EU-Risk Management Plan for AYVAKYT (avapritinib)

RMP version to be assessed as part of this application:

RMP version number:	4.4
Data lock point for this RMP:	08 July 2022
Date of final sign off	07 November 2023

Rationale for submitting an updated RMP:

To support a Type II variation application for a new indication in the EU (indolent systemic mastocytosis [ISM]).

Summary of significant changes in this RMP:

- **Part I Product(s) Overview**

Product(s) overview was amended with an updated wording on the proposed indication for ISM.

- **Part II Safety Specification**

Module SI was amended with the epidemiology of ISM.

Module SII was amended with safety margins for avapritinib clinical doses of 25 mg, 200 mg, and 300 mg.

Module SIII was amended with patient exposure from the ISM clinical development programme.

Modules SVII.2 and SVIII were amended to reflect the differences in the safety profile of avapritinib in patients with gastrointestinal stromal tumour (GIST)/ advanced systemic mastocytosis (AdvSM) and ISM.

Module SVII.3 was updated with available data relevant to the clinical development programme for ISM.

- **Part V Risk Minimisation Measures**

Routine risk minimisation activities recommending specific clinical measures to address the risk included were revised in Part V.3 in line with the Guidance on the format of the RMP in the EU.

All changes made to the body of the document were reflected in Part VI of the RMP.

Other RMP versions under evaluation:

RMP version number:	Not applicable.
Submitted on:	Not applicable.
Procedure number:	Not applicable.

Details of the currently approved RMP:

RMP version number:	3.1
Approved within procedure:	EMEA/H/C/005208/II/0022
Date of approval (opinion date):	26 May 2023

QPPV name: Tereza Dušková

The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

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List of Abbreviations

AdvSM	Advanced systemic mastocytosis
AE	Adverse event
AST	Aspartate aminotransferase
ASM	Aggressive systemic mastocytosis
ATC	Anatomical therapeutic chemical classification system
AUC	Area under the plasma concentration-time curve
AUC0-∞	Area under the plasma concentration-time curve from time 0 to infinity
BMI	Body mass index
BSC	Best supportive care
CI	Confidence interval
CLcr	Creatinine clearance
C_{max}	Maximum plasma concentration
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CXDX	Cycle X, day X
CYP	Cytochrome P450
DDI	Drug-drug interaction
ddPCR	Digital-droplet polymerase chain reaction
DLP	Data lock point
EC50	Half-maximal effective concentration
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
EEG	Electroencephalographic
EMA	European Medicines Agency
EPAR	European public assessment report
EU	European Union
FDA	United States Food and Drug Administration
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumour
GLP	Good laboratory practice
hERG	Human ether-à-go-go-related gene
IBD	International Birth Date
IC50	Half-maximal inhibitory concentration

IgE	Immunoglobulin E
INN	International non-proprietary name
ISM	Indolent systemic mastocytosis
ISM-SAF	Indolent Systemic Mastocytosis-Symptom Assessment Form
IWG-MRT-ECNM	International Working Group-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis
MAF	Mutant allele fraction
Max	Maximum
MC	Mast cell
MCL	Mast cell leukaemia
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MRI	Magnetic resonance imaging
NaV 1.2	Type 2 sodium channel
NOAEL	No-observed-adverse-effect level
NSAID	Nonsteroidal anti-inflammatory drug
ORR	Overall response rate
PAES	Post-authorisation efficacy study
PDGFR	Platelet-derived growth factor receptor
PDGFRA	Platelet-derived growth factor receptor alpha
PDGFRB	Platelet-derived growth factor receptor beta
PFS	Progression-free survival
PL	Package leaflet
PPI	Proton pump inhibitor
PT	Preferred term (of MedDRA)
QD	Once daily
QPPV	Qualified person for pharmacovigilance
QTc	Corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
RMP	Risk management plan
SM	Systemic mastocytosis
SM-AHN	Systemic mastocytosis with an associated haematological neoplasm
SSM	Smoldering systemic mastocytosis
$t_{½}$	Elimination half-life
TKI	Tyrosine kinase inhibitor
SD	Standard deviation
SmPC	Summary of product characteristics

SMQ	Standardised MedDRA Query
TSS	Total symptom score
ULN	Upper limit of normal
US	United States
UV	Ultraviolet
WHO	World Health Organization

PART I: Product(s) Overview

Active substance (INN or common name)	Avapritinib
Pharmacotherapeutic groups (ATC code)	Antineoplastic agents, protein kinase inhibitors (L01EX18)
Marketing authorisation holder	Blueprint Medicines (Netherlands) B.V.
Medicinal product(s) to which this RMP refers	5
Invented name(s) in the European Economic Area (EEA)	AYVAKYT
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class Avapritinib is a small-molecule tyrosine kinase inhibitor (TKI) with chemical name (S)-1-(4-fluorophenyl)-1-(2-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)piperazin-yl)pyrimidin-5-yl)ethan-1-amine.
	Summary of mode of action Avapritinib is a Type 1 tyrosine kinase inhibitor that binds to the active conformation and inhibits a broad range of platelet-derived growth factor receptor alpha (PDGFRA) and KIT mutant kinases at clinically relevant concentrations. This includes the activity of PDGFRA exon 18 mutants (D842V, D842I and D842Y) and KIT exon 11, 17 (including KIT D816V) and 11/17 mutants.
	Important information about its composition None
Hyperlink to the Product Information	eCTD Module 1.3.1
Indication(s) in the EEA	Current: AYVAKYT is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the PDGFRA D842V mutation. 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.
	Proposed: AYVAKYT is indicated for the treatment of adult patients with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment.

Dosage in the EEA	Current: **Adult patients with GIST and AdvSM** The recommended dose of avapritinib for the GIST indication is 300 mg orally once daily (QD). The recommended dose of avapritinib for the advanced systemic mastocytosis (AdvSM) indication is 200 mg orally QD. The dose should be adjusted as recommended based on safety and tolerability.
	Proposed: **Adult patients with ISM** The recommended dose of avapritinib for the ISM indication is 25 mg orally QD.
Pharmaceutical form(s) and strength(s)	Current Film-coated tablet Each film-coated tablet contains 25, 50, 100, 200 or 300 mg of avapritinib.
	Proposed: None
Is the product subject to additional monitoring in the EU?	Yes

Abbreviations: ATC = anatomical therapeutic chemical classification system; EU = European Union; INN = international non-proprietary name; RMP = risk management plan.

PART II: Safety Specification

PART II: Module SI- Epidemiology of Indication and Target Population

SI.1 Unresectable or Metastatic Gastrointestinal Stromal Tumour

GISTs are the most common mesenchymal tumours, probably arising from the precursors of the interstitial tissue cells of Cajal in the gastrointestinal tract [1, 2]. GISTs represent approximately 0.1%-0.3% of all gastrointestinal malignancies [3].

Activating mutations of *KIT* or *PDGFRA* are found in the vast majority of GISTs [4]. These mutations lead to continuous activation of tyrosine kinases, leading to cell proliferation and inhibition of apoptosis.

Most cases of GIST (75%) harbour a mutation in *KIT* in exon 11 (90%), exon 9 (8%), and less frequently in exon 13 (1%) and exon 17 (1%). Disease progression during treatment with TKIs is often associated with development of new mutations, with an increasing prevalence of mutations in exon 17 of *KIT* to approximately 95%-99% following a second-line TKI therapy [5-8].

PDGFRA gene mutations represent approximately 10%-20% of GISTs [5-10]. The most common mutation of *PDGFRA* occurs in exon 18 which leads to a mutant PDGFRA with valine (V) substituting for an aspartic acid (D) at position 842 (D842V mutation); however, mutations may also occur in exons 12 and 14 [7-10].

Approximately 10% of adult GISTs (and about 85% of paediatric cases) are not associated with *KIT* or *PDGFRA* mutations and stromal tumours do not harbour any known gene mutations (these cases are known as “wild-type” tumours) [8, 11-13].

Incidence:

The estimated age-standardised annual GIST incidence ranged from 0.1 per 100,000, based on a study combining data from 64 European cancer registries [14], to 1.94 per 100,000, based on a nationwide pathology registry study conducted in the Netherlands [15].

Based on the most recent data, the estimated worldwide incidence of GISTs is 1.0 per 100,000 population [16, 17]. About 85% of GISTs, depending on the source of data, have a KIT (~75% of cases), or PDGFRA (~10% of cases) mutation which drive tumour growth [5-10].

Prevalence:

The most recent estimated prevalence of GISTs in Europe is 28.0 cases per 100,000 population [15, 16]. This estimate is higher than other literature estimates, which may be explained by the source of the data, representing a nationwide pathology registry study conducted in the Netherlands. This registry study included all GISTs, regardless of malignancy type and/or tumour size.

Previous European estimates ranged from 8.0 per 100,000 in Norway [18] to 12.9 per 100,000 in Sweden [19] and 15.0 per 100,000 population in the United Kingdom [20].

Demographics of the Population in the proposed Indication and Risk Factors for the Disease:

GIST is most commonly diagnosed between 50 and 80 years of age with the median age of patients being about 60-65 years [9, 21]. In the GIST natural history study conducted

retrospectively in Italy on 929 imatinib-naïve patients diagnosed with GIST between 1980 and 2000 [2], the age of the patients ranged from 12 to 95 years, with the median of 66 years.

Less than 1% of GISTs occur in the paediatric population. Paediatric GIST mainly affects females at or under the age of 16 years [3].

In the natural history study conducted by Blueprint in the United States (US) in patients with a D842V mutation in PDGFRA, diagnosed between 01 January 2000 and 01 July 2016 (Study BLU-285-1002), most patients were males (68%), with a median age at the time of diagnosis of 57 years (ranging from 31 to 72 years) [8]. This is consistent with the epidemiology of GIST reported in other studies conducted in the US and Europe [2, 22].

Main existing Treatment Options:

Prior to the initial marketing approval of avapritinib, unresectable PDGFRA D842V mutant-driven GIST represented a high unmet medical need as there were no approved therapies specifically targeting this mutation [12, 17, 23]. PDGFRA D842V mutations are insensitive to imatinib treatment as well as the other available treatment regimens for GIST [3, 12, 24-26]. Due to the lack of effective treatment options at the time, patients had a poor prognosis with the median progression free-survival (PFS) of only 3 to 5 months, and the overall survival of 15 months after diagnosis [24, 26]. In refractory KIT mutant-driven GIST, PFS with best supportive care (BSC), after failure of available therapies, is approximately 0.9 months [27, 28].

Surgery is the standard primary treatment option for patients with localised GIST and can provide long-term disease control [17]. However, surgery is not recommended for locally recurrent or metastatic GISTs, which also respond poorly to conventional therapies such as chemotherapy (e.g., doxorubicin, ifosfamide) [29] and radiation therapy [30]. Thus, targeted therapy with TKIs has emerged as the standard treatment for advanced disease, including imatinib as the first-line, sunitinib as the second-line and regorafenib as the third-line therapy [17]. Despite these advances with the introduction of TKIs, the majority of patients develop resistance over time which is mainly driven by the acquisition of a secondary mutation in the activation loop of KIT [17].

Imatinib is the standard first-line treatment for locally advanced inoperable and/or metastatic GIST [7, 9, 10]. Current European guidelines (i.e., Clinical Practice Guidelines of the European Society for Medical Oncology and the European Network for Rare Adult Solid Cancer on Gastrointestinal Stromal Tumours) recommend that imatinib should be considered as the treatment of choice, even for *KIT* exon 9 mutated GIST [17].

Sunitinib is the standard second-line therapy for unresectable and/or metastatic GIST, and treatment is routinely initiated upon lack of response to imatinib therapy [17]. Sunitinib and the third-line therapy regorafenib offer limited sustained disease control, with the median PFS ranging from 5 to 6 months and overall response rates (ORRs) ranging from 4% to 7% [27, 31].

An analysis of patient registry data and post-marketing prescription information collected from patients with GIST receiving treatment for metastatic disease [32] showed that only about 50% of these patients receive a second-line treatment. While the first-line treatment with imatinib is used in about 85% of patients seeking first-line treatment for metastatic disease, sunitinib is utilised in the second-line setting only in approximately 50% of patients and approximately 15% of patients still receive imatinib at different doses in the second-line setting. In the third-line setting, regorafenib is used in approximately 45% of patients. These real-world data indicate that although sunitinib and regorafenib are approved for second- and third-line treatment, respectively, neither is used in the majority of patients, and there is no dominant

standard of care or preferred treatment regimen after first-line therapy with imatinib [32]. This is consistent with the low response rates and short PFS seen with these agents.

Natural History of the Indicated Condition in the Population, Including Mortality and Morbidity:

The malignant potential of GISTs varies greatly from indolent tumours to rapidly progressing cancers [8]. A retrospective natural history study of GIST conducted in Italy showed that 59.7% of patients were diagnosed with gastric tumours, 26.3% with ileal/jejunal tumours, 3.4% with rectal tumours, 3.1% with duodenal tumours, and 3.1% with peritoneal tumours (including mesenteric, omental, pelvic, and abdominal wall GIST tumours). The status of the disease at diagnosis was localised in 88% of patients and metastatic in 12% of patients [2]. Study BLU-285-1002 showed that the primary tumour location was in the stomach in 68% of patients [8]. A US retrospective population-based epidemiological study showed similar results with the most common tumour sites involving the stomach (55% of cases) and small intestine (29% of cases) [22].

Studies have reported that up to 20% of patients with GIST have metastases. GIST usually metastasises within the abdominal cavity, affecting mostly the liver or peritoneum [1]. Less common metastatic sites are in the gastrointestinal tract, including the oesophagus and stomach, lymph nodes, or reproductive or renal systems [2]. Central nervous system (CNS) metastases are extremely rare in patients with GIST [1]. In the natural history Study BLU-285-1002, metastases occurred predominantly in the peritoneum in 9% of patients receiving the first-line therapy, 17% of patients receiving the second-line therapy, and 33% of patients receiving the third-line therapy [8]. Peritoneal and/or liver metastases may occur even after complete excision of the tumour.

Mortality rates for GIST differ based on existing co-morbidities and risk factors associated with them. Patients with localised GIST and no additional cancers, such as sporadic patients with GIST, were shown to be at increased risk of synchronous or metachronous malignancies [22], with the 5-year mortality rate being estimated at 12.9 % [33]. The mortality rate is three times higher in patients with concomitant regionally advanced or metastatic GIST [33].

In natural history Study BLU-285-1002, the overall study population included 22 patients, all of whom had previously received at least first-line therapy. Nineteen (86%) of these patients had also received second-line therapy and 16 (73%) had also received third-line therapy. Out of the 22 patients, only 1 achieved a complete response after first-line therapy with imatinib. No other responses (complete or partial response) were reported following the first-, second- or third-line therapies. The ORR for first-line therapy was 4.5% (95% confidence interval [CI]: 0.1–22.8). The median PFS was 5.6 months (95% CI: 3.1–16.2) with first-line therapy, 2.6 months (95% CI: 1.4–5.9) with second-line therapy and 5.6 months (95% CI: 2.1–11.5) with third-line therapy. The median overall survival was 44.5 months (95% CI: 20.4–69.6) with first-line therapy, 28.1 months (95% CI: 12.6–56.7) with second-line therapy, and 25.5 months (95% CI: 10.5-55.0) with third-line therapy [8]. Similar ORRs were calculated for patients who received first-line treatment in other published studies [24, 26, 34]; in these studies, none of the patients achieved an objective response to treatment following second- and third-line treatment (refer to Table 1). These trends are consistent with the real-world experience showing that median overall survival in patients with metastatic disease decreases quickly with multiple lines of therapy from 7 to 8 years after starting initial treatment for metastatic disease to only 1.4 years after starting treatment with fourth line of therapy [32].

Table 1:Comparison of Overall Response Rates in Patients with PDGFRA D842V GIST Following Multiple Lines of Treatment

Line of treatment	Overall Response Rate (95% Confidence Interval)			
	BLU-285-1002	Cassier et al [24]	Yoo et al [26]	Farag et al [34]
	N=22	N=32	N=9	N=17
1st line	4.5% (0.1–22.8)	0% (0.0–10.9)	0% (0.0–33.6)	11.8% (0.1–22.8)
2nd line	0% (0.0–17.7)	Not reported	0% (0.0–36.9)	Not reported
3rd line	0% (0.0–20.6)	Not reported	Not reported	Not reported
Any line	9.1% [a] (1.1–29.2)	0% (0.0–10.9)	0% (0.0–33.6)	Not reported

Abbreviation: N = number of subjects.

a One patient had an unconfirmed response during the fourth line of treatment with an investigational drug crenolanib.

Source: CSR BLU-285-1002, Table 14.2.1.1a, Table 14.2.1.1b, and Table 14.2.1.1c, CSR BLU-285-1101, Table 14.2.1.1.2.

The epidemiological studies on the US population concluded that Black race, older age, and advanced stage of the disease were associated with worse disease prognoses [22, 35]. The characteristics of paediatric GIST differ from that of GIST in adult patients in respect to morphology, prognosis and pathology, as *KIT* or *PDGFRA* mutations are not commonly seen in this population [3]. Rare cases of familial GIST were reported in the literature associated with autosomal dominant transmission of germline *KIT* or *PDGFRA* mutation [30].

Important Co-Morbidities:

GIST is predominantly diagnosed in patients older than 60 years of age [9]. As such, comorbidities are common and may include conditions commonly seen in this population such as heart disease, pulmonary disease, diabetes, and arthritis.

A natural history study of GIST conducted in Italy showed that 61% of patients with GIST reported other significant diseases. Malignancies other than GIST occurred in 28% of patients with GIST at any point in time and were concomitant with GIST in 15.8% of cases (most commonly colorectal or gastric carcinoma) [2].

A US population-based study on 6,112 patients with GIST showed that malignancies occurring with significantly increased incidence both before and after GIST diagnoses included other sarcomas, neuroendocrine-carcinoid tumours, non-Hodgkin's lymphoma, and colorectal adenocarcinoma. Oesophageal adenocarcinoma, bladder adenocarcinoma, melanoma, and prostate adenocarcinoma were significantly more common before the GIST diagnosis. Ovarian carcinoma, small intestine adenocarcinoma, papillary thyroid cancer, renal cell carcinoma, hepatobiliary adenocarcinoma, gastric adenocarcinoma, pancreatic adenocarcinoma, uterine adenocarcinoma, non-small cell lung cancer, and transitional cell carcinoma of the bladder were significantly more common than the background rates after the GIST diagnosis [22].

Among concomitant non-malignant conditions, the most frequent diseases were gastrointestinal disorders (7.8%), such as duodenal ulcers, gastric ulcers, intestinal obstruction, and Crohn's disease [2].

SI.2 Advanced Systemic Mastocytosis

Systemic mastocytosis (SM) is a 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 proliferation, infiltration, and abnormal activation of MCs, leading to debilitating MC-mediated symptoms, and in a subset of patients, organ damage and poor survival [36, 37]. SM can be broadly divided into non-advanced and AdvSM, the latter encompassing a group of high-risk subtypes with a poor prognosis, including ASM, SM-AHN, and MCL [38]. SM-AHN accounts for approximately 75% of patients diagnosed with AdvSM [39].

Patients with both non-advanced and AdvSM suffer from a wide variety of severe and unpredictable symptoms and reduced quality of life with limited treatment options. Low awareness of SM results in suboptimal patient care and a highly unmet medical need in this population. Although heterogeneity characterises the clinical presentation and prognosis of SM, ~95% of all SM cases are driven by the activating *KIT D816V* mutation, regardless of a subtype [40, 41].

Among SM patients, the majority (95%) are considered to have non-AdvSM, which primarily includes the World Health Organization variant of ISM and a small number of patients with smoldering SM (SSM) [42]. ISM patients have minimal signs of organ infiltration and have a generally normal life expectancy; however, they often suffer from severe, or even life threatening, mediator symptoms and a poor quality of life. Importantly, ISM patients can progress to more serious forms, including SSM and AdvSM [36, 43].

In addition to severe mediator symptoms, patients with any of the AdvSM subtypes characteristically experience organ damage from MC infiltration and have adverse pathological features that are associated with poor overall survival [42]. Organ systems typically involved (and associated findings) are bone marrow (marked cytopenia), liver (hepatomegaly, ascites, increased liver enzymes), bones (osteolysis, pathologic fractures), and the gastrointestinal tract (malabsorption, weight loss) [44].

Incidence:

The estimated annual incidence rate of SM in the EU is 0.2 to 0.9 cases per 100,000 population [45, 46].

In a retrospective cohort study of 548 adults with SM diagnosed from 1997–2010 constructed using linked Danish national health registries, the incidence rate for all SM types was 0.9 per 100,000 per year [45]. The most common subtype was ISM (450 patients; 82%), followed by SM with subtype unknown (61 patients; 11%), SM-AHN (24 patients; 4%), ASM (8 patients; 2%), and MCL (5 patients; 1%). Among AdvSM patients, the incidence rates were 0.04 per 100,000 for SM-AHN, and 0.01 per 100,000 for ASM and MCL [45].

In a retrospective cohort study of 35 adults with SM diagnosed from 2001–2013 in a single centre in Hungary, the cumulative incidence rate for all SM types was 2.7 per 100,000 [46], corresponding to an annual incidence rate of 0.2 per 100,000.

Prevalence:

The estimated prevalence of SM in the EU is 9.6 to 50.0 cases per 100,000 population [45, 47]. The prevalence of AdvSM has been reported to be 0.052 cases per 10,000 [48].

In the retrospective Danish cohort study [45], the 14-year limited-duration prevalence as of 01 January 2011 was 9.6 cases of any type of SM per 100,000. Among AdvSM patients, the

prevalence rates were 3.1 per 100,000 for SM-AHN, 0.1 per 100,000 for ASM, and 0.0 per 100,000 for MCL [45].

Based on latest estimates, the prevalence is 1.0-9.0 cases per 100,000 population for SM-AHN [49], 0.1-0.9 per 100,000 for ASM [47], and < 0.1 per 100,000 for MCL [50].

Demographics of the Population in the Proposed Indication and Risk Factors for the Disease:

SM preferentially affects Caucasians and there is no sex predominance. It is mainly observed in older adults and elderly (average age at diagnosis is 60 years) and it is very rare in the paediatric population [47].

Main existing Treatment Options:

Standard of Care

Prevention of further organ damage by reducing MC burden is the current goal in treating AdvSM. However, prior to the approval of avapritinib patients with AdvSM had very limited therapeutic options, and patients with ISM and SSM have no approved treatment options. Historically, the treatment of AdvSM relies on systemic therapies such as cladribine, hydroxyurea, and interferon-alpha being used off-label. Based on small case series these agents have partial response rates of 35-70% (using the Valent criteria), but responses are often not durable and complete remission is rare [37]. Bone marrow MC burden and elevations in serum tryptase typically persist both during and after therapy.

Mediator effects of MC degranulation are treated symptomatically, with antihistamines used to control the widespread cutaneous manifestations, pruritus, and excessive gastric acid secretion, and corticosteroids to reduce inflammation. Corticosteroids can reduce MC burden and hence serum tryptase levels; however, most symptomatic treatments have no effect on MC burden.

Importantly, currently used systemic therapies often come at a cost of significant and potentially life-threatening side effects. In the case of interferon-alpha, one third of patients experience depression and the adverse effects of therapy can be similar to the symptoms of mastocytosis. For cladribine, nearly half of patients experience Grade 3 or 4 neutropenia, and 80% experience prolonged lymphopenia, increasing the risk of life-threatening opportunistic infections [37].

Although many *KIT* inhibitors of various mutations exist for other indications, the *D816V* mutation in the activation loop is particularly challenging to target as it locks the kinase in an active conformation. Most *KIT* inhibitors target the inactive conformation and are therefore not effective against the *KIT D816V* mutation. Several approved TKIs, such as imatinib and nilotinib, have activity against wild-type *KIT* but lack activity against *KIT D816V*. Imatinib's approval in the US in SM is limited to the small number of patients with ASM lacking the *KIT D816V* mutation [51]. Based on a Phase 2, multicentre study of SM patients with or without *KIT D816V* treated with nilotinib, it is reasonable to assume that only *KIT D816V*-negative patients may benefit. Dasatinib's poor in vivo effectiveness despite the substantial in vitro activity may reflect its short half-life. Based on these disappointing results, dasatinib was not developed further for the treatment of mastocytosis [37].

Midostaurin

Midostaurin is a multikinase inhibitor that was approved for *FLT3* mutated acute myeloid leukaemia and is the only agent approved specifically for all subtypes of AdvSM. It inhibits *D816V* mutated KIT with a biochemical half maximal inhibitory concentration (IC_{50}) of 2.9 nM [52]. It was approved by the US Food and Drug Administration (FDA) in April 2017 and by the European Medicines Agency (EMA) in September 2017 based on an open label, single arm,

Phase 2 clinical study in 116 patients (89 evaluable for primary efficacy analysis) [53] with AdvSM and an open label single arm investigator sponsored Phase 2 study in 26 patients with AdvSM [54, 55].

The objective response rate reported in the US prescribing information is 21% using modified Valent criteria. Based on an FDA post-hoc assessment using International Working Group-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis (IWG-MRT-ECNM) criteria, the objective response rate (complete and partial response, excluding CI) is 17% [56]. The EU summary of product characteristics (SmPC) for midostaurin reports an objective response rate as high as 60% [54]. These differences are primarily driven by the depth of response that was considered to be clinically significant by various response criteria and the agencies.

Sixty percent of patients treated with midostaurin experienced some improvement in C-findings (including thrombocytopenia, anaemia, and neutropenia due to bone marrow involvement; splenomegaly with hypersplenism due to spleen infiltration; hepatomegaly with impaired liver function, ascites and portal hypertension; malabsorption with significant weight loss due to gastrointestinal involvement; and large osteolytic bone lesions) [53, 54]; however, many of these responses involved only minor or partial improvement and only 28% of patients achieved full resolution in one or more C-findings [54]. Importantly, only 17% to 21% of patients had substantial (≥ 50%) reductions in MC burden [56] and complete remissions were rare (0% to 2%) [53, 54, 56].

Midostaurin is frequently associated with gastrointestinal side effects, including nausea (82%, 6% Grade ≥3) and vomiting (68%, 6% Grade ≥3), and treatment with prophylactic antiemetics is recommended. In addition, there is significant pulmonary toxicity associated with midostaurin, including dyspnoea (18%, 6% Grade ≥3) and pneumonia (9%, 7% Grade ≥3), as well as cases of fatal interstitial pneumonitis. Treatment discontinuation due to adverse events (AEs) occurred in 24% of patients [54]. Given the modest activity and tolerability of the available agents prior to the approval of avapritinib, there was a need for more efficacious and better-tolerated agents.

Natural History of the Indicated Condition in the Population, Including Mortality and Morbidity:

Patients with AdvSM may have fewer mediator-release symptoms compared to other forms of SM (such as ISM), but much poorer survival outcomes [37, 57]. In patients with AdvSM, the median overall survival is 41 to 68 months for ASM, 24 to 35 months for SM-AHN, and 2 to 23 months for MCL [38, 39]. Prognostic factors that have been associated with inferior survival of SM patients include history of weight loss, anaemia, thrombocytopenia, and excess bone marrow blasts [39].

In SM patients, activated MCs release potent mediators that induce pathologic responses in various organs, causing various symptoms including skin reactions, gastrointestinal symptoms, cardiovascular symptoms, musculoskeletal pain, and neuropsychiatric disturbances [37, 57].

MC mediator release is promoted by minimal triggers such as temperature changes, exercise, or emotional stress [37, 58, 59]. Certain types of food may also cause severe vasomotor responses and lead to anaphylaxis [37, 60], and even some of the same medications used to treat symptoms (e.g., non-steroidal anti-inflammatory drugs and opiate analgesics) may increase histamine release from mutated MCs [37, 61]. For these reasons, substantial morbidity, diminished quality of life, and inability to perform activities of daily living are common.

Malignant MCs may infiltrate every tissue, but typical target organs in AdvSM are the hematopoietic system (bone marrow, spleen, and lymph nodes), liver, and gastrointestinal tract. C-findings describe typical consequences of MC-induced end organ damage [37, 44].

Important Co-Morbidities:

As the average age when SM is diagnosed is 60 years [47], comorbidities are common, and as in the case of GIST patients, may include heart disease, pulmonary disease, diabetes, and arthritis. Other relevant co-morbidities in SM patients include immunoglobulin E-dependent allergies, psychiatric or psychological problems, and vitamin D deficiency [62]. MC-induced symptoms in SM patients may also be aggravated by infections, chronic inflammation or food intolerance [62].

Approximately 75% of patients with AdvSM have an associated haematologic neoplasm contributing to their disease course [39], and 16% to 18% of patients with AdvSM show disease transformation to acute myeloid leukaemia [38].

In a retrospective study of 342 adult patients with SM, 123 of 138 patients (89%) diagnosed with SM-AHN had an associated myeloid neoplasm, while the remainder had lymphoma (7 patients), myeloma (5 patients), chronic lymphocytic leukaemia (2 patients), or primary amyloidosis (1 patient) [36, 39]. Of the patients with an associated myeloid malignancy, 55 patients (45%) had SM-myeloproliferative neoplasm, 36 (29%) had SM-chronic myelomonocytic leukaemia and 28 (23%) had SM-myelodysplastic syndrome. A significant proportion (42 patients; 34%) exhibited prominent eosinophilia ($\geq 1.5 \times 10^9$/L), especially those with SM-myeloproliferative neoplasms (31 patients; 56%). Of the latter, 12 patients (39%) harboured the *FIP1L1-PDGFRA* fusion [36, 39].

In the same study, 24 of 41 ASM patients (59%) frequently displayed constitutional symptoms including weight loss, fever, chills, and night sweats. Patients also displayed hepatosplenomegaly (50%), lymphadenopathy (30%), severe anaemia (haemoglobin < 10 g/dL; 24%) or thrombocytopenia (platelets $< 100 \times 10^9$/L; 27%), leucocytosis (41%), and markedly elevated serum tryptase levels (> 200 ng/mL; 40%) [36, 39].

Due to the rarity of MCL in the aforementioned study (4 patients; 1%) [36, 39], no pattern of co-morbidities could be established for this patient sub-population.

SI.3 Indolent Systemic Mastocytosis

Patients with ISM suffer from a broad spectrum of persistent and debilitating symptoms [63-66]. Mutant KIT drives the accumulation and hyperactivity of aberrant MCs, leading to excessive signalling of vasoactive and inflammatory cytokines, including leukotrienes, prostaglandins, and interleukins [67]. Aggregates of activated proliferating MCs, driven by mutant KIT, result in a constellation of symptoms leading to a significant reduction in quality of life caused by recurrent diarrhoea, pruritus, abdominal pain, nausea, headache, flushing, cognitive impairment, fatigue, bone pain, and disfiguring skin lesions that are observed across the spectrum of the disease [68, 69]. In one study, 93% of patients reported ≥ 10 SM-related symptoms in their lifetime, with patients experiencing an average of 14 SM-related symptoms, the most bothersome of which were reported to be anaphylaxis and abdominal pain, followed by diarrhoea and fatigue [64]. Among patients with ISM, 46% experience anaphylaxis [70, 71], and the majority of patients report they carry adrenaline auto-injectors at all times [64, 72].

MC mediator release can be triggered by normal daily activities including but not limited to food, infection, natural and chemical odours, physical stimuli (heat, cold, friction, sunlight, etc.), physical exertion, bacterial proteins, venom, medication (non-steroidal anti-inflammatory

drugs, general anaesthetics), and stress [61, 70]. The triggers for mediator release can be unpredictable with patients sometimes reacting to triggers they have not reacted to in the past. More than half of patients with ISM report being limited at work or during other daily activities, living in fear of attacks and anaphylaxis, finding it difficult to work or attend school, leading to isolation to protect against unpredictable triggers and manage diarrhoea [63, 64].

Incidence:

In a retrospective cohort study of adult patients with SM in Denmark [45], the estimated incidence rate for ISM was estimated at 0.7 per 100,000 population per year.

Prevalence:

The estimated prevalence of all types of SM in the EU is 9.6 to 50.0 cases per 100,000 population [45, 47], with the estimated prevalence of ISM accounting for approximately 8.2 cases per 100,000 population [45].

In the Groningen region of the Netherlands, a major referral area for patients with SM, the prevalence of ISM was estimated at 13.0 cases per 100,000 population [73].

Demographics of the Population in the Proposed Indication and Risk Factors for the Disease:

In a study of 333 Medicare beneficiaries with newly diagnosed moderate to severe ISM, the mean age was 67 years and 76% of the patients were female [74]. The female predominance was consistent with prior studies in SM [75, 76]. Approximately 94% of the beneficiaries were white [74].

Both advanced and non-advanced SM are characterised by the uncontrolled proliferation and activation of MCs, which are present as aggregates in the skin, bone marrow, spleen, liver, gastrointestinal tract, and other organs [73]. All forms of SM can compromise quality of life and be accompanied by significant symptom burden, due to the direct infiltration of MCs in various organs, significant aberrant cell signalling, and release of highly bioactive mediators.

SM can be fatal in its advanced form, but in the non-advanced form, survival is typically not compromised [77]. Despite this, patients with non-advanced disease face life-long daily challenges associated with aberrant MC functioning, such as significant, burdensome symptoms and compromised quality of life, or even recurrent life-threatening anaphylaxis.

The main risk factor for the development of ISM is acquisition of the somatic driver mutation, KIT D816V. The causes of KIT D816V development are unknown; however, an increased likelihood of harbouring an autosomal dominant increased copy number of the TPSAB1 gene duplications, also called hereditary α-tryptasaemia, has been found in ISM patients and continues to be investigated [78]. Increasing levels of serum tryptase over time have been demonstrated to be associated with poor prognosis disease features and disease progression in ISM [79].

Due to the broad range of nonspecific symptoms, patients with SM present to a diverse group of healthcare specialists (e.g., primary care, dermatologists, emergency medicine, allergists, gastroenterologists), many of whom are not familiar with this rare disorder, leading to underdiagnosis and potentially years of symptoms prior to diagnosis. The median time from symptom onset to diagnosis for patients with ISM is 9 years [63]. In the 12 months prior to diagnosis, Medicare beneficiaries with newly diagnosed moderate to severe ISM were found to have high rates of specialty physician visits (mean specialty physician visits of 15.3 visits per person) [74].

Main Existing Treatment Options:

Therapies currently recommended for ISM are considered palliative, administered with the intent of only improving symptoms. Currently no therapies treat the underlying driver of ISM or impact the ISM disease course. Treatments for ISM include both prescription and non-prescription medications (Table 2) that represent the BSC. As patients with ISM harbour a wide spectrum of symptoms that range from being episodic to continuous with fluctuating severity, patients' symptoms are typically managed with multiple medications and with dosing regimens and duration largely individualised for each patient. These medications are typically taken in both a maintenance and breakthrough setting and are often given at doses or frequency higher than typically used in a non-SM setting. On average, SM patients are reported to routinely use ≥3 BSC medications to treat their symptoms [64].

Table 2:Commonly Used Therapies Directed for Treatment of ISM Symptoms

Symptom	Drug Class
Pruritus, flushing	H1 antihistamines, leukotriene inhibitors, NSAIDs
Abdominal pain, cramping, diarrhoea, heartburn, nausea, vomiting	H2 antihistamines, PPI, cromolyn, corticosteroid
Headache, cognitive impairment, depression	H1 antihistamine, cromolyn
Hypotension	H1 antihistamine, corticosteroid
Osteoporosis	Bisphosphonate
Anaphylaxis	Corticosteroid, anti-IgE antibody, epinephrine

Abbreviations: IgE = Immunoglobulin E; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor.

Given that none of these supportive care medications significantly decrease MC burden in tissues, more than 70% of patients with ISM continue to report frequent moderate to severe symptoms despite BSC and avoidance of known triggers [80, 81]. Many of the BSC medications are also given at high doses and concomitantly, hence are often accompanied by side effects that can negatively impact patient quality of life [82].

In some cases, there are additional challenges in administrating or obtaining medications for ISM patients [64, 83, 84]. For example, cromolyn is commercially available in powder-containing ampules, which require compounding by specialty pharmacies into a large volume liquid formulation that is not available to all patients. In addition to the potential challenges of obtaining cromolyn, dosing of large number of liquids up to 4 times daily may cause AEs such as vomiting, abdominal pain/discomfort, constipation, erythema, photosensitivity, urticaria, and angioedema [83, 85]. Additionally, none of these medications have been demonstrated to control ISM symptoms in randomised controlled studies. Several case reports and small observational studies of omalizumab, an injected anti-immunoglobulin E antibody that has been approved for treatment of allergic asthma and chronic spontaneous urticaria, suggested that omalizumab might decrease ISM symptoms. Therefore, a double-blind, randomised placebo controlled study with predominantly ISM patients was conducted, which failed to show statistically significant improvement in symptoms, including anaphylaxis [86]. Thus, there remains an unmet medical need in patients who do not adequately respond to existing symptomatic treatments.

Current treatment with symptom-directed medications remains ineffective in a majority of patients and off-label or investigational use of cytoreductive therapies are often poorly tolerated. Patients report they still have to avoid known triggers. Therefore, there is a high unmet need for treatments that address the underlying mechanisms of this debilitating hematologic disease that provides a more effective and better tolerated treatment for patients with ISM.

Natural History of the Indicated Condition in the Population, Including Mortality and Morbidity:

As a non-advanced form of SM, ISM typically does not usually significantly compromise survival. A study found that the median OS of ISM patients was 198 months, which was not significantly different than that of the age-matched and sex-matched US control population [36, 39].

Patients with ISM are at risk for progression of their disease. The cumulative probability of disease progression in ISM ranges from $1.7 \pm 1.2\%$ at 5 to 10 years to $8.4 \pm 5.0\%$ at 20 to 25 years [43]. In an analysis of a large European registry, the cumulative probability of ISM disease progression was 4.9% with a median follow-up of 4.2 years [87]. Serum β2-microglobulin level and multilineage KIT D816V involvement were found to be predictors of disease progression [36, 43].

Important Co-Morbidities:

As presented in SI.2, comorbidities in SM patients include heart disease, pulmonary disease, diabetes, and arthritis. Other relevant co-morbidities include immunoglobulin E-dependent allergies, psychiatric or psychological problems, vitamin D deficiency, and osteoporosis [62]. Infections, chronic inflammation or food intolerance may also aggravate MC-induced symptoms in SM patients [62].

Hypertension and malignancy were the most observed comorbidities in Medicare beneficiaries with moderate to severe ISM [74]. The observed prevalence of comorbidities among the ISM patients due to non-age-related factors was higher than among all ISM patients for select mental health conditions (anxiety: 43% vs. 29%; depression 38% vs. 27%), pulmonary diagnoses (asthma 43% vs. 29%; chronic obstructive pulmonary disease 51% vs. 36%), and migraine (27% vs. 11%) [74].

PART II: Module SII - Non-Clinical Part of the Safety Specification

Key Safety Findings from Non-Clinical Studies and Relevance to Human Usage

Repeat-Dose Toxicity Studies

The Good Laboratory Practice (GLP)-compliant 28-day and 3-month toxicology studies of avapritinib were conducted in both Sprague Dawley rats and Beagle dogs, as well as chronic 6-month rat and 9-month dog studies, using the intended clinical regimen of avapritinib daily dosing per os (Studies WIL-124507, WIL-124525, WIL-124522, WIL-124508, WIL-124523, WIL-124815, and WIL-124816).

The key organs of toxicity in rat and/or dog included the CNS, haematopoietic, lymphoid, gastrointestinal, reproductive (testes and ovaries), and hepatobiliary systems, as well as the bones. These studies showed predominantly mechanism-related toxicities, except for convulsions in rats which was potentially secondary to inhibition of the type 2 sodium channel (Na_V 1.2).

Avapritinib-related clinical findings in rats included mortality, moribundity (with related observations of hunched posture and hypothermia), and CNS effects such as convulsions, tremors, hyperreactivity, body weight loss and lower food consumption.

Clinical pathology findings included reduced haematology parameters among which red blood cells, white blood cells (lymphocyte, neutrophil, monocyte, and eosinophil counts), haematocrit and haemoglobin, increased platelet counts and prothrombin time. Significant microscopic findings included haemorrhagic luteal cysts, most likely secondary to platelet-derived growth factor receptor beta (PDGFRB) inhibition and previously reported as a class effect with TKIs [88].

Avapritinib-related clinical findings in dogs included mortality, moribundity, inanition and metabolic perturbations with vomiting, diarrhoea, decreased food intake, body weight loss, haematologic and serum chemistry perturbations and microscopic alterations in several tissues, especially oedema and haemorrhage in the brain. Avapritinib-related changes in haematology in dogs included lower red blood cell counts, haemoglobin, haematocrit, absolute reticulocytes, altered red cell calculated indices, lymphocyte counts and eosinophil counts.

In the 28-day dog study, the main causes of early death in dogs following short-term (9 days) dosing at higher avapritinib doses (45-60 mg/kg/day) were inanition, reduced body weight, and poor toleration. Brain lesions were not noted in these early decadents; however, single foci of brain haemorrhage were noted at terminal necropsy after 28 days of dosing.

In the 3-month dog study, mild to moderate haemorrhage and/or minimal to mild choroid plexus oedema were noted within the brain at 15 and 30 mg/kg/day resulting in pre-terminal moribundity and euthanasia within the first month of dosing. The brain haemorrhage was multifocal, acute to subacute, and was often perivascular or periventricular. Brain haemorrhage was the main cause of death in these animals.

Minimal haemorrhage in the spinal cord was also noted in the affected dogs. The spinal cord haemorrhage was multifocal, acute, perivascular, and was often located in the spinal cord grey matter. In comparing the 28-day and 3-month dog studies, the brain haemorrhage exacerbated from single foci in the 28-day study to multi-focal lesions in the 3-month study, indicating progression of the lesions with increasing duration of treatment. Brain haemorrhage was not noted in the 9-month dog study up to the maximum dose tested, 5 mg/kg/day.

It was presumed that the oedema and haemorrhage noted in the brain in dogs was potentially secondary to inhibition of PDGFRB on pericytes, thereby compromising vascular integrity [89-91].

The underlying mechanism that would explain the increased sensitivity of dogs to brain haemorrhage, despite their relatively lower exposure compared to rats, remains unclear. Non-clinical studies in rats have demonstrated that avapritinib penetrates the blood-brain barrier and results in measurable levels of avapritinib in the brain.

– Relevance to human use: Haemorrhage in the brain and spinal cord occurred in dogs at doses greater than or equal to 15 mg/kg/day (approximately 9.0, 1.8, and 0.8 times the human exposure based on the area under the plasma concentration-time curve (AUC) at 25 mg, 200 mg, and 300 mg dose once daily, respectively) and choroid plexus oedema in the brain occurred in dogs at doses greater than or equal to 7.5 mg/kg/day (approximately 4.7, 1.0, and 0.4 times the human exposure based on AUC at the clinical dose of 25 mg, 200 mg, and 300 mg once daily, respectively). These findings were not accompanied by consistent, clinically translatable prodromal CNS-related clinical signs such as tremors, ataxia, or convulsions in the absence of overall moribundity.

  Intracranial bleeding, including subdural haematoma, haemorrhage intracranial and cerebral haemorrhage occurred in the avapritinib clinical trials in GIST and AdvSM patients, suggesting a potential correlation between the preclinical findings and human use in these patient populations.

  The potential mechanism for brain haemorrhage in dogs and ovarian haemorrhage in rats is considered to be inhibition of PDGFRB. Thrombocytopenia is a risk factor in AdvSM patients but was not observed in rats or dogs.

  Based on the preclinical findings correlated with the clinical data, intracranial haemorrhage is an important identified risk associated with avapritinib in patients with GIST and AdvSM, while it represents an important potential risk in patients with ISM (refer to PART II: Module SVII).

Genotoxicity

Five GLP-compliant assays were conducted for avapritinib: bacterial reverse mutation assay (Study WIL-124504); in vitro chromosome aberration test in cultured human peripheral blood lymphocytes (Study WIL-124505); and in vivo bone marrow micronucleus (Study WIL-124506) and liver comet (Studies 9800604 and 9800938) assays in Sprague Dawley rats. In addition, GLP-compliant bacterial reverse mutation assays were conducted for three impurities of avapritinib drug substance (Study 00124800, Study 00124801, Study 00124802).

Avapritinib was not mutagenic in the bacterial reverse mutation assay. In the in-vitro mammalian cell chromosome aberration test, avapritinib demonstrated minimal potential to cause structural chromosomal aberrations. However, avapritinib did not induce micronuclei in the bone marrow or the liver in the repeated-dose chromosomal aberration studies in rats.

Overall, avapritinib is non-genotoxic. Three specific impurities identified in avapritinib drug substance were also tested and shown to be non-mutagenic in the bacterial reverse mutation assay.

– Relevance to human use: There was little to no evidence of genotoxicity in in-vitro and in-vivo non-clinical toxicology studies conducted within the non-clinical development programme for avapritinib. No genotoxic potential is expected in humans.

Carcinogenicity

Two GLP-compliant assays were conducted for avapritinib: a dose-range finding 5-day and 28-day toxicity study in wild type CByB6F1-Tg(HRAS)2Jic mice (Study 00124989) and a 26-week carcinogenicity study in transgenic CByB6F1/Tg rasH2 hemizygous mice (Study 01499039).

The objective of the dose-range finding 5-day and 28-day toxicity study was to identify doses suitable for the subsequent 26-week transgenic mouse carcinogenicity study. In the 26-week study, higher incidences of lower thymic cortical cellularity were noted at the 10 and 20 mg/kg/day doses.

– Relevance to human use: A 2-year carcinogenicity study with avapritinib is ongoing.

Reproductive and Developmental Toxicity

The effects of avapritinib on fertility and early embryonic development to implantation were assessed in a repeated-dose GLP-compliant study in rats (Study 00124844), and the effects on developmental toxicity and maternal toxicity study were assessed in a repeat-dose range finding GLP-compliant study in gravid Sprague Dawley rats exposed to avapritinib during the critical period of organogenesis (Study 124704).

Avapritinib did not affect male or female fertility in rats up to the highest tested dose of 30 mg/kg/day (180 mg/m^2/day) in males and 20 mg/kg/day (120 mg/m^2/day) in females. The no-observed-adverse-effect level (NOAEL) for early embryonic toxicity was at the lowest dose tested of 3 mg/kg/day (18 mg/m^2/day) due to effects on implantation and intrauterine survival at higher doses.

In gravid rats, avapritinib was tolerated up to the highest tested dose of 30 mg/kg/day (180 mg/m^2/day). Based on adverse ovarian haemorrhages that resulted in an increased frequency of resorptions at ≥10 mg/kg/day (60 mg/m^2/day), a dose of 5 mg/kg/day (30 mg/m^2/day) was the NOAEL for maternal toxicity.

Based on the adverse decreases in foetal weights, viability (higher mean litter proportions of post-implantation loss and lower mean litter proportions and/or mean numbers of viable foetuses), and/or increases in visceral and skeletal malformations at ≥10 mg/kg/day (60 mg/m^2/day), a dose of 5 mg/kg/day (30 mg/m^2/day) was the NOAEL for embryofoetal developmental toxicity.

– Relevance to human use: Avapritinib was teratogenic and embryotoxic in rats at doses 31.4, 6.3, and 2.7-times greater than the human exposure at the therapeutic doses of 25 mg, 200 mg, and 300 mg avapritinib, respectively. There were no direct effects on fertility in either sex at the highest dose levels tested in this study (100.8 and 62.6 times the human exposure (AUC) at 25 mg, 20.3 and 9.5 times the human exposure (AUC) at 200 mg, and 8.7 and 4.1 times the human exposure (AUC) at 300 mg).

  No pregnancies occurred during the clinical development programme for avapritinib. Avapritinib-related embryotoxicity and teratogenicity is a mechanism-related class effect reported with other TKIs, such as imatinib [92]. Embryofoetal toxicity is an important potential risk associated with avapritinib (refer to PART II: Module SVII).

Safety Pharmacology

Effects on CNS

In vitro safety pharmacology studies (Studies 100013720 and 100014090) demonstrated that avapritinib inhibits Na_V 1.2 with IC_{50} of the free drug at 280 nM. Inhibition of Na_V 1.2 is considered to be the cause of convulsions noted in rats.

Oral administration of avapritinib at a dose of 30 mg/kg/day for 15 consecutive days resulted in increased corneal reflex and increased pinna reflex in 1 of 6 animals in an in-vivo neurofunctional safety pharmacology study (Study WIL-124502) in rats. These signs were first observed on Study Day 7 and had resolved by Study Day 10. A dose of 45 mg/kg/day resulted in increased touch response, increased corneal reflex, increased pinna reflex, head flicking, exophthalmos, increased startle response, aggressiveness, vocalisation, increased pain response, and/or tremors in up to 2 of 6 animals. These signs were first observed on Day 11, peaked at Day 13 and were still present on Day 14, the last day of the study. These findings indicate an increase in sensitivity to stimuli and are potentially underlying indictors of pre-convulsive activity. No avapritinib–related effects on the gross behavioural, physiological, or neurological state of the animals were noted at a dose level of 15 mg/kg/day which was the NOAEL in this study.

Two non-GLP compliant studies were conducted in Sprague Dawley rats using subcutaneously implanted electroencephalographic (EEG) electrodes (Studies WIL-124530 and WIL-124538). The studies demonstrated that EEG changes correlated with an avapritinib-induced increase in seizure potential or decreased seizure threshold in rats, and that avapritinib-mediated seizures were ameliorated by diazepam.

– Relevance to human use: Seizures or convulsions were observed in rats at high, poorly tolerated doses exceeding the highest non-severely toxic dose in this species. Seizures in rats occurred at systemic exposures ≥8-fold higher than the exposure in patients at the 300 mg/day avapritinib dose level, and there were no microscopic correlates in the brains of these rats.

  The pooled safety analysis of data from the clinical trials did not reveal any related risks in humans. In the overall safety population (N = 749), seizure was reported in only 3 patients (< 1%; serious in 1 patient, non-serious in 2 patients), whereas epilepsy was reported in 2 patients (< 1%; serious in both patients, neither of whom were in the AdvSM patient group). In all patients but in 1 patient who had seizure, the events were assessed as related to avapritinib.

  Even though the potential of avapritinib to cause seizures in humans cannot be fully excluded, based on data collected from the clinical development programme, this potential risk is not considered important for inclusion in the RMP as further discussed in PART II: Module SVII.

  Neurocognitive effects of avapritinib were seen in the clinical development programme as events of cognitive impairment. Memory impairment studies in rats failed to provide a translatable model for the neurocognitive defects seen in patients, nor were they able to evaluate the effectiveness of risk mitigation strategies (e.g., patient monitoring with EEG, dose cessation or reduction, or co-treatment with a neurostimulant antidote). In addition, the potential role of any metabolites of avapritinib in causing memory impairment in patients is not known. It is unlikely that the levels of free avapritinib in the brain of affected patients would be high enough to cause meaningful inhibition of Na_V 1.2 (IC_{50} = 280 nM), therefore, it is unlikely that inhibition of Na_V 1.2 in the brain may cause neurocognitive

effects. Overall, the mechanism of neurocognitive effects is unknown. Nevertheless, based on the clinical data, cognitive effects (e.g., memory impairment, cognitive disorder, confusional state, amnesia, somnolence, speech disorder, encephalopathy, delirium, mental impairment, hallucination, mood altered, agitation, disorientation, personality change, dementia, mental status change, and psychotic disorder) is an important identified risk associated with avapritinib in patients with GIST and AdvSM, and important potential risk in patients with ISM (refer to PART II: Module SVII).

Effects on Cardiovascular System

Avapritinib inhibited the human ether-à-go-go-related gene (hERG) channel activity with IC_{50} of 2.4 µM in vitro in a GLP-compliant hERG assay (Study 140717.XSM). This concentration is more than 100-fold above the free geometric mean maximum plasma concentration (C_{max}) at steady state of 0.018 µM at the recommended human dose of 300 mg/day in patients with GIST.

In a GLP-compliant cardiopulmonary safety pharmacology study in radiotelemetry-implanted dogs (Study WIL-124501), no avapritinib-related effects were observed on any cardiovascular parameter (heart rate, mean arterial blood pressure, and systolic, diastolic, and pulse pressure), body temperature, electrocardiogram (ECG) waveform morphology, duration of PR, QRS, RR, QT, and heart rate corrected QT interval (QTc), respiratory parameters, or the clinical condition of the animals. The observed steady state geometric mean C_{max} of approximately 1,500 ng/mL observed at the high dose of 45 mg/kg in the dog cardiopulmonary study was approximately 2-fold greater than the steady state geometric mean C_{max} of 813 ng/mL at the recommended human dose of 300 mg QD in Study BLU-285-1101.

There were no observations of QT prolongation in the 28-day and 3-month dog toxicology studies (Study WIL-124508 and Study WIL-124523).

A single-dose, whole body autoradiography study in rats did not indicate preferential distribution of avapritinib in the heart (Study 124696).

– Relevance to human use: The non-clinical studies did not show any effects of avapritinib on the cardiovascular system.

  In clinical Study BLU-285-1101, a small increase in the QTc interval (6.55 ms [(90% CI: 1.80 to 11.29)] at 300/400 mg QD clinical dose) was observed in a subset of GIST patients; however, this increase was not clinically relevant.

  The mechanism for this slight QTc prolongation in certain patients treated with avapritinib is not understood. Based on the preclinical Study 124696, there is no evidence of a preferential distribution of avapritinib in the heart to suggest any cardiovascular effect due to high local concentrations in the heart.

  Cardiac toxicity and the potential for QT prolongation is considered a class effect of small-molecule TKIs; however, the impact differs between individual agents [93-96].

  Cardiac toxicity seen mostly with multitarget TKIs ranged from asymptomatic QT prolongation to reduction in left ventricular ejection fraction, symptomatic congestive heart failure, acute coronary syndromes, and myocardial infarction. Hypertension and sudden death have also been associated mostly with multitarget TKIs [93-95]. The relevance of these findings to avapritinib remains unknown.

  Considering the existing potential of TKIs to cause cardiac effects, including QT prolongation, cardiac toxicity, including QT prolongation is considered an important potential risk associated with avapritinib (refer to PART II: Module SVII).

Interactions with Other Medicinal Products

In-vitro studies showed that avapritinib phase I metabolism is predominantly mediated by cytochrome P450 (CYP) isozyme 3A4 (CYP3A4), CYP3A5, and to a minor extent by CYP2C9 (Studies 140415, CYP0915-R3, and CYP0915-R4).

In vitro, avapritinib inhibited CYP3A4 with the IC_{50} values of 21.6 µM (testosterone 6β-hydroxylation) and 27.9 µM (midazolam 1'-hydroxylation), respectively. The R_1 values for CYP3A4 inhibition and $R_{1,gut}$ value for CYP3A4 inhibition for avapritinib are either at or above the threshold for a potential clinical drug-drug interaction (DDI) ($R_1 \geq 1.02$ and $R_{1,gut} > 11$) (Study CYP0915-R3) [97, 98].

In vitro, avapritinib demonstrated a time-dependent inhibition of CYP3A4 with a K_I of 12.3 µM and k_{inact} of 0.0301 min^{-1}. The resulting inactivation efficiency (k_{inact}/K_I) for CYP3A4 was 2.45 mL/min/µmol. The estimated R_2 value is above the threshold for a potential DDI ($R_2 \geq 1.25$) (Study CYP0915-R4).

In human hepatocytes, avapritinib increased CYP3A4 messenger ribonucleic acid expression with an EC_{50} of 0.36 µM and a maximal induction effect of 5.7-fold. However, no corresponding increase in CYP3A4 enzyme activity was observed, likely due to concurrent time-dependent inhibition of CYP3A4. The estimated R_3 value is ≤ 0.8, hence DDIs with comedications that are predominantly metabolised by CYP3A are possible, causing them to be ineffective due to decreased exposure.

Using the basic models of reversible inhibition, the time-dependent inhibition and induction, avapritinib is anticipated to alter the pharmacokinetics of CYP3A4 substrate drugs at clinically relevant exposure via its time-dependent inhibition ($R_2 \geq 1.25$) or induction of CYP3A4 ($R_3 \leq 0.8$).

– Relevance to human use: The non-clinical data showed that in vitro, avapritinib is a time-dependent inhibitor of CYP3A and an inducer of CYP3A. Therefore, DDIs with comedications for which CYP3A-mediated metabolism constitutes the primary mechanism of clearance are likely to occur, resulting in increased exposure to the comedication.

  Avapritinib phase I metabolism is primarily mediated by CYP3A4, thus, concomitant treatment with drugs that are moderate or strong CYP3A4 inhibitors or inducers may alter avapritinib plasma concentrations and may result in increased frequency or severity of adverse reactions.

  The non-clinical findings were consistent with the results of the clinical Study BLU-285-0104 conducted in healthy volunteers, which showed that plasma exposure of avapritinib was modulated in the presence of the strong CYP3A4 inducer rifampicin and strong CYP3A4 inhibitor itraconazole.

  Nonetheless, the exact clinical outcomes of these interactions in clinical practice, their severity and impact on patient's quality of life are not established.

  The DDIs with moderate or strong CYP3A inhibitors or inducers represent an important identified risk of avapritinib. In the absence of any clinical data, DDIs with CYP3A substrates represent missing information of avapritinib (refer to PART II: Module SVII).

Phototoxicity

Two GLP-compliant studies were conducted to evaluate the in vitro neutral red uptake phototoxicity of avapritinib in Balb/c 3T3 mouse fibroblasts (Study 20137416) and the in vivo

avapritinib phototoxicity potential after oral administration in pigmented Long Evans rats (Study 20142828).

Avapritinib showed a weak potential for phototoxicity in the in vitro 3T3 mouse fibroblast assay. Avapritinib demonstrated minimal potential for dermal phototoxicity in the phototoxicity study in pigmented Long Evans rats. These effects are consistent with the ultraviolet (UV) light absorption characteristics of avapritinib (Molar Extinction Coefficient in UV range > 1,000 L mol^{-1} cm^{-1}).

– Relevance to human use:

  Non-clinical in-vitro and in-vivo studies showed that avapritinib has a potential for phototoxicity, consistent with the UV absorption characteristics and the preferential distribution in the uvea of the eye likely due to melanin binding.

  In the clinical development programme, patients were advised to wear protective clothing and sunscreen, and to avoid direct sun exposure. Overall, 2.1% of the 749 patients who received treatment with avapritinib for the indications of GIST and AdvSM experienced photosensitivity reaction, representing 10 patients (1.7%) with GIST and 6 patients (4.1%) with AdvSM. In 14 patients (1.9%), the events were treatment related. All photosensitivity reactions were Grade 1 or 2 in severity and assessed as non-serious. Phototoxicity events occurred with low incidence and low severity, without any serious clinical consequences and as such, it is considered that the risk of phototoxicity has minimal clinical impact on patients and on the benefit-risk profile of avapritinib (refer to PART II: Module SVII for further details).

PART II: Module SIII - Clinical Trial Exposure

The clinical development programme evaluating the efficacy and safety of avapritinib in patients with GIST and AdvSM included data from studies BLU-285-1101, BLU-285-1303, BLU-285-2101, and BLU-285-2202, and therefore, the safety population was represented by the pooled safety analyses set of these four clinical trials.

Given the less-aggressive course of ISM, the difference in the recommended dose for patients with ISM (25 mg QD) as compared to those in patients with AdvSM (200 mg QD) and GIST (300 mg QD) as well as the different benefit-risk considerations, the evidence of safety for patients with ISM is based on the ongoing study BLU-285-2203.

Detailed information on the clinical development programme for avapritinib is available in eCTD Module 2.5.

Table 3:Exposure to Avapritinib by Dose and Duration of Treatment (GIST and AdvSM)

Parameter	GIST [a]		AdvSM [b]			Overall Safety Population [c]
	300 mg N=525	All doses N=610	200 mg N=126	≥300 mg N=50	All doses N=193	All doses N=803
Duration of treatment (weeks) [d]						
Mean (SD)	32.24 (34.576)	37.06 (43.437)	51.09 (35.420)	105.74 (68.059)	75.82 (64.281)	46.37 (51.930)
Median	20.00	21.50	41.00	95.86	60.29	25.71
Min, Max	0.1, 191.4	0.1, 255.4	0.9, 188.1	14.1, 218.0	0.9, 266.9	0.1, 266.9
Treatment interval, n (%)						
≤4 weeks	38 (7.2)	43 (7.0)	2 (1.6)	0	2 (1.0)	45 (5.6)
> 4 to ≤ 8 weeks	96 (18.3)	106 (17.4)	7 (5.6)	0	8 (4.1)	114 (14.2)
> 8 to ≤ 12 weeks	55 (10.5)	63 (10.3)	1 (0.8)	0	1 (0.5)	64 (8.0)
> 12 to ≤ 16 weeks	41 (7.8)	46 (7.5)	7 (5.6)	1 (2.0)	8 (4.1)	54 (6.7)
> 16 to ≤ 20 weeks	38 (7.2)	41 (6.7)	11 (8.7)	2 (4.0)	13 (6.7)	54 (6.7)
> 20 to ≤ 24 weeks	29 (5.5)	32 (5.2)	9 (7.1)	4 (8.0)	13 (6.7)	45 (5.6)
> 24 to ≤ 28 weeks	31 (5.9)	35 (5.7)	9 (7.1)	0	11 (5.7)	46 (5.7)
> 28 to ≤ 32 weeks	23 (4.4)	25 (4.1)	5 (4.0)	1 (2.0)	6 (3.1)	31 (3.9)
> 32 to ≤ 36 weeks	23 (4.4)	27 (4.4)	5 (4.0)	4 (8.0)	9 (4.7)	36 (4.5)
> 36 to ≤ 40 weeks	9 (1.7)	10 (1.6)	6 (4.8)	1 (2.0)	7 (3.6)	17 (2.1)
> 40 to ≤ 44 weeks	11 (2.1)	14 (2.3)	5 (4.0)	3 (6.0)	8 (4.1)	22 (2.7)
> 44 to ≤ 48 weeks	16 (3.0)	19 (3.1)	1 (0.8)	1 (2.0)	2 (1.0)	21 (2.6)
> 48 to ≤ 52 weeks	17 (3.2)	19 (3.1)	3 (2.4)	0	3 (1.6)	22 (2.7)
> 52 to ≤ 56 weeks	8 (1.5)	8 (1.3)	1 (0.8)	1 (2.0)	2 (1.0)	10 (1.2)
> 56 weeks	90 (17.1)	122 (20.0)	54 (42.9)	32 (64.0)	100 (51.8)	222 (27.6)

Parameter	GIST [a]		AdvSM [b]			Overall Safety Population [c]
	300 mg N=525	All doses N=610	200 mg N=126	≥300 mg N=50	All doses N=193	All doses N=803
Cumulative dose (mg)						
Mean (SD)	48315.24 (50398.104)	54826.66 (62487.574)	43916.87 (41041.467)	113719.00 (80514.677)	68506.66 (66087.281)	58114.63 (63599.073)
Median	32700.00	34150.00	31000.00	81325.00	47300.00	36200.00
Min, Max	300.0, 289000.0	300.0, 453600.0	1200.0, 262000.0	16400.0, 322500.0	1200.0, 322500.0	300.0, 453600.0
Average daily dose (mg)						
Mean (SD)	259.44 (53.087)	260.13 (64.426)	137.75 (51.459)	181.84 (62.159)	145.26 (58.249)	232.52 (79.853)
Median	287.04	287.37	124.10	198.28	128.82	241.12
Min, Max	110.8, 383.0	30.0, 478.0	31.7, 289.2	71.1, 316.7	30.0, 316.7	30.0, 478.0
Dose intensity (mg/day) [e]						
Mean (SD)	241.48 (62.345)	241.56 (70.021)	126.27 (55.024)	167.49 (59.734)	133.84 (58.595)	215.67 (81.648)
Median	253.99	253.85	111.41	161.00	117.81	214.29
Min, Max	68.0, 375.2	29.0, 400.0	30.3, 284.8	67.4, 316.7	30.0, 316.7	29.0, 400.0
Relative dose intensity [e]						
Mean (SD)	0.97 (0.396)	0.99 (0.579)	0.63 (0.275)	0.54 (0.203)	0.67 (0.378)	0.92 (0.555)
Median	0.95	0.95	0.56	0.51	0.58	0.87
Min, Max	0.2, 2.0	0.2, 7.8	0.2, 1.4	0.2, 1.1	0.2, 3.0	0.2, 7.8
Relative dose intensity category, n (%) [e]						
< 75%	169 (32.2)	199 (32.6)	85 (67.5)	43 (86.0)	128 (66.3)	327 (40.7)
≥ 75% to < 90%	69 (13.1)	79 (13.0)	8 (6.3)	4 (8.0)	16 (8.3)	95 (11.8)
≥ 90% to < 120%	192 (36.6)	221 (36.2)	32 (25.4)	3 (6.0)	41 (21.2)	262 (32.6)

Parameter	GIST [a]		AdvSM [b]			Overall Safety Population [c]
	300 mg N=525	All doses N=610	200 mg N=126	≥300 mg N=50	All doses N=193	All doses N=803
≥ 120% to < 150%	31 (5.9)	35 (5.7)	1 (0.8)	0	5 (2.6)	40 (5.0)
≥ 150%	64 (12.2)	76 (12.5)	0	0	3 (1.6)	79 (9.8)

Abbreviations: AdvSM = advanced systemic mastocytosis; GIST = gastrointestinal stromal tumour; Max = maximum; Min = minimum; SD = standard deviation.

a ‘300 mg’ includes patients from Studies BLU-285-1101 and BLU-285-1303 who received a 300 mg starting dose of avapritinib and patients from Study BLU-285-1303 who received a 300 mg starting dose of avapritinib during Period 2; and ‘All doses’ includes all patients from Studies BLU-285-1101 and BLU-285-1303 who received avapritinib. GIST patients who received a starting dose of 600 mg are included in the GIST ‘All doses’ and Overall Safety Population columns.

b ‘200 mg’ includes patients from Studies BLU-285-2101 and BLU-285-2202 who received a 200 mg starting dose of avapritinib; ‘≥300 mg’ includes patients from Study BLU-285-2101 who received a starting dose of avapritinib ≥300 mg; and ‘All doses’ includes all patients from Studies BLU-285-2101 and BLU-285-2202 who received avapritinib.

c Includes all GIST and AdvSM patients who received avapritinib.

d Duration of treatment (weeks) = (treatment end date – treatment start date + 1)/7.

e Relative dose intensity was defined as the ratio of dose intensity/planned dose intensity. Dose intensity was defined as the cumulative dose divided by the treatment duration. Planned dose intensity was based on the initially assigned daily dose.

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

Data cut-off dates: 25 January 2021 for Study BLU-285-1101, 03 December 2020 for Study BLU-285-1303, and 20 April 2021 for Studies BLU-285-2101 and BLU-285-2202.

Source: Table 18.3.2.1.

Table 4:Exposure to Avapritinib by Age Group, Gender, and Race/Ethnicity, History of TKI Use, and Other Demographic Parameters (GIST and AdvSM)

Parameter	GIST [a]		AdvSM [b]			Overall Safety Population [c]
	300 mg N=525	All doses N=610	200 mg N=126	≥300 mg N=50	All doses N=193	All doses N=803
Age at informed consent (years) [d]						
Mean (SD)	60.4 (11.14)	60.2 (11.06)	66.7 (10.91)	62.8 (11.03)	65.1 (11.36)	61.4 (11.32)
Median	61.0	61.0	68.0	66.0	67.0	62.0
Min, Max	29, 91	25, 91	31, 88	34, 83	31, 88	25, 91
Age group (years), n (%) [d]						
< 65	324 (61.7)	378 (62.0)	47 (37.3)	23 (46.0)	81 (42.0)	459 (57.2)
≥ 65	201 (38.3)	232 (38.0)	79 (62.7)	27 (54.0)	112 (58.0)	344 (42.8)
Sex, n (%)						
Female	173 (33.0)	207 (33.9)	52 (41.3)	23 (46.0)	85 (44.0)	292 (36.4)
Male	352 (67.0)	403 (66.1)	74 (58.7)	27 (54.0)	108 (56.0)	511 (63.6)
Race, n (%)						
American Indian or Alaska Native	1 (<1)	2 (<1)	0	0	0	2 (<1)
Asian	123 (23.4)	123 (20.2)	1 (<1)	2 (4.0)	3 (1.6)	126 (15.7)
Black or African American	19 (3.6)	23 (3.8)	0	1 (2.0)	1 (<1)	24 (3.0)
Native Hawaiian or Other Pacific Islander	3 (<1)	3 (<1)	0	0	0	3 (<1)
White	322 (61.3)	390 (63.9)	109 (86.5)	43 (86.0)	166 (86.0)	556 (69.2)
Other	20 (3.8)	20 (3.3)	14 (11.1)	0	15 (7.8)	35 (4.4)
Unknown	37 (7.0)	49 (8.0)	2 (1.6)	4 (8.0)	8 (4.1)	57 (7.1)

Parameter	GIST [a]		AdvSM [b]			Overall Safety Population [c]
	300 mg N=525	All doses N=610	200 mg N=126	≥300 mg N=50	All doses N=193	All doses N=803
Ethnicity, n (%)						
Hispanic or Latino	16 (3.0)	17 (2.8)	3 (2.4)	1 (2.0)	5 (2.6)	22 (2.7)
Not Hispanic or Latino	453 (86.3)	522 (85.6)	108 (85.7)	46 (92.0)	170 (88.1)	692 (86.2)
Unknown	24 (4.6)	32 (5.2)	1 (<1)	3 (6.0)	4 (2.1)	36 (4.5)
Not reported	32 (6.1)	39 (6.4)	14 (11.1)	0	14 (7.3)	53 (6.6)
Region, n (%)						
Asia	113 (21.5)	113 (18.5)	0	0	0	113 (14.1)
Europe or Australia	222 (42.3)	270 (44.3)	63 (50.0)	8 (16.0)	76 (39.4)	346 (43.1)
North America	190 (36.2)	227 (37.2)	63 (50.0)	42 (84.0)	117 (60.6)	344 (42.8)
Height (cm)						
Mean (SD)	170.71 (9.615)	170.97 (9.706)	170.85 (10.086)	168.83 (9.566)	170.48 (9.907)	170.85 (9.750)
Median	170.20	170.50	172.00	169.50	170.75	170.60
Min, Max	142.0, 207.0	142.0, 207.0	146.0, 196.0	149.9, 192.8	146.0, 196.0	142.0, 207.0
Weight (kg)						
Mean (SD)	74.38 (18.710)	75.12 (19.095)	73.36 (15.675)	74.20 (17.605)	74.04 (16.528)	74.86 (18.505)
Median	72.00	73.00	70.15	74.50	71.00	72.75
Min, Max	41.0, 156.3	39.5, 156.3	42.7, 107.0	42.5, 104.5	42.5, 115.8	39.5, 156.3
BMI (kg/m^2)						
Mean (SD)	25.42 (5.622)	25.58 (5.660)	25.18 (4.954)	25.26 (4.590)	25.31 (4.881)	25.52 (5.483)
Median	24.43	24.65	24.36	25.09	24.63	24.64
Min, Max	15.6, 55.6	15.3, 55.6	16.3, 41.2	17.3, 33.1	16.3, 41.2	15.3, 55.6

Parameter	GIST [a]		AdvSM [b]			Overall Safety Population [c]
	300 mg N=525	All doses N=610	200 mg N=126	≥300 mg N=50	All doses N=193	All doses N=803
BMI (kg/m^2), n (%)						
< 25	266 (50.7)	298 (48.9)	64 (50.8)	22 (44.0)	93 (48.2)	391 (48.7)
≥ 25 to < 30	140 (26.7)	167 (27.4)	36 (28.6)	12 (24.0)	52 (26.9)	219 (27.3)
≥ 30	87 (16.6)	106 (17.4)	17 (13.5)	11 (22.0)	33 (17.1)	139 (17.3)
ECOG performance status, n (%)						
0	243 (46.3)	279 (45.7)	27 (21.4)	13 (26.0)	43 (22.3)	322 (40.1)
1	269 (51.2)	315 (51.6)	66 (52.4)	23 (46.0)	101 (52.3)	416 (51.8)
2	13 (2.5)	16 (2.6)	23 (18.3)	9 (18.0)	34 (17.6)	50 (6.2)
3	0	0	10 (7.9)	5 (10.0)	15 (7.8)	15 (1.9)
Prior midostaurin, 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; GIST = gastrointestinal stromal tumour; ISM = indolent systemic mastocytosis; Max = maximum; MCL = mast cell leukaemia; Min = minimum; SD = standard deviation; SM-AHN = systemic mastocytosis with an associated haematological neoplasm; SSM = smoldering systemic mastocytosis; TKI = tyrosine kinase inhibitor.

a '300 mg' includes patients from Studies BLU-285-1101 and BLU-285-1303 who received a 300 mg starting dose of avapritinib and patients from Study BLU-285-1303 who received a 300 mg starting dose of avapritinib during Period 2; and 'All doses' includes patients from Studies BLU-285-1101 and BLU-285-1303 who received avapritinib. GIST patients who received a starting dose of 600 mg are included in the GIST 'All doses' and Overall Safety Population columns.

b '200 mg' includes patients from Studies BLU-285-2101 and BLU-285-2202 who received a 200 mg starting dose of avapritinib; '≥300 mg' includes patients from Study BLU-285-2101 who received a starting dose of avapritinib ≥300 mg; and 'All doses' includes patients from Studies BLU-285-2101 and BLU-285-2202 who received avapritinib.

c Includes all GIST and AdvSM patients who received avapritinib.

d Age was calculated as [(year of consent) – (year of birth)] – [(month of consent) ≤ (month of birth)] + [(month of consent) = (month of birth) and (day of consent) ≥ (day of birth)].
Note: Percentages are based on the number of patients in the Safety Population in each column.
Data cut-off dates: 25 January 2021 for Study BLU-285-1101, 03 December 2020 for Study BLU-285-1303, and 20 April 2021 for Studies BLU-285-2101 and BLU-285-2202.
Source: Table 18.3.1.3.

Table 5:Exposure to Avapritinib by Dose and Duration of Treatment (ISM)

Parameter	Part 2	Overall Safety Population (Part 1/2/3)	
	Avapritinib 25 mg N=141	All Avapritinib 25 mg [a] N=226	All Avapritinib Doses N=246
Number of doses administered			
Mean (SD)	163.6 (24.30)	311.4 (216.31)	353.1 (269.02)
Median (min, max)	169.0 (20, 195)	269.5 (11, 1113)	288.0 (4, 1113)
Duration of treatment (months) [b]			
Mean (SD)	5.46 (0.726)	10.41 (7.167)	11.84 (8.997)
Median (min, max)	5.55 (0.7, 6.5)	8.87 (0.5, 36.7)	9.74 (0.2, 36.7)
< 6 months, n (%)	135 (95.7)	53 (23.5)	55 (22.4)
≥ 6 months, n (%)	6 (4.3)	173 (76.5)	191 (77.6)
≤ 12 months, n (%)	141 (100.0)	155 (68.6)	158 (64.2)
> 12 months, n (%)	0	71 (31.4)	88 (35.8)
Cumulative dose (total dose taken) (mg) [c]			
Mean (SD)	4,085.0 (608.93)	7,786.4 (5,407.69)	9,788.5 (9,556.05)
Median (min, max)	4,225.0 (500, 4875)	6,750.0 (263; 27,825)	7,300.0 (263; 56,900)
Average daily dose (mg) [d]			
Mean (SD)	25.0 (0.37)	25.0 (0.02)	26.6 (7.57)
Median (min, max)	25.0 (21, 25)	25.0 (25, 25)	25.0 (25, 100)
Dose intensity (mg/day) [e]			
Mean (SD)	24.6 (1.66)	24.6 (1.59)	25.9 (6.49)
Median (min, max)	25.0 (14, 25)	25.0 (12, 25)	25.0 (12, 88)
Relative dose intensity [f]			

Parameter	Part 2	Overall Safety Population (Part 1/2/3)	
	Avapritinib 25 mg N=141	All Avapritinib 25 mg [a] N=226	All Avapritinib Doses N=246
Mean (SD)	99.7 (1.99)	99.7 (1.83)	99.5 (2.54)
Median (min, max)	100.0 (83, 101)	100.0 (75, 100)	100.0 (75, 101)

Abbreviations: max = maximum; min = minimum; SD = standard deviation.

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

b Duration of treatment is defined as (treatment end date-treatment start date + 1)/30.4375.

c Cumulative dose (mg) is defined as the sum of all doses actually taken.

d Average daily dose (mg): cumulative dose/number of days actually dosed.

e Dose intensity (mg/day): cumulative dose/treatment duration (days).

f Relative dose intensity: dose intensity/planned dose intensity. Planned dose intensity is based on initial assigned daily dose.

Note: The table includes all avapritinib-treated patients from Parts 1, 2 and 3 of Study BLU-285-2203 (safety population).

Data cut-off date: 23 June 2022.

Sources: Tables 14.1.5.1a and 14.1.5.1c.

Table 6:Exposure to Avapritinib by Age Group, Gender, and Race/Ethnicity, Baseline Disease Characteristics, and Other Demographic Parameters (ISM)

Parameter	Part 2	Overall Safety Population (Part 1/2/3)	
	Avapritinib 25 mg N=141	All Avapritinib 25 mg [a] N=226	All Avapritinib Doses N=246
Age at informed consent (years) [b]			
Mean (SD)	48.7 (11.70)	49.8 (12.28)	49.7 (12.23)
Median (min, max)	50.0 (18, 77)	51.0 (18, 79)	51.0 (18, 79)
Age group (years), n (%)			
< 65	132 (93.6)	203 (89.8)	222 (90.2)
≥ 65	9 (6.4)	23 (10.2)	24 (9.8)
Sex, n (%)			
Female	100 (70.9)	166 (73.5)	179 (72.8)
Male	41 (29.1)	60 (26.5)	67 (27.2)
Ethnicity, n (%)			
Hispanic or Latino	6 (4.3)	7 (3.1)	8 (3.3)
Not Hispanic or Latino	99 (70.2)	170 (75.2)	189 (76.8)
Not reported	22 (15.6)	32 (14.2)	32 (13.0)
Unknown	14 (9.9)	-	-
Race (%)			
Asian	1 (0.7)	1 (0.4)	1 (0.4)
White	109 (77.3)	185 (81.9)	202 (82.1)
Unknown	27 (19.1)	35 (15.5)	37 (15.0)
Other	4 (2.8)	5 (2.2)	5 (2.0)

Parameter	Part 2	Overall Safety Population (Part 1/2/3)	
	Avapritinib 25 mg N=141	**All Avapritinib 25 mg [a] N=226**	**All Avapritinib Doses N=246**
Height (cm)			
N	137	221	241
Mean (SD)	169.05 (9.726)	168.25 (9.495)	168.30 (9.626)
Median (min, max)	167.00 (152.4, 194.0)	165.60 (150.2, 195.0)	165.90 (142.2, 195.6)
Weight (kg)			
Mean (SD)	81.12 (17.915)	81.31 (18.634)	81.29 (18.375)
Median (min, max)	80.20 (45.0, 126.4)	80.10 (44.1, 148.9)	80.60 (44.1, 148.9)
BMI (kg/m^2)[c]			
N	137	221	241
Mean (SD)	28.31 (5.400)	28.61 (5.644)	28.58 (5.499)
Median (min, max)	27.84 (17.6, 42.0)	28.10 (17.6, 51.4)	28.18 (17.6, 51.4)
Baseline ISM-SAF TSS [d] (Range: 0-110)			
N	139	224	244
Mean (SD)	50.17 (19.145)	48.08 (19.465)	48.48 (19.621)
Median (min, max)	47.86 (12.1, 102.7)	45.04 (5.2, 102.7)	45.62 (5.2, 102.7)
Baseline ISM severity based on ISM-SAF TSS [d], n(%)			
≥ 42 (severe)	87 (61.7)	131 (58.0)	145 (58.9)
< 42 (moderate)	52 (36.9)	93 (41.2)	99 (40.2)
Baseline serum tryptase (ng/mL) [e]			
Mean (SD)	57.57 (54.371)	63.38 (70.265)	67.02 (77.548)
Median (min, max)	38.40 (3.6, 256.0)	39.20 (3.6, 590.4)	40.25 (3.6, 590.4)

Parameter	Part 2	Overall Safety Population (Part 1/2/3)	
	Avapritinib 25 mg N=141	All Avapritinib 25 mg [a] N=226	All Avapritinib Doses N=246
Baseline *KIT D816V* mutation allele burden as measured by MAF using ddPCR from blood (central assay) [e]			
Mean (SD)	2.570 (6.1287)	3.097 (6.9739)	3.154 (7.0658)
Median (min, max)	0.390 (0.00, 41.29)	0.385 (0.00, 41.29)	0.350 (0.00, 41.29)
Presence of *KIT D816V* mutation (central and local assay)			
Mutation detected (central assay) [f] Yes (local assay) [g] No (local assay) [g]	 104 (73.8) 14 (9.9)	 -	 -
No mutation detected (central assay) [f] Yes (local assay) [g] No (local assay) [g]	 13 (9.2) 10 (7.1)	 -	 -
Baseline percent bone marrow mast cells (central pathology review) [e]			
Mean (SD)	11.03 (11.087)	11.14 (11.229)	11.58 (11.761)
Median (min, max)	7.00 (1.0, 50.0)	7.00 (1.0, 60.0)	7.00 (1.0, 60.0)
Mast cell (counts/mm^2) in skin by central lab (lesional)			
N	107	180	197
Mean (SD)	561.2 (399.65)	568.3 (439.20)	579.7 (509.79)
Median (min, max)	459.0 (89, 2870)	451.5 (83, 2870)	446.0 (53, 4300)
Mast cell (counts/mm^2) in skin by central lab (non-lesional)			
N	106	179	196
Mean (SD)	152.2 (76.28)	166.4 (112.11)	160.5 (109.68)
Median (min, max)	131.5 (35, 659)	133.0 (35, 837)	130.0 (10, 837)

Parameter	Part 2	Overall Safety Population (Part 1/2/3)	
	Avapritinib 25 mg N=141	All Avapritinib 25 mg [a] N=226	All Avapritinib Doses N=246
Baseline concomitant BSC use [h]			
Mean (SD)	3.7 (1.94)	3.8 (2.00)	3.9 (2.02)
Median (min, max)	3.0 (0, 11)	4.0 (0, 12)	4.0 (0, 12)

Abbreviations: BMI = body mass index; BSC = best supportive care; CXDX = cycle X, day X; ddPCR = digital-droplet polymerase chain reaction; GI = gastrointestinal; ISM = indolent systemic mastocytosis; ISM-SAF = Indolent Systemic Mastocytosis-Symptom Assessment Form; MAF = mutant allele fraction; Max = maximum; Min = minimum; SD = standard deviation; TSS = total symptom score; WHO = World Health Organization.

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

b Age at the time of informed consent.

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

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

e Baseline refers to the last assessment value prior to C1D1 dosing in the study.

f Baseline *KIT D816V* mutation allele burden as measured by MAF using ddPCR from blood.

g History of *KIT D816V* detection by blood or bone marrow.

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

Note: The table includes all avapritinib-treated patients from Parts 1, 2 and 3 of Study BLU-285-2203 (safety population).

Baseline is defined as the day the first avapritinib dose was received. For the 25 mg avapritinib and all groups, this would be either Part 1 C1D1, Part 2 C1D1, or Part 3 C1D1.

Data cut-off date: 23 June 2022.

Sources: Tables 14.1.3.1.2a, 14.1.3.1.2c, 14.2.2.1.1a, 14.2.1.2.1c, 14.1.4.7a, 14.1.4.7c, 99.2.4.5.1a.

PART II: Module SIV - Populations not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

The important exclusion criteria from the pivotal studies BLU-285-1101, BLU-285-1303, BLU-285-2101 and BLU-285-2202 in patients with GIST and AdvSM, and BLU-285-2203 in patients with ISM are summarised below.

1. Hepatically impaired patients

As defined by alanine aminotransferase and aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN); > 5 × ULN if hepatic metastases are present (GIST only); total bilirubin > 1.5 × ULN; and in presence of Gilbert's disease, total bilirubin > 3 × ULN or direct bilirubin > 1.5 × ULN (GIST and ISM only) or > 2.0 × ULN (AdvSM only).

- **Reason for exclusion:**

  This exclusion criterion was established to minimise the potential confounding factors for evaluation of the efficacy, pharmacokinetics and safety of avapritinib.

- **Is it considered to be included as missing information?** Yes

- **Rationale:**

  Not applicable.

2. Renally impaired patients

As defined by persistent proteinuria of Grade 3 or higher (according to the National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] version 5.0); or as defined by estimated (per institutional standard; e.g., Cockcroft-Gault formula and Modification of Diet in Renal Disease equation) and measured creatinine clearance (CLcr) < 40 mL/min.

- **Reason for exclusion:**

  This exclusion criterion was established to minimise potential confounding factors for evaluation of the efficacy, pharmacokinetics and safety of avapritinib.

  Avapritinib is primarily metabolised in the liver, with unchanged avapritinib representing as little as 11.00% and 0.23% of the administered dose in faeces and urine, respectively.

- **Is it considered to be included as missing information?** No

- **Rationale:**

  Following a single oral dose of ~310 mg (~100 μCi) [^{14}C]-avapritinib, faecal excretion was the predominant route of elimination of drug-related material (70.3%) and excretion in urine was the secondary route of elimination (17.9%). Based on a population pharmacokinetic analysis, avapritinib exposures were similar among 88 subjects with mild renal impairment (CLcr 60 to 89 mL/min), 24 subjects with moderate renal impairment (CLcr 30 to 59 mL/min) and 230 subjects with normal renal function (CLcr ≥ 90 mL/min), suggesting that no dose adjustment is necessary in patients with mild to moderate renal impairment.

  The pharmacokinetics and safety of avapritinib in patients with severe renal impairment (CLcr 15 to 29 mL/min) or end-stage renal disease (CLcr < 15 mL/min) have not been studied.

The impact of reduced renal function on avapritinib's protein binding capacity was investigated. Plasma protein binding of avapritinib was tested at 3 concentrations (0.1, 1 and 10 µM) in plasma from healthy subjects (N=3) and patients with chronic kidney disease (N=3). The 3 patients with chronic kidney disease had estimated glomerular filtration rate < 30 mL/min. The concentrations at 0.1 µM were below the lower limit of quantification, therefore, the extent of protein binding could not be determined. At 1 and 10 µM, the plasma protein binding was similar between healthy subjects and patients with chronic kidney disease. Thus, reduced renal function does not impact avapritinib's protein binding capacity. Therefore, no further analysis or investigation, including pharmacokinetic study, is deemed necessary in subjects with reduced renal function.

3. Patients requiring therapy with a concomitant medication that is a strong inhibitor, strong inducer, or moderate inducer of CYP3A4

- **Reason for exclusion:**

  Data from non-clinical studies (refer to PART II: Module SII) revealed that phase I metabolism of avapritinib is predominantly mediated by CYP3A4, CYP3A5, and with minor contribution from CYP2C9. Thus, plasma levels of avapritinib can be affected when administered concomitantly with a strong CYP3A inhibitor or strong CYP3A inducer. As such, this exclusion criterion was established as a precautionary measure to minimise potentially confounding factors for evaluation of the efficacy and safety of avapritinib.

  The initial exclusion criterion was further amended based on findings from the clinical pharmacology Study BLU-285-0104, which showed that co-administration of a strong CYP3A4 inducer, rifampicin (600 mg QD for 18 days), with a single 400 mg dose of avapritinib on Day 9 decreased avapritinib C_{max} by 74% and AUC from time 0 to infinity ($AUC_{0\text{-}inf}$) by 92%, relative to a 400 mg dose of avapritinib administered alone. Additionally, co-administration of a strong CYP3A4 inhibitor itraconazole (200 mg twice daily on Day 1 followed by 200 mg QD for 13 days) with a single 200 mg dose of avapritinib on Day 4 increased avapritinib C_{max} by 1.4-fold and $AUC_{0\text{-}inf}$ by 4.2-fold, relative to a 200 mg dose of avapritinib administered alone.

- **Is it considered to be included as missing information?** No.

- **Rationale:**

  It is expected that administration of avapritinib together with a moderate or strong CYP3A inhibitor or inducer will lead to changes in the avapritinib plasma concentration, resulting in either an increased risk of adverse reactions or decreased efficacy. Although not observed in clinical trials due to the exclusion criterion as mentioned above, these changes might have significant clinical outcomes with impact on the patients treated with avapritinib. As such, the DDIs with moderate or strong CYP3A inhibitors or inducers represent an important identified risk of avapritinib for all indications (refer to PART II: Module SVII).

4. Patients with a QT interval corrected using Fridericia's formula (QTcF) of > 450 ms (GIST and ISM only) or > 480 ms (AdvSM only);

Patients with a history of prolonged QT syndrome or Torsade de pointes;

Patients with a family history of prolonged QT syndrome

– **Reason for exclusion:**

The potential for QT interval prolongation has been observed with the use of small-molecule TKIs [96, 99, 100]. As such, these exclusion criteria were established as a precautionary measure, to decrease the number of patients that could potentially develop severe cardiovascular events.

– **Is it considered to be included as missing information?** No

– **Rationale:**

The ability of avapritinib to prolong the QT interval was assessed in 27 patients from Study BLU-285-1101, who were administered avapritinib at doses of 300/400 mg QD (i.e., 12 to 16 times the 25 mg dose recommended for ISM patients, 1.33 times the 300 mg dose recommended for GIST patients). The estimated mean change from baseline in QTcF was 6.55 ms (90% CI: 1.80-11.29) at the observed steady state geometric mean C_{max} of 899 ng/mL. No effect on heart rate or cardiac conduction (PR, QRS, and RR intervals) was observed.

Considering the class potential of certain small-molecule TKIs to cause QTc prolongation [96] and cardiac toxicity associated with multitarget TKIs [93-95], cardiac toxicity, including QT prolongation is considered an important potential risk for avapritinib (refer to PART II: Module SVII for further details).

5. Patients with a history of a cerebrovascular accident or transient ischaemic attack within 1 year prior to the first dose of study drug;

Patients with a known risk of intracranial bleeding, such as a brain aneurysm or history of subdural or subarachnoid bleeding;

Patients with a primary brain malignancy or metastases to the brain.

– **Reason for exclusion:**

In non-clinical studies (refer to PART II: Module SII), CNS haemorrhage was observed at subtherapeutic exposure multiples (30 mg/kg/day in dogs).

In addition, intracranial haemorrhage was associated with use of other TKIs such as dasatinib or imatinib [101], including their use in patients with GIST [102]. As such, patients considered at higher risk of experiencing intracranial bleeding were excluded from clinical trials.

– **Is it considered to be included as missing information?** No

– **Rationale:**

Intracranial haemorrhage (e.g., haemorrhage intracranial, cerebral haemorrhage, and subdural haematoma) is considered an important identified risk associated with the use of avapritinib in patients with GIST and AdvSM, while an important potential risk in patients with ISM. The risk factors and special populations at risk for such events are presented in detail in PART II: Module SVII.

6. Female patients who are unwilling, if not postmenopausal or surgically sterile, to abstain from sexual intercourse or employ contraception from the first dose of study drug to at least 6 weeks after the last dose of study drug;

Female patients who are pregnant, as documented by a serum beta human chorionic gonadotropin pregnancy test consistent with pregnancy obtained within 7 days (GIST and ISM only) or 15 days (AdvSM only) before the first dose of study drug

- **Reason for exclusion:**

  Avapritinib was teratogenic and embryotoxic in rats at doses approximately 31.4, 6.3, 2.7 times greater than the human exposure at the therapeutic dose of 25 mg, 200 mg, and 300 mg avapritinib, respectively (refer to PART II: Module SII). Therefore, the above exclusion criteria represented a standard measure to avoid any adverse effects on pregnancy.

- **Is it considered to be included as missing information?** No

- **Rationale:**

  Pregnant or lactating women were excluded from the clinical development programme, and women of child-bearing potential were required to use appropriate methods of contraception during the treatment course with avapritinib and for 6 weeks for females and 2 weeks for males after the last administered dose. As such, there are no data on the use of avapritinib in this special patient population.

  However, non-clinical studies showed that avapritinib is teratogenic and embryotoxic and it is expected to have similar effects in humans. Foetal toxicity has been reported with post-marketing use of other TKIs [92, 103]. As such, embryofoetal toxicity is considered as an important potential risk for all indications (refer to PART II: Module SVII).

7. Women who are breastfeeding

- **Reason for exclusion:**

  Exclusion of breastfeeding women represents a standard ethical measure.

  No non-clinical studies were conducted to evaluate whether avapritinib or its metabolites are excreted in the milk of a lactating female. As such, the effects of avapritinib on this population could not be anticipated, and a risk to the breastfed child could not be excluded (refer to PART II: Module SII).

- **Is it considered to be included as missing information?** No

- **Rationale:**

  There are no data regarding the secretion of avapritinib or its metabolites in human milk nor on their effects on the breastfed infant or on milk production. Because of the potential for adverse reactions in breastfed infants from avapritinib, breastfeeding should be discontinued during treatment with avapritinib and for 2 weeks after the last administered dose. As such, it is expected that avapritinib will not be used by breastfeeding women, and no data on use in this population are expected to be collected from the post-marketing setting.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programme

The data set pooled for evaluation of the clinical safety of avapritinib in patients with GIST and AdvSM originates from studies BLU-285-1101, BLU-285-1303, BLU-285-2101, and BLU-285-2202, whereas the clinical development programme in patients with ISM includes data from study BLU-285-2203 only.

Avapritinib has an orphan designation for treatment of GIST and for treatment of mastocytosis. The clinical development programme is unlikely to detect certain types of adverse reactions such as uncommon and rare adverse reactions (considering the overall safety population of 803 patients with GIST and AdvSM, and 246 patients with ISM), adverse reactions with a long latency, or those caused by prolonged exposure.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table 7:Exposure of Special Populations Included or not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant and breastfeeding women	Not included in clinical development programme
Elderly patients	Refer to Table 4 and Table 6 for exposure figures by age groups for patients with GIST/AdvSM and ISM, respectively.
Patients with different races or ethnic origins	Refer to Table 4 and Table 6 for exposure figures by race and ethnic origin for patients with GIST/AdvSM and ISM, respectively.
Patients with relevant comorbidities:	
– Advanced cardiac disorders	Not included in the clinical development programme.
– Advanced hepatic impairment	Not included in the initial clinical development programme but included in a separate pharmacokinetic study.
– Renal impairment	Not included in the clinical development programme.

Abbreviations: AdvSM = advanced systemic mastocytosis; GIST = gastrointestinal stromal tumour; ISM = indolent systemic mastocytosis.

PART II: Module SV - Post-Authorisation Experience

SV.1 Post-Authorisation Exposure

Avapritinib received the first marketing authorisation approval in the US on 09 January 2020 under the trade name AYVAKIT for the treatment of adults with unresectable or metastatic GIST harbouring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations. The date of this initial marketing authorisation represents the International Birth Date (IBD) for avapritinib. AYVAKIT was subsequently approved in the US for the treatment of adult patients with AdvSM, including patients with ASM, SM-AHN, and MCL on 16 June 2021.

In the EU/EEA, avapritinib received the marketing authorisation on 24 September 2020 under the trade name AYVAKYT for the treatment of adult patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation. AYVAKYT was subsequently approved in the EU/EEA on 24 March 2022 for the treatment of adult patients with ASM, SM-AHN or MCL, after at least one systemic therapy.

At the data lock point (DLP) of the latest periodic benefit-risk evaluation report (PBRER) (08 July 2022), avapritinib was marketed in 9 countries, including 5 EU countries (Denmark, France, Italy, Germany, and the Netherlands).

SV.1.1 Method Used to Calculate Exposure

The following points are considered when estimating the patient exposure from the post-marketing experience with avapritinib:

- Patient-years are calculated based on the actual number of dispensed tablets and not the number of bottles dispensed (each bottle contains 30 tablets of avapritinib).
- The number of patient-days is the same as the number of dispensed tablets, i.e., it is assumed that 1 tablet is taken per day regardless of the tablet strength.
- 365 represents the number of days in a year.

SV.1.2 Patient Exposure from Marketing Experience

Since the IBD until the DLP of the latest PBRER (08 July 2022), the overall estimated post-marketing exposure to avapritinib is 1,222.72 patient-years.

Cumulatively until the DLP of the latest PBRER (08 July 2022), 22,710 tablets of avapritinib were dispensed in the EU/EEA. This corresponds to an estimated 62.22 patient-years.

Data by age, sex, or other demographic characteristics are not available for the exposure from the post-marketing experience with avapritinib.

PART II: Module SVI - Additional EU Requirements for Safety Specification

Potential for misuse for illegal purposes

Considering the mechanism of action of avapritinib, the potential for misuse for illegal purposes is negligible and does not constitute a safety concern.

PART II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

– **Risks with minimal clinical impact on patients (in relation to the severity of the indication treated) or on the benefit-risk profile of avapritinib:**

Seizures

Seizures or convulsions were observed in rats at high, poorly tolerated doses exceeding the highest non-severely toxic dose (refer to PART II: Module SII). Seizures in rats occurred at systemic exposures ≥8-fold higher than the exposure in patients at the 300 mg/day dose level, and there were no microscopic correlates in the brains of these rats.

Overall, in the clinical development programme as of the DLP of the initial RMP (18 December 2018), 2 (0.6%) of the 335 patients who received treatment with avapritinib experienced events of seizure. Both patients were part of the GIST group, with a starting dose of < 300 mg.

One patient experienced a Grade 2 event of 'seizure', and one patient experienced a Grade 1 event of 'epilepsy'. Both events were non-serious. None of the patients had a prior medical history of seizures or epilepsy, however, the event of seizure occurred in a patient with cerebral haemorrhage. No change in study drug dosing was made as a result of these events. At the time of this RMP, the event of 'seizure' resolved, and the event of 'epilepsy' was ongoing. The Investigators assessed the events as possibly related to study drug. Given the limited amount of information available for these 2 non-serious events, a causal association to study drug cannot be ruled out.

In addition, by the time of the of the 08 July 2019 data cut-off, one additional non-serious event of 'seizure' occurred. Therefore, 3 (0.6%) of the overall 506 patients who received avapritinib experienced events of seizure. All 3 events occurred in GIST patients.

Events of seizure may have a significant impact on patients' quality of life and can lead to long-term sequelae if not managed in a timely manner. However, in spite of the findings in animal models showing avapritinib at high doses can cause seizures, these findings were not replicated in humans, with only two non-serious events of seizure occurring as of the DLP of the initial RMP (18 December 2018). As such, the risk is considered acceptable in relation to the severity of the indication treated. No risk minimisation measures are deemed necessary at this time and routine pharmacovigilance is considered sufficient for further characterising this risk.

Phototoxicity

Non-clinical in-vitro and in-vivo studies showed that avapritinib has a potential for phototoxicity, consistent with the UV absorption characteristics and the preferential distribution in the uvea of the eye likely due to melanin binding.

Overall, as of the DLP of the initial RMP (18 December 2018), 3% of the 335 patients who received treatment with avapritinib for the indications of GIST and AdvSM, experienced photosensitivity reaction, representing 9 patients with GIST and 1 patient with AdvSM. All events were treatment related, Grade 1 or 2 in severity and assessed as not serious.

Patients in the avapritinib clinical development programme were advised to avoid or minimise sun exposure through use of sunscreen and clothing. Phototoxicity events occurred with low incidence and low severity, without any serious clinical consequences. As such, it is considered that the risk has minimal clinical impact on patients and on the benefit-risk profile of avapritinib.

– **Risks with clinical consequences, even serious (but occurring with a low frequency), considered to be acceptable in relation to the severity of the indication treated:**

Fluid retention (pleural effusion)

Overall as of the DLP of the initial RMP (18 December 2018), 11.3% of the 335 patients who received treatment with avapritinib for the indications of GIST and AdvSM, experienced events of pleural effusion, representing 31 patients with GIST and 7 patients with AdvSM. The majority of events were Grade 1 or 2 in severity, but events ≥Grade 3 also occurred, in 2.1% of the patients. Only 2.6% of patients with GIST and 4.4% of patients with AdvSM experienced serious events of pleural effusion. One patient experienced a fatal event but was assessed as not related to the treatment. One patient discontinued the treatment in response to the event of pleural effusion.

Pleural effusions are an expected and manageable toxicity in advanced GIST, most likely related to inhibition of wild-type *KIT/PDGFRA* [104, 105]. Although the events of pleural effusion occurred with a high frequency in the clinical development programme, the serious or clinically significant cases were infrequent. The risk is easily manageable through routine, well-established clinical measures, including administration of diuretics and interventional procedures for fluid removal. As such, the risk is considered acceptable in relation to the severity of the indication treated.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important identified risks:

– **Intracranial haemorrhage (e.g., haemorrhage intracranial, cerebral haemorrhage, and subdural haematoma)**

Risk-benefit impact:

As of the DLP of the initial RMP (18 December 2018), events of intracranial haemorrhage, including haemorrhage intracranial, cerebral haemorrhage, and subdural haematoma have been reported in the overall safety population with a 3% frequency in the clinical development programme for avapritinib (1.1% of all patients with GIST and 10.3% of patients with AdvSM). None of the reported events were fatal at the DLP of the initial RMP (one patient who had intracranial bleeding died of disease progression while the event of intracranial haemorrhage was ongoing), but in almost one third of the patients, it led to discontinuation of treatment.

Intracranial haemorrhage is a serious, life-threatening event, leading to dose interruptions when occurring with mild severity, or even permanent discontinuation of the drug when occurring with increased severity. Considering the known association of intracranial haemorrhage with other TKIs, including imatinib, and the seriousness of these events, intracranial haemorrhage has a significant impact on the benefit-risk profile of avapritinib.

- **Cognitive effects (e.g., memory impairment, cognitive disorders, confusional state, and encephalopathy)**

  Risk-benefit impact:

  Cases of cognitive effects, including memory impairment, cognitive disorder, confusional state and encephalopathy had been frequently reported in the clinical development programme for avapritinib (36.4%) as of the DLP of the initial RMP (18 December 2018). However, the majority of the cognitive effects were non-serious and of low severity.

  Cognitive effects have been identified in association with other authorised TKIs (such as larotrectinib and lorlatinib), but the mechanism of occurrence, as well as long-term outcomes remain unknown. Considering the frequency of cognitive effects in avapritinib-treated patients and the potential for affecting patient's quality of life, this risk is considered important for the risk management.

- **Drug-drug interactions with moderate or strong CYP3A inhibitors or inducers**

  Risk-benefit impact:

  The data from the non-clinical studies showed that plasma levels of avapritinib can be affected when administered concomitantly with a strong CYP3A inhibitor or strong CYP3A inducer (refer to PART II: Module SII). The only clinical data available originated from a single-dose, pharmacology Study BLU-285-0104, where the overall findings indicated that strong CYP3A inhibitors and inducers will have marked effects on the pharmacokinetics of avapritinib after a single oral dose. Although not observed in clinical trials, such changes in pharmacokinetics of avapritinib might have potentially significant clinical outcomes in treated patients.

Important potential risks:

- **Cardiac toxicity, including QT prolongation**

  Risk-benefit impact:

  The non-clinical studies did not show any effects of avapritinib on the cardiovascular system. In the clinical Study BLU-285-1101, a small increase in the QTc interval (6.55 ms [(90% CI: 1.80 to 11.29)] at 300/400 mg QD clinical dose) that was not clinically relevant was observed in a subset of GIST patients. In addition, the slope of the avapritinib concentration-QTc relationship was very shallow: 0.007 ms per ng/mL (90% CI: 0.003 to 0.012), with a small and not statistically significant intercept of -0.2 ms (90% CI: -2.26 to 1.89).

  Based on preclinical data, there is no evidence of a preferential distribution of avapritinib in the heart to suggest any cardiovascular effect due to high local concentrations in the heart. However, considering the existing potential of mainly multitarget TKIs to cause QT prolongation [96] and cardiac toxicity [93-96], cardiac toxicity, including QT prolongation is considered an important potential risk associated with avapritinib.

- **Embryofoetal toxicity**

  Risk-benefit impact:

  Avapritinib demonstrated the potential for developmental toxicity in an embryofoetal development study in pregnant rats (refer to PART II: Module SII).This is consistent with the known effects of TKIs on pregnancy in humans, collected from the post-marketing experience with these agents [92, 103].

No data are available on the safety of avapritinib use in pregnant women; however, published data on imatinib use showed adverse effects on foetal development in humans. As pregnant women were excluded from the clinical programme for avapritinib, there are no data on use of avapritinib during pregnancy. Based on the non-clinical embryotoxic evidence and the experience with other TKIs, a risk to the pregnant woman and the foetus cannot be excluded.

Missing information:

– **Use in patients with severe hepatic impairment**

Risk-benefit impact:

Patients with severe hepatic impairment (total bilirubin > 3.0 × ULN and any AST) were excluded from the clinical development programme for avapritinib. Based on a population pharmacokinetic analysis, avapritinib exposure levels in patients with mild and moderate hepatic impairment are similar to those in patients with normal hepatic function. However, given that hepatic elimination is a major route of excretion for avapritinib, severe hepatic impairment may result in alteration of plasma avapritinib concentrations that cannot be predicted based on available data. As such, use in patients with severe hepatic impairment is considered missing information.

– **Drug-drug interaction with CYP3A substrates**

Risk-benefit impact:

The non-clinical data showed that in vitro, avapritinib is a time dependent inhibitor and inducer of CYP3A. As such, avapritinib is anticipated to alter the pharmacokinetics of CYP3A substrate drugs at clinically relevant exposure via its time dependent inhibition or induction of CYP3A (refer to PART II: Module SII). In the absence of any clinical data, these interactions and their clinical relevance represent missing information of avapritinib.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

No new safety concerns for avapritinib are proposed with this RMP update. However, the important identified and important potential risks were revised in light of the application for the treatment of ISM in the EU. Namely, in this updated RMP, intracranial haemorrhage and cognitive effects are considered important identified risks for avapritinib in patients with GIST and AdvSM, and important potential risks in patients with ISM, reflecting the different safety profiles of avapritinib in these patient populations and recommended avapritinib doses in these indications (i.e., 25 mg QD for patients with ISM as compared to 200 mg QD in patients with AdvSM and 300 mg QD in patients with and GIST).

Intracranial haemorrhage

In patients with AdvSM, who received a higher starting dose of 200 mg avapritinib, severe thrombocytopenia (defined as $< 50 \times 10^9$/L) was identified as the primary risk factor for intracranial haemorrhage. Patients with AdvSM are at higher risk of developing intracranial haemorrhage, considering that the underlying disease often causes haematopoietic insufficiency leading to severe thrombocytopenia. Therefore, platelet count monitoring and dose modifications are very important measures in the setting of AdvSM and have been shown to reduce the occurrence of intracranial haemorrhage in AdvSM clinical trials.

No events of intracranial haemorrhage were reported during study BLU-285-2203 in patients with ISM, and treatment with avapritinib was not associated with an increased risk of

developing thrombocytopenia. By definition, thrombocytopenia is not observed in patients with ISM, as this would be considered a C-finding that would be indicative of advanced disease.

During study BLU-285-2203, treatment-emergent thrombocytopenia was rarely reported in patients with ISM and was only Grade 1 in severity. One patient receiving 25 mg avapritinib in Part 2 of the study and 2 patients in Part 3 (both with prior placebo) had Grade 1 thrombocytopenia. Shifts in platelet count decreased (in 3.5% of patients receiving 25 mg avapritinib and 2.8% of patients receiving placebo) were also to Grade 1 only. Additionally, across all study parts, the frequency and severity of shifts in platelet decrease in patients over time with longer exposure were similar to what was observed in Part 2 of the study. These shifts were transient with platelet counts returning to normal values in most of the patients. No patient experienced a shift to ≥Grade 2 platelet count decrease.

It can be concluded that patients with ISM do not have baseline thrombocytopenia and when treated with 25 mg avapritinib QD, are not at risk of developing clinically significant thrombocytopenia. Therefore, platelet monitoring in this patient population is not deemed necessary as a risk minimisation measure.

Taking the above considerations into account, intracranial haemorrhage is considered an important potential risk in the ISM patient population.

Cognitive effects

In study BLU-285-2203, treatment with 25 mg avapritinib in patients with ISM was not associated with an increased risk of developing cognitive effect events. These events were infrequent in both treatment groups (avapritinib and placebo) and slightly lower in the 25 mg avapritinib group (2.8%) compared with the placebo group (4.2%). This lower incidence in the avapritinib group suggests that these events are most likely due to the patients' underlying disease and other treatments patients were receiving as part of their BSC.

Cognitive effects have been observed in the clinical studies in patients with GIST and AdvSM, following treatment with avapritinib at higher doses. The exposure-response analyses of safety in patients with GIST and AdvSM showed that increased avapritinib exposure was associated with an increased risk of cognitive effect events.

Taking the above considerations into account, cognitive effects are considered an important potential risk in the ISM patient population.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1 Important Identified Risk 1: Intracranial Haemorrhage (GIST and AdvSM)

Potential Mechanisms:

The mechanism by which avapritinib may increase the risk of intracranial haemorrhage is not yet understood. It is hypothesised that there are two main mechanisms by which TKIs may cause intracranial haemorrhage:

- TKIs can alter platelet function which may predispose patients to intracranial haemorrhage [101]. Imatinib is believed to cause platelet dysfunction which may not be detectable by standard testing, leading to intracranial haemorrhage [106].
- The other postulated aetiology for risk of intracranial haemorrhage is linked to the TKIs/avapritinib's mechanism of action, targeting platelet-derived growth factor receptor

(PDGFR). Inhibition of PDGFRB was linked with the under-development of microvascular pericytes in mice, thus compromising the mechanical stability of the blood vessels [90].

An in-vitro assessment revealed that there were no effects of avapritinib in vitro on platelets isolated from normal volunteers and platelet aggregation and activation were unaffected by treatment with avapritinib at concentrations spanning the clinically relevant range (Study 6000714).

In the AdvSM population, severe thrombocytopenia was identified as the primary risk factor for intracranial haemorrhage and is further discussed below.

Evidence Sources and Strength of Evidence:

This risk is based on the events of intracranial haemorrhage observed in patients treated with avapritinib in the clinical development programme, even though the causality evaluation of the events was confounded by alternative aetiologies or other risk factors.

The non-clinical data from the avapritinib development programme showed the development of choroid plexus oedema in dogs with exposure margins of 4.7, 1.0, and 0.4 times the human exposure at the 25 mg, 200 mg, and 300 mg clinical doses, respectively, as well as brain haemorrhage in dogs with exposure margins of 9.0, 1.8, and 0.8 times the human exposure at the 25 mg, 200 mg, and 300 mg clinical doses, respectively (refer to PART II: Module SII).

In addition, intracranial haemorrhage was associated with use of other TKIs such as dasatinib or imatinib [101], including their use in patients with GIST [102, 106].

Lastly, a majority of AdvSM patients with intracranial haemorrhage had severe thrombocytopenia, preceding or at the time of the event.

Characterisation of the Risk:

In general, intracranial haemorrhage is an important public health problem leading to marked mortality and morbidity [107]. However, the causes for intracranial haemorrhage differ in the cancer population from that in the general population as will be further discussed in the 'Risk factors and risk groups' part of this sub-section [108, 109].

Clinical Trials

GIST and AdvSM

Frequency

In the avapritinib clinical trials, events of intracranial haemorrhage occurred in 25 patients (3.1%) within the overall safety population (refer to distribution of events per indication in Table 8). The incidence of intracranial haemorrhage was 2.5% in patients with AdvSM without pre-existing severe thrombocytopenia and treated at a starting dose of 200 mg QD.

Table 8:Adverse Events of Intracranial Haemorrhage in the Safety Population by MedDRA PT (GIST and AdvSM)

Adverse Event (MedDRA PT)	GIST (All Doses, N=610)	AdvSM (All Doses, N=193)	Overall Safety Population (N=803)
	n (%)	n (%)	n (%)
Subdural haematoma	5 (<1)	7 (3.6)	**12 (1.5)**
Haemorrhage intracranial	6 (<1)	5 (2.6)	**11 (1.4)**

Adverse Event (MedDRA PT)	GIST (All Doses, N=610)	AdvSM (All Doses, N=193)	Overall Safety Population (N=803)
	n (%)	n (%)	n (%)
Cerebral haemorrhage	3 (<1)	0	**3 (<1)**
Total Unique Patients	**13[a] (2.1)**	**12 (6.2)**	**25 (3.1)**

Abbreviations: AdvSM = advanced systemic mastocytosis; GIST = gastrointestinal stromal tumour; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term.
If a patient experienced more than 1 event within a given adverse event category or preferred term, that patient was counted only once for that category or term.
a 1 patient with GIST had two events: subdural haematoma and haemorrhage intracranial.
A discrepancy in the number of intracranial haemorrhage events for patients with GIST was noted. An additional event of nonserious Grade 2 haemorrhage intracranial was captured in the safety database but was not reflected in the clinical database or in the source table listed below. Numbers shown in the table above include this additional patient.
Percentages are based on the number of patients in the Safety Population in each column.
Data cut-off dates: 25 January 2021 for Study BLU-285-1101, 03 December 2020 for Study BLU-285-1303, and 20 April 2021 for Studies BLU-285-2101 and BLU-285-2202.
Source: Table 18.3.3.2.1.1.

Severity, Reversibility, and Long-Term Outcomes

GIST

In the GIST patient group, subdural haematoma was reported in 5 patients (< 1%). Grade 1 subdural haematoma was reported in 2 patients and 1 patient each reported Grade 2, Grade 3, and Grade 4 subdural haematoma. In 3 patients, the events of subdural haematoma were assessed as serious. In 3 patients, the events of subdural haematoma were assessed as related to avapritinib.

A total of 6 patients (< 1%) had events of haemorrhage intracranial. Grade 1 haemorrhage intracranial was reported in 2 patients, Grade 2 in 1 patient, Grade 3 in 1 patient, and Grade 4 in 2 patients. In 4 patients, the events of haemorrhage intracranial were serious. In all 6 patients, the haemorrhage intracranial events were assessed as related to avapritinib. One patient had two events (subdural haematoma and haemorrhage intracranial).

A total of 3 patients (< 1%) had events of cerebral haemorrhage. Grade 3 cerebral haemorrhage was reported in 2 patients and Grade 4 in 1 patient, and all were serious. In all 3 patients, the events of cerebral haemorrhage were assessed as related to avapritinib.

Events of intracranial haemorrhage (all grades) occurred in a range from 8 weeks to 84 weeks after initiating avapritinib, with a median time to onset of 22 weeks.

Avapritinib treatment was permanently discontinued in 7 patients with GIST (1.1%) with intracranial haemorrhage events (3 patients with cerebral haemorrhage, 2 patients with subdural haematoma, and 2 patients with haemorrhage intracranial) and it was temporarily interrupted in 4 patients (< 1%) (2 patients with subdural haematoma and 2 patients with haemorrhage intracranial).

The ≥Grade 2 intracranial haemorrhage events were reported as resolved in 6 patients (1.0%), resolved with sequelae in 3 patients (< 1%), and ongoing in 1 patient (< 1%). None of the intracranial haemorrhage events in the GIST patient group were fatal. The median time to improvement and resolution was 25 weeks for intracranial haemorrhage of ≥ Grade 2.

Confounding factors were reported in 11 of 13 patients with GIST with intracranial haemorrhage events and included history of hypertension in 9 patients, angiopathies in 2 patients, brain structural/vascular abnormalities (e.g., cavernous haemangiomas or cavernous arteriovenous fistula) in 4 patients, likely head trauma in 2 patients, and aspirin use in 1 patient.

AdvSM

In the AdvSM patient group, subdural haematoma was reported in 7 patients (3.6%). Grade 1 subdural haematoma was reported in 4 patients and 1 patient each had Grade 2, Grade 3, and Grade 4 subdural haematoma. In 6 patients, the events of subdural haematoma were assessed as serious. In 5 patients, the events of subdural haematoma were assessed as related to avapritinib.

A total of 5 patients (2.6%) had events of haemorrhage intracranial. Grade 1 haemorrhage intracranial was reported in 1 patient, Grade 2 in 2 patients, Grade 3 in 1 patient, and Grade 5 in 1 patient. In 4 patients, the events of haemorrhage intracranial were serious. In 4 patients, the haemorrhage intracranial events were assessed as related to avapritinib. One serious event of haemorrhage intracranial was Grade 5 in severity and assessed as related to avapritinib. This fatal event occurred in an elderly patient with SM-myelodysplastic syndrome as a result of prior head trauma and in the setting of severe thrombocytopenia (platelet count on admission: 40×10^9/L; normal range 130-400 [units not specified]).

No events of cerebral haemorrhage were reported in patients with AdvSM in the clinical trials with avapritinib.

Events of intracranial haemorrhage (all grades) occurred in a range from 12.0 weeks to 15.0 weeks after initiating avapritinib, with a median time to onset of 12.1 weeks.

Avapritinib treatment was permanently discontinued in 6 patients with AdvSM (3.1%) with intracranial haemorrhage events (3 patients with haemorrhage intracranial and 3 patients with subdural haematoma) and was temporarily interrupted in 4 patients (2.1%) (3 patients with subdural haematoma and 1 patient with haemorrhage intracranial).

The events that resulted in temporary interruption and restarting at a reduced dose and those that resulted in no change in study drug dosing occurred prior to the protocol amendment that required permanent discontinuation of treatment in the setting of intracranial haemorrhage of any severity.

The ≥Grade 2 intracranial haemorrhage events were reported as resolved in 5 patients (2.6%) and as resolved with sequelae in 1 patient. One of the intracranial haemorrhage events was fatal as described above.

Confounding factors were reported in all 12 patients with AdvSM with intracranial haemorrhage events and included severe thrombocytopenia preceding or at the time of the event in 10 patients, history of hypertension in 6 patients, concurrent use of aspirin in 2 patients, prior falls with head trauma in 2 patients, history of coagulopathy in 1 patient, history of alcohol abuse, chronic myelomonocytic leukaemia, and an increased international normalisation ratio in 1 patient.

Impact on Quality of Life

Intracranial haemorrhage is a potentially life-threatening event which may lead to or prolong hospitalisation, residual neurological damage or may even result in death.

Post-Authorisation Experience (Data Lock Point of 08 July 2022)

A comprehensive analysis of data collected during the post-marketing experience in patients with GIST and AdvSM does not indicate a change in the characterisation of the risk.

Risk Factors and Risk Groups:

Intracranial haemorrhage occurs in 7% of patients with cancer, and subdural haematoma has been estimated to account for 26% of intracranial haemorrhage found at autopsy in this population of patients [109].

Intracranial haemorrhage accounts for nearly one half of all cerebrovascular events in cancer patients, but the risk factors vary between types of cancer [108]. Intracranial haemorrhage is common in haematological malignancies or in the presence of brain metastases. However, brain metastases are extremely rare in GIST [4] and only 16 cases of brain metastases in patients with GIST were reported in the literature until 2014 [1].

Events of subdural haematoma in patients with GIST treated with imatinib were reported in the literature [102, 106] in the absence of other obvious causes such as head trauma, brain metastases, thrombocytopenia or anticoagulation which represent the most common general risk factors for such events, and the suspected cause was imatinib-related platelet dysfunction. It has been estimated that the rate of imatinib-related intracranial haemorrhage in the absence of other obvious causes may be between 1.9 and 5.7% [106].

Thrombocytopenia is a known risk factor for bleeding events, including intracranial haemorrhage. In patients with GIST, thrombocytopenia AEs were observed at a low frequency (18 patients; 3.0%). Grade 1 thrombocytopenia was reported in 16 patients, and Grade 2 and Grade 3 in 1 patient each. However, thrombocytopenia AEs were reported in more than a third of the patients with AdvSM (77 patients; 39.9%) and in more than a half of these patients, the thrombocytopenia AEs were ≥Grade 3 in severity (43 of 77 patients; 56%).

Severe thrombocytopenia (platelet count $< 50 \times 10^9$/L) was identified as the primary risk factor for intracranial haemorrhage in AdvSM. Prior to or at the time of the intracranial haemorrhage events, 10 of the 12 patients with AdvSM with intracranial haemorrhage had severe thrombocytopenia with platelet counts below 50×10^9/L, and 2 patients had mild thrombocytopenia (platelet counts between less than lower limit of normal and 75×10^9/L) at the time of the event.

As severe thrombocytopenia is a known complication associated with AdvSM, due to bone marrow infiltration by MCs, this likely explains the higher frequency of intracranial haemorrhage seen in patients with AdvSM compared with patients with GIST treated with avapritinib.

In addition to severe thrombocytopenia prior to or at the time of the intracranial haemorrhage, a review of case reports of patients with intracranial haemorrhage events identified several other potential risk factors for such events including the use of concomitant anti-platelet or anti-thrombotic therapy any time from the date of first dose of study drug to the date of last dose of avapritinib + 30 days, inclusive; elevated international normalised ratio prior to the intracranial haemorrhage event; elevated activated partial thromboplastin time prior to the intracranial haemorrhage event; and avapritinib starting dose > 200 mg QD.

A multivariate logistic regression model to evaluate the association between intracranial haemorrhage and each of these 5 potential risk factors identified severe thrombocytopenia (platelet counts $< 50 \times 10^9$/L) as the only statistically significant risk factor (p-value: 0.0292) for intracranial haemorrhage in the AdvSM population.

Risk mitigation strategies were implemented for all AdvSM patients to minimise the risk for intracranial haemorrhage. These measures included exclusion of patients with a platelet count $< 50 \times 10^9$/L at baseline, monitoring of platelet count at every treatment cycle, detailed guidance on dose modification, and defining the starting dose of avapritinib to be 200 mg QD. Additionally, to mitigate against a second bleed, protocols were amended such that patients who experienced an intracranial haemorrhage of any toxicity grade permanently discontinued avapritinib treatment. With these risk minimisation measures the current intracranial haemorrhage incidence is 2.5% in patients with AdvSM who did not have pre-existing severe thrombocytopenia and were treated at a starting dose of 200 mg QD.

Preventability:

Due to the potential link to the mechanism of action of avapritinib, the risk of intracranial haemorrhage may not be entirely preventable, but the incidence may be reduced if patients with risk factors are not treated with avapritinib and if risk factors emerging during treatment are managed appropriately. Severe thrombocytopenia is a significant risk factor for intracranial haemorrhage, and in case of occurrence, it is expected to be managed through dose interruptions and corrected by platelet support. Furthermore, in patients developing intracranial haemorrhage, the outcome may be improved if diagnosis is made early.

Before initiating avapritinib at any dose the risk for intracranial haemorrhage should be carefully considered in patients with potential increased risk including those with a history of vascular aneurysm, intracranial haemorrhage, cerebrovascular accident within the prior year, concomitant use of anticoagulants or thrombocytopenia. Other factors that may contribute to the risk of haemorrhage events at an individual patient level should also be considered, including history of coagulopathy, prolonged international normalised ratio, and concomitant use of medicinal products that increase the risk of haemorrhage. Physical examination, blood counts, and coagulation parameters should be monitored in order to reduce the risk of severe haemorrhage events during treatment with avapritinib.

In patients with AdvSM, platelet count must be performed prior to initiating therapy. Avapritinib is not recommended in patients with severely low platelet counts ($< 50 \times 10^9$/L). Following treatment initiation, platelet counts must be performed every 2 weeks for the first 8 weeks regardless of baseline platelet count. After 8 weeks of treatment, platelet counts should be monitored every 2 weeks (or more frequently as clinically indicated) if values are less than 75×10^9/L, every 4 weeks if values are between 75 and 100×10^9/L, and as clinically indicated if values are $\geq 100 \times 10^9$/L.

In case of severe thrombocytopenia ($< 50 \times 10^9$/L) occurring during avapritinib treatment, avapritinib should be withheld until platelet counts are $\geq 50 \times 10^9$/L. Platelet support may be necessary. Appropriate diagnostic evaluations (e.g., neuroimaging) should be performed at the first sign or symptom suggestive of intracranial haemorrhage, regardless of the severity at the initial presentation. Patients who experience clinically relevant neurological signs and symptoms (e.g., severe headache, vision problems, somnolence, or focal weakness) during treatment with avapritinib should interrupt dosing of avapritinib and immediately inform their treating physician. Treating physicians should have a low threshold for ordering diagnostic tests in patients presenting with relevant complaints. Brain magnetic resonance imaging (MRI) or computed tomography (CT) is recommended in cases of suspected intracranial haemorrhage.

Avapritinib should be permanently discontinued in any patient experiencing an intracranial haemorrhage, regardless of severity. Patients with suspected intracranial haemorrhage should withhold treatment until the appropriate diagnostic evaluations are performed.

Impact on the Risk-Benefit Balance of the Product:

While the overall incidence of intracranial haemorrhage events in GIST patients was low (2.1%), it was higher in AdvSM patients (6.2%), mainly due to an increased incidence of severe thrombocytopenia in the latter patient population. In line with that, the incidence of intracranial haemorrhage was 2.5% in AdvSM patients without pre-existing severe thrombocytopenia and treated at a starting dose of 200 mg QD. In general, intracranial haemorrhage events observed in the clinical development program for avapritinib were reversible and Grade 3 or lower in severity. Thirteen out of the 25 patients that experienced intracranial haemorrhage permanently discontinued the drug.

Close monitoring of patients for clinical signs of intracranial haemorrhage as part of routine clinical practice and regular platelet monitoring is expected to allow for early diagnosis and intervention, thus improving the outcomes of these events and minimising the impact on patients.

Based on a thorough review of the clinical data and taking into consideration the poor prognosis, high mortality, and unmet need in patients with advanced, unresectable or metastatic GIST or with AdvSM, the risk of intracranial haemorrhage associated with exposure to avapritinib is considered acceptable and outweighed by the anticipated benefits of avapritinib therapy.

Public Health Impact:

Not applicable.

SVII.3.1.2 Important Identified Risk 2: Cognitive Effects (GIST and AdvSM)

Potential Mechanism:

The mechanism by which avapritinib may cause cognitive effects is not known. Cognitive effects in patients from the avapritinib development programme were not associated with structural changes in the brain that would potentially explain their aetiology.

Non-clinical mechanistic studies of memory impairment were conducted. Parameters of short-term memory assessment were unaffected by treatment with avapritinib in rats. In mice, however, avapritinib treatment resulted in reduction in short term memory as assessed by the novel object recognition test. The effect of avapritinib on the blood brain barrier has not been specifically studied in non-clinical studies. However, a possible effect on the integrity of the blood brain barrier can be inferred from choroid plexus oedema noted in dogs treated with avapritinib and from the mechanistic hypothesis of inhibition of PDGFRB which regulates pericyte function; pericytes maintain the integrity of the vasculature as well as the blood brain barrier (refer to PART II: Module SII).

Cognitive impairment has been described in patients with a variety of cancers, independent of the chemotherapeutic agent administered, the stage of the disease or the stage of the therapeutic protocol [110]. Studies suggest that up to 33% of patients exhibit some degree of cognitive deficiency prior to any chemotherapy, including impairments in verbal learning and memory function [111], reaction time and global cognitive function [112]. This indicates a potential mechanism which is not dependent on the chemotherapeutic agent. Similarly, in SM, neuropsychiatric disturbances, including memory impairment, anxiety, and depression, have been observed [37, 57].

Other potential mechanisms that could explain the development of cognitive impairment in cancer patients have been hypothesized, based on the pharmacological activity of some chemotherapeutic agents. Cognitive changes through deoxyribonucleic acid damage and increases in oxidative stress, as well as cytokine deregulation and inflammatory processes can

contribute to occurrence of cancer-related cognitive impairment [113, 114]. However, as in most cases this is a direct consequence of a specific mechanism of action of an individual chemotherapeutic agent, this aetiology may not be pertinent for avapritinib.

Anxiety, depression, and confusion have been seen with PI3K inhibitors, particularly with buparlisib [115, 116]. Neuropsychiatric effects such as anxiety and depression were seen in up to one-third of patients receiving buparlisib, with Grade 3 or higher confusion seen in up to 10% [117].

Alternatively, certain genetic factors can provide an explanation which is independent of the chemotherapeutic agent. Variability in genes that regulate neural repair or plasticity, such as apolipoprotein E and brain-derived neurotrophic factor, and neurotransmission, such as catechol-O-methyltransferase, have been shown to increase the vulnerability of cancer patients to cognitive changes [113, 114].

Evidence Source and Strength of Evidence:

This risk is based on the events of cognitive effects (e.g., memory impairment, cognitive disorder, confusional state, amnesia, somnolence, speech disorder, encephalopathy, delirium, mental impairment, hallucination, mood altered, agitation, disorientation, personality change, dementia, mental status change, and psychotic disorder) observed with high frequency in subjects exposed to avapritinib in the clinical development programme for GIST and AdvSM. In addition, cognitive effects have been identified in association with other TKIs such as larotrectinib [118] and lorlatinib [119].

Characterisation of the Risk:

Clinical Trials

GIST and AdvSM

Frequency

In the avapritinib clinical trials, 321 patients (40.0%) experienced cognitive effects (all indications, all doses, N=803; refer to distribution of events per indication in Table 9).

In the GIST patient group (all doses; N=610), 262 patients (43.0%) experienced cognitive effects (Table 9) and the most common cognitive effect was memory impairment (21.6%).

In the AdvSM patient group (all doses; N=193), 59 patients (30.6%) experienced cognitive effects (Table 9) and similarly to the GIST population, the most common cognitive effect was memory impairment (14.5%).

Table 9:Adverse Events of Cognitive Effects in the Safety Population by MedDRA PT (GIST and AdvSM)

Adverse Event (MedDRA PT)	GIST (All Doses, N=610)	AdvSM (All Doses, N=193)	Overall Safety Population (N=803)
	n (%)	n (%)	n (%)
Memory impairment	132 (21.6)	28 (14.5)	160 (19.9)
Cognitive disorder	78 (12.8)	27 (14.0)	105 (13.1)
Confusional state	35 (5.7)	12 (6.2)	47 (5.9)
Amnesia	20 (3.3)	4 (2.1)	24 (3.0)

Adverse Event (MedDRA PT)	GIST (All Doses, N=610)	AdvSM (All Doses, N=193)	Overall Safety Population (N=803)
	n (%)	n (%)	n (%)
Somnolence	16 (2.6)	3 (1.6)	19 (2.4)
Speech disorder	14 (2.3)	0	14 (1.7)
Delirium	8 (1.3)	2 (1.0)	10 (1.2)
Encephalopathy	7 (1.1)	3 (1.6)	10 (1.2)
Mental impairment	8 (1.3)	0	8 (<1)
Hallucination	5 (<1)	1 (<1)	6 (<1)
Mood altered	6 (<1)	0	6 (<1)
Agitation	5 (<1)	1 (<1)	6 (<1)
Dementia	3 (<1)	2 (1.0)	5 (<1)
Disorientation	2 (<1)	2 (1.0)	4 (<1)
Personality change	4 (<1)	0	4 (<1)
Mental status change	2 (<1)	2 (1.0)	4 (<1)
Psychotic disorder	3 (<1)	0	3 (<1)
Total Unique Patients	**262 (43.0)**	**59 (30.6)**	**321 (40.0)**

Abbreviations: AdvSM = advanced systemic mastocytosis; GIST = gastrointestinal stromal tumour; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term.
If a patient experienced more than 1 event within a given adverse event category or preferred term, that patient was counted only once for that category or term
Data cut-off dates: 25 January 2021for Study BLU-285-1101, 03 December 2020 for Study BLU-285-1303, and 20 April 2021 for Studies BLU-285-2101 and BLU-285-2202.
Source: Table 18.3.3.2.1.1.

Severity, Reversibility and Long-Term Outcomes

In terms of severity, 24.6% of patients with GIST (all doses; N=610) experienced Grade 1 cognitive effects (predominantly events of memory impairment [15.4%]), with 13.6%, 3.9%, and <1% of patients experiencing Grade 2, Grade 3, and Grade 4 cognitive effects, respectively. No patients experienced Grade 5 cognitive effects.

Similarly, most patients with AdvSM (all doses; N=193) experienced Grade 1 cognitive effects (18.1%; predominantly events of memory impairment [11.9%]), and 8.8% and 3.6% of patients experienced Grade 2 and Grade 3 cognitive effects, respectively. No patients experienced Grade 4 or Grade 5 cognitive effects.

Serious AEs of cognitive effects were reported for 3.6% of patients within the overall safety population (all indications, all doses, N=803). The majority of the serious cognitive effects in both indications were Grade 3 (in 2.4% of patients) and assessed as related to avapritinib (in 2.2% of patients).

Twenty-four patients with GIST (3.9%) and 5 patients with AdvSM (2.6%) experienced serious AEs of cognitive effects. Approximately a half of the serious events resolved or resolved with sequelae.

In the avapritinib clinical trials (all indications, all doses, N=803), the majority of patients with cognitive effects continued dosing with avapritinib with only 3.0% of patients experiencing cognitive effects leading to permanent discontinuation of study treatment (3.1% and 2.6% of patients with GIST and AdvSM, respectively) and 13.1% of patients interrupting the study treatment (14.1% and 9.8% of patients with GIST and AdvSM, respectively). This observation indicates that the cognitive effects appeared to be tolerated by the patients and that physicians believe the benefit-risk balance of avapritinib was positive and recommended continued treatment.

Kaplan-Meier analyses were conducted to assess the probability of experiencing a cognitive effect at a certain point in time, and the time window needed for improvement. Approximately half of patients treated with avapritinib are expected to have an event by the 40th week of treatment. The probability of experiencing a cognitive effect increases over the first 1.5 year of treatment and then reaches a plateau. The median time to onset among patients who experienced a cognitive effect of any grade was 8.4 weeks in GIST (all doses; N=249), 13.3 weeks in AdvSM (all doses; N=42), and 8.9 weeks in the overall safety population (all doses; N=291).

For patients with GIST and AdvSM who experienced a cognitive effect of ≥Grade 2, the probability of improvement to Grade ≤1 was high (approximately 80%). Focusing on patients with GIST whose starting dose was 300/400 mg and who experienced a ≥Grade 2 cognitive effect, the probability of improvement to ≤Grade 1 was 80% at 28 weeks after the event onset; the median time to improvement to ≤Grade 1 was 7.9 weeks. In patients with AdvSM whose starting dose was 200 mg and who experienced a ≥Grade 2 cognitive effect, the probability of improvement to ≤Grade 1 was 50% at 24.1 weeks and 75% by 24.1 weeks after the event onset; the median time to improvement to ≤Grade 1 was 24.1 weeks.

In many cases, the events of cognitive effects started as Grade 1 in severity and worsened to higher grades over time, with dose interruption or reduction not occurring until the event was Grade 2 or worse.

Cognitive effects were not associated with structural changes in the brain. Forty-four patients with GIST experienced cognitive effect events during the first 3 cycles of treatment with avapritinib when routine monthly brain imaging was performed. Among those 44 patients, 42 had brain imaging at baseline and none had a new abnormality compared to the baseline imaging.

Impact on Quality of Life

Of the patients experiencing cognitive effects, 24.6% of patients with GIST and 18.1% of patients with AdvSM experienced Grade 1 (mild) cognitive effects, which according to the CTCAE definition do not interfere with activities of daily living.

In general, cognitive effects of ≥Grade 2 in severity may lead to impairment of quality of life and represent a risk factor for accidents and injuries. However, just 13.6% of patients with GIST and 8.8% of patients with AdvSM experienced Grade 2 cognitive effects, and only 3.9% of patients with GIST and 3.6% of patients with AdvSM experienced Grade 3 cognitive effects, defined as limiting self-care. Grade 4 (life threatening) cognitive effects were reported in < 1% patients with GIST and no patients with AdvSM. No patients reported Grade 5 (fatal) cognitive effects.

Post-Authorisation Experience (Data Lock Point of 08 July 2022)

A comprehensive analysis of data collected during the post marketing experience in patients with GIST and AdvSM does not indicate a change in the characterisation of the risk.

Risk Factors and Risk Groups:

Several risk factors and risk groups prone to develop cognitive effects have been identified, based on quantitative and qualitative analysis of available data. These include increased age, medical history of cognitive effects, together with polypharmacy and use of CNS medications, increased avapritinib dosage, and other concurrent pathologies or disease progression.

Analyses of patients in the overall GIST and AdvSM safety population (N = 803) showed that the incidence of cognitive effects was slightly higher in patients aged ≥65 years compared with patients aged < 65 years (42.4% vs 38.1%). This difference is not unexpected because cognitive issues are known to increase with age [120]. Furthermore, this is in accordance with other studies that found similar correlation between the age of the patient and development of cognitive effects while undergoing anti-cancer therapy [121].

In the GIST and AdvSM safety population, there appeared to be a slightly higher incidence of cognitive effects in female compared to male patients (44.9 vs. 37.2%) and in white compared to non-white patients (41.4% vs 36.8%).

The incidence of events of cognitive effects in patients with GIST and AdvSM was higher in patients from North America compared with patients from Europe or Australia and Asia (51.5% vs 31.2% and 31.9%, respectively). This difference appears to be driven by a higher incidence of events of memory impairment in North American patients compared with patients from the above regions (31.1% vs 10.7% and 14.2%, respectively). The cause of this observation is not clear.

The incidence of cognitive effects was also found to be higher in patients with prior regorafenib use compared with patients with no regorafenib use in the GIST population.

Other variables that did not appear to show a significant impact on the incidence of cognitive effects in the GIST and AdvSM safety population included prior number of TKI therapies and total duration of prior TKI therapy.

A multivariable logistic regression analysis performed for cognitive effects of any grade in the GIST and AdvSM safety population showed that the odds of experiencing a cognitive effect were increased by a multiplier of 167% if a patient had medical history of cognitive effects. This is in accordance with publications indicating that the level of cognitive reserve prior to treatment plays a role in development of cognitive effects during anti-cancer therapy [121]. This refers to the innate and developed cognitive capacity, which is influenced by various factors, including genetics, education, occupational attainment, and lifestyle. Results of one longitudinal study showed that patients who had lower pre-treatment cognitive reserve performed worse on measures of Processing Speed compared with patients not exposed to chemotherapy and healthy controls [121]. As such, patients with higher baseline cognitive performance may have more cushion against cognitive detriments than individuals with a lower baseline cognitive performance.

Preventability:

Guidelines for management of oncology geriatric patients recommend several supportive care interventions for alleviating cognitive impairment, which can be routinely used in everyday medical management of cancer patients. These include caregiver involvement, minimising complexity of treatment and medications, delirium prevention, social work involvement, capacity assessment, health-care proxy identification, and additional cognitive testing or neuropsychological assessment [122]. Actual management of cognitive effects can be done through non-pharmacologic interventions that include exercise and physical activity, as well as cognitive trainings. A small number of studies showed that some pharmacologic agents can be

used for management of cognitive effects, but no recommendation can be made in this respect [123].

For patients under treatment with avapritinib who experience signs and symptoms of cognitive effects, different managing strategies are recommended, based on the severity of the adverse reactions.

Patients experiencing events of Grade 1 in severity should continue at the same or reduced dose or interrupt until improvement to baseline or resolution and resume at the same or reduced dose. If events of Grade 2 or 3 in severity occur, treatment with avapritinib should be interrupted until improvement to baseline, Grade 1 or complete resolution. Therapy can be resumed at the same dose or at a reduced dose. Patients experiencing cognitive effects of Grade 4 should permanently discontinue treatment with avapritinib.

Impact on the Risk-Benefit Balance of the Product:

Cases of cognitive effects have been reported with increased frequency within the clinical development programme of avapritinib. However, the AEs of cognitive effects have not been associated with any fatal outcomes, the majority of which were of Grade 1 severity which did not affect patient's quality of life and allowed for continuation of therapy.

For events of Grade ≥2 in severity, clinical measures such as dose reductions and treatment interruptions were shown effective for improvements. Data from the clinical development programmes indicate that the cognitive effects appeared to be tolerated by patients and accepted by physicians, as the benefit-risk profile of continued treatment with avapritinib remains positive. As such, the risk of cognitive effects associated with exposure to avapritinib is considered acceptable.

Public Health Impact:

Not applicable.

SVII.3.1.3 Important Identified Risk 3: Drug-Drug Interactions with Moderate or Strong CYP3A Inhibitors or Inducers (All Indications)

Potential Mechanisms:

In-vitro studies showed that avapritinib phase I metabolism is predominantly mediated by CYP3A4 and is a time dependent inhibitor and inducer of CYP3A4. As such, the plasma levels of avapritinib or comedication that is moderate or strong CYP3A inhibitor/inducer can be affected, and co-administration of such medication with avapritinib may lead to increased risks of adverse effects or decreased efficacy.

Evidence Sources and Strength of Evidence:

The data from the non-clinical studies showed that in vitro, avapritinib is predominantly metabolised by CYP3A, and thus, plasma levels of avapritinib can be affected when administered concomitantly with a moderate or strong CYP3A inhibitor or inducer (refer to PART II: Module SII). The only clinical data available originated from the single-dose, pharmacology Study BLU-285-0104 conducted in healthy volunteers, which showed that plasma exposure of avapritinib was modulated in the presence of the strong CYP3A4 inducer rifampicin and strong CYP3A4 inhibitor itraconazole.

The clinical outcomes of such effects and the overall impact on patients treated with avapritinib remains unknown.

Characterisation of the Risk:

Clinical Trials

GIST, AdvSM, and ISM

Frequency

Not yet established for avapritinib in any patient population (i.e., GIST, AdvSM, and ISM).

Severity

Not yet established for avapritinib in any patient population (i.e., GIST, AdvSM, and ISM).

In general, the outcomes of DDIs between avapritinib and CYP3A inhibitors/inducers can range from asymptomatic changes in pharmacokinetics of the drug to clinically meaningful outcomes, including increased incidence and/or severity of adverse effects and decreased efficacy of avapritinib therapy.

Reversibility and Long-Term Outcomes

The effects of CYP3A inhibitors/inducers on avapritinib plasma levels are expected to be fully reversed upon discontinuation of the perpetrator drugs.

The long-term outcomes are not yet established for avapritinib in any patient population (i.e., GIST, AdvSM, and ISM).

Impact on Quality of Life

The clinically meaningful outcomes of DDIs could have a marked impact on patients, especially if leading to increased severity of adverse effects or decreased efficacy.

Post-Authorisation Experience (Data Lock Point of 08 July 2022)

A comprehensive analysis of data collected during the post marketing experience in patients with GIST and AdvSM does not indicate a change in the characterisation of the risk.

Risk Factors and Risk Groups:

No specific risk factors or risk groups have yet been established for avapritinib in any patient population (i.e., GIST, AdvSM, and ISM).

Preventability:

For patients with GIST and AdvSM, 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 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.

For patients with ISM, concomitant use of avapritinib with strong or moderate CYP3A inhibitors must be avoided.

Co-administration of avapritinib with strong and moderate CYP3A inducers should be avoided in all patient populations.

Impact on the Risk-Benefit Balance of the Product:

The non-clinical and clinical data from a single-dose healthy volunteer study showed that plasma levels of avapritinib can be affected by co-administration with a strong CYP3A inhibitor or inducer. Although not observed in clinical trials, the changes in pharmacokinetics of avapritinib might have potentially serious clinical outcomes in treated patients.

Public Health Impact:

Not applicable.

SVII.3.1.4 Important Potential Risk 1: Intracranial Haemorrhage (ISM)

Potential Mechanisms:

The mechanism of action by which avapritinib may predispose patients to intracranial haemorrhage is unknown.

Evidence Sources and Strength of Evidence:

No intracranial haemorrhages were reported in patients with ISM receiving avapritinib in the clinical development programme. However, intracranial haemorrhage represents a known risk for avapritinib in patients with GIST and AdvSM and has been observed in these patient populations treated with avapritinib at the higher starting doses of 300 mg and 200 mg QD, respectively, with severe thrombocytopenia identified as the primary risk factor in patients with AdvSM (refer to SVII.3.1.1).

Characterisation of the Risk:

Clinical Trials

ISM

Frequency

No intracranial haemorrhage events were reported in avapritinib-treated patients in the ISM safety population (all doses; N = 246).

Severity

No intracranial haemorrhage events were reported in the avapritinib clinical development programme in patients with ISM.

Reversibility and Long-Term Outcomes

No intracranial haemorrhage events were reported in the avapritinib clinical development programme in patients with ISM.

Impact on Quality of Life

Intracranial haemorrhage is a potentially life-threatening event which may lead to or prolong hospitalisation, residual neurological damage or may even result in death. However, considering the characteristics of ISM and the recommended avapritinib dose of 25 mg QD, events of intracranial haemorrhage are not expected to occur in the ISM patient population.

Post-Authorisation Experience (Data Lock Point of 08 July 2022)

Not yet applicable in the ISM patient population.

Risk Factors and Risk Groups:

Not yet established in the ISM patient population.

Preventability:

Due to the fact that the mechanism of action of avapritinib predisposing patients to intracranial haemorrhage is unknown, the risk of intracranial haemorrhage may not be entirely preventable.

Severe thrombocytopenia is a significant risk factor for intracranial haemorrhage in patients with AdvSM, and in case of occurrence, it is expected to be managed through dose interruptions

and corrected by platelet support. However, patients with ISM do not have baseline thrombocytopenia and based on the available clinical data, when treated with 25 mg avapritinib QD, are not at risk of developing thrombocytopenia. Therefore, routine platelet monitoring in this patient population is not deemed necessary.

Before initiating avapritinib at any dose the risk for intracranial haemorrhage should be carefully considered in patients with potential increased risk including those with a history of vascular aneurysm, intracranial haemorrhage, cerebrovascular accident within the prior year, concomitant use of anticoagulants or thrombocytopenia. Patients who experience clinically relevant neurological signs and symptoms during treatment with avapritinib must interrupt dosing of avapritinib and inform their healthcare professional immediately. Brain imaging by MRI or CT may be performed at the discretion of the physician based on severity and the clinical presentation.

Avapritinib should be permanently discontinued in any patient experiencing an intracranial haemorrhage, regardless of severity. Patients with suspected intracranial haemorrhage should withhold treatment until the appropriate diagnostic evaluations are performed.

Impact on the Risk-Benefit Balance of the Product:

There have been no intracranial haemorrhage events in patients with ISM and treatment with avapritinib was not associated with an increased risk of developing thrombocytopenia in this patient population in the clinical development programme for avapritinib. Additionally, thrombocytopenia is not observed in patients with ISM, as this would be considered a C-finding that would be indicative of advanced disease.

There are no approved therapies for this patient population and current treatment consists of symptom-directed therapies that do not address the underlying cause of ISM. As a result, patients suffer from life-long debilitating symptoms that adversely affect their quality of life.

In light of the currently available data, patients with ISM are not anticipated to develop intracranial haemorrhage. Given the efficacy observed in this target population and the potential risk for experiencing intracranial haemorrhage, the impact on the benefit-risk balance of avapritinib is acceptable.

Public Health Impact:

Not applicable.

SVII.3.1.5 Important Potential Risk 2: Cognitive Effects (ISM)

Potential Mechanisms:

The mechanism by which avapritinib may cause cognitive effects is not known.

Patients with ISM typically have a higher incidence of neurocognitive symptoms related to the underlying disease [70] compared to the general population.

High prevalence of morphological and functional brain abnormalities (mainly abnormal punctuated white matter abnormalities) with neuropsychiatric complaints have also been observed in this patient population [124].

Evidence Sources and Strength of Evidence:

Cognitive effects were reported at a low frequency in patients receiving avapritinib in patients with ISM in Part 2 of study BLU-285-2203, and the frequency was slightly lower in the 25 mg avapritinib group compared with the placebo group. In this study, treatment with 25 mg

avapritinib in patients with ISM was not associated with an increased risk of developing cognitive effect events.

However, cognitive effects represent a known risk for avapritinib in patients with GIST and AdvSM and have been observed in these patient populations treated with avapritinib at higher doses, despite that the causality of the events was confounded by alternative aetiologies or other risk factors (refer to SVII.3.1.2).

Characterisation of the Risk:

Clinical Trials

ISM

Frequency

In Part 2 of study BLU-285-2203 (avapritinib 25 mg, N = 141; placebo, N = 71), cognitive effect AEs were overall infrequent in the 25 mg avapritinib and placebo groups. The incidence of cognitive effect AEs was slightly lower in the 25 mg avapritinib group (4 patients [2.8%]) than in the placebo group (3 patients [4.2%]). The most commonly reported event was memory impairment, in 2 patients (1.4%) in the 25 mg avapritinib group and 1 patient (1.4%) in the placebo group. Amnesia and mood altered occurred in 1 patient (0.7%) each in the 25 mg avapritinib group, and mental impairment and mental status changes occurred in 1 patient (1.4%) each in the placebo group (Table 10).

In the overall safety population (all doses; N = 246), 16 (6.5%) of all avapritinib-treated patients experienced cognitive effects. The most common event was memory impairment in 7 patients (2.8%) (Table 10).

Table 10: Adverse Events of Cognitive Effects in the Safety Population by MedDRA PT (ISM)

Adverse Event (MedDRA PT)	Part 2		Overall Safety Population (Part 1/2/3)	
	Avapritinib 25 mg (N=141)	Placebo (N=71)	All Avapritinib 25 mg [a] (N=226)	All Avapritinib Doses (N=246)
	n (%)	n (%)	n (%)	n (%)
Memory impairment	2 (1.4)	1 (1.4)	5 (2.2)	7 (2.8)
Amnesia	1 (0.7)	0	1 (<1)	2 (<1)
Mood altered	1 (0.7)	0	1 (<1)	1 (<1)
Mental impairment	0	1 (1.4)	0	0
Mental status changes	0	1 (1.4)	0	0
Cognitive disorder	0	0	1 (<1)	4 (1.6)
Agitation	0	0	1 (<1)	2 (<1)
Confusional state	0	0	0	2 (<1)
Disorientation	0	0	0	1 (<1)

Adverse Event (MedDRA PT)	Part 2		Overall Safety Population (Part 1/2/3)	
	Avapritinib 25 mg (N=141)	Placebo (N=71)	All Avapritinib 25 mg [a] (N=226)	All Avapritinib Doses (N=246)
	n (%)	n (%)	n (%)	n (%)
Somnolence	0	0	0	1 (<1)
Delirium	0	0	0	1 (<1)
Total Unique Patients	**4 (2.8)**	**3 (4.2)**	**8 (3.5)**	**16 (6.5)**

Abbreviations: ISM = indolent systemic mastocytosis; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term.

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

If a patient experienced more than 1 event within a given adverse event category or preferred term, that patient was counted only once for that category or term.

Data cut-off date: 23 June 2022.

Source: Table 14.3.1.11.1a, Table 14.3.1.11.1c.

Severity, Reversibility and Long-Term Outcomes

In Part 2 of study BLU-285-2203 (avapritinib 25 mg, N = 141; placebo, N = 71), most of the cognitive effects AEs were Grade 1 in severity in the 25 mg avapritinib group with only 1 patient experiencing a Grade 2 AE (memory impairment). In the placebo group, 1 patient experienced a Grade 3 event, which was reported as serious (mental status changes); all other events were reported as Grade 1 events. None of the events led to study drug discontinuation in either treatment group, whereas 1 patient in each group experienced events leading to dose reduction.

In the overall safety population (all doses; N = 246), ≥ Grade 3 cognitive effects were reported in 2 patients (< 1%) (delirium [serious] and cognitive disorder) receiving higher doses of avapritinib (50 and 100 mg, respectively). A serious AE of delirium that occurred in a patient receiving 50 mg avapritinib, led to study drug discontinuation.

Impact on Quality of Life

Based on the available data from study BLU-285-2203, treatment with 25 mg avapritinib is not associated with an increased risk of cognitive effects in patients with ISM. Of the patients with ISM experiencing cognitive effects, most experienced Grade 1 (mild) cognitive effects, which according to the CTCAE definition do not interfere with activities of daily living.

In general, cognitive effects of ≥Grade 2 in severity may lead to impairment of quality of life and represent a risk factor for accidents and injuries. However, < 1% of patients with ISM in the 25 mg avapritinib group experienced Grade 2 cognitive effects and none experienced Grade 3 cognitive effects, defined as limiting self-care. No Grade 4 (life-threatening) or Grade 5 (fatal) cognitive effects were reported.

Post-Authorisation Experience (Data Lock Point of 08 July 2022)

Not yet applicable in the ISM patient population.

Risk Factors and Risk Groups:

No specific risk factors or risk groups for cognitive effects have been established for avapritinib in the ISM patient population. The lower incidence of cognitive effects in patients receiving 25 mg avapritinib compared with placebo in the clinical development programme suggests that these events are most likely due to the patients' underlying disease and other treatments patients were receiving as part of their BSC.

Preventability:

For patients under treatment with avapritinib who experience signs and symptoms of cognitive effects, different managing strategies are recommended, based on the severity of the adverse reactions.

Patients experiencing events of Grade 1 in severity should continue at the same or reduced dose or interrupt until improvement to baseline or resolution and resume at the same or reduced dose. If events of Grade 2 or 3 in severity occur, treatment with avapritinib should be interrupted until improvement to baseline, Grade 1 or complete resolution. Therapy can be resumed at the same dose or at a reduced dose. Patients experiencing cognitive effects of Grade 4 should permanently discontinue treatment with avapritinib.

Impact on the Risk-Benefit Balance of the Product:

Data from study BLU-285-2203 indicated that avapritinib at the 25 mg dose was not associated with an increased risk for developing cognitive effects in patients with ISM compared with placebo. The lower incidence of cognitive effects in the 25 mg avapritinib group suggests that these events are most likely due to the patients' underlying disease and other treatments patients were receiving as part of their BSC.

Given the efficacy observed in this target population and the potential risk of cognitive effects, the impact on the benefit-risk balance of avapritinib is acceptable.

Public Health Impact:

Not applicable.

SVII.3.1.6 Important Potential Risk 3: Cardiac Toxicity, Including QT Prolongation (All Indications)

Potential Mechanisms:

Inhibition of tyrosine kinases may cause cardiotoxicity by several different mechanisms [95]. However, not all mechanisms underlying development of cardiotoxicity have been fully elucidated and not all TKIs are predicted to exert the same level of toxicity on the heart [93, 94].

Several multitarget inhibitors targeting tyrosine kinase receptors, including PDGFR, have been associated with cardiac dysfunction in treated patients, including sorafenib, sunitinib or imatinib [125].

PDGFRs are expressed in cardiomyocytes and are unregulated in response to mechanical stress in animal model. Inhibition of PDGFRs has been reported to play a protective role in hearts exposed to ischaemic injury in the same animal model [126]. PDGFRB is required for angiogenesis and preservation of cardiac function in the presence of stress overload [125].

The mechanism for a slight increase in QTc interval seen in the clinical programme for avapritinib is not understood. Based on preclinical study, there is no evidence of a preferential

distribution of avapritinib in the heart to suggest any cardiovascular effect due to high local concentrations in the heart.

QT prolongation of cancer drugs, including small-molecule TKIs, has been linked to an off-target effect of some of these therapies, causing abnormalities in cardiac repolarisation resulting in QT prolongation [96].

Evidence Sources and Strength of Evidence:

The non-clinical studies did not show any effects of avapritinib on the cardiovascular system. In clinical Study BLU-285-1101, a minor increase in QTc interval was reported at 300/400 mg QD dose of avapritinib in 3.9% of patients (13/335). The estimated mean change from baseline in QTcF was 6.55 ms (90% CI: 1.80 to 11.29) at the observed steady state geometric mean C_{max} of 899 ng/mL. These increases were not clinically relevant and no effect on heart rate or cardiac conduction (PR, QRS, and RR intervals) was observed.

The potential for QT prolongation was assessed in the context of the lower 25 mg QD dose of avapritinib for the treatment of ISM. As no clinically relevant effect on QTc was observed with avapritinib when administered at a dose of 300 or 400 mg QD, no clinically relevant effect is anticipated when avapritinib is administered at the 12- to 16-times lower dose of 25 mg QD in patients with ISM (12.8-fold lower geometric mean Cmax at the 25 mg QD dose [70.2 ng/mL]).

Cardiac toxicity seen mostly with multitarget TKIs ranged from asymptomatic QT prolongation to reduction in left ventricular ejection fraction, symptomatic congestive heart failure, acute coronary syndromes and myocardial infarction. Hypertension and sudden death have also been associated with treatment with these agents [93-95]. The relevance of these findings to avapritinib remains unknown.

The potential for QT prolongation is considered a class effect of small-molecule TKIs despite potential differences between individual agents. While dasatinib, vandetanib, sorafenib, nilotinib, or sunitinib showed QT prolongation frequently (> 5% of patients), based on the large systematic review of commonly used cancer drugs to determine the incidence of QT prolongation and clinically relevant arrhythmias [96], QT prolongation was infrequent or absent with afatinib, crizotinib, ceritinib, dovitinib, imatinib, lapatinib, lenvatinib, nintedanib, pazopanib, and ponatinib. However, when present, QT prolongation had only rarely clinically relevant consequences, defined as arrhythmias and sudden cardiac death [96].

Characterisation of the Risk:

Clinical Trials

GIST and AdvSM

Frequency

In the avapritinib clinical trials (GIST and AdvSM; all doses, N = 803), 39 patients (4.9%) experienced AEs within the Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) Torsade de pointes/QT prolongation (refer to distribution of events per indication in Table 11).

In the GIST patient group (all doses; N = 610), 25 patients (4.1%) experienced torsade de pointes/QT prolongation events (Table 11). The most common AE was electrocardiogram QT prolonged (2.6%).

In the AdvSM patient group (all doses; N = 193), 14 patients (7.3%) experienced torsade de pointes/QT prolongation events (Table 11). Similar to the GIST population, the most common AE was electrocardiogram QT prolonged (3.6%).

No patients in the overall safety population experienced an AE of Torsade de pointes.

Table 11: Adverse Events of Cardiac Toxicity, Including QT Prolongation in the Safety Population by MedDRA PT (GIST and AdvSM)

Adverse Event (MedDRA PT)	GIST (All Doses, N=610)	AdvSM (All Doses, N=193)	Overall Safety Population (N=803)
	n (%)	n (%)	n (%)
Electrocardiogram QT prolonged	16 (3.0)	7 (3.6)	**23 (2.9)**
Syncope	5 (<1)	5 (2.6)	**10 (1.2)**
Ventricular arrhythmia	3 (<1)	0	**3 (<1)**
Cardiac arrest	0	2 (1.0)	**2 (<1)**
Ventricular tachycardia	1 (<1)	1 (<1)	**2 (<1)**
Loss of consciousness	1 (<1)	0	**1 (<1)**
Total Unique Patients	**25 (4.1)**	**14 (7.3)**	**39 (4.9)**

Abbreviations: AdvSM = advanced systemic mastocytosis; GIST = gastrointestinal stromal tumour; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term.
If a patient experienced more than 1 event within a given adverse event category or preferred term, that patient was counted only once for that category or term
Data cut-off dates: 25 January 2021for Study BLU-285-1101, 03 December 2020 for Study BLU-285-1303, and 20 April 2021 for Studies BLU-285-2101 and BLU-285-2202.
Source: Table T.99.4.1.1.

The ability of avapritinib to prolong the QT interval was assessed in 27 patients that were administered avapritinib at doses of 300 mg and 400 mg QD in Study BLU-285-1101 (Cardiac Safety Report, Appendix 16.1.13; BLU-285-1101 CSR). The results showed that avapritinib had a small effect on the QTc interval at steady-state plasma concentrations. At steady state (Day 15), the mean ΔQTcF was 7.0 ms (90% CI: 2.84, 11.14) at the time point before dosing, and above 5 ms at all time points after dosing, except at 4 hours after dosing (4.6 ms; 90% CI: 0.50, 8.65). The largest mean ΔQTcF was observed at 1 hour and 8 hours after dosing: 9.9 and 9.5 ms, respectively (90% CIs: 5.72, 14.03 and 5.30, 13.62, respectively). No patient had a QTcF > 450 ms. In the concentration-QTc analysis of data, a linear model with an intercept provided the best fit to the observed QTcF data and was, therefore, used to establish the relationship between plasma concentrations of avapritinib and ΔQTcF. The concentration-QTc analysis confirmed that avapritinib at doses of 300/400 mg QD resulted in a small increase in QTcF of 6.55 ms (90% CI: 1.80 to 11.29) at the observed steady state geometric mean C_{max} of 899 ng/mL with a shallow slope of the concentration-QTc relationship. A QT effect (ΔQTcF) exceeding 20 ms can be excluded at avapritinib plasma concentrations up to 1,645 ng/mL. No effect on heart rate or cardiac conduction (PR, RR, and QRS intervals) was observed.

Based on the analysis of QT prolongation/ventricular arrhythmias events in Study BLU-285-1303 (data cut-off 09 March 2020), the frequency of patients who reported QT prolongation/ventricular arrhythmia events was the same in each of the treatment arms (3%). Almost all of these events were Grade 1 or Grade 2 in severity and non-serious. There was only 1 serious AE reported (ventricular arrhythmia) which occurred in the regorafenib

arm. Based on the data presented, there is no evidence that avapritinib is associated with events of QT prolongation or ventricular arrhythmias.

ISM

In Part 2 of study BLU-285-2203 (avapritinib 25 mg, N = 141; placebo, N = 71), 3 patients (2.1%) in the 25 mg avapritinib group and 1 patient (1.4%) in the placebo group experienced events within the SMQ Torsade de pointes/QT prolongation. The reported events included electrocardiogram QT prolonged (2 patients in the 25 mg avapritinib group and 1 patient in the placebo group) and syncope (2 patients in the 25 mg avapritinib group) (Table 12).

In the ISM patient group (all doses; N=246), 8 (3.3%) of all avapritinib-treated patients experienced events within the SMQ Torsade de pointes/QT prolongation. The most common event was electrocardiogram QT prolonged in 5 patients (2.0%) (Table 12).

Table 12: Adverse Events of Cardiac Toxicity, Including QT Prolongation in the Safety Population by MedDRA PT (ISM)

Adverse Event (MedDRA PT)	Part 2		Overall Safety Population (Part 1/2/3)	
	Avapritinib 25 mg (N=141)	Placebo (N=71)	All Avapritinib 25 mg [a] (N=226)	All Avapritinib Doses (N=246)
	n (%)	n (%)	n (%)	n (%)
Electrocardiogram QT prolonged	2 (1.4)	1 (1.4)	4 (1.8)	5 (2.0)
Syncope	2 (1.4)	0	4 (1.8)	4 (1.6)
Loss of consciousness	0	0	1 (<1)	1 (<1)
Total Unique Patients	**3 (2.1)**	**1 (1.4)**	**7 (3.1)**	**8 (3.3)**

Abbreviations: ISM = indolent systemic mastocytosis; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term.

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

If a patient experienced more than 1 event within a given adverse event category or preferred term, that patient was counted only once for that category or term.

Data cut-off date: 23 June 2022.

Source: 99.3.1.18.1a, Table 99.3.1.18.1c.

Severity

GIST and AdvSM

The majority of the reported events were non-serious and only < 1% of patients in the overall safety population (GIST and AdvSM; all doses; N = 803) experienced serious QT prolongation/ventricular arrhythmia AEs. These included syncope and ventricular tachycardia (1 patient each in both GIST and AdvSM patient groups).

Approximately half of the AEs were Grade 1 in severity, resolved, and were assessed as not related to avapritinib. All but 4 events were non-serious (see above) and none of the serious events were assessed as related to avapritinib.

ISM

None of the reported events within the SMQ Torsade de pointes/QT prolongation in the overall safety population (ISM; all doses; N = 246) were serious.

In Part 2 of study BLU-285-2203 (avapritinib 25 mg, N = 141; placebo, N = 71), 1 patient each in the 25 mg avapritinib group had QTcF > 480 msec and > 500 msec compared to no patients in the placebo group.

An increased QTcF > 60 msec from baseline was reported in 3 (2.1%) patients (all female) in the 25 mg avapritinib group and no patients in the placebo group. QTcF was > 500 msec in only 1 patient and was not associated with any relevant AEs. In the remaining 2 patients, QTcF did not increase beyond 470 msec, which is considered to be within the upper normal range in female patients and therefore not clinically meaningful.

In Part 2 of study BLU-285-2203 (avapritinib 25 mg, N = 141; placebo, N = 71), 1 patient in the avapritinib 25 mg group with a medical history of intermittent dizziness experienced a Grade 3 syncope assessed as not related to avapritinib. The event was not associated with QT prolongation at the time of the occurrence. The patient continued treatment with no new episodes reported. Syncope, Grade 1 in severity, was not associated with QT prolongation in the other patient in the avapritinib 25 mg group either. It is important to note that patients with ISM frequently suffer from MC mediator-related symptoms that include syncope.

Reversibility and Long-Term Outcomes

Not yet established for avapritinib in any patient population (i.e., GIST, AdvSM, and ISM).

QT prolongation has been linked to an increased risk of life-threatening ventricular arrhythmia or events of sudden cardiac death [96]. Moreover, a modest QTc prolongation was shown to be linked to an increased risk of cardiovascular events, stroke and all-cause mortality in variety of patient population [127, 128].

Impact on Quality of Life

The impact of clinically relevant QT prolongation effects may be significant. In general, the impact of QT prolongation on patients depends on patients' risk factors and clinical consequences of such prolongation, which may be life-threatening or fatal.

Post-Authorisation Experience (Data Lock Point of 08 July 2022)

A comprehensive analysis of data collected during the post-marketing experience in patients with GIST and AdvSM does not indicate a change in the characterisation of the risk.

Risk Factors and Risk Groups:

Patients with a prior history of cardiac disease are in general at higher risk of cardiac damage associated with TKIs [95].

Patients with underlying ECG or cardiac abnormalities, including patients with a prolonged QTc, defined as QTcF of > 480 ms, with a history of prolonged QT syndrome or torsade de pointes or patients with a family history of prolonged QT syndrome may be at higher risk of effects on QT interval and were, therefore, excluded from the clinical trials with avapritinib but are expected in clinical practice within the target population of avapritinib.

Concomitant treatment with drugs with a known potential to prolong QT interval such as azole antifungals, fluoroquinolones, macrolides and others may increase the risk.

Additionally, elderly patients or patients with electrolyte imbalance are at higher risk of QTc prolongation [129].

Preventability:

Patients with GIST and AdvSM at-risk of QT prolongation (e.g., patients with electrolyte imbalance) should avoid concomitant treatment with medication with a known potential to prolong QT interval (e.g., azole antifungals, fluoroquinolones, macrolides).Patients with GIST and AdvSM with pre-existing cardiac abnormalities should be closely monitored for any signs of QT prolongation during therapy with avapritinib.

Treatment with 25 mg avapritinib was not associated with an increased risk of QT prolongation and no clinically relevant effect is anticipated when avapritinib is administered in patients with ISM.

In patients with ISM, QT interval assessments by ECG should be considered, in particular in patients with concurrent factors that could prolong QT (e.g., age, pre-existing heart rhythm disorders, etc.).

Impact on the Risk-Benefit Balance of the Product:

Prolonged QT interval can lead to life-threatening ventricular arrhythmias or sudden cardiac death in patients with predisposing factors, including concomitant use of medication with known potential for QT prolongation. In light of currently available non-clinical and clinical data related to potential for QT prolongation and anticipated benefits of avapritinib in the target population, the impact on avapritinib is acceptable.

Public Health Impact:

Not applicable.

SVII.3.1.7 Important Potential Risk 4: Embryofoetal Toxicity (All Indications)

Potential Mechanisms:

The embryofoetal toxicity of avapritinib is a consequence of its mechanism of action causing inhibition of wild-type KIT and PDGFRA activity.

Loss of function studies in mice demonstrated that KIT activity is required for proper development of the red blood cell lineage, as well as reproductive and melanocyte function [130-132], thus inhibition of KIT could cause disturbances of the embryogenesis process.

Similarly, inhibition of tyrosine kinase receptor PDGFRA was shown to result in birth defects, including facial clefting, severe spina bifida occulta, cardiac defects, omphalocele, renal and urogenital anomalies, and vertebral and rib fusion abnormalities [133].

Evidence Sources and Strength of Evidence:

Data from the rodent embryofoetal development studies showed that avapritinib has embryotoxic effects (refer to PART II: Module SII). These results are further supported by the post-marketing data for other TKI agents such as imatinib in pregnant women showing that maternal exposure during the first trimester of pregnancy can lead to foetal development complications and spontaneous abortion [92, 103]. No data on the use of avapritinib during pregnancy are available.

Characterisation of the Risk:

Clinical Trials

GIST, AdvSM, and ISM

Frequency

Not yet established in any patient population (i.e., GIST, AdvSM, and ISM).

Pregnant women were excluded from the clinical development programme and no events of pregnancy occurred during the avapritinib clinical trials.

Post-marketing reports of use of other approved TKI agents, such as imatinib, during pregnancy, showed that the apparent rate of malformations following exposure to imatinib in the first trimester is 11% [92, 103]. No malformations were observed in the liveborn infants when in utero exposure to imatinib took place during the second and/or third trimester of pregnancy [92, 103].

Severity

In non-clinical studies (refer to PART II: Module SII), avapritinib was teratogenic and embryotoxic in rats at doses 2.4 times greater than the human exposure at a dose of 400 mg.

Exposure to other TKI agents during the first trimester of pregnancy led to spontaneous foetal death and malformations, including exomphalos, skeletal malformation including hemivertebrae and scoliosis, meningocele, kidney agenesis, hypospadias, and to premature death of the newborns [92, 103].

Reversibility

None

Long-Term Outcomes

Not yet established in any patient population (i.e., GIST, AdvSM, and ISM).

Impact on Quality of Life

Embryofoetal toxicity is a significant complication of pregnancy with marked impact on both the mother and the foetus/child [92, 103].

In TKI-exposed pregnancies which completed to term, severe malformations were seen in the newborns, requiring medical care, surgical intervention and in some cases, culminating in premature death [92, 103].

Post-Authorisation Experience (Data Lock Point of 08 July 2022)

No case reports of embryofoetal toxicity were received from the post-marketing experience with avapritinib.

Post-marketing reports of use of other approved TKI agents, such as imatinib, during pregnancy, showed that the apparent rate of malformations following exposure to imatinib in the first trimester is 11% [92, 103]. No malformations were observed in the liveborn infants when in utero exposure to imatinib took place during the second and/or third trimester of pregnancy [92, 103].

Risk Factors and Risk Groups:

No specific risk factors or risk groups, other than exposure in pregnant women during the first trimester of pregnancy, have yet been identified.

Preventability:

All women of child-bearing potential treated with avapritinib, or men treated with avapritinib who have female partners of child-bearing potential, must use effective contraception methods during treatment and for at least 6 weeks for females and 2 weeks for males after the last dose of avapritinib.

Adherence to these recommendations should limit the cases of avapritinib exposure in pregnant women and thus prevent any potential malformations that foetal exposure might cause.

Impact on the Risk-Benefit Balance of the Product:

If pregnancy were to occur while receiving treatment with avapritinib, therapy should be withheld unless the potential benefits to the mother outweigh the potential risk to the foetus. Even though the nature and severity of embryofoetal toxicity events cannot be anticipated based on the currently available data, occurrence of such events would have a significant impact on individual patients. Routine risk minimisation measures should suffice for informing the patients in this respect.

Public Health Impact:

Not applicable.

SVII.3.2 Presentation of the Missing Information

SVII.3.2.1 Missing Information 1: Use in Patients with Severe Hepatic Impairment (All Indications)

Evidence Source:

Following a single oral dose of ~310 mg (~100 μCi) [^{14}C]-avapritinib, faecal excretion was the predominant route of elimination of drug-related material (70.3%) and excretion in urine was the secondary route of elimination (17.9%). Unchanged avapritinib represented 11.0% and 0.23% of the administered dose in faeces and urine, respectively.

Based on a population pharmacokinetics analysis, avapritinib exposures were similar among 53 subjects with mild hepatic impairment (total bilirubin within the ULN and AST above the ULN or total bilirubin above 1 to 1.5 × ULN and any AST), 6 subjects with moderate hepatic impairment (total bilirubin of above 1.5 to 3.0 × ULN and any AST), and 284 subjects with normal hepatic function (total bilirubin and AST within the ULN).

In the completed category 3 PASS BLU-285-0107, investigating the effect of severe hepatic impairment (score of 10 to 15 on the Child-Pugh scale) on the pharmacokinetics of avapritinib following administration of a single oral dose of 100 mg avapritinib in 8 subjects with severe hepatic impairment and 8 matched control subjects with normal hepatic function, the unbound concentrations of avapritinib were higher in patients with severe hepatic impairment compared to healthy matched control subjects with normal hepatic function.

Anticipated Risk/Consequence of the Missing Information:

Analyses of data from a small set number of patients with mild or moderate hepatic impairment demonstrated that exposure levels in this subpopulation were similar to those in patients with normal hepatic function. As such, no avapritinib dose adjustments are recommended in patients with mild or moderate hepatic impairment.

However, given that hepatic elimination is a major route of excretion for avapritinib and based on the results of the completed category 3 PASS BLU-285-0107, severe hepatic impairment may result in alteration of plasma avapritinib concentrations. Following results of the

BLU-285-0107 study, dose modification recommendations are proposed in the product information (i.e., modified starting dose of avapritinib for patients with severe hepatic impairment) to result in comparable avapritinib unbound concentrations in patients with severe hepatic impairment and patients with normal hepatic function. The safety profile and potential long-term effects of avapritinib use in patients with severe hepatic impairment require further characterisation.

SVII.3.2.2 Missing Information 2: Drug-Drug Interaction with CYP3A Substrates (All Indications)

Evidence Source:

In vitro studies demonstrated that avapritinib is a direct inhibitor of CYP3A and a time-dependent inhibitor of CYP3A. Therefore, avapritinib may have the potential to increase plasma concentrations of co-administered medicinal products that are substrates of CYP3A (refer to PART II: Module SII).

The pharmacokinetics of avapritinib in patients using avapritinib concomitantly with CYP3A substrates has not yet been established.

Anticipated Risk/Consequence of the Missing Information:

The concomitant use of avapritinib with CYP3A substrates (especially those with narrow therapeutic index) may result in alteration of their plasma concentrations that cannot be predicted based on available data.

PART II: Module SVIII - Summary of Safety Concerns

Table 13: Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Intracranial haemorrhage (GIST and AdvSM) Cognitive effects (GIST and AdvSM) Drug-drug interactions with moderate or strong CYP3A inhibitors or inducers (all indications)
Important potential risks	Intracranial haemorrhage (ISM) Cognitive effects (ISM) Cardiac toxicity, including QT prolongation (all indications) Embryofoetal toxicity (all indications)
Missing information	Use in patients with severe hepatic impairment (all indications) Drug-drug interactions with CYP3A substrates (all indications)

Abbreviations: AdvSM = advanced systemic mastocytosis; GIST = gastrointestinal stromal tumour; ISM = indolent systemic mastocytosis.

PART III: Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine Pharmacovigilance Activities beyond Adverse Reactions Reporting and Signal Detection

- **Specific Adverse Reaction Follow-up Questionnaires for Intracranial Haemorrhage and Cognitive Effects:**

  The structured follow-up forms are designed to optimise collection of data needed for a better understanding and characterisation of these safety concerns.

  The forms aim to collect information relevant to the patient (e.g., demographics, biometrics, medical history), the suspected medicinal product (e.g., duration of therapy, route of administration) and the AE/adverse drug reaction (e.g., date of onset, detailed description, action taken, outcome). Specific information on medical history and co-medication relevant to each of the risks will also be collected, including history of haemorrhage, intracerebral vascular anomaly, brain metastases, hypertension, stroke, and use of anticoagulants, aspirin or non-steroidal anti-inflammatory drugs for patients experiencing intracranial haemorrhage and history of psychiatric conditions, stroke, dementia, Alzheimer's disease or COVID-19, and (prior) use of other TKIs, psychiatric and opioid medication.

The respective follow-up forms are provided in Annex 4 of the RMP.

III.2 Additional Pharmacovigilance Activities

Observational Safety and Efficacy Study

Study Short Name and Title:

BLU-285-1406: Observational study evaluating the long-term safety and efficacy of avapritinib in the first-line treatment of patients with platelet-derived growth factor alpha D842V-mutated gastrointestinal stromal tumour.

Rationale and Study Objectives:

To address the specific obligation of the conditional marketing authorisation in Europe and to provide further evidence of the positive benefit-risk profile of avapritinib in patients with metastatic and unresectable GIST harbouring D842V mutations in PDGFRA, an excessively rare disease with high unmet medical need, this study aims to collect additional long-term safety and efficacy data in the first-line population.

- List of Addressed Safety Concerns:

  Intracranial haemorrhage
  Cognitive effects
  DDIs 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

The overall objective is to collect long-term safety and efficacy data for avapritinib in first-line patients with PDGFRA D842V-mutated GIST.

Primary Objective:

– To describe types, severity, and rates of AEs, serious AEs, AEs leading to discontinuation or decreased dosing of avapritinib, AEs of special interest, and deaths.

Secondary Objective:

– To evaluate efficacy in terms of disease response to treatment, PFS, and overall survival, as well as duration of treatment and duration of response.

Study Design:

This is a multinational, open-label, observational PASS that will evaluate the long-term safety and efficacy of avapritinib in first-line or following < 4 months of imatinib treatment at least 50 patients with PDGFRA D842V-mutated GIST.

Study Population:

Patients will be included from multiple sites worldwide. Three patient populations are planned to be enrolled:

- Patients with PDGFRA D842V-mutated GIST who are scheduled to receive avapritinib in the first line (or have received imatinib for < 4 months).
- Patients with PDGFRA D842V-mutated GIST who are already receiving treatment with avapritinib (in the first-line or following ≤ 4 months of imatinib treatment).
- Patients with PDGFRA D842V-mutated GIST who previously received treatment with avapritinib in the first line or following ≤ 4 months of imatinib treatment and have discontinued treatment.

In addition to evaluating safety and efficacy of first-line avapritinib treatment, patients who were initially treated with imatinib for ≤ 4 months are also being included in this study to allow for practical, real-world, clinical experience with use of avapritinib in the PDGFRA D842V-mutated GIST population setting and increase the feasibility of study completion in this ultra-rare patient population.

Milestones:

– Annual progress reports: annually starting from August 2022 until August 2025

– Interim report: February 2025

– Final clinical study report: Q1 2027

DDI Study

Study Short Name and Title:

BLU-285-1107: Clinical drug-drug interaction study of avapritinib with a CYP3A4 substrate

Rationale and Study Objectives:

The primary objective is to investigate the net effect of CYP3A4 inhibition and induction by avapritinib on midazolam pharmacokinetics in patients.

The effect of avapritinib on the pharmacokinetic parameters of midazolam as well as safety will be assessed.

– List of Addressed Safety Concerns:

  Drug-drug interactions with CYP3A substrates

Study Design:

Open-label, fixed sequence

Study Population:

It is expected that this study will be conducted in patients rather than healthy volunteers due to the need for multiple dosing of avapritinib to reach steady state.

Milestones:

– Study completion: December 2024

– Final clinical study report: May 2025

Tabulated summary of ongoing pharmacovigilance study programme is provided in Annex 2.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 14: Ongoing 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 BLU-285-1406 "Observational study evaluating the long-term safety and efficacy of avapritinib in the first-line treatment of patients with platelet-derived growth factor alpha D842V mutated gastrointestinal stromal tumour" Ongoing	The overall objective is to collect long-term safety and efficacy data for avapritinib in first-line patients with PDGFRA D842V-mutated GIST. Primary objective: – To describe types, severity, and rates of adverse events, serious adverse events, adverse events leading to discontinuation or decreased dosing of avapritinib, adverse events of special interest, and deaths. Secondary objective: – To evaluate efficacy in terms of disease response to treatment, progression-free survival, and overall survival, as well as duration of treatment and duration of response.	– Intracranial haemorrhage – Cognitive effects – Drug-drug interactions with moderate or strong CYP3A inhibitors or inducers – Cardiac toxicity, including QT prolongation – Embryofoetal toxicity – Use in patients with severe hepatic impairment – Drug-drug interactions with CYP3A substrates	– Annual progress reports	– Annually starting from August 2022 until August 2025
			– Interim report	– February 2025
			– Final clinical study report	– Q1 2027

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 – required additional pharmacovigilance activities				
Study BLU-285-1107 "Clinical drug-drug interaction study of avapritinib with a CYP3A substrate" Ongoing	– To investigate net effect of CYP3A inhibition and induction by avapritinib on midazolam pharmacokinetics in patients	– Drug-drug interactions with CYP3A substrates	– Study completion	– December 2024
			– Final clinical study report	– May 2025

Abbreviations: CYP3A = cytochrome P450 isozyme 3A; GIST = gastrointestinal stromal tumour; PDGFRA = platelet-derived growth factor receptor alpha; Q = quarter.

PART IV: Plans for Post-authorisation Efficacy Studies

None.

PART V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk minimisation plan

V.1 Routine Risk Minimisation Measures

Table 15: Description of Routine Risk Minimisation Measures by Safety Concern

Safety Concern	Routine Risk Minimisation Activities
Intracranial haemorrhage (GIST and AdvSM)	**Routine risk communication**: – SmPC sections 4.2, 4.4, and 4.8 – PL sections 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: 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. **Other routine risk minimisation measures beyond the Product Information:** – Restricted medical prescription
Cognitive effects (GIST and AdvSM)	**Routine risk communication**: – SmPC sections 4.2, 4.4, 4.7, and 4.8 – PL sections 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: 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. **Other routine risk minimisation measures beyond the Product Information:** – Restricted medical prescription

Safety Concern	Routine Risk Minimisation Activities
Drug-drug interactions with moderate or strong CYP3A inhibitors or inducers (all indications)	**Routine risk communication:** – SmPC sections 4.2, 4.4, 4.5, and 5.2 – PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: For patients with GIST and AdvSM, concomitant use with strong CYP3A inhibitors must be avoided. Concomitant use with moderate CYP3A inhibitors should be avoided. If concomitant use with moderate CYP3A inhibitor cannot be avoided, the starting dose of avapritinib must 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. For patients with ISM, concomitant use with strong or moderate CYP3A inhibitors must be avoided, as stated in SmPC section 4.2. **Other routine risk minimisation measures beyond the Product Information:** – Restricted medical prescription
Intracranial haemorrhage (ISM)	**Routine risk communication:** – SmPC sections 4.2, 4.4 and 4.8 – PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: Recommendation to permanently discontinue treatment if intracranial haemorrhage of any grade occurs is included in SmPC sections 4.2 and 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. 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. **Other routine risk minimisation measures beyond the Product Information:** – Restricted medical prescription
Cognitive effects (ISM)	**Routine risk communication**: – SmPC sections 4.2, 4.4, 4.7 and 4.8 – PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk**: 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.

Safety Concern	Routine Risk Minimisation Activities
	Other routine risk minimisation measures beyond the Product Information: – Restricted medical prescription
Cardiac toxicity, including QT prolongation (all indications)	**Routine risk communication:** – SmPC sections 4.4, 4.8, and 5.1 – PL sections 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** For patients with GIST and AdvSM, 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. For patients with ISM, recommendation for interval assessments of QT by ECG should be considered, in particular in patients with concurrent factors that could prolong QT (e.g., age, pre-existing heart rhythm disorders, etc.). **Other routine risk minimisation measures beyond the Product Information:** – Restricted medical prescription
Embryofoetal toxicity (all indications)	**Routine risk communication:** – SmPC sections 4.6 and 5.3 – PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendation for female patients of childbearing potential to use effective contraception during treatment and for 6 weeks after the last dose of avapritinib and for male patients with female partners of childbearing potential to use effective contraception during treatment and for 2 weeks after the last dose of avapritinib, is included in SmPC section 4.6 and PL section 2. **Other routine risk minimisation measures beyond the Product Information:** – Restricted medical prescription
Use in patients with severe hepatic impairment (all indications)	**Routine risk communication:** – SmPC sections 4.2 and 5.2 – PL section 3 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendation for patients with severe hepatic impairment (Child-Pugh Class C) to reduce the starting dose from 300 mg to 200 mg orally QD for patients with GIST, from 200 mg to 100 mg orally QD for patients with AdvSM, and from 25 mg QD to 25 mg every other day for patients with ISM is included in SmPC section 4.2. **Other routine risk minimisation measures beyond the Product Information:**

Safety Concern	Routine Risk Minimisation Activities
	– Restricted medical prescription
Drug-drug interaction with CYP3A substrates (all indications)	**Routine risk communication:** – SmPC sections 4.5 and 5.2 – PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** – Restricted medical prescription

Abbreviations: AdvSM = advanced systemic mastocytosis; CT = computed tomography; CYP3A = cytochrome P450 isozyme 3A; GIST = gastrointestinal stromal tumour; ISM = indolent systemic mastocytosis; MRI = magnetic resonance imaging; PL = package leaflet; QD = once daily; SmPC = summary of product characteristics.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table 16: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Intracranial haemorrhage (GIST and AdvSM)	Routine risk minimisation measures: – SmPC sections 4.2, 4.4, and 4.8 – PL sections 2 and 4 SmPC section 4.2 contains recommendation on dose interruptions, permanent discontinuation, and platelet support. SmPC section 4.4 provides guidance on MRI/CT, platelet count monitoring, and recommendation on permanent drug discontinuation. PL section 2 gives recommendation on treatment interruption. PL section 4 provides guidance on MRI/CT. Restricted prescription medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting: – Follow-up questionnaire Additional pharmacovigilance activities: – Study BLU-285-1406 (final study report: Q1 2027)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Cognitive effects (GIST and AdvSM)	Routine risk minimisation measures: – SmPC sections 4.2, 4.4, 4.7, and 4.8 – PL sections 2 and 4 SmPC section 4.2 contains recommendations on dose modifications and permanent discontinuation of therapy. Restricted prescription medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting: – Follow-up questionnaire Additional pharmacovigilance activities: – Study BLU-285-1406 (final study report: Q1 2027)
Drug-drug interactions with moderate or strong CYP3A inhibitors or inducers (all indications)	Routine risk minimisation measures: – SmPC sections 4.2, 4.4, 4.5, and 5.2 – PL section 2 SmPC section 4.2 contains recommendation on concomitant use of avapritinib with moderate or strong CYP3A inhibitors. Restricted prescription medicine Additional risk minimisation measures: None	Additional pharmacovigilance activities: – Study BLU-285-1406 (final study report Q1 2027)
Intracranial haemorrhage (ISM)	Routine risk minimisation measures: – SmPC sections 4.2, 4.4 and 4.8 – PL section 2 SmPC section 4.4 provides guidance on MRI/CT and permanent drug discontinuation. PL section 2 gives recommendation on treatment interruption. Restricted prescription medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting: – Follow-up questionnaire Additional pharmacovigilance activities: – None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Cognitive effects (ISM)	Routine risk minimisation measures: – SmPC sections 4.2, 4.4, 4.7 and 4.8 – PL section 2 SmPC section 4.2 contains recommendations on dose modifications and permanent discontinuation of therapy. Restricted prescription medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting: – Follow-up questionnaire Additional pharmacovigilance activities: – None
Cardiac toxicity, including QT prolongation (all indications)	Routine risk minimisation measures: – SmPC sections 4.4, 4.8, and 5.1 – PL sections 2 and 4 SmPC section 4.4 includes recommendation for interval assessment of QT interval. Restricted prescription medicine Additional risk minimisation measures: None	Additional pharmacovigilance activities: – Study BLU-285-1406 (final study report: Q1 2027)
Embryofoetal toxicity (all indications)	Routine risk minimisation measures: – SmPC sections 4.6 and 5.3 – PL section 2 SmPC section 4.6 and PL section 2 includes recommendation on the use of effective contraception during therapy. Restricted prescription medicine Additional risk minimisation measures: None	Additional pharmacovigilance activities: – Study BLU-285-1406 (final study report Q1 2027)
Use in patients with severe hepatic impairment (all indications)	Routine risk minimisation measures: – SmPC sections 4.2 and 5.2 – PL section 3 SmPC section 4.2 includes dosing recommendations in patients with severe hepatic impairment.	Additional pharmacovigilance activities: – Study BLU-285-1406 (final study report Q1 2027)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
	Restricted prescription medicine Additional risk minimisation measures: None	
Drug-drug interaction with CYP3A substrates (all indications)	Routine risk minimisation measures: – SmPC sections 4.5 and 5.2 – PL section 2 Restricted prescription medicine Additional risk minimisation measures: None	Additional pharmacovigilance activities: – Study BLU-285-1406 (final study report: Q1 2027) – Study BLU-285-1107 (final study report: May 2025).

Abbreviations: AdvSM = advanced systemic mastocytosis; CT = computed tomography; CYP3A = cytochrome P450 isozyme 3A; GIST = gastrointestinal stromal tumour; ISM = indolent systemic mastocytosis; MRI = magnetic resonance imaging; PL = package leaflet; Q = quarter; SmPC = summary of product characteristics.

PART VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for AYVAKYT (avapritinib)

This is a summary of the risk management plan (RMP) for AYVAKYT. The RMP details important risks of AYVAKYT, how these risks can be minimised, and how more information will be obtained about AYVAKYT's risks and uncertainties (missing information).

AYVAKYT's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how AYVAKYT should be used.

This summary of the RMP for AYVAKYT should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of AYVAKYT's RMP.

I. The Medicine and What it is Used for

AYVAKYT is authorised as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the PDGFRA D842V mutation, 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, and for the treatment of adult patients with indolent systemic mastocytosis (ISM) (see SmPC for the full indications). It contains avapritinib as the active substance administered via oral route.

Further information about the evaluation of AYVAKYT's benefits can be found in AYVAKYT's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of AYVAKYT, together with measures to minimise such risks and the proposed studies for learning more about AYVAKYT's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of AYVAKYT is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of AYVAKYT are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of AYVAKYT. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Intracranial haemorrhage (GIST and AdvSM) Cognitive effects (GIST and AdvSM) Drug-drug interactions with moderate or strong CYP3A inhibitors or inducers (all indications)
Important potential risks	Intracranial haemorrhage (ISM) Cognitive effects (ISM) Cardiac toxicity, including QT prolongation (all indications) Embryofoetal toxicity (all indications)
Missing information	Use in patients with severe hepatic impairment (all indications) Drug-drug interactions with CYP3A substrates (all indications)

II.B Summary of Important Risks

Identified Risk: Intracranial Haemorrhage (GIST and AdvSM)	
Evidence for linking the risk to the medicine	This risk is based on the events of intracranial haemorrhage (subdural haematoma, haemorrhage intracranial, and cerebral haemorrhage) observed in subjects exposed to avapritinib in the clinical development programme, even though the causality evaluation of the events was confounded by alternative aetiologies or other risk factors. The non-clinical data from the avapritinib development programme showed the development of choroid plexus oedema in dogs with exposure margins of 4.7, 1.0, and 0.4 times the human exposure at the 25 mg, 200 mg, and 300 mg clinical doses, respectively, as well as brain haemorrhage in dogs with exposure margins of 9.0, 1.8, and 0.8 times the human exposure at the 25 mg,

Identified Risk: Intracranial Haemorrhage (GIST and AdvSM)	
	200 mg, and 300 mg clinical doses of avapritinib, respectively. In addition, intracranial haemorrhage was associated with use of other tyrosine kinase inhibitors (TKIs) such as dasatinib or imatinib (Mustafa Ali et al. 2015), including their use in patients with GIST (Feki et al. 2015, Theodotou et al. 2016). Lastly, a majority of AdvSM patients with intracranial haemorrhage had severe thrombocytopenia, preceding or at the time of the event.
Risk factors and risk groups	Intracranial haemorrhage occurs in 7% of patients with cancer, and subdural haematoma has been estimated to account for 26% of intracranial haemorrhage found at autopsy in this population of patients (Reichman et al. 2012). Intracranial haemorrhage accounts for nearly one half of all cerebrovascular events in cancer patients, but the risk factors vary between types of cancer (Navi et al. 2010). Intracranial haemorrhage is common in haematological malignancies or in the presence of brain metastases. However, brain metastases are extremely rare in GIST (Naoe et al. 2011) and only 16 cases of brain metastases in patients with GIST were reported in the literature until 2014 (Sato et al. 2014). Events of subdural haematoma in patients with GIST treated with imatinib were reported in the literature (Feki et al. 2015, Theodotou et al. 2016) in the absence of other obvious causes such as head trauma, brain metastases, thrombocytopenia or anticoagulation which represent the most common general risk factors for such events, and the suspected cause was imatinib-related platelet dysfunction. It has been estimated that the rate of imatinib-related intracranial haemorrhage in the absence of other obvious causes may be between 1.9 and 5.7% (Theodotou et al. 2016). Thrombocytopenia is a known risk factor for internal haemorrhage, including intracranial haemorrhage. In patients with GIST, thrombocytopenia adverse events (AEs) were observed at a low frequency (18 patients; 3.0%). Grade 1 thrombocytopenia was reported in 16 patients, and Grade 2 and Grade 3 in 1 patient each. However, thrombocytopenia adverse events (AEs) were reported in more than a third of the patients with AdvSM (77 patients; 39.9%) and in more than half of these patients the thrombocytopenia AEs were ≥Grade 3 in severity (43 of 77 patients; 56%). Severe thrombocytopenia (platelet count $< 50 \times 10^9$/L) was identified as the primary risk factor for intracranial haemorrhage in AdvSM. Prior to or at the time of the intracranial haemorrhage events, 10 of

Identified Risk: Intracranial Haemorrhage (GIST and AdvSM)	
	the 12 patients with AdvSM with intracranial haemorrhage had severe thrombocytopenia with platelet counts below 50 × 10^9/L, and 2 patients had mild thrombocytopenia (platelet counts between less than lower limit of normal and 75 × 10^9/L) at the time of the event. As severe thrombocytopenia is a known complication associated with AdvSM, due to bone marrow infiltration by MCs, this likely explains the higher frequency of intracranial haemorrhage seen in patients with AdvSM compared with patients with GIST treated with avapritinib. In addition to severe thrombocytopenia prior to or at the time of the intracranial haemorrhage, a review of case reports of patients with intracranial haemorrhage events identified several other potential risk factors for such events including use of concomitant anti-platelet or anti-thrombotic therapy any time from the date of first dose of study drug to the date of last dose of study drug + 30 days, inclusive; elevated international normalised ratio prior to the intracranial haemorrhage event; elevated activated partial thromboplastin time prior to the intracranial haemorrhage event; and avapritinib starting dose > 200 mg once daily (QD). A multivariate logistic regression model to evaluate the association between intracranial haemorrhage and each of these 5 potential risk factors identified severe thrombocytopenia (platelet counts < 50 × 10^9/L) as the only statistically significant risk factor (p-value: 0.0292) for intracranial haemorrhage in the AdvSM population. Risk mitigation strategies were implemented for all AdvSM patients to minimise the risk for intracranial haemorrhage. These measures included exclusion of patients with a platelet count < 50 × 10^9/L at baseline, monitoring of platelet count at every treatment cycle, detailed guidance on dose modification, and defining the starting dose of avapritinib to be 200 mg QD. Additionally, to mitigate against a second bleed, protocols were amended such that patients who experienced an intracranial haemorrhage of any toxicity grade permanently discontinued avapritinib treatment. With such risk minimisation measures, the current intracranial haemorrhage incidence is 2.5% in patients with AdvSM who did not have pre-existing severe thrombocytopenia and were treated at a starting dose of 200 mg QD.

Identified Risk: Intracranial Haemorrhage (GIST and AdvSM)	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.2, 4.4, and 4.8 PL sections 2 and 4 SmPC section 4.2 contains recommendation on dose interruptions, permanent discontinuation, and platelet support. SmPC section 4.4 provides guidance on MRI/CT, platelet count monitoring, and recommendation on permanent drug discontinuation. PL section 2 gives recommendation on treatment interruption. PL section 4 provides guidance on MRI/CT. Restricted medical prescription Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study BLU-285-1406 See section II.C of this summary for an overview of the post-authorisation development plan.

Feki J, Marrekchi G, Boudawara T, Rekik N, Maatouq S, Boudawara Z, et al. (2015). "Subdural hematoma during therapy of gastro-intestinal stromal tumor (GIST) with Imatinib mesylate." Gulf J Oncolog 1(17): 92-5.

Kantarjian H, Giles F, List A, Lyons R, Sekeres MA, Pierce S, et al. (2007). "The incidence and impact of thrombocytopenia in myelodysplastic syndromes." Cancer 109(9): 1705-14.

Mustafa Ali MK, Sabha MM, Al-Rabi KH (2015). "Spontaneous subdural hematoma in a patient with Philadelphia chromosome-positive acute lymphoblastic leukemia with normal platelet count after dasatinib treatment." Platelets 26(5): 491-4

Naoe H, Kaku E, Ido Y, Gushima R, Maki Y, Saito H, et al. (2011). "Brain metastasis from gastrointestinal stromal tumor: a case report and review of the literature." Case Rep Gastrointest Med 5(3): 583-9.

Navi BB, Reichman JS, Berlin D, Reiner AS, Panageas KS, Segal AZ, et al. (2010). "Intracerebral and subarachnoid hemorrhage in patients with cancer." Neurology 74(6): 494-501.

Reichman J, Singer S, Navi B, Reiner A, Panageas K, Gutin PH, et al. (2012). "Subdural hematoma in patients with cancer." Neurosurgery 71(1): 74-9.

Sato K, Tanaka T, Kato N, Ishii T, Terao T, Murayama Y (2014). "Metastatic cerebellar gastrointestinal stromal tumor with obstructive hydrocephalus arising from the small intestine: a case report and review of the literature." Case Rep Oncol Med 2014: 343178.

Theodotou CB, Shah AH, Ivan ME, Komotar RJ (2016). "Subdural hematoma in a patient taking imatinib for GIST: a case report and discussion of risk with other chemotherapeutics." Anticancer Drugs 27(3): 259-63.

Tornebohm E, Lockner D, Paul C (1993). "A retrospective analysis of bleeding complications in 438 patients with acute leukaemia during the years 1972-1991." Eur J Haematol 50(3): 160-7.

Identified Risk: Cognitive Effects (GIST and AdvSM)	
Evidence for linking the risk to the medicine	This risk is based on the events of cognitive effects (e.g., memory impairment, cognitive disorder, confusional state, amnesia, somnolence, speech disorder, encephalopathy, delirium, mental impairment, hallucination, mood altered, agitation, disorientation, personality change, dementia, mental status change, and psychotic disorder) observed with

Identified Risk: Cognitive Effects (GIST and AdvSM)	
	increased frequency in subjects exposed to avapritinib in the clinical development programme. In addition, cognitive effects have been identified in association with other authorised TKIs such as larotrectinib (Vitrakvi SmPC, 2019) and lorlatinib (Lorviqua SmPC, 2019).
Risk factors and risk groups	Several risk factors and risk groups prone to develop cognitive effects have been identified based on quantitative and qualitative analysis of available data. These include increased age, medical history of cognitive effects, together with polypharmacy and use of central nervous system medications, increased avapritinib dosage and other concurrent pathologies or disease progression. Analyses of patients in the overall safety population (N=803) showed that the incidence of cognitive effects was slightly higher in patients aged ≥65 years compared with patients aged < 65 years (42.4% vs 38.1%). This difference is not unexpected because cognitive issues are known to increase with age (Harada et al. 2013). Furthermore, this is in accordance with other studies that found similar correlation between the age of the patient and development of cognitive effects while undergoing anti-cancer therapy (Ahles et al. 2010). There appeared to be a slightly higher incidence of cognitive effects in female compared to male patients (44.9 vs. 37.2%) and in white compared to non-white patients (41.4% vs. 36.8%). The incidence of events of cognitive effects was higher in patients from North America compared with patients from Europe or Australia and Asia (51.5% vs 31.2% and 31.9%, respectively). This difference appears to be driven by a higher incidence of events of memory impairment in North American patients compared with patients from the above regions (31.1% vs 10.7% and 14.2%). The cause of this observation is not clear. The incidence of cognitive effects was also found to be higher in patients with prior regorafenib use compared with patients with no regorafenib use in the GIST population. Other variables that did not appear to show a significant impact on the incidence of cognitive effects included prior number of TKI therapies and total duration of prior TKI therapy. A multivariable logistic regression analysis performed for cognitive effects of any grade showed that the odds of experiencing a cognitive effect were increased by a multiplier of 167% if a patient had medical history of cognitive effects. This is in accordance with publications

Identified Risk: Cognitive Effects (GIST and AdvSM)	
	indicating that the level of cognitive reserve prior to treatment plays a role in development of cognitive effects during anti-cancer therapy (Ahles et al. 2010). This refers to the innate and developed cognitive capacity, which is influenced by various factors, including genetics, education, occupational attainment, and lifestyle. Results of one longitudinal study showed that patients who had lower pre-treatment cognitive reserve performed worse on measures of Processing Speed compared with patients not exposed to chemotherapy and healthy controls (Ahles et al. 2010). As such, patients with higher baseline cognitive performance may have more cushion against cognitive detriments than individuals with a lower baseline cognitive performance.
Risk minimisation measures	<u>Routine risk minimisation measures</u> SmPC sections 4.2, 4.4, 4.7, and 4.8 PL sections 2 and 4 SmPC section 4.2 contains recommendations on dose modifications and permanent discontinuation of therapy. Restricted medical prescription <u>Additional risk minimisation measures</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> Study BLU-285-1406 See section II.C of this summary for an overview of the post-authorisation development plan.

Vitrakvi (larotrectinib) Summary of Product Characteristics. Leverkusen, Germany: Bayer AG; 2019. Available from: https://www.ema.europa.eu/en/documents/product-information/vitrakvi-epar-product-information_en.pdf [accessed 11 May 2020].

Lorviqua (lorlatinib) Summary of Product Characteristics. Bruxelles, Belgium: Pfizer Europe MA EEIG; 2019. Available from: https://www.ema.europa.eu/en/documents/product-information/lorviqua-epar-product-information_en.pdf [accessed 11 May 2020].

Harada CN, Natelson Love MC, Triebel KL (2013). "Normal cognitive aging." Clin Geriatr Med 29(4): 737-52.

Ahles TA, Saykin AJ, McDonald BC, Li Y, Furstenberg CT, Hanscom BS, et al. (2010). "Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve." J Clin Oncol 28(29): 4434-40.

Identified Risk: Drug-Drug Interactions with Moderate or Strong CYP3A Inhibitors or Inducers (All Indications)	
Evidence for linking the risk to the medicine	The data from the non-clinical studies showed that in vitro, avapritinib is predominantly metabolised by CYP3A, and thus, plasma levels of avapritinib can be affected when administered concomitantly with a moderate or strong CYP3A inhibitor or inducer. The only clinical data available originated from the single-dose,

Identified Risk: Drug-Drug Interactions with Moderate or Strong CYP3A Inhibitors or Inducers (All Indications)	
	pharmacology Study BLU-285-0104 conducted in healthy volunteers, which showed that plasma exposure of avapritinib was modulated in the presence of the strong CYP3A4 inducer rifampicin and strong CYP3A4 inhibitor itraconazole. The clinical outcomes of such effects and the overall impact on patients treated with avapritinib remains unknown.
Risk factors and risk groups	No specific risk factors or risk groups have yet been established for avapritinib.
Risk minimisation measures	<u>Routine risk minimisation measures</u> SmPC sections 4.2, 4.4, 4.5, and 5.2 PL section 2 SmPC section 4.2 contains recommendation on concomitant use of avapritinib with moderate or strong CYP3A inhibitors. Restricted medical prescription <u>Additional risk minimisation measures</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> Study BLU-285-1406 See section II.C of this summary for an overview of the post-authorisation development plan.

Potential Risk: Intracranial Haemorrhage (ISM)	
Evidence for linking the risk to the medicine	No intracranial haemorrhages were reported in patients with ISM receiving avapritinib in the clinical development programme. However, intracranial haemorrhage represents a known risk for avapritinib in patients with GIST and AdvSM and has been observed in these patient populations treated with avapritinib at the higher starting doses of 300 mg and 200 mg QD, respectively, with severe thrombocytopenia identified as the primary risk factor in patients with AdvSM.
Risk factors and risk groups	Not yet established in the ISM patient population.

Potential Risk: Intracranial Haemorrhage (ISM)	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.2, 4.4 and 4.8 PL section 2 SmPC section 4.4 provides guidance on MRI/CT and permanent drug discontinuation. PL section 2 gives recommendation on treatment interruption. Restricted medical prescription Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Potential Risk: Cognitive Effects (ISM)	
Evidence for linking the risk to the medicine	Cognitive effects were reported at a low frequency in patients receiving avapritinib in patients with ISM in Part 2 of study BLU-285-2203, and the frequency was slightly lower in the 25 mg avapritinib group compared with the placebo group. In this study, treatment with 25 mg avapritinib in patients with ISM was not associated with an increased risk of developing cognitive effect events. However, cognitive effects represent a known risk for avapritinib in patients with GIST and AdvSM and have been observed in these patient populations treated with avapritinib at higher doses, despite that the causality of the events was confounded by alternative aetiologies or other risk factors.
Risk factors and risk groups	No specific risk factors or risk groups for cognitive effects have been established for avapritinib in the ISM patient population. The lower incidence of cognitive effects in patients receiving 25 mg avapritinib compared with placebo in the clinical development programme suggests that these events are most likely due to the patients' underlying disease and other treatments patients were receiving as part of their best supportive care.

Potential Risk: Cognitive Effects (ISM)	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.2, 4.4, 4.7 and 4.8 PL section 2 SmPC section 4.2 contains recommendations on dose modifications and permanent discontinuation of therapy. Restricted medical prescription Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Potential Risk: Cardiac Toxicity, Including QT Prolongation (All Indications)	
Evidence for linking the risk to the medicine	The non-clinical studies did not show any effects of avapritinib on the cardiovascular system. In clinical Study BLU-285-1101, a minor increase in QTc interval was reported at 300/400 mg QD dose of avapritinib in 3.9% of patients (13/335). The estimated mean change from baseline in QTcF was 6.55 ms (90% CI: 1.80 to 11.29) at the observed steady state geometric mean maximum plasma concentration of 899 ng/mL. These increases were not clinically relevant and no effect on heart rate or cardiac conduction (PR, QRS, and RR intervals) was observed. The potential for QT prolongation was applied to the lower 25 mg QD dose of avapritinib for the treatment of ISM. As no clinically relevant effect on QTc was observed with avapritinib when administered at a dose of 300 or 400 mg QD, no clinically relevant effect is anticipated when avapritinib is administered at the 12- to 16-times lower dose of 25 mg QD in patients with ISM (12.8-fold lower geometric mean maximum plasma concentration at the 25 mg QD dose [70.2 ng/mL]). Cardiac toxicity seen mostly with multitarget TKIs ranged from asymptomatic QT prolongation to reduction in left ventricular ejection fraction, symptomatic congestive heart failure, acute coronary syndromes and myocardial infarction. Hypertension and sudden death have also been associated with treatment with these agents (Chen, 2016; Lee, 2018; Orphanos, 2009). The relevance of these findings to avapritinib remains unknown.

Potential Risk: Cardiac Toxicity, Including QT Prolongation (All Indications)	
	The potential for QT prolongation is considered a class effect of small molecule TKIs despite potential differences between individual agents. While dasatinib, vandetanib, sorafenib, nilotinib, or sunitinib showed QT prolongation frequently (> 5% of patients), based on the large systematic review of commonly used cancer drugs to determine the incidence of QT prolongation and clinically relevant arrhythmias (Porta-Sanchez, 2017), QT prolongation was infrequent or absent with afatinib, crizotinib, ceritinib, dovitinib, imatinib, lapatinib, lenvatinib, nintedanib, pazopanib, and ponatinib. However, when present, QT prolongation had only rarely clinically relevant consequences, defined as arrhythmias and sudden cardiac death (Porta-Sanchez, 2017).
Risk factors and risk groups	Patients with a prior history of cardiac disease are in general at higher risk of cardiac damage associated with TKIs (Lee and Kim 2018). Patients with underlying electrocardiogram or cardiac abnormalities, including patients with a prolonged QTc, defined as QTcF of > 480 ms, with a history of prolonged QT syndrome or torsade de pointes or patients with a family history of prolonged QT syndrome may be at higher risk of effects on QT interval and were, therefore, excluded from the clinical trials with avapritinib but are expected in clinical practice within the target population of avapritinib. Concomitant treatment with drugs with a known potential to prolong QT interval such as azole antifungals, fluoroquinolones, macrolides and others may increase the risk. Additionally, elderly patients or patients with electrolyte imbalance are at higher risk of QTc prolongation (Kloth et al. 2015).
Risk minimisation measures	<u>Routine risk minimisation measures</u> SmPC sections 4.4, 4.8, and 5.1 PL sections 2 and 4 SmPC section 4.4 includes recommendation for interval assessment of QT interval. Restricted medical prescription <u>Additional risk minimisation measures</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> Study BLU-285-1406

Potential Risk: Cardiac Toxicity, Including QT Prolongation (All Indications)	
	See section II.C of this summary for an overview of the post-authorisation development plan.

Chen ZI, Ai DI (2016). "Cardiotoxicity associated with targeted cancer therapies." Mol Clin Oncol 4(5): 675-81.

Kloth JSL, Pagani A, Verboom MC, Malovini A, Napolitano C, Kruit WHJ, et al. (2015). "Incidence and relevance of QTc-interval prolongation caused by tyrosine kinase inhibitors." Br J Cancer 112(6): 1011-6.

Lee W-S, Kim J (2018). "Cardiotoxicity associated with tyrosine kinase-targeted anticancer therapy." Mol Cell Toxicol 14(3): 247-54.

Orphanos GS, Ioannidis GN, Ardavanis AG (2009). "Cardiotoxicity induced by tyrosine kinase inhibitors." Acta Oncol 48(7): 964-70.

Porta-Sanchez A, Gilbert C, Spears D, Amir E, Chan J, Nanthakumar K, et al. (2017). "Incidence, Diagnosis, and Management of QT Prolongation Induced by Cancer Therapies: A Systematic Review." J Am Heart Assoc 6(12).

Potential Risk: Embryofoetal Toxicity (All Indications)	
Evidence for linking the risk to the medicine	Data from the rodent embryofoetal development studies showed that avapritinib has embryotoxic effects. These results are further supported by the post-marketing data for other TKI agents such as imatinib in pregnant women showing that maternal exposure during the first trimester of pregnancy can lead to foetal development complications and spontaneous abortion (National Toxicology Program 2013, Abruzzese et al. 2014). No data on the use of avapritinib during pregnancy are available.
Risk factors and risk groups	No specific risk factors or risk groups, other than exposure in pregnant women during the first trimester of pregnancy, have yet been identified.
Risk minimisation measures	<u>Routine risk minimisation measures</u> SmPC sections 4.6 and 5.3 PL section 2 SmPC section 4.6 and PL section 2 includes recommendation on the use of effective contraception during therapy. Restricted medical prescription <u>Additional risk minimisation measures</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> Study BLU-285-1406 See section II.C of this summary for an overview of the post-authorisation development plan.

Abruzzese E, Trawinska MM, Perrotti AP, De Fabritiis P (2014). "Tyrosine kinase inhibitors and pregnancy." J Cereb Blood Flow Metab 6(1): e2014028-e.

National Toxicology Program (2013). "Monograph. Developmental Effects and Pregnancy Outcomes Associated With Cancer Chemotherapy Use During Pregnancy." (2): i-214.

Missing Information: Use in Patients with Severe Hepatic Impairment (All Indications)	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.2 and 5.2 PL section 3 SmPC section 4.2 includes dosing recommendations in patients with severe hepatic impairment. Restricted medical prescription Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study BLU-285-1406 See section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Drug-Drug Interactions with CYP3A Substrates (All Indications)	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.5 and 5.2 PL section 2 Restricted medical prescription Additional risk minimisation measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study BLU-285-1406 Study BLU-285-1107 See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-Authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

Post-authorisation safety study

Observational safety and efficacy study (Study BLU-285-1406)

Purpose of the study:

To address the specific obligation of the conditional marketing authorisation in Europe and to provide further evidence of the positive benefit-risk profile of avapritinib in patients with metastatic and unresectable GIST harbouring D842V mutations in PDGFRA, an excessively rare disease with high

unmet medical need, this study aims to collect additional long-term safety and efficacy data in the first-line population.

The primary objective is a long-term safety of avapritinib while the secondary objective is a long-term efficacy of avapritinib.

II.C.2 Other Studies in Post-authorisation Development Plan

Drug-Drug Interaction Study (Study BLU-285-1107)

Purpose of the study:

The primary objective is to investigate the net effect of CYP3A inhibition and induction by avapritinib on midazolam pharmacokinetics in patients.

The effect of avapritinib on the pharmacokinetic parameters of midazolam as well as safety will be assessed.

PART VII: Annexes

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Intracranial Haemorrhage Follow-up Questionnaire

Cognitive Effects Follow-up Questionnaire

Intracranial Bleeding Data Collection Tool for Avapritinib

1. Patient Information

Patient Name: _____

Date of Birth: ___/____/_____(DD/MMM/YYYY) Age:_____ (YY) Height:_____□cm □in Weight: _____ □cm □in

Gender: Male ☐ Female ☐ Country: _____

Prescribing Physician Name: _____

2. Indication

□ AdvSM

Initial AdvSM diagnosis Date: ___/____/_____(DD/MMM/YYYY)

Previous lines of therapy for AdvSM:

Line: _____/Drug: _____/ Date start/Stop: _____

□ GIST

Initial GIST diagnosis Date: ___/____/_____(DD/MMM/YYYY)

GIST- associated mutations (specify mutation type):

KIT: _____ PDGFRa: _____

Previous lines of Tyrosine kinase inhibitors for **metastatic or unresectable** GIST:

Line: _____/Drug: _____/ Date start/Stop: _____

□ ISM

Initial ISM diagnosis Date: ___/____/_____(DD/MMM/YYYY)

Previous therapy for ISM:

Drug: _____/ Date start/Stop: _____

□ Other Diagnosis: _____ Previous treatment: _____

3. Risk Factors for Intracranial Bleeding

History of Prior Intracranial Bleeding: Yes ☐ No ☐

History of Bleeding disorder, Thrombocytopenia or other Bleeding event: Yes ☐ No ☐

History of Intracerebral Vascular Anomaly (e.g. Cavernous Hemangioma, Aneurysm, etc): Yes ☐ No ☐

History of Brain Metastases: Yes ☐ No ☐

History of Hypertension: Yes ☐ No ☐

History of Stroke: Yes ☐ No ☐

History of COVID-19: Yes ☐ No ☐

If Yes to any of the above, please provide event type, onset date, treatment, brain imaging findings, lab results, etc (use additional sheets of paper if necessary)

_____

_____

_____

_____

4. Concomitant Medications

Anticoagulant Con-Meds: Yes ☐ No ☐

Aspirin or NSAID Con-Meds: Yes ☐ No ☐

Other Con-Med that may cause bleeding or affect ability to clot: Yes ☐ No ☐

If Yes to any of the above, please provide medication name, start/stop dates and dosing strength and frequency (use additional sheets of paper if necessary)

_____

_____

_____

_____

5. Avapritinib Dose Information

Avapritinib Start Date: ___/____/_____(DD/MMM/YYYY) Starting Dose:_____

Avapritinib Dose at time of Event: _____ Date of last dose before event: ___/____/_____(DD/MMM/YYYY)

***Note, avapritinib is to be permanently discontinued in patients experiencing intracranial haemorrhage of any severity grade.**

Permanent discontinuation: Yes ☐ No ☐ Date of permanent discontinuation: ___/____/_____(DD/MMM/YYYY)

6. Event Information

Event Type: _____ Onset Date: ___/____/_____(DD/MMM/YYYY)

Did Head Trauma precede the event: Yes ☐ No ☐ Date of Head Trauma: ___/____/_____(DD/MMM/YYYY)

Was patient asymptomatic and/or was bleeding identified as an incidental finding on brain imaging: Yes ☐ No ☐

Description of Event:
(include symptoms, associated testing (provide results of brain imaging, abnormal lab test results [e.g. platelets, INR]), treatment, and any other details thought to be relevant to the event. (Use additional sheets of paper if necessary)

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

□ CT head: Yes ☐ No ☐ Date of CT head ___/____/_____(DD/MMM/YYYY)

□ MRI brain: Yes ☐ No ☐ Date of MRI brain ___/____/_____(DD/MMM/YYYY)

Brain imaging findings: *(please provide results of brain imaging below or attach de-identified imaging report)*

_____
_____
_____

Severity of Event (CTCAE Grade): Grade 1 ☐ Grade 2 ☐ Grade 3 ☐ Grade 4 ☐ Grade 5 ☐

Causality to Avapritinib: Related ☐ Not Related ☐

Did event improve after dose stopped (De-challenge): Yes ☐ No ☐

7. Outcome

Resolved: Yes ☐ No ☐ Date of resolution: ___/____/_____(DD/MMM/YYYY)

Resolved with sequelae: Yes ☐ No ☐ List sequelae: _____ *(provide CTCAE grade if applicable)*

Ongoing: Yes ☐ No ☐

Fatal: Yes ☐ No ☐ Date of death: ___/____/_____(DD/MMM/YYYY) Cause of Death: _____

Did Death occur in the setting of Progressive Disease: Yes ☐ No ☐

Please provide autopsy results and copy of death certificate if available

Cognitive Effects Data Collection Tool for Avapritinib

1. Patient Information

Patient Name: _____

Date of Birth: ___/____/_____(DD/MMM/YYYY) Age:_____ (years) Height:_____□cm □in Weight: _____ □cm □in

Gender: Male ☐ Female ☐ Country: _____

Prescribing Physician Name: _____

2. Indication

□ AdvSM

Initial AdvSM diagnosis Date: ___/____/_____(DD/MMM/YYYY)

Previous lines of therapy for AdvSM GIST:

Line: _____/Drug: _____/ Date start/Stop: _____

□ GIST

Initial GIST diagnosis Date: ___/____/_____(DD/MMM/YYYY)

GIST- associated mutations (specify mutation type):

KIT: _____ PDGFRa: _____

Previous lines of Tyrosine kinase inhibitors for **metastatic or unresectable** GIST:

Line: _____/Drug: _____/ Date start/Stop: _____

□ ISM

Initial ISM diagnosis Date: ___/____/_____(DD/MMM/YYYY)

Previous therapy for ISM:

Drug: _____/ Date start/Stop: _____

□ Other Diagnosis: _____ Previous treatment: _____

3. Risk factors for Cognitive Effects

History of Prior Cognitive Effects: Yes ☐ No ☐

History of other Psychiatric Conditions (e.g. depression, anxiety, insomnia): Yes ☐ No ☐

History of Stroke/TIA: Yes ☐ No ☐ History of Dementia/Alzheimer's disease: Yes ☐ No ☐

History of COVID-19: Yes ☐ No ☐

If Yes to any of the above, please provide event type, onset date, treatment, brain imaging findings, cognitive testing results, etc (use additional sheets of paper if necessary)

_____
_____
_____
_____
_____
_____

4. Concomitant Medications or Prior TKI Use

Prior TKI Use: Yes ☐ No ☐

Psychiatric Con-Meds (e.g. antidepressants, anxiolytics, antipsychotics, sedatives/hypnotics): Yes ☐ No ☐

Opioid Analgesic Con-Meds or Other Pain Treatment: Yes ☐ No ☐

Antihistamines Con-Meds: Yes ☐ No ☐

Corticosteroids Con-Meds: Yes ☐ No ☐

If Yes to any of the above, please provide medication name, start/stop dates and dosing strength and frequency (use additional sheets of paper if necessary)

_____
_____
_____
_____

5. Avapritinib Dose Information

Avapritinib Start Date: ___/____/_____(DD/MMM/YYYY) Starting Dose:_____

Avapritinib Dose at time of Event: _____ Date of last dose before event: ___/____/_____(DD/MMM/YYYY)

6. Event Information

Event Type: _____ Onset Date: ___/____/_____(DD/MMM/YYYY)

Description of Event:
(include symptoms, associated testing (provide results of brain imaging, cognitive testing, abnormal lab test results), treatment, impact on activities of daily living, and any other details thought to be relevant to the event. (Use additional sheets of paper if necessary)

_____
_____
_____
_____
_____
_____
_____
_____
_____

□ CT head: Yes ☐ No ☐ Date of CT head ___/____/_____(DD/MMM/YYYY)

□ MRI brain: Yes ☐ No ☐ Date of MRI brain ___/____/_____(DD/MMM/YYYY)

Brain imaging findings: *(please provide results of brain imaging below or attach de-identified imaging report)*

_____
_____
_____

Severity of Event (CTCAE Grade): Grade 1 ☐ Grade 2 ☐ Grade 3 ☐ Grade 4 ☐ Grade 5 ☐

Causality to Avapritinib: Related ☐ Not Related ☐

Action taken with Avapritinib:

No change in dosing: Yes ☐ No ☐ Dose reduction without interruption: Yes ☐ No ☐ If yes, new dose: _____

Temporary interruption: Yes ☐ No ☐ Did event improve after dose stopped (De-challenge): Yes ☐ No ☐

Was dose restarted after interruption: Yes ☐ No ☐

If yes, new dose: _____ Date of restart: ___/____/_____(DD/MMM/YYYY)

Did event recur after dose restarted (Re-challenge): Yes ☐ No ☐

Permanent discontinuation: Yes ☐ No ☐ Cause of permanent discontinuation:

7. Outcome

Resolved: Yes ☐ No ☐ Date of resolution: ___/____/_____(DD/MMM/YYYY)

Resolved with sequelae: Yes ☐ No ☐ List sequelae: _____ *(provide CTCAE grade if applicable)*

Ongoing: Yes ☐ No ☐

Fatal: Yes ☐ No ☐ Date of death: ___/____/_____(DD/MMM/YYYY) Cause of Death: _____

Did Death occur in the setting of Progressive Disease: Yes ☐ No ☐

Please provide autopsy results and copy of death certificate if available

Annex 6 - Details of Proposed Additional Risk Minimisation Measures

Not applicable.