MAA) is for the use of avapritinib for the treatment of adult patients with AdvSM, including ASM, SM-AHN, and MCL, after at least one systemic therapy. This application is based on the efficacy results from the ongoing phase 2, open-label, single-arm, 2-cohort **study BLU-285-2202** (PATHFINDER) supported by the phase 1, open-label dose escalation **study BLU-285-2101** (EXPLORER). Both studies include patients with prior systemic therapy as well as treatment-naïve patients.

Studies comprising the clinical development program for AdvSM are shown in the table below, according to the latest data cut-off date of 20 April 2021.

Table 10 Studies comprising the clinical development program for AdvSM

Study Identifier/ Status	Number of Study Centers/ Countries	Study Objective(s)	Study Design	Disease Population	Dose/Dosing Regimen	Number of Patients
Advanced Systemic Mastocytosis						

Study Identifier/ Status	Number of Study Centers/ Countries	Study Objective(s)	Study Design	Disease Population	Dose/Dosing Regimen	Number of Patients
BLU-285-2101 (NCT02561988, EudraCT number: 2015-001661-12) Part 1: Complete Part 2: Ongoing, enrollment complete; data cut-off date of 20 April 2021	11 centers/ 2 countries (UK, US)	Primary objectives: - MTD and RP2D - Safety and tolerability Secondary objectives: - PK - Changes in serum tryptase concentration and KIT D816V MAF - Changes in PROs and QoL - Reduction in spleen and liver volumes - Preliminary antineoplastic activity (efficacy)	Phase 1, open-label, dose escalation with expansion at the MTD/RP2D	Male or female patients ≥ 18 years old; Part 1: AdvSM, histologically or cytologically-confirmed myeloid malignancy that is relapsed or refractory to standard treatments, or other relapsed or refractory, potentially avapritinib-responsive neoplasms, based on WHO diagnostic criteria Part 2: - Patients with AdvSM based on WHO diagnostic criteria	Part 1: 3 + 3 dose-escalation 30 to 400 mg QD Part 2: Initially avapritinib 300 mg QD (RP2D), changed to 200 mg QD [a]	Part 1: 32 patients Part 2: 54 patients

Study Identifier/ Status	Number of Study Centers/ Countries	Study Objective(s)	Study Design	Disease Population	Dose/Dosing Regimen	Number of Patients
BLU-285-2202 (NCT03580655, EudraCT number: 2017-004836-13) Ongoing; data cutoff date of 20 April 2021	33 centers/ 11 countries (Canada, Denmark, France, Germany, Italy, Netherlands, Norway, Poland, Spain, UK, US)	<u>Primary objective:</u> - Adjudicated ORR (CR/CRh + PR + CI) based on mIWG-MRT-ECNM criteria <u>Secondary objectives:</u> - Change in AdvSM-SAF TSS - Investigator-assessed ORR - Time to event outcomes (TTR, DOR, PFS, OS) - Morphologic response (CR/CRh + PR) based on PPR criteria - ORR, DOR, PFS, and OS by prior therapy and genotype - Changes in measures of MC burden - Changes in PROs and QoL - Assess safety and PK - Correlate exposure with safety and efficacy endpoints	Phase 2, open-label, single-arm, 2-cohort	Male or female patients ≥ 18 years old with AdvSM as confirmed by WHO diagnostic criteria and by the SSC - *Cohort 1:* ≥ 1 measurable C-finding per mIWG-MRT-ECNM, attributed to SM unless diagnosis was MCL (C-findings not required) - *Cohort 2:* ASM, SM-AHN, or MCL and no measurable C-findings per mIWG-MRT-ECNM	Cohort 1 and 2: 200 mg QD [b]	Cohort 1: 85 patients Cohort 2: 22 patients

Study Identifier/ Status	Number of Study Centers/ Countries	Study Objective(s)	Study Design	Disease Population	Dose/Dosing Regimen	Number of Patients
BLU-285-2405 (NCT04695431) Complete	6 centers/ 5 countries (Austria, Germany, Spain, UK, US)	Primary objective: -Comparative evaluation of overall survival (OS) between real-world patients receiving best available therapy versus patients receiving avapritinib in Studies 285-2101 and BLU-285-2202 Secondary objectives: -Comparative evaluation between real-world patients receiving best available therapy versus patients receiving avapritinib in studies BLU-285-2101 and BLU-285-2202, of: ---DOT ---TtNTL ---Change in serum tryptase - Safety profile	External control, observational, retrospective study	Patients diagnosed with AdvSM (ASM, SM-AHN or MCL)	observational	176 patients from avapritinib studies 141 patients from real world group

Abbreviations: AdvSM = advanced systemic mastocytosis; AdvSM-SAF = Advanced Systemic Mastocytosis-Symptom Assessment Form; ASM = aggressive systemic mastocytosis; CI = clinical improvement; CR = complete remission; CRh = complete remission with partial recovery of peripheral blood counts; DOR = duration of response; DOT = duration of treatment; EudraCT = European Clinical Trials Database; MAF = mutant allele fraction; MCL = mast cell leukemia; mIWG-MRT-ECNM = modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis International Working Group; MTD = maximum tolerated dose; NCT = a unique identification code given to each clinical study record registered on ClinicalTrials.gov; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK= pharmacokinetic; PPR = pure pathologic response; PR = partial remission; PRO = patient-reported outcome; QD = once daily; QoL = quality of life; RP2D = recommended Phase 2 dose; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm; SSC = Study Steering Committee; TtNTL = time to next treatment line; TSS = total symptom score; TTR = time to response; WHO = World Health Organization; UK = United Kingdom; US = United States.

[a] A dose of 300 mg QD was initially determined as RP2D based on data from Part 1 of Study BLU-285-2101 and later reduced to 200 mg QD based on new data demonstrating efficacy and improved tolerability at this dose level.

[b] Patients were treated at a starting dose of 200 mg QD, with the exception of patients with platelet counts ranging from 25,000 to 50,000/μL at baseline who were treated at a starting dose of 100 mg QD. With Protocol Amendment 5, patient with platelet counts < 50,000/μL were excluded from enrolment.

Source: CSR BLU-285-2101, CSR BLU-285-2202, CSR BLU-285-2405, data on file.

Initial Scientific Advice from the CHMP regarding the SM program for avapritinib was received on 31 May 2018 (procedure EMEA/H/SA/3738/2/2018/SME/III). Later, Simultaneous National Scientific Advice was obtained from the Spanish Agency of Medicines and Medical Products and the Norwegian Medicines Agency for a planned external-control, observational, retrospective study (BLU-285-2405). SA is further discussed under "The development programme/compliance with CHMP guidance/scientific advice".

2.6.5.1. Dose response study(ies)

Study BLU-285-2101 is an ongoing, open-label, Phase 1 study designed to evaluate the safety, tolerability, PK, pharmacodynamics, and antineoplastic activity (efficacy) of avapritinib, administered orally, in adult patients with AdvSM and relapsed or refractory myeloid malignancies. As of the data cut-off date of 27 May 2020, enrolment in the study is complete at 86 patients and patients remaining on study are being followed for response and safety assessments.

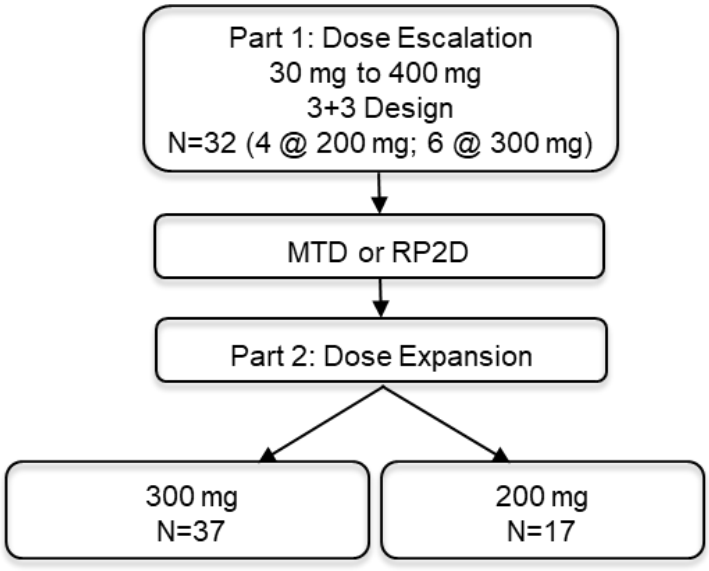
The primary objective was to establish the maximum tolerated dose and the recommended Phase 2 dose.

This 2-part study included:

- an initial **dose escalation** (**Part 1**, complete) to evaluate safety and tolerability of increasing doses of avapritinib (from 30 to 400 mg QD) in patients with a local diagnosis of AdvSM or other relapsed or refractory myeloid malignancies,
- and an **expansion** (**Part 2**, ongoing) to further evaluate the safety, PK, pharmacodynamics, and efficacy (according to mIWG-MRT-ECNM response criteria) of avapritinib in the treatment of AdvSM when administered at starting doses of 200 or 300 mg QD.

Part 2 enrolled patients with a WHO diagnosis of AdvSM. A central pathologic review was implemented to confirm diagnosis for all patients and to assess response for patients in Parts 1 and 2 of the study.

Figure 2 Study Schematic of BLU-285-2101



Abbreviations: MTD = maximum tolerated dose; RP2D = recommended Phase 2 dose. Source: adapted from CSR BLU-285-2101.

Part 1: Dose Escalation (with enrichment)

The primary objectives of Part 1 were to determine the MTD, RP2D as well as the initial safety and tolerability of avapritinib. Part 1 was designed to enroll patients with a local diagnosis of AdvSM or relapsed or refractory myeloid malignancy. Patients had a confirmed diagnosis of 1 of the following, based on WHO diagnostic criteria:

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

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

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

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

Table 11 **Dose Escalation Results**

Avapritinib Dose Level, mg QD	Dose Escalation		Enrichment Cohorts		DLTs/Total Evaluable (N)
	Enrolled/Evaluable (N/N)	Number of DLTs	Additional Accrual/Evaluable (N)	Number of DLTs	
30	3/3	0	0	0	0/3
60	6/6	0[a]	0	0	0[a]/6
100	3/3	0	0	0	0/3
130	3/3	0	0	0	0/3
200	4/3	0	0	0	0/3
300	3/3	0	3/3	0	0/6
400	7/6	1	0/0	0	1/6

Abbreviations: DLT = dose-limiting toxicity; QD = once daily.
[a]One patient had a Grade 3 increased alkaline phosphatase, which was initially assessed by the Investigator to be a DLT and the cohort was expanded to 6 patients; however, it was later revised to not be a DLT.
Source: Dose escalation meeting minutes on file.

Part 2: Expansion

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

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

Based on data demonstrating efficacy at all tested dose levels and emerging safety data showing improved tolerability at the 200 mg QD, a second expansion cohort (Cohort 2) with a starting dose of 200 mg QD was added in Part 2 enrolling patients with AdvSM (regardless of subtype) who had ≥ 1 measurable C-finding by mIWG-MRT-ECNM criteria.

This change was introduced with Protocol Amendment 6. With Protocol Amendment 7, all patients newly enrolling into Cohort 1 received a starting dose of 200 mg QD.

As of the data cut-off date, 54 patients had been enrolled in Part 2 of the study (CSR BLU-285-2101). Of these, 37 patients received avapritinib at the RP2D of 300 mg QD and **17 patients received avapritinib at a starting dose of 200 mg QD (in addition to the 4 patients enrolled in Part 1 of the study).**

Dose modifications in Study 2101. Source: Table 14.1.6.1 2101-CSR

	Starting Dose (QD)				
	<200 mg (N=15)	200 mg (N=21)	300 mg (N=43)	200 mg + 300mg (N=64)	All Doses (N=86)
Number of Dose Increases (n (%))					
0	7 (46.7)	17 (81.0)	38 (88.4)	55 (85.9)	69 (80.2)
1	4 (26.7)	3 (14.3)	3 (7.0)	6 (9.4)	10 (11.6)
2	4 (26.7)	1 (4.8)	1 (2.3)	2 (3.1)	6 (7.0)
>2	0	0	1 (2.3)	1 (1.6)	1 (1.2)
Number of Dose Reductions due to AE (n (%))					
0	12 (80.0)	7 (33.3)	4 (9.3)	11 (17.2)	23 (26.7)
1	2 (13.3)	9 (42.9)	15 (34.9)	24 (37.5)	28 (32.6)
2	1 (6.7)	4 (19.0)	20 (46.5)	24 (37.5)	27 (31.4)
>2	0	1 (4.8)	4 (9.3)	5 (7.8)	8 (9.3)
Time to First Dose Reduction (weeks)					
n	5	15	40	55	67
Mean (StdDev)	63.17 (31.509)	8.84 (8.148)	14.39 (17.229)	12.88 (15.422)	16.49 (20.983)
Median	68.14	4.86	10.64	8.14	9.71
Min, Max	25.0, 109.4	2.9, 27.1	0.4, 108.9	0.4, 108.9	0.4, 109.4
Number of Dose Interruption/Missing due to AE (n (%))					
0	5 (33.3)	5 (23.8)	9 (20.9)	14 (21.9)	19 (22.1)
1	5 (33.3)	10 (47.6)	11 (25.6)	21 (32.8)	27 (31.4)
2	2 (13.3)	3 (14.3)	7 (16.3)	10 (15.6)	14 (16.3)
>2	3 (20.0)	3 (14.3)	16 (37.2)	19 (29.7)	26 (30.2)

Source: Listing 16.2.5.1

Note by assessor: The 7 patients with 400 mg QD starting dose are included in the "All Doses" group.

Results

Overall, in the safety population (N=69: 8 ASM, 48 SM-AHN; 13 MCL), median (range) treatment duration was 18.79 (1.0 to 50.6) months. Median (range) relative dose intensity was 62% (20% to 293%) in patients treated at all doses, 64% (20% to 139%) in patients treated at 200 mg QD, and 56% (25% to 106%) in patients treated at 300 mg QD.

Overall, the ORR (CR + CRh + PR + CI) was 75.5% (40/53), which was higher than the prespecified null hypothesis of 28% ($p < 0.0001$, Wald test). No patient had PD as their best response. Responses occurred in all subtypes of AdvSM. The CR + CRh + PR rate was 69.8% with 37 of 53 AdvSM patients achieving a best confirmed response of CR, CRh, or PR. The CR + CRh + PR rate of 69.8% was significant compared to the prespecified null of 17% ($p < 0.0001$, Wald test).

Table 12 **Summary of Centrally Adjudicated Response Rates and Event Analyses by mIWG-MRT-ECNM Criteria (RAC-RE Population)**

Parameter	All Doses			
	ASM N=3	SM-AHN N=37	MCL N=13	All AdvSM N=53
Response analyses, responders (%) [95% confidence interval]				
ORR (CR + CRh + PR + CI)	3 (100) [29.2, 100]	28 (75.7) [58.8, 88.2]	9 (69.2) [38.6, 90.9]	40 (75.5) [61.7, 86.2)] $p < 0.0001$ (H_0=28%)
CR + CRh + PR rate	3 (100) [29.2, 100]	27 (73.0) [55.9, 86.2]	7 (53.8) [25.1, 80.8]	37 (69.8) [55.7, 81.7] $p<0.0001$ (H_0=17%)
CR + CRh rate	2 (66.7) [9.4, 99.2]	14 (37.8) [22.5, 55.2]	3 (23.1) [5.0, 53.8]	19 (35.8) [23.1, 50.2]
Time to event analyses, median (range) in months				
Time to response (CR + CRh + PR + CI)	1.84 (0.3 to 1.9)	1.89 (0.7 to 26.7)	1.87 (1.3 to 26.7)	1.87 (0.3 to 26.7)
Time to CR + CRh + PR	1.87 (1.9 to 5.6)	2.37 (1.8 to 26.7)	1.87 (1.6 to 26.7)	2.04 (1.6 to 26.7)
Time to CR + CRh	7.20 (1.9 to 12.5)	10.05 (5.5 to 32.2)	5.65 (2.1 to 37.9)	9.43 (1.9 to 37.9)
Time to event analyses, median (95% confidence interval)				
DOR	NE (NE, NE)	38.3 (21.7, NE)	NE (9.2, NE)	38.3 (21.7, NE)
Censored, n (%)	3 (100)	19 (67.9)	6 (66.7)	28 (70.0)
KM estimate at 12 months, %	100	84.3	75.0	83.6
Duration of CR + CRh + PR	NE (NE, NE)	38.3 (19.4, NE)	NE (21.6, NE)	38.3 (21.6, NE)
KM estimate at 12 months, %	100	83.6	100	88.1
PFS, median (95% confidence interval)	NE (NE, NE)	30.5 (21.4, NE) months	NE (23.8, NE)	40.3 (23.8, NE) months
KM estimate at 12 months, %	100	79.6	91.7	83.5
OS, median (95% confidence interval)[a]	NE (NE, NE)	46.9 (24.5, NE) months	NE (31.2, NE)	NE (46.9, NE) months
KM estimate at 12 months, %	100	81.9	91.7	85.8

Abbreviations: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; CI = clinical improvement; CR = complete remission; CRh = complete remission with partial recovery of peripheral blood counts; DOR = duration of response; KM = Kaplan-Meier; mIWG-MRT-ECNM = modified International Working Group-Myeloproliferative Neoplasm Research and Treatment and European Competence Network on Mastocytosis; MCL = mast cell leukemia; NE = not evaluable; ORR = overall response rate; OS = overall survival;

PFS = progression-free survival; PR = partial remission; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm.
[a] Overall survival in the safety population (N=69, 8 ASM, 48 SM-AHN, and 13 MCL).
Sources: CSR BLU-285-2101, Table 28, Table 39, Table 41, Table 46, Table 48, and Table 49.

Updated results from this study pertaining to the population of interest, i.e. RE patients according to modified IWG-MRT-ECNM following at least one prior systemic therapy and receiving a starting dose of 200 mg QD were submitted during the procedure and are included below:

Table 13 Updated results from this study pertaining to the population of interest, i.e. RE patients according to modified IWG-MRT-ECNM following at least one prior systemic therapy and receiving a starting dose of 200 mg QD

Efficacy parameter	Data cut-off date 27 May 2020		Data cut-off date 20 April 2021	
	Regardless of prior systemic therapy	At least one prior systemic therapy	Regardless of prior systemic therapy	At least one prior systemic therapy
Response Evaluable Population N	**13**	**9**	**16**	**11**
Median follow-up (months) (95% confidence interval)	15.2 (9.0, 38.7)	16.1 (9.5, 19.0)	22.4 (18.2, 29.7)	26.0 (18.2, 29.7)
ORR, N (%)[1] (CR+CRh+PR+CI) (95% confidence interval)	7 (53.8) (25.1, 80.8)	4 (44.4) (13.7, 78.8)	11 (68.8) (41.3, 89.0)	8 (72.7) (39.0, 94.0)
CR+CRh	2 (15.4)	2 (22.2)	3 (18.8)	3 (27.3)
CR	0	0	1 (6.3)	1 (9.1)
CRh	2 (15.4)	2 (22.2)	2 (12.5)	2 (18.2)
PR	5 (38.5)	2 (22.2)	8 (50)	5 (45.4)
CI	0	0	0	0
DOR[2] (months), median (95% confidence interval)	21.6 (11.2, 21.6)	NE (11.2, NE)	NE (21.6, NE)	NE (NE, NE)
DOR rate at 12 months, %	75.0	66.7	88.9	83.3
DOR rate at 24 months, %	NE	NE	59.3	83.3
Time to response (months), median	1.9	1.9	2.2	6.1
Time to CR/CRh (months), median	20.7	20.7	9.3	9.3
Median OS (months), AdvSM Population (95% confidence interval)	N = 20 NE (13.0, NE)	N = 12 NE (13.0, NE)	N = 20 NE (NE, NE)	N = 12 NE (13.0, NE)
OS rate at 12 months, %	81.2	82.5	80.0	83.3

Efficacy parameter	Data cut-off date 27 May 2020		Data cut-off date 20 April 2021	
	Regardless of prior systemic therapy	At least one prior systemic therapy	Regardless of prior systemic therapy	At least one prior systemic therapy
OS rate at 24 months, %	67.7	66.0	74.7	74.1
OS rate at 36 months, %	67.7	66.0	74.7	74.1

Abbreviations: CI = clinical improvement, CR = complete remission, CRh = complete hematologic remission, DOR = duration of response, IA = interim analysis, IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis, NE = not estimable, ORR = overall response rate, OS = overall survival, PR = partial remission, TTR = time to response, QD – once daily
Source: Original ISE (SN0012): Table 14.2.4.2, Table 14.2.1.1, Table 14.2.1.1.f , Table 14.2.2.1, Table 14.2.2.1b, Table 14.2.2.4, and Table 14.2.4.1
Original ISE (Annex 1): Table 99.2.4.2.1, Table 99.2.2.4.1, Table 99.2.4.1.1
Updated ISE 20 April 2021 (Annex 1): Table 14.2.4.2, Table 99.2.4.2.1, Table 14.2.1.1, Table 14.2.1.1f, Table 14.2.2.1, Table 14.2.2.1b, Table 14.2.2.4, Table 99.2.2.4.1, Table, 14.2.4.1, and Table 99.2.4.1.1

Overall, in the RAC-RE population the median follow-up increased from 16.1 months (27 May 2020) to 26.0 months (20 April 2021) for patients who had received prior systemic therapy and were treated with an avapritinib starting dose of 200 mg QD. Results by disease subtype are included in the table below.

Table 14 Summary of Centrally Adjudicated Response Rates and Event Analyses by mIWG-MRT-ECNM Criteria in Patients with Prior Systemic Therapy (20 April 2021, BLU-285-2101, RAC-RE Population, 200 mg)

Parameter	ASM N=1	SM-AHN N=6	MCL N=4	All AdvSM N=11
Response analyses, responders (%) [95% confidence interval]				
ORR (CR + CRh + PR + CI)	1 (100) [2.5, 100]	4 (66.7) [22.3, 95.7]	3 (75.0) [19.4, 99.4]	8 (72.7) [39.0, 94.0]
CR + CRh + PR rate	1 (100) [2.5, 100]	4 (66.7) [22.3, 95.7]	3 (75.0) [19.4, 99.4]	8 (72.7) [39.0, 94.0]
CR + CRh rate	1 (100) [2.5, 100]	2 (33.3) [4.3, 77.7]	0	3 (27.3) [6.0, 61.0]
Time to Response median (range) in months				
Time to response (CR + CRh + PR + CI)	N = 1 9.30 (9.3 to 9.3)	N = 4 2.32 (0.3 to 26.7)	N = 3 9.46 (1.6 to 9.5)	N = 8 6.05 (0.3 to 26.7)
Time to CR + CRh + PR	N = 1 9.30 (9.3 to 9.3)	N = 4 4.19 (1.8 to 26.7)	N = 3 9.46 (1.6 to 9.5)	N = 8 7.44 (1.6 to 26.7)
Time to CR + CRh	N = 1 9.30 (9.3 to 9.3)	N = 2 20.73 (9.2 to 32.2)	-	N = 3 9.30 (9.2 to 32.2)
Duration of Response median (95% confidence interval)				
DOR, months	N = 1 NE (NE, NE)	N = 4 NE (11.2, NE)	N = 3 NE (NE, NE)	N = 8 NE (NE, NE)
Censored, n (%)	1 (100)	3 (75)	4 (100)	7 (87.5)
KM estimate at 12 months, %	-	75.0	100.0	83.3
KM estimate at 24 months, %	-	-	100	83.3

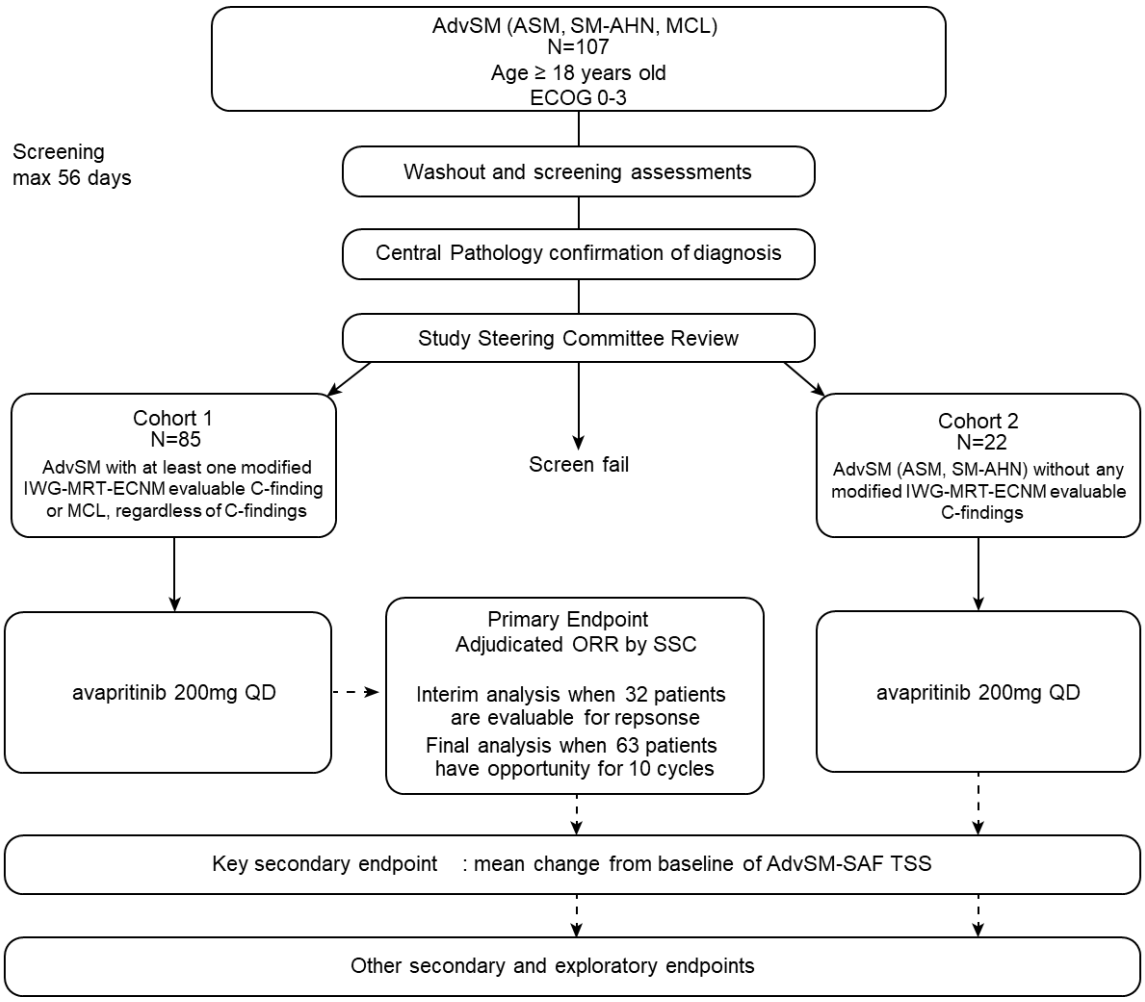
Parameter	ASM N=1	SM-AHN N=6	MCL N=4	All AdvSM N=11
Duration of CR + CRh + PR	N = 1 NE (NE, NE)	N = NE (11.2, NE)	N = 3 NE (21.6, NE)	N = 8 NE (NE, NE)
KM estimate at 12 months, %	-	75.0	100.0	83.3
KM estimate at 24 months, %	-	-	100.0	83.3
PFS, median, months (95% confidence interval)	NE (NE, NE)	NE (8.0, NE)	NE (NE, NE)	NE (13.0, NE)
KM estimate at 12 months, %	100	66.7	100.0	81.8
KM estimate at 24 months, %	-	50.0	100	71.6
OS, median, months (95% confidence interval)[a]	NE (NE, NE)	NE (8.0, NE)	NE (NE, NE)	NE (13.0, NE)
KM estimate at 12 months, %	100	66.7	100	81.8
KM estimate at 24 months, %	-	50.0	100	71.6

Abbreviations: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; CI = clinical improvement; CR = complete remission; CRh = complete remission with partial recovery of peripheral blood counts; DOR = duration of response; KM = Kaplan-Meier; mIWG-MRT-ECNM = modified International Working Group-Myeloproliferative Neoplasm Research and Treatment and European Competence Network on Mastocytosis; MCL = mast cell leukemia; NE = not evaluable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial remission; RAC-RE = Response Assessment Committee Response-Evaluable; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm.
Source Updated ISE, 20 April 2021:Table 14.2.1.1f, Table 99.2.2.4.1, Table 14.2.2.1b, Table 99.2.3.1a and, Table 99.2.4.2.1

2.6.5.2. Main study(ies)

An open-label, single arm, Phase 2 study evaluating the efficacy and safety of avapritinib (BLU-285) in patients with advanced systemic mastocytosis (AdvSM), including patients with aggressive SM (ASM), SM with associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL)

Study schematic of BLU-285-2202 (DCO date of 20 April 2021)



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

Methods

- **Study Participants**

Inclusion criteria at the latest global amendment (Amendment 7.1)

Patients meeting the following criteria will be eligible for participation in the study:

1. Patients who are ≥ 18 years of age.
2. Patients must have 1 of the following diagnoses as confirmed by WHO diagnostic criteria. Before enrolment, the SSC must confirm the diagnosis of AdvSM based on Central Pathology Laboratory assessment of BM).
   - Aggressive systemic mastocytosis (ASM).
   - Systemic mastocytosis with an associated hematologic neoplasm (SM-AHN).
     - The AHN must be myeloid, with the following exceptions that are excluded:

- AML.
- Myelodysplastic syndrome that is very high- or high-risk, as defined by the International Prognostic Scoring System for Myelodysplastic Syndromes (Greenberg et al, 2012).
- A myeloid AHN with ≥ 10% BM or PB blasts.
- Philadelphia chromosome-positive malignancies.

▪ Incidental indolent, low-grade lymphoid AHNs (eg, chronic lymphocytic leukemia) not requiring treatment are eligible.

o MCL, including diagnoses with an AHN component.

3. Patients with SM-AHN should have received prior treatment for the AHN component of disease if, in the opinion of the Investigator, such therapy was appropriate.
4. Patient must have a BM biopsy taken within 56 days of C1D1, assessed by the Central Pathology Laboratory.
5. **Cohort 1 only**: Patient must have at least 1 of the following measurable C-findings, per modified IWG-MRT-ECNM criteria, attributed to SM (*Appendix 6*, unless diagnosis is MCL, which does not require a C-finding). Laboratory abnormality C-findings should not be assessed until the required washout period from last cytoreductive therapy has been met. If a C-finding improves during the screening period, prior to dosing, and no longer meets criteria for evaluability, it can no longer be counted as a C-finding.

Table 15 Modified IWG-MRT-ECNM Definition of Evaluable C-Findings

Nonhematologic C-findings	
Ascites or pleural effusions	Symptomatic ascites or pleural effusion requiring medical intervention such as (1) Use of diuretics (Grade 2) *or* (2) ≥ 2 therapeutic paracenteses *or* thoracenteses (Grade 3) at least 28 days apart over 12 weeks before C1D-8 with 1 procedure performed during the 6 weeks before C1D-8
Liver function abnormalities	• ≥ Grade 2 abnormalities in direct bilirubin (> 1.5 × ULN), AST (> 3.0 × ULN), ALT (> 3.0 × ULN) or AP (> 2.5 × ULN) in the presence of: o Ascites *and/or* o Clinically relevant portal hypertension, *and/or* o Liver MC infiltration that is biopsy-proven *or* o No other identified cause of abnormal liver function
Hypoalbuminemia	≥ Grade 2 hypoalbuminemia (< 3.0 g/dL)
Marked splenomegaly	A spleen that is palpable ≥ 5 cm below the left costal margin
Hematologic C-findings	
ANC	≥ Grade 3 ANC (< 1.0×10^9/L)
Anemia (transfusion-independent)	≥ Grade 2 Hgb (< 10 g/dL)
Anemia (transfusion-dependent)	• Transfusion of ≥ 6 units PRBCs in the 12 weeks before C1D-8 *and* • Most recent transfusion occurring during the 4 weeks before C1D-8 *and* • Transfusions administered for Hgb ≤ 8.5 g/dL *and* • Reason for transfusions is not bleeding, hemolysis, or therapy-related
Thrombocytopenia (transfusion-independent)	≥ Grade 2 thrombocytopenia (< 75×10^9/L)
Thrombocytopenia (transfusion-dependent)	• Transfusion of ≥ 6 units of apheresed platelets (or ≥ 6 pools of random donor or buffy coat) 12 weeks before C1D-8 *and* • ≥ 2 units transfused 4 weeks before C1D-8 *and* • Transfusions administered for platelet count < 20×10^9/L

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AP = alkaline phosphatase; AST = aspartate aminotransferase; C1D1 = Cycle 1 Day 1; Hgb = hemoglobin; IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasms Research and Treatment; MC = mast cell; PBRC = packed red blood cell; ULN = upper limit of normal.
Notes: One or more C-findings is required for eligibility. Grade is based on the Common Terminology Criteria for Adverse Events, Version 5.0.
Source: Adapted from (Gotlib et al, 2013).

In addition,

- Patients must have documented evidence of MC aggregates in the bone marrow or other extracutaneous organ based on central pathology
- Patient must be willing to have follow up biopsies of affected organ(s) to document response.

Measurable C-findings:

- Cytopenias:

- ANC < 1.0 × 10^9/L or
- Hemoglobin < 10 g/dL or
- Platelet count < 75 × 10^9/L.

NOTE: Cytopenias attributable to prior cytoreductive therapy or causes other than SM may not be used as C-findings.

- Symptomatic ascites or pleural effusion requiring medical intervention such as:
  - Use of diuretics (Grade 2) or
  - ≥ 2 therapeutic paracenteses or thoracenteses (Grade 3) at least 28 days apart over the 12 weeks before C1D-8 and 1 of the procedures is performed during the 6 weeks before C1D-8.
- ≥ Grade 2 abnormalities in direct bilirubin (> 1.5 × upper limit of normal [ULN]), aspartate aminotransferase (AST; > 3.0 × ULN), alanine aminotransferase (ALT; > 3.0 × ULN), or alkaline phosphatase (> 2.5 × ULN) with 1 of the following present:
  - Ascites or
  - Clinically relevant portal hypertension or
  - Liver MC infiltration that is biopsy-proven or
  - No other identified cause of abnormal liver function.
- ≥ Grade 2 hypoalbuminemia (< 3.0 g/dL).
- A spleen that is palpable ≥ 5 cm below the left costal margin.
- Transfusion-dependent anemia defined as:
  - Transfusion of ≥ 6 units packed red blood cells (PRBCs) in the 12 weeks
  - before C1D-8 and
  - Most recent transfusion occurring during the 4 weeks before C1D-8 and
  - Transfusion administered for hemoglobin ≤ 8.5 g/dL and
  - Reason for transfusion is not bleeding, hemolysis, or therapy related.

6. Patient must have a serum tryptase ≥ 20 ng/mL.
7. Patients receiving cytoreductive therapy within the preceding 12 weeks must have discontinued therapy due to disease progression, refractory disease, lack of efficacy, or intolerance.
8. Patient's non-antineoplastic SM therapies (ie, BSC; eg, H1 and H2 blockers) must be stable (same dose, no new medications for SM) for ≥ 14 days C1D-8. This criterion is not applicable if a patient has progressive disease and it is in the patient's best interest to enrol in the study rapidly with Medical Monitor approval.
9. If the patient is receiving corticosteroids, the dose must be ≤ 20 mg/d prednisone or equivalent and dose must be stable for ≥ 14 days before C1D-8. This criterion is not applicable if the patient has progressive disease, and it is in the patient's best interest to enrol in the study rapidly with Medical Monitor approval.
10. Patient has Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 3.
11. Patient must be able to give written informed consent.

<u>Main exclusion Criteria</u>

1. Patients meeting any of the following criteria will not be eligible for participation in the study:
2. Patient has received prior treatment with avapritinib.

3. Patient has received any cytoreductive therapy (including midostaurin and other TKIs, hydroxyurea, azacitidine) or an investigational agent less than 14 days, and for cladribine, interferon alpha, pegylated interferon and any antibody therapy (eg, brentuximab vedotin) less than 28 days before obtaining screening BM biopsy for this study. If the patient has progressive disease and it is in the patient's best interest to enrol in the study rapidly, cytoreductive therapy may be discontinued 1 day before the screening BM biopsy with approval from the Medical Monitor. Cytoreductive therapy may not be restarted during Screening or while on study.
4. Patient has received prior radiotherapy within 14 days before the screening BM biopsy, unless given to palliate specific sites of disease (eg, bone lesion).
5. Patient received any hematopoietic growth factor within 14 days of screening BM biopsy.
6. Patient requires therapy with a concomitant medication that is a strong inhibitor, strong inducer, or moderate inducer of CYP3A4.
7. Patient has had a major surgical procedure within 14 days of the first dose of study drug. Surgical procedures such as central venous catheter placement, BM biopsy, and feeding tube placement are considered minor surgical procedures.
8. Patient is a candidate for allogeneic hematopoietic stem cell transplantation for treatment of SM, in the opinion of the Investigator.
9. Patient has eosinophilia and known positivity for the *FIP1L1-PGDFRA* fusion, unless the patient has demonstrated relapse or PD on prior imatinib therapy. Patients with eosinophilia (> 1.5 × 109/L), who do not have a detectable *KIT* D816 mutation, must be tested for a *PDGFRA* fusion mutation by fluorescence in situ hybridization (FISH) or PCR.
10. Patient has history of another primary malignancy that has been diagnosed or required therapy within 3 years before the first dose of study drug. The following are exempt from the 3-year limit: completely resected basal cell and squamous cell skin cancer, curatively treated localized prostate cancer, and completely resected carcinoma in situ of any site.
11. Patient meets any of the following laboratory criteria:
    - AST or ALT > 3.0 × ULN; no restriction if due to suspected liver infiltration by MCs.
    - Bilirubin > 1.5 × ULN; no restriction if due to suspected liver infiltration by MCs or Gilbert's disease. (In the case of Gilbert's disease, a direct bilirubin > 2.0 × ULN would be an exclusion.)
    - Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m2 or creatinine> 1.5 × ULN.
    - Platelet count < 50,000/µL (within 4 weeks of the first dose of study drug) or receiving platelet transfusion(s)
12. Patient has a QT interval corrected using Fridericia's formula (QTcF) > 480 msec.
13. Patient has a history of a seizure disorder (eg, epilepsy) or requirement for antiseizure medication.
14. Patient has a history of a cerebrovascular accident or transient ischemic attacks within 1 year before the first dose of study drug.
15. Patient has a known risk or recent history (12 months before the first dose of study drug) of intracranial bleeding (eg, brain aneurysm, concomitant vitamin K antagonist use).

- **Treatments**

Avapritinib was administered orally, at a starting dose of **200 mg QD** (Amendment 1), from **D1 to D28 in 28-day cycles**. Dosing was continuous, with **no inter-cycle rest periods**.

Initially, to manage thrombocytopenia and bleeding risk avapritnib was reduced to 100 mg QD for patients with platelet counts from 25,000 to 50,000/μL at baseline (Amendment 3). This was later updated to exclude patients with platelet counts <50,000/μL at baseline from enrolment (Amendment 5). In total, 2 patients received a starting dose of 100 mg QD.

Avapritinib doses were administered with a glass of water (≥ 8 ounces or 250 mL) in a fasted state, with no food intake from 2 hours before until 1 hour after avapritinib administration. Each dose was administered at approximately the same time each day.

Patients were instructed to not chew but swallow the tablets whole. Antacids were not to be taken within 3 hours before or after avapritinib administration.

If a patient forgot to take a dose, he/she had to take it until 4:00 PM (morning dose schedule) or 12:00 AM (evening dose schedule) that day. If the dose was not taken by the specified time, then that dose was omitted, and the patient resumed treatment with the next scheduled dose. If the patient switched from a morning dose schedule to an evening dose schedule, he/she had to ensure the doses were taken ≥ 8 hours apart. If a patient vomited during or after taking avapritinib, redosing was not permitted and the patient should resume treatment with the next scheduled dose.

- **Objectives**

Primary:

To determine adjudicated **ORR** (CR+CRh+PR+CI) based on mIWG-MRT-ECNM consensus response criteria in patients with AdvSM treated with avapritinib and enrolled in Cohort 1.

The ORR is tested for superiority versus midostaurin (see Statistical methods)

Response criteria applied for assessment:

Table 16 **Modified IWG-MRT-ECNM Consensus Response Criteria in Advanced Systemic Mastocytosis**

Response	Criteria for Response	
Complete remission (CR)[a]	Requires all 4 of the following criteria, and response duration must be ≥ 12 weeks: • No presence of compact neoplastic MC aggregates in the BM or other biopsied extracutaneous organ • Serum tryptase level < 20 ng/mL[b] • Peripheral blood count remission defined as: o ANC ≥ 1 × 10^9/L with normal differential (absence of neoplastic MCs and blasts < 1%) *and* o Platelet count ≥ 100 × 10^9/L *and* o Hgb level ≥ 11 g/dL • Complete resolution of palpable hepatosplenomegaly and all biopsy-proven or suspected SM-related organ damage (C-findings)[c]	
CR with partial recovery of peripheral blood counts (CRh)[a]	Requires all criteria for CR be met and response duration must be ≥ 12 weeks; however, patient may have residual cytopenias. The following minimum recovery of peripheral blood counts is required: • ANC > 0.5 × 10^9/L with normal differential (absence of neoplastic MCs and blasts < 1%) *and* • Platelet count > 50 × 10^9/L *and* • Hgb level > 8.0 g/dL	
Partial remission (PR)[a]	Requires all 3 of the following criteria, and response duration must be ≥ 12 weeks, in the absence of CR/CRh and PD: • Reduction by ≥ 50% in neoplastic MCs in the BM[d] *and/or* other extracutaneous organ at biopsy demonstrating eligible SM-related organ damage • Reduction of serum tryptase level by ≥ 50%[b] • Resolution of 1 or more biopsy-proven or suspected SM-related organ damage (C-finding[s])[c]	
Clinical improvement (CI)[a]	Response duration must be ≥ 12 weeks Requires 1 or more of the nonhematologic and/or hematologic response criteria to be fulfilled (refer to Appendix 9) in the absence of CR, CRh, PR, or PD	
Stable disease (SD)	Not meeting criteria for CR/CRh, PR, CI, or PD	
Progressive disease (PD)[e]	Requires at least 1 element from the criteria below; duration must be ≥ 4 weeks:	
	Baseline	**Postbaseline**
	Any Grade 2 nonhematologic organ damage	• Worsening by 1 grade *and* • Minimum 100% increase (doubling) of laboratory abnormality
	≥ Grade 2 albumin	• Worsening by 1 grade *and* • Decrease by ≥ 0.5 g/dL
	≥ Grade 3 nonhematologic organ damage	Minimum 100% increase (doubling) of laboratory abnormality
	≥ Grade 2 transfusion-independent anemia or thrombocytopenia	New transfusion dependence for an 8-week period of ≥ 4 units of PRBCs or platelets

Response	Criteria for Response	
	Transfusion-dependent anemia or thrombocytopenia	• ≥ 100% increase in the average transfusion frequency for an 8-week period compared with the 12-week pretreatment period
	≥ Grade 3 neutropenia	• > 50% decrease in neutrophil count *and* • Absolute decrease of neutrophil count of ≥ 0.25 x 10^9/L *and* • Grade 4 (< 0.5 x 10^9/L)
	Baseline spleen size of not palpable or < 5 cm	• Development of at least 10 cm palpable symptomatic splenomegaly *or* • Increase in spleen volume ≥ 25%
	Splenomegaly ≥ 5 cm	• > 50% worsening *and* • Development of ≥ 10 cm of palpable symptomatic splenomegaly compared with the baseline value *or* • Increase in spleen volume ≥ 25%
Loss of response (LOR)	Loss of a documented CR/CRh, PR, or CI that must be for ≥ 8 weeks. Downgrading of CR/CRh to PR or PR to CI is considered as such but is not considered a loss of response unless CI is also lost for a minimum of 8 weeks. The baseline value for LOR is the pretreatment measurement(s) and not the nadir values during response.	

Abbreviations: ANC = absolute neutrophil count; BM = bone marrow; CI = clinical improvement; CR = complete remission; CRh = complete remission with partial recovery of peripheral blood counts; Hgb = hemoglobin; IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasms Research and Treatment; LOR = loss of response; MC = mast cells; PBRCs = packed red blood cells; PD = progressive disease; PR = partial remission; SD = stable disease; SM = systemic mastocytosis.

Note: Guidelines for assessing response are as follows: (A) Only disease-related ≥ Grade 2 organ damage is evaluable as a primary endpoint. (B) Response assessments of CR, CRh, PR, SD, PD, and LOR should only be applied to these ≥ Grade 2 organ damage findings in the context of trials. (C) Disease status at the time of patient removal from the study singularly relates to the updated status of initial ≥ Grade 2 organ damage finding(s). (D) Exclusion of drug-related toxicity and/or other clinical issues (eg, gastrointestinal tract bleeding in the case of worsening anemia/transfusion-dependence) should be undertaken before assigning the designation PD or LOR in a patient with worsening of baseline ≥ Grade 2 organ damage.

[a] Responses that are not maintained for a period of at least 12 weeks do not fulfill criteria for CR/CRh, PR, or CI; however, both maintained and unmaintained (< 12 weeks duration) responses should be recorded in the electronic case report form each time they are observed in order to measure duration of response.

[b] Only valid as a response criterion if the pretreatment serum tryptase level is ≥ 40 ng/mL (ie, if pretreatment serum tryptase is < 40 ng/mL, it will not be considered as a criterion in evaluation of response).

[c] Biopsy of organ(s) in addition to the bone marrow to evaluate for SM-related organ damage may be considered.

[d] Only valid as a response criterion if the pretreatment BM MCs are ≥ 5% (ie, if pretreatment BM MCs are < 5%, BM MCs will not be considered as a criterion in evaluation of response).

[e] Preservation of at least 1 CI finding permits a patient to maintain the response of CI if 1 or more CI findings are lost but none meet criteria for PD. However, if 1 or more of the CI findings become PD, then the CI finding assignment is lost and the patient meets criteria for PD. The baseline value for

evaluating PD is the pretreatment measurement(s). The PD findings must be considered related to the underlying disease and not to other clinical factors. Progression of an underlying chronic myeloid neoplasm to acute myeloid leukemia is also considered PD.

Source: Adapted from (Gotlib et al, 2013).

Definition of clinical improvement:

Table 17 : Modified IWG-MRT-ECNM Clinical Improvement Criteria for Response

Criteria	Baseline criteria	Criteria for response
Nonhematologic		
Ascites or pleural effusions	(1) Symptomatic ascites or pleural effusion requiring medical intervention such as use of diuretics (Grade 2) or (2) ≥ 2 therapeutic paracenteses or thoracenteses at least 28 days apart over 12 weeks before C1D-8 (Grade 3) and 1 of the procedures is performed 6 weeks before C1D-8	(1) Complete resolution of symptomatic ascites or pleural effusion (including trace or minimal on radiographic imaging) and no longer in need of diuretics for ≥ 12 weeks and no longer in need of diuretics for ≥ 12 weeks or (2) No therapeutic paracenteses or thoracentesis for ≥ 12 weeks
Liver function test abnormalities	≥ Grade 2 abnormalities in direct bilirubin (> 1.5 × ULN), AST (> 3.0 × ULN), ALT (> 3.0 × ULN) or AP (> 2.5 × ULN) in the presence of: ascites and/or clinically relevant portal hypertension and/or liver MC infiltration that is biopsy-proven or other causes of abnormal liver function are not identified	Reversion of ≥ 1 LFTs to normal range for ≥ 12 weeks
Hypoalbuminemia	≥ Grade 2 hypoalbuminemia (< 3.0 g/dL)	Reversion of albumin to normal range for ≥ 12 weeks
Marked splenomegaly	A spleen that is palpable ≥ 5 cm below left costal margin	≥ 35% reduction in spleen volume based on 3D MRI for ≥ 12 weeks
Hematologic		
ANC	≥ Grade 3 ANC (< 1.0×10^9/L)	≥ 100% increase and an absolute increase ≥ 0.5×10^9/L for ≥ 12 weeks
Anemia (transfusion-independent)	≥ Grade 2 Hgb (< 10 g/dL)	An increase in Hgb ≥ 2 g/dL that is maintained for ≥ 12 weeks
Anemia (transfusion-dependent)	Transfusion of ≥ 6 units PRBCs in the 12 weeks before C1D-8 *and* Most recent transfusion occurring in the 4 weeks before C1D-8 *and* Transfusions administered for Hgb ≤ 8.5 g/dL *and* Reason for transfusions is not bleeding, hemolysis or therapy-related	Transfusion independence for ≥ 12 weeks and maintenance of Hgb ≥ 8.5 g/dL at the end of the 12-week period of response duration
Thrombocytopenia (transfusion-independent)	≥ Grade 2 thrombocytopenia (< 75×10^9/L)	≥ 100% increase and an absolute increase ≥ 50×10^9/L and no need for platelet transfusion for ≥ 12 weeks

Criteria	Baseline criteria	Criteria for response
Thrombocytopenia (transfusion-dependent)	(1) Transfusion of ≥ 6 units of spheresed (or ≥ 6 pools of random donor or buffy coat) platelets during the 12 weeks before C1D-8, and (2) ≥ 2 units transfused in the 4 weeks before C1D-8, and (3) Transfusions given for platelet count < 20×10^9/L	Transfusion independence for ≥ 12 weeks and maintenance a platelet count ≥ 20×10^9/L

Abbreviations: 3D = 3 dimension; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AP = alkaline phosphatase; AST = aspartate aminotransferase; Hgb = hemoglobin; IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; MC = mast cell; MRI = magnetic resonance imaging; LFT = liver function test; PRBC = packed red blood cell; ULN = upper limit of normal.
Note: Toxicity grading is based on Common Terminology Criteria for Adverse Events, Version 5.0.
Source: Adapted from (Gotlib et al, 2013).

Key secondary:

To assess mean change from baseline in AdvSM-SAF total symptom score (TSS) in patients in Cohorts 1 and 2;

- **Outcomes/endpoints**

Primary:

- Adjudicated **ORR** (CR+CRh+PR+CI) based on mIWG-MRT-ECNM criteria, confirmed **12 weeks after initial response in patients in Cohort 1 only**;

  Sensitivity analyses defined as secondary endpoints were conducted for ORR using algorithm-derived IWG-MRT-ECNM responses and investigator-assessed responses based on mIWG-MRT-ECNM criteria, and for pathologic ORR using Pure Pathologic Response (PPR) criteria.

  Algorithm-derived IWG-MRT-ECNM responses were based on a computer algorithm that derived responses per the original, published IWG-MRT-ECNM without modifications. The computer algorithm used the same source data as the SSC, including adjudicated diagnosis by SSC.

  Morphologic response by PPR criteria proposed by the SSC were used for all patients with measurable MC burden. PPR was derived by a computer algorithm using the same assessments that were used for mIWG-MRT-ECNM derivation and additionally KIT D816V Mutant Allele Fraction by central assay. The PPR criteria define responses as a direct measure of the disease burden. The PPR criteria are a modification of the mIWG-MRT-ECNM criteria and focus on objective changes (bone marrow MC burden, serum tryptase, and complete blood count).

  This study was the first to use the IWG-MRT-ECNM criteria, and some issues were identified that led to modification of the published criteria, leading to the modified IWG-MRT-ECNM criteria as shown in the following table:

Table 18 Original and Modified IWG-MRT-ECNM Criteria

Assessment	Original Criteria	Modified Criteria
Evaluable C-findings		

Symptomatic splenomegaly	Patient endorses symptoms of discomfort and/or early satiety	Symptoms not required
Splenomegaly	> 5 cm below left costal margin	≥ 5 cm below left costal margin
Response Criteria		
Pretreatment bone marrow MCs required for valid response criterion	NA	≥ 5%
CRh category of response	NA	Included
Duration for Confirmation of PD	8 weeks	4 weeks

Abbreviations: CRh = CR with partial recovery of peripheral blood counts; IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; MC = mast cells; NA = not applicable; PD = progressive disease.

Key secondary:

- Mean change from baseline in Advanced Systemic Mastocytosis-Symptom Assessment Form Total symptom score (AdvSM-SAF TSS) in patients in Cohorts 1 and 2;

Additional secondary:

- Local Investigator-assessed ORR (CR+CRh+PR+CI) based on mIWG-MRT-ECNM criteria, using C-findings when present, confirmed 12 weeks after initial response;
- Time to event outcomes including time to response, DOR, PFS, and OS;
- Objective response rate (CR+CRh+PR) based on PPR criteria;
- CR+CRh+PR and clinical benefit (CR+CRh+PR+CI+SD) based on mIWG-MRT-ECNM criteria;
- ORR and other clinical outcome measures (DOR, PFS, OS) analyzed by prior therapy and by genotype;
- Changes in bone marrow MCs, serum tryptase, KIT mutation burden (eg, D816V) in PB and bone marrow, and liver and spleen volume by imaging;
- Mean change from baseline in AdvSM-SAF domain and individual symptom scores;
- Changes in PGIS and EORTC QLQ-C30 (global health status, functional scales, and symptom scales/items) scores;
- Safety of avapritinib as assessed by AEs, changes in vital signs, ECGs, and laboratory testing;
- PK of avapritinib;
- Correlations between avapritinib exposure and safety and efficacy endpoints;

Exploratory:

- Additional measures of clinical benefit including:
    - Changes in transfusion-dependent anaemia and transfusion-dependent thrombocytopenia;
    - Changes in bone density;
    - Changes in cutaneous disease in patients with mastocytosis in skin;

- Changes in BSC medication use;
- AHN response rate in patients with SM-AHN;

- Potential correlations between efficacy and safety endpoints and AdvSM-SAF, PGIS, and EORTC QLQ-C30;
- Changes in other mutations in PB and bone marrow;
- Changes in levels of exploratory biomarkers (DNA, RNA, protein) in PB;
- Platelet aggregation

- **Sample size**
- **Randomisation and Blinding (masking)**

This is an open-label, single-arm study with no randomization or stratification and no blinding. All eligible patients who consented to participate and were enrolled in the study received avapritinib. Patients were assigned to 1 of the 2 cohorts based on SSC confirmation of eligibility by mIWG-MRT-ECNM and AdvSM subtype.

- **Statistical methods**

A pre-planned interim analysis for superiority against the null hypothesis of ORR 28% was conducted to determine whether avapritinib is effective in treating patients with AdvSM. Analyses are presented by starting dose of 200 mg QD and all doses for the safety population and/or by disease subtype for RE (Response evaluable) and PPRE (Pure pathologic response-evaluable) populations.

The null hypothesis was generated using midostaurin ORR of 28.3% by IWG-MRT-ECNM criteria (Rydapt 2017b). With the initial application only results of the interim analysis as of data cut-off date of 23 June 2020 were submitted. Additional data were however submitted later during the procedure from a later cut-off (additional 10 months of follow up, DCO date of 20 April 2021) and including additional patients.

Disease subtypes are presented separately for Investigator-reported diagnosis and SSC-determined disease diagnosis.

Analyses of demographics, baseline disease characteristics, and prior therapies for the underlying malignancy were performed for all 3 analyses populations.

Efficacy data presentation: The primary efficacy endpoint analysis is presented for RE population, with sensitivity analyses performed in both the RE and PPRE populations. All other secondary/exploratory efficacy endpoints analyses were performed for the RE population, PPRE population, and/or the safety population. The primary endpoint was SSC-adjudicated ORR (CR+CRh+PR+CI) based on mIWG-MRT-ECNM criteria, a modified version of the original, published IWG-MRT-ECNM criteria that were modified in consultation with experts and regulatory authorities.

The key secondary endpoint as well as secondary analyses of bone marrow mast cells, serum tryptase, KIT D816V MAF, spleen and liver measurements, PGIS, EORTC QLQ-C30, and all exploratory endpoints are

presented for the safety population. Time to event analyses, DOR, and PFS are presented for RE population, with sensitivity analyses performed in RE and PPRE populations.

Overall survival is presented for both safety and RE populations. Event-free survival is presented for RE population. Subgroup analyses are presented for RE population (ORR, DOR, and PFS) and for safety population (OS).

Summary statistics for continuous variables included n (non-missing observations), mean, StdDev, minimum, median, and maximum. Summary statistics for categorical variables were presented in terms of frequencies and percentages. Time to event data were summarized and analyzed using the Kaplan-Meier method, including the estimated median with 95% confidence intervals, and 25th and 75th percentiles.

Unless otherwise specified, baseline was defined as the last observation before first dose date of avapritinib, including predose assessments on the first dose date.

Sample size

The sample size of approximately 63 patients in Cohort 1 was estimated based on the primary objective and was intended to provide 93.5% power at the 1-sided significance level of 0.025 for testing the assumption of the null hypothesis ORR of 28% vs the alternative ORR of 50%.

Enrolment of the SM-AHN subgroup was capped at 70% of 63 patients (ie, maximum of 45 patients) to ensure the study population reflects the general AdvSM patient population.

This sample size also allowed statistical testing of the key secondary objective and was intended to provide > 90% power at the 1-sided significance level of 0.025 for testing the assumption of the null hypothesis mean change of TSS ≥ 0 vs the alternative mean change of TSS ≤ −10. All treated patients in Cohort 1 and Cohort 2 were included in the analysis. Testing for this key secondary endpoint was sequential to ensure control of the study wise type I error rate (ie, it was only performed when the null hypothesis for the primary objective was rejected).

The non-mIWG-MRT-ECNM evaluable cohort (Cohort 2) of approximately 40 patients, for a total of 103, was intended for an approximate 88% probability of observing ≥ 1 AE at 2% frequency, instead of 3.5% frequency with 60 patients.

Interim analysis

As per Protocol, an interim analysis was planned once the first 32 patients (with the SM-AHN subgroup capped at approximately 70%) were enrolled in the mIWG-MRT-ECNM-evaluable cohort and were evaluable for response. The results initially presented for this submission were those corresponding to the interim analysis, DCO date 23 June 2020.

The final analysis of the primary efficacy endpoint was planned to occur after all 63 patients (with the SM-AHN subgroup capped at approximately 70%) were enrolled in the cohort 1 and have had the opportunity to receive avapritinib treatment for at least 10 cycles or had discontinued treatment earlier, and was to be tested at a 1-sided alpha level of 0.02178.

Analysis Populations – Data Sets Analysed

The following analysis populations were defined as follows:

- Safety Population: All patients who received ≥ 1 dose of avapritinib;

- Response-evaluable (RE) Population: All patients who received ≥ 1 dose of avapritinib, were deemed evaluable per mIWG-MRT-ECNM criteria at baseline as assessed by SSC review, and had 1 of the following conditions:

  – ≥ 2 complete postbaseline bone marrow assessments, and had been on study for ≥ 6 cycles (6 x 28 days);

  – had an EOS Visit;

- Pure Pathologic Response-evaluable (PPRE) Population: All patients who received

  - ≥ 1 dose of avapritinib, and had 1 of the following conditions:

  – ≥ 2 complete postbaseline bone marrow assessments, and had been on study for ≥ 6 cycles (6 x 28 days);

  – had an EOS Visit.

The safety population was used for the key secondary analysis and all safety analyses, patient reported outcome analyses, and efficacy analyses that are not based on mIWG-MRT-ECNM response criteria.

The **RE population was used for the primary efficacy analysis and for all secondary efficacy analyses related to response**, such as objective response, time to response, DOR, PFS, CI rate, and clinical benefit rate.

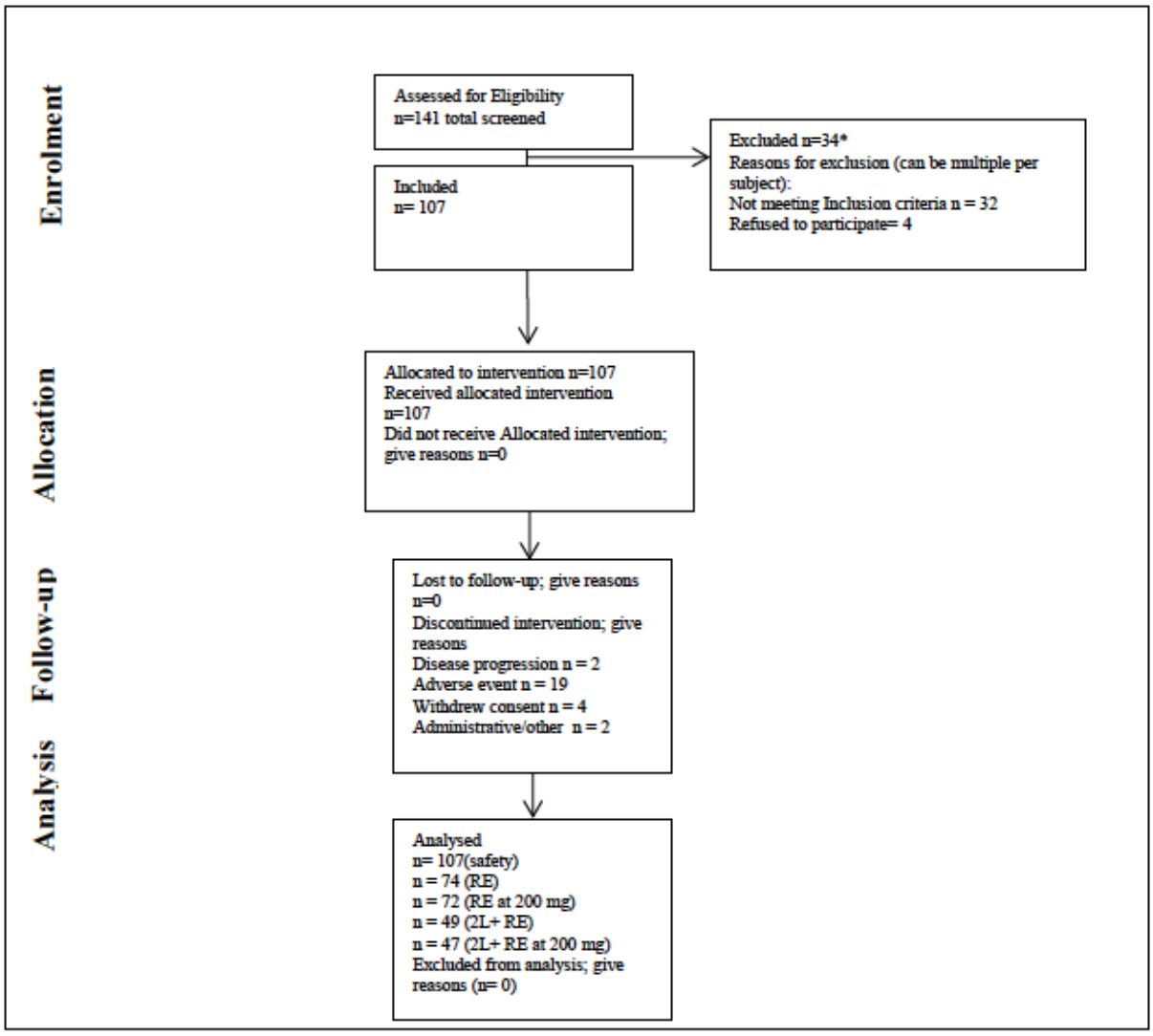
The PPRE population was used as analysis population for PPR, such as objective response rate, time to response, DOR, and PFS.

Results

Results from the pre-planned IA, DCO date of 23 June 2020, for 32 response evaluable patients (23 having received at least one systemic therapy, which corresponds to the target indication) were initially presented in the application.

During the procedure, updated efficacy data from study BLU-285-2202 were submitted from a later data cut-off (20 April 2021) including additional RE patients (post IA population), i.e. up to 47 patients having received prior systemic therapy and a starting dose of 200 mg QD of avapritinib, who are considered the primary efficacy population in the context of the applied indication. Data/results from this subset of patients are presented below.

- **Participant flow** (DCO 20 April 2021)



Abbreviations: 2L+ = following prior systemic therapy; RE = response evaluable
*NOTE –patients may be excluded for more than one reason. The number of reasons for exclusion does not match the number of patients excluded
Source: Updated ISE, 20 April 2021 Table 14.1.2.1 and data on file.

Patient Disposition

Patient Disposition in Patients with Prior Systemic Treatment (DCO 20 April 2021, BLU-285-2202, RE Population). Out of 107 patients enrolled in the study, 67 patients had at least one prior systemic therapy and were treated at a starting dose of 200 mg orally once daily

Table 19 Disposition Category (20 April 2021, BLU-285-2202, RE Population, 200 mg)

Disposition Category	200 mg (N=47)
Discontinued from treatment	16 (34.0)
Continuing on treatment	31 (66.0)
Discontinued from study	15 (31.9)
Disease progression	2 (4.3)
AML	1 (2.1)
Adverse event(s)	11 (23.4)
Related	3 (6.4)
Withdrew consent	2 (4.3)
Administrative/other	1 (2.1)
Death	11 (23.4)
Withdrew consent	4 (8.5)

Abbreviations: AML = acute myeloid leukemia; RE = response evaluable
Source: Updated ISE, 20 April 2021 Table 14.1.2.1.2b

- **Recruitment**

- Date first patient enrolled (C1D1): 21 November 2018
- Date last patient enrolled (C1D1) for the interim analysis: 17 June 2020
- Data cut-off date for the interim analysis: 23 June 2020
- Data cut-off date for the updated analysis: 20 April 2021
- Date last patient enrolled in the study: 21 January 2021

At the time of data cut-off, **18 sites** enrolled patients and entered data, including **10 sites in North America** (1 site in Canada and 9 in the United States) and **8 sites in Europe** (3 in Germany, 1 in Italy, 1 in Norway, 1 in Poland, 1 in Spain and 1 in the UK).

At the time of the initial DCO, enrolment was still ongoing. Data from additional patients were submitted during the procedure.

- **Conduct of the study**

- Protocol amendments
- There were a total of 10 amendments to the original Protocol (09 January 2018). Amendments 1, 3 and 5 referred to changes in the starting dose of avapritinib. The recommended Phase 2 dose was initially identified as 300 mg QD, which was finally not selected given the observed higher toxicity and lower tolerability. With Protocol Amendment 1, the starting dose of avapritinib was reduced from 300 mg to 200 mg QD with no patient in study BLU-285-2202 enrolled under the initial protocol. With Protocol Amendment 3, a 100 mg QD starting dose was permitted for patients with platelet counts from 25,000 to 50,000/μL at baseline. However, with Protocol Amendment 5, patients with platelet

counts <50,000/µL at baseline were excluded from enrolment. Amendments 1, 3, 5, 7, and 7.1 were incorporated globally. All patients contributing data to analyses in this CSR were enrolled under Protocol Amendment 1 or later. The amendments to the protocol do not seem to adversely affect the interpretability of the study.

-
- Protocol deviations

- No patient was excluded from any analysis population as a result of a protocol deviation.

- The observed protocol deviations were considered unlikely to affect the study efficacy or safety conclusions.

- **Baseline data**

Demographic Characteristics

Table 20 Demographic Characteristics in Patients with Prior Systemic Therapy (20 April 2021, BLU-285-2202, RE Population, 200 mg)

Category	**200 mg (N=47)**
Age (years)	
Mean (StdDev)	66.3 (11.68)
Median (min, max)	69.0 (31, 86)
Age group, n (%)	
< 65 years	17 (36.2)
≥ 65 years	30 (63.8)
Sex, n (%)	
Female	14 (29.8)
Male	33 (70.2)
Ethnicity, n (%)	
Hispanic or Latino	2 (4.3)
Not Hispanic or Latino	42 (89.4)
Unknown	3 (6.4)
Race, n (%)	
White	43 (91.5)
Unknown/other	4 (8.5)
Height (cm)	
n	44
Mean (StdDev)	172.48 (9.624)

Category	200 mg (N=47)
Median (min, max)	172.00 (150.0, 192.0)
Weight (kg)	
n	47
Mean (StdDev)	71.20 (13.228)
Median (min, max)	68.90 (48.2, 103.1)
BMI (kg/m^2)	
n	44
Mean (StdDev)	23.94 (3.877)
Median (min, max)	23.29 (18.1, 34.8)

Abbreviations: BMI = body mass index; max = maximum; min = minimum; RE = Response-Evaluable; StdDev = standard deviation.

Source: Updated ISE, 20 April 2021 Table 14.1.4.1.2b

Baseline Disease Characteristics

Table 21 Disease Characteristics in Patients with Prior Systemic Therapy (20 April 2021, BLU-285-2202, RE Population, 200 mg)

Category	200 mg (N=47)
Extracutaneous organ involvement, n (%)	
Yes	33 (70.2)
No	14 (29.8)
ECOG performance status	
0	9 (19.1)
1	22 (46.8)
2	11 (23.4)
3	5 (10.6)
Corticosteroid therapy use for SM	
Yes	19 (40.4)
No	28 (59.6)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; RE = Evaluable; SM = systemic mastocytosis.
Source: Updated ISE, 20 April 2021 Table 14.1.4.2.2b

Table 22 Summary of Baseline Disease Assessment in Patients with Prior Systemic Therapy (20 April 2021, BLU-285-2202, RE Population, 200 mg)

Category	200 mg (N=47)
Mutation Status*, n (%)	
KIT Exon 17 mutation	

Category	200 mg (N=47)
Positive	45 (95.7)
Negative	2 (4.3)
SRSF2/ASXL1/RUNX1 mutation (S/A/R)	
Positive	17 (36.2)
Negative	30 (63.8)
Number of co-mutations	
0	5 (10.6)
1	4 (8.5)
2-3	15 (31.9)
4-5	16 (34.0)
≥ 6	7 (14.9)
Median (min, max)	3 (0, 21)
KIT D816V MAF (%) - blood Median (min, max)	N=46 26.215 (0.00, 46.68)
Serum tryptase (ng/mL) Median (min, max)	325.20 (23.8, 1600.0)
BM MC (%) Median (min, max)	N=46 70.0 (1, 95)
Spleen volume (mL) Median (min, max)	1018.42 (44.2, 2652.2)

Abbreviations: BM MC = bone marrow mast cells; MAF = mutant allele fraction; max = maximum; min = minimum; RE = response evaluable
*Central assay
Source: Updated ISE, 20 April 2021 Table 14.1.4.3.2.b

As shown in the table above by central assessment, in the RE population almost all patients, ~95.7% were positive for the KIT D816V mutation and ~ 36 % carried 1 of the S/A/R mutations. Except for 9 patients, all had ≥ 2 non-KIT co-mutations with a median (range) number of co-mutations of 3 (0 to 21).

Prior Systemic treatment

Table 23 Summary of Prior Systemic Therapies in Patients with Prior Systemic Therapy (20 April 2021, BLU-285-2202, RE, 200 mg dose)

Category	ASM (N=8)	SM-AHN (N=29)	MCL (N=10)	All AdvSM (N=47)
Number of lines of prior antineoplastic therapy, n (%)				
1	4 (50.0)	17 (58.6)	6 (60.0)	27 (57.4)
2	4 (50.0)	8 (27.6)	1 (10.0)	13 (27.7)
3	0	2 (6.9)	1 (10.0)	3 (6.4)
4	0	1 (3.4)	2 (20.0)	3 (6.4)

Category	ASM (N=8)	SM-AHN (N=29)	MCL (N=10)	All AdvSM (N=47)
5	0	0	0	0
6	0	1 (3.4)	0	1 (2.1)
Best response to prior antineoplastic therapy, n (%)[a] (95% confidence interval)				
CR	0	0	0	0
PR	1 (12.5) (0.3, 52.7)	5 (17.2) (5.8, 35.8)	2 (20.0) (2.5, 55.6)	8 (17.0) (7.6, 30.8)
CI	2 (25.0) (3.2, 65.1)	4 (13.8) (3.9, 31.7)	4 (40.0) (12.2, 73.8)	10 (21.3) (10.7, 35.7)
SI	0	0	0	0
SD	3 (37.5) (8.5, 75.5)	10 (34.5) (17.9, 54.3)	2 (20.0) (2.5, 55.6)	15 (31.9) (19.1, 47.1)
LOR	0	0	0	0
PD	1 (12.5) (0.3, 52.7)	5 (17.2) (5.8, 35.8)	1 (10.0) (0.3, 44.5)	7 (14.9) (6.2, 28.3)
Other	1 (12.5) (0.3, 52.7)	1 (3.4) (0.1, 17.8)	1 (10.0) (0.3, 44.5)	3 (6.4) (1.3, 17.5)
Unknown	0	3 (10.3) (2.2, 27.4)	0	3 (6.4) (1.3, 17.5)
Missing	0	1 (3.4) (0.1, 17.8)	0	1 (2.1) (0.1, 11.3)
Best response to last prior antineoplastic therapy, n (%)[a] (95% confidence interval)				
CR	0	0	0	0
PR	1 (12.5) (0.3, 52.7)	5 (17.2) (5.8, 35.8)	1 (10.0) (0.3, 44.5)	7 (14.9) (6.2, 28.3)
CI	2 (25.0) (3.2, 65.1)	2 (6.9) (0.8, 22.8)	4 (40.0) (12.2, 73.8)	8 (17.0) (7.6, 30.8)
SI	0	0	0	0
SD	2 (25.0) (3.2, 65.1)	9 (31.0) (15.3, 50.8)	2 (20.0) (2.5, 55.6)	13 (27.7) (15.6, 42.6)
LOR	0	0	0	0
PD	1 (12.5) (0.3, 52.7)	5 (17.2) (5.8, 35.8)	1 (10.0) (0.3, 44.5)	7 (14.9) (6.2, 28.3)
Other	1 (12.5) (0.3, 52.7)	4 (13.8) (3.9, 31.7)	2 (20.0) (2., 55.6)	7 (14.9) (6.2, 28.3)

Category	ASM (N=8)	SM-AHN (N=29)	MCL (N=10)	All AdvSM (N=47)
Unknown	1 (12.5) (0.3, 52.7)	3 (10.3) (2.2, 27.4)	0	4 (8.5) (2.4, 20.4)
Missing	0	1 (3.4) (0.1, 17.8)	0	1 (2.1) (0.1, 11.3)
Reason for discontinuation of last prior antineoplastic therapy, n (%) (95% confidence interval)				
Completed scheduled cycles of treatment	1 (12.5) (0.3, 52.7)	2 (6.9) (0.8, 22.8)	0	3 (6.4) (1.3, 17.5)
PD/Relapse	1 (12.5) (0.3, 52.7)	11 (37.9) (20.7, 57.7)	7 (70.0) (34.8, 93.3)	19 (40.4) (26.4, 55.7)
Refractory	0	3 (10.3) (2.2, 27.4)	1 (10.0) (0.3, 44.5)	4 (8.5) (2.4, 20.4)
Toxicity	3 (37.5) (8.5-75.5)	5 (17.2) (5.8-35.8)	0	8 (17.0) (7.6-30.8)
Other	3 (37.5) (8.5, 75.5)	7 (24.1) (10.3, 43.5)	2 (20.0) (2.5, 55.6)	12 (25.5) (13.9, 40.3)
Unknown	0	1 (3.4) (0.1, 17.8)	0	1 (2.1) (0.1, 11.3)
Missing	0	0	0	0
Duration of treatment on last prior antineoplastic therapy (months)				
n	8	29	10	47
Mean (StdDev)	11.36 (6.526)	12.54 (17.048)	30.25 (36.210)	16.11 (22.255)
Median	12.35	4.01	19.60	8.08
Min, Max	0.0, 21.0	0.2, 67.4	1.7, 121.8	0.0, 121.8

Abbreviations: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; CI = clinical improvement; CR = complete remission; IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasm Research and Treatment and European Competence Network on Mastocytosis; LOR = loss of response, MCL = mast cell leukemia; PD = progressive disease; PR = partial remission; RAC-RE = Response Assessment Committee Response-Evaluable; SAP = statistical analysis plan; SD = stable disease; SI = symptomatic improvement.
[a] Response is not per IWG-MRT-ECNM response criteria.
Note: Duration of treatment on prior antineoplastic therapy was derived based on the first start date and the last end date of treatment. Partial dates were imputated according to SAP.
Source: Updated ISE Table 99.1.10.1a (attached).

The assessment of the primary efficacy endpoint was based on a total of 47 AdvSM patients, evaluable according to the modified IWG-MRT-ECNM response criteria, enrolled in the study, who received at least one prior systemic therapy and a starting dose of 200 mg AYVAKYT once daily **with 78.7% of patients having received prior midostaurin, 17.0% prior cladribine, 14.9 % prior interferon alpha, 10.6% prior hydroxycarbamide and 6.4% prior azacytidine. Thirty seven (79%) out of the 47 patients with AdvSM who received at least one prior systemic therapy and a starting dose of 200 mg AYVAKYT had one or more dose reductions during the course of therapy with a median time to dose**

reduction of 6 weeks.

- **Numbers analysed**

Table 24 Analysis Populations (20 April 2021, BLU-285-2202, RE, 200 mg dose)

Analysis Population	**200 mg n (%)**
RE population	47 (100.0)
ASM	8 (17.0)
SM-AHN	29 (61.7)
MCL	10 (21.3)
PPRE population	59 (100.0)
ASM	13 (22.0)
SM-AHN	36 (61.0)
MCL	10 (16.9)
AdvSM/Safety population*	67 (100.0)
ASM	14 (20.9)
SM-AHN	41 (61.2)
MCL	12 (17.9)

Abbreviations: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; MCL = mast cell leukemia; PPRE = pure pathological response evaluable.
Source: Updated BLU-285-2202, 20 April 2021 Table 14.2.1.1f, Table 14.2.1.4a, and Table 14.2.6.1c
*For Study BLU-285-2202 the Safety Population and the AdvSM population are the same. In the ISE this patient population is referred to as the AdvSM population.

- **Outcomes and estimation**

Primary Endpoint

Overall Response Rate by Centrally Adjudicated mIWG-MRT-ECNM Criteria

The ORR (CR+CRh+PR+CI) by centrally adjudicated mIWG-MRT-ECNM criteria was **59.6 %** (95% confidence interval: 44.3, 73.6) in all AdvSM patients in the RE population having received prior systemic therapy and treated with a starting 200 mg QD dose (see table above), with 28 of the 47 evaluable patients achieving a best confirmed response of CR (1), CRh (4), PR (19), or CI (4). The ORR was statistically significant compared to the prespecified null hypothesis of 28% ($p < 0.0001$, Wald test). One patient achieved a CR as of the time of data cut-off (20 April 2021), and 4 (8.5%) patients achieved a CRh. Responses occurred in all subtypes of AdvSM. The ORR was 62.5% and 65.5% in patients with ASM (5 of 8 patients) and SM-AHN (19 of 29 patients),

respectively. The ORR in the MCL group was 40%, based on 3/10 MCL patients, who showed PR, and one patient achieving best response of CI.

The CR+CRh+PR rate by centrally adjudicated mIWG-MRT-ECNM criteria was **51.1%** (95% confidence interval: 36.1, 65.9) in patients with AdvSM treated at all doses in the RE population, with 24 of 47 patients achieving a best confirmed response of CRh or PR. This was statistically significant compared to the prespecified null hypothesis of 17% ($p < 0.0001$, Wald test). Responses occurred in all subtypes of AdvSM.

Table 25 Adjudicated Best Response by mIWG-MRT-ECNM Criteria in Patients with Prior Systemic Therapy by Disease Subtype (20 April 2021, BLU-285-2202, RE Population, 200 mg)

Parameter	ASM N=8	SM-AHN N=29	MCL N=10	All AdvSM N=47
ORR (CR + CRh + PR + CI), n (%)	5 (62.5)	19 (65.5)	4 (40.0)	28 (59.6)
95% confidence interval	(24.5, 91.5)	(45.7, 82.1)	(12.2, 73.8)	(44.3, 73.6)
CR + CRh + PR, n (%)	5 (62.5)	16 (55.2)	3 (30.0)	24 (51.1)
95% confidence interval	(24.5, 91.5)	(35.7, 73.6)	(6.7, 65.2)	(36.1, 65.9)
CR + CRh, n (%)	2 (25.0)	3 (10.3)	0	5 (10.6)
95% confidence interval	(3.2, 65.1)	(2.2, 27.4)	-	(3.5, 23.1)
Best response, n (%)				
CR	0	1 (3.4)	0	1 (2.1)
CRh	2 (25.0)	2 (6.9)	0	4 (8.5)
PR	3 (37.5)	13 (44.8)	3 (30.0)	19 (40.4)
CI	0	3 (10.3)	1 (10.0)	4 (8.5)
SD	3 (37.5)	4 (13.8)	4 (40.0)	11 (23.4)
PD	0	1 (3.4)	1 (10.0)	2 (4.3)
NE	0	5 (17.2)	1 (10.0)	6 (12.8)

Abbreviations: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; CI = clinical improvement; CR = complete remission; CRh = complete remission with partial recovery of peripheral blood counts; mIWG-MRT-ECNM = modified International Working Group-Myeloproliferative Neoplasm Research and Treatment and European Competence Network on Mastocytosis International Working Group; MCL = mast cell leukemia; NE = not evaluable; ORR = overall response rate; PD = progressive disease; PR = partial remission; RE = response evaluable; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm.
Source: Updated ISE, 20 April 2021 Table 14.2.1.1f

Table 26 Sensitivity Analysis*: Summary of Investigator Assessed Best Response by mIWG MRT ECNM Criteria in Patients with Prior Systemic Therapy by Disease Subtype (20 April 2021, BLU 285 2202, AdvSM Population, 200 mg)*

Parameter	ASM N=14	SM-AHN N=41	MCL N=12	All AdvSM N=67
ORR (CR + CRh + PR + CI), n (%)	6 (42.9)	21 (51.2)	5 (41.7)	32 (47.8)
95% confidence interval	(17.7, 71.1)	(35.1, 67.1)	(15.2, 72.3)	(35.4, 60.3)
CR + CRh + PR, n (%)	1 (7.1)	8 (19.5)	4 (33.3)	13 (19.4)

95% confidence interval	(0.2, 33.9)	(8.8, 34.9)	(9.9, 65.1)	(10.8, 30.9)
CR + CRh, n (%)	0	3 (7.3)	1 (8.3)	4 (6.0)
95% confidence interval		(1.5, 19.9)	(0.2, 38.5)	(1.7, 14.6)
Best response, n (%)				
CR	0	1 (2.4)	0	1 (1.5)
CRh	0	2 (4.9)	1 (8.3)	3 (4.5)
PR	1 (7.1)	5 (12.2)	3 (25.0)	9 (13.4)
CI	5 (35.7)	13 (31.7)	1 (8.3)	19 (28.4)
SD	5 (35.7)	16 (39.0)	5 (41.7)	26 (38.8)
PD	0	0	0	0
NE	3 (21.4)	4 (9.8)	2 (16.7)	9 (13.4)

Abbreviations: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; CI = clinical improvement; CR = complete remission; CRh = complete remission with partial recovery of peripheral blood counts; mIWG-MRT-ECNM = modified International Working Group-Myeloproliferative Neoplasm Research and Treatment and European Competence Network on Mastocytosis International Working Group; MCL = mast cell leukemia; NE = not evaluable; ORR = overall response rate; PD = progressive disease; PR = partial remission; RE = response evaluable; SM-AHN = systemic mastocytosis with an associated hematologic neoplasm.

Source: Updated ISE, 20 April 2021 Table 14.2.1.2

Sensitivity Analysis: Best Response by Pure Pathologic Response Criteria (PPRE Population)

Table 27 Best Response by Pure Pathologic Response Criteria and Disease Subtype in Patients with Prior Systemic Therapy (BLU-285-2202, PPRE Population, 200 mg)

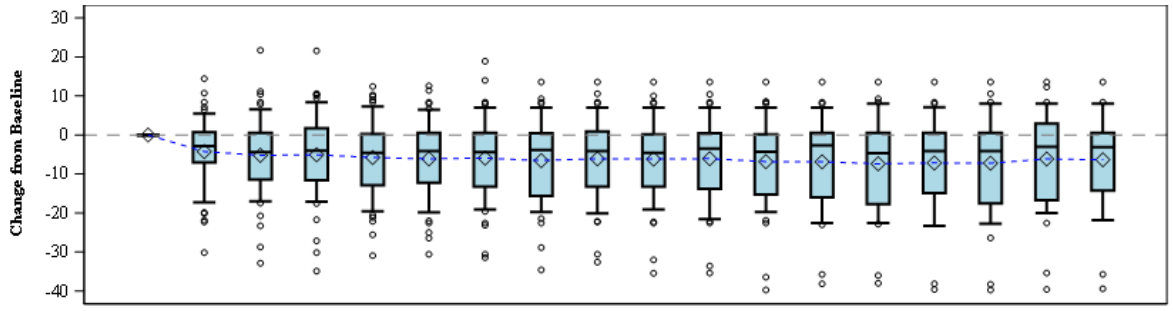
	200 mg			
Parameter	**ASM N=13**	**SM-AHN N=36**	**MCL N=10**	**All AdvSM N=59**
Pathologic ORR (mCR + mCRh + mPR), n (%)	7 (53.8)	20 (55.6)	4 (40.0)	31 (52.5)
95% confidence interval	(25.1, 80.8)	(38.1, 72.1)	(12.2, 73.8)	(39.1, 65.7)
mCR + mCRh, n (%)	3 (23.1)	10 (27.8)	1 (10.0)	14 (23.7)
95% confidence interval	(5.0, 53.8)	(14.2, 45.2)	(0.3, 44.5)	(13.6, 36.6)
Best response, n (%)				
mCR	1 (7.7)	5 (13.9)	0	6 (10.2)
mCRh	2 (15.4)	5 (13.9)	1 (10.0)	8 (13.6)
mPR	4 (30.8)	10 (27.8)	3 (30.0)	17 (28.8)
TF	0	0	0	0
SD	6 (46.2)	15 (41.7)	6 (60.0)	27 (45.8)
PD	0	0	0	0
NE	0	1 (2.8)	0	1 (1.7)

Key Secondary Endpoint

Total Symptom Score (TSS)

As shown in the figure below (DCO date 20 April 2021), in patients with a starting dose of 200 mg QD, the mean (StdDev) TSS score at baseline was 17.60 (11.81) out of 80 maximal points (10 points per symptom), where 0 represents absence of symptoms and 80 the most severe symptom experience. In patients on treatment for >10 cycles, mean change in AdvSM SAF TSS from baseline to C11D1 was statistically significant ($p < 0.001$) with a mean reduction from baseline of –-6.07 points (95% confidence interval: –9.45 to –2.69). A decrease on C11D1 was also seen in the skin and GI domains as well as the symptoms abdominal pain, nausea, spots, itching, flushing, fatigue, diarrhoea count, and diarrhoea severity.

Figure 3 Change of Total Symptom Score from Baseline to Day 1 of Each Cycle in Patients with Prior Therapy (20 April 2021, BLU-285-2202, Safety Population, 200 mg)



	Baseline	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	C9 D1	C10 D1	C11 D1	C12 D1	C13 D1	C14 D1	C15 D1	C16 D1	C17 D1	C18 D1
MIN	0	-30.14	-32.86	-34.88	-30.9	-30.57	-31.43	-34.57	-32.57	-35.43	-35.38	-39.71	-38.14	-38	-39.57	-39.71	-39.57	-39.4
Q1	0	-7.095	-11.43	-11.57	-12.86	-12.29	-13.29	-15.64	-13.29	-13.29	-13.79	-15.29	-16	-17.71	-14.86	-17.57	-16.71	-14.29
MEDIAN	0	-2.857	-4.429	-4	-4.571	-4.129	-4.4	-3.857	-4.143	-4.557	-3.521	-4.343	-2.686	-4.714	-4.143	-4.143	-3	-3.143
Q3	0	0.7143	0.5143	1.7143	0.2857	0.5143	0.5143	0.4595	0.8571	0.1429	0.4	0.1667	0.5143	0.5143	0.5143	0.5143	2.8571	0.5143
MAX	0	14.429	21.714	21.571	12.429	12.571	18.905	13.571	13.571	13.571	13.571	13.571	13.571	13.571	13.571	13.571	13.571	13.571
MEAN	0	-4.26	-5.217	-5.078	-5.771	-6.13	-5.924	-6.572	-6.097	-6.183	-6.069	-6.83	-6.887	-7.381	-7.176	-7.231	-6.147	-6.345
STD	0	8.5614	9.7483	10.546	9.7508	10.141	10.703	10.647	10.448	10.584	11.113	11.512	11.816	12.326	12.576	12.945	12.992	12.657
N	59	57	59	58	58	54	51	48	47	46	44	42	39	38	37	35	31	29
P-VALUE							<0.001***				<0.001***							

Source: Updated BLU-285-2202, 20 April 2021 Figure 15.2.2.1b

Time to Response

Median (range) time to response (TTR) by centrally adjudicated mIWG-MRT-ECNM criteria in the 28 AdvSM responders treated in the 200 mg QD group in the previously treated RE population was rapid and occurred at 1.94 (0.5, 12.2) months.

Responses deepened over time.

Median (range) time to CR+CRh (5 patients) was 3.71 (1.8, 14.8) months.

Median time to response was similar in patients with ASM, SM-AHN, but median time to response and CR + CRh +PR was slightly longer for MCL, the more aggressive disease subtype with a higher MC burden (3.6 months and 5.59 months respectively).

Table 28 Time to Response in Patients with Prior Systemic Treatment (20 April 2021, BLU-285-2202, RE population 200 mg, Responders [CR+CRh+PR+CI] by mIWG-MRT-ECNM Criteria)

Parameter	200 mg			
	ASM N=5	**SM-AHN N=19**	**MCL N=4**	**All AdvSM N=28**
Median (range) in months				
Time to response (CR + CRh + PR + CI)	2.30 (1.8, 5.5)	1.94 (0.5, 5.5)	3.60 (1.7, 12.2)	1.94 (0.5, 12.2)
Time to CR + CRh + PR	2.30 (1.8, 5.5)	3.19 (1.7, 14.8)	5.59 (1.7, 12.2)	3.19 (1.7, 14.8)
Time to CR + CRh	2.76 (1.8, 3.7)	5.59 (1.8, 14.8)		3.71 (1.8, 14.8)

Abbreviations: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; CI = clinical improvement; CR = complete remission; CRh = complete remission with partial recovery of peripheral blood counts; MCL = mast cell leukemia, PR = partial remission; RE = Response-Evaluable; SM-AHN = systemic mastocytosis with an associated hematological neoplasm;
Note: Time to response is defined as the time in months from the start of treatment to the time criteria for response (CR/CRh/PR/CI) are first met. Patients without confirmed response were excluded from this analysis. Time to CR is defined as the time from the start of treatment to the time a CR/CRh is first met. Patients without a confirmed CR/CRh were excluded from this analysis.
Source: Updated ISE, 20 April 2021 Table 99.2.2.4.1 and Table 14.2.2.1b

Duration of Response

At the time of the 20 April 2021 data cut-off, response was ongoing in 26 (92.9%) of the 28 responders. who had received prior systemic therapy and were treated with an avapritinib starting dose of 200 mg QD. The Kaplan-Meier estimate of probability of an ongoing response was 100.0% at 12 months and 85.6% at 24 months.

Table 29 Duration of Response in Patients with Prior Systemic Treatment (20 April 2021, BLU-285-2202, RE Population 200 mg, Responders [CR+CRh+PR+CI] by mIWG-MRT-ECNM Criteria)

Parameter	200 mg			
	ASM N=5	**SM-AHN N=19**	**MCL N=4**	**All AdvSM N=28**
Duration analyses, median (95% confidence interval)				
DOR	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Censored, n (%)	5 (100)	17 (89.5)	4 (100)	26 (92.9)
KM estimate at 12 months, %	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)
KM estimate at 24 months, %	NA	83.3 (62.2-100.0)	NA	85.6 (66.9-100.0)
Duration of CR + CRh + PR	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
KM estimate at 12 months, %	100.0 (100.0, 100.0)	90.0 (71.4-100.0)	100.0 (100.0, 100.0)	92.3 (77.8-100.0
KM estimate at 24 months, %	NA	90.0 (71.4-100.0)	NA	92.3 (77.8-100.0

Abbreviations: AdvSM = advanced systemic mastocytosis; ASM = aggressive systemic mastocytosis; CI = clinical improvement; CR = complete remission; CRh = complete remission with partial recovery of peripheral blood counts; DOR = duration of response; KM = Kaplan-Meier; mIWG-MRT-ECNM = modified International Working Group-Myeloproliferative Neoplasm Research and Treatment and European Competence Network on Mastocytosis; MCL = mast cell leukemia, max = maximum; min = minimum; NE = not evaluable; PR = partial remission; RE = Response-Evaluable; SM-AHN = systemic mastocytosis with an associated hematological neoplasm;

Source: Updated ISE, 20 April 2021 Table 99.2.2.4.1 and Table 14.2.2.1b

Progression-free Survival

In the RE population of patients who had received prior systemic therapy and were treated with an avapritinib starting dose of 200 mg QD, 35 of 47 patients (74.5%) were censored for the analysis and 12 (25.5%) had a PFS event (DCO date 20 April 2021). Median PFS by centrally adjudicated mIWG MRT ECNM criteria in the 47 AdvSM patients was NE at the time of data cut-off (95% confidence interval: 17.5, NE). The estimated PFS rate was 87.2% at 3 months and 65.5% at 24 months. Median PFS was not reached in any disease subtype.

Table 30 Progression-free Survival in Patients with Prior Systemic Treatment (20 April 2021, BLU-285-2202, RE Population, 200 mg)

Parameter	200 mg			
	ASM N=8	**SM-AHN N=29**	**MCL N=10**	**All AdvSM N=47**
Progression-free Survival (PFS)				
Events	0	9 (31.0)	3 (30.0)	12 (25.5)
Censors	8 (100)	20 (69.0)	7 (70.0)	35 (74.5)
PFS, median (95% confidence interval)	NE (NE, NE)	NE (17.4, NE)	NE (10.5, NE)	NE (17.5, NE)
KM estimate at 12 months, %	100.0 (100.0, 100.0)	75.2 (59.3, 91.2)	68.6 (38.9, 98.3)	77.5 (65.0, 89.9)
KM estimate at 24 months, %	-	61.6 (40.0, 83.1)	68.6 (38.9, 98.3)	65.5 (47.1, 84.0)

Abbreviations: AdvSM = advanced systemic mastocytosis; ASM aggressive systemic mastocytosis; KM = Kaplan-Meier; MCL = mast cell leukemia; NE = not evaluable; PFS = progression-free survival; RE = response evaluable; SM-AHN = systemic mastocytosis with an associated hemotologic neoplasm.
Source: Updated ISE, 20 April 2021, Table 99.2.3.1a

Overall Survival

Most AdvSM patients (91.9%) in the safety population were alive at the time of data cut-off (Table 24). **Kaplan-Meier estimate for median OS could not be determined** (NE [95% confidence interval: NE, NE]). The estimated OS rate was **94.1%** at 6 months and **86.2%** at 9 and 12 months. Median (range) OS follow-up duration was 7 (5.6 to 8.1) months. Overall survival was similar among patients with ASM, SM-AHN, and MCL.

In the RE population, with a median follow up of 14.6 months, 36 (76.6%) of the 47 patients who had received prior systemic therapy and were treated with an avapritinib starting dose of 200 mg QD were alive at the time of the DCO (20 April 2021). The Kaplan-Meier estimates for proportion of AdvSM patients alive were 82.7% at 12 months and 67.8% at 24 months.

Median OS follow-up was longer in RE patients with SM-AHN (17.8 months; 95% confidence interval: 13.2, 20.7) and MCL (14.6 months; 95% confidence interval: 11.1, 17.9) who had received prior systemic therapy as compared to patients with ASM (8.6 months; 95% confidence interval: 7.3, 16.9,).

Table 31 Overall Survival in Patients with Prior Systemic Therapy (20 April 2021, BLU-285-2202, RE Population, 200 mg)

Parameter	200 mg			
	ASM N=8	**SM-AHN N=29**	**MCL N=10**	**All AdvSM N=47**
Overall Survival (OS) months				
Events	0	8 (27.6)	3 (30.0)	11 (23.4)
Censors	8 (100.0)	21 (72.4)	7 (70.0)	36 (76.6)
Median Follow-up (95% confidence interval)[a]	8.6 (7.3, 16.9)	17.8 (13.2, 20.7)	14.6 (11.1, 17.0)	14.6 (11.2, 17.8)
OS, median (95% confidence interval)[a]	NE (NE, NE)	NE (17.5, NE)	NE (13.5, NE)	NE (17.5, NE)
KM estimate at 12 months, %	100.0 (100.0, 100.0)	79.0 (64.0, 94.0)	80.0 (55.2, 100.0)	82.7 (71.8, 93.6)
KM estimate at 24 months, %	-	65.8 (45.0, 86.6)	66.7 (35.1, 98.2)	67.8 (49.8, 85.8)

Abbreviations: AdvSM = advanced systemic mastocytosis; ASM aggressive systemic mastocytosis; KM = Kaplan-Meier; MCL = mast cell leukemia; NE = not evaluable; OS = overall survival; RE = response evaluable; SM-AHN = systemic mastocytosis with an associated hemotologic neoplasm.
Note: Overall survival is defined as the time in months from the start of treatment to the date of death. Patients who died before or on the data cutoff date were considered to have had an overall survival event. Patients who did not have a death record before or on the cutoff date were censored at the last date known alive.
Source: Updated ISE, 20 April 2021, Table 99.2.4.2.1

Change in Bone Marrow Mast Cells

The mean (StdDev) percentage of BM MC at baseline in the 65 patients who had received prior systemic therapy and were treated with an avapritinib starting dose of 200 mg QD in the Safety population who had BM MC measurements at baseline was 51.2% (26.92, 20 April 2021). A total of 54 (83.1%) patients in the Safety population (200 mg) had a ≥ 50% reduction in BM MC and 38 (58.5%) patients had complete elimination of BM MC aggregates. Of the 54 patients with a ≥ 50% decrease in BM MC 36 (55.5%) patients sustained the decrease for ≥ 2 consecutive biopsies (20 April 2021). Results were generally similar between ASM and SM-AHN patients and lower for MCL patients.

Over time, bone marrow response deepened. By the time of the first bone marrow biopsy on C3D1, 41.2% of patients had CR in bone marrow while by C7D1, 55.3% of patients who reached that time point had a bone marrow CR. Patients with ASM and SM-AHN had deeper responses compared with MCL patients.

Change in Serum Tryptase Level

The mean (StdDev) serum tryptase at baseline in the 67 patients who had received prior systemic therapy and were treated with an avapritinib starting dose of 200 mg QD in the Safety population was 338.4 µg/L (259.68) (20 April 2021). A total of 59 (88.1%) patients had a ≥ 50% decrease in serum tryptase and 43 patients (64.2%) had sustained the decrease for ≥2 cycles (20 April 2021). In 34 (49.3%) patients, serum tryptase level was reduced to < 20 ng/mL. A total of 64 patients with AdvSM had baseline serum tryptase ≥40 ng/mL. Of those 56 (87.5%) patients had ≥50% reduction in serum tryptase from baseline, 41 (64.1%) patients sustained the decrease for ≥2 cycles, and 31 (48.4%) had reduced serum tryptase <20 ng/mL. Results were generally similar between ASM, SM-AHN, and MCL patients (20 April 2021).

Change in KIT D816V Mutant Allele Fraction

The mean (StdDev) KIT D816V MAF at baseline in the 67 patients with AdvSM who had received prior systemic therapy and were treated with an avapritinib starting dose of 200 mg QD in the Safety population was 20.4 (16.67). Of the 67 patients with a baseline assessment in blood, 46 (68.7%) patients had a ≥ 50% decrease and 28 (41.8%) sustained the decrease for ≥2 cycles. Thirteen (19.4%) patients had a reduction to MAF < 0.17% and 24 (35.5%) patients had a decrease to < 1%. A total of 57 patients with AdvSM had baseline assessments of MAF ≥ 1% in blood, of those, 16 (28.1%) had a reduction to MAF < 1%. A total of 41 (71.9%) patients had ≥ 50% reduction in MAF from baseline and 26 (45.6%) patients sustained the decrease for ≥ 2 cycles. Results were generally similar between ASM and SM-AHN patients and lower for MCL patients.

Responses deepened over time, with 52.2% of patients with KIT D816V MAF experienced a ≥ 50% reduction from baseline by C3D1.

Change in Spleen and Liver Volume

Mean (StdDev) spleen volume at baseline in 65 AdvSM patients who had received prior systemic therapy and were treated with an avapritinib starting dose of 200 mg QD in the Safety population and who had spleen measurement at baseline was 968.03 mL (582.831). A total of 39 of the 65 (60.0%) AdvSM patients with baseline spleen volume assessments and 11 of the 20 (55.0%) AdvSM patients with baseline spleen palpation ≥ 5 cm had ≥ 35% spleen volume reduction from baseline. Of the 34 AdvSM patients with palpable spleen at baseline, the spleen became non-palpable in 23 (67.6%) patients. Results were generally similar between ASM, SM-AHN, and MCL patients.

Patient-reported Outcomes

Results included below correspond to patients enrolled in study BLU-285-2202 following prior systemic therapy (AdvSM/safety population, all doses). **Patient's Global Impression of Symptom Severity**

Mean (StdDev) PGIS score in AdvSM patients treated in the safety population decreased (improved) **from 2.6 (1.11) out of 4 maximal points** at baseline **to 0.9 (1.00)** points at C17D1, where 0 represents no symptoms and 4 very severe symptoms.

Decreases were reported over the entire course of the study. Results were generally similar among patients with ASM, SM-AHN, and MCL.

Among patients with a baseline PGIS score greater than the median, a greater improvement of the score was noted compared with all patients.

Quality of Life Assessment

Mean (StdDev) global health status score in all AdvSM patients in the safety population improved **from 37.90** (24.549) out of 100 maximal points **to 59.72** (18.060) points at C17D1, where 0 represents low quality of life and 100 high quality of life. Increases were reported over the entire course of the study (Table 35.2.11.1, attached)

Results were generally similar among patients with ASM, SM-AHN, and MCL.

Among patients with baseline values below the median, a greater improvement of the score was noted compared with all patients (Figures 35.2.11.2 and 35.2.11.2a, attached).

Ancillary analyses

Subgroup Analyses

Results included below correspond to data from response evaluable patients enrolled in study BLU-285-2202 following prior systemic therapy (200 mg starting dose) based on the 20 April 2021 data cut-off date.

Subgroup analyses were performed for ORR by prior midostaurin treatment, baseline S/A/R genotype, age group, sex, and geographic regions. Subgroup analyses used centrally adjudicated data by mIWG-MRT-ECNM criteria.

Overall there are no clinically meaningful differences in ORR between the respective subgroups. The 95% confidence intervals were generally wide and overlapping. See table below.

Table 32 Adjudicated Best Response by Modified IWG-MRT-ECNM Criteria in Patients with Prior Systemic Therapy (20 April 2021, BLU-285-2202, RE Population, 200 mg)

Response Category,	All Patients with AdvSM									
	Age (years)		Sex		Region		Genotype – S/A/R[a]		Prior Midostaurin	
	< 65 N=17	≥ 65 N=30	Female N=14	Male N=33	North Am. N=22	Europe N=25	With N=17	Without N=30	Yes N=37	No N=10
ORR (CR + CRh + PR + CI), n (%)	7 (41.2)	21 (70.0)	11 (78.6)	17 (51.5)	13 (59.1)	15 (60.0)	11 (64.7)	17 (56.7)	23 (62.2)	5 (50.0)
95% confidence interval	(18.4, 67.1)	(50.6, 85.3)	(49.2-95.3)	(33.5, 69.2)	(36.4, 79.3)	(38.7, 78.9)	(38.3, 85.8)	(37.4, 74.5)	(44.8, 77.5)	(18.7, 81.3)
Best Response										
CR	0	1 (3.3)	0	1 (3.0)	1 (4.5)	0	0	1 (3.3)	1 (2.7)	0
CRh	0	4 (13.3)	2 (14.3)	2 (6.1)	2 (9.1)	2 (8.0)	1 (5.9)	3 (10.0)	4 (10.8)	0
PR	4 (23.5)	15 (50.0)	7 (50.0)	12 (36.4)	8 (36.4)	11 (44.0)	7 (41.2)	12 (40.0)	14 (37.8)	5 (50.0)
CI	3 (17.6)	1 (3.3)	2 (14.3)	2 (6.1)	2 (9.1)	2 (8.0)	3 (17.6)	1 (3.3)	4 (10.8)	0
SD	6 (35.3)	5 (16.7)	3 (21.4)	8 (24.2)	5 (22.7)	6 (24.0)	2 (11.8)	9 (30.0)	7 (18.9)	4 (40.0)
PD	2 (11.8)	0	0	2 (6.1)	1 (4.5)	1 (4.0)	0	2 (6.7)	1 (2.7)	1 (10.0)
NE	2 (11.8)	4 (13.3)	0	6 (18.2)	3 (13.6)	3 (12.0)	4 (23.5)	2 (6.7)	6 (16.2)	0
CR + CRh, n (%)	0	5 (16.7)	2 (14.3)	3 (9.1)	3 (13.6)	2 (8.0)	1 (5.9)	4 (13.3)	5 (13.5)	0
95% confidence interval	-	(5.6, 34.7)	(1.8, 42.8)	(1.9, 24.3)	(2.9, 34.9)	(1.0, 26.0)	(0.1-28.7)	(3.8, 30.7)	(4.5, 28.8)	-
CR+CRh+PR, n (%)	4 (23.5)	20 (66.7)	9 (64.3)	15 (45.5)	11 (50.0)	13 (52.0)	8 (47.1)	16 (53.3)	19 (51.4)	5 (50.0)
95% confidence interval	(6.8, 49.9)	(47.2, 82.7)	(35.1, 87.2)	(28.1, 63.6)	(28.2, 71.8)	(31.3, 72.2)	(23.0, 72.2)	(34.3, 71.7)	(34.4, 68.1)	(18.7, 81.3)

Abbreviations: AdvSM = advanced systemic mastocytosis; CI = clinical improvement; CR = complete remission; CRh = complete remission with a partial hematologic recovery; IWG-MRT-ECNM = International Working Group-Myeloproliferative

Neoplasms Research and Treatment and European Competence Network on Mastocytosis; NE = not evaluable; North Am. = North America; ORR = overall response rate; PD = progressive disease; PR = partial remission; RAC-RE = Response Assessment Committee Response-Evaluable; S/A/R = SRSF2/ASXL1/RUNX1; SD = stable disease.
[a] Genotype at Baseline.
Note: All doses represent combined data for patients with starting avapritinib doses of (30, 60, 100, 130, 200, 300, and 400 mg).
Source Tables: 20 April 2021 Table 99.2.1.1a, Table 99.2.1.1b, Table 99.2.1.1c, Table 99.2.1.1d, Table 99.2.1.1e, Table 99.2.1.1f (attached)

- **Summary of main efficacy results**

The following table summarises the efficacy result from Study BLU-285-2202 in the RE patients having received prior systemic therapy and treated with a starting dose of 200 mg QD of avapritinib, i.e. 47 AdvSM patients; corresponding to the most recent DCO date of 20 April 2021.

Table 33 Summary of efficacy for trial BLU-285-2202

Title: An Open-label, Single Arm, Phase 2 Study to Evaluate Efficacy and Safety of Avapritinib (BLU-285), A Selective KIT Mutation-targeted Tyrosine Kinase Inhibitor, in Patients with Advanced Systemic Mastocytosis		
Study identifier	BLU-285-2202 EudraCT number: 2017-004836-13 PATHFINDER	
Design	BLU-285-2202: Multi-centre, open-label, single-arm, Phase 2, 2-cohort study.	
	Duration of main phase:	Date first patient enrolled (C1D1): 21 November 2018 Data cut-off date for the interim analysis: 23 June 2020 Data cut-off date for updated data: 20 April 2021
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Ongoing, patients may continue to receive avapritinib until precluded by toxicity, noncompliance, withdrawal of consent, physician decision, progressive disease, death, or closure of the study by the Sponsor
Hypothesis	Exploratory - Superiority To evaluate efficacy and safety of avapritinib in patients with a WHO diagnosis of AdvSM, including patients with ASM, SM-AHN, and MCL. The primary analyses were performed for the RE population and performed according to AdvSM disease subtype and by starting daily dose 200 mg and all doses.	
Treatments groups	All patients received avapritinib at a starting dose of 200 mg QD except for two patients who were treated at a starting dose of 100 mg QD, which was introduced for patients with platelet counts between 25,000 and 50,000/μL. A total of 107 AdvSM patients were enrolled. In this summary, only patients who	

	received at least one prior systemic therapy are presented (N = 69, all doses and N = 67, 200 mg QD starting dose).		
	Overall population after at least one systemic therapy		Oral dose of avapritinib QD, presented for all doses Overall AdvSM population: N = 69 N varies depending on the analysis population, further information is included in the results and analysis section.
	ASM population after at least one systemic therapy		Oral dose of avapritinib QD, presented for all doses Overall AdvSM population: N = 14 N varies depending on the analysis population, further information is included in the results and analysis section.
	SM-AHN population after at least one systemic therapy		Oral dose of avapritinib QD, presented for all doses Overall AdvSM population: N = 43 N varies depending on the analysis population, further information is included in the results and analysis section.
	MCL population after at least one systemic therapy		Oral dose of avapritinib QD, presented for all doses Overall AdvSM population: N = 12 N varies depending on the analysis population, further information is included in the results and analysis section.
Endpoints and definitions	Primary endpoint: Overall response rate by mIWG-MRT-ECNM	ORR by mIWG-MRT-ECNM (Response in Organ Damage)	ORR is defined as the proportion of patients with a confirmed best response of CR, CRh, PR or CI by mIWG criteria. Primary ORR analysis was based on SSC adjudicated responses in the RE Population. ORR was estimated using frequency, percentage, and two-sided 95% confidence intervals based on the exact binomial distribution (Clopper-Pearson). Statistical test on binomial proportion against a null of 28% were performed using one sided α=0.025. Wald test p-value was presented. There is one interim analysis when 32 patients who are evaluable for response enrolled in the cohort 1. If the 1-sided p-value is < 0.00625, the null hypothesis is rejected, and avapritinib will be deemed effective in treating patients

			with AdvSM. The interim analysis is used to support a marketing application. CR + CRh + PR rate was summarized similarly as ORR. Statistical test on binomial proportion against a null of 17% were performed using one sided α=0.025. Wald test p-value was presented.
	Secondary endpoint: Overall response rate by PPR criteria	ORR by PPR (Response in Disease Burden)	Pathologic ORR is defined as the proportion of patients with a confirmed best response of morphologic CR (mCR), morphologic CRh (mCRh), or morphologic PR (mPR) by PPR criteria. Pathologic ORR is analyzed in the PPRE Population and RE Population. Pathologic ORR is estimated using frequency, percentage, and two-sided 95% confidence intervals based on the exact binomial distribution (Clopper-Pearson).
	Secondary endpoint: Time to response	TTR	Time to response (TTR) is defined as the time from the start of treatment to the time a response (CR/CRh/PR/CI) by mIWG or PPR criteria is first met. Patients without confirmed response are excluded from this analysis.
	Secondary endpoint: Time to CR/CRh	TTCR/CRh	Time to CR is defined as the time from the start of treatment to the time a CR/CRh by mIWG is first met. Patients without confirmed CR/CRh are excluded from this analysis.
	Secondary endpoint: Duration of response	DOR	DOR is defined as the time from first documented response (CR/CRh/PR/CI) to the date of first documented PD/LoR or death due to any cause, whichever occurs first. Responses are determined by mIWG or PPR criteria.
	Secondary endpoint: Mast cell burden reduction	≥50% Decrease in Marrow Mast Cells (%)	Percent of patients who achieved total clearance of neoplastic MC aggregates who had neoplastic MC at baseline among all patients (IWG CR) and percent of patients who achieved ≥50 % reduction from baseline (IWG PR) are tabulated.
		≥50% Decrease in Serum Tryptase (%)	Percent of patients who achieved serum tryptase < 20 ng/mL (IWG CR) who had baseline serum tryptase ≥ 40 ng/mL (IWG CR) among all patients and percent of patients who achieved ≥50 % reduction from baseline (IWG PR) are tabulated.
		≥50% Decrease in KIT D816V allele fraction (%)	Percent of patients with MAF <0.02%who had baseline MAF ≥1 % among all patients, percent of patient with<1% who had baseline MAF ≥1 % among all patients and percent of patients with≥50 % reduction from baseline among patients with baseline KIT D816V MAF are tabulated.
		≥50% Decrease in	Percent of patients who achieved ≥35 % reduction from baseline among patients with

		Spleen Volume (%)	baseline spleen volume assessment are tabulated.
	Secondary endpoint: Overall survival	OS	OS is defined as the time from the start of treatment to the date of death. Patients who die before or on the data cut-off date are considered to have had an OS event. All Patients who do not have a death record prior to or on the cut-off date are censored at the last date known alive.
Database lock	Data cut-off for analyses = 20 April 2021		
Results and Analysis			
Analysis description	**Primary Analysis: ORR by mIWG-MRT-ECNM criteria in RAC-RE population**		
Analysis population and time point description	The primary efficacy analysis of ORR by mIWG-MRT-ECNM criteria is primarily based on assessment of resolution of evaluable organ damage (C-findings). Therefore, enrolled AdvSM patients must be assessed by central review as having one or more baseline evaluable C-findings (except for MCL, which is evaluable regardless of C-findings). In addition, patients must have sufficient follow up for response assessment, which is on study for 6 months (with at least 2 post-baseline marrow assessments) or off study. These patients are the Response Assessment Committee-Response Evaluable (RAC-RE) population. Patients were analyzed according to AdvSM disease subtype and the starting dose. Other secondary/exploratory efficacy endpoints analyses were performed for the RAC-RE population, AdvSM PPRE population, and/or the safety population.		

Descriptive statistics and estimate variability	Treatment group (200 mg starting dose)	**ASM** after at least 1 systemic therapy	**SM-AHN** after at least 1 systemic therapy	**MCL** after at least 1 systemic therapy	**Overall** after at least 1 systemic therapy
	Number of subjects	8	29	10	47
	ORR by mIWG-MRT-ECNM criteria, (%), (95% CI)	62.5 (24.5, 91.5)	65.5 (45.7, 82.1)	40.0 (12.2, 73.8)	59.6 (44.3, 73.6)
	CR+CRh+PR rate (%), (95% CI)	62.5 (24.5, 91.5)	55.2 (35.7, 73.6)	30.0 (6.7, 65.2)	51.1 (36.1, 65.9)
	CR (%)	0	3.4	0	2.1
	CRh (%)	25.0	69	0	8.5
	PR (%)	37.5	44.8	30	40.4
	CI (%)				

		0	10.3	10.0	8.5
Effect estimate per comparison	Not applicable – single arm studies.				
Analysis description	**Secondary analyses: mIWG-MRT-ECNM responses: Duration of response, Time to Response, Time to Complete Remission, and Overall Survival in RAC-RE population**				
Analysis population and time point description	As for the primary analysis, RAC-RE population.				
Descriptive statistics and estimate variability	Treatment group (200 mg starting dose)	**ASM** after at least 1 systemic therapy	**SM-AHN** after at least 1 systemic therapy	**MCL** after at least 1 systemic therapy	**Overall** after at least 1 systemic therapy
		N = 5	N = 19	N = 4	N = 28
	DOR (months) median (95%CI)	- (-,-)	- (-,-)	- (-,-)	- (-,-)
	DOR rate at 12 months (%)	100.0	100.0	100.0	100.0
	DOR rate at 24 months (%)	-	83.3	-	85.6
		N = 5	N = 19	N = 4	N = 28
	TTR (months), median	2.30	1.94	3.60	1.94
		N = 5	N = 19	N = 4	N = 28
	TTCR/CRh (months), median	2.76	5.59	-	3.71
		N = 8	N = 29	N = 10	N = 47
	OS (months) median (95% CI)	- (-,-)	- (17.5,-)	- (13.5,-)	- (17.5,-)
Effect estimate per comparison	Not applicable. Single arm study.				
Analysis description	**Secondary analyses: PPR responses: Overall Response Rate by Pure Pathologic Response (PPR) criteria, Duration of Response, Time to Response, and Time to Complete Remission in AdvSM PPRE population**				
Analysis population and time point description	The secondary efficacy analysis of response by PPR criteria is based on assessment of disease burden, including bone marrow mast cells and serum tryptase. AdvSM patients must have sufficient follow up for response assessment, which is on study for 6 months (with at least 2 post-baseline marrow assessments) or off study. These patients are the AdvSM PPR Evaluable (PPRE) population. Patients were analyzed according to AdvSM disease subtype and the starting dose.				
	Treatment group	**ASM** after at least 1	**SM-AHN** after at least	**MCL** after at least 1	**Overall** after at least 1

Descriptive statistics and estimate variability	(200 mg starting dose)	systemic therapy	1 systemic therapy	systemic therapy	systemic therapy
		N = 13	N = 36	N = 10	N = 59
	ORR by PPR, (%), (95% CI)	53.8 (25.1, 80.8)	55.6 (38.1, 72.1)	40.0 (12.2, 73.8)	52.5 (39.1, 65.7)
	mCR (%)	7.7	13.9	0	10.2
	mCRh (%)	15.4	13.9	10.0	13.6
	mPR (%)	30.8	27.8	30.0	28.8
		N = 7	N = 20	N = 4	N = 31
	DOR (months) median (95%CI)	- (-,-)	13.0 (-,-)	- (-,-)	- (-,-)
	DOR rate at 12 months (%)	100.0	90.9	100.0	92.9
	DOR rate at 24 months (%)	-	90.9	-	92.9
		N = 7	N = 20	N = 4	N = 31
	TTR (months), median	1.87	1.94	3.83	1.91
		N = 3	N = 10	N = 1	N = 14
	TT mCR/mCRh (months), median	1.94	4.58	1.74	3.63
Effect estimate per comparison	Not applicable - single arm studies.				
Analysis description	**Secondary analyses: Reductions in Mast Cell Burden and Overall Survival in AdvSM population**				
Analysis population and time point description	Reductions in mast cell burden, including bone marrow mast cells, serum tryptase, KIT D816V allele fraction and spleen volume were performed in all enrolled patients and are presented for patients with a central diagnosis of AdvSM after at least one systemic therapy below. Overall survival for AdvSM patients is also presented. Patients were analyzed according to AdvSM disease subtype and the starting dose.				
Descriptive statistics and estimate variability	Treatment group (200 mg starting dose)	**ASM** after at least 1 systemic therapy	**SM-AHN** after at least 1 systemic therapy	**MCL** after at least 1 systemic therapy	**Overall** after at least 1 systemic therapy
	Reductions in Mast Cell Burden				
		N = 13	N = 40	N = 12	N = 65

	≥50% Decrease in Marrow Mast Cells (%)	100.0	80.0	75.0	83.1
	≥50% Decrease in Serum Tryptase (%)	N = 14 100	N = 41 82.9	N = 12 91.7	N = 67 88.1
	≥50% Decrease in KIT D816V allele fraction (%)	N = 14 71.4	N = 41 73.2	N = 12 50.0	N = 67 68.7
	≥35% Decrease in Spleen Volume (%)	N = 14 57.1	N = 39 64.1	N = 12 50.0	N = 65 60.0
	Overall Survival				
	Treatment group (200 mg starting dose)	**ASM** after at least 1 systemic therapy	**SM-AHN** after at least 1 systemic therapy	**MCL** after at least 1 systemic therapy	**Overall** after at least 1 systemic therapy
	OS (months) median (95% CI)	N = 14 - (-,-)	N = 41 - (-,-)	N = 12 - (13.5,-)	N = 67 - (-,-)
	% OS at 12 months	100.0	84.0	81.5	86.9
	% OS at 24 months	-	71.1	67.9	72.5
Effect estimate per comparison	Not applicable - single arm studies.				

Further details of data submitted in between the initial submission and the responses to the D120 LoQ are included below as they are considered informative.

Table 34 Study BLU-285-2202: Summary of Primary Efficacy Endpoints (Response Evaluable Population, According to modified IWG-MRT-ECNM)

Population (data cut-off date)	**IA Population (23 June 2020)**		**IA Population (Updated) (20 April 2021)**		**Post-IA Population (20 April 2021)**		**Combined IA and post-IA (20 April 2021)**	
	Regardless of prior systemic therapy	At least one prior systemic therapy	Regardless of prior systemic therapy	At least one prior systemic therapy	Regardless of prior systemic therapy	At least one prior systemic therapy	Regardless of prior systemic therapy	At least one prior systemic therapy
N	32[1]	23[1]	32[1]	23[1]	42[2]	26[2]	74[3]	49[3]
Median follow-up, months (95% confidence interval)	10.4 (8.1-11.6)	10.4 (8.3-12.3)	20.7 (18.0-22.6)	20.7 (18.0-24.7)	9.6 (8.0-11.2)	9.9 (7.3-13.9)	14.3 (11.2-16.9)	14.6 (11.2-18.0)

ORR, N (%)[1]	24 (75.0)	17 (73.9)	26 (81.3)	17 (73.9)	24 (57.1)	12 (46.2)	50 (67.6)	29 (59.2)
(CR+CRh+PR+CI)	(56.6, 88.5)	(51.6, 89.8)	(63.6, 92.8)	(51.6, 89.8)	(41.0 72.3)	(26.6, 66.6)	(55.7, 78.0)	(44.2, 73.0)
(95% confidence interval)								
CR+CRh	6 (18.8)	3 (13)	10 (31.3)	4 (17.4)	3 (7.1)	1 (3.8)	13 (17.6)	5 (10.2)
CR	0	0	3 (9.4)	1 (4.3)	0	0	3 (4.1)	1 (2.0)
CRh	6 (18.8)	3 (13.0)	7 (21.9)	3 (13.0)	3 (7.1)	1 (3.8)	10 (13.5)	4 (8.2)
PR	10 (31.3)	7 (30.4)	13 (40.6)	10 (43.5)	18 (42.9)	9 (34.6)	31 (41.9)	19 (38.8)
CI	8 (25.0)	7 (30.4)	3 (9.4)	3 (13.0)	3 (7.1)	2 (7.7)	6 (8.1)	5 (10.2)

[1] Includes 1 patient treated with avapritinib 100 mg QD starting dose in the IA population
[2] Includes 1 patient treated with avapritinib 100 mg QD starting dose in the post-IA population
[3] Includes 2 patients treated with avapritinib 100 mg QD starting dose
Abbreviations: CI = clinical improvement, CR = complete remission, CRh = complete hematologic remission, IA = interim analysis, IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis, ORR = overall response rate, PR = partial remission
Source: Original ISE (SN0012): Table 14.2.4.2, Table 99.2.4.2.1, 14.2.1.1 and 14.2.1.1f
Study BLU-285-2202 20 April 2021 (Annex 1): Table14.2.6.2, Table 14.2.6.2c, Table 14.2.1.1 and Table 14.2.1.1f

Table 35 Study BLU-285-2202: Summary of Secondary Efficacy Endpoints (Response Evaluable Population, According to modified IWG-MRT-ECNM)

Population (data cut-off date)	**IA Population (23 June 2020)**		**IA Population (Updated) (20 April 2021)**		**Post-IA Population (20 April 2021)**		**Combined IA and post-IA (20 April 2021)**	
Efficacy parameter Median (months)	Regardless of prior systemic therapy	At least one prior systemic therapy	Regardless of prior systemic therapy	At least one prior systemic therapy	Regardless of prior systemic therapy	At least one prior systemic therapy	Regardless of prior systemic therapy	At least one prior systemic therapy
Median TTR (months)	2.04	2.56	2.04	2.10	1.92	1.92	1.95	1.94
Median Time to CR/CRh[1] (months)	5.55	3.71	5.57	4.64	2.10	1.81	5.55	3.71
Median DOR (months) (95% confidence interval)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
DOR rate at 12 months, %	100	100	100	100	100	100	100	100
DOR rate at 24 months, %	NA	NA	85.2	86.2	NA	NA	86.2	86.2
Median PFS (months) (95% confidence interval)	NE (NE, NE)	NE (10.5, NE)	NE (NE, NE)	NE (17.5, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (17.5, NE)
PFS rate at 12 months, %	79.0	70.4	83.9	77.5	87.8	80.4	85.4	78.3

PFS rate at 24 months, %	NA	NA	71.2	66.5	NA	NA	73.1	67.1

[1] Includes 1 patient treated with avapritinib 100 mg QD starting dose in the IA population
[2] Includes 1 patient treated with avapritinib 100 mg QD starting dose in the post-IA population
[3] Includes 2 patients treated with avapritinib 100 mg QD starting dose
Abbreviations: CR = complete remission, CRh = complete hematologic remission, DOR = duration of response, IA = interim analysis, IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis, NA = not available, NE = not estimable, PFS = progression free survival, TTR = time to response
Source Data: Original ISE (SN0012): Table 14.2.2.4, Table 99.2.2.4.1, Table 14.2.2.1, Table 14.2.2.1b, and Table 14.2.3.1
Study BLU-285-2202 CSR (SN0012): Table 14.2.5.1c
Study BLU-285-2202 20 April 2021 (Annex 1): Table 14.2.3.1, Table 14.2.3.1a, Table 14.2.4.1, Table 14.2.4.1c, Table 14.2.5.1 and Table 14.2.5.1c

Analysis performed across trials (pooled analyses and meta-analysis)

A pooled analysis of data obtained from patients treated with prior systemic therapy from the two ongoing clinical studies BLU-285-2101 and BLU-285-2202 was submitted as part of the initial application. The data for Study BLU-285-2202 were derived from a pre-specified interim analysis and additionally, pooled efficacy results for all patients regardless of prior therapy were provided. The comparability of the two pooled populations were however not conclusively demonstrated and details from this pooled analysis are not shown in this report.

2.6.5.3. Clinical studies in special populations

Table 36 Age groups of older patients in clinical studies

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
BLU-285-2101	30/86	12/86	0
BLU-285-2202	47/107	20/107	3/107

Of the 47 patients who received AYVAKYT at a starting dose of 200 mg and who received at least one prior systemic therapy in PATHFINDER, 64% were 65 years or older, while 21% were 75 years and older. No overall differences in efficacy were observed between patients ≥65 years and those <65 years

2.6.5.4. Analysis performed across trials (pooled analyses and meta-analysis)

A pooled analysis of data obtained from patients treated with prior systemic therapy from the two ongoing clinical studies BLU-285-2101 and BLU-285-2202 was submitted as part of the initial application. The data for Study BLU-285-2202 were derived from a pre-specified interim analysis and additionally, pooled efficacy results for all patients regardless of prior therapy were provided. The comparability of the two pooled populations were however not conclusively demonstrated and details from this pooled analysis are not shown in this report.

2.6.5.5. Supportive study(ies)

BLU-285-2101 has been submitted as dose response study (see section 3.2)

BLU-285-2405

Study Design

Study BLU-285-2405 was designed as an external control, observational, retrospective study to compare the effectiveness of avapritinib in patients treated in studies BLU-285-2101 and BLU-285-2202 and real-world patients treated with Best Available Therapy (BAT). The primary endpoint was OS, while secondary endpoints included: duration of therapy (DOT), change in serum tryptase from baseline to two months and the maximum reductions in serum tryptase. Subgroup analyses for the primary endpoint of OS were conducted in patients who initiated avapritinib at dose ⩽200mg compared to patients who received BAT as 1L+, in patients who initiated avapritinib at a ⩽200 mg dose compared to all patients who received BAT, in the 2L+ setting; and in patients who received avapritinib at a starting dose of 200 mg QD in both trials compared to all patients who received BAT in the 2L+ setting.

Individual patient-level data for the BAT cohort were collected retrospectively up to October 4, 2021, from the medical charts of adult patients with AdvSM, who received systemic treatment at participating study sites in Europe and the US on or after January 1, 2009. The avapritinib cohort consisted of patients treated with avapritinib in studies BLU-285-2101 and BLU-285-2202, at any dose, included in the data cut as of April 20, 2021.

Inverse probability of treatment weights (IPTW)-weighted Cox proportional hazards models were used to assess the association between receiving avapritinib vs. BAT and outcomes of OS and DOT, adjusting for differences in key covariates defined *a priori*, between the two treatment groups. Key covariates included, but were not limited to, age, sex, Eastern Cooperative Oncology Group (ECOG) score, number of prior lines of therapy (LOTs), and types of prior therapy.

Results

Primary Analysis

Overall, 176 patients from studies BLU-285-2101 and BLU-285-2202 in the avapritinib cohort and 141 real-world patients in the BAT cohort were included in the comparative analysis. Patients in the BAT cohort could have received multiple LOTs at participating sites, and data on all eligible LOTs was collected, therefore the 141 patients in this cohort contributed data on 250 LOTs. Among 196 LOTs with agent-level information available, midostaurin and cladribine were the most commonly used, representing 50.5% and 25.0% of these LOTs, respectively. Of note, midostaurin was only approved for treatment of AdvSM in 2017. Other treatments included TKIs (ripretinib (2.0%), ibrutinib (1.5%), dasatinib (1.0%), and imatinib (1.0%)), cytotoxic treatments (hydroxyurea (8.7%) and azacitidine (1.5%)), and biologics (interferon-alpha (5.6%), pegylated interferon (4.1%), brentuximab vedotin (2.0%), and gemtuzumab ozogamicin (0.5%)).

Based on an unweighted Kaplan-Meier (KM) analysis, median OS was not reached (95% confidence interval [CI]: 46.9, not estimable [NE]) for the avapritinib cohort and was 23.4 months (95% CI: 19.5, 32.6) for the BAT cohort (log-rank $P<0.001$). In the IPTW-weighted, adjusted analysis, OS was improved in the avapritinib cohort compared with the BAT cohort (hazard ratio [HR] [95% CI]: 0.48 [0.29, 0.79]; $P=0.004$), after adjustment for key covariates. Similar results were obtained in the subgroup analyses (see table below).

Table 37 Summary of Overall Survival in Patient Subgroups

	Unweighted sample[b]				IPTW-Weighted sample[c]			
	Avapritinib	BAT	HR (95% CI)	p	Avapritinib effective sample size	BAT effective sample size	HR (95% CI)	p
Overall: Avapritinib vs. BAT 1L+								
Unique patients, n	176	141			172	136		
LOTs, n	176	222			172	210		
HR (95% CI)[d]	--	--	0.39 (0.26, 0.58)	<0.001*	--	--	0.48 (0.29, 0.79)[e]	0.004*
Subgroup 1: Avapritinib (≤200 mg) vs. BAT, 1L+								
Unique patients, n	136	141			133	135		
LOTs, n	136	222			133	212		
HR (95% CI)[d]	--	--	0.37 (0.23, 0.60)	<0.001*	--	--	0.43 (0.26, 0.72)[f]	0.001*
Subgroup 2: Avapritinib (≤200 mg) vs. BAT, 2L+								
Unique patients, n	85	73			83	64		
LOTs, n	85	104			83	95		
HR (95% CI)[d]	--	--	0.32 (0.17, 0.60)	<0.001*	--	--	0.34 (0.17, 0.69)[g]	0.003*
Subgroup 3: Avapritinib (200 mg) vs. BAT, 2L+								
Unique patients, n	79	73			77	66		
LOTs, n	79	104			77	96		
HR (95% CI)[d]	--	--	0.39 (0.21, 0.74)	0.004*	--	--	0.37 (0.18, 0.75)[h]	0.006*

*P<0.05 **Abbreviations:** AdvSM: advanced systemic mastocytosis; BAT: best available therapy; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; IPTW: inverse probability of treatment weighting; RAC-RE: response assessment committee-response evaluable. **Notes:** [a] For the BAT cohort, overall survival was defined as the interval of time between initiation of each included line of therapy and death due to any cause. Patients who had not died by the study end date were censored at the date of last contact. For avapritinib patients, overall survival was defined as the time from the first dose of avapritinib to the date of death due to any cause. Patients who were still alive or lost to follow-up were censored at the last known alive date.[b] Patients from the BAT cohort could contribute multiple lines of therapy. A total of 222 lines of therapy were contributed by 141 real-world patients in the unweighted BAT cohort. [c] Stabilized weights were generated using the following baseline characteristics: age, sex, region, ECOG score, anemia (hemoglobin less than 10 g/dL), thrombocytopenia (platelet count less than 100 x 10^9/L), AdvSM subtype, skin involvement, leukocyte count of 16 × 10^9 per L or higher, serum tryptase concentration of 125 ng/mL or higher, number of mutated genes within the SRSF2/ASXL1/RUNX1 panel, number of prior lines of therapy, and prior use of tyrosine kinase inhibitor, cytotoxic, biologic or other systemic therapy. To reduce variability, stabilized weights were capped at the 1st and 99th percentiles. [d] Both unweighted and IPTW-weighted Cox proportional hazards models with a robust sandwich variance estimator were used to model overall survival. IPTW-weighted Cox proportional hazards model further adjusted for covariates with a standardized difference of greater than 10% after weighting, using a doubly robust approach. [e] IPTW-weighted multivariable Cox proportional hazards model further adjusted for age, ECOG score, AdvSM subtype, and skin involvement. [f] IPTW-weighted multivariable Cox proportional hazards model further adjusted for region, presence of thrombocytopenia at baseline, serum tryptase concentration of 125 ng/mL or higher, and prior use of tyrosine kinase inhibitor therapy. [g] IPTW-weighted multivariable Cox proportional hazards model further adjusted for sex, region, ECOG score, presence of thrombocytopenia at baseline, leukocyte count of 16 × 10^9 per L or higher, prior use of tyrosine kinase inhibitor therapy, and prior use of cytotoxic therapy.[h] IPTW-weighted multivariable Cox proportional hazards model further adjusted for sex, region, ECOG score, presence of thrombocytopenia at baseline, leukocyte count of 16 × 10^9 per L or higher, serum tryptase concentration of 125 ng/mL or higher, prior use of tyrosine kinase inhibitor therapy, and prior use of cytotoxic therapy.[i] IPTW-weighted multivariable Cox proportional hazards model further adjusted for sex, region, presence of anemia at baseline, presence of thrombocytopenia at baseline, AdvSM subtype, prior use of tyrosine kinase inhibitor therapy, and prior use of cytotoxic therapy. [j] IPTW-weighted multivariable Cox proportional hazards model further adjusted for age, region, ECOG score, presence of thrombocytopenia at baseline, leukocyte count of 16 × 10^9 per L or higher, serum tryptase concentration of 125 ng/mL or higher, and prior use of tyrosine kinase inhibitor therapy.
Source: CSR BLU-285-2405 Section 4

2.6.6. Discussion on clinical efficacy

The MAH applied for the addition of two new strengths (25mg and 50 mg film-coated tablets) and for a new therapeutic indication. This new claimed indication is for the use of daily avapritinib 200 mg, administered orally in 28 day-cycles, for the "*treatment of adult patients with advanced systemic mastocytosis (AdvSM), including aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN), and mast cell leukaemia (MCL), after at least one systemic therapy*".

This application is based on the efficacy results from the ongoing phase 2, open-label, single-arm, 2-cohort **study BLU-285-2202** (PATHFINDER) and supported by the phase 1, open-label dose escalation **study BLU-285-2101** (EXPLORER) as described below. Both studies were conducted in countries in Europe and North America. Data of study BLU-285-2202 (PATHFINDER) in the initial submission came from a pre-specified interim analysis (n=32 in the mIWG-MRT-ECNM-evaluable cohort 1).

Results from these two studies, and from a pooled analysis including patients previously treated with at least one systemic therapy and who have received various avapritinib starting doses (ranging from below 200 mg to 400 mg) were the initial basis proposed to support efficacy (and safety) of avapritinib in the intended indication. Differences were noted in the baseline characteristics and prognostic factors in the relevant

populations (200mg, focus on 2L+), which constitutes an important drawback of this pooled analysis. Efficacy data from the pooled analysis are therefore not presented in this report.

Additionally, results from a Real-World Evidence (RWE) trial (study BLU-285-2405) designed as an external control, observational, retrospective study assessing the effect of avapritinib compared with best available therapy (BAT) for patients with AdvSM have been provided during this procedure. Inclusion of these RWE data in the SmPC is however not accepted.

Design and conduct of clinical studies

Dose response study

Study BLU-285-2101 (EXPLORER) is an ongoing, open-label, Phase 1 study designed to evaluate the safety, tolerability, PK, pharmacodynamics, and antineoplastic activity (efficacy) of avapritinib, administered orally, in adult patients with AdvSM and relapsed or refractory myeloid malignancies. As of the data cut-off date of 27 May 2020, enrolment in the study was complete at 86 patients and patients remaining on study are being followed for response and safety assessments. Its primary objective was to establish the maximum tolerated dose (MTD) and the recommended Phase 2 dose.

The BLU-285-2101 two-part study included:

- an initial dose escalation (**Part 1**, complete) to evaluate safety and tolerability of increasing doses of avapritinib (from 30 to 400 mg QD) in patients with a local diagnosis of AdvSM or other relapsed or refractory myeloid malignancies,

- and an expansion (**Part 2**, ongoing) to further evaluate the safety, PK, pharmacodynamics, and **efficacy** (according to mIWG-MRT-ECNM response criteria) of avapritinib in the treatment of AdvSM when administered at starting doses of 200 or 300 mg QD.

The recommended Phase 2 dose was initially identified as 300 mg QD; however, based on efficacy, time to response, and long-term safety and dosing data from the Phase 1 study (BLU-285-2101), a starting dose of 200 mg QD was selected. Therefore, a dose of 200 mg QD was used in the BLU-285-2202 study for the treatment of patients with AdvSM. This is considered acceptable, although the trial design limits the possibility to quantify how the risk potentially changes in relation to different dose- and exposure levels. The 3+3 design with the allowance of intrapatient dose increases, and abundant dose modifications, makes it difficult to assess any relationship between dose and response. For efficacy, relationships cannot be determined since patients were not kept at lower dose levels for sufficient periods to assess objective responses at the actual starting dose levels. The separate exposure-efficacy analyses (presented in 3.3.2 Pharmacodynamics) are also inconclusive.

A total of 53 patients from BLU-285-2101 study were considered as response evaluable for the pooled efficacy analysis initially provided, of whom 32 received prior systemic therapy and 9 were treated with a starting dose of 200 mg QD (DCO 27 May 2020). Of note, three additional patients previously treated with systemic therapy and receiving a starting dose 200 mg QD became RE at a later DCO of 20 April 2021.

Main clinical study

Study BLU-285-2202 (PATHFINDER) is an ongoing, open-label, single-arm, Phase 2 study evaluating the efficacy and safety of avapritinib 200 mg QD in patients with a WHO diagnosis of AdvSM, who were enrolled into 1 of 2 cohorts:

- **Cohort 1:** patients with ≥ 1 mIWG-MRT-ECNM criteria for evaluable disease (with an evaluable C-finding or MCL), as determined by the Study Steering Committee (SSC).
- **Cohort 2:** patients who were not considered eligible for an adjudicated mIWG-MRT-ECNM response, as determined by the SSC.

At the first data cut-off date the study was ongoing with 62 patients across both cohorts having received ≥ 1 avapritinib dose through the data cut-off of 23 June 2020 (safety population). Screening in study BLU-285-2202 was completed on 17 Nov/2020, with the last patient enrolled on 21 Jan/2021.

Patients in Cohort 1 support the primary objective of determining SSC-adjudicated ORR by mIWG-MRT-ECNM criteria (primary endpoint). The RE population was used for the primary efficacy analysis and for all secondary efficacy analyses related to response. Data from both cohorts were used in the analyses of the remaining secondary and exploratory endpoints.

During the study a total of ten **amendments** to the original protocol (09 January 2018) were issued. A number of deviations were also noted, primarily due to the large number of assessments required to adjudicate response by mIWG-MRT-ECNM criteria, as well as the COVID-19 pandemic. However, the amendments to and deviations from the protocol do not seem to adversely affect the interpretability of the study.

As mentioned, no patient in study BLU-285-2202 received a **starting dose** of 300 mg QD. There were two patients who received 100 mg as an initial dose at the time of the interim analysis data cut-off. Of the two patients, one met the criteria for response evaluable population and was included in the primary analysis. This patient never received a 200 mg dose during following cycles. The patient was continuing on 100 mg at the time of the data cut-off (20 April 2021, cycle 26) with ongoing CI (TTR 5.8 months) and DOR of 15.7 months. In addition, one patient who received a starting dose of 100 mg became response evaluable at the time of the most recent data cut-off (20 April 2021).

The **proposed inclusion and exclusion criteria** are considered overall acceptable. Of note, with the exception of study sites in Germany, midostaurin-naïve patients were enrolled in the study based on encouraging results from study BLU-285-2101 where the majority of patients were midostaurin-naïve as study BLU-285-2101 was initiated before the approval of midostaurin. In study BLU-285-2202, 9 patients, out of the 32 response evaluable patients at the time of the IA, were treatment naïve. None of them had a clear absolute or relative contraindication to midostaurin, as reported by the MAH following a review they conducted on data available from patients (the specific information was not recorded in the CRFs).

The **primary endpoint** in the study is adjudicated ORR (CR+CRh+PR+CI) based on mIWG-MRT-ECNM response criteria, confirmed 12 weeks after initial response, which is considered an acceptable primary endpoint in the context of a single arm trial, indicating drug activity. The use of the modified IWG-MRT-ECNM response criteria was discussed and agreed at the time when scientific advice was sought. Inclusion of clinical improvement, in line with what was done in the midostaurin trials, was also agreed at that time and is considered acceptable.

The IWG-MRT-ECNM criteria were used for the first time in BLU-285-2101, and based on this experience, the applicant modified the IWG-MRT-ECNM criteria to construct the mIWG-MRT-ECNM criteria. The modified criteria have not been published, although requested at the time when SA was sought. The main difference in the mIWG-MRT-ECNM criteria compared to the original was the revision and expansion of the definition of a C-finding, which likely led to the inclusion of a larger patient population compared to the patient group that would have been eligible according to the original IWG-MRT-ECNM criteria. This could lead to an observed enhancement of effect compared with evaluation by IWG-MRT-ECNM criteria. The applicant has provided

sensitivity analyses with the IWG-MRT-ECNM criteria to address this issue (data not shown). Another modification in the mIWG-MRT-ECNM criteria was the introduction of the CRh (Complete remission with partial recovery of peripheral blood counts) response category, which required the absence of neoplastic MC aggregates, serum tryptase < 20ng/mL, complete resolution of all evaluable C-findings, partial hematologic recovery with ANC≥0.5x10^9/L, Hgb≥8g/dL and Platelets≥50x10^9/L. In the SA it was stated that this response should be considered in the category of partial response and not be taken into account as a CR.

Overall, in the absence of a RCT, an indirect comparison of ORR rates in the precedent midostaurin study and BLU-285-2202, although not exempt from limitations, does provide information about avapritinib efficacy. In this regard, the validity of comparing ORR for the current study, assessed by the mIWG-MRT-ECNM criteria, against ORR for midostaurin, assessed by the unmodified IWG-MRT-ECNM criteria, was questioned, and for a better comparison, the MAH was asked to provide an analysis where the response for avapritinib treated patients was assessed according to similar unmodified IWG-MRT-ECNM criteria. The MAH provided the requested analyses (data not shown) of ORR for avapritinib compared to the ORR observed for midostaurin, i.e. 28%, using unmodified IWG-MRT-ECNM criteria. Again, ORR for avapritinib was found to be statistically significantly superior to an ORR of 28%. While it is necessary to recognize that midostaurin is an external control group and the results of this comparison should be interpreted with caution, the comparison seems overall favourable for avapritinib.

Secondary endpoints include among others: time to event outcomes (including time to response, DOR, PFS, and OS) as well as changes in bone marrow mast cells and serum tryptase which are related to disease activity. All are considered reasonable. Of particular relevance in the context of the conducted single arm trial is the duration of response (DOR) as it provides relevant information on the clinical value of the achieved responses.

From a methodological perspective the **targeted sample size** of 63 patients in cohort 1 can be considered adequate also taking into account that AdvSM is a very rare disease. At the time when scientific advice was sought (EMEA/H/SA/3738/2/2018/SME/III) the CHMP expressed concerns regarding the intended sample size of only 60 patients, especially since three different disease entities with different prognosis are included. The MAH increased the target for enrolment in study BLU-285-2202 (up to 103 patients, approximately 63 patients in cohort 1 and 40 patients in cohort 2) but only cohort 1 will provide data on the primary endpoint of ORR based on mIWG-MRT-ECNM response criteria. As reported above, study enrolment completed with a total of 107 patients enrolled, including 85 (74 currently RE) in Cohort 1 and 22 in Cohort 2.

The statistical analysis plan (SAP) is dated 29th June 2020, whereas the data cut-off date is 23rd June 2020: the statistical analysis plan was therefore finalised after the data cut-off date. Ideally in an open label study (with confirmatory intent) the SAP should have been finalised before.

An **interim analysis** was planned and added to the protocol as part of amendment 3, to be conducted once the first 32 patients (with the SM-AHN subgroup capped at approximately 70%) were enrolled in the mIWG-MRT-ECNM-evaluable cohort and were evaluable for response. Only ORR results (primary efficacy endpoint) from the 23 previously treated patients (out of the 32 patients evaluable for response at the time of the IA) were initially considered for efficacy evaluation together with data from additional patients in study BLU-285-2101. Additional data was however submitted during the procedure as reported below.

<u>RWE study</u>

Study BLU-285-2405 was designed as an external control, observational, retrospective study to compare the effectiveness of avapritinib in patients treated in studies BLU-285-2101 and BLU-285-2202 and real-world patients treated with BAT. Individual patient-level data for the BAT cohort were collected retrospectively up to October 4, 2021, from the medical charts of adult patients with AdvSM, who received systemic treatment

at participating study sites in Europe and the US on or after January 1, 2009. The primary endpoint was overall OS, while secondary endpoints included: duration of therapy, change in serum tryptase from baseline to two months and the maximum reductions in serum tryptase (data for secondary endpoints not shown). Subgroup analyses were performed, reflecting the indication and posology applied for. The final CSR for this study was submitted during the procedure.

Efficacy data and additional analyses

Study BLU-285-2202

The updated dataset (DCO date of 20 April 2021) included 42 additional response evaluable (RE) patients from study BLU-285-2202 so that the current sample size is more than double of the previous submitted IA-population. The combined IA and post IA population (n=74 patients, 49 received at least one prior systemic therapy) showed a slightly lower ORR in both subpopulations compared to that reported in the initial submission (ORR 67.6% vs. 75% in the "Regardless of prior systemic therapy population" / ORR 59.2% vs. 73.9% in the "After at least one prior systemic therapy population"), with a median follow-up of 14 months which remains short particularly for the post-IA population where median follow is 9.6-9.9 months. The lower response rate, in spite of similar follow-up time, reported in the post-IA population compared to the initially reported IA population, in patients who received at least one prior therapy (46.2% vs. 73.9%), is explained by the MAH as being driven by fewer CI responses but with a similar rate of deeper responses (CR/CRh/PR), i.e. 38.4% vs.43.4%. This is acknowledged though it should also be noted that a lower number of CRh is also reported (13% in the IA population vs. 3.8% in the post-IA population). In addition, the point estimate in the IA analysis falls outside the 95% CI in the post-IA population. The lower limit of the confidence interval is also clearly lower in the 2L+ post-IA population, extending down to 26.6%. Patient numbers are, however, small and follow-up too short to conclude on whether these differences are of concern. Overall, the updated data from the BLU-285-2202 study supports previously reported results from the IA population.

Median (range) **time to response** by centrally adjudicated mIWG-MRT-ECNM criteria in the 24 AdvSM responders treated in the all doses group in the RE population, initial dataset, was rapid and **occurred at 2.04** (0.3 to 12.2) **months**.

Median **DOR** by centrally adjudicated mIWG-MRT-ECNM criteria in the 24 AdvSM responders treated in the all doses group in the RE population **was not reached** at the time of data cut-off (nor for the updated analysis). Median **PFS was also not reached** at the time of data cut-off (nor for the updated analysis), with an estimated PFS rate of 78.3% at 12 months (combined IA and post-IA population, patients having received at least one prior therapy, DCO date 20 April 2021). OS at 12 months was 87.3% (combined IA and post-IA population, DCO date 20 April 2021).

Efficacy data for the 3 subdiagnoses of AdvSM have also been presented for the 200mg, 2L+ RE population (n=47) which is considered the main efficacy population in the context of the applied indication. Data/results for this subset of patients are presented in the efficacy section of this report and are reflected in section 5.1 of the SmPC instead of the originally proposed pooled analysis. There are 8 patients with ASM, 10 patients with MCL and 29 patients with SM-AHN in the updated analysis. The numbers of patients are still very low especially for ASM and MCL. From the results in the subgroups, it may however be concluded that clinically relevant response can be obtained with avapritinib in all subgroups, although MCL seems to be the most difficult to treat.

Results from secondary endpoints, albeit exploratory, can be considered to support the reported ORR findings. Of special relevance are data on DOR which are critical to judge the expectation of a reported very high ORR to translate into clinically meaningful benefit. Follow-up is limited and, as noted, median DOR is still not reached with a median updated follow–up of 14 months, which remains limited particularly in the newly enrolled patients / post-IA patient population.

Besides data being currently immature, interpretation of time to event endpoints, in particular PFS and OS, is hampered in the context of a single arm trial and should therefore be considered with caution.

Results on other secondary endpoints e.g. the observed reduction of bone marrow mast cells and changes observed in serum tryptase level are also encouraging. Both endpoints are related to the level of disease activity with maintenance of observed reductions over time associated with control of the disease.

Notwithstanding the above outlined limitations, it can be concluded that clinically relevant responses can be obtained with avapritinib treatment in AdvSM patients after at least one systemic therapy and in whom an improvement in symptoms and control of the disease can be considered to represent clinical benefit. Provision, post-approval, of the final CSR of study BLU-285-2202, for further confirmation of currently reported results and of long-term benefit is in any case expected (**REC**).

Subgroup analyses were performed for ORR by prior antineoplastic therapy, prior midostaurin treatment, baseline S/A/R genotype, age group, sex, and geographic regions (data presented in this report corresponds to the original dataset). The submission of results from subgroup analyses is acknowledged. However, given the low numbers results from these analyses are difficult to interpret. Of note, according to the submitted subgroup analysis by prior midostaurin treatment, patients previously treated with midostaurin seem to have better outcomes that those who did not received previous treatment with midostaurin though the 95% CIs are wide and overlapping.

No dedicated studies have been conducted in special populations: **elderly** patients and patients with renal or hepatic impairment. However, 67.7% of patients from the safety population (n=62) of the main study (BLU-285-2202) were 65 years old or older. The MAH has included information in the SmPC, i.e. of the percentages of patients above 65 years of age and 75 years and older among patients who received avapritinib (all doses) and who received at least one prior systemic therapy in EXPLORER or in PATHFINDER highlighting that no overall differences in efficacy were observed between these patients and younger adult patients.

RWE Study: BLU-285-2405

Analysis of the primary endpoint, OS, showed improved OS for avapritinib compared to BAT (HR [95% CI]: 0.48 [0.29, 0.79]; *P*=0.004), after adjusting for differences in key prognostic factors and confounders between the patients who received avapritinib in clinical trials and patients who received BAT in real-world practice. Subgroup analyses agreed with the primary analysis. In particular, the subgroup of patients who received an avapritinib starting dose of 200mg in 2L+ had a 63% decreased risk of death (adjusted HR [95% CI]: 0.37 [0.18, 0.75]; P=0.006) compared to BAT patients in 2L+. However, there are several limitations to study BLU-285-2405 and these analyses should therefore be interpreted with caution. For one, BLU-285-2405 was not able to fully recapitulate the inclusion/exclusion criteria from BLU-285-2101 and BLU-285-2202. Further, AdvSM diagnoses for the avapritinib cohort were centrally confirmed, while diagnoses in the BAT cohort were not. In BLU-285-2405, patients were included from January 1, 2009. Treatment options for advanced systemic mastocytosis have improved during this time, most notably through the introduction of Rydapt (midostaurin) in 2017. Thus, though median OS appears better for avapritinib than for BAT in BLU-285-2405, it cannot be concluded from the study whether avapritinib also gives better median OS than midostaurin, which has shown good results in patients with AdvSM. Further possible biases in BLU-285-2405 may arise from the censoring of

patients upon starting avapritinib treatment and from the inclusion of several lines of therapy from some patients, though sensitivity analyses to assess these two issues show results consistent with the main analysis. Overall, study BLU-285-2405 provides some support for an improved median OS in the avapritinib cohort compared with the BAT cohort, bearing in mind that there are several uncertainties surrounding study BLU-285-2405 and the comparison between BLU-285-2405 and BLU-285-2101/BLU-285-2202.

Wording of the indication

A slight rewording of the indication was proposed for clarity. This was accepted by the MAH and the final indication reads:

"AYVAKYT is indicated as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), after at least one systemic therapy"

2.6.7. Conclusions on the clinical efficacy

Efficacy data submitted to support the new claimed indication for avapritinib come from two uncontrolled single arm studies where a relevant ORR by centrally adjudicated mIWG-MRT-ECNM criteria in patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) and mast cell leukaemia (MCL) after at least one systemic therapy, have been reported. These ORR results, which are supported by secondary endpoints, including duration of response, are expected to translate into clinically meaningful benefit, and appear to be rather consistent regardless of prior systemic therapy, subtype of the disease and starting dose cohort, though data are limited. A number of methodological limitations are identified that are considered to be outweighed by the relevance of the reported efficacy results in the context of a very rare disease with limited treatment alternatives. Even if follow-up time is limited, particularly for the post-IA population, currently available updated efficacy data show that clinically relevant responses can be obtained with avapritinib treatment in AdvSM patients after at least one systemic therapy in whom an improvement in symptoms and control of the disease can be considered to represent clinical benefit. Final data from study BLU-285-2202 (CSR), anticipated to be available in December 2026, will be submitted as a post-authorization commitment (REC).

2.6.8. Clinical safety

The safety database to support this indication expansion consists of 2 studies in patients with AdvSM (studies BLU-285-2101 and BLU-285-2202) and updated safety data from 2 studies in patients with GIST (studies BLU-285-1101 and BLU-285-1303). Safety data from these 4 studies were pooled for analysis (Table 1). Several other ongoing and completed avapritinib studies were considered out of scope for the integration of safety data into pooled analyses, including 5 clinical pharmacology studies (all subjects were healthy volunteers), study BLU-285-2203 (ongoing Phase 2 study in ISM using smaller doses of avapritinib), an EAP, and data from individual patients treated under a CUP.

Data presented with the initial submission included events occurring up to 27 May 2020 for Studies BLU-285-1101, BLU-285-1303, and BLU-285-2101, and through 23 June 2020 for BLU-285-2202, the data cut-off dates for this marketing application. During the procedure, the MAH provided a safety update for studies BLU-285-2101 and BLU-285-2202, with a cut-off date of 21 Apr 2021. Pooled safety data were also updated

and provided. For some of the analyses concerning the 200mg QD group (also referred to as "extended" or "overall" group), separate data for the 81 original patients were also provided at the CHMP's request.

Table 38 Completed and Ongoing Clinical Studies with Avapritinib Included in the Pooled Safety Set

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

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

Abbreviations: AdvSM = advanced systemic mastocytosis; CSR = clinical study report; F = female; GIST = gastrointestinal stromal tumor; M = male; mIWGMRT-ECNM = modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; MTD = maximum tolerated dose; ORR = objective response rate; PD = progressive disease; PDGFRA = platelet derived growth factor receptor alpha; PK = pharmacokinetics; PO = per os, by mouth, oral; QD = once daily; QoL = quality of life; RP2D = recommended Phase 2 dose; TKI = tyrosine kinase inhibitor. [a] Only data from patients assigned to Arm A and treated with avapritinib are included in the integrated summary of safety pooled analysis; patients in Arm B who received regorafenib only or those who crossed over from Arm B (regorafenib) to Arm A are excluded from the pooled ISS analysis. [b] Emerging safety and efficacy data resulted in the RP2D being reduced from 300 mg to 200 mg in Cohort 1. Source: Table 18.3.1, Table 99.1.1.1, Table 99.1.1.2, Table 99.1.1.3, Table 99.1.1.4, CSR BLU-285-2101, CSR BLU-285-2202, data on file.

2.6.8.1. Patient exposure

In the initial submission, a total of 148 AdvSM patients across all doses of avapritinib were included in the Safety Population. Of them, 81 patients received a starting dose of 200 mg QD, 50 patients received a starting dose of ≥ 300 mg QD, and 17 patients received a starting dose of < 200 mg QD. Studies BLU-285-2101 and BLU-285-2202 contributed 86 and 62 AdvSM patients, respectively to the Safety Population.
During the procedure, the MAH provided an integrated analysis of safety with a data cut-off date of 20 April 2021. The updated safety population included 193 patients (i.e., extended population) that had received avapritinib in studies BLU-285-2101 and BLU-285-2202, including 126 patients who initiated treatment with avapritinib at 200 mg once daily (QD) and 50 patients who initiated dosing at ≥ 300 mg QD.

- **Disposition**

A total of 193 AdvSM patients received ≥ 1 dose of avapritinib as of 21 April 2021. Overall, 99/126 (78.6%) of patients starting with avapritinib 200mg QD continued on treatment. The updated patient disposition is shown in the table below.

Table 39 Updated patient disposition as of 21 April 2021

Table 18.3.1.2
Summary of Patient Disposition
Safety Population

Patient Disposition	SM 200mg N=126 n (%)	SM ≥ 300mg N=50 n (%)	SM All N=193 n (%)	Ava All N=803 n (%)
Patients Continuing Study	99 (78.6)	30 (60.0)	141 (73.1)	141 (17.6)
Patients Discontinued Study	27 (21.4)	20 (40.0)	52 (26.9)	662 (82.4)
Reason for Discontinuation of Study				
Disease Progression	0	1 (2.0)	1 (<1)	10 (1.2)
Adverse Event	0	1 (2.0)	1 (<1)	5 (<1)
Adverse Event Related to Study Drug	0	1 (2.0)	1 (<1)	3 (<1)
Death	18 (14.3)	11 (22.0)	33 (17.1)	303 (37.7)
Lost to Follow-up	0	0	0	15 (1.9)
Protocol Deviation	0	0	0	0
Withdrew Consent	8 (6.3)	5 (10.0)	14 (7.3)	57 (7.1)
Pregnancy	0	0	0	0
Investigator's Decision	1 (<1)	0	1 (<1)	11 (1.4)
Administrative/Other	0	0	0	50 (6.2)
Sponsor Decision	0	0	0	208 (25.9)
Initiation of New Antineoplastic Therapy	0	2 (4.0)	2 (1.0)	3 (<1)

Abbreviations: GIST = Gastrointestinal Stromal Tumor; SM = Systemic Mastocytosis
Note: Percentages are based on the number of patients in the Safety Population in each column.

Source (Date): Program: t-18-3-1-2-ds.sas Date: 12:01/18AUG2021

- **Study Drug Exposure**

In the original submission, median treatment duration for the all-doses safety population (n=148) was 41.29 (range: 0.9 to 220.0) weeks for all AdvSM patients (n= 148) treated at all doses of avapritinib, with 39.2% having been exposed to avapritinib for > 56 weeks.

During the procedure, the Applicant indicated that median treatment duration for the all-doses safety population (n=193) was 60.29 weeks (range: 0.9-266.9). Median duration in the 200mg QD group (n=126) was 41.00 (0.9 to 188.1) weeks for patients with AdvSM treated at 200 mg QD, with 42.9% having been exposed to avapritinib for > 56 weeks. As expected, due to the addition of new patients in the 200 mg "extended" group (that included the original 81 patients and the new patients), the median duration for the 81 original patients in the 200mg QD group was slightly higher (67.14 week, range: 0.9-188.1).

Most recent patient exposure data are shown in table 12, below.

Table 40: Summary of Study Treatment (Updated Safety Population)

Parameter	AdvSM 200 mg N=126	AdvSM ≥ 300 mg N=50	AdvSM All N=193
Duration of Treatment [a] (weeks)			
Mean (StdDev)	51.09 (35.420)	105.74 (68.059)	75.82 (64.281)
Median	41.00	95.86	60.29
Min, max	0.9, 188.1	14.1, 218.0	0.9, 266.9
Treatment Interval, n (%)			
≤ 4 weeks	2 (1.6)	0	2 (1.0)

Parameter	AdvSM		
	200 mg N=126	**≥ 300 mg N=50**	**All N=193**
> 4 to ≤ 8 weeks	7 (5.6)	0	8 (4.1)
> 8 to ≤ 12 weeks	1 (0.8)	0	1 (0.5)
> 12 to ≤ 16 weeks	7 (5.6)	1 (2.0)	8 (4.1)
> 16 to ≤ 20 weeks	11 (8.7)	2 (4.0)	13 (6.7)
> 20 to ≤ 24 weeks	9 (7.1)	4 (8.0)	13 (6.7)
> 24 to ≤ 28 weeks	9 (7.1)	0	11 (5.7)
> 28 to ≤ 32 weeks	5 (4.0)	1 (2.0)	6 (3.1)
> 32 to ≤ 36 weeks	5 (4.0)	4 (8.0)	9 (4.7)
> 36 to ≤ 40 weeks	6 (4.8)	1 (2.0)	7 (3.6)
> 40 to ≤ 44 weeks	5 (4.0)	3 (6.0)	8 (4.1)
> 44 to ≤ 48 weeks	1 (0.8)	1 (2.0)	2 (1.0)
> 48 to ≤ 52 weeks	3 (2.4)	0	3 (1.6)
> 52 to ≤ 56 weeks	1 (0.8)	1 (2.0)	2 (1.0)
> 56 weeks	54 (42.9)	32 (64.0)	100 (51.8)
Relative Dose Intensity [b]			
Mean (StdDev)	0.63 (0.275)	0.54 (0.203)	0.67 (0.378)
Median	0.56	0.51	0.58
Min, Max	0.2, 1.4	0.2, 1.1	0.2, 3.0
Relative Dose Intensity Category, n (%)			
< 75%	85 (67.5)	43 (86.0)	128 (66.3)
≥ 75% to < 90%	8 (6.3)	4 (8.0)	16 (8.3)
≥ 90% to < 120%	32 (25.4)	3 (6.0)	41 (21.2)
≥ 120% to < 150%	1 (0.8)	0	5 (2.6)
≥ 150%	0	0	3 (1.6)

Abbreviations: AdvSM = advanced systemic mastocytosis; Max = maximum; Min = minimum; StdDev = standard deviation.
[a] Duration of treatment (weeks) = (treatment end date - treatment start date + 1)/7.
[b] Relative dose intensity was defined as the ratio of dose intensity/planned dose intensity. Dose intensity was defined as the cumulative dose/treatment duration. Planned dose intensity was based on the initially assigned daily dose.
Notes: Percentages are based on the number of patients in the Updated Safety Population in each column.
Source: Updated Table 18.3.2.1.

In the Updated Safety Population (all doses), 159 of the patients (82.4%) with AdvSM had ≥ 1 dose modification 129 patients (66.8%) had ≥ 1 dose interruption due to an AE, and 140 patients (72.5%) had ≥ 1 dose reduction due to an AE. In the 200mg QD group, the proportion of patients requiring ≥ 1 dose modification/interruption was slightly lower (Table 41).

There were no meaningful differences in dose modifications between the 200 mg QD original group and 200 mg extended group.

Table 41: Summary of Dose Modifications (Updated Safety Population)

Parameter	AdvSM		
	200 mg N=126	**≥ 300 mg N=50**	**All N=193**
Patients with dose modification, n (%)	99 (78.6)	48 (96.0)	159 (82.4)
Patients with dose increases, n (%) [a]	25 (19.8)	6 (12.0)	41 (21.2)

Parameter	AdvSM		
	200 mg N=126	**≥ 300 mg N=50**	**All N=193**
1 dose increase	23 (18.3)	4 (8.0)	33 (17.1)
2 dose increases	2 (1.6)	1 (2.0)	7 (3.6)
3+ dose increases	0	1 (2.0)	1 (0.5)
Patients with dose interruptions due to AE, n (%) [a]	77 (61.1)	40 (80.0)	129 (66.8)
1 dose interruption	32 (25.4)	11 (22.0)	47 (24.4)
2 dose interruptions	26 (20.6)	7 (14.0)	38 (19.7)
3+ dose interruptions	19 (15.1)	22 (44.0)	44 (22.8)
Patients with dose reductions due to AE, n (%) [a]	90 (71.4)	46 (92.0)	140 (72.5)
1 dose reduction	52 (41.3)	17 (34.0)	71 (36.8)
2 dose reductions	27 (21.4)	21 (42.0)	50 (25.9)
3+ dose reductions	11 (8.7)	8 (16.0)	19 (9.8)
Time to dose reduction in patients with dose reduction			
Patients with events, n (%)	94 (74.6)	47 (94.0)	147 (76.2)
Kaplan-Meier estimates of time to the first dose reduction (months) [b]			
Median (95% CI)	1.91 (1.64, 3.06)	2.71 (1.87, 3.09)	2.83 (1.91, 3.19)
25th, 75th percentiles	0.99, 5.45	1.45, 4.14	1.18, 7.43
3 months (95% CI)	0.42 (0.34, 0.51)	0.38 (0.25, 0.51)	0.46 (0.39, 0.53)
6 months (95% CI)	0.24 (0.16, 0.32)	0.16 (0.06, 0.26)	0.27 (0.21, 0.34)
9 months (95% CI)	0.21 (0.13, 0.29)	0.06 (0.00, 0.13)	0.23 (0.16, 0.29)
12 months (95% CI)	0.20 (0.12, 0.27)	0.06 (0.00, 0.13)	0.21 (0.15, 0.27)
18 months (95% CI)	0.20 (0.12, 0.27)	0.06 (0.00, 0.13)	0.19 (0.13, 0.25)

Abbreviations: AdvSM = advanced systemic mastocytosis; AE = adverse event; CI = confidence interval
[a] Patients may have experienced more than 1 type of dose modification.
[b] Kaplan-Meier CIs are calculated using Greenwood's formula and linear/plain transformation.
Notes: Percentages are based on the number of patients in the Updated Safety Population in each column.
Source: Updated Table 18.3.2.2.

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

Demographics and Baseline disease characteristics

Among the 126 patients with AdvSM treated at 200 mg QD, 74 were male (58.7%) and 52 were female (41.3%). Median (range) age was 68.0 (31 to 88) years, with 37.3% of patients < 65 years of age (Table 42). Most patients self-identified as white (86.5%) and not Hispanic or Latino (85.7%).

A total of 52.4% of patients with AdvSM treated at 200 mg QD had received prior midostaurin. In Studies BLU-285-2101 and BLU-285-2202, 79 patients had prior antineoplastic therapy and 46 had not.

Most patients with AdvSM treated at 200 mg QD (96%) had a baseline platelet count ≥ 50,000/μL during screening.

Demographics in the overall population were comparable to those of the 200mg QD group. (Table 42).

There were no meaningful differences in demographics and baseline characteristics between the 200 mg original and the 200 mg extended groups.

Table 42: Summary of Demographics and Baseline Disease Characteristics (Updated Safety Population)

	AdvSM		
	200 mg N=126	**≥ 300 mg N=50**	**All N=193**
Age (years) [a]			
Mean (StdDev)	66.7 (10.91)	62.8 (11.03)	65.1 (11.36)
Median	68.0	66.0	67.0
Min, max	31, 88	34, 83	31, 88
Age group (years), n (%) [a]			
< 65	47 (37.3)	23 (46.0)	81 (42.0)
≥ 65	79 (62.7)	27 (54.0)	112 (58.0)
Sex, n (%)			
Female	52 (41.3)	23 (46.0)	85 (44.0)
Male	74 (58.7)	27 (54.0)	108 (56.0)
Race, n (%)			
Asian	1 (< 1)	2 (4.0)	3 (1.6)
Black or African American	0	1 (2.0)	1 (< 1)
White	109 (86.5)	43 (86.0)	166 (86.0)
Other	14 (11.1)	0	15 (7.8)
Unknown	2 (1.6)	4 (8.0)	8 (4.1)
Ethnicity, n (%)			
Hispanic or Latino	3 (2.4)	1 (2.0)	5 (2.6)
Not Hispanic or Latino	108 (85.7)	46 (92.0)	170 (88.1)
Unknown	1 (< 1)	3 (6.0)	4 (2.1)
Not reported	14 (11.1)	0	14 (7.3)
Region, n (%)			
Europe or Australia	63 (50.0)	8 (16.0)	76 (39.4)
North America	63 (50.0)	42 (84.0)	117 (60.6)
Height (cm)			
n	117	45	178
Mean (StdDev)	170.85 (10.086)	168.83 (9.566)	170.48 (9.907)
Weight (kg)			
n	126	50	193
Mean (StdDev)	73.36 (15.675)	74.20 (17.605)	74.04 (16.528)
BMI (kg/m^2)			
n	117	45	178
Mean (StdDev)	25.18 (4.954)	25.26 (4.590)	25.31 (4.881)

	AdvSM		
	200 mg N=126	**≥ 300 mg N=50**	**All N=193**
ECOG performance status, n (%)			
0	27 (21.4)	13 (26.0)	43 (22.3)
1	66 (52.4)	23 (46.0)	101 (52.3)
2	23 (18.3)	9 (18.0)	34 (17.6)
3	10 (7.9)	5 (10.0)	15 (7.8)
Prior midostaurin use, n (%)			
Yes	66 (52.4)	13 (26.0)	83 (43.0)
No	60 (47.6)	37 (74.0)	110 (57.0)
Nadir platelet count in screening, n (%)			
< 50,000/µL	5 (4.0)	7 (14.0)	14 (7.3)
≥ 50,000/µL	121 (96.0)	43 (86.0)	179 (92.7)

Abbreviations: AdvSM = advanced systemic mastocytosis; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; Max = maximum; Min = minimum; StdDev = standard deviation; TKI = tyrosine kinase inhibitor.

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

[b] Number of prior distinct TKIs was defined as the number of unique TKIs received. A combination of 2 TKIs counted as 2 distinct TKIs.

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

Source: Updated Table 18.3.1.3.

Medical history and concomitant medication

Most patients with AdvSM (98.4%) treated at 200 mg dose had ongoing events from their medical histories. The most commonly reported (≥ 20% of patients) ongoing medical conditions were similar between patients with AdvSM treated at all doses and at 200 mg QD (Table 43).

Table 43: Medical History Reported in ≥ 20% of Patients with AdvSM Treated at 200 mg Dose by Preferred Term, Indication, and Dose Level (Updated Safety Population)

	AdvSM		
Preferred Term	**200 mg N=126 n (%)**	**≥ 300 mg N=50 n (%)**	**All N=193 n (%)**
Anaemia	54 (42.9)	28 (56.0)	87 (45.1)
Fatigue	47 (37.3)	36 (72.0)	91 (47.2)
Hypertension	47 (37.3)	19 (38.0)	71 (36.8)
Diarrhoea	39 (31.0)	29 (58.0)	77 (39.9)
Blood alkaline phosphatase increased	35 (27.8)	13 (26.0)	53 (27.5)
Splenomegaly	33 (26.2)	17 (34.0)	52 (26.9)
Nausea	33 (26.2)	22 (44.0)	59 (30.6)
Gastrooesophageal reflux disease	29 (23.0)	18 (36.0)	55 (28.5)
Ascites	28 (22.2)	13 (26.0)	44 (22.8)
Thrombocytopenia	26 (20.6)	18 (36.0)	49 (25.4)
Postmenopause	26 (20.6)	11 (22.0)	40 (20.7)

Abbreviations: AdvSM = advanced systemic mastocytosis.

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

Preferred terms are sorted in decreasing order of frequency using the AdvSM 200 mg column.
This table includes ongoing medical history only.
Source: Updated Table 18.3.1.4.

There were no meaningful differences in medical history findings between the 200 mg original group and 200 mg extended group.

Concomitant Medications

All patients took ≥ 1 concomitant medication during study treatment (first dose date to last dose date + 30 days). The most commonly reported (≥ 25% of patients) concomitant medications summarized in Table 44.

Table 44: Concomitant Medications Reported in ≥ 25% of Patients with AdvSM Treated at All Doses by Preferred Drug Name, Indication, and Dose Level (Updated Safety Population)

	AdvSM		
ATC Class Preferred Drug Name	**200 mg N=126 n (%)**	**≥ 300 mg N=50 n (%)**	**All N=193 n (%)**
High-ceiling diuretics			
Furosemide	52 (41.3)	22 (44.0)	83 (43.0)
Other analgesics and antipyretics			
Paracetamol	35 (27.8)	24 (48.0)	69 (35.8)
Antiemetics and antinauseants			
Ondansetron	35 (27.8)	24 (48.0)	64 (33.2)
Corticosteroids for systemic use, plain			
Prednisone	27 (21.4)	17 (34.0)	53 (27.5)
Drugs for peptic ulcer and gastro-oesophageal reflux disease			
Famotidine	41 (32.5)	15 (30.0)	61 (31.6)
Omeprazole	32 (25.4)	15 (30.0)	52 (26.9)
Vitamin A and D, incl. combinations of the two			
Colecalciferol	33 (26.2)	13 (26.0)	50 (25.9)

Abbreviations: AdvSM = advanced systemic mastocytosis; ATC = anatomical therapeutic chemical.
Notes: Percentages are based on the number of patients in the Safety Population in each column.
Source: Updated Table 18.3.1.5.

There were no meaningful differences in concomitant medications received by patients between the original 200 mg group and extended 200 mg group.

2.6.8.2. Adverse events

Overall Adverse Event

Table below provides information on overall adverse event experience in all AdvSM safety populations, including, both, the 200 mg QD and the overall population.

Table 45: Summary of Adverse Events (Updated Safety Population)

Patients with any:	AdvSM 200 mg N=126 n (%)	≥ 300 mg N=50 n (%)	All N=193 n (%)
AE	126 (100.0)	50 (100.0)	193 (100.0)
SAE	48 (38.1)	37 (74.0)	97 (50.3)
Grade ≥ 3 AE	95 (75.4)	47 (94.0)	158 (81.9)
Related AE	120 (95.2)	50 (100.0)	186 (96.4)
Related SAE	15 (11.9)	16 (32.0)	34 (17.6)
Grade ≥ 3 related AE	75 (59.5)	37 (74.0)	123 (63.7)
AE leading to discontinuation from study drug	23 (18.3)	13 (26.0)	40 (20.7)
Related AE leading to discontinuation from study drug	9 (7.1)	8 (16.0)	19 (9.8)
AE leading to dose interruption	84 (66.7)	41 (82.0)	137 (71.0)
AE leading to dose reduction	91 (72.2)	46 (92.0)	141 (73.1)
AESI of intracranial bleeding	4 (3.2)	8 (16.0)	12 (6.2)
Related AESI of intracranial bleeding	3 (2.4)	6 (12.0)	9 (4.7)
Serious AESI of intracranial bleeding	4 (3.2)	6 (12.0)	10 (5.2)
AESI of intracranial bleeding leading to discontinuation from study drug	3 (2.4)	3 (6.0)	6 (3.1)
AESI of cognitive effects	24 (19.0)	28 (56.0)	59 (30.6)
Related AESI of cognitive effects	23 (18.3)	22 (44.0)	51 (26.4)
Serious AESI of cognitive effects	1 (< 1)	4 (8.0)	5 (2.6)
AESI of cognitive effects leading to discontinuation from study drug	2 (1.6)	2 (4.0)	5 (2.6)
AE leading to death	8 (6.3)	6 (12.0)	15 (7.8)
Related AE leading to death	0	1 (2.0)	1 (< 1)

Abbreviations: AdvSM = advanced systemic mastocytosis; AE = adverse event; AESI = adverse event of special interest; SAE = serious adverse event.
Notes: Percentages are based on the number of patients in the Updated Safety Population in each column.
If a patient experienced more than 1 event in a given category, that patient was counted only once.
Source: Updated Table 18.3.3.1.1.

There were no meaningful differences in overall adverse events observed between the original 200 mg group and extended 200 mg group.

The most commonly reported AE reported in ≥ 20% of patients) in the 200 mg QD and all-doses groups were oedema peripheral, anaemia, periorbital oedema and thrombocytopenia, diarrhoea, and nausea (Table 46).

Table 46: Adverse Events Reported in ≥ 10% of Patients with AdvSM Treated at 200 mg Dose by Preferred Term, and Dose Level (Updated Safety Population)

Preferred Term	AdvSM 200 mg N=126 n (%)	≥ 300 mg N=50 n (%)	All N=193 n (%)
Patients with at least one adverse event	126 (100.0)	50 (100.0)	193 (100.0)
Oedema peripheral	54 (42.9)	22 (44.0)	82 (42.5)
Anaemia	51 (40.5)	32 (64.0)	91 (47.2)
Periorbital oedema	50 (39.7)	40 (80.0)	100 (51.8)

Preferred Term	AdvSM 200 mg N=126 n (%)	AdvSM ≥ 300 mg N=50 n (%)	AdvSM All N=193 n (%)
Thrombocytopenia	50 (39.7)	21 (42.0)	77 (39.9)
Diarrhoea	35 (27.8)	21 (42.0)	67 (34.7)
Nausea	30 (23.8)	22 (44.0)	60 (31.1)
Vomiting	24 (19.0)	22 (44.0)	51 (26.4)
Neutropenia	24 (19.0)	7 (14.0)	36 (18.7)
Dysgeusia	22 (17.5)	11 (22.0)	35 (18.1)
Fatigue	21 (16.7)	22 (44.0)	51 (26.4)
Hair colour changes	19 (15.1)	16 (32.0)	41 (21.2)
Headache	19 (15.1)	7 (14.0)	33 (17.1)
Eyelid oedema	18 (14.3)	0	19 (9.8)
Constipation	17 (13.5)	13 (26.0)	34 (17.6)
Face oedema	17 (13.5)	6 (12.0)	25 (13.0)
Arthralgia	16 (12.7)	17 (34.0)	39 (20.2)
Pruritus	16 (12.7)	11 (22.0)	34 (17.6)
Abdominal pain	16 (12.7)	11 (22.0)	32 (16.6)
Epistaxis	16 (12.7)	9 (18.0)	27 (14.0)
Blood alkaline phosphatase increased	16 (12.7)	5 (10.0)	25 (13.0)
Dizziness	15 (11.9)	10 (20.0)	28 (14.5)
Cognitive disorder	15 (11.9)	9 (18.0)	27 (14.0)
Blood bilirubin increased	15 (11.9)	9 (18.0)	25 (13.0)
Blood creatinine increased	15 (11.9)	5 (10.0)	21 (10.9)
Platelet count decreased	14 (11.1)	2 (4.0)	18 (9.3)
Weight increased	13 (10.3)	3 (6.0)	19 (9.8)

Abbreviations: AdvSM = advanced systemic mastocytosis
Notes: Percentages are based on the number of patients in the Updated Safety Population in each column.
Preferred terms are sorted in decreasing order of frequency using the AdvSM 200 mg column.
If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term.
Source: Updated Table 18.3.3.1.2.2.

There were no meaningful differences in the incidences of the most commonly reported AEs between the 200 mg original group and 200 mg extended group.

--AEs by severity

A summary of Grade ≥ 3 AEs by PT reported in > 2% of AdvSM patients treated at all doses is provided in (Table 3).

Table 47 **Grade 3 or Higher Adverse Events Reported in > 2% of AdvSM Patients Treated at All Doses by Preferred Term and Dose Level (Safety Population)**

Preferred Term	AdvSM		
	200 mg N=126 n (%)	SM ≥ 300 mg N=50 n (%)	SM All N=193 n (%)
Patients with at least one event	95 (75.4)	47 (94.0)	158 (81.9)
Anaemia	27 (21.4)	19 (38.0)	47 (24.4)
Thrombocytopenia	23 (18.3)	15 (30.0)	43 (22.3)
Neutropenia	21 (16.7)	6 (12.0)	31 (16.1)
Neutrophil count decreased	10 (7.9)	4 (8.0)	14 (7.3)
Blood alkaline phosphatase increased	4 (3.2)	2 (4.0)	10 (5.2)
Fatigue	3 (2.4)	6 (12.0)	10 (5.2)
Platelet count decreased	8 (6.3)	1 (2.0)	10 (5.2)
White blood cell count decreased	4 (3.2)	2 (4.0)	8 (4.1)
Hypokalaemia	4 (3.2)	3 (6.0)	7 (3.6)
Periorbital oedema	5 (4.0)	1 (2.0)	7 (3.6)
Diarrhoea	5 (4.0)	0	6 (3.1)
Pneumonia	1 (<1)	5 (10.0)	6 (3.1)
Vomiting	3 (2.4)	1 (2.0)	6 (3.1)
Ascites	3 (2.4)	2 (4.0)	5 (2.6)
Back pain	2 (1.6)	2 (4.0)	5 (2.6)
Blood bilirubin increased	2 (1.6)	3 (6.0)	5 (2.6)
Hypophosphataemia	1 (<1)	3 (6.0)	5 (2.6)
Syncope	3 (2.4)	1 (2.0)	5 (2.6)
Abdominal pain	1 (<1)	2 (4.0)	4 (2.1)
Acute kidney injury	2 (1.6)	2 (4.0)	4 (2.1)
Acute myeloid leukaemia	1 (<1)	0	4 (2.1)
Arthralgia	1 (<1)	2 (4.0)	4 (2.1)
Cardiac failure	2 (1.6)	1 (2.0)	4 (2.1)
Cholecystitis	1 (<1)	2 (4.0)	4 (2.1)
Gastric haemorrhage	0	3 (6.0)	4 (2.1)
Gastrointestinal haemorrhage	2 (1.6)	2 (4.0)	4 (2.1)
Hypertension	1 (<1)	3 (6.0)	4 (2.1)
Leukocytosis	2 (1.6)	2 (4.0)	4 (2.1)
Nausea	1 (<1)	2 (4.0)	4 (2.1)
Pleural effusion	2 (1.6)	2 (4.0)	4 (2.1)
Pyrexia	1 (<1)	3 (6.0)	4 (2.1)
Weight increased	3 (2.4)	1 (2.0)	4 (2.1)

Abbreviations: AdvSM = advanced systemic mastocytosis; SM = systemic mastocytosis.
Notes: Percentages are based on the number of patients in the Safety Population in each column.
Preferred terms are sorted in decreasing order of frequency using the AdvSM All column.
If a patient experienced more than 1 event within a given preferred term, that patient was counted only once under that preferred term.
Source: Table 18.3.3.1.4.2

There were no meaningful differences in the incidences of Grade 3 or higher AEs in the 200 mg original group and 200 mg extended group.

Adverse Drug Reactions

A comprehensive approach was undertaken to identify potential adverse drug reactions for avapritinib to be used in the proposed product label. Medical review of the AEs reported for patients with AdvSM who received treatment with avapritinib was performed with a focus on events assessed as related to study treatment (as assessed by the investigator). PTs that represented the same or a similar medical concept were grouped as appropriate. In addition, events that may be related to nonclinical findings were assessed for plausibility as adverse drug reactions.

A summary of related AEs (as assessed by the Investigator) by PT reported in ≥ 10% of AdvSM patients is provided in table 34.

Table 48: Related Adverse Events Reported in ≥ 10% of Patients with AdvSM Treated at 200 mg Dose by Preferred Term, Indication, and Dose Level (Updated Safety Population)

	AdvSM		
Preferred Term	**200 mg N=126 n (%)**	**≥ 300 mg N=50 n (%)**	**All N=193 n (%)**
Patients with at least one event	120 (95.2)	50 (100.0)	186 (96.4)
Periorbital oedema	48 (38.1)	39 (78.0)	96 (49.7)
Thrombocytopenia	47 (37.3)	15 (30.0)	66 (34.2)
Oedema peripheral	42 (33.3)	17 (34.0)	64 (33.2)
Anaemia	28 (22.2)	26 (52.0)	58 (30.1)
Hair colour changes	19 (15.1)	16 (32.0)	41 (21.2)
Dysgeusia	19 (15.1)	9 (18.0)	29 (15.0)
Diarrhoea	18 (14.3)	12 (24.0)	36 (18.7)
Neutropenia	18 (14.3)	7 (14.0)	28 (14.5)
Eyelid oedema	18 (14.3)	0	19 (9.8)
Fatigue	17 (13.5)	12 (24.0)	36 (18.7)
Nausea	16 (12.7)	18 (36.0)	38 (19.7)
Face oedema	16 (12.7)	4 (8.0)	22 (11.4)
Cognitive disorder	15 (11.9)	7 (14.0)	25 (13.0)
Platelet count decreased	13 (10.3)	2 (4.0)	15 (7.8)

Abbreviations: AdvSM = advanced systemic mastocytosis
Notes: Percentages are based on the number of patients in the Updated Safety Population in each column.
Preferred terms are sorted in decreasing order of frequency using the AdvSM 200 mg column.
If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term.
Source: Updated Table 18.3.3.1.3.2.

There were no meaningful differences in the incidences of treatment-related AEs between the 200 mg original group and 200 mg extended group.

2.6.8.3. Serious adverse event/deaths/other significant events

Summaries of SAEs and related SAEs by PT reported in > 1% of AdvSM patients are provided in Table 41 and Table 42, respectively.

Table 49: Serious Adverse Events Reported in > 1% of AdvSM Patients Treated at 200 mg Dose by Preferred Term, Indication, and Dose Level (Updated Safety Population)

	AdvSM		
Preferred Term	**200 mg N=126 n (%)**	**≥ 300 mg N=50 n (%)**	**All N=193 n (%)**
Patients with any serious adverse event	48 (38.1)	37 (74.0)	97 (50.3)
Anaemia	4 (3.2)	4 (8.0)	8 (4.1)
Subdural haematoma	4 (3.2)	2 (4.0)	6 (3.1)
Ascites	3 (2.4)	3 (6.0)	6 (3.1)
Pleural effusion	2 (1.6)	4 (8.0)	6 (3.1)
Acute kidney injury	2 (1.6)	2 (4.0)	4 (2.1)
Gastrointestinal haemorrhage	2 (1.6)	2 (4.0)	4 (2.1)
Diverticulitis	2 (1.6)	1 (2.0)	3 (1.6)
Haemorrhage	2 (1.6)	0	2 (1.0)
Intra-abdominal haemorrhage	2 (1.6)	0	2 (1.0)
Osteomyelitis	2 (1.6)	0	2 (1.0)
Pneumothorax	2 (1.6)	0	2 (1.0)

Abbreviations: AdvSM = advanced systemic mastocytosis.
Notes: Percentages are based on the number of patients in the Updated Safety Population in each column.
Preferred terms are sorted in decreasing order of frequency using the AdvSM 200 mg column.
If a patient experienced more than 1 event within a given preferred term, that patient was counted only once under that preferred term.
Source: Updated Table 18.3.3.1.6.2.

Table 50: Related Serious Adverse Events Reported in > 1% of Patients with AdvSM Treated at 200 mg Dose by Preferred Term, Indication, and Dose Level (Updated Safety Population)

	AdvSM		
Preferred Term	**200 mg N=126 n (%)**	**≥ 300 mg N=50 n (%)**	**All N=193 n (%)**
Patients with any related serious adverse event	15 (11.9)	16 (32.0)	34 (17.6)
Subdural haematoma	3 (2.4)	2 (4.0)	5 (2.6)
Anaemia	2 (1.6)	3 (6.0)	5 (2.6)
Haemorrhage	2 (1.6)	0	2 (1.0)

Abbreviations: AdvSM = advanced systemic mastocytosis.
Notes: Percentages are based on the number of patients in the Updated Safety Population in each column.
Preferred terms are sorted in decreasing order of frequency using the AdvSM 200 mg column.
If a patient experienced more than 1 event within a given preferred term, that patient was counted only once under that preferred term.
Source: Updated Table 18.3.3.1.7.2.

Deaths

Table 37 provides a summary of AEs leading to death for all patients in the Safety Population. Overall, 15 patients (7.8%) treated with avapritinib died during the studies due to AEs. Most deaths were related to the patients' underlying disease.

Eight (6.3%) patients with AdvSM who initiated treatment at 200 mg QD died during the study due to AEs compared with 6 patients (12.0%) who initiated treatment at ≥ 300 mg QD. In the 200 mg group, no patients

died due to a related AE compared with 1 patient in the ≥ 300 mg QD group. The single fatal event that was assessed as avapritinib-related was a case of intracranial bleeding.

Table 51: Adverse Events Leading to Death (Updated Safety Population)

	AdvSM		
Preferred Term	**200 mg N=126 n (%)**	**≥ 300 mg N=50 n (%)**	**All N=193 n (%)**
Patients with any adverse event leading to death	8 (6.3)	6 (12.0)	15 (7.8)
Acute kidney injury	1 (< 1)	0	1 (< 1)
Disease progression	1 (< 1)	0	1 (< 1)
Endocarditis	1 (< 1)	0	1 (< 1)
Gastritis erosive	1 (< 1)	0	1 (< 1)
Intra-abdominal haemorrhage	1 (< 1)	0	1 (< 1)
Ischaemic stroke	0	1 (2.0)	1 (< 1)
Necrotising fasciitis	1 (< 1)	0	1 (< 1)
Pneumonia aspiration	1 (< 1)	0	1 (< 1)
Sepsis	1 (< 1)	0	1 (< 1)
Shock haemorrhagic	1 (< 1)	0	1 (< 1)
Acute myeloid leukaemia	0	0	1 (< 1)
Cardiac arrest	0	1 (2.0)	1 (< 1)
Gastric haemorrhage	0	1 (2.0)	1 (< 1)
Haemorrhage intracranial	0	1 (2.0)	1 (< 1)
Septic shock	0	1 (2.0)	1 (< 1)
Staphylococcal sepsis	0	1 (2.0)	1 (< 1)

Abbreviations: AdvSM = advanced systemic mastocytosis.
Notes: On-treatment death was defined as arising between the first dose and last dose + 30 days, inclusive.
Percentages are based on the number of patients in the Updated Safety Population in each column and treatment group.
Preferred terms are sorted in decreasing order of frequency using the AdvSM 200 mg column.
In each treatment group, if a patient experienced more than 1 event within a given preferred term, that patient was counted only once under that preferred term.
Source: Updated Table 18.3.3.1.8.2.

There were no meaningful differences in the incidences of AEs leading to death between the 200 mg original group and 200 mg extended group.

Adverse Events of Special Interest

- **Intracranial Bleeding**

Intracranial bleeding is an important identified risk in avapritinib-treated patients.

In the overall clinical development of avapritinib, the incidence of intracranial bleeding was considerably higher in patients with AdvSM treated at all doses (updated data: 6.2%, initial submission: 7.4 %) than in patients with GIST treated at all doses (updated data: 2.1%, initial submission: 1.8 %, SmPC: 1.7 %) (Table 11). Most of the intracranial bleeding events in avapritinib-treated patients (76.0%; 19 of 25 events) were serious, and 36% (9 of 25 events) were Grade 1 in severity. The majority of the intracranial bleeding events resolved or resolved with sequelae (88%; 22 of 25 events).

Kaplan-Meier analyses of time to resolution demonstrated that, for patients with AdvSM treated at all doses who experienced Grade ≥ 2 intracranial bleeding, the probability of resolution was 25% by 2.4 weeks and 50% by 8.1 weeks

Table 56: Intracranial Bleeding Adverse Events of Special Interest by Category, Preferred Term, Indication, and Dose Level (Safety Population)

Category Preferred Term	AdvSM			Ava (AdvSM +GIST)	GIST	
	200 mg N=126 n (%)	≥ 300 mg N=50 n (%)	All N=193 n (%)	All N=803 n (%)	300 mg N=525 n (%)	All N=610 n (%)
Intracranial bleeding	4 (3.2)	8 (16.0)	12 (6.2)	25 (3.1)[a]	12 (2.3)[a]	13 (2.1)[a]
Subdural haematoma	4 (3.2)	3 (6.0)	7 (3.6)	12 (1.5)	5 (< 1)	5 (< 1)
Haemorrhage intracranial	0	5 (10.0)	5 (2.6)	11 (1.4)[a]	6 (< 1)[a]	6 (< 1)[a]
Cerebral haemorrhage	0	0	0	3 (< 1)	3 (1.1)	3 (< 1)
Grade ≥ 3 intracranial bleeding	2 (1.6)	2 (4.0)	4 (2.1)	11 (1.4)	6 (1.1)	7 (1.1)
Haemorrhage intracranial	0	2 (4.0)	2 (1.0)	5 (< 1)	3 (< 1)	3 (< 1)
Subdural haematoma	2 (1.6)	0	2 (1.0)	4 (< 1)	2 (< 1)	2 (< 1)
Cerebral haemorrhage	0	0	0	3 (< 1)	2 (< 1)	3 (< 1)
Serious intracranial bleeding	4 (3.2)	6 (12.0)	10 (5.2)	19 (2.4)	9 (1.5)	9 (1.5)
Subdural haematoma	4 (3.2)	2 (4.0)	6 (3.1)	9 (1.1)	3 (< 1)	3 (< 1)
Haemorrhage intracranial	0	4 (8.0)	4 (2.1)	8 (< 1)	4 (< 1)	4 (< 1)
Cerebral haemorrhage	0	0	0	3 (< 1)	3 (< 1)	3 (< 1)
Intracranial bleeding leading to permanent discontinuation of study treatment	3 (2.4)	3 (6.0)	6 (3.1)	13 (1.6)	6 (1.1)	7 (1.1)
Haemorrhage intracranial	0	3 (6.0)	3 (1.6)	5 (< 1)	2 (< 1)	2 (< 1)
Subdural haematoma	3 (2.4)	0	3 (1.6)	5 (< 1)	2 (< 1)	2 (< 1)
Cerebral haemorrhage	0	0	0	3 (< 1)	3 (< 1)	3 (< 1)

[a] A discrepancy in the number of intracranial bleeding events for GIST patients was noted. An additional event of nonserious haemorrhage intracranial Grade 2 was captured in the safety database which was not reflected in the clinical database or in the source tables listed below. Numbers shown in the table above include this patient.

During Study BLU-285-2101, a significantly higher frequency of intracranial bleeding events was observed in AdvSM patients initiating treatment at the 300 mg dose (16.0 %, n = 8) as compared with GIST patients (1.8 %), most of whom were treated at ≥300 mg.

With all risk minimization measures, at the data cut-off date (27 May 2020/23 June 2020) for the initial application the intracranial bleeding incidences in AdvSM patients in the 200 mg group were overall 3.7 % (n = 3) and 2.6 % (n = 2) when patients with pre-existing severe thrombocytopenia were excluded. With the most recent data cut-off date (April 2021), the corresponding incidences were 3.2 % and 2.5%, respectively.

Table 52: Intracranial Bleeding Adverse Events of Special Interest by Category, Preferred Term, Indication, and Dose Level Sorted by AdvSM All (Updated Safety Population)

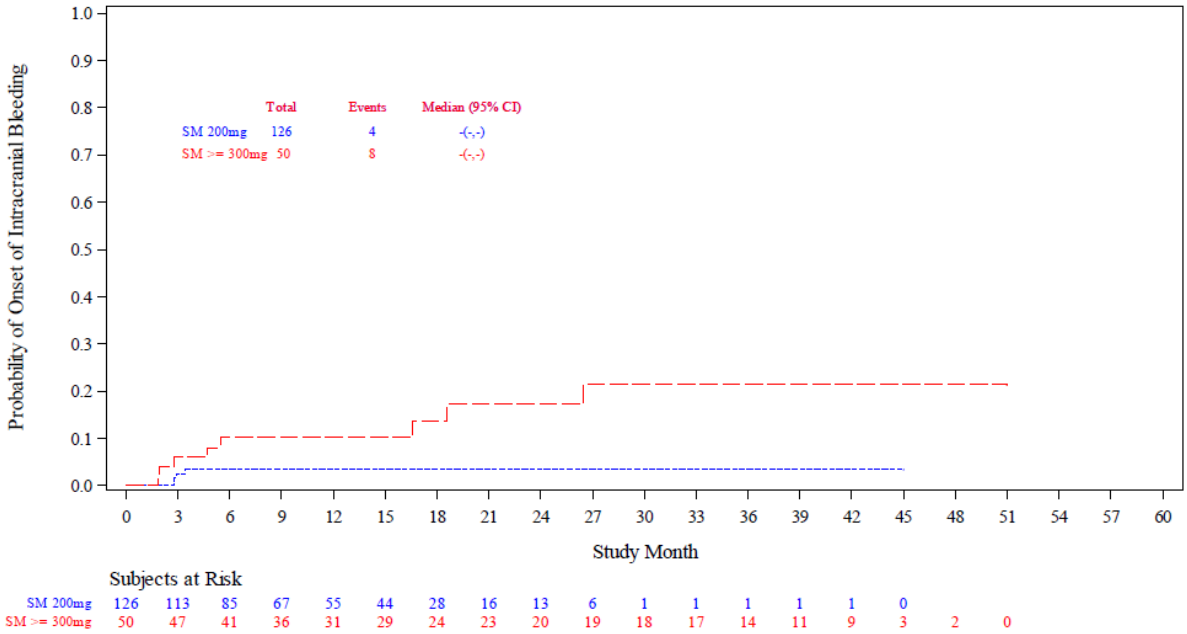
Category Preferred Term	AdvSM 200 mg N=126 n (%)	AdvSM ≥ 300 mg N=50 n (%)	AdvSM All N=193 n (%)
Intracranial bleeding	4 (3.2)	8 (16.0)	12 (6.2)
Subdural haematoma	4 (3.2)	3 (6.0)	7 (3.6)
Haemorrhage intracranial	0	5 (10.0)	5 (2.6)
Cerebral haemorrhage	0	0	0
Grade ≥ 3 intracranial bleeding	2 (1.6)	2 (4.0)	4 (2.1)
Haemorrhage intracranial	0	2 (4.0)	2 (1.0)
Subdural haematoma	2 (1.6)	0	2 (1.0)
Cerebral haemorrhage	0	0	0
Serious intracranial bleeding	4 (3.2)	6 (12.0)	10 (5.2)
Subdural haematoma	4 (3.2)	2 (4.0)	6 (3.1)
Haemorrhage intracranial	0	4 (8.0)	4 (2.1)
Cerebral haemorrhage	0	0	0
Intracranial bleeding leading to permanent discontinuation of study treatment	3 (2.4)	3 (6.0)	6 (3.1)
Haemorrhage intracranial	0	3 (6.0)	3 (1.6)
Subdural haematoma	3 (2.4)	0	3 (1.6)
Cerebral haemorrhage	0	0	0

Abbreviations: AdvSM = advanced systemic mastocytosis; AESI = adverse event of special interest.
Notes: Percentages are based on the number of patients in the Safety Population in each column.
Preferred terms are sorted in decreasing order of frequency using the AdvSM All column.
If a patient experienced more than 1 event in a given AESI category, that patient is counted once for the category. If a patient experienced more than 1 event within a given preferred term, that patient is counted only once for that term.
Sources: Updated Table 18.3.3.2.1.1, Updated Table 18.3.3.2.2.1, Updated Table 18.3.3.2.3, Updated Table 99.2.1.1.

No notable differences in the frequency of intracranial bleeding events were seen through the update period compared to what was reported in the initial application. One patient in study BLU 285-2202 had an ICB (grade 3 haematoma) following the original data cut-off dates. This patient initiated at 200 mg, experienced on-treatment severe thrombocytopenia and interrupted dosing; however, the event was confounded by accidental head trauma and concomitant use of aspirin.

Kaplan-Meier analyses of TTO of any grade of intracranial bleeding for all patients with AdvSM are summarized in figure below:

Figure 4: Kaplan Meier Plot of Time to Onset for Intracranial Bleeding AESI (Updated Safety Population)



Abbreviations: AdvSM = advanced systemic mastocytosis, CI = confidence interval, QD = once daily, SM = systemic mastocytosis.
Source: Updated Figure 99.2.2.1.1

A side-by-side comparison of intracranial bleeding AEs reported in the 200 mg original group and 200 mg extended group is provided in Table 53. There were no meaningful differences in the incidences of intracranial bleeding AEs between both groups. Pre-existing severe thrombocytopenia was present in an equal proportion of patients experiencing intracranial bleeding events in the 200 mg original group and in the 200 mg extended group (Table 54).

Table 53: Intracranial Bleeding Adverse Events of Special Interest in 200 mg Original Group and 200 mg Extended Group

	AdvSM	
AESI Category Preferred Term	**200 mg Original[a] (N=81) n (%)**	**200 mg Extended[b] (N=126) n (%)**
Intracranial Bleeding	**3 (3.7)**	**4 (3.2)**
Subdural haematoma	3 (3.7)	4 (3.2)
Grade ≥ 3 intracranial bleeding	1 (1.2)	2 (1.6)
Subdural haematoma	1 (1.2)	2 (1.6)
Serious intracranial bleeding	3 (3.7)	4 (3.2)
Subdural haematoma	3 (3.7)	4 (3.2)
Intracranial bleeding leading to permanent discontinuation of study treatment	2 (2.5)	3 (2.4)
Subdural haematoma	2 (2.5)	3 (2.4)

Abbreviations: AdvSM = advanced systemic mastocytosis; AESI = adverse event of special interest.
[a] Original 200 mg safety population from initial submission (data cut-off date 20 April 2021)
[b] Updated safety population (data cut-off date 20 April 2021)

Source: Table 99.20.3.3.2.1.1, Table 99.20.99.2.1.1, Table 99.20.3.3.2.2.1, Table 99.20.3.3.2.3

Table 54: Intracranial Bleeding Adverse Events of Special Interest by Pre-existing Severe Thrombocytopenia in 200 mg Original Group and 200 mg Extended Group

Pre-existing Severe Thrombocytopenia (Platelets < 50,000/µL in Screening)	AdvSM 200 mg Original[a] N=81		AdvSM 200 mg Extended[b] N=126	
	Number of Patients	Incidence of ICB n (%)	Number of Patients	Incidence of ICB n (%)
Yes	5	1 (20.0)	5	1 (20.0)
No	76	2 (2.6)	121	3 (2.5)

Abbreviations: AdvSM = advanced systemic mastocytosis; ICB = intracranial bleeding.
[a] Original 200 mg safety population from initial submission (data cut-off date 20 April 2021)
[b] Updated safety population (data cut-off date 20 April 2021)
Notes: Percentages are based on the number of patients in the Safety Population in each column.
Preexisting thrombocytopenia refers to the nadir platelet count during screening up to Cycle 1 Day 1.
Source: Table 99.20.3.3.2.1.1g.

The updated data are consistent with what was presented in the initial submission, and the incidence of ICB appear to be reliably constant in the 200 mg group. The estimates of the incidence of this important safety issue are considered to be acceptably accurate.

- **Cognitive Effects**

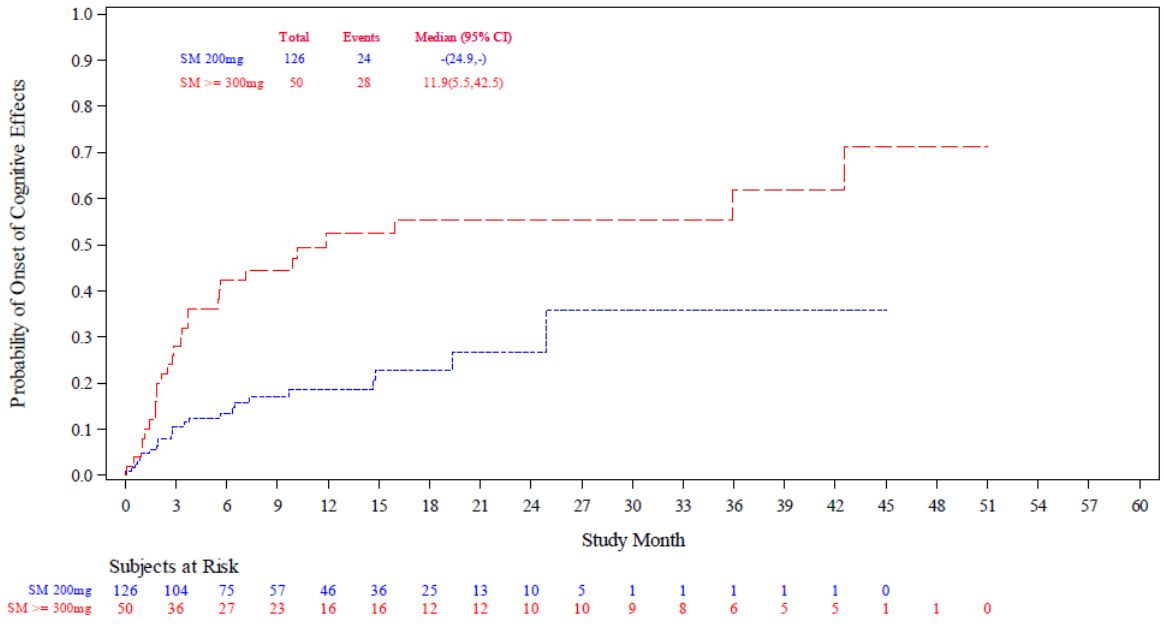
A systematic approach was used by the MAH in the identification of cognitive effects events comprising the AESI of cognitive effects. Based on this methodology, the current PTs comprising the AESI cognitive effects are as follows: Memory impairment, Cognitive disorder, Confusional state, Amnesia, Somnolence, Speech disorder, Delirium, Hallucination, Mood altered, Agitation, Personality change, Dementia, Mental status changes, Psychotic disorder, Disorientation, Mental impairment, and Encephalopathy.

Among the 193 patients with AdvSM, 59 patients (30.6%) experienced cognitive effects (Table 55). The most commonly reported event was memory impairment (14.5%), followed by cognitive disorder (14.0%). Thirty-five patients (18.1%) reported Grade 1 events, 17 patients (8.8%) reported Grade 2 events, and 7 patients (3.6%) reported Grade 3 events, which according to the CTCAE definition had clinical relevance (eg, interfered with activities of daily living or self-care); ≥Grade 4 events were reported. Five patients (2.6%) reported cognitive effects that led to permanent discontinuation of avapritinib (Table 55).

Of the 59 patients who experienced cognitive effects, 5 patients reported serious cognitive effects. Confounders for serious cognitive effects were reported in all 5 patients and included advanced age > 70 years in 3 patients; a history of psychiatric conditions or insomnia in 4 patients; and psychiatric or opioid medication use in 5 patients.

In general, the incidence of cognitive effects was lower in the AdvSM patients treated at 200 mg QD compared with AdvSM patients treated at ≥ 300 mg QD, largely attributed to the differences in exposure and in its duration (41 weeks vs ~96 weeks, respectively) which was supported by findings in the exposure-response analysis, that included data from patients with AdvSM or GIST (original submission). In addition, with longer treatment durations the probability of experiencing a cognitive effect event increases, see figure below:

Figure 5: Kaplan-Meier Plot of TTO for Cognitive Effects AESI (Updated Safety Population)



Abbreviations: AdvSM = advanced systemic mastocytosis; AESI = adverse event of special interest; QD = once daily, SM = systemic mastocytosis; TTO = time to onset.
Source: Updated Figure 99.2.1.1.1

The median time to occurrence of cognitive effects was 12.1 weeks and 13.3 weeks for the 200 mg and ≥ 300 mg groups, respectively. There are cases of cognitive effects reported later then 24 months, which is important information to convey.

Kaplan-Meier analyses of **time to improvement** (defined as a reduction from Grade ≥ 2 to Grade < 2) showed that, for patients with AdvSM treated at all doses who experienced Grade ≥ 2 cognitive effects, the probability of improvement was 50% by 8.0 weeks and 75% by 24.1 weeks. For patients treated at 200 mg QD, the probability of improvement was 50% by 6.1 weeks and 75% by 9.1 weeks.

Kaplan-Meier analyses of **time to resolution** demonstrated that, for patients with AdvSM treated at all doses who experienced Grade ≥ 2 cognitive effects, the probability of resolution was 25% by 5.4 weeks and 50% by 13.1 weeks. For patients at 200 mg QD, the probability of resolution was 50% at 6.1 weeks and 75% at 9.1 weeks.

The majority of AdvSM patients with cognitive effects events continued treatment with avapritinib, with only 2.6% of all AdvSM patients and 1.6% of patients who initiated treatment at 200 mg experiencing cognitive effects leading to permanent discontinuation of study treatment.

Table 55: Cognitive Effects Adverse Events of Special Interest by Category, Preferred Term, Indication, and Dose Level Sorted by AdvSM All (Updated Safety Population)

	AdvSM		
Category Preferred Term	**200 mg N=126 n (%)**	**≥ 300 mg N=50 n (%)**	**All N=193 n (%)**
Cognitive effects	24 (19.0)	28 (56.0)	59 (30.6)

Category Preferred Term	AdvSM 200 mg N=126 n (%)	≥ 300 mg N=50 n (%)	All N=193 n (%)
Cognitive disorder	15 (11.9)	9 (18.0)	27 (14.0)
Somnolence	1 (< 1)	2 (4.0)	3 (1.6)
Delirium	1 (< 1)	1 (2.0)	2 (1.0)
Dementia	1 (< 1)	1 (2.0)	2 (1.0)
Disorientation	1 (< 1)	0	2 (1.0)
Mental status changes	1 (< 1)	1 (2.0)	2 (1.0)
Memory impairment	7 (5.6)	16 (32.0)	28 (14.5)
Confusional state	3 (2.4)	6 (12.0)	12 (6.2)
Amnesia	0	3 (6.0)	4 (2.1)
Encephalopathy	0	3 (6.0)	3 (1.6)
Agitation	0	0	1 (< 1)
Hallucination	0	1 (2.0)	1 (< 1)
Grade ≥ 3 cognitive effects	4 (3.2)	3 (6.0)	7 (3.6)
Cognitive disorder	2 (1.6)	1 (2.0)	3 (1.6)
Mental status changes	1 (< 1)	1 (2.0)	2 (1.0)
Delirium	1 (< 1)	0	1 (< 1)
Dementia	1 (< 1)	0	1 (< 1)
Encephalopathy	0	2 (4.0)	2 (1.0)
Confusional state	0	1 (2.0)	1 (< 1)
Serious cognitive effects	1 (< 1)	4 (8.0)	5 (2.6)
Dementia	1 (< 1)	1 (2.0)	2 (1.0)
Mental status changes	1 (< 1)	1 (2.0)	2 (1.0)
Encephalopathy	0	2 (4.0)	2 (1.0)
Confusional state	0	1 (2.0)	1 (< 1)
Cognitive effects leading to permanent discontinuation of study treatment	2 (1.6)	2 (4.0)	5 (2.6)
Cognitive disorder	1 (< 1)	1 (2.0)	3 (1.6)
Dementia	1 (< 1)	1 (2.0)	2 (1.0)
Encephalopathy	0	1 (2.0)	1 (< 1)

Abbreviations: AdvSM = advanced systemic mastocytosis; AESI = adverse event of special interest.
Notes: Percentages are based on the number of patients in the Updated Safety Population in each column.
Preferred terms are sorted in decreasing order of frequency using the AdvSM 200 mg column.
If a patient experienced more than 1 event in a given AESI category, that patient is counted once for the category. If a patient experienced more than 1 event within a given preferred term, that patient is counted only once for that term.
Sources: Updated Table 18.3.3.2.1.1, Updated Table 18.3.3.2.2.1, Updated Table 18.3.3.2.3, Updated Table 99.2.1.1.

There were no meaningful differences in the incidences of cognitive effects AEs between the 200 mg original group and 200 mg extended group.

Analysis of Adverse Events by Organ System or Syndrome

Table 56 summarizes AEs in any SOC with ≥ 10% incidence in patients with AdvSM treated at 200 mg dose. The following sections present more details for selected organ systems or syndromes, based on frequency and medical importance.

Table 56: Adverse Events Reported in ≥ 10% of Patients with AdvSM Treated at 200 mg Dose by System Organ Class, Indication, and Dose Level Sorted by AdvSM All (Updated Safety Population)

System Organ Class	AdvSM		
	200 mg N=126 n (%)	≥ 300 mg N=50 n (%)	All N=193 n (%)
Patients with any adverse event	126 (100.0)	50 (100.0)	193 (100.0)
Gastrointestinal disorders	96 (76.2)	49 (98.0)	161 (83.4)
Blood and lymphatic system disorders	87 (69.0)	43 (86.0)	144 (74.6)
General disorders and administration site conditions	84 (66.7)	39 (78.0)	135 (69.9)
Eye disorders	80 (63.5)	43 (86.0)	134 (69.4)
Investigations	74 (58.7)	31 (62.0)	116 (60.1)
Nervous system disorders	68 (54.0)	42 (84.0)	123 (63.7)
Skin and subcutaneous tissue disorders	63 (50.0)	39 (78.0)	115 (59.6)
Infections and infestations	55 (43.7)	42 (84.0)	111 (57.5)
Respiratory, thoracic and mediastinal disorders	46 (36.5)	36 (72.0)	95 (49.2)
Musculoskeletal and connective tissue disorders	45 (35.7)	35 (70.0)	91 (47.2)
Metabolism and nutrition disorders	42 (33.3)	28 (56.0)	81 (42.0)
Injury, poisoning and procedural complications	34 (27.0)	25 (50.0)	70 (36.3)
Psychiatric disorders	27 (21.4)	23 (46.0)	57 (29.5)
Vascular disorders	27 (21.4)	23 (46.0)	54 (28.0)
Renal and urinary disorders	15 (11.9)	15 (30.0)	35 (18.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	13 (10.3)	10 (20.0)	30 (15.5)

Abbreviations: AdvSM = advanced systemic mastocytosis.
Notes: Percentages are based on the number of patients in the Updated Safety Population in each column.
System organ classes are sorted in decreasing order of frequency using the AdvSM 200 mg column.
If a patient experienced more than 1 event within a given system organ class, that patient was counted only once for that class.
Source: Updated Table 18.3.3.1.2.1.

A higher proportion of patients in the 200 mg original group experienced AEs in the SOC of General Disorders and Administration Site Conditions compared to those in the 200 mg extended group (Table 57). This increase was primarily driven by higher incidence of peripheral edema (51.9% vs 42.9%) and fatigue (19.8% vs 16.7%) in the original 200 mg group as compared to extended 200 mg group, respectively.

Table 57: Adverse Events Reported in 200 mg Original group and 200 mg Extended Group by System Organ Class

System Organ Class	AdvSM	
	200 mg Original[a] (N=81) n (%)	200 mg Extended[b] (N=126) n (%)
Patients with any adverse event	81 (100)	126 (100)
Gastrointestinal disorders	64 (79.0)	96 (76.2)
Blood and lymphatic system disorders	56 (69.1)	87 (69.0)
General disorders and administration site	61 (75.3)	84 (66.7)
Eye disorders	57 (70.4)	80 (63.5)
Investigations	48 (59.3)	74 (58.7)
Nervous system disorders	47 (58.0)	68 (54.0)
Skin and subcutaneous tissue disorders	43 (53.1)	63 (50.0)
Infections and infestations	42 (51.9)	55 (43.7)
Respiratory, thoracic and mediastinal disorders	34 (42.0)	46 (36.5)

System Organ Class	AdvSM	
	200 mg Original[a] (N=81) n (%)	200 mg Extended[b] (N=126) n (%)
Musculoskeletal and connective tissue disorders	34 (42.0)	45 (35.7)
Metabolism and nutrition disorders	31 (38.3)	42 (33.3)
Injury, poisoning and procedural complications	25 (30.9)	34 (27.0)
Psychiatric disorders	22 (27.2)	27 (21.4)
Vascular disorders	21 (25.9)	27 (21.4)
Renal and urinary disorders	11 (13.6)	15 (11.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	13 (16.0)	13 (10.3)

Abbreviations: AdvSM = advanced systemic mastocytosis.
Note: System organ classes with ≥ 10% incidence in the 200 mg extended group are presented.
[a] Original 200 mg safety population from initial submission (data cut-off date 20 April 2021)
[b] Updated safety population (data cut-off date 20 April 2021)
Source: Table 99.20.3.3.1.2.1

- **Gastrointestinal Disorders**

In AdvSM, mast cells can accumulate in the GI tract and GI symptoms are expected. Nausea, diarrhea, vomiting, abdominal pain, and gastric hemorrhage are commonly reported in patients with AdvSM (Jensen, 2000).

Overall, 161 of the patients with AdvSM treated at all doses (83.4%) experienced AEs in the SOC of Gastrointestinal Disorders; the most common AEs were diarrhoea (34.7%), nausea (31.1%), vomiting (26.4%), constipation (17.6%), and abdominal pain (16.6%).

Regarding intensity,

In this SOC, the majority of patients experienced grade <3 AEs (n=124, 64.3%).

A total of 31 patients (16.1%) experienced SAE in this SOC, most commonly ascites (3.1%), gastrointestinal haemorrhage (2.1%), abdominal pain, gastric haemorrhage, and vomiting (1.6% each), and intra-abdominal haemorrhage, large intestine perforation, pancreatitis, and upper gastrointestinal haemorrhage (1.0% each).

Three patients died due to an AE in this SOC (gastric haemorrhage, gastritis erosive, and intra-abdominal haemorrhage), none of them were considered treatment-related.

A total of 30 patients (15.5%) experienced AEs in this SOC that led to dose interruption, most commonly vomiting (2.6%), ascites (2.1%), gastrointestinal haemorrhage and nausea (1.6% each).

A total of 15 patients (7.8%) experienced AEs in this SOC that led to dose reduction, most commonly diarrhoea and nausea (2.1% each), ascites and vomiting (1.6% each).

The most common AEs, related AEs, SAEs, and AEs leading to dose interruption or reduction experienced by patients with AdvSM treated at 200 mg QD were similar to those experienced by patients with AdvSM treated at all doses.

- **Blood and Lymphatic System Disorders**

Anemia, leukopenia, and other cytopenias are features of AdvSM resulting from dense mast cell infiltrates within the bone marrow (Pardanani 2016) and expected toxicities of avapritinib related to on-target KIT

inhibition (Demetri et al, 2002; Gleevec, 2016). These findings are generally manageable with supportive treatment and/or dose interruption/reduction when related to treatment and may improve as the mast cell burden decreases.

Overall, 144 (74.6%) of the patients treated at all doses experienced AEs in this SOC. The most common AEs were anaemia (47.2%), thrombocytopenia (39.9%), and neutropenia (18.7%). Regarding intensity, 91 (47.2%) patients experienced grade ≥ 3; the most common (≥ 5%) Grade 3 events were anaemia (23.8%), thrombocytopenia (15.0%), and neutropenia (10.9%). The most common (≥ 5%) Grade 4 event was thrombocytopenia (7.3%) and neutropenia (5.2%).

A total of 12 patients (6.2%) experienced SAEs in this SOC, most commonly anaemia (4.1%). No patient died due to an AE in this SOC.

A total of 59 patients (30.6%) experienced AEs in this SOC that led to dose interruption, most commonly thrombocytopenia (15.5%), neutropenia (8.8%), anaemia (8.3%). A total of 63 patients (32.6%) experienced AEs in this SOC that led to dose reduction, most commonly thrombocytopenia (15.5%), neutropenia, (8.8%), anaemia (8.3%).

The most common AEs, related AEs, SAEs, and AEs leading to dose interruption or reduction experienced by patients with AdvSM treated at 200 mg QD were similar to those experienced by patients with AdvSM treated at all doses.

The incidence of Blood and Lymphatic System Disorders was lower in AdvSM patients treated at 200 mg QD (69.0%) as compared with AdvSM patients treated at ≥ 300 mg QD (86.0%).

- **General Disorders and Administration Site Conditions**

Overall, 135 of the patients with AdvSM treated at all doses (69.9%) experienced AEs in this SOC; the most common AEs were oedema peripheral (42.5%), fatigue (26.4%), and face oedema (13.0%).

Fatigue is a prominent feature in patients with AdvSM (Jennings et al, 2018). Oedema is an expected and manageable toxicity related to on-target KIT/PDGFRA inhibition, which was first demonstrated with imatinib treatment (Demetri et al, 2002).

In this SOC, the majority of patients (n=114, 59%) experienced Grade <3 AEs. The most common (≥ 5%) Grade 3 event was fatigue (5.2%).

Eight patients (4.1%) experienced SAEs in this SOC, namely pyrexia (2.1%) and disease progression, oedema, oedema peripheral, and pain (< 1% each).

One patient died due to an AE in this SOC (disease progression).

A total of 18 patients (9.3%) experienced AEs in this SOC that led to dose interruption, most commonly fatigue (2.1%), influenza like illness, oedema peripheral and pyrexia (1.6% each), and asthenia (1.0%). A total of 24 patients (12.4%) experienced AEs in this SOC that led to dose reduction, most commonly oedema peripheral (5.7%), fatigue (3.1%), asthenia (2.1%), and pain (1%).

The most common AEs, related AEs, SAEs, and AEs leading to dose interruption or reduction experienced by patients with AdvSM treated at 200 mg QD were similar to those experienced by patients with AdvSM treated at all doses.

- **Eye Disorders**

A summary of AEs in the Eye disorders and Infections and Infestations SOCs is provided in Tables 20 and 21 (data cut-off date 20 April 2021).

Table 20: Summary of Adverse Events by SOC (AdvSM Safety Population) for Eye Disorders and Infections & Infestations

Patients with any:	AdvSM	
	200 mg N=126 n (%)	All N=193 n (%)
EYE DISORDERS		
AE	80 (63.5)	134 (69.4)
SAE	0	1 (<1)
Grade ≥ 3 AE	7 (5.6)	12 (6.2)
Related AE	73 (57.9)	123 (63.7)
Related SAE	0	1 (<1)
Grade ≥ 3 related AE	6 (4.8)	10 (5.2)
AE leading to dose interruption	5 (4.0)	8 (4.1)
AE leading to dose reduction	12 (9.5)	26 (13.5)
AE leading to treatment discontinuation	0	0
INFECTIONS & INFESTATIONS		
AE	55 (43.7)	111 (57.5)
SAE	17 (13.5)	32 (16.6)
Grade ≥ 3 AE	16 (12.7)	34 (17.6)
Related AE	9 (7.1)	21 (10.9)
Related SAE	1 (<1)	1 (<1)
Grade ≥ 3 related AE	1 (<1)	1 (<1)
AE leading to dose interruption	4 (3.2)	15 (7.8)
AE leading to dose reduction	0	1 (<1)
AE leading to treatment discontinuation	2 (1.6)	2 (1.0)

Abbreviations: AdvSM = advanced systemic mastocytosis; AE = adverse event; SAE = serious adverse event; SOC = system organ class.
Notes: Percentages are based on the number of patients in the Safety Population in each column. If a patient experienced more than 1 event in a given category, that patient was counted only once.
Source: Table.18.3.3.1.2.1; Table.18.3.3.1.6.1; Table.18.3.3.1.4.1; Table.18.3.3.1.3.1; Table.18.3.3.1.7.1; Table.18.3.3.1.5.1; Table.18.3.3.1.10.1; Table.18.3.3.1.9.1; Table.18.3.3.1.11.1.

Table 58 Summary of Eye disorders and ≥ Grade 3 Eye disorders SOC AEs for the AdvSM Safety Population

Patients with any:	AdvSM	
	200 mg N=126 n (%)	All N=193 n (%)
Eye disorders AEs in > 1% (PT)	80 (63.5)	134 (69.4)
Periorbital oedema	50 (39.7)	100 (51.8)
Eyelid oedema	18 (14.3)	19 (9.8)
Lacrimation increased	8 (6.3)	17 (8.8)
Vision blurred	3 (2.4)	9 (4.7)
Conjunctival haemorrhage	3 (2.4)	7 (3.6)
Ocular hyperaemia	2 (1.6)	6 (3.1)
Eye swelling	3 (2.4)	5 (2.6)
Dry eye	2 (1.6)	4 (2.1)
Eye haemorrhage	3 (2.4)	4 (2.1)
Blepharitis	1 (<1)	3 (1.6)
Conjunctival oedema	1 (<1)	3 (1.6)
Eye pruritus	0	3 (1.6)
≥ Grade 3 Eye disorders in ≥ 1% (PT)	7 (5.6)	12 (6.2)
Periorbital oedema	5 (4.0)	7 (3.6)
Lacrimation increased	0	1 (<1)
Ocular hyperaemia	0	1 (<1)
Retinal haemorrhage	1 (<1)	1 (<1)
Uveitis	0	1 (<1)
Vitreous haemorrhage	1 (<1)	1 (<1)

Abbreviations: AdvSM = advanced systemic mastocytosis; AE = adverse event; PT = preferred term; SAE = serious adverse event; SOC = system organ class.
Notes: Percentages are based on the number of patients in the Safety Population in each column. If a patient experienced more than 1 event in a given category, that patient was counted only once.
Source : Table 18.3.3.1.2.1 ; Table 18.3.3.1.4.1

- **Infections and Infestations**

A summary of AEs in the Eye disorders and Infections and Infestations SOCs is provided in Table 20 (above) and is also further described in Table 22 (data cut-off date 20 April 2021).

Table 59 Summary of Infections and Infestations and ≥ Grade 3 Infections and Infestations SOC AEs for the AdvSM Safety Population

Patients with any:	AdvSM	
	200 mg N=126 n (%)	All N=193 n (%)
Infections and Infestations AEs in > 1% (PT)	55 (43.7)	111 (57.5)
Urinary tract infection	8 (6.3)	21 (10.9)
Upper respiratory tract infection	7 (5.6)	20 (10.4)
Gastroenteritis	3 (2.4)	12 (6.2)
Conjunctivitis	4 (3.2)	10 (5.2)
Herpes zoster	4 (3.2)	10 (5.2)
Oral candidiasis	3 (2.4)	9 (4.7)
Sinusitis	4 (3.2)	9 (4.7)
Cellulitis	3 (2.4)	8 (4.1)
Nasopharyngitis	2 (1.6)	7 (3.6)
Pneumonia	2 (1.6)	7 (3.6)
Diverticulitis	2 (1.6)	6 (3.1)
Oral herpes	3 (2.4)	5 (2.6)
Corona virus infection	1 (<1)	3 (1.6)
Ear infection	1 (<1)	3 (1.6)
Gastroenteritis viral	0	3 (1.6)
Influenza	0	3 (1.6)
Respiratory tract infection	2 (1.6)	3 (1.6)
Rhinitis	2 (1.6)	3 (1.6)
Sepsis	1 (<1)	3 (1.6)
Vaginal infection	1 (<1)	3 (1.6)
≥ Grade 3 Infections and Infestations in > 1% (PT)	16 (12.7)	34 (17.6)
Pneumonia	1 (<1)	6 (3.1)
Cellulitis	1 (<1)	2 (1.0)
Clostridium difficile infection	1 (<1)	2 (1.0)
Diverticulitis	2 (1.6)	2 (1.0)
Gastroenteritis	0	2 (1.0)
Osteomyelitis	2 (1.6)	2 (1.0)
Pneumonia viral	1 (<1)	2 (1.0)

Abbreviations: AdvSM = advanced systemic mastocytosis; AE = adverse event; PT = preferred term; SOC = system organ class.
Notes: Percentages are based on the number of patients in the Safety Population in each column. If a patient experienced more than 1 event in a given category, that patient was counted only once.
Source : Table 18.3.3.1.2.1 ; Table 18.3.3.1.4.1

- **Nervous System Disorders**

Overall, 123 of the patients with AdvSM treated at all doses (63.7%) experienced AEs in the SOC of Nervous System Disorders (Table 56). The most common AEs were dysgeusia (18.1%), headache (17.1%), dizziness and memory impairment (14.5% each), and cognitive disorder (14.0%)

In this SOC, the majority of patients (n=103, 54.4%) experienced Grade <3 AEs.

A total of 13 patients (6.7%) experienced SAEs in this SOC, most commonly haemorrhage intracranial (2.1%), dementia and encephalopathy (1.0% each).
Two patients (1.0%) died due to haemorrhage intracranial and ischaemic stroke.

A total of 23 patients (11.9%) experienced AEs in this SOC that led to dose interruption, most commonly cognitive disorder (5.7%), memory impairment (2.1%), and dementia (1.0%). Twenty-two patients (11.4%)

experienced AEs in this SOC that led to dose reduction, most commonly cognitive disorder (6.2%), memory impairment (3.6%), and dysgeusia (1.0%).

In this SOC, the most common AEs experienced by patients treated at 200 mg QD were generally lower than those experienced by patients with AdvSM treated at all doses AEs leading to dose interruption or reduction experienced in this group were similar to those experienced by patients treated at all doses.

- **Renal and urinary disorders**

Eleven (5.7%) of the 193 patients with AdvSM who received treatment with avapritinib (all doses) in clinical trials reported 12 events of acute kidney injury (AKI), and 1 (<1%) patient reported 1 event of renal failure. All but 1 patient (grade 5) reported events that were Grade 1-3 in severity, and the majority of the events resolved and did not lead to permanent discontinuation of treatment. Risk factors/confounders were present in 11 of the 12 patients, (predominantly hypertension, diabetes, pre-renal azotaemia or infections). Two of the thirteen reported events were designated as related.

In the AdvSM 200 mg group, acute kidney injury is reported in 5 patients (4.0 %, considered related in 1 patient) and renal failure in 1 patient (< 1 %, not considered related). One patient in the 200 mg group had AKI that led to discontinuation of avapritinib.

For the GIST indication, the reported frequencies are: AKI (n=17, 2.8 %) and renal failure (n=7, 1.1 %). Risk factors/confounders were present in all these 24 patients, but half of the events were considered related to treatment.

2.6.8.4. Laboratory findings

Serum Chemistry

Shift analyses from baseline to worst value on treatment based on the NCI CTCAE were conducted for serum chemistry parameters.

Shifts in selected serum chemistry parameters from Grade ≤ 2 at baseline to Grade ≥ 3 at the worst value on treatment are summarized in Table 68.

Table 60: Proportion of Patients with Shifts in Selected Serum Chemistry Parameters from Grade ≤ 2 at Baseline to Grade ≥ 3 at Worst Value on Study Sorted by AdvSM All (Updated Safety Population)

	AdvSM		
Parameter	**200 mg N=126 n (%)**	**≥ 300 mg N=50 n (%)**	**All N=193 n (%)**
ALP increased	7/126 (5.6)	3/50 (6.0)	14/193 (7.3)
Bilirubin increased	7/126 (5.6)	4/50 (8.0)	14/193 (7.3)
Potassium decreased	8/126 (6.3)	3/50 (6.0)	12/193 (6.2)
Phosphate decreased	1/126 (< 1)	6/50 (12.0)	9/193 (4.7)
AST increased	1/126 (< 1)	2/50 (4.0)	3/193 (1.6)
ALT increased	1/126 (< 1)	1/50 (2.0)	2/193 (1.0)

Abbreviations: AdvSM = advanced systemic mastocytosis; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase.
Parameters are sorted in decreasing order of frequency using the AdvSM All column.
Baseline value was defined as the last observation before the first dose of study drug.

There were no meaningful differences observed in serum chemistry results between the original 200 mg group and the extended 200 mg group.

Hematology

Shift analyses from baseline to worst value on treatment based on the NCI CTCAE were conducted for hematology parameters. Shifts in selected hematology parameters from Grade ≤ 2 at baseline to Grade ≥ 3 at the worst value on treatment are summarized in Table 71.

Table 61: Proportion of Patients with Shifts in Selected Hematology Parameters from Grade ≤ 2 at Baseline to Grade ≥ 3 at Worst Value on Study Sorted by AdvSM All (Updated Safety Population)

	AdvSM		
Parameter	**200 mg N=126 n (%)**	**≥ 300 mg N=50 n (%)**	**All N=193 n (%)**
Hemoglobin decreased	31/126 (24.6)	24/50 (48.0)	58/193 (30.1)
Platelets decreased	30/126 (23.8)	14/50 (28.0)	50/193 (25.9)
Neutrophils decreased	29/126 (23.0)	14/50 (28.0)	49/193 (25.4)
Lymphocytes decreased	20/126 (15.9)	14/50 (28.0)	37/193 (19.2)
Leukocytes decreased	14/126 (11.1)	9/50 (18.0)	27/193 (14.0)

Abbreviations: AdvSM = advanced systemic mastocytosis.
Parameters are sorted in decreasing order of frequency using the AdvSM All column.
Baseline value was defined as the last observation before the first dose of study drug.
Source: Updated Table 18.3.4.2.2.

There were no meaningful differences observed in hematology results between the original 200 mg group and the extended 200 mg group.

- **Summary of AEs of Torsade de Pointes/QT Prolongation**

A search of the clinical database for AdvSM studies (BLU-285-2101 and BLU-285-2202) and GIST studies (BLU-285-1101 and BLU-285-1303) was performed using the standardized MedDRA query (SMQ) Torsade de pointes/QT Prolongation. The search revealed 39 patients (4.9%) overall (14 patients with AdvSM and 25 patients with GIST) who experienced 41 events including Electrocardiogram QT prolonged, syncope, cardiac arrest, ventricular tachycardia, loss of consciousness, and ventricular arrhythmia. Serious events were reported in 4 patients (< 1%), (2 patients with AdvSM and 2 patients with GIST), and included cardiac arrest, syncope, and ventricular tachycardia. These events were all assessed as not related to avapritinib and were described in the initial AdvSM submission. There were no new serious events reported during the update period. Eighteen patients (2.2%) reported Grade 1 events; 6 patients (< 1%) reported Grade 2 events, 13 patients (1.6%) reported Grade 3 events, and 1 patient each (< 1%) reported Grade 4 and Grade 5 events.

Events from the SMQ Torsade de pointes/QT Prolongation are summarized in Table 23.

Table 62 Summary of Torsade de Pointes/QT Prolongation SMQ Adverse Events by Preferred Term (Safety Population)

Preferred Term	AdvSM			Ava (AdvSM+GIST)	GIST	
	200 mg N=126 n (%)	≥ 300 mg N=50 n (%)	All N=193 n (%)	All N=803 n (%)	300 mg N=525 n (%)	All N=610 n (%)
Patients with treatment-emergent torsade de pointes/QT prolongation SMQ adverse event	6 (4.8)	4 (8.0)	14 (7.3)	39 (4.9)	22 (4.2)	25 (4.1)
Electrocardiogram QT prolonged	2 (1.6)	2 (4.0)	7 (3.6)	23 (2.9)	16 (3.0)	16 (2.6)
Syncope	3 (2.4)	1 (2.0)	5 (2.6)	10 (1.2)	2 (< 1)	5 (< 1)
Cardiac arrest	1 (< 1)	1 (2.0)	2 (1.0)	2 (< 1)	0	0
Ventricular tachycardia	1 (< 1)	0	1 (< 1)	2 (< 1)	1 (< 1)	1 (< 1)
Loss of consciousness	0	0	0	1 (< 1)	1 (< 1)	1 (< 1)
Ventricular arrhythmia	0	0	0	3 (< 1)	3 (< 1)	3 (< 1)

Abbreviations: AdvSM = advanced systemic mastocytosis; Ava = avapritinib; GIST = gastrointestinal stromal tumor; MedDRA = Medical Dictionary for Regulatory Activities; QT = the time interval between the start of the Q wave and the end of the T wave in the heart's electrical cycle; SMQ = standardised MedDRA query.
Notes: Percentages are based on the number of patients in the Safety Population in each column.
Preferred terms are sorted in decreasing order of frequency using the AdvSM All column.
GIST patients who received a starting dose of 600 mg are included in the GIST All and Ava All columns.
If a patient experienced more than 1 event within a given SMQ category or preferred term, that patient was counted only once for that category or term.
Source: Table 99.4.1.1.

One patient with AdvSM had 3 events of electrocardiogram (ECG) QT prolonged; 1 patient with GIST had 2 events of ventricular arrhythmia and an event of electrocardiogram QT prolonged. One patient with AdvSM had a Grade 4 event of cardiac arrest that occurred in the context of haemorrhagic shock with massive blood loss due to oesophageal varices haemorrhage; the event was managed with massive transfusion protocol and was assessed as not related to avapritinib. The majority of the events (30 of 44; 68.2%) resolved, 13 events were ongoing, and 1 event had a fatal outcome. Twenty-one events (47.7%) were assessed as related to avapritinib, and 23 events (52.3%) were assessed as not related to avapritinib. All but 4 events were nonserious and there were no new serious events during this update period.

-- Information from Post-Marketing Sources

Cumulatively as of 20 April 2021, there has been 1 case report containing 1 serious event within the Torsade de Pointes/QT prolongation SMQ since marketing authorization. The event was not HCP-confirmed.

Table 63 Summary of Torsade de pointes/QT prolongation SMQ Adverse Events by Preferred Term (Safety Population)

Preferred Term	AdvSM			Ava (AdvSM +GIST)	GIST	
	200 mg N=81 n (%)	≥ 300 mg N=50 n (%)	All N=148 n (%)	All N=749 n (%)	300 mg N=516 n (%)	All N=601 n (%)
Patients with treatment-emergent torsade de pointes/QT prolongation SMQ adverse event	2 (2.5)	4 (8.0)	9 (6.1)	33 (4.4)	21 (4.1)	24 (4.0)
Electrocardiogram QT prolonged	1 (1.2)	2 (4.0)	5 (3.4)	20 (2.7)	15 (2.9)	15 (2.5)
Syncope	1 (1.2)	1 (2.0)	3 (2.0)	8 (1.1)	2 (< 1)	5 (< 1)
Cardiac arrest	0	1 (2.0)	1 (< 1)	1 (< 1)	0	0
Loss of consciousness	0	0	0	1 (< 1)	1 (< 1)	1 (< 1)
Ventricular arrhythmia	0	0	0	3 (< 1)	3 (< 1)	3 (< 1)
Ventricular tachycardia	0	0	0	1 (< 1)	1 (< 1)	1 (< 1)

Abbreviations: AdvSM = advanced systemic mastocytosis; Ava = avapritinib; GIST = gastrointestinal stromal tumor; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standardised MedDRA query.
Notes: Percentages are based on the number of patients in the Safety Population in each column.
Preferred terms are sorted in decreasing order of frequency using the AdvSM All column.
GIST patients who received a starting dose of 600 mg are included in the GIST All and Ava All columns.
If a patient experienced more than 1 event within a given SMQ category or preferred term, that patient was counted only once for that category or term.
Source: Table 99.4.1.1.

2.6.8.5. Safety in special populations

Intrinsic and Extrinsic Factors

Subgroup analyses of AEs and AESIs were performed for intrinsic factors (age, gender, race, nadir platelet count during screening and extrinsic factors (region, prior midostaurin).

Interpretation of these individual analyses is limited given the small number of patients within certain subgroups, which may be influenced by the differences in design and populations across studies in the pooled Safety Population. Due to the risk mitigation strategies implemented to minimize the risk for intracranial bleeding, the analysis of nadir platelet count during screening was uninterpretable as most patients had platelet counts ≥ 50,000/μL.

Subgroup analyses relevant for AdvSM are discussed in this section.

Table 81 summarizes the incidence of AEs, related AEs, Grade ≥ 3 AEs, related Grade ≥ 3 AEs, SAEs, and related SAEs in the subgroup analyses performed for AdvSM patients treated at 200 mg QD.

Table 64: Summary of Adverse Events by Subgroup (Updated Safety Population – Patients with AdvSM Treated at 200 mg QD, N=126)

Subgroup	N	Any AE	Related AE	Grade ≥ 3 AE		SAE	
				All	Related	All	Related
Nadir platelet count during screening							
< 50,000/μL	5	5 (100.0)	5 (100.0)	3 (60.0)	2 (40.0)	2 (40.0)	1 (20.0)
≥ 50,000/μL	121	121 (100.0)	115 (95.0)	92 (76.0)	73 (60.3)	46 (38.0)	14 (11.6)
Age							
< 65 years	47	47 (100.0)	43 (91.5)	33 (70.2)	25 (53.2)	14 (29.8)	7 (14.9)

Subgroup	N	Any AE	Related AE	Grade ≥ 3 AE		SAE	
				All	Related	All	Related
≥ 65 years	79	79 (100.0)	77 (97.5)	62 (78.5)	50 (63.3)	34 (43.0)	8 (10.1)
Prior midostaurin							
Yes	66	66 (100.0)	61 (92.4)	49 (74.2)	39 (59.1)	28 (42.4)	9 (13.6)
No	60	60 (100.0)	59 (98.3)	46 (76.7)	36 (60.0)	20 (33.3)	6 (10.0)
Gender							
Male	74	74 (100.0)	68 (91.9)	52 (70.3)	39 (52.7)	35 (47.3)	10 (13.5)
Female	52	52 (100.0)	52 (100.0)	43 (82.7)	36 (69.2)	13 (25.0)	5 (9.6)
Race							
White	109	109 (100.0)	103 (94.5)	82 (75.2)	65 (59.6)	43 (39.4)	14 (12.8)
Non-White	15	15 (100.0)	15 (100.0)	11 (73.3)	9 (60.0)	3 (20.0)	0
Unknown	2	2 (100.0)	2 (100.0)	2 (100.0)	1 (50.0)	2 (100.0)	1 (50.0)
Region							
North America	63	63 (100.0)	59 (93.7)	49 (77.8)	40 (63.5)	23 (36.5)	6 (9.5)
Europe or Australia	63	63 (100.0)	61 (96.8)	46 (73.0)	35 (55.6)	25 (39.7)	9 (14.3)

Abbreviations: AdvSM = advanced systemic mastocytosis; AE = adverse event; QD = once daily; SAE = serious adverse event.
Notes: Percentages are based on the number of patients with AdvSM treated at 200 mg QD in the Updated Safety Population in each column.
If a patient experienced more than 1 event within a given system organ class or preferred term, that patient was counted only once for that class or term.
Sources: Any AE: Updated Table 18.3.3.1.2.1a, Updated Table 18.3.3.1.2.1b, Updated Table 18.3.3.1.2.1c, Updated Table 18.3.3.1.2.1d, Updated Table 18.3.3.1.2.1f, Updated Table 18.3.3.1.2.1g; Any related AE: Updated Table 18.3.3.1.3.1a, Updated Table 18.3.3.1.3.1b, Updated Table 18.3.3.1.3.1c, Updated Table 18.3.3.1.3.1d, Table 18.3.3.1.3.1f, Updated Table 18.3.3.1.3.1g; Any Grade ≥ 3: Updated Table 18.3.3.1.4.1a, Updated Table 18.3.3.1.4.1b, Updated Table 18.3.3.1.4.1c, Updated Table 18.3.3.1.4.1d, Updated Table 18.3.3.1.4.1f, Table 18.3.3.1.4.1g; Any related Grade ≥ 3: Updated Table 18.3.3.1.5.1a, Updated Table 18.3.3.1.5.1b, Updated Table 18.3.3.1.5.1c, Updated Table 18.3.3.1.5.1d, Updated Table 18.3.3.1.5.1f, Updated Table 18.3.3.1.5.1g; Any SAE: Updated Table 18.3.3.1.6.1a, Updated Table 18.3.3.1.6.1b, Updated Table 18.3.3.1.6.1c, Updated Table 18.3.3.1.6.1d, Updated Table 18.3.3.1.6.1f, Updated Table 18.3.3.1.6.1g; Any related SAE: Table 18.3.3.1.7.1a, Updated Table 18.3.3.1.7.1b, Updated Table 18.3.3.1.7.1c, Updated Table 18.3.3.1.7.1d, Updated Table 18.3.3.1.7.1f, Updated Table 18.3.3.1.7.1g.

- Age

Among the 126 patients with AdvSM treated at 200 mg QD, 47 patients (37.3%) were < 65 years and 79 patients (62.7%) were ≥ 65 years. A summary of AEs by age for patients with AdvSM treated at 200 mg QD is presented in Table 25.

Table 65 Summary of Adverse Events for AdvSM 200 mg group by age

Patients with any:	< 65 Years N=47 n (%)	≥ 65 Years N=79 n (%)
AE	47 (100.0)	79 (100.0)
SAE	14 (29.8)	34 (43.0)
Grade ≥3 AEs	33 (70.2)	62 (78.5)
Related AE	43 (91.5)	77 (97.5)
Related SAE	7 (14.9)	8 (10.1)
Grade ≥ 3 related AE	25 (53.2)	50 (63.3)
AESI intracranial bleed	2 (4.3)	2 (2.5)
AESI cognitive effects	7 (14.9)	17 (21.5)

Abbreviations: AdvSM = advanced systemic mastocytosis; AE = adverse event; AESI = adverse event of special interest; SAE = serious adverse event.
Notes: Percentages are based on the number of patients in the Safety Population in each column. If a patient experienced more than 1 event in a given category, that patient was counted only once.
Source: Table 18.3.3.1.2.2a; Table 18.3.3.1.6.2a; Table 18.3.3.1.4.2a; Table 18.3.3.1.3.2a; Table 18.3.3.1.7.2a; Table 18.3.3.1.5.2a; Table 18.3.3.2.1.1a

Differences between the subgroups for the most commonly reported AEs are summarized in Table 66.

Table 66: Summary of the Events with a Difference in Incidence of ≥ 10% Between Age Groups for Adverse Events Reported in ≥ 20% of Patients with AdvSM Treated at 200 mg QD (Updated Safety Population)

Preferred Term	< 65 Years N=47 n (%)	≥ 65 Years N=79 n (%)	Total N=126 n (%)
Oedema peripheral	17 (36.2)	37 (46.8)	54 (42.9)
Anaemia	16 (34.0)	35 (44.3)	51 (40.5)
Periorbital oedema	24 (51.1)	26 (32.9)	50 (39.7)
Thrombocytopenia	13 (27.7)	37 (46.8)	50 (39.7)
Diarrhoea	16 (34.0)	19 (24.1)	35 (27.8)

Abbreviations: AdvSM = advanced systemic mastocytosis; QD = once daily.
Note: If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term.
Source: Updated Table 18.3.3.1.2.2a.

The overall incidence of Grade ≥ 3 AEs was similar between the younger (70.2%) and older (78.5%) patients. The overall incidence of SAEs was higher among older patients (43.0% and 29.8%, respectively).
The incidence of intracranial bleeding was similar for younger patients (2 patients; 4.3%) and older patients (2 patients; 2.5%). The incidence of cognitive effects was higher in the older subgroup (14.9% and 21.5%, respectively).

Table 67 Summary of safety findings in elderly patients with AdvSM treated at 200 mg

MedDRA Terms	Age < 65 N = 47 number (percentage)	Age 65-74 N = 52 number (percentage)	Age 75-84 N = 24 number (percentage)	Age 85+ N = 3 number (percentage)
Total AEs	47 (100)	52 (100)	24 (100)	3 (100)
Serious AEs – Total[a]	13 (27.6)	22 (42.3)	16 (66.6)	3 (100)
- Fatal	4 (8.5)	6 (11.5)	1 (4.1)	0
- Life-threatening	2 (4.2)	0	2 (8.3)	0
- Hospitalization/prolong existing hospitalization	7 (14.8)	16 (30.7)	13 (54.1)	3 (100)
- Disability/incapacity	0	0	0	0
- Other (medically significant)	0	0	0	0
AE leading to drop-out	8 (17.0)	10 (19.2)	4 (16.7)	1 (33.3)
Psychiatric disorders (SOC)	10 (21.3)	10 (19.2)	7 (29.2)	0
Nervous system disorders (SOC)	28 (59.6)	24 (46.2)	14 (58.3)	2 (66.7)
Accidents and injuries[b]	8 (17.0)	16 (30.8)	9 (37.5)	1 (33.3)
Cardiac disorders (SOC)	1 (2.1)	9 (17.3)	2 (8.3)	0
Vascular disorders (SOC)	10 (21.3)	11 (21.2)	6 (25.0)	0
Cerebrovascular disorders[c]	4 (8.5)	0	2 (8.3)	0
Infections and infestations (SOC)	17 (36.2)	24 (46.2)	13 (54.2)	1 (33.3)
Anticholinergic syndrome (PT)	0	0	0	0
Quality of life decreased (PT)	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	7 (14.9)	6 (11.5)	9 (37.5)	1 (33.3)
MedDRA Terms	**Age < 65 N = 47 number (percentage)**	**Age 65-74 N = 52 number (percentage)**	**Age 75-84 N = 24 number (percentage)**	**Age 85+ N = 3 number (percentage)**
<other AE appearing more frequently in older patients>				
Oedema peripheral	17 (36.2)	25 (48.1)	9 (37.5)	3 (100.0)
Anemia	16 (34.0)	22 (42.3)	12 (50.0)	1 (33.3)
Periorbital oedema	24 (51.1)	19 (36.5)	6 (25.0)	1 (33.3)
Thrombocytopenia	13 (27.7)	24 (46.2)	12 (50.0)	1 (33.3)
Diarrhoea	16 (34.0)	13 (25.0)	5 (20.8)	1 (33.3)

[a] Information on SAEs and outcomes is taken from the safety database
[b] "Injury, poisoning and procedural complications" SOC used for analysis.
[c] "Haemorrhagic central nervous system vascular conditions" (SMQ) + "Ischaemic central nervous system vascular conditions" (SMQ)
Abbreviations: AdvSM = advanced systemic mastocytosis, AE = adverse event, MedDRA = medical dictionary for regulatory activities, PT = preferred term, SOC = system organ class.
Source: Table 99.16.2.1, Table 99.16.2.3, Table 99.16.2.4

- **Prior Midostaurin**

Among the 126 patients with AdvSM treated at 200 mg QD, 66 patients (52.4%) had received prior midostaurin.

The incidence of AEs overall was the same (100%) for patients who had received prior midostaurin or not and the incidence of related AEs was similar (92.4% vs 98.3%) (Table 64).

Differences between the subgroups for the most commonly reported AEs are summarized in Table 68.

Table 68: Summary of the Events with a Difference in Incidence of ≥ 10% Between Prior Midostaurin Groups for Adverse Events Reported in ≥ 20% of Patients with AdvSM Treated at 200 mg QD (Updated Safety Population)

Preferred Term	Prior Midostaurin		Total
	Yes N=66 n (%)	No N=60 n (%)	N=126 n (%)
Periorbital oedema	22 (33.3)	28 (46.7)	50 (39.7)
Diarrhoea	15 (22.7)	20 (33.3)	35 (27.8)

Abbreviations: AdvSM = advanced systemic mastocytosis; QD = once daily.
Note: If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term.
Source: Updated Table 18.3.3.1.2.2f.

The overall incidence of Grade ≥ 3 AEs was similar between patients who had received prior midostaurin (74.2%) and patients who had not (76.7%).

Serious AEs were more frequently reported for patients who had received prior midostaurin (42.4%) than for patients who had not (33.3%). However, there were no trends for specific PTs.

The incidence of intracranial bleeding was similar for patients who had received prior midostaurin (3.0%) and for patients who had not (3.3%). The incidence of cognitive effects was also similar between the subgroups (16.7% and 21.7%, respectively).

- Gender

Among the 126 patients with AdvSM treated at 200 mg QD, 74 patients (58.7%) were male, and 52 patients (41.3%) were female. The incidence of AEs overall was the same (100%) for both subgroups and the incidence of related AEs was similar (91.9% vs 100.0%) (Table 64). Differences between the subgroups for the most commonly reported AEs are summarized in Table 69.

Table 69: Summary of the Events with a Difference in Incidence of ≥ 10% Between Gender Groups for Adverse Events Reported in ≥ 20% of Patients with AdvSM Treated at 200 mg QD (Updated Safety Population)

Preferred Term	Male N=74 n (%)	Female N=52 n (%)	Total N=126 n (%)
Oedema peripheral	28 (37.8)	26 (50.0)	54 (42.9)
Periorbital oedema	23 (31.1)	27 (51.9)	50 (39.7)
Thrombocytopenia	33 (44.6)	17 (32.7)	50 (39.7)
Nausea	14 (18.9)	16 (30.8)	30 (23.8)

Abbreviations: AdvSM = advanced systemic mastocytosis; QD = once daily.
Note: If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term.
Source: Updated Table 18.3.3.1.2.2b.

The overall incidence of Grade ≥ 3 AEs was lower in males (70.3%) than females (82.7%); the greater incidence in females was driven by Grade ≥ 3 AEs of neutrophil count decreased (17.3% in females, 1.4% in males).

Serious AEs were reported more frequently in males (47.3%) than in females (25.0%).

The incidence of intracranial bleeding was similar for males (2.7%) and females (3.8%). The incidence of cognitive effects was lower for males (12.2%) than females (28.8%). Memory impairment was experienced only by females (13.5%), and more females experienced cognitive disorder (17.3%) than males (8.1%).

- Race

Among the 126 patients with AdvSM treated at 200 mg QD, 109 patients (86.5%) were white, 1 patient (< 1%) was Asian, 14 patients (11.1%) were other race, and 2 patients (1.6%) were of unknown race. The incidence of AEs overall was the same (100%) across the 3 racial groups of white, non-white, and unknown race and the incidence of related AEs was similar (94.5%, 100%, and 100%, respectively) (Table 64).

Differences across the subgroups for the most commonly reported AEs are summarized in Table 70.

Table 70: Summary of the Events with a Difference in Incidence of ≥ 10% Among Racial Groups for Adverse Events Reported in ≥ 20% of Patients with AdvSM Treated at 200 mg QD (Updated Safety Population)

Preferred Term	White N=109 n (%)	Non-white N=15 n (%)	Unknown Race N=2 n (%)	Total N=126 n (%)
Oedema peripheral	44 (40.4)	9 (60.0)	1 (50.0)	54 (42.9)
Anaemia	40 (36.7)	9 (60.0)	2 (100.0)	51 (40.5)
Periorbital oedema	47 (43.1)	3 (20.0)	0	50 (39.7)
Thrombocytopenia	42 (38.5)	8 (53.3)	0	50 (39.7)
Diarrhoea	31 (28.4)	4 (26.7)	0	35 (27.8)
Nausea	28 (25.7)	2 (13.3)	0	30 (23.8)

Abbreviations: AdvSM = advanced systemic mastocytosis; QD = once daily.
Note: If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term.
Source: Updated Table 18.3.3.1.2.2d.

Grade ≥ 3 AEs were experienced by all patients of unknown race (100.0%) and most white and non-white patients (75.2% and 73.3%, respectively); the small number of patients of unknown race (n=2) should be considered in evaluating these comparisons. Serious AEs were more frequently reported for patients of unknown race (100.0%) and white patients (39.4%) than for non-white patients (20.0%).

Intracranial bleeding events were reported for 3.7% of white patients. No intracranial bleeding events were reported for non-white patients and patients of unknown race. The incidence of cognitive effects was similar for white (20.2%) and non-white (13.3%) patients, and no patients of unknown race reported this event.

- Region

Among the 126 patients with AdvSM treated at 200 mg QD, 63 patients (50.0%) were enrolled in North American sites, 63 patients (50.0%) in European or Australian sites, and none in Asian sites.

The incidence of AEs overall was the same (100%) for North American and European and Australian sites and the incidence of related AEs was similar (93.7% vs 96.8%) (Table 64). Differences between the subgroups for the most commonly reported AEs are summarized in Table 71.

Table 71: Summary of the Events with a Difference in Incidence of ≥ 10% Between Regional Groups for Adverse Events Reported in ≥ 20% of Patients with AdvSM Treated at 200 mg QD (Updated Safety Population)

Preferred Term	North America N=63 n (%)	Europe or Australia N=63 n (%)	Total N=126 n (%)
Periorbital oedema	30 (47.6)	20 (31.7)	50 (39.7)
Thrombocytopenia	17 (27.0)	33 (52.4)	50 (39.7)
Nausea	19 (30.2)	11 (17.5)	30 (23.8)

Abbreviations: AdvSM = advanced systemic mastocytosis; QD = once daily.
Note: If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term.
Source: Updated Table 18.3.3.1.2.2c.

The overall incidence of Grade ≥ 3 AEs was similar between North American patients (77.8%) and European or Australian patients (73.0%). Anaemia was reported by more North American (30.2%) than European patients (12.7%). The incidence of SAEs was similar for North American (36.5%) and European or Australian patients (39.7%).

The incidence of intracranial bleeding was similar for North American patients (4.8%) and European or Australian patients (1.6%). The incidence of cognitive effects was the same for North American patients and European or Australian patients (19.0%).

2.6.8.6. Immunological events

N/A

2.6.8.7. 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.

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, Original Application.

Overdose

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

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

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.

2.6.8.8. Discontinuation due to adverse events

- **Adverse Events Leading to Study Drug Discontinuation**

A total of 40 of the patients with AdvSM (20.7%) treated at all doses experienced AEs leading to permanent discontinuation of study drug (including "disease progression" reported as an AE term and AEs that represented symptoms of disease progression). The most common AEs (occurring in > 1% of patients) were acute myeloid leukaemia and thrombocytopenia (2.1% each) and ascites, cognitive disorder, haemorrhage intracranial, and subdural haematoma (1.6% each).
The incidence of AEs leading to permanent discontinuation of study drug for AdvSM patients treated at 200 mg QD (18.3%) was lower than for AdvSM patients treated at ≥ 300 mg QD (26.0%). There were no meaningful differences in the incidences of AEs leading to treatment discontinuation between the 200 mg original group and 200 mg extended group.

- **Adverse Events Leading to Dose Modification**

Summaries of AEs leading to dose interruption or dose reduction are provided in Table 50 and Table 51, respectively.

Table 72: Adverse Events Leading to Dose Interruption in ≥ 2% of AdvSM Patients Treated at 200 mg Dose Regardless of Causality by Preferred Term, Indication, and Dose Level (Updated Safety Population)

Preferred Term	AdvSM		
	200 mg N=126 n (%)	≥ 300 mg N=50 n (%)	All N=193 n (%)
Patients with any adverse event leading to dose interruption	84 (66.7)	41 (82.0)	137 (71.0)
Thrombocytopenia	22 (17.5)	8 (16.0)	30 (15.5)
Neutropenia	14 (11.1)	2 (4.0)	17 (8.8)
Anaemia	8 (6.3)	8 (16.0)	16 (8.3)
Cognitive disorder	8 (6.3)	2 (4.0)	11 (5.7)
Neutrophil count decreased	7 (5.6)	2 (4.0)	9 (4.7)
Platelet count decreased	6 (4.8)	0	7 (3.6)
Periorbital oedema	4 (3.2)	0	5 (2.6)
White blood cell count decreased	4 (3.2)	0	5 (2.6)
Oedema peripheral	3 (2.4)	0	3 (1.6)

Abbreviations: AdvSM = advanced systemic mastocytosis.
Notes: Percentages are based on the number of patients in the Updated Safety Population in each column.
Preferred terms are sorted in decreasing order of frequency using the AdvSM 200 mg column.
If a patient experienced more than 1 event within a given preferred term, that patient was counted only once under that preferred term.
Source: Updated Table 18.3.3.1.10.2.

Table 73 Adverse Events Leading to Dose Reduction in ≥ 2% of AdvSM Patients Treated at 200 mg Dose Regardless of Causality by Preferred Term, Indication, and Dose Level (Updated Safety Population)

Preferred Term	AdvSM		
	200 mg N=126 n (%)	≥ 300 mg N=50 n (%)	All N=193 n (%)
Patients with at least one event	91 (72.2)	46 (92.0)	141 (73.1)
Thrombocytopenia	24 (19.0)	6 (12.0)	30 (15.5)
Neutropenia	12 (9.5)	4 (8.0)	17 (8.8)
Periorbital oedema	10 (7.9)	9 (18.0)	20 (10.4)
Oedema peripheral	9 (7.1)	2 (4.0)	11 (5.7)
Cognitive disorder	8 (6.3)	3 (6.0)	12 (6.2)
Platelet count decreased	8 (6.3)	0	8 (4.1)
Neutrophil count decreased	7 (5.6)	1 (2.0)	8 (4.1)
Anaemia	6 (4.8)	10 (20.0)	16 (8.3)
Fatigue	3 (2.4)	3 (6.0)	6 (3.1)
Asthenia	3 (2.4)	1 (2.0)	4 (2.1)

Preferred Term	AdvSM		
	200 mg N=126 n (%)	**≥ 300 mg N=50 n (%)**	**All N=193 n (%)**
Blood alkaline phosphatase increased	3 (2.4)	0	3 (1.6)

Abbreviations: AdvSM = advanced systemic mastocytosis.
Notes: Percentages are based on the number of patients in the Updated Safety Population in each column.
Preferred terms are sorted in decreasing order of frequency using the AdvSM 200 mg column.
If a patient experienced more than 1 event within a given preferred term, that patient was counted only once under that preferred term.
Source: Updated Table 18.3.3.1.9.2.

There were no meaningful differences in the incidences of AEs leading to dose interruption and dose reduction between the 200 mg original group and 200 mg extended group.

2.6.8.9. Post marketing experience

Avapritinib was first approved in the US on 09 January 2020 by the FDA for the treatment of adults with unresectable or metastatic GIST harbouring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations. The approved pharmaceutical strengths of avapritinib are 100 mg, 200 mg, and 300 mg tablets.
Cumulatively as of 20 April 2021, 238 unique patients (verified unique through specialty pharmacy and HUB) have received commercial AYVAKIT/AYVAKYT globally, for an overall estimated exposure of 125.08 patient-years. Overall, 3,021 AEs in 768 case reports have been reported for avapritinib in the post-marketing setting through 20 April 2021. The most frequently reported AEs are fatigue (146 case reports), nausea (120 case reports) and diarrhoea (96 case reports), similar to observations in clinical trials of GIST and AdvSM. AEs reported in ≥ 20 case are shown in Table 16. The majority of AEs reported in the post-marketing setting are consumer reports that are not medically confirmed, and therefore, AE severity is not usually reported. No data can be provided on Grade ≥ 3 AEs. Additional details on the post-marketing safety of avapritinib will be provided in Periodic Safety Update Report #02 (data lock point 08 July 2021), which was submitted on 16 September 2021.

Table 74 Post-Marketing AEs reported in ≥ 20 Case Reports

Preferred Terms	PT Count & Case reports N=768
Fatigue	146
Nausea	120
Diarrhoea	96
Off label use	81
Memory impairment	64
Swelling face	53
Vomiting	53
Decreased appetite	53
Peripheral swelling	48
Drug ineffective	48
Dizziness	47
Asthenia	44
Insomnia	41
Lacrimation increased	40
Headache	38
Eye swelling	35
Rash	32
Cognitive disorder	29
Fall	26
Anaemia	26
Confusional state	25
Product dose omission issue	24
Hair colour changes	23
Death	23
Abdominal distension	22
Abdominal pain upper	21
Constipation	21
Feeling abnormal	21
Neoplasm progression	20

Abbreviations: AE = adverse event, PT = preferred terms
Source: Safety database

All Serious Post-Marketing AEs:

Cumulatively, 366 SAEs in 205 case reports have been reported in the post-marketing setting of avapritinib. The most frequently reported SAEs are death (23 case reports), fall (9 case reports) and dementia (9 case reports). Most death cases contain very limited information and do not provide consent for follow-up; therefore, complete medical assessment cannot be performed. SAEs reported in ≥ 5 case reports are shown in Table 17.

Table 75 Post-Marketing SAEs reported ≥ 5 Case Reports

Preferred Term	PT Count & Case reports N=768
Death	23
Fall	9
Dementia	9
Vomiting	8
Diarrhoea	8
Pleural effusion	7
Anaemia	7
Tumour excision	7
Hospitalisation	6
Neoplasm	6
Hallucination	6
Cataract	5
Pulmonary oedema	5
Diabetes mellitus	5
Seizure	5
Dyspnoea	5
Haemorrhage	5

Abbreviations: PT = preferred term, SAE = serious adverse events
Source: Safety database

2.6.9. Discussion on clinical safety

The present application is seeking approval for an extension of the indication to treatment of adult patients with AdvSM, including ASM, SM-AHN, and MCL, after at least 1 systemic therapy. The recommended dose of avapritinib is 200 mg once daily (QD), with the possibility to perform dose adjustment down based on tolerability.

To support this variation, the Applicant originally provided safety data from 2 studies in patients with AdvSM (studies BLU-285-2101 and BLU-285-2202) and updated safety data from patients with GIST. For the purpose of the present assessment, the subset of AdvSm patients treated with avapritinib 200mg QD is considered to be the main safety population, whereas data pooling all avapritinib doses used in patients with AdvSM are considered supportive.

During the procedure, the Applicant has provided a safety update with a cut-off date of 20 April 2021, which amounts to approximately 10 additional months of follow-up for the patients included in the original submission. As a result, the safety population is now composed by 193 patients that received at least one avapritinib dose, 126 of them treated with 200mg QD (81 from the original submission, 45 new ones), and 50 patients treated with 300mg QD. The 23-patient difference between the "all treated" patient cohort and the sum of the dose cohorts appears to be due to only 176 patients having their diagnoses confirmed centrally. No new patients have been included in the 300mg QD starting dose group.

Patient exposure

Among the 126 patients treated with 200mg QD (the "200mg QD extended group"), the median duration of treatment with avapritinib was 41.00 weeks (range 0.9-188.1); for the 81 patients originally treated with 200mg QD, the median updated treatment duration was 67.14 weeks (range: 0.9-188.1), which amounts to approximately 37 additional weeks of exposure.

Although the overall size of the AdvSM safety database is small, the inclusion of 45 new patients to the 200 mg QD group is welcomed. The safety update also increased follow-up time and median treatment duration. Nevertheless, the uncontrolled nature of the study design poses some limitations for an adequate characterization of the safety profile of avapritinib in the intended indication, in particular, making the AE causality assessment difficult.

With the most recent cut-off date, a total of 38 (30.2%) of the 126 patients treated with avapritinib 200mg QD had discontinued treatment, the primary reason for discontinuation of treatment being AE (23 patients, 18.3%), followed by withdrawal of consent (6 patients, 4.8%) and disease progression (5 patients, 4.0%).

Overall, avapritinib appears to be tolerated acceptably at the 200mg QD dose (intended for this indication), while the 300mg QD dose is no longer sought by the MAH due to poor tolerance. The possibility to decrease/interrupt doses, permitted as a way to manage toxicities, appears to be a useful tool, with treatment discontinuations due to AE around 18% (for the 200mg QD extended group).

Regarding the population included, it appears to be representative of the intended target population, although some baseline differences in medical history were noted between the ≥300 mg and 200 mg AdvSM populations, which could be interpreted as a better baseline status in 200 mg AdvSM population and could contribute to the apparent higher tolerability of 200 mg compared to ≥300 mg. Even if differences in health status cannot be excluded as a contributing factor, the same types of AEs are observed in both dose groups. Apart from the AESIs that are discussed separately, uncertainties in assigned frequencies to AEs due to other health factors are not expected to affect the characterization of risks in a clinically significant manner.

Adverse events

All **AdvSM patients treated at 200 mg QD** in the updated safety analysis experienced at least 1 AE, and 78 (96.3 %) experienced AEs related to avapritinib, which is similar to data from the initial submission.

In comparison with the original data, the frequencies of AEs, grade ≥3 AEs and SAEs appeared to increase over time. For example, the frequencies in the original 200 mg group (updated/initial data) of SAEs (44.4%/33.3%), related SAEs (16.0%/11.1%), grade ≥3 AEs (79.0%/71.6%) and related grade ≥3 AEs (63.0%/54.3%) have all increased. However, these numbers are lower than the numbers in the ≥300 mg group, both compared to initial and updated data, which are similar: SAEs (updated/initial 74.0%/72.0%), related SAEs (32.0%/32.0%), grade ≥3 AEs (94.0%/94.0%) and related grade ≥3 AEs (74.0%/74.0%).

The most **common AEs** (reported in > 20% of 200mg QD patients) were peripheral oedema (42.9%), anaemia (40.5%), periorbital oedema (39.7%), thrombocytopenia (39.7%), diarrhoea (27.8 %) and nausea (23.8 %).

The most common (≥ 5%) **Grade ≥ 3 AEs** in the 200mg QD extended group were anaemia (21.4%), thrombocytopenia (18.3%), and neutropenia (16.7%), , neutrophil count decreased (57.9%), and platelet count decreased (6.3 %)

The most **common SAEs** were anaemia (4 patients, 3.2 %), subdural haematoma (4 patients, 3.2 %), ascites (3 patients, 2.4 %). The most common **related SAEs** were subdural haematoma (3 patients, 2.4 %), anaemia and hamorrhage (2 patients, 1.6 % each).

Overall, 18.5% of patients (200mg QD extended group) experience an **AE leading to treatment discontinuation**, the most frequent were thrombocytopenia and subdural haematoma (3 patients, 2.4 % each), while the proportion of patients with any **AEs leading to dose interruption or dose reductions** were 69.1% and 74.1%, respectively. The most common AEs leading to dose interruptions were: thrombocytopenia (17.5%), neutropenia (11.1%), anaemia (6.3%) and cognitive disorder (6.3%). The most common AEs leading

to dose reductions were: thrombocytopenia (19.0%), periorbital oedema (7.9 %), neutropenia (9.5%), oedema peripheral (7.1 %), cognitive disorder (6.3%) and platelet count decreased (6.3 %).

In this (200 mg) dose group, 5 (6.2%) patients **died due to AEs**, none of them considered related to avapritinib. One avapritinib-related death was reported in the ≥300 mg group (intracranial bleeding).

The incidence of SAEs, Grade ≥ 3 AEs, AEs leading to discontinuation of treatment, AEs leading to dose interruption, AEs leading to dose reduction, was generally higher for AdvSM patients treated with ≥300 mg QD (and all-dose group) compared with patients treated at 200 mg QD. Likewise, the incidence of AEs leading to death was slightly lower for AdvSM patients treated at 200 mg QD than for AdvSM patients treated at ≥300 mg QD.

Overall, these findings point to a worse tolerance for the ≥300mg QD dose, supporting the proposed initial dosing of 200mg QD.

The safety profile of avapritinib in AdvSM patients appears to be mostly consistent with the one previously observed in the GIST indication and in line with other TKIs.

AESIs

Intracranial bleeding is an important identified risk for avapritinib treatment, included in the RMP and followed in the post-marketing by means of routine Pharmacovigilance and 2 PAES. In general, intracranial haemorrhage can lead to marked mortality and morbidity. This type of event is a serious adverse event that has been reported for certain other TKIs and could, hypothetically, be pharmacologically driven through the inhibition of PDGFRβ, which plays a role in pericyte development and integrity.

In the original submission, 7.4% of AdvSM patients (11/148) experienced intracranial bleeding events (6 AE subdural haematoma and 5 haemorrhage intracranial). Eight patients experienced ≥1 serious events, most of them grade 1-2. The incidence of intracranial bleeding was significantly higher in patients with AdvSM (≥300 mg: 16.0 %, 200 mg: 3.7 %, All doses: 7.4%) than the one observed in patients with GIST (1.8%), which is a worrisome safety concern. For the AdvSM studies, the Applicant implemented some risk mitigation strategies (exclusion of patients with a platelet count < 50,000/μL at baseline, periodic platelet count monitoring, dose modifications, and defining a lower starting dose [200 mg QD]). To validate the effectiveness of these risk minimization measures (RMM) and to exclude the possibility that the frequency of ICB in the 200 mg group was underestimated compared to the ≥300 mg group due to shorter treatment duration (200 mg: 30.29 weeks vs ≥300 mg: 89.64 weeks), the Applicant was requested to provide updated safety data in the response.

With the provided safety update, only one additional case of ICB has been reported (occurred in the AdvSM 200 mg extended group). Severe thrombocytopenia (platelet count < 50,000/μL) was identified as the primary risk factor for intracranial bleeding in AdvSM. Most intracranial bleeding events in AdvSM patients (83.3%; 10 of 12 patients) have been associated with severe thrombocytopenia (platelet count < 50,000/μL) prior to or at the time of the event. Two additional reports were received in the post-marketing setting, both of them after the patients had experienced a fall. The review of the individual ICB cases occurred in the AdvSM and GIST studies (data not shown) indicated that most patients had confounders.

In the original safety analysis, the incidences of ICB in the 200 mg AdvSM group were 3.7 % (n = 3) overall and 2.6 % (n = 2) when patients with pre-existing severe thrombocytopenia were excluded. In the updated analysis, the corresponding numbers were 3.2 % and 2.5%, respectively. This supports the effectiveness of the risk minimization measures implemented, since a lower number of cases were observed after their implementation into the studies. Further, the incidence of ICB appears to be reliably constant in the 200 mg group, which is reassuring. Although follow up is longer in the ≥ 300 mg group overall, greater, or similar

numbers of patients have experienced the 200 mg starting dose up to almost 20 months of therapy, the time frame in which nearly all ICB events occurred (usually within 6 months). The overall shorter duration of treatment for patients in the 200 mg group was unlikely to lead to underestimation of the incidence of ICBs. Thus, the estimates of the incidences are considered to be acceptably accurate.

Since the risk of ICB is an important safety issue, the wording originally included in the SmPC was revised during the procedure in order to properly reflect this risk and the importance of platelet monitoring and (starting and maximum) dose.

Further, since determining causality in cases of ICB in AdvSM patients is particularly challenging, and in order to account for any uncertainties considering the gravity of these events, in the final text agreed for the SmPC all cases (all causality) and related cases are presented.

Cognitive effects are also an important identified risk, incidence in the 200mg QD group went from 14.8% in the original submission to 19.0% in the update, compared to 56 % in the ≥300 mg group. The most frequent AESIs in this group were cognitive disorder (11.9%), memory impairment (5.6%) and confusional state (2.4%). Most of these AESI were mild-moderate in intensity and very few led to the permanent discontinuation of avapritinib. The MAH has provided a listing with the individual cognitive effect AESIs occurred in the AdvSM and GIST indications (data not shown). A large proportion of the patients presented confounders, such as prior neuropsychiatric history or medicines with a CNS depressor effect. At this time, the mechanism behind these effects is not known. Currently available data suggest that for the most part, they are mild-moderate in intensity, manageable by dose adjustment with a very low incidence of permanent discontinuations, but resolution may be slow (weeks to months).

Safety data in **elderly patients** (≥65 years old) is limited. Data suggest that avapritinib could be worse tolerated in the elderly population than in younger adults, however, the numbers in some of the subgroups are small, particularly for patients over 75 years of age. It is agreed that some of the risks identified for avapritinib (e.g., oedema, cognitive effects, cytopenias, among others) may also occur more frequently in the elderly population than in younger adults. These risks and their management have been addressed either in the SmPC (sections 4.2, 4.4, 4.8) or the RMP (e.g., as important identified or potential risks). Overall, no new signals or concerning findings have been identified. The SmPC has been revised to reflect that grade ≥3 AEs occur more frequently in the elderly.

Changes in laboratory parameters, including liver function parameters (i.e., bilirubin, transaminases, alkaline phosphatase), blood counts (anemia, neutropenia, mainly) have been observed during avapritinib therapy. No new or alarming concerns have been identified.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

The characterization of the safety prolife of avapritinib in the intended indication present two main limitations: the size of the safety database in patients with AdvSM is small and the AdvSM safety database mainly derives from 2 uncontrolled, on-going studies. As a result, there are some uncertainties related to these limitations. Prior knowledge on the safety of avapritinib in the GIST indication and its similarities to other TKIs may alleviate these concerns to some extent.

The overall incidence of adverse events (100%), severe AEs (81.9%) and SAEs (50.3%) in the overall AdvSM patient population was high, suggesting that avapritinib is poorly tolerated, especially at higher doses. Toxicities due to the 200mg QD, for the most part, appear to be acceptably tolerated and manageable with dose modification. In addition, the safety profile is mostly consistent to that previously reported for other TKIs, with the exception of intracranial bleedings and cognitive disorders. The incidences of these events are concerning, but they have been addressed through risk mitigation measures (dose adjustments and platelet monitoring in the case of ICBs), which are considered acceptable.

In summary, the overall safety profile of avapritinib appears consistent with that seen in other indications and similar to other TKIs.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 76 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Intracranial haemorrhage Cognitive effects Drug-drug interactions with moderate or strong CYP3A inhibitors or inducers
Important potential risks	Cardiac toxicity, including QT prolongation Embryofoetal toxicity
Missing information	Use in patients with severe hepatic impairment Drug-drug interactions with CYP3A substrates

2.7.2. Pharmacovigilance plan

Table 77 Ongoing and Planned Additional Pharmacovigilance Activities

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/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Study BLU-285-1406 "Observational study evaluating safety and efficacy of avapritinib in the first-line treatment of patients with Platelet derived Growth Factor Alpha D842V mutated gastrointestinal stromal tumor" Planned	Primary objective: – To evaluate long-term safety Secondary objective: – To evaluate long-term efficacy	– 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	– Interim reports	– Annually within the annual renewal (starting with the second annual renewal)
			– Final clinical study report	– December 2027
Category 3 – required additional pharmacovigilance activities				
Study BLU-285-0107 "A Phase 1, open-label, single-dose study to investigate the influence of severe hepatic impairment on the pharmacokinetics of avapritinib (BLU-285)" Planned	Primary objective: – To characterise the pharmacokinetics of avapritinib in patients with severe hepatic impairment Secondary objective: – To evaluate the safety and tolerability of avapritinib in subjects with severe hepatic impairment	– Use in patients with severe hepatic impairment	– Study completion	– Q3 2023
			– Final clinical study report	– March 2024
DDI study "Clinical drug-drug interaction study of avapritinib with a CYP3A substrate" Planned	– 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 2023
			– Final clinical study report	– May 2024

2.7.3. Risk minimisation measures

Table 78 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Intracranial haemorrhage	Routine risk minimisation measures: – SmPC sections 4.2, 4.4 and 4.8 – PL sections 2 and 4 Recommendation to perform brain imaging by MRI or CT if the patient experiences clinically relevant neurological signs and symptoms (e.g. severe headache, vision problems, somnolence, or focal weakness) is included in SmPC section 4.4 and PL section 4. Recommendation to permanently discontinue treatment if intracranial haemorrhage of any grade occurs is included in SmPC sections 4.2 and 4.4. Recommendation to interrupt dosing in patients with AdvSM until platelet count is ≥50 × 10^9/L, then resume at reduced dose, is included in SmPC section 4.2. Recommendation for platelet support in patients with AdvSM if the platelet count does not recover above 50 × 10^9/L is included in SmPC section 4.2. Recommendations for platelet count monitoring in patients with AdvSM are included in SmPC section 4.4. Recommendation to temporarily stop treatment and contact treating physician if symptoms such as severe headache, vision problems, severe sleepiness, or severe weakness on one side of the body (signs of bleeding in the brain) occur is included in 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: – Study BLU-285-1406 (final study report: December 2027) This risk will be evaluated in Study BLU-285-1406. The PAES BLU-285-1101 will provide further information.
Cognitive effects	Routine risk minimisation measures: – SmPC sections 4.2, 4.4, 4.7 and 4.8 – PL sections 2 and 4 Recommendations for dose modification in case of Grade 1-Grade 3 events is included in SmPC section 4.2 . Recommendation to permanently discontinue therapy if Grade 4 cognitive effects occur is included in SmPC section 4.2. Restricted prescription medicine	Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting: – Follow-up questionnaire Additional pharmacovigilance activities: – Study BLU-285-1406 (final study report: December 2027) This risk will be evaluated in Study BLU-285-1406. The PAES

Table 78 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Additional risk minimisation measures: None	BLU-285-1101 will provide further information.
Drug-drug interactions with moderate or strong CYP3A inhibitors or inducers	Routine risk minimisation measures: – SmPC sections 4.2, 4.4, 4.5, and 5.2 – PL section 2 If concomitant use with a moderate CYP3A inhibitor cannot be avoided, the starting dose of avapritinib should be reduced from 300 mg orally QD to 100 mg orally QD for patients with GIST, and from 200 mg orally QD to 50 mg orally QD for patients with AdvSM, as stated in SmPC section 4.2. Restricted prescription medicine Additional risk minimisation measures: None	Additional pharmacovigilance activities: – Study BLU-285-1406 (final study report: December 2027) This risk will be evaluated in Study BLU-285-1406. The PAES BLU-285-1101 will provide further information.
Cardiac toxicity, including QT prolongation	Routine risk minimisation measures: – SmPC sections 4.4, 4.8 and 5.1 – PL sections 2 and 4 Recommendation for interval assessments of QT by electrocardiography if avapritinib is taken concurrently with medicinal products that can prolong the QT interval, is included in SmPC section 4.4. Restricted prescription medicine Additional risk minimisation measures: None	Additional pharmacovigilance activities: – Study BLU-285-1406 (final study report: December 2027) This risk will be evaluated in Study BLU-285-1406. The PAES BLU-285-1101 will provide further information.
Embryofoetal toxicity	Routine risk minimisation measures: – SmPC sections 4.6 and 5.3 – PL section 2 Recommendation for use of effective contraception during and after treatment in SmPC section 4.6 and PL section 2. Restricted prescription medicine Additional risk minimisation measures: None	Additional pharmacovigilance activities: – Study BLU-285-1406 (final study report: December 2027) This risk will be evaluated in Study BLU-285-1406. The PAES BLU-285-1101 will provide further information.
Use in patients with severe hepatic impairment	Routine risk minimisation measures: – SmPC sections 4.2 and 5.2 Restricted prescription medicine Additional risk minimisation measures: None	Additional pharmacovigilance activities: – Study BLU-285-1406 (final study report: December 2027) – Study BLU-285-0107 (final study report: March 2024) This missing information will be evaluated in studies outlined

Table 78 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		above. The PAES BLU-285-1101 will provide further information.
Drug-drug interaction with CYP3A substrates	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: December 2027) – DDI study (final study report: May 2024) This missing information will be evaluated in studies outlined above. The PAES BLU-285-1101 will provide further information.

2.7.4. Conclusion

The CHMP considered that the risk management plan version 1.3 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

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.

2.9. Product information

2.9.1. 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.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, AYVAKYT (avapritinib) is included in the additional monitoring list as it is approved under a conditional marketing authorisation [REG Art 14-a]

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

The current MAA is a grouped application involving both a line extension for two additional strengths (25 mg and 50 mg) of avapritinib and an extension of indication (AdvSM). For the benefit risk assessment concerning the extension of indication, see section below.

Line extension

Avapritinib is currently available as an immediate-release tablet for the following strengths 100, 200 and 300 mg.

The MAH has now applied for two additional strengths to be approved: 25 mg and 50 mg in order to approve the dosing scheme required for the EoI in advanced systemic mastocytosis. The supporting clinical data showed that dose-reductions based on tolerability are recommended, with the dose reduction scheme 200mg-100mg-50mg-25mg. These scheme explains the need for the new strengths

The new strengths are considered approvable from a quality perspective.

In order to demonstrate that the new strengths are bioequivalent to the currently approved strengths, the MAH has not submitted clinical bioequivalence studies, but instead presented a rationale for a strength-based waiver for the 25 mg and 50 mg tablets. The CHMP Guideline on investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) lists general criteria that must be met for a strength-based biowaiver to be approvable. The MAH has demonstrated that these are met: i.e.: same manufacturing process, identical qualitative composition of the different strengths, quantitatively proportional compositions between the previously approved strengths and the two new strengths, and appropriate *in vitro* dissolution data. Dose proportionality of avapritinib was confirmed over the dose rage of 25 – 100 mg and supports the biowaiver for 25 and 50 mg tablet strength.

Based on the above the new strengths i.e. avapritinib 25 mg and 50 mg immediate-release tablets, are considered approvable.

Extension of indication

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication is:

"AYVAKYT is indicated as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), after at least one systemic therapy."

Systemic mastocytosis (SM) is a clonal mast cell neoplasm, driven by the KIT D816V mutation, where abnormal activation of MC leads to debilitating and life-threatening symptoms. To set the diagnosis of systemic mastocytosis, certain criteria must be met. Either one major plus one minor criterium or 3 minor criteria have to be fulfilled. Major criterion: dense infiltrates of >15 mast cells in the bone marrow or an extracutaneous organ. Minor criteria: aberrant phenotype on the mast cells (positivity for CD2 and/or CD25), aberrant mast cell morphology (spindle-shaped), finding of mutation in KIT(D816V) and S-tryptase >20 ng/ml.

SM can be broadly divided into non-advanced and advanced SM, on the basis of so-called B- and C-findings in these patients. AdvSM encompasses a group of high-risk subtypes with a poor prognosis, including ASM, SM-AHN, and MCL. SM with the copresence of an associated haematological neoplasm (SM-AHN) comprises the

majority of AdvSM cases. The AHN component is typically myeloid, including CMML, MDS, MPN, CEL, and AML. SM-AHN commonly presents with C-findings. SM with C-findings, but without additional adverse pathologic features, is rare and known as aggressive systemic mastocyotsis (ASM). The presence of excess (≥ 20%) MCs in the BM aspirate smear is characteristic of a rare, highly aggressive SM variant known as MCL. MCL commonly presents with C-findings and can co-occur with AHN.

Although heterogeneity characterizes the clinical presentation and prognosis of SM, the pathogenesis is largely shared, with D816 mutations in KIT found in 93% of SM cases, regardless of subtype (Garcia-Montero et al, 2006).

3.1.2. Available therapies and unmet medical need

Patients with AdvSM have limited treatment options. Current recommended therapies include midostaurin (approved in the EU and the US), cladribine and interferon alfa (both used off-label), and imatinib (approved in the US only for a small subset of adult patients with ASM without KIT D816V or with unknown KIT mutation status).

Despite the approval of midostaurin for treatment of AdvSM in 2017, cladribine is still recommended for patients who need rapid debulking or have to discontinue midostaurin due to toxicity, and interferon is recommended for patients with slow PD without the need for rapid cytoreduction (Pardanani, 2019).

However, MC burden has proven difficult to eradicate with current therapies, and thus improvement in symptoms of organ damage, rather than MC burden reduction, has historically been the endpoint used in assessing response in AdvSM. Current therapies improve organ damage in 35% to 70% of patients (per Valent consensus criteria), but these responses are often not durable, and CR is rare. BM MC burden and elevations in serum tryptase typically persist both during and after therapy (Pardanani, 2021)..Cladribine, interferon alfa, and imatinib may be effective in some patients with AdvSM, but complete responses are rarely achieved and the symptom relief they provide is often transitory. On the other hand, currently used systemic therapies are often associated with significant, sometimes life-threatening, side effects. (Pardanani, 2021).

While midostaurin provides proof of principle for targeting KIT D816V as a disease-driver mutation in AdvSM, most responses to treatment are incomplete and/or not sustained

Overall, given the poor survival with the current standard of care, and the modest activity and tolerability of currently used therapies, there is a need for more treatment options for patients with AdvSM.

3.1.3. Main clinical studies

This application is based on the efficacy results from the ongoing phase 2, open-label, single-arm, 2-cohort **study BLU-285-2202** (PATHFINDER) n=107) and supported by the phase 1, open-label dose escalation **study BLU-285-2101** (EXPLORER) (n=86) as described below. The studies were conducted in countries in Europe and North America. Both studies include patients with prior systemic therapy as well as treatment-naïve patients.

Study BLU-285-2101 (EXPLORER) is an ongoing, open-label, Phase 1 study designed to evaluate the safety, tolerability, PK, pharmacodynamics, and antineoplastic activity (efficacy) of avapritinib, administered orally, in adult patients with AdvSM and relapsed or refractory myeloid malignancies. As of the data cut-off date of 27 May 2020, enrolment in the study is complete at 86 patients and patients remaining on study are being followed for response and safety assessments.

The primary objective was to establish the maximum tolerated dose and the recommended Phase 2 dose.

This 2-part study included:

- an initial **dose escalation** (**Part 1**, complete) to evaluate safety and tolerability of increasing doses of avapritinib (from 30 to 400 mg QD) in patients with a local diagnosis of AdvSM or other relapsed or refractory myeloid malignancies,
- and an **expansion** (**Part 2**, ongoing) to further evaluate the safety, PK, pharmacodynamics, and efficacy (according to mIWG-MRT-ECNM response criteria) of avapritinib in the treatment of AdvSM when administered at starting doses of 200 or 300 mg QD.

Part 2 enrolled patients with a WHO diagnosis of AdvSM.

The main **study BLU-285-2202** (PATHFINDER) is an ongoing, open-label, single-arm, Phase 2 study evaluating the efficacy and safety of avapritinib 200 mg QD in patients with a WHO diagnosis of AdvSM. Patients with a centrally confirmed WHO diagnosis of AdvSM were enrolled into 1 of 2 cohorts:

- **Cohort 1:** patients with ≥ 1 mIWG-MRT-ECNM criteria for evaluable disease (with an evaluable C-finding or MCL), as determined by the Study Steering Committee (SSC) (n=85).
- **Cohort 2:** patients who were not considered eligible for an adjudicated mIWG-MRT-ECNM response, as determined by the SSC (n=22).

Patients in **Cohort 1 support the primary objective of determining SSC-adjudicated ORR by mIWG-MRT-ECNM criteria.** Both cohorts are included in the analyses of secondary and exploratory efficacy objectives.

A pre-planned **interim analysis** was performed when 32 patients enrolled in Cohort 1 were considered evaluable for response. Results of this interim analysis were included as part of the initial submission. At that time the population evaluable for the primary endpoint (RE Population), i.e. ORR by mIWG-MRT-ECNM criteria, included 32 patients (Cohort 1), (DCO for the interim analysis 23 June 2020), with 23 patients having received prior systemic therapy and enrolment ongoing. Follow-up was limited. Updated data with a DCO of 20 April 2021 and including 42 additional RE patients, , were submitted during the procedure, thus providing approximately 10 months of additional follow-up. Twenty six out of the new 42 patients had received prior systemic therapy. The combined IA and post IA population (n=74 patients) therefore includes 49 patients who had received at least one prior systemic therapy out of which 47 patients at an initial dose of 200 mg, which is the population of interest. Median follow-up for the updated IA population, post-IA population and combined populations (having received at least one prior systemic therapy) are 20.7, 9.9 and 14.6 months, respectively.

3.2. Favourable effects

Pivotal study BLU-285-2202 – combined IA and post IA RE population having received at least one prior systemic therapy, DCO 20 April 2021

- ORR by mIWG-MRT-ECNM criteria (primary endpoint): 59.6% (95%CI=44.3, 73.6) (n=47)
- DOR was not reached, with a probability of ongoing response at 12 months of 100%.
- ORR by pure pathological response (PPR) criteria was 52.5% (95%CI=39.1, 65.7%) (n=59)
- Individual measures of mast cell burden, including bone marrow mast cells, serum tryptase, KIT D816V mutant allele fraction and spleen and liver volume, showed improvement.

Supportive study BLU-285-2101 – RE patients having received at least one prior systemic therapy, starting dose 200 mg QD, DCO 20 April 2021.

- ORR by mIWG-MRT-ECNM criteria of 72.7% (95%CI=39.0, 94.0%) (n=11)
- DOR was not reached

.

3.3. Uncertainties and limitations about favourable effects

Both studies BLU-285-2101 and BLU-285-2202 are uncontrolled single arm trials with associated well known limitations, e.g. risk of selection bias and potential overestimation of the effect. In addition, the number of patients, even considering data from new patients submitted during the procedure, is low, especially considering the three different disease entities/subgroups (of very different prognosis) that have been included. The reported ORR data from study BLU-285-2202 submitted in the initial application and updated data submitted during the procedure are considered to be overall consistent although follow-up time remains limited particularly in the newly enrolled patients / post-IA patient population. Median DoR is still not reached. Therefore, the applicant is recommended to submit the final clinical study report from study BLU-285-2202, anticipated to be available in December 2026 (REC).

Besides data being currently immature, interpretation of time to event endpoints, in particular PFS and OS, is hampered in the context of a single arm trial and should therefore be considered with caution. Even if follow-up is still short, particularly in newly included patients, with median DOR not yet reached, (updated) efficacy data currently available show that clinically relevant responses can be obtained with avapritinib treatment in AdvSM patients after at least one systemic treatment in whom an improvement in symptoms and control of the disease can be considered to represent clinical benefit

In the absence of an RCT, comparison with an external control, efficacy data from the midostaurin registrational trial (CPKC412D2201), was performed. The direct comparability of the patients in these two trials, as well as their management, cannot be ensured. In addition, the criteria used for assessment of response in the avapritinib trials (mIWG-MRT-ECNM) are distinct from the criteria used for evaluation of efficacy in the midostaurin trial (IWG-MRT-ECNM). For the RWE retrospective trial, BLU-285-2405, similar issues with ensuring comparability of the patient populations apply.

The addition of an interim analysis for the phase 2 trial was triggered post-hoc. The interim analysis was included in the protocol plan almost 7 months after the start of the recruitment (protocol amendment 3, 18 June 2019). The single arm design poses further concerns since this change can be considered data-driven, and therefore, no formal adjustment for inference is feasible. Consequently, results should be interpreted with caution since there is no type I error control in this scenario.

In the SmPC, dose-reductions based on tolerability are recommended, with the dose reduction scheme 200mg-100mg-50mg-25mg. No exposure-response relationship has been characterised, and there are limited data available for the efficacy at the lower doses in patients that have received dose reductions. However ORR in study BLU-285-2202 was promising despite the majority of patients had a dose reduction”

3.4. Unfavourable effects

The most common adverse reactions of any grade during treatment with AYVAKYT at a starting dose of 200 mg were periorbital oedema (38%), thrombocytopenia (37%), oedema peripheral (33%), and anaemia (22%).

Serious adverse reactions occurred in 12% of patients receiving avapritinib. The most common serious adverse reactions during treatment with avapritinib were subdural haematoma (2%), anaemia (2%), and haemorrhage (2%).

In AdvSM patients treated at 200 mg, 7.1% had adverse reactions leading to permanent treatment discontinuation. In two patients (1.6%), subdural haematoma occurred. Cognitive disorder, depressed mood, diarrhoea, disturbance in attention, haemoglobin decreased, hair colour changes, libido decreased, nausea, neutropenia, premature menopause and thrombocytopenia occurred in one patient (0.8% each). Adverse reactions leading to a dose reduction included thrombocytopenia, neutropenia, periorbital oedema, cognitive disorder, oedema peripheral, platelet count decreased, neutrophil count decreased, anaemia, asthenia, fatigue, arthralgia, blood alkaline phosphatase increased, blood bilirubin increased, and white blood cell count decreased."

Overall, 18.5% of patients (200mg QD extended group) experience an **AE leading to treatment discontinuation**, while the proportion of patients with any **AEs leading to dose interruption or dose reductions** were 69.1% and 74.1%, respectively.

The most common AEs leading to discontinuation were thrombocytopenia and subdural haematoma (3 patients, 2.4 % each). The most common AEs leading to dose interruptions were thrombocytopenia (17.5%), neutropenia (11.1%), anaemia (6.3%) and cognitive disorder (6.3%). The most common AEs leading to dose reductions were thrombocytopenia (19.0%), periorbital oedema (7.9 %), neutropenia (9.5%), oedema peripheral (7.1 %), cognitive disorder (6.3%) and platelet count decreased (6.3 %).

Cognitive effects and intracranial bleedings were considered AESI and were reported by 24 (19.0%) and 4 (3.2%) of AdvSM patients treated in the 200mg QD extended group, respectively, a majority of the cases were considered as treatment-related.

3.5. Uncertainties and limitations about unfavourable effects

The main limitations of the safety database are related to the small size (126 AdvSM patients treated with the intended 200mg QD dose, 193 overall), and difficulties in establishing a causal relationship with avapritinib for key adverse events in the context of non-controlled, on-going studies and of a severe underlying condition.

Thus, there are some uncertainties related to these limitations. However, prior knowledge on the GIST indication and similarities observed in the safety profile alleviate this concern to some extent.

Events of intracranial bleedings (ICB) can cause severe morbidity and mortality. Underlying mechanisms of how avapritinib cause intracranial haemorrhage are not understood. The increased prevalence of intracranial bleedings in AdvSM patients (≥300 mg group: 16.0 %, 200 mg group: 3.2 %) compared to GIST patients (1.8 %) is attributed, in part, to thrombocytopenia. Reduction of the starting dose to 200 mg, platelet monitoring and treatment interruption for levels < 50,000/µL were implemented to mitigate the risk of ICB (see section 4.2 and 4.4 of the SmPC).

A mechanistic understanding of how avapritinib induces cognitive effects is lacking, but these AEs are very frequently reported. It appears that cognitive effects manifest for many patients within study week 30, but may debut late (> 1 year). Resolution is slow and partial (the probability of resolution of a grade ≥2 event was 50 % by 24.1 weeks). It is not fully elucidated to what extent this affects normal life.

Overall, the safety profile is consistent to that previously reported for the GIST indication, with the exception of ICBs and cognitive effects. These events are important safety concerns, but they are now considered to be adequately addressed with the proposed risk minimisation measures, updated text in the SmPC and through post-marketing studies

3.6. Effects Table

Table 79 Effects Table for avapritinib in patients with advanced systemic mastocytosis (data cut-off: 20 April 2021).

Effect Short Description	Unit	Avapritinib				Uncertainties/ Strength of evidence	References
Favourable Effects - Data correspond to the RE population according to modified IWG-MRT-ECNM following at least one prior systemic therapy, starting dose 200 mg QD*							
		ASM	**SM-AHN**	**MCL**	**Overall**		
Number of subjects	**N**	8	29	10	47		
ORR by mIWG-MRT-ECNM criteria Overall response rate by mIWG-MRT-ECNM criteria	n (%) (95% CI)	5 (62.5) (24.5, 91.5)	19 (65.5) (45.7, 82.1)	4 (40.0) (12.2,73.8)	28 (59.6) (44.3, 73.6)	Data coming from BLU-285-2202, i.e.uncontrolled, open-label study of small sample size. Overestimation of the effect cannot be ruled out	Updated data provided
CR+CRh+PR rate	n (%) (95% CI)	5 (62.5) (24.5, 91.5)	16 (55.2) (35.7,73.6)	3 (30.0) (6.7-65.2)	24 (51.1) (36.1, 65.9)		
CR Complete remission	n (%)	0	1 (3.4)	0	1 (2.1)		
CRh CR with partial recovery of peripheral blood counts	n (%)	2 (25)	2 (6.9)	0	4 (8.5)		
PR Partial remission	n (%)	3 (37.5)	13 (44.8)	3 (30)	19 (40.4)		
CI Clinical improvement	n (%)	0	3 (10.3)	1 (10)	4 (8.5)		
DOR (months) Duration of response	median, (95%CI)	NE	NE	NE	NE		
DOR rate at 12 months	(%)	100	100	100	100		

Effect Short Description		Unit	Avapritinib				Uncertainties/ Strength of evidence	References
TTR (months) Time to Response		median (range)	2.30 (1.8, 5.5)	1.94 (0.5, 5.5)	3.60 (1.7, 12.2)	1.94 (0.5, 12.2)		
		Unfavourable Effects						
General Safety profile (200mg QD)		%						
	≥G3 AEs	75.4						
	SAEs	38.1						
	AEs leading to death	3.7						
	AE leading to treatment discontinuation	18.3)[1]						
	AE leading to dose reductions	72.2						
	AE leading to dose interruptions	69.1						
Adverse events of special interest	Intracranial bleedings	3.2						
	Cognitive effects	19.0						

Abbreviations: DOR = duration of response, CR = complete remission, CRh = complete hematologic remission, DOR = duration of response, IWG-MRT-ECNM = International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis, NA = not available, NE = not estimable, ORR = overall response rate, PFS = progression free survival, PR = partial remission, TTR = time to response

[1] see Table 45

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The reported ORR by centrally adjudicated mIWG-MRT-ECNM criteria for avapritinib in patients with a rare and aggressive disease such as AdvMS previously treated with at least one systemic therapy, i.e. with limited treatment alternatives, is considered promising and expected to translate into clinically meaningful benefit, in particular if supported by long duration of achieved responses. Median DOR has not been reached which can be interpreted as encouraging but also reinforces the need for additional follow-up data to confirm long-term benefit. This noted, currently available efficacy data show that clinically relevant responses can be obtained with avapritinib treatment in AdvSM patients after at least one systemic therapy in whom an improvement in

symptoms and control of the disease can be considered to represent clinical benefit. Observation of clinically relevant responses apply to all included disease entities, although MCL seems to be the most difficult to treat with also less representation in the efficacy dataset.

In the absence of an RCT, the applicant has compared the response in the main study against that observed for midostaurin. The comparison seems overall favourable to avapritinib. However, patients treated with midostaurin are an external control group and therefore the results of this comparison should be interpreted with caution, particularly in view of differences in the patient populations and assessment criteria used for evaluation of efficacy (See EPAR for midostaurin).

Data on time to event endpoints, PFS and OS, are currently immature and their evaluation is hampered in the context of a single arm trial.

The applicant has provided results from a retrospective RWE trial showing an improved median OS in the avapritinib cohort compared with the BAT cohort. The results of this indirect comparison are only to be considered supportive, for contextualization purposes, in view of the well-known limitations with ensuring comparability between populations and overall interpretation.

The overall safety database for avapritinib is small and based on on-going, non-controlled studies, making any causality assumption challenging. Thus, there are some uncertainties related to these limitations. However, prior knowledge on the GIST indication and similarities observed in the safety profile alleviate this concern to some extent. The overall incidence of adverse events (100%), including serious (38.1%), and severe (grade ≥3) AEs (75.4%) is high for the intended dose (i.e., 200mg QD). Avapritinib was poorly tolerated based on the high frequency of AEs leading to dose interruptions/reductions (66.7%, and 72.5% of patients, respectively). The recommendations for dose adjustments (to 200 mg) appeared to mitigate these toxicities to an acceptable level, with only 18.5% discontinuing study treatment due to an AE.

The tolerability profile and benefit/risk balance could potentially be improved with even lower initial avapritinib doses. However, as lower starting doses have not been prospectively tested, and the dose-response relationship is not characterised, it is unknown whether lower initial doses would maintain similar clinical benefit. In general, the toxicities appear to be manageable with dose adjustment/temporary treatment interruptions. Considering the severity of the study disease, this safety profile could be considered favourable/acceptable in front of outstanding benefits.

3.7.2. Balance of benefits and risks

The reported ORR by centrally adjudicated mIWG-MRT-ECNM criteria for avapritinib in patients with AdvMS previously treated with at least one systemic therapy, i.e. in a rare disease setting with limited treatment alternatives, is considered promising and expected to translate into clinically meaningful benefit in the long-term, in particular if supported by long duration of achieved responses. Even if follow-up is short in many patients and a median DOR not yet reached, efficacy data currently available show that clinically relevant responses can be obtained with avapritinib treatment in AdvSM patients after at least one systemic therapy in whom an improvement in symptoms and control of the disease can be considered to represent clinical benefit.

The overall safety profile of avapritinib appears consistent with that seen in the GIST indication and similar of that for other TKIs. Avapritinib is tolerable, with a safety profile that appears to be manageable.

With this in mind, it is considered that the benefit reported with avapritinib in the intended patient population in the context of a manageable safety profile, translates in a positive benefit risk ratio with (outstanding) efficacy results outweighing/mitigating the methodological concerns discussed.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall benefit/risk balance of AYVAKYT is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

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. 847/2000. See appendix on similarity.

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, AYVAKYT new strengths 25 and 50 mg and existing strengths 100 and 200 mg film coated tablets is favourable in the following indication(s):

Unresectable or metastatic gastrointestinal stromal tumour (GIST)

AYVAKYT is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation.

Advanced systemic mastocytosis (AdvSM)

AYVAKYT is indicated as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), after at least one systemic therapy.

The CHMP therefore recommends the extension(s) of the marketing authorisation for AYVAKYT subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to further confirm the safety and efficacy of avapritinib in the treatment of adult patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation, the MAH should submit the results of study BLU-285-1101, an ongoing single-arm, open-label multiple-cohort Phase 1 study in patients with GIST and other relapsed and refractory solid tumours.	December 2021
In order to further confirm the safety and efficacy of avapritinib in the treatment of adult patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation, the MAH should submit the results of an observational safety and efficacy study in patients with unresectable or metastatic PDGFRA D842V-mutant GIST.	December 2027

Additional Marketing protection

Furthermore, the CHMP reviewed the data submitted by the Blueprint Medicines (Netherlands) B.V., taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004 considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix on Article 14(11)).

In addition, CHMP recommends the variation to the terms of the marketing authorisation, concerning the

following change(s):

Variations 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 application to add two new strengths of film-coated tablets (25 mg and 50 mg), grouped with a type II variation (C.I.6.a) to introduce a new therapeutic indication for AYVAKYT. Extension of indication to include monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), after at least one systemic therapy based on the results of the BLU-285-2101 and BLU-285-2202 studies. The new indication is applicable to the new and existing presentations (25 mg, 50 mg, 100 mg and 200 mg film-coated tablets). As a consequence, sections 1, 2, 3, 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.2, 5.3, 6.1 and 8 of the SmPC are updated. The Labeling and Package Leaflet are updated in accordance. Version 1.2 of the RMP has also been submitted.

5. Appendix

1. Product information