EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2020
EMA/451735/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

AYVAKYT

International non-proprietary name: avapritinib

Procedure No. EMEA/H/C/005208/0000

Note

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

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List of abbreviations

Abbreviation	Definition
4L+	Fourth-line or later
ADLs	Activities of daily living
AdvSM	Advanced systemic mastocytosis
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
API	Active Pharmaceutical Ingredient
AST	Aspartate aminotransferase
ATR	Attenuated Total Reflection
AUC	Area under the plasma concentration-time curve
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BSEP	Bile salt export pump
Cave	Average plasma concentration
CBR	Clinical benefit rate
CI	Confidence interval
CMA	Conditional Marketing Approval
Cmax	Maximum plasma concentration
CQAs	Critical Quality Attributes
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTAB	Cetyl Trimethylammonium Bromide
CTCAE	Common Terminology Criteria for Adverse Events
CUP	Compassionate use program
Cx	Cycle x
CYP	Cytochrome P450
DCR	Disease control rate
DD	Dose-Determining
DDI	Drug-drug interaction
DIPEA	Di-isopropylethylamine
DLT	Dose-limiting toxicity
DLT	Dose-limiting toxicity
DoE	Design of Experiment
DOR	Duration of response
DSp	Design Space
DTPEA	Diisopropylethylamine
Dx	Day x
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEG	Electroencephalogram
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FDA	Food and Drug Administration
FMEA	Failure mode effects analysis
FPT	First-line of Prior Treatment
FTIR	Fourier Transform Infrared Spectroscopy
GC	Gas Chromatography
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumor
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HPLC	High Pressure Liquid Chromatography
HS-GC	Headspace Gas Chromatography
IC50	Half-maximal inhibitory concentration

ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPCs	In-Process Controls
IR	Infrared Radiation
ISS	Integrated Summary of Safety
ITT	Intent-to-Treat
JP	Japanese Pharmacopoeia
KF	Karl Fischer titration
KIT	V-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
KM	Kaplan-Meier
LDPE	Low Density Polyethylene
MAA	Marketing Authorization Application
MATE	Multidrug and toxin extrusion protein
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	Magnetic resonance imaging
MS	Mass Spectrometry
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NF	National Formulary
NMR	Nuclear Magnetic Resonance
NMT	Not More Than
NORs	Normal Operating Ranges
ORR	Overall response rate
OS	Overall survival
OVAT	One-Variable-At-A-Time
PARs	Proven Acceptable Ranges
PBPK	Physiologically-based pharmocokinetic
PD	Progressive disease
PDE	Permitted Daily Exposure
PDGFRA	Platelet-derived growth factor receptor alpha
PFS	Progression free survival
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PO	Orally (per os)
PR	Partial response
PSD	Particle Size Distribution
PT	Preferred term
QbD	Quality by Design
QD	Once daily
QP	Qualified Person
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTTP	Quality target product profile
RBC	Red blood cell
RoW	Rest of the world
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCS	Summary of Clinical Safety
SD	Stable disease
SM	Systemic mastocytosis
SmPC	Summary of Product Characteristics
SMQ	Standardised Medical Dictionary for Regulatory Activities query
SOC	System organ class
SPT	Second-line of Prior Treatment
TKI	Tyrosine kinase inhibitor
TPT	Third-line of Prior Treatment

TTP	Time to tumor progression
US	United States
USP	United States Pharmacopeia
UV	Ultraviolet
XRPD	X-Ray Powder Diffraction
ΔQTcF	Change in QT interval corrected for heart rate using Fridericia's formula

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Blueprint Medicines (Netherlands) B.V. submitted on 1 July 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Avapritinib Blueprint Medicines, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 October 2018 -

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

The applicant applied for the following indication "treatment of adult patients with unresectable or metastatic GIST who have been treated with at least 3 prior lines of therapy" and "treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation, regardless of prior therapy."

The name of Avapritinib Blueprint Medicines was changed to Ayvakyt during the procedure. Reference of both names appear throughout the assessment.

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

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0026/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0026/2019 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with

authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance avapritinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
25 January 2018	EMEA/H/SA/3738/1/2017/PA/SME/III	Dr David Brown, Dr Serena Marchetti

The Applicant received Protocol Assistance on the development relevant for the approved indication from the CHMP, on 25 January 2018 (EMEA/H/SA/3738/1/2017/PA/SME/III). The Protocol Assistance pertained to the following quality and clinical aspects of the dossier:

- the designation of starting materials for the synthesis of the drug substance, the proposed approach to their respective specifications and registration stability plan;
- the drug product specifications, including the proposed qualification threshold for the organic impurities (degradation products), the selected analytical tests and the general approach for the acceptance criteria for release and stability;
- the strength-based biowaivers for the intermediate strength tablets;
- Whether study BLU-285-1101, benchmarked against historical data to current treatment options, shows relevant activity that can fulfil an unmet medical need and whether the data package could support a conditional marketing authorization (CMA);
- Whether the planned randomized, regorafenib-controlled Phase 3 trial in patients with unresectable or metastatic GIST that have progressed after imatinib and 1 or 2 TKI's enrolling also patients with unresectable or metastatic GIST that harbor a PDGFRα D842 mutation, can provide the confirmatory and comprehensive data set to support full approval of BLU-285 for the indication of treatment of unresectable or metastatic GIST patients that have progressed after prior therapy or for whom effective therapy is not available;
- the proposed safety database for the CMA and the full MA.

1.2. Steps taken for the assessment of the product

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

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

The application was received by the EMA on	1 July 2019
The procedure started on	18 July 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	14 October 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	7 October 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	21 October 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 November 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 February 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	08 April 2020
The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product: A GCP inspection at two investigator sites located in South Korea and Poland was performed between October and December 2019. The outcome of the inspection carried out was issued on	27 April 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	30 April 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 June 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	08 July 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ayvakyt on	23 July 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The intended indication is:

"treatment of adult patients with unresectable or metastatic GIST who have been treated with at least 3 prior lines of therapy" And "treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation, regardless of prior therapy."

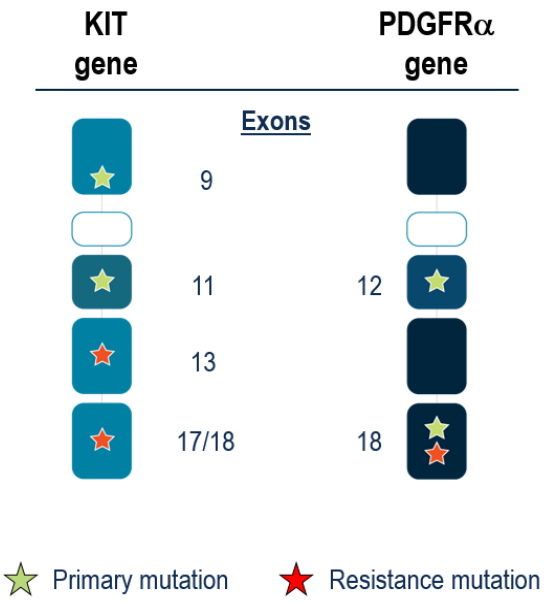
2.1.2. Epidemiology

Gastrointestinal stromal tumour is a rare sarcoma that arises from the interstitial cells of Cajal and occurs throughout the gastrointestinal (GI) tract (Miettinen and Lasota, 2006; Rammohan et al, 2013). Gastrointestinal stromal tumour is most commonly diagnosed between the ages of 50 and 80 years and represents approximately 0.1% to 3.0% of all GI malignancies (Nilsson et al, 2005).

2.1.3. Biologic features

More than 85% of patients with GIST have an oncogenic KIT (~75% of cases), or PDGFRA (~10% of cases) mutation that drives tumour growth (Antonescu, 2011). While patients with metastatic GIST clearly benefit from imatinib and may derive some benefit with other available TKIs, as described above; this advantage is limited to patients with KIT-mutant GIST. Importantly, patients with disease bearing the PDGFRA D842V [substitution of aspartic acid with valine at 842 position] mutation typically do not obtain clinical benefit with any of the approved therapies, including imatinib, and the degree of activity in patients with disease bearing other mutations in exon 18 of PDGFRA, which encodes the activation loop, is uncertain, as these mutations are very rare.

Figure 2: Primary and Acquired Mutations in *KIT* and *PDGFRA*



Source: (Heinrich et al, 2003a; Heinrich et al, 2003b; Hirota et al, 2003; Cassier et al, 2012; Yoo et al, 2016)

Primary and acquired KIT and PDGFRA resistance mutations (Figure 2) appear closely linked with therapeutic failure in advanced GIST. The presence of mutations in specific regions of the KIT and PDGFRA genes are correlated with response (or lack of response) to specific tyrosine kinase inhibitors (NCCN, 2018). Acquired resistance occurs after initial response or disease stabilization in KIT-driven GIST and relates to acquisition of a second mutation that impairs binding of approved TKIs. Acquired/secondary resistance mutations involving the adenosine triphosphate binding pocket (exons 13 and 14) and activation loop (exons 17 and 18) of KIT are common (Heinrich et al, 2008). Activation loop mutations accumulate with increasing frequency after second-line therapy (sunitinib), which also has inadequate activity on activation loop mutant proteins (Heinrich et al, 2008; Liegl et al, 2008). By fourth line therapy, multiple resistance mutations are often present, and no agents have demonstrated significant clinical activity. Primary resistance due to mutation in the PDGFRA activation loop, particularly the D842V mutation occurs in 5-6% of patients with advanced GIST.

2.1.4. Clinical presentation, diagnosis

Some GISTs are asymptomatic and are discovered incidentally during an endoscopic study (where they typically present as subepithelial masses) or on cross-sectional imaging done for another purpose. More often, they are associated with nonspecific symptoms (ie, early satiety, bloating), unless they ulcerate, bleed, or grow large enough to cause pain or obstruction.

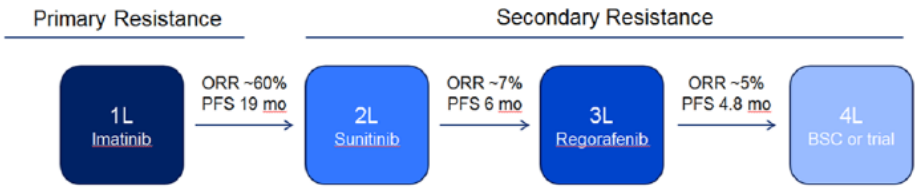
The median overall survival (OS) in patients with metastatic disease decreases quickly with multiple lines of therapy from 7 to 8 years after starting initial treatment for metastatic disease to only 1.4 years after starting treatment with fourth line therapy (Life Raft Group Patient Registry; data on file). The short survival may account for the fact that only about 50% of patients receive treatment with a second line of therapy. Imatinib is the clear standard of care for first-line therapy being used in about 85% of patients seeking first-line treatment for metastatic disease. Sunitinib is the most commonly used agent in the second-line setting, with utilization in approximately 50% of patients; however, 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 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 (Kantar Health 2018). This is consistent with the low response rates and short PFS seen with these agents.

2.1.5. Management

For localized, potentially resectable disease, initial treatment includes surgery, followed by adjuvant therapy with imatinib for patients with increased risk of recurrence due to poor prognostic factors, such as high mitotic index and large tumour size (NCCN, 2018). As chemotherapy and radiation are ineffective, the current treatment paradigm (Figure 1) for advanced GIST involves sequential administration of the tyrosine kinase inhibitors (TKIs), imatinib, sunitinib, and regorafenib (Antonescu, 2011; Casali et al, 2018; NCCN, 2018). First-line treatment with imatinib is effective with a 60% response rate and median progression free survival (PFS) of 18 to 24 months (Demetri et al, 2002; Blanke et al, 2008). Subsequent treatment with sunitinib and regorafenib is markedly less effective with a response rate of 5% to 7%, and a median PFS of 5-6 months. Once patients experience progressive disease (PD) following treatment with imatinib, sunitinib, and regorafenib, no agents are effective; therefore, the National Comprehensive Cancer Network and European Society for Medical Oncology guidelines recommend a clinical trial or palliative care for fourth-line patients (Casali et al, 2018; ESMO, 2018; NCCN, 2018). For example, in a randomized study imatinib re-treatment in the third or fourth-line setting resulted in an overall response rate (ORR) of zero and a median PFS of 1.8 months compared to 0.9 months for placebo (Kang et al, 2013). Therefore, there remains a high medical need for the development of novel therapies for fourth-line patients with GIST. The D842V mutation is insensitive to imatinib and other approved agents (Heinrich et al, 2003a; Cassier et al, 2012), which rarely induce response, and provide a median PFS of only 3 to 5 months, OS of approximately 15 months (Cassier et al, 2012; Yoo et al, 2016).

Figure 1: Treatment Paradigm for Advanced GIST



Abbreviations: BSC=best supportive care; GIST=gastrointestinal stromal tumor; L=line of therapy; mo=months; ORR=overall response rate; PFS=progression-free survival.
Source: (Demetri et al, 2002; Demetri et al, 2006; Demetri et al, 2013; Casali et al, 2018; NCCN, 2018)

About the product

All oncogenic kinases signal via the active conformation of the kinase. Avapritinib is a Type 1 kinase inhibitor designed to potently and selectively inhibit oncogenic KIT and PDGFRA mutants by targeting the active conformation of the kinase. Avapritinib shows broad inhibitory activity against both primary and secondary KIT and PDGFRA mutants with most potent activity against activation loop mutants, which approved therapies do not inhibit. Based on nonclinical models, exposures achieved in the clinical studies are projected to be active across a broad range of mutations seen in patients with GIST. Avapritinib

shows marked selectivity for KIT and PDGFRA within the kinome, as demonstrated via comprehensive kinome screening.

The indication approved by the CHMP is:

Ayvakyt is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation.

Therapy should be initiated by a physician experienced in the administration of anticancer therapy.

Patient selection for treatment of unresectable or metastatic GIST harbouring the PDGFRA D842V mutation should be based on a validated test method. The recommended starting dose of avapritinib is 300 mg orally once daily, on an empty stomach. The dose should be adjusted based on safety and tolerability

Treatment should be continued until disease progression or unacceptable toxicity.

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 once daily to 100 mg orally once daily (see section 4.5 of the SmPC).

If vomiting occurs after taking a dose of avapritinib, the patient should not take an additional dose but continue with the next scheduled dose.

If a dose of avapritinib is missed, the patient should make up for the missed dose unless the next scheduled dose is within 8 hours (see Method of administration of the SmPC). If the dose has not been taken at least 8 hours prior to the next dose, then that dose should be omitted and the patient should resume treatment with the next scheduled dose.

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

Patients may have their dose reduced by 100 mg increments to a minimum dose of 100 mg once daily.

Recommended dose modifications are indicated in Table 1.

Table 1: Recommended dose modifications for Ayvakyt for adverse reactions

Adverse reaction	**Severity***	**Dosage modification**
Intracranial haemorrhage (see section 4.4)	All Grades	Permanently discontinue Ayvakyt.
Cognitive effects** (see section 4.4)	Grade 1	Continue at the same dose or interrupt until improvement to baseline or resolution. Resume at the same dose or a reduced dose.
	Grade 2 or Grade 3	Interrupt therapy until improved to baseline, Grade 1, or resolution. Resume at the same dose or at a reduced dose.
	Grade 4	Permanently discontinue Ayvakyt.
Other (also see section 4.4 and section 4.8)	Grade 3 or Grade 4	Interrupt therapy until less than or equal to Grade 2. Resume at the same dose or at a reduced dose, if warranted.

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

Type of Application and aspects on development

The applicant requested consideration of its application intended for the treatment of gastrointestinal stromal tumor, a life threatening disease, for a Conditional Marketing Authorisation in accordance with Article 14-a of the above mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data. The Applicant claims that for both populations included in the intended indication, longer term follow-up data from the Phase 1 study BLU-285-1101 would be available and were planned to be submitted during the evaluation. In addition, a confirmatory Phase 3 randomized controlled study BLU-285-1303 is currently ongoing. The study is designed to demonstrate the efficacy and safety of avapritinib compared to regorafenib in patients with locally advanced unresectable or metastatic GIST previously treated with at least 2 TKIs including imatinib (3L and 4L). Approximately 5% of patients (n=20) in the confirmatory study are expected to carry the D842V mutation.
- Unmet medical needs will be addressed, as there are no approved and appropriate therapies for patients with unresectable or metastatic GIST harboring the PDGFRA D842V mutation nor for the 4L+ GIST patients who are at their last line of therapy.
- The benefits to public health of the immediate availability of avapritinib outweigh the risks inherent in the fact that additional data are still required. The Applicant claims that the overall safety profile consistent with inhibition of KIT and PDGFRA, oral kinase inhibitors in general, and underlying disease and the unprecedented activity observed in the PDGFRA D842V-mutant GIST population and significant activity in the 4L+ population, immediate availability of avapritinib, outweighs the risk to wait until the confirmatory data are fully available.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film coated tablets containing 100, 200 and 300 mg of avapritinib as active substance.

Other ingredients are:

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

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

Printing ink: shellac glaze 45% (20% esterified) in ethanol, brilliant blue FCF (E133), titanium dioxide (E171), black iron oxide (E172), and propylene glycol

The product is available in high-density polyethylene (HDPE) bottle with child-resistant cap with foiled induction seal liner and a desiccant in canister as described in section 6.5 of the SmPC. Each carton contains one bottle with 30 film-coated tablets.

2.2.2. Active Substance

General information

The chemical name of avapritinib is (S)-1-(4-fluorophenyl)-1-(2-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)piperazin-1-yl)pyrimidin-5-yl)ethan-1-amine corresponding to the molecular formula $C_{26}H_{27}FN_{10}$ has a relative molecular mass of 498.57 g/mol and the following structure:

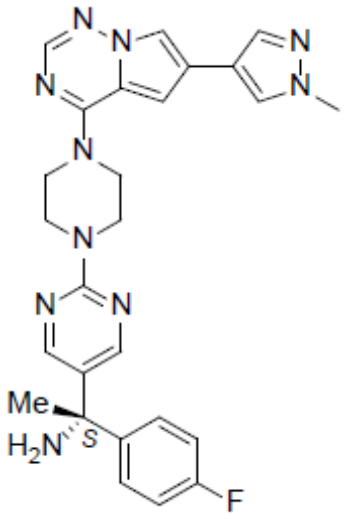


Figure 1: Active substance structure

The chemical structure of active substance was elucidated by a combination of single crystal X-ray crystallography, nuclear magnetic resonance spectroscopy (NMR), mass spectrometry (MS), elemental analysis, Fourier transform infrared spectroscopy (FT-IR), and ultraviolet absorption spectroscopy (UV). The solid state properties of the active substance were measured by XRPD.

The active substance is a non-hygroscopic white to off-white to light yellow solid, practically insoluble in water and slightly or very slightly soluble in buffer solutions of pH 1 to 5. At higher pHs the solubility of the molecule decreases. Avapritinib is very soluble in acetonitrile and methanol.

Avapritinib contains a single asymmetrically substituted tetrahedral carbon of the 'S' absolute configuration.

Polymorphism has been observed for the active substance. Two polymorphs have been observed, Form A is the polymorph which is manufactured consistently using the commercial process and is the form that was used exclusively throughout the development process. Form A is also the thermodynamically stable form.

Manufacture, characterisation and process controls

The active substance is manufactured in one manufacturing site.

Avapritinib is manufactured via a convergent route, sub-divided into three major process steps using commercially available well-defined starting materials with acceptable specifications.

The manufacturing process consists of three starting materials. There are multiple isolated intermediates, the manufacturing process uses multiple purifications including precipitations, organic-aqueous extractions, crystallizations, recrystallizations, and triturations to generate a highly pure active substance.
Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Acceptable information on impurities (covering starting materials, intermediates, reagents, catalysts, solvents, and other related potential impurities arising from the synthesis) and the proposed control strategy for these impurities have been provided. The identified impurities are limited either through the starting materials and intermediates specifications or by in-process controls. The active substance is intended for cancer therapy, so is outside of the scope of ICH M7. Nevertheless, the presence of potential genotoxic impurities arising from the active substance manufacture has been addressed. Potential and actual impurities were well discussed with regards to their origin and characterised.

The development history of the active substance has been described. Throughout development, avapritinib has been produced by two different multi-step, convergent synthetic routes. The process development studies for each step of the manufacturing process included laboratory experiments performed to optimise reaction and isolation conditions. Spike, fate, and purge studies that demonstrated the capability of the manufacturing process to remove the impurities were also performed. A combination of both traditional (one-variable-at-a-time, OVAT) and multi-variate process mapping studies (DoE) were conducted to identify critical process parameters during development. Parameters included in the process mapping studies were those identified (in a prior risk analysis) as presenting potential risks to the critical material attributes (CMAs) or active substance CQAs. Interaction effects within different PARs have been analysed. In order to support the designation of PARs and CPPs confirmatory runs (at manufacture scale) were carried out. No design space is claimed.

The active substance is packaged in LDPE bags which complies with the Regulation (EU) 10/2011. The LDPE bags are closed with cable ties (with one bag inside the other) and placed into a HDPE secondary container.

Specification

The active substance specification includes tests for description (visual), identity (FTIR, HPLC), assay (HPLC), impurities (HPLC), chiral impurity (chiral HPLC) residual solvents (HS-GS), residual diisopropylethylamine (GC), residue on ignition (Ph. Eur.), solid form confirmation (PXRD), and particle size distribution (laser diffraction).

Impurities are controlled in accordance with ICH Q3A and Q6A. A single impurity present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set

An assessment of the manufacturing process for avapritinib active substance concludes that the risk for the presence of nitrosamines impurities is low in the current manufacturing process. There are no recommended process or analytical method changes required to further mitigate this risk.
Water content is not included in the active substance specification as the active substance is non-hygroscopic. A review of the available microbial enumeration data alongside results from water activity testing and the lack of hygroscopicity of avapritinib indicates that the amount of water available in the active substance is insufficient to support the growth of microorganisms and therefore the risk of microbial contamination is low, therefore microbial enumeration is not part if the commercial specification of the active substance. Class 1 and 2A elements (Cd, Pb, As, Hg, Co, V, and Ni) are not

used in the avapritinib manufacturing process. Based on release data from avapritinib clinical batches and upstream control of metals used in manufacturing process, elemental impurities testing is not included in the commercial specification.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used testing has been presented.

Batch analysis data 26 pilot and commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 pilot scale batches of active substance from the manufacturer stored in the intended commercial package for up to 24 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.

In addition, supportive stability data is provided in one batch manufactured prior to implementation of optimised recrystallisation step through 36 months and 6 months at the long term and accelerated storage conditions, respectively.

The parameters included in the stability program and their acceptance criteria are the same as those used for release testing. In addition, water content and microbial enumeration are tested during stability studies. The analytical methods used were the same as for release and were stability indicating. Results from stability studies under long term and accelerated stability conditions show no changes in any of the parameters tested.

Stress study results demonstrated sensitivity to oxidative and acidic stress conditions, however, the finished product is stable.

Photostability testing following the ICH guideline Q1B was performed on one batch. No significant degradation was observed after exposure to light stress.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period, when stored at 15 - 25°C in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is an immediate release tablet for oral administration. It is a white film-coated tablet, printed in blue ink with "BLU" on one side and the tablet strength on the other side.

All tablet strengths are manufactured using a common blend and are therefore quantitatively proportional in active substance and excipient content.

The active substance has low solubility and high permeability and is classified as a Biopharmaceutical Classification System (BCS) Class 2 based on criteria for solubility and intestinal permeability in the ICH M9 Guideline Biopharmaceutics Classification System-based Biowaivers. Avapritinib is slightly soluble to practically insoluble in aqueous media. Avapritinib shows polymorphism, Form A being the most thermodynamically stable form. Solid Form A is used for the finished product manufacturing.

Compatibility studies were undertaken to assess the compatibility of the active substance with a range of commonly used pharmaceutical excipients. The data obtained were used to aid selection of appropriate excipients during formulation development. The excipients compatibility study was designed to focus on excipients that are commonly used in dry granulation, immediate release tablet formulations. Binary blends of avapritinib and the excipients were prepared and stored at 60°C/75% RH through 4 weeks. After chemical and manufacturability assessments were completed, the excipients selected for the finished product were microcrystalline cellulose (diluent), copovidone (binder), croscarmellose sodium (disintegrant), magnesium stearate (lubricant) and Opadry II (film-coat).

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Based on the clinical development program, a solid oral dosage form was the starting point and initial objective of pharmaceutical development for the finished product. The quality target product profile (QTPP) was an integral part of the development process that expanded on the initial objective to guide the selection and optimisation of desirable attributes and quality targets for the finished product. The QTPP connects the desired product attributes with specific development targets and then links them to the resulting qualities of the intended commercial product.

Potential finished product critical quality attributes (CQA) have been derived from the QTPP and/or prior knowledge to design a quality product and a manufacturing process which consistently delivers the intended performance of the product. The preliminary identification of finished product CQAs was performed with consideration for relevant quality attributes of the finished product components (e.g. active substance), process development studies, and process knowledge based on previous experience. In addition, ICH Harmonised Guidelines Q8 (R2), Q9 and Q10 were used as benchmarks to guide development with the aim of enabling continuous improvement in the context of a lifecycle approach to product development and process validation.

Based on these assessments, the following qualities were identified as potentially critical to finished product: description, identification, assay, degradants, uniformity of dosage units, moisture content, dissolution, and microbial purity. These attributes were selected in accordance with ICH Q6A *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*, including consideration of analytical and manufacturing capabilities, desired product quality attributes, and intended product performance with regard to safety and efficacy. All finished product CQAs were monitored by means of a comprehensive control strategy that includes process design and validated methods for process inputs, in-process controls and final product release tests.

The development of the dissolution method was described. The data provided confirm that the method is able to discriminate between batches showing differences in those parameters/attributes.

The finished product is manufactured using a common blend which is prepared through intragranular blending of diluent, binder, disintegrant and lubricant, followed by dry granulation using roller compaction and then extragranular blending with diluent, disintegrant and lubricant. The common blend is compressed into the different tablet strengths that are then aesthetically film-coated and printed with a unique identifier for each tablet strength.
The initial tablets were manufactured in one manufacturing site. The manufacturing process was transferred to the manufacturing site of the commercial finished product. The manufacturing process flow remained unchanged and the equipment was similar with some exceptions. During the manufacturing process transfer, the data from in-process testing and release testing was used to determine if the tablets manufactured by both manufacturers were comparable.

Characterisation and optimisation studies were performed to ensure that the process was suitably robust and well-controlled prior to validation. After the completion of the process transfer, the manufacturing process was evaluated from a technical perspective before manufacturing the registration batches. Observations from the process transfer and the results of the technical risk assessment were used to design experiments to further optimise the process. The details of each unit operation were considered along with the QTPP, and the manufacturing process was evaluated to identify potential risk to drug product CQAs. A FMEA based approach with a defined process was used to rank all potential risks for each unit operation. The applicant has applied QbD principles in the development of the finished product and the manufacturing process. However, the process description is traditional, and no design space was claimed for the manufacturing process of the finished product.

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

Manufacture of the product and process controls

All three tablet strengths are dose-weight proportional and are manufactured using a common blend. The manufacturing process of avapritinib tablets consists of 6 main steps. The process is considered to be a standard manufacturing process

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process**.** The in-process controls are adequate for this type of manufacturing process.

Product specification

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

Degradants were evaluated according to procedures described in ICH Q6A.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. In compliance with ICH Q3D, all Class 1 and 2A elements and intentionally added or those with the potential to be present were considered in the risk assessment. The risk assessment has concluded that the potential risk of elemental impurities in the finished product is low and no additional controls are required to further minimize this risk.

In the context of the on-going review under Article 5(3) of Regulation (EC) No 726/2004 related to the potential presence of nitrosamine impurities in human medicinal products applicants were requested by CHMP to review their products for potential presence of nitrosamine impurities and to conduct risk evaluations/risk assessments as appropriate. Risk assessments from the suppliers of the active substances, excipients and finished product manufacturer were provided. Based on the risk assessments provided, a risk for nitrosamine formation can be excluded.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for 23 commercial and pilot scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 pilot scale batches of finished product for 100 mg and 400 mg tablet strengths stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Four strengths (100 mg, 200 mg, 300 mg and 400 mg) of the finished product were developed initially, although only 100 mg, 200 mg and 300 mg strengths will be authorised / marketed. Since all strengths are dose-weight proportional, manufactured with a common blend and the container closure system and units per container are the same across all strengths, a bracketing design has been applied in which the 100 mg and 400 mg represent the extremes of the design, i.e. 100 mg and 400 mg are placed on formal stability studies where the intermediate strengths (i.e. 200 mg and 300 mg) are considered bracketed. Taking into account the principles defined in the ICH Q1D guideline, the proposed bracketing design is acceptable. The fact that the 400 mg strength will not be commercialised does not impact the validity of the proposed design. In addition, the applicant commits to place production batches of the marketed extremes (i.e. 100 mg and 300 mg) on stability studies post-approval.

In addition to the parameters included in the product specifications, enantiomer impurity, hardness, and solid form are tested in the stability studies. The analytical procedures used are stability indicating. All the stability results comply with the proposed specifications.

A photostability study using Option 2 as described in ICH Q1B was performed on two batches (100 mg and 400 mg strength). The photostability data shows that the finished product is not sensitive to light.

A simulated in-use study was initiated for the 100 mg and 300 mg strengths to study the effect of use of the product in practice via opening and closing the bottle daily at 15.0 – 25.0°C over 75 days. Negligible change was seen in assay, moisture, and dissolution results. No degradant growth was detected.

Based on available stability data, the proposed shelf-life of 24 months without special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

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

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

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

The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation(s) for future quality development

Not applicable

2.3. Non-clinical aspects

2.3.1. Introduction

In vivo and in vitro studies were submitted, additionally toxicology studies were also presented. Avapritinib showed broad inhibitory activity against a panel of GIST relevant KIT and PDGFRα mutant enzymes including the KIT exon 11 mutants found in >60% of newly diagnosed GIST, all KIT exon 17 and 18 mutants tested and all PDGFRα exon 18 mutants tested. While potent on these KIT and PDGFRα mutants, avapritinib was demonstrated to be selective against a panel of 456 human kinases and disease-relevant mutants.

Avapritinib demonstrated inhibition of KIT and PDGFRα mutant activity in the cellular setting and efficacy in some KIT mutant-driven mouse xenograft models.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Inhibition of KIT and PDGFRα Mutants *In Vitro*

Avapritinib has demonstrated biochemical *in vitro* activity on KIT exon 17 mutant enzymes including KIT D816V (IC_{50}= 0.27 nM) and PDGFRα exon 18 mutant enzymes including D842V (IC_{50}= 0.24 nM). Imatinib, sunitinib, and regorafenib, all approved to treat patients with GIST, were over 400-fold less potent against these clinically relevant mutations (Table 1).

Table 1. Biochemical activity of avapritinib and approved GIST agents against KIT D816V and PDGFRα D842V Mutants

Compound	KIT D816V IC_{50} (nM)	PDGFRα D842V IC_{50} (nM)
Avapritinib	0.27	0.24
Sunitinib	191	118
Regorafenib	3619	825
Imatinib	8481	656

Abbreviations: IC_{50}, half-maximal inhibitory concentration of enzyme activity; KIT, V-Kit Hardy-Zuckerman 4 Feline Sarcoma Viral Oncogene Homolog; PDGFRα, platelet-derived growth factor receptor alpha.
Source: Reports BPM-0001 and BPM-0006

Further biochemical testing against a panel of GIST relevant KIT and PDGFRα mutant enzymes demonstrated avapritinib was potent against all KIT mutants tested, with subnanomolar IC_{50} on KIT exon

11, 17 and 18 mutants (Table 2). In addition, avapritinib demonstrated potent subnanomolar activity against all PDGFRα exon 18 mutants tested (Table 2).

Table 2: Biochemical Activity of Avapritinib and Imatinib Against a Panel of GIST relevant mutants

Enzyme	Mutant Exon	Avapritinib IC_{50} (nM)	Imatinib IC_{50} (nM)
PDGFRα wildtype	Non Mutant	1.4	41
PDGFRα D842V	Exon 18	0.24	656
PDGFRα D842I	Exon 18	0.13	2055
PDGFRα D842Y	Exon 18	0.12	115
KIT wildtype	Non Mutant	73	261
KIT d557-558	Exon 11	0.60	11.9
KIT V560G	Exon 11	0.97	86.6
KIT D816E	Exon 17	0.21	135
KIT D816F	Exon 17	0.19	>10000
KIT D816H	Exon 17	0.35	4825
KIT D816I	Exon 17	0.16	>10000
KIT D816V	Exon 17	0.22	>10000
KIT D816Y	Exon 17	0.11	7065
KIT D820E	Exon 17	1.77	58.8
KIT D820Y	Exon 17	0.44	76.5
KIT Y823D	Exon 17	1.49	253
KIT A829P	Exon 18	0.54	122
KIT V559D/T670I	Exon 11/14	27.6	>10000
KIT V559D/V654A	Exon 11/13	11.1	>10000
KIT V560G/D816V	Exon 11/17	0.10	>10000
KIT V560G/N822K	Exon 11/17	0.30	406
VEGFR-2	Non-mutant	544	>10000

Abbreviations: IC_{50}, half-maximal inhibitory concentration of enzyme activity; KIT, V-Kit Hardy-Zuckerman 4 Feline Sarcoma Viral Oncogene Homolog; PDGFRα,platelet-derived growth factor receptor alpha; VEGFR-2, vascular endothelial growth factor receptor 2

Source: Report BPM-0050, BPM-0016, BPM-0006

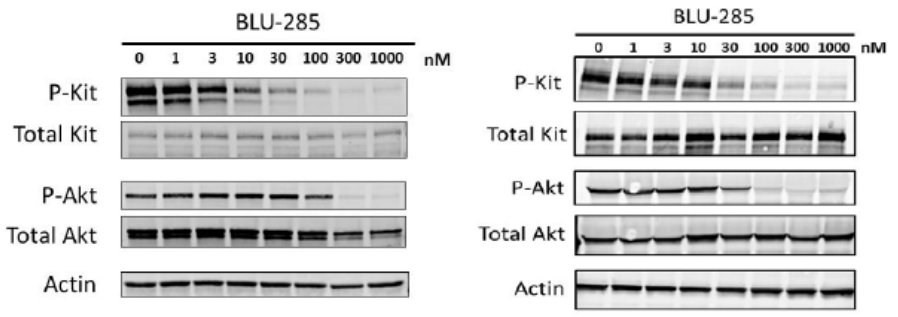
The selectivity of avapritinib was characterized by profiling its binding across a panel of over 450 human kinases and disease-relevant kinase mutants at 3 µM. Avapritinib had a high degree of selectivity for the KIT exon 11, 13 and 17 mutant proteins in this assay. As a control, four reference compounds were included in the study and the obtained data were comparable to historic percent of control values for each reference control in all 456 assays.

The dissociation constant (K_d) was determined for wild-type kinases that avapritinib significantly bound (i.e., < 10% of control) in the human kinome screen. Measurement of K_d demonstrated that in addition to the KIT exon 17 mutants (KIT D816V K_d= 0.3 nM, KIT D816H K_d= 0.4 nM), avapritinib demonstrated binding affinity for the small group of highly related class III receptor tyrosine kinases to which KIT belongs: KIT wild type (K_d= 17 nM), PDGFRα wild type (K_d= 1 nM), platelet-derived growth factor receptor beta (PDGFRβ) (K_d= 1 nM), colony stimulating factor 1 receptor (CSF1R) (K_d= 6 nM) and Fms-like tyrosine kinase 3 (FLT3) (K_d= 31 nM). All other kinases demonstrated K_d greater than 50 nM. These data demonstrate that avapritinib has limited potential for kinome activity outside of the related class III receptor tyrosine kinases.

Avapritinib cellular activity was measured by inhibition of KIT exon 17 mutant autophosphorylation and inhibition of cellular proliferation. In the human mast cell leukemia (MCL) cell line HMC1.2, which harbours an activated KIT exon 11/exon 17 (V560G/D816V) mutant kinase, treatment with low nanomolar concentrations of avapritinib potently inhibited the KIT V560G/D816V mutant protein measured by both AlphaLISA® and immunoblotting (IC_{50}=4.0 nM). Avapritinib antiproliferative activity was also demonstrated in this KIT mutant dependent cell line (IC_{50}= 125 nM). In P815 cells, a mouse

mastocytoma cell line driven by a KIT exon 17 mutation (mouse KIT D814Y) equivalent to the human KIT D816Y mutation, avapritinib potently inhibited signalling of mutant KIT measured by inhibition of KIT autophosphorylation (IC_{50}= 22 nM) or cellular proliferation (IC_{50}= 202 nM) and induced caspase activation (half maximal effective concentration [EC_{50}=36 nM]), indicating apoptosis was induced with avapritinib. Consistent with the selectivity observed in biochemical binding and enzymatic assays, avapritinib inhibited SCF-stimulated KIT wild type activity in M-07e cells less potently as measured by KIT autophosphorylation with IC_{50}= 192 nM (Figure 1), compared to the autophosphorylation IC_{50}= 4 and 22 nM in the KIT exon 17 mutant cell lines HMC1.2 and P815 cells, respectively. Inhibition of proliferation in the non-stem cell factor/KIT-driven cell line UT7 grown in the presence of granulocyte-macrophage colony-stimulating factor (GM-CSF) demonstrated avapritinib lacked nonspecific antiproliferative activity and was not broadly cytotoxic.

Figure 1: Activity of Avapritinib on KIT Exon 17 Mutants in HMC 1.2 and P815 Cells

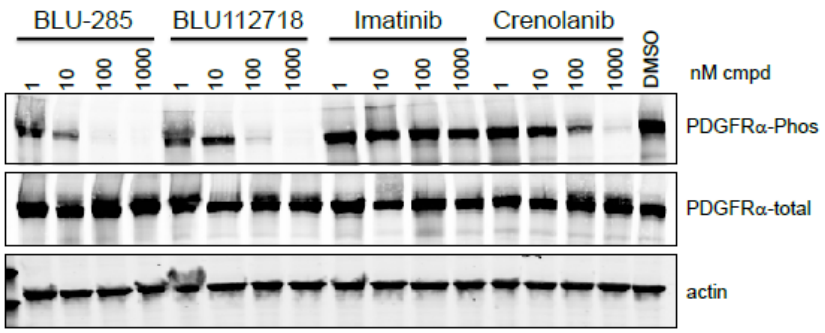


Abbreviations: AKT, v-akt murine thymoma viral oncogene homolog; KIT, v-Kit Hardy-Zuckerman 4 Feline Sarcoma Viral Oncogene Homolog
Immunoblot data are shown for both HMC1.2 (**left panel**) and P815 cells (**right panel**) treated with avapritinib (BLU-285) at the indicated concentrations. Phosphorylated (P-KIT) and total protein levels of KIT D816V mutant (HMC1.2 cells) and the mouse KIT D814Y mutant (P815 cells) and downstream biomarkers are shown.
Source: Reports BPM-0003 and BPM-0004

The circulating metabolite M499, formed by oxidative deamination of avapritinib, has been shown to be pharmacologically active. Compared to avapritinib (IC_{50}=4 nM), the (S) - and (R) - enantiomers of M499 (BLU-111208; IC_{50}=12.4 nM and BLU-111207; IC_{50}=41.8 nM) are 3.1- and 10.5-fold less potent against KIT D816V in HMC1.2 cell assay. Metabolites M484 (formed by N-demethylation) and M485 (formed by oxidative deamination, N-demethylation) also demonstrated activity against KIT D816V. The IC_{50} values for M484 and the (S) - and (R)-enantiomers of M485 were 7.1, 16.1 and 94.5 nM, respectively.

KIT and PDGFRα are 2 highly-related class III receptor tyrosine kinases. The KIT exon 17 D816V activating mutation occurs at the same amino acid position structurally as the PDGFRα exon 18 D842V mutation that is found in 5% of unresectable or metastatic GISTs (Liang et al., 2016). Avapritinib potently inhibited signalling of the oncogenic PDGFRα D842V mutant protein when expressed in an engineered cell line as measured by inhibition of autophosphorylation (IC_{50}= 30 nM) (Figure 2). In contrast, the approved GIST therapy imatinib was unable to inhibit the mutant kinase in the cellular setting, even at concentrations of 1 μM, consistent with imatinib's reported inactivity in this patient population.

Figure 2: Activity of Avapritinib on PDGFRα D842V Mutant Cellular Activity



Abbreviations: CHO, Chinese hamster ovary; DMSO, dimethylsulfoxide; PDGFRα, platelet-derived growth factor receptor alpha

Immunoblot data are shown measuring P-PDGFRα D842V inhibition with avapritinib (BLU-285), imatinib, and the multi-kinase inhibitor crenolanib at the indicated concentrations. BLU112718 is a separate molecule from Blueprint Medicines that was evaluated in this assay. BLU112718 is not the subject of this NDA and will not be discussed further. Mutant PDGFRα D842V was transiently expressed in CHO cells and kinase activity detected by the presence of PDGFRα autophosphorylation as shown. Avapritinib potently and dose-dependently inhibited the activity of PDGFRα D842V.

Source: Report BPM-0006

Inhibition of KIT Mutant Activity *In Vivo*

Antitumor efficacy with avapritinib was demonstrated in a P815 mouse mastocytoma cell line xenograft model in which tumour growth was driven by a KIT exon 17 mutation (D816Y). Avapritinib administered orally at doses including 0.3, 1, 3, 10 or 30 mg/kg/day resulted in robust and dose-dependent growth inhibition of P815 xenograft tumours when assayed after 10 days. At doses of 10 mg/kg and 30 mg/kg QD, avapritinib caused complete tumour growth inhibition and regression (Table 3, Figure 3). Avapritinib 10 mg/kg treatment lasted for 17 days. Tumour growth was inhibited from day 0 to day 9, and the tumours began to grow rapidly from day 10 to day 16. Avapritinib 30 mg/kg treatment lasted for 31 days. Tumours almost disappeared as early as day 4, but began to reappear at day 18 and grew to the end of the study (Figure 3).

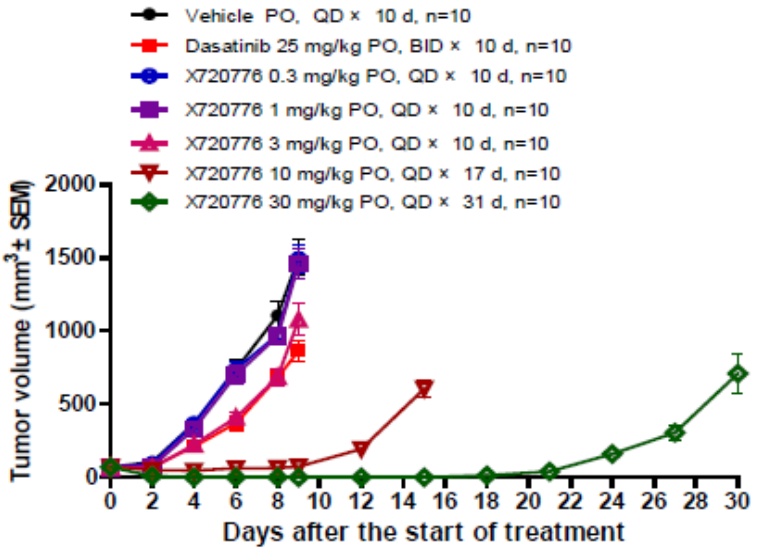
Table 3. Tumour growth inhibition by avapritinib (X720776) and dasatinib in a KIT Exon 17 Mutant Driven P815 Xenograft Model measured on Day 9 of treatment.

Treatment	Tumor Size (mm^3)[a] at Day 9	TGI (%)	T/C (%)	T-C (days) at 1,000 mm^3	*p* value
Vehicle	1,498±43	--	--	--	--
Dasatinib 25 mg/kg BID	865±23	44	58	2	<0.001
X720776 0.3 mg/kg QD	1,491±32	1	100	0	ns
X720776 1 mg/kg QD	1,457±35	3	97	0	ns
X720776 3 mg/kg QD	1,075±37	30	72	1	<0.01
X720776 10 mg/kg QD	74±3	100	5	10	<0.001
X720776 30 mg/kg QD	0±0	105	0	24	<0.001

Abbreviations: BID = twice daily, QD = once daily, T/C = tumor growth inhibition ratio, TGI = tumor growth inhibition

a. Mean ± SEM.

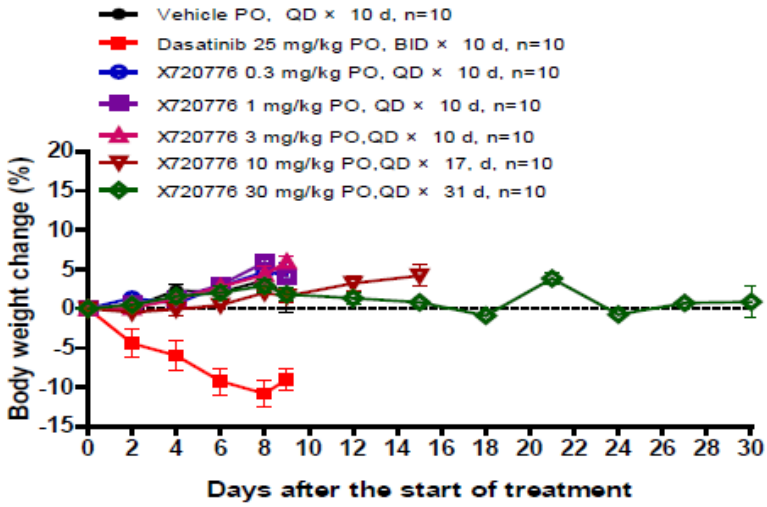
Figure 3. Efficacy of avapritinib (X720776) in a KIT Exon 17 Mutant Driven P815 Xenograft Model



Data points represent group mean of 10 mice per cohort, error bars represent standard error of the mean (SEM).

Two mice in vehicle and avapritinib 0.3 mg/kg groups, one mouse in avapritinib 1 mg/kg and 3 mg/kg groups died on day 9 and one mouse in avapritinib 3 mg/kg group died on day 8. All other animals tolerated the treatment well with no impact on animal body weight (Figure 4). In contrast, the maximum tolerated dose (MTD) of the nonselective kinase inhibitor dasatinib (25 mg/kg twice daily [BID]) resulted in only marginal tumor growth inhibition and rapid body weight loss throughout the course of the experiment (Figure 4).

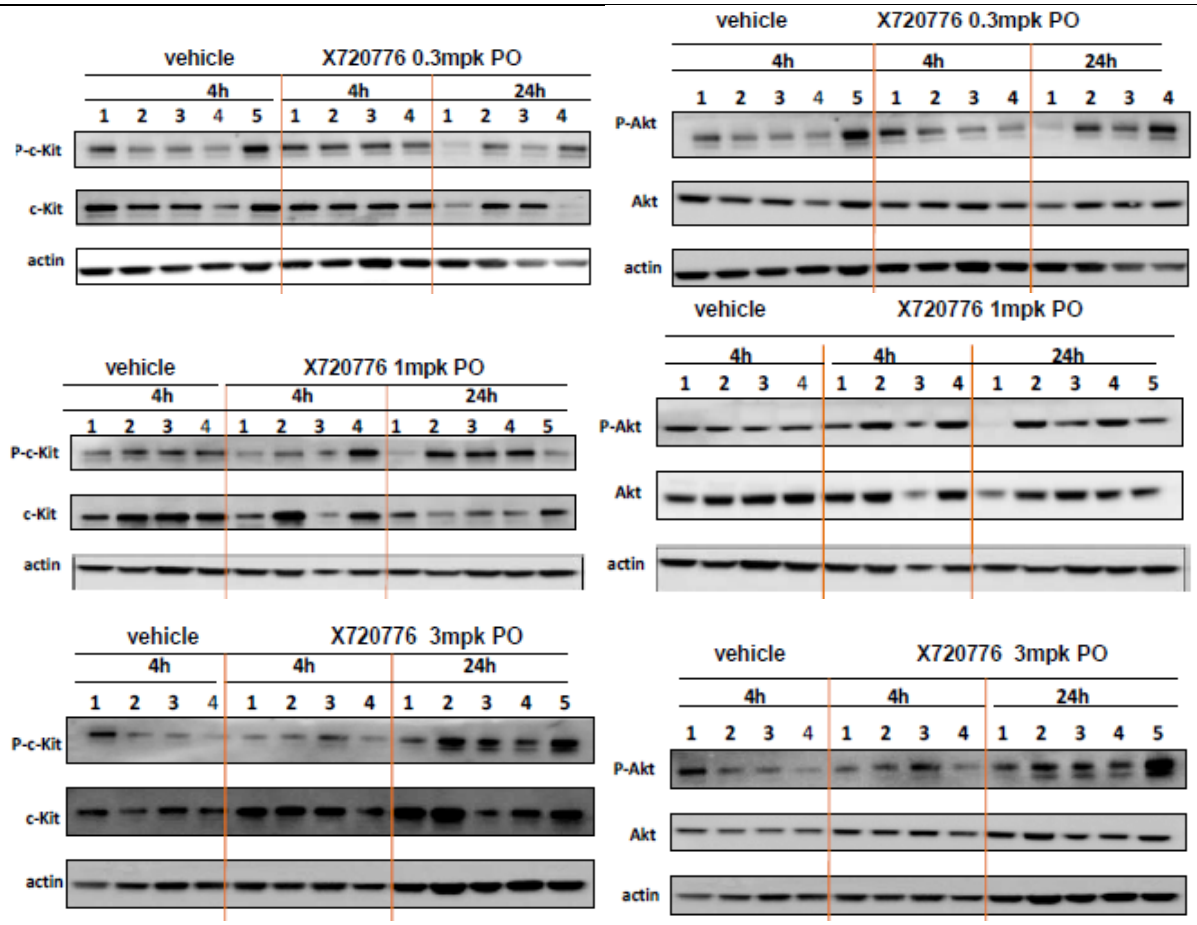
Figure 4. Body weight change in a KIT Exon 17 Mutant Driven P815 Xenograft Model dosed with avapritinib and dasatinib.



BW change was calculated based on animal weight on the first day of dosing. Data points represent percent group mean change in BW. Error bars represent standard error of the mean (SEM).

Direct inhibition of mutant KIT activity in P815 xenograft tumours was assessed after oral administration of 0.3, 1 and 3 mg/kg of avapritinib to tumour bearing mice. Avapritinib did not show significant inhibition on both p-c-kit and p-Akt at 4 hours and 24 hours post administration as compared with vehicle controls at these doses. The PD results were consistent with the *in vivo* efficacy in-life part (Figure 5).

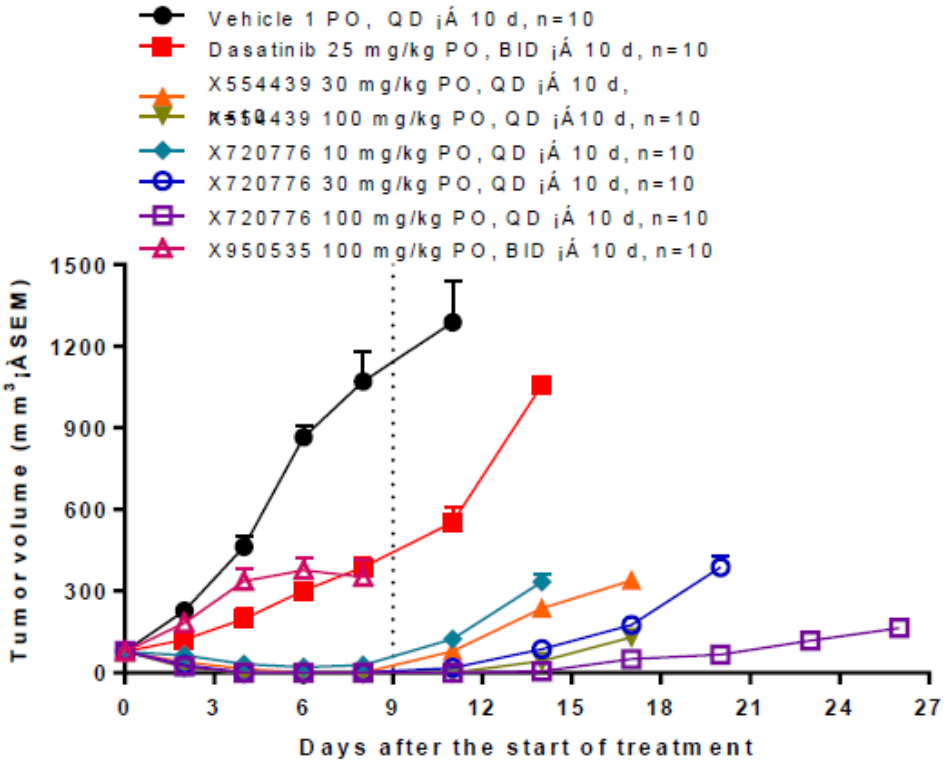
Figure 5. Inhibition of KIT Exon 17 Mutant Signaling *In Vivo*



Western blotting analysis of p-c-kit (right) and p-Akt (left) expression in groups of vehicle collected at 4 hours post administration, avapritinib (X720776) at 0.3, 1 and 3 mg/kg at 4 and 24 hours post administration.

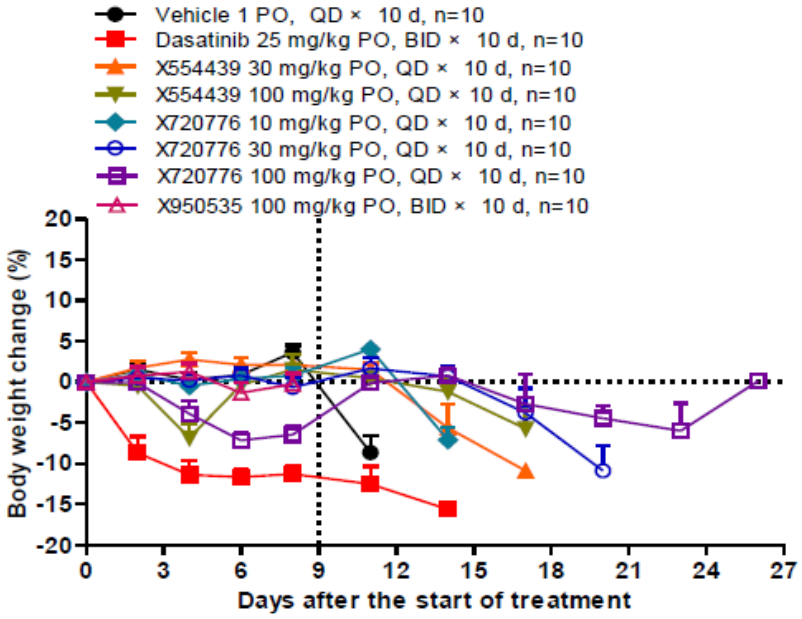
In the same mouse model, the therapeutic efficacy of avapritinib at 10, 30 and 100 mg/kg was evaluated after nine days of treatment. The mean tumour sizes of avapritinib 10 mg/kg, 30 mg/kg, and 100 mg/kg QD groups were 28 mm^3, 0 mm^3 and 0 mm^3 on Day 8, respectively. The tumors in avapritinib 30 mg/kg and 100 mg/kg QD groups almost disappeared both on Day 4, while these tumours began to reappear on Day 11 and Day 14, respectively, after the Day 9 treatment termination (Figure 6). All the mice in avapritinib 10 mg/kg, 30 mg/kg and 100 mg/kg QD groups died on Day 16, Day 22, and Day 27, respectively. The median survival times of avapritinib 10 mg/kg, 30 mg/kg, and 100 mg/kg QD groups were 14 days, 19 days, and 22 days, respectively. Avapritinib-treated groups statistically prolonged survival time in comparison with the vehicle group ($p < 0.001$). Avapritinib 10 mg/kg and 30 mg/kg were well tolerated during the dosing period, while avapritinib 100 mg/kg caused 7.2% body weight loss on Day 6 after the start of treatment (Figure 7).

Figure 6. Efficacy of avapritinib (X720776) in a KIT Exon 17 Mutant Driven P815 Xenograft Model



Data points represent group mean of 10 mice per cohort, error bars represent standard error of the mean (SEM). The last dosing was delivered on Day 9.

Figure 7. Body weight change in a KIT Exon 17 Mutant Driven P815 Xenograft Model dosed with avapritinib and dasatinib.

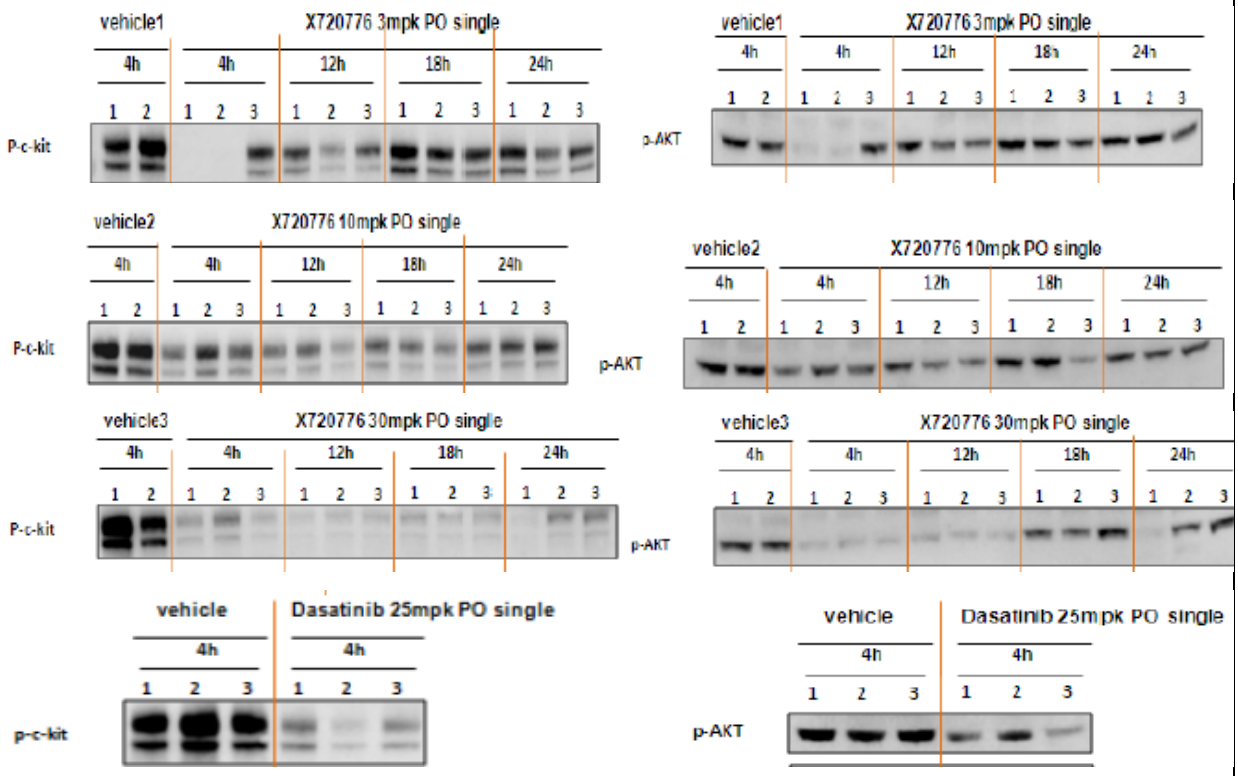


BW change was calculated based on animal weight on the first day of dosing. Data points represent percent group mean change in BW. Error bars represent standard error of the mean (SEM).

A different study was performed to investigate the PK and PD characteristics of dasatinib (25 mg/kg) and avapritinib (3, 10 and 30 mg/kg) after single dose administration in the P815 cell xenograft model. Plasma and tumours were collected from individual mice 4, 12, 18, or 24 hours after dosing. Avapritinib concentrations in plasma were determined by liquid chromatography/tandem mass spectrometry and

inhibition of KIT mutant signaling in the tumour tissue was assessed by immunoblot. Quantitation of the phospho-KIT signal on the immunoblot determined the percent KIT mutant inhibition in avapritinib-treated animals as compared with vehicle-treated control animals. A dose- and time-dependent correlation was observed between the concentration of avapritinib in mouse plasma and the level of phosphorylated KIT. When dosed with 3 mg/kg avapritinib orally, *in vivo* KIT mutant activity was inhibited by at least 44% over the 24-hour dosing period. At 10 and 30 mg/kg avapritinib, doses that produced 100% tumour growth inhibition in efficacy studies, sustained inhibition of KIT activity reached 75% and 90%, respectively (Figure 8). Dose-dependent inhibition of the downstream biomarker phospho-AKT was also detected in P815 tumour homogenates after treatment with avapritinib (Figure 8).

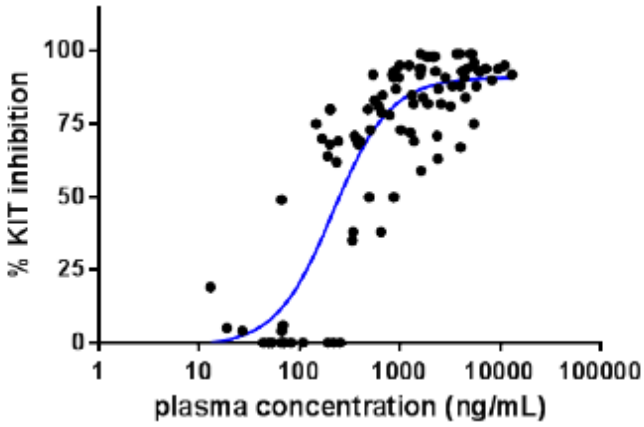
Figure 8. Inhibition of KIT Exon 17 Mutant Signaling *In Vivo*



Western blotting analysis of p-c-kit (right) and p-Akt (left) expression in groups of vehicle collected at 4 hours post administration, avapritinib (X720776) at 0.3, 1, 3, 10 and 30 mg/kg and dasatinib at 25 mg/kg collected at 4, 12, 18 and 24 hours post administration.

A compilation of 97 pharmacokinetic/pharmacodynamic (PK/PD) data points collected after oral administration of avapritinib in multiple P815 xenograft experiments is shown in Figure 9 and demonstrates a robust decrease in KIT mutant activity with increasing plasma drug levels. As efficacy was associated with doses producing at least 75% KIT mutant inhibition, the plasma concentration required for 75% inhibition in all experiments was calculated using 4-parameter nonlinear regression curve fitting and was determined to be 448 ng/mL. Similarly, the plasma concentration of avapritinib required for 90% KIT mutant inhibition was determined to be 923 ng/mL (Figure 9).

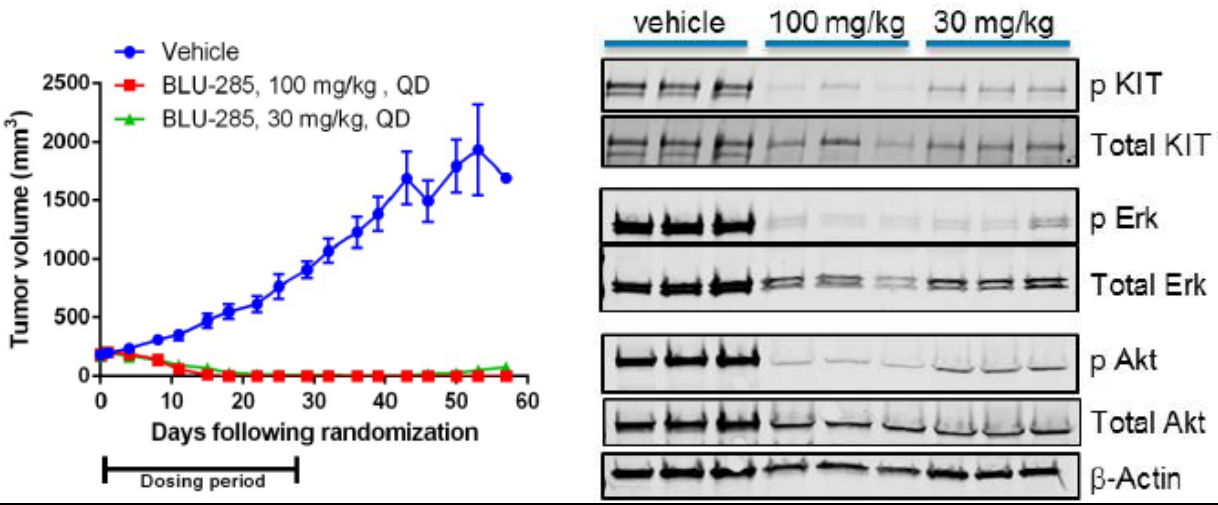
Figure 9. Pharmacokinetic/Pharmacodynamic Profile in a KIT Exon 17 Mutant Xenograft Model



Compilation of avapritinib pharmacokinetic and pharmacodynamic measurements in P815-tumor bearing mice. P815 tumors were collected after oral administration of avapritinib. Tumor homogenates were assayed for KIT inhibition with specific phospho-KIT antibodies by immunoblot analysis. The plasma concentration of each sample was determined by liquid chromatography/tandem mass spectrometry. Percent KIT inhibition and plasma concentrations from 97 tumor/plasma pairs from multiple individual experiments were plotted. The plasma concentrations required for 75% or 90% KIT mutant inhibition were calculated using 4-parameter nonlinear regression curve fitting.

Antitumor efficacy was demonstrated in an imatinib-resistant GIST PDX model that was driven by an activated KIT exon 11/exon 17 double mutant (delW557K558/Y823D). In this model, the KIT exon 17 mutant was an alternate amino acid substitution at residue 823 (Y823D) that is also observed in imatinib-relapsed/refractory KIT-driven GIST. Two experiments were performed in this model. In the first, avapritinib administered orally for 27 days at either 30 or 100 mg/kg QD, resulted significant tumour growth suppression compared to vehicle treatment. Tumour growth inhibition was not significantly different between 30 mg/kg and 100 mg/kg doses. Tumour suppression that was observed in all mice treated with 100 mg/kg dose of avapritinib was maintained for at least 4 weeks after the completion of avapritinib dosing. Tumour regrowth was observed in 6 of 8 mice treated with 30 mg/kg dose of avapritinib, at the end of the study (study day 57) (Figure 10). Direct inhibition of KIT activity and downstream signalling (Erk and Akt phosphorylation) in the PDX tumour was measured by immunoblot in tumour lysates collected after 7 days of avapritinib oral dosing, 24 hours after the last dose. Immunoblot analysis of tumour homogenate revealed that avapritinib maintained >75% inhibition of KIT mutant activity with the 100 mg/kg dose and > 40% inhibition at the 30 mg/kg dose, 24 hours after the last dose. Similarly, downstream signalling components p-ERK and p-AKT were also inhibited in a dose-dependent manner (Figure 10).

Figure 10. Efficacy and Inhibition of KIT Exon 11/Exon 17 Mutant Signaling with Avapritinib in a GIST Patient-Derived Xenograft Model



Abbreviations: Akt, v-akt murine thymoma viral oncogene homolog; ERK, extracellular signal-regulated kinase; KIT, v-Kit Hardy-Zuckerman 4 Feline Sarcoma Viral Oncogene Homolog; p, phosphorylated; PDX, patient-derived xenograft; QD, once daily.

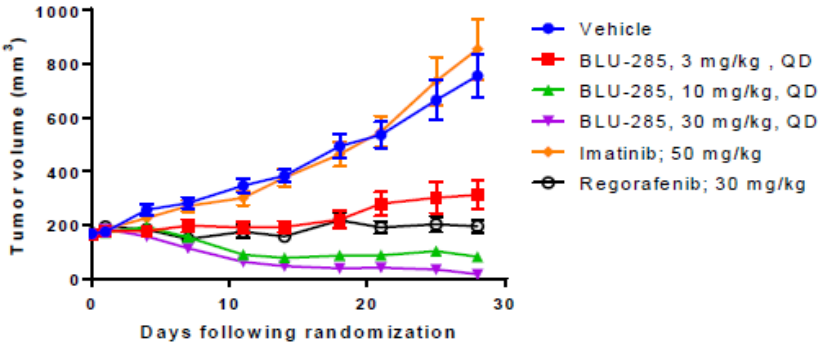
Mice bearing KIT exon 11/exon 17 mutant GIST PDXs were dosed once daily, orally with vehicle, 30 mg/kg, or 100 mg/kg avapritinib for 27 days.

Left panel: Tumor growth was measured twice weekly for the 27-day dosing period followed by a 28-day observation period. Avapritinib induced tumor regression and sustained tumor growth inhibition at both doses tested. Avapritinib antitumor activity was highly statistically significant ($P < 0.0001$ by one-way analysis of variance). Data points represent group mean and error bars represent standard error of the mean for 9 mice per cohort.

Right panel: After 7 days of once-daily dosing with vehicle, 30 mg/kg avapritinib, or 100 mg/kg avapritinib, tumors were harvested from 3 mice per group, 24 hours after the last dose. Tumor homogenates demonstrated inhibition of KIT signaling by analysis of KIT autophosphorylation and downstream signaling markers p-ERK and p-AKT.

A second experiment performed in the KIT exon 11/exon 17 mutant (delW557K558/Y823D) imatinib-resistant GIST PDX model demonstrated antitumor activity with avapritinib at doses similar to that seen in the KIT D816Y driven P815 allograft tumors. Avapritinib administered orally for 27 days with 3, 10 or 30 mg/kg QD, resulted in significant dose dependent antitumor activity compared to vehicle treatment. Treatment with the low dose of avapritinib (3 mg/kg, QD) resulted in minimal tumor growth over the 28-day period whereas treatment with higher doses of avapritinib (10 mg/kg and 30 mg/kg, QD) produced tumor regression. Avapritinib was well tolerated with no adverse effect on body weight observed at any dose level. As expected, imatinib was not active in this model; regorafenib produced only tumor stasis and > 5% body weight loss at its maximum tolerated dose in mice.

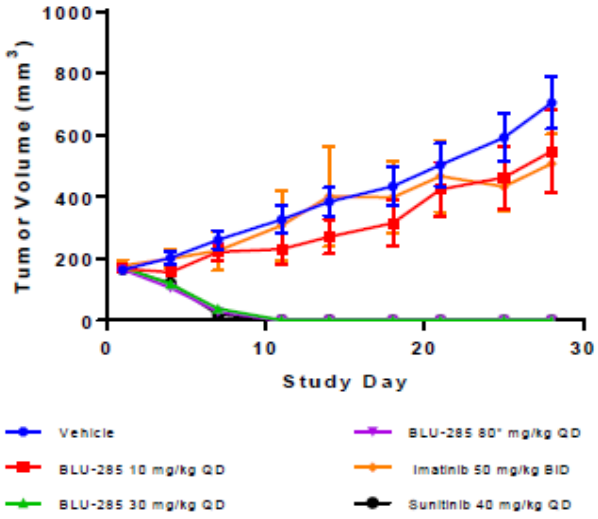
Figure 11. Dose Dependent Efficacy in a KIT Exon 11/17 Mutant GIST PDX Model



Mice bearing KIT exon 11/exon 17 mutant GIST PDXs were dosed once daily, orally with vehicle, 3, 10 or 30 mg/kg avapritinib, 50 mg/kg imatinib BID or 30 mg/kg QD regorafenib for 28 days. Tumor growth was measured twice weekly for the 28-day dosing period. Avapritinib induced tumor regression at either 10 mg/kg or 30 mg/kg. Avapritinib antitumor activity at 10 and 30 mg/kg QD was highly statistically significant ($P < 0.001$ by one-way analysis of variance). Data points represent group mean and error bars represent standard error of the mean for 8 mice per cohort.

In a KIT exon 11/exon 13 mutant (delW557K558/V654A) imatinib-resistant GIST PDX model, avapritinib demonstrated antitumor activity with doses of 30 mg/kg QD. Treatment with a 10 mg/kg QD dose of avapritinib resulted in minimal tumour growth inhibition over the 28-day period whereas treatment with 30 mg/kg QD of avapritinib produced tumour regression. At 30 mg/kg QD, avapritinib was well tolerated with no adverse effect on body weight. As expected, imatinib was not active in this model; 40 mg/kg QD sunitinib produced tumour regression (Figure 12).

Figure 12. Dose Dependent Efficacy in a KIT Exon 11/13 Mutant GIST PDX Model

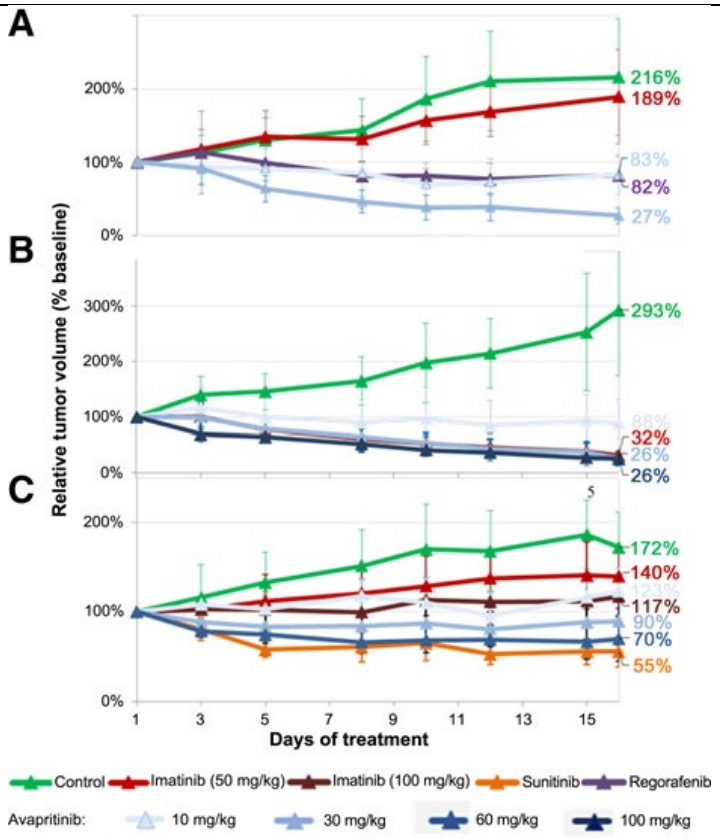


Mice bearing KIT exon 11/exon 13 mutant GIST PDXs were dosed once daily, orally with vehicle, 10, 30, or 80* mg/kg avapritinib, 50 mg/kg imatinib BID or 40 mg/kg QD sunitinib for 28 days. Tumour growth was measured twice weekly for the 28-day dosing period. Avapritinib induced tumour regression at either the 30 mg/kg or 80* mg/kg QD dose. Avapritinib antitumor activity at 30 and 80* mg/kg QD was statistically significant (Tukey's multiple comparisons test). Data points represent group mean and error bars represent standard error of the mean for 8 mice per cohort.

Avapritinib also demonstrated *in vivo* anti-tumour activity against GIST xenografts with other KIT mutant genotypes including primary exon 9 and exon 11 mutant models (UZLX-GIST9$^{KIT\ 11+17}$ [p.P577del; W557LfsX5;D820G], UZLX-GIST3$^{KIT\ 11}$ [p.W557_V559delinsF] and UZLX-GIST2B$^{KIT\ 9}$ [p.A502_Y503dup]). In all three xenograft models, avapritinib (10 mg/kg) resulted in tumour volume stabilization compared with the baseline value. This effect was comparable to the effects induced by the higher dose of imatinib in UZLX-GIST2B$^{KIT\ 9}$ (100 mg/kg) or to regorafenib in UZLX-GIST9$^{KIT\ 11+17}$ (Fig. 10). Remarkably, at the dose of 30 mg/kg, avapritinib treatment resulted in substantial tumour regression as compared with baseline in two of the tested models, to 27% in UZLX-GIST9$^{KIT\ 11+17}$ (P = 0.005) and to 26% in GIST3$^{KIT\ 11}$ (P = 0.008, both WMP), and tumour volume stabilization (90%) in UZLX-GIST2B$^{KIT\ 9}$ (P = 0.08, WMP). Similarly, in UZLX-GIST3$^{KIT\ 11}$, higher dose of avapritinib (100 mg/kg), led to a significant tumour regression to 26% of baseline value (P = 0.005, WMP), which was similar to the effect of imatinib in this model (Fig. 13B). In addition, in UZLX-GIST2B$^{KIT\ 9}$, avapritinib at a dose of 60 mg/kg led to tumour shrinkage, which was significantly better than imatinib (at both doses) and comparable with sunitinib (Fig. 13C). Taken together, avapritinib induced remarkable and dose-dependent effects on tumor volume in all three models.

During the course of this study, the treatment with avapritinib was well tolerated, and mice had a stable body weight within ethically acceptable limits.

Figure 13. Activity of Avapritinib in Patient-derived Xenograft Models of Gastrointestinal Stromal Tumors (UZLX-GIST9$^{KIT\ 11+17}$, UZLX-GIST3$^{KIT\ 11}$ and UZLX-GIST2B$^{KIT\ 9}$)



Evolution of tumor volume during the treatment, presented as relative tumor volume (% change compared with normalized, baseline value) ± SD in UZLX-GIST9$^{KIT\ 11+17}$ (A), -GIST3 $^{KIT\ 11}$ (B), and –GIST2B$^{KIT\ 9}$ (C).

Secondary pharmacodynamic studies

The pharmacologic specificity of avapritinib was assessed against a panel of pharmacological targets including receptors, transporters, and enzymes. Compound binding was calculated as a percent inhibition of the binding of a radioactively labelled ligand specific for each target. Assays for the following targets showed >50% inhibition by avapritinib at a 10 µM screening concentration: 5- hydroxytryptamine transporter, adenosine A2A receptor, gamma aminobutyric acid-gated chloride channel, dopamine transporter, histamine H2 receptor, kappa opioid receptor, muscarinic acetylcholine M2 and M3 receptors, norepinephrine transporter, mu opioid receptor, and the type 2 sodium channel. In subsequent studies, avapritinib had biochemical IC_{50} values of 280, 2900, 5800, and 2200 nM against the type 2 sodium channel, histamine H2 receptor, muscarinic acetylcholine M2 receptor, and the norepinephrine transporter, respectively.

Safety pharmacology programme

Effect of avapritinib on cloned hERG potassium channels expressed in human embryonic kidney cells.

Avapritinib inhibited hERG current by 20.0±1.0% at 1 µM (n= 3), 37.5±1.5% at 2 µM (n= 3), 62.2±2.3% at 3 µM (n= 3) and 59.4±1.2% at 10 µM (n= 3) versus 3.0±0.5% (n= 3) in control. The hERG inhibition at all concentrations tested was statistically significant ($P < 0.05$) when compared with vehicle control values. The IC_{50} for the inhibitory effect of avapritinib on hERG potassium current was 2.4 µM (Hill coefficient= 1.8).

Under identical conditions, the positive control (60 nM terfenadine) inhibited hERG potassium current by (Mean±SD; n= 2) 85.4±2.5%.

Irwin test assessment following 15-day oral administration of avapritinib to Sprague-Dawley rats.

Oral (gavage) administration of avapritinib to female Sprague-Dawley rats at a dose level of 30 mg/kg for 15 consecutive days resulted in increased corneal reflex and increased pinna reflex in 1 of 6 animals. These signs were first observed on Day 7 and had resolved by Day 10. A dose level of 45 mg/kg resulted in increased touch response, increased corneal reflex, increased pinna reflex, head flicking, exophthalmos, increased startle response, aggressiveness, vocalization, 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 show an increase in sensitivity to stimuli and are potentially underlying indicators of preconvulsive activity. These signs, although observed in a minority of treated animals, were considered test article-related. No avapritinib–related effects on the gross behavioral, physiological, or neurological state of the animals were noted at a dose level of 15 mg/kg. Based on the results of this study, the no-observed-effect level was 15 mg/kg avapritinib.

Cardiovascular and respiratory assessment following oral gavage administration of avapritinib to conscious, radiotelemetry instrumented Beagle dogs.

Administration of avapritinib via oral gavage to male Beagle dogs at dose levels of 15, 30, or 45 mg/kg did not result in avapritinib–related effects on any cardiovascular parameter (heart rate, mean arterial blood pressure, and systolic, diastolic, and pulse pressure), body temperature, ECG waveform morphology, duration of PR, QRS, RR, QT, and QTcV intervals, respiratory parameters (respiratory frequency, tidal volume, and minute volume), or the clinical condition of the animals. Based on these results, the no-observed-effect level (NOEL) for cardiovascular and respiratory function following oral gavage administration of avapritinib to male radiotelemetry-instrumented Beagle dogs was 45 mg/kg.

Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies have not been performed with avapritinib.

2.3.3. Pharmacokinetics

The absorption, distribution, metabolism, and excretion profiles of avapritinib have been characterized in nonclinical species both in vitro and in vivo and in human in vitro studies.

Avapritinib is expected to be well absorbed from the gastrointestinal tract in humans, as suggested by the high oral bioavailability (77-81%) and high fraction absorbed (fa*fg) in nonclinical species. Furthermore, based on these findings from MDCK-MDR1 and Caco-2 assays, efflux transport in gut is not expected to limit the oral bioavailability of avapritinib in humans. In addition, the plasma PK of avapritinib was not altered by pretreatment with pentagastrin or famotidine in dogs.

Plasma clearance (CLplasma) of avapritinib was low in mouse and rat (≤ 10% liver blood flow) and was moderate in dog and monkey (≤ 40% liver blood flow). The apparent volume of distribution at a steady state (Vdss) was moderate to high in every species.

Avapritinib displayed dose-proportional pharmacokinetics over a range of doses in rats and dogs including and above the therapeutic range. Accumulation was evident in rats after repeated doses. Difference in plasma exposure of avapritinib after repeated oral administrations was observed between male and female rats where the exposure was higher in female rats. On the other hand, plasma exposures in dogs were similar among the sexes.

After single-dose administration of avapritinib across the dose range of 30 to 400 mg in patients with GIST, the mean t1/2 was longer than in animals, ranging from 32 to 57 hours (Study BLU-285-1101). A longer half-life is expected to result in a higher accumulation ratio after repeated dosing. Steady state is however established in patients within 15 consecutive days of daily treatment.

Plasma protein binding is high (>99 %) across all species tested (mouse, rat, dog, monkey, and human). Overall, the fraction unbound in plasma from human and dog was similar, and 2-3 fold higher than in plasma from mouse and rat. Distribution of avapritinib to red blood cells is low (blood to plasma ratio < 1). Avapritinib was found to be stable in human, rat and dog plasma.

Avapritinib was widely distributed to majority of tissues. The distribution of [^{14}C]-avapritinib-related radioactivity in nonpigmented rats was the highest in the lung, adrenal gland, and liver, and was the lowest in uveal tract and adipose. In gastrointestinal tissues like stomach wall, small intestine and large intestine, tissue to plasma ratios of 3.5, 5.8 and 6.8, respectively, are reported. The concentration of [^{14}C]-avapritinib-derived radioactivity in the uveal tract and skin of pigmented Long Evans rats was eliminated more slowly and was approximately 2 to 330-fold higher than in these tissues in nonpigmented rats. These results suggest that avapritinib may have an affinity to these melanin-containing tissues. In rats, unbound avapritinib brain-to-plasma ratio was approximately 8, which indicated a potential for high brain penetration of avapritinib.

The metabolic pathways in vitro for avapritinib are comparable between rat, dog, and human. It included N-demethylation (M484), oxidation of the primary amine to a tertiary alcohol (M499) whereby the primary amine was oxidized to an alcohol, and oxidized N-demethylated metabolite (M485) and hydroxylation/oxidation (M514a/b). CYP3A4 (84.9%) and CYP2C9 (15.1%) are the main enzyme involved in the metabolism of avapritinib in vitro.

The major component in plasma of rat, dog and human was unchanged avapritinib. Data from the [14C] avapritinib human ADME study, indicates that metabolites M690 (34.8%; hydroxy glucuronide) and M499 (14.1%) are major circulating radioactive components. M499 was observed in rat plasma (31% of total radioactivity), and at lower levels in dog.M690 was detected in trace amounts in rats and dog plasma.

Concomitant treatment with drugs that are strong or moderate CYP3A4 inhibitors or inducers may alter the PK of avapritinib by either increasing or decreasing plasma concentrations. The potential for avapritinib to inhibit or induce activity of human CYP enzymes and to inhibit human transporters has been assessed in the Clinical part. PK interactions mediated by M690 and M499 were studied.

The excretion data indicate that biliary excretion is the major route of elimination; however, the reproducible detection of [^{14}C]-avapritinib-derived radioactivity in the feces of BDC rats also indicates active intestinal epithelial excretion. There are no data on excretion routes in dog.

Excretion studies in milk have not been conducted in animals.

2.3.4. Toxicology

Single dose toxicity

Although dedicated single-dose toxicity studies were not conducted, clinical observations of poor toleration were noted in the single-dose PK studies in rats and dogs. In a non–GLP-compliant PK study, 4 groups of male Sprague Dawley rats (n= 3/group) were administered single oral gavage doses of 10, 30, 100, or 300 mg/kg of avapritinib. No clinical signs were noted in rats at doses up to 100 mg/kg; at

a dose of 300 mg/kg, clinical signs of twitching, unsteady gait, hypersensitivity to touch, and vocalization upon handling were noted at the 24-hour time point.

In a non–GLP-compliant PK study, 2 groups of male Beagle dogs (n= 3/group) were administered single oral gavage doses of 25 or 50 mg/kg of avapritinib. Emesis was noted in 5 of 6 dogs 1-hour postdose and 2 of 3 dogs at 50 mg/kg had loose stools 4-hours postdose.

Repeat dose toxicity

The following table resume the findings in repeat dose toxicity studies**.**

28-day oral (gavage) toxicity and toxicokinetic study in Sprague Dawley rats with a 14-day recovery period (WIL-124507)

Species/strain/GLP/Duration/Route of administration	**Number/Sex/Group**	**Dose (mg/kg/day) /vehicle**	**HNSTD (mg/kg/day)**
Rat/Crl:CD(SD)/GLP/28 days/PO gavage	3-15M+3-15F/group	M: 0, 30/20/10, 75/50/30, 150/100 F: 0, 20/10/5, 50/40/20, 100/75 (Doses were reduced as result of poor tolerance during the 28-day dosing period) 0.5% CMC-Na (w/v) and 1% Tween® 80 (v/v) in water (pH 2-3)/suspension	M: ≥30 F: ≥20
Clinical signs: Clinical observations included central nervous system findings (tremors, clonic convulsions, vocalization, vocalization upon handling, and hyper-reactivity to touch), cardio-pulmonary findings (cool and pale extremities and cool body), hunched posture, thin body condition, dermal atonia, and coloured material on various body surfaces. These avapritinib-related effects were generally noted with greatest incidence and/or severity in high dose group males and females, and took less time to be expressed in comparison to the mid-dose groups, suggesting that the effects were the result of total drug exposure over time. *Food consumption, body weight and weight gain:* Lower body weight gains and and/or body weight losses in the mid and high dose groups were accompanied by lower food consumption and frequently preceded death. *Haematology:* Alterations in the low, mid and high-dose groups, included reduced RBC, WBC (lymphocyte, neutrophil, monocyte, and eosinophil counts), haematocrit and haemoglobin; increased reticulocytes; increased platelet counts and prothrombin time (PT). At the recovery necropsy, avapritinib-related lower RBC counts and higher MCV, MCH, and RDW values persisted in the low-dose groups with partial improvement compared with the primary necropsy. *Clinical chemistry and urinalysis:* Alterations in all avapritinib groups, included increased serum chemistry parameters (ALP, ALT, AST, total bilirubin, glucose (not the low dose group), cholesterol, bicarbonate (not the low dose group)) and decreased phosphorus; change in cation/anion clearance in urine (total and corrected total increases in sodium, potassium, and chloride clearance values). Most changes in serum			

chemistry were completely reversed in recovery though a few parameters (specifically phosphorus) were reversing, but not complete. Urine perturbations were reversed in recovery.

Organ weight changes: Avapritinib-related changes in organ weights noted at the primary necropsy included higher adrenal gland, ovaries/oviducts, and uterus weights, and lower spleen and thymus weights.

Microscopic changes: Microscopic changes were found in the hematopoietic and lymphoid systems (bone marrow with decreased cellularity and haemorrhage, spleen with increased extramedullary haematopoiesis, thymic cortex with decreased cellularity and increased apoptosis, and lymph nodes with decreased cellularity); in the femur with medullary hyperostosis and fibrosis and growth plate perturbation; in the adrenal cortex with hypertrophy; in reproductive tissues with reduced sperm in epididymis and seminal vesicles and prostate atrophy, ovaries with haemorrhagic luteal cysts, vagina with evidence of altered cyclicity; and, stomach with atrophy (only in unscheduled deaths). At the recovery necropsy, minimal increased extramedullary hematopoiesis in the spleen (1 male rat), severe bilateral testicular degeneration (1 male rat), and severe reduced luminal sperm and mild luminal cellular debris in the epididymis (1 male rat) were noted in the low-dose group males, and minimal to moderate hemorrhagic and cystic degeneration of the corpora lutea in the ovaries were noted in the low-dose group females. In the main study recovery groups, all anatomic pathologic changes were reversed, reversing, or compensatory to the effects of treatment, with the potential exceptions of the female gonadal effects, likely requiring a longer recovery period for return to normal.

Toxicokinetics: The severely toxic dose with lethality in 10% of the animals (STD10) was greater than 30 mg/kg/day in males and 20 mg/kg/day in female rats, based on the supplemental study and absence of convulsions (or other neurologic signs) or lethality after dose adjustment (in the final 2 weeks) in the main study at the mid dose of 75/50/30 mg/kg/day in males and 50/40/20 mg/kg/day in female rats. The dose levels of 30 mg/kg/day in male rats and 20 mg/kg/day in female rats did not result in severe toxicity, thus representing the HNSTD level and exposure values. The female rat is confirmed as the more sensitive sex, based on the dose administered. After 28-days of dosing, the exposure values at the HNSTD in the main study mid-dose group with ending dose of 30/20 mg/kg/day (males/females) are 7760/7500 ng/mL for C_{max} and 136,000/137,000 ng·h/mL for AUC_{0-24}.

28-day oral (gavage) toxicity and toxicokinetic study in Sprague Dawley rats with a 14-day recovery period (WIL-124525)

Species/strain/GLP/Duration/Route of administration	**Number/Sex/Group**	**Dose (mg/kg/day) /vehicle**	**STD10 (mg/kg/day)**
Rat/Crl:CD(SD)/GLP/28 days/PO gavage	3-9F/group	F: 0, 30, 45/30 (Doses were reduced as result of poor tolerance during the 28-day dosing period) 0.5% CMC-Na (w/v) and 1% Tween® 80 (v/v) in water (pH 2-3)/suspension	F: 30
Mortality: Several toxicological effects were observed in the animals that were found dead or euthanized, including body weight losses, clinical observations (behavioural/central nervous system findings (tremors, prostration, hunched posture, vocalization upon handling, and hyper-reactivity to touch), cardio-pulmonary findings (cool body to touch), decreased defecation, red discharge on the eye, red material on various body surfaces (forelimbs, hindlimbs, nose, and/or mouth), and yellow material on the urogenital area), and			

haematological changes (lower red blood cell counts (RBC), haemoglobin values, and haematocrit values, higher mean corpuscular haemoglobin (MCH) values, mean corpuscular volume (MCV) values, and platelet counts), lower total leukocyte counts (white blood cell) and/or lower absolute lymphocyte and monocyte counts. Serum chemistry alterations included higher total bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and/or gamma glutamyltransferase (GGT) values, lower chloride, and higher potassium and bicarbonate values. Macroscopic test article-related changes in the unscheduled death animals were confined to the ovaries and consisted of dark red discoloration, enlargement, and/or cysts. These changes correlated with microscopic changes of haemorrhagic and cystic degeneration in the ovaries. Microscopic changes included hypertrophy of the zona fasciculata in the adrenal gland; decreased hematopoietic cellularity in the femoral or sternal bone marrow; increased thickness of the zone of hypertrophy or the primary spongiosa of the physeal growth plate in the femur; hyperostosis in the femur; haemorrhagic and cystic degeneration of the ovaries, lymphoid depletion of the thymus, spleen, and/or lymph nodes; increased extramedullary haematopoiesis in the spleen; and increased mucification with or without neutrophilic infiltrates in the vaginal mucosa.

Food consumption, body weight and weight gain: There were no test article-related effects on body weights or food consumption in the animals that survived to the scheduled necropsies.

Coagulation: There were no test article-related effects on coagulation.

Ophthalmology: There were no test article-related effects on ophthalmology.

Clinical observations: Test article-related clinical observations for animals in the 45/30 mg/kg/day group that survived to the scheduled necropsies included red material around the nose in a single animal from study days 14-26. Test article-related clinical observations for animals in the 30 mg/kg/day group that survived to the scheduled necropsies included vocalization upon handling and hyper-reactivity to touch in a single animal on study day 28, and red material around the eye in a different animal from study days 24-28.

Haematology: Test article-related alterations in haematology parameters included the following: red blood cell parameters (minimally to mildly lower RBC counts, haemoglobin values, haematocrit values, and lower/higher reticulocyte [45/30 mg/kg/day group only; lower on study day 14 and mildly higher on study day 28] and platelet counts [45/30 mg/kg/day group only on study day 14]; and minimal to mild higher MCV, MCH, and red blood cell distribution width [RDW], and/or haemoglobin distribution width [HDW] values) were noted in the 30 and 45/30 mg/kg/day groups on study day 14 and at the study day 28 primary necropsy. At the study day 42 recovery necropsy, minimally lower RBC counts were noted in the 30 and 45/30 mg/kg/day groups indicating partial recovery. In addition, higher reticulocyte counts and MCV, MCH, RDW, and HDW values were noted in the 30 and 45/30 mg/kg/day groups, indicating continued bone marrow response consistent with a rebound effect, consistent with a partial recovery.

Serum chemistry: Test article-related alterations in serum chemistry parameters noted in the 30 and 45/30 mg/kg/day groups on study day 14 and/ at the study day 28 primary necropsy included higher ALP (45/30 mg/kg/day group only on study day 28), ALT, AST, GGT (study day 28 only), total bilirubin, cholesterol, and triglyceride values. At the study day 42 recovery necropsy, these alterations had reversed with the exception of higher cholesterol values in the 30 and 45/30 mg/kg/day groups, which had partially reversed.

Urine chemistry parameters: Test article-related alterations in urine chemistry parameters on study day 28 in the 30 and 45/30 mg/kg/day groups included higher mean total sodium, corrected total sodium, total potassium, corrected total potassium, total chloride, and corrected total chloride values. At the study day 42 recovery necropsy, these alterations had reversed in the 30 mg/kg/day group, with the exception of higher sodium values. At the study day 42 necropsy, none of the alterations in urine chemistry parameters in the 45/30 mg/kg/day group had reversed.

Macroscopic findings: Test article-related macroscopic findings noted at the primary necropsy included an enlarged adrenal gland in a single 30 mg/kg/day group animal, and dark red discoloration and enlarged ovaries in the 30 and 45/30 mg/kg/day groups. Findings of dark red discoloration and enlarged ovaries in the ovaries persisted, and cysts in the ovaries were noted in the 30 and 45/30 mg/kg/day groups at the recovery necropsy.

Organ weights: Test article-related higher adrenal gland and ovaries/oviduct weights and lower spleen and thymus weights were noted in the 30 and 45/30 mg/kg/day groups at the primary necropsy at approximately the same magnitude. Lower ovaries/oviducts weights were noted in the 30 and 45/30 mg/kg/day groups on study day 42, but were partially recovered.

Microscopic changes: Test article-related microscopic changes were noted at a similar incidence and severity in the 30 and 45/30 mg/kg/day groups at the primary necropsy and included the following: mild haemorrhagic and cystic degeneration in the ovaries (marked in a single 45/30 mg/kg/day animal), minimal to mild increased mucification and neutrophilic infiltrates in the vagina; mild increased mucification of the cervix in the 45/30 mg/kg/day group only; minimal to moderate decreased hematopoietic cellularity of the femoral and sternal bone marrow, and minimal hyperostosis (45/30 mg/kg/day group only) of the femoral bone marrow; increased thickness of the hypertrophic zone cartilage and primary spongiosa of the femur and minimally increased thickness of the physeal growth plate of the femur; minimal to mild hypertrophy of the zona fasciculata of the adrenal cortex; minimal increased extramedullary haematopoiesis in the spleen in the 30 mg/kg/day group only; and minimal lymphoid depletion of the axillary lymph node and minimal to mild lymphoid depletion of the spleen and thymus (30 mg/kg/day group only). At the study day 42 recovery necropsy, mild to moderate haemorrhagic and cystic degeneration in the ovaries was noted in the 30 and 45/30 mg/kg/day groups (partially reversed), and minimal hyperostosis in the femoral bone marrow was noted in a single 45/30 mg/kg/day group animal.

Toxicokinetics: All rats dosed orally by gavage with avapritinib were systemically exposed to avapritinib. Exposure increased with increasing dosage on study day 0 in terms of $AUC_{0\text{-}24}$ and C_{max}. The increase in exposure to avapritinib was nearly proportional to the increase in dosage. The T_{max} for avapritinib in plasma was generally observed at 3 or 6 hours post-dose for rats. Based on the unscheduled deaths in 2 female rats, including an additional animal with a single incidence of neurologic signs (vocalization and hypersensitivity to touch), the STD10 dose in female rats is 30 mg/kg/day. The terminal Day 27 steady state $AUC_{0\text{-}24}$ and C_{max} at the STD10 dose of 30 mg/kg/day are 208,000 ng·h/mL and 11,200 ng/mL, respectively.

3-month oral (gavage) toxicity and toxicokinetic study in Sprague Dawley rats (WIL-124522)

Species/strain/GLP/Duration/Route of administration	Number/Sex/Group	Dose (mg/kg/day) /vehicle	HNSTD (mg/kg/day)
Rat/Crl:CD(SD)/GLP/3 months/PO gavage	3-9M+3-9F/group	M: 0, 10, 20, 30 F: 0, 5, 15, 25 0.5% CMC-Na (w/v) and 1% Tween® 80 (v/v) in water (pH 2-3)/suspension	M: ≥30 F: ≥25
General toxicological considerations: Test article-related findings generally increased in incidence and/or severity with increasing dosage with even the lowest dosage levels in males and females having multiple, albeit less severe, test article-related effects. At the 10 mg/kg/day dosage level in males and 5 mg/kg/day dosage level in females, test article-related findings still included minimal to mild haematology, coagulation,			

and urinalysis parameter alterations; presence of gross observations (limited to ovaries); and minimal to mild histologic changes in multiple tissues.

Food consumption and body weight/weight gain: There were no test article-related effects on food consumption. Test article-related higher body weights were noted in all test article-treated male and female groups.

Ophthalmology: There were no test article-related effects on ophthalmic findings.

Clinical observations: Test article-related clinical observations included red material around the eyes (mid and high dose males) and red material around the nose (low, mid and high dose males). The incidence of these observations increased with increasing dosage level.

Haematology: Red blood cell parameter alterations (lower RBC count, haemoglobin, and haematocrit values; reticulocyte value alterations; higher MCV, MCH, RDW, and HDW values); coagulation parameter alterations (higher platelet count and MPV); leukogram parameter alterations (lower monocyte and eosinophil counts);

Serum chemistry: Serum chemistry parameter alterations (higher total protein, albumin, globulin, A/G ratio, ALT, AST, GGT, total bilirubin, and cholesterol);

Urine chemistry parameters: Urinalysis parameter alterations (higher urine pH and increased leukocytes on macroscopic urinalysis)

Macroscopic findings: Gross observations of enlarged adrenal glands, small thymus, and several ovarian changes (cysts, dark red areas, dark red discoloration, and enlarged)

Organ weights: Organ weight differences including higher adrenal gland, heart, kidney, liver, and ovaries/oviducts weights

Microscopic changes: Histologic changes involving the hematopoietic and lymphoid systems (decreased cellularity of hematopoietic cells and haemorrhage in the bone marrow [femur and sternum], increased bone formation and fibroplasia in the bone marrow [femur], increased extramedullary haematopoiesis and increased pigmented macrophages in the spleen, and decreased lymphoid cellularity in the thymic cortex), femur (increased thickness of the zone of hypertrophic cartilage), adrenal cortex (hypertrophy and cystic degeneration), and reproductive tissues (haemorrhagic and cystic degeneration of the ovarian corpora lutea, reproductive cycle alteration, and vaginal mucification).

Toxicokinetics: The increase in exposure to avapritinib, in terms of AUC_{0-24} and C_{max}, was nearly proportional to the increase in dosage from 10 to 30 mg/kg/day for males, except on study day 90, where the relationship was less than dose-proportional. For females, the increase in exposure to avapritinib was nearly proportional to the increase in dosage. Accumulation was evident at all dosage levels, with accumulation ratios that ranged from 1.6 to 2.4 for males and from 1.7 to 2.1 for females. Exposure (AUC_{0-24}) was higher in females than in males at all dosage levels on both evaluation days. The T_{max} for avapritinib in plasma was generally observed at 3 or 6 hours post-dose for both genders at all dosage levels. The severely toxic dose in 10% of animals (STD10) was not defined. The highest nonseverely toxic dose (HNSTD) was considered to be ≥30 mg/kg/day for the males and ≥25 mg/kg/day for the females, the highest dose administered in this study. This dosage corresponded to mean AUC_{0-24} values of 68,100 and 117,000 ng*h/mL and mean C_{max} values of 3870 and 6740 ng/mL for males and females, respectively, on study day 90.

28-day oral (gavage) toxicity and toxicokinetic study in Beagle Dogs with a 14-day recovery period (WIL-124508)

Species/strain/GLP/Duration/Route of administration	Number/Sex/Group	Dose (mg/kg/day) /vehicle	HNSTD (mg/kg/day)
Dog/Beagle/GLP/28-day/PO gavage	3-5M+3-5F/group	M: 0, 15/7.5, 30/15, 60/45/15 F: 0, 15/7.5, 30/15, 60/45/15 (Due to mortality and signs of excessive toxicity, the dosage level was lowered for all test article-treated groups) 0.5% CMC-Na (w/v) and 1% Tween® 80 (v/v) in water (pH 2-3)/suspension	M: 7.5 F: 7.5

Mortality: Prior to euthanasia, pertinent clinical observations noted in these animals included emesis, injected sclera, thin body condition, dermal atonia, changes in faecal consistency (diarrhoea), wet clear material on various body surfaces (mouth, ventral neck, and/or forelimbs), salivation, and/or reddened ears. Test article-related changes in haematology parameters for these early death animals included lower red blood cell (RBC) counts, haemoglobin, haematocrit, absolute reticulocytes (females only), red cell distribution width, haemoglobin distribution width, and mean corpuscular volume (females only) and higher mean corpuscular haemoglobin concentration. In addition, both animals showed lower absolute lymphocytes and eosinophils. Changes in serum chemistry parameters included lower values for albumin, globulin, total protein, alkaline phosphatase, phosphorus, and calcium and higher values for total bilirubin, aspartate aminotransferase, gamma glutamyltransferase, and creatine kinase in both animals, and higher sorbitol dehydrogenase and chloride in the female. Small thymus was noted in the male which correlated with test article-related thymic atrophy, decreased lymphoid cellularity, and increased lymphoid apoptosis. A microscopic finding specific to animals euthanized in extremis was minimal to mild oesophageal erosion at the junction of the oesophagus and stomach. Other avapritinib-related changes in the 2 early death animals consisted of increased severity of hypospermatogenesis of the testis, decreased cellularity and haemorrhage in the bone marrow, and a plethora of changes in lymphoid organs (decreased lymphoid cellularity, increased lymphoid apoptosis, decreased germinal centers, decreased size of lymphoid follicles, and/or atrophy). The cause of moribundity necessitating euthanasia was considered to be due to inanition.

Ophthalmology: There were no test article-related ophthalmic findings.

ECG: There were no test article-related effects on electrocardiographic parameters.

Clinical observations: In the mid- and high-dose groups (M and F), avapritinib-related clinical observations included emesis (containing white material, yellow material, and/or food), clear material on various body surfaces (mouth, ventral neck, and/or forelimbs), and/or salivation generally from study day 0 through 12. These clinical observations were generally not noted after lowering the dosage level to 15 mg/kg/day and were not noted during the recovery period.

Food consumption, body weight gain and body weight: Avapritinib-related mean body weight losses and corresponding lower mean food consumption were generally noted in both high-dose groups through study day 10. Lower food consumption was also noted for a single female in the mid dose group. To limit the

impact of body weight loss and low food consumption, the daily feed ration for all animals was supplemented with moist food.

Haematology: On study day 28 lower red blood cells (RBC), haemoglobin, and haematocrit values and higher haemoglobin distribution width (HDW) were seen at all dosage levels. In the low dose group, higher absolute reticulocytes and red cell distribution width (RDW) were observed. In the mid and high-dose groups, lower reticulocyte values and higher corpuscular haemoglobin concentration (MCHC) were seen. A lower total white blood cells counts (WBC), neutrophil, eosinophil, and basophil values, and higher platelet counts were observed at all dosage levels. After the 14-day recovery period, reduced eosinophil and monocyte (males only) values and higher platelet values in males and females were still observed. Higher RBC, haemoglobin, haematocrit, absolute reticulocytes, RDW, HDW, MCV (females only), WBC, absolute neutrophils, and absolute eosinophil (females only) values were also observed as rebound effects.

Clinical chemistry: Avapritinib-related changes in serum chemistry parameters on study day 28 were noted as lower calcium, phosphorus, total protein, albumin, globulin, creatinine, alkaline phosphatase (ALP), cholesterol, and triglyceride values and higher chloride, total bilirubin, and urea nitrogen values at all dosage levels; and higher aspartate aminotransferase (AST), and creatine kinase (CK), sorbitol dehydrogenase (SDH), and glucose values in the mid and high-dose groups. All changes were slight. After the 14-day recovery period, lower albumin, cholesterol, triglyceride, and ALP values and a higher urea nitrogen value were still observed in the mid-dose group.

Urinalysis: A possible avapritinib-related change on study day 28 was observed as lower urine osmolality in the mid and high-dose group males and females. The urine osmolality value in the mid-dose group males remained lower on study day 42.

Necropsy and organ weight changes: Avapritinib-related small spleen and small thymus were each observed in a high-dose group male. There were no macroscopic observations noted at the study day 42 recovery necropsy. Avapritinib-related organ weight changes included the following: higher heart weights in the mid-dose group females and the high-dose group males and females; lower spleen weights in all avapritinib-treated male and females groups; lower thymus weights in all test article-treated male groups and the mid and high-dose group females; and lower testes weights in all test article-treated male groups. At the study day 42 recovery necropsy, avapritinib-related organ weight changes consisted of lower thymus weights in males and females and lower spleen weights in males, and higher heart weights in males and higher spleen weights in females in the mid dose-group.

Microscopic findings: Avapritinib-related microscopic findings consisted of the following: mild haemorrhage of the brain in the mid-dose group; minimal or mild erosion of the oesophagus at high-dose group; and minimal to severe hypospermatogenesis in the testis, minimal increased lymphoid apoptosis, minimal or mild decreased lymphoid cellularity, and minimal extramedullary hematopoiesis in the spleen, mild to severe decreased cellularity of hematopoietic cells and minimal or mild haemorrhage in the femoral and/or sternal bone marrow, minimal or mild increased lymphoid apoptosis, mild decreased lymphoid cellularity, and minimal to moderate decreased germinal centers in the axillary lymph nodes, minimal or mild increased lymphoid apoptosis, minimal or mild decreased size of lymphoid follicles, and minimal or mild neutrophil infiltrate in the Peyer's patches, minimal increased apoptosis and minimal or mild decreased lymphoid cellularity in the gut associated lymphoid tissue (GALT) in the stomach, and/or minimal to severe atrophy, minimal increased lymphoid apoptosis, and minimal decreased lymphoid cellularity in the thymus at all dosage levels. At the study day 42 recovery necropsy, avapritinib-related microscopic findings consisted of the following: mild haemorrhage of the brain, mild to severe hypospermatogenesis in the testis, immature epididymis, minimal increased cellularity of hematopoietic cells in the femoral bone marrow, minimal and/or mild extramedullary haematopoiesis in the spleen and axillary lymph node, minimal or mild decreased size of the lymphoid follicles in the Peyer's patches, and minimal to moderate atrophy and minimal increased

lymphoid apoptosis in the thymus in the mid-dose group. In 1 dog, a mature thrombus was in the plane of section, suggesting infarction as the cause of the haemorrhage.

Toxicokinetics: Exposure (AUC_{0-24} and C_{max}), increased with increasing dosage on study day 0 and study day 27 for male and female dogs. The increase in exposure was less than proportional to the increase in dosage from 15 to 60 mg/kg/day on study day 0, and nearly dose proportional to the increase in dosage from 7.5 to 15 mg/kg/day on study day 27. Exposure (AUC_{0-24}) was similar between genders. The T_{max} was generally observed at 1 or 2 hours post-dose for male and female dogs. Plasma avapritinib concentrations increased through 1 or 2 hours post-dose and remained relatively level or decreased slowly through 24 hours post-dose. The terminal elimination phase was inadequate to determine half-life for all groups. Based on the results of this study and given the indication of the test article, the highest non-severely-toxic dosage (HNSTD) level was considered to be 7.5 mg/kg/day. At this dosage level, mean C_{max} values were 462 and 475 ng/mL and mean AUC_{0-24} values were 5820 and 6410 ng·hr/mL for males and females, respectively, on study day 27.

3-month oral (gavage) toxicity and toxicokinetic study in Beagle Dogs (WIL-124523)

Species/strain/GLP/Duration/Route of administration	Number/Sex/Group	Dose (mg/kg/day) /vehicle	HNSTD (mg/kg/day)
Dog/Beagle/GLP/3-month/PO gavage	4M+4F/group	0, 7.5, 15, 30 0.5% CMC-Na (w/v) and 1% Tween® 80 (v/v) in water (pH 2-3)/suspension	M: 7.5 F: 7.5

Mortality: Prior to death or euthanasia, these animals were noted with avapritinib-related clinical observations of laboured respiration, clear ocular discharge, emesis (containing food, white material, or yellow material), salivation, tremors, hypoactivity, partial closure of the eyes, prominent nictitating membranes, ataxia, vocalization, vocalization upon handling, hunched posture, injected sclerae, cool extremities, white frothy material around the mouth, and/or pale nose, gums, body, and/or extremities. In addition, these animals were noted with macroscopic findings in the adrenal glands, brain, gastrointestinal tract, gingiva, joint, liver, pituitary gland, skin, spleen, thymus, and/or trachea and microscopic findings in the brain, spinal cord, bone marrow, spleen, thymus, lymph nodes, Peyer's patches, adrenal cortex, adrenal medulla, gastrointestinal tract, and/or testes. Brain haemorrhage was considered the cause of death or moribundity for all animals in the high-dose groups. A single mid-dose group male was found dead on study day 80; however, the cause of death for this male was oral gavage error and was not test article-related.

Clinical observations: Avapritinib-related clinical observations were noted for the low and mid-dose group males and females and included clear ocular discharge, emesis (containing white material), and pale nose, gums, and extremities. In addition, test article-related pale body was noted for two mid-dose group males.

Food consumption and body weight: Test article-related lower body weights and corresponding lower food consumption values were noted for the high-dose group females beginning during the second week of dosing. Mean body weights in this group were 6.3% to 10.0% lower than the control group during study weeks 4-6.

Ophthalmology: There were no avapritinib-related ophthalmic findings.

ECG: There were no avapritinib-related alterations in electrocardiography parameters.

Urinalysis: There were no test article-related alterations in urinalysis parameters.

Haematology and clinical chemistry: Avapritinib-related clinical pathology alterations were noted in all groups, and included lower red blood cells, haemoglobin, haematocrit, white blood cells, neutrophils, lymphocytes, total protein, albumin, cholesterol, and calcium and higher platelets, prothrombin time and aspartate aminotransferase for males and/or females. Higher red cell distribution width, haemoglobin distribution width, activated partial thromboplastin time, and sorbitol dehydrogenase values were also noted for the high-dose group males and/or females. In addition, higher mean corpuscular volume was higher and reticulocytes, monocytes, eosinophils, basophils were lower for the low and mid-dose group males and/or females; phosphorus and globulin were lower for the low-dose group males and females and the high-dose group males; potassium was higher for the mid-dose group males and females and the high-dose group males and lower for the high-dose group females; and alkaline phosphatase was lower for the mid-dose group males and females. The high-dose group males and females were also noted with higher or lower reticulocyte values in several animals.

Necropsy and organ weight changes: Avapritinib-related macroscopic findings were noted for the low and mid-dose group males and females at the scheduled necropsy and included small thymus, oedematous thymus, and pale gingiva, skin, thymus, and/or thyroid. Avapritinib-related organ weight alterations included lower spleen weights for the low and mid-dose group males and females and lower thymus weights for the mid-dose group males and females.

Microscopic findings: Avapritinib-related microscopic findings in the following tissues were noted for the low and mid-dose groups at the scheduled necropsy: bone marrow (decreased cellularity of hematopoietic cells and/or haemorrhage), spleen (increased extramedullar hematopoiesis and/or increased pigmented macrophages), Peyer's patches (decreased lymphoid cellularity and/or increased lymphoid apoptosis), thymus (decreased lymphoid cellularity and/or increased lymphoid apoptosis), lymph nodes (increased pigmented macrophages, increased lymphoid apoptosis, decreased lymphoid cellularity, sinus erythrocytosis, and/or brown pigment), gastrointestinal tract (mucosal oedema, neutrophil infiltrate, and/or glandular dilation), testes (hypospermatogenesis), and brain (choroid plexus oedema). Males and/or females in the mid-dose group were also noted with additional findings in the brain (haemorrhage), adrenal cortex (angiectasis, haemorrhage, and brown pigment), pituitary gland (angiectasis), and gastrointestinal tract (mucosal atrophy).

Toxicokinetics: The increase in exposure to avapritinib was nearly proportional to the increase in dosage from 7.5 to 30 mg/kg/day in terms of AUC_{last} and C_{max} on study days 0 and 41. On study day 90, the increase in AUC_{last} and C_{max} was approximately 2-fold in males and <1.5-fold in females over the 2-fold increase in dosage from 7.5 to 15 mg/kg/day. Exposure (AUC_{last}) was similar between genders, differences were <2-fold. The T_{max} for avapritinib in plasma was observed at 1, 2, or 4 hours following dose administration for individual male and female dogs. The terminal elimination phase was inadequate to determine half-life for both genders and all groups on all evaluation days. The highest non-severely toxic dose (HNSTD) was considered to be 7.5 mg/kg/day for males and females. The dosage level of 7.5 mg/kg/day corresponded to mean AUC_{last} values of 6090 ng·hr/mL and 6330 ng·hr/mL and C_{max} values of 456 ng/mL and 485 ng/mL for males and females, respectively, on study day 90.

Genotoxicity

Avapritinib was not genotoxic overall when tested in a panel of *in vitro* and *in vivo* genotoxicity studies.

A standard genotoxicity program in line with ICH S2 was provided and summarised in the following table:

Table 2: *In vitro* and *in vivo* genotoxicity studies with avapritinib

Type of test/study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
In vitro Ames test/WIL-124504/Yes	Salmonella strains, TA1537, TA98, TA100, and TA1535, E.coli WP2uvrA	Up to 5000 µg/plate +/- S9	Negative Precipitates were observed at ≥100 µg/plate without metabolic activation and at ≥250 µg/plate with metabolic activation in all strains. Cytotoxicity was observed at ≥100 µg/plate in TA1537 without metabolic activation; at ≥250 µg/plate in TA100 and TA1535 both with and without metabolic activation; and in TA1537 with metabolic activation and TA98 without metabolic activation; and at ≥500 µg /plate in TA98 with metabolic activation. Hence, plates with concentrations ≥100 µg/plate were not counted. This apply for TA98, 100, 1535, 1537 without metabolic activation, and more or less the same were observed in the same strains with metabolic activation. The plate 5000 µg/plate WP2 uvrA were not counted due to precipitating. These cytotoxic findings limit the sensitivity of the test.
In vitro Chromosomal aberrations (CA) test/WIL-124505/Yes	HPBL-cells	Concentrations tested in the range-finding assay ranged from 0.977 to 500 µg/mL. Concentrations tested in the CA assay were 0.625, 1.25, 2.50, 5.00, 10.0, 20.0, 35.0, 50.0, 75.0, 125, and 250 µg/mL, with DMSO as control. short (3-hour) and long (22-hour) incubations +/- S9	Positive 3 h treatment without metabolic activation: A statistically significant increase of CA at 20.0 µg/mL. 22 h treatment without metabolic activation: A non-statistically significant increase of CA at 5.00 µg/mL. 3 h treatment with metabolic activation: A statistically significant increase of CA at 20.0 µg/mL. All treatments revealed no increases in numerical aberrations (percent of cells with polyploidy and/or endoreduplication) compared to vehicle control. Cytotoxicity: Reduction in mitotic index of 56% at 20.0 µg/mL in 3 h –S9; 54% at 5.00

			µg/mL in 22 h –S9; and 53% at 20.0 µg/mL in 3 h +S9 Precipitates were observed at ≥125 µg/mL in the 3-h treatments with and without metabolic activation and at 250 µg/mL in the 22-h treatment without metabolic activation.
In vivo Micronucleus test/ WIL-124506/Yes	Micronuclei in (PCE) in Sprague Dawley Rats bone marrow/ oral gavage	Males 0, 30, 75, and 150 mg/kg/day Female 0, 10, 20, and 50 mg/kg/day All groups consisted of 6 animals/sex except high-dose with 9 animals/sex 0.5% carboxymethylcellulose [CMC; medium viscosity]-sodium [w/v]: 1% Tween® 80 [v/v] in deionized water [pH 2-3] Duration of dosing: QD for 3 days	Negative

Avapritinib was not mutagenic in the bacterial reverse mutation assay. The Ames test was negative up to maximal tested concentration, but limited by cytotoxicity. It was positive in the in vitro chromosomal aberration assay, however, no evidence of clastogenicity was noted in vivo in the repeated dose rat bone marrow micronucleus assay. Therefore, taking into consideration all the three genotoxicity studies, avapritinib is not mutagenic and nonclastogenic in vivo, and thus, overall non-genotoxic.

Carcinogenicity

No carcinogenicity studies have been conducted with avapritinib.

Reproduction Toxicity

No studies to investigate fertility and early embryonal development have been conducted.

The objectives of the GLP-compliant embryo-foetal developmental toxicity study were to determine the potential of avapritinib to induce developmental toxicity after maternal exposure during the critical period of organogenesis and to characterize maternal toxicity at the exposure levels tested. In addition, a TK assessment of avapritinib was performed on Gestation Days 6 and 17 in a satellite group of 8 animals/dose.

Avapritinib was administered orally by gavage to 4 groups (n=10/group) of time-mated female Crl:CD(SD) rats once daily from Gestation Days 6-17. Dose levels were 0 (vehicle control), 5, 10, 20, and 30 mg/kg/day. The female rats were approximately 12–13 weeks of age at the initiation of dose administration.

All rats survived to the scheduled necropsy. There were no avapritinib-related clinical observations noted at the daily examinations at any dose level. Mean body weight losses and/or lower mean body weight gains, and corresponding lower mean food consumption were variably noted in the 10, 20 and 30

mg/kg/day groups during the dosing phase, but comparable to control and 5 mg/kg/day groups. The lower mean body weight gains late in gestation in the 10, 20, and 30 mg/kg/day groups were attributed to avapritinib-related higher mean post-implantation loss and/or lower mean fetal body weights. Furthermore, the 10, 20, and 30 mg/kg/day doses resulted in lower mean gravid uterine weights than the control group in a dose-related manner as a result of the post-implantation loss and/or lower mean fetal body weights. The 5 mg/kg/day group was unaffected. Dark red discoloration and/or enlargement (30 mg/kg/day group only) were noted in the ovaries of 2, 2, and 4 nongravid rats in the 10, 20, and 30 mg/kg/day groups, respectively, and in one rat in the 20 mg/kg/day group that was determined to be gravid (single implantation that resulted in an early resorption). Dark red discoloration and the enlarged ovary corresponded to ovarian hemorrhages based on microscopic examinations. Avapritinib-related minimal to marked hemorrhages were observed microscopically in the ovaries and were characterized by enlarged corpora lutea with central, dilated blood-filled cavities, dilated vasculature throughout the ovarian tissue, and rarely extravasated red blood cells that were present free in the ovarian tissue. A clear dose response was apparent.

As a result of the reduced fetal viability noted in the current study at doses >10 mg/kg/day, 10 mg/kg/day dose was determined to be the highest feasible dose from a fetal assessment standpoint. Intrauterine growth and survival and fetal morphology at 5 mg/kg/day were unaffected by test article administration.

Following oral administration of avapritinib to pregnant rats, all animals were exposed to avapritinib in a dose-dependent manner. Exposure was nearly dose proportional in terms of $AUCl_{ast}$ and C_{max} over the 6-fold increase in dose from 5 to 30 mg/kg/day on Gestation Days 6 and 17. There was no notable accumulation of avapritinib in terms of AUC_{last} following repeated administration for 12 days. The TK parameters are summarized in Table 15.

Table 15. Summary of Toxicokinetic Parameters

Dose (mg/kg/day)	AUC_{last} (ng·h/mL)	C_{max} (ng/mL)
Gestation Day 6		
5	12,700	802
10	30,100	2040
20	62,200	4290
30	89,800	5880
Gestation Day 17		
5	19,300	1190
10	41,700	2660
20	83,200	5400
30	110,000	6490

Based on adverse ovarian hemorrhages that likely resulted in an increase in non-gravid rats in the 10, 20, and 30 mg/kg/day groups, a dose level of 5 mg/kg/day was the NOAEL for maternal toxicity. Based on adverse avapritinib related effects on fetal weights, viability (higher mean litter proportions of post-implantation loss and lower mean litter proportions and/or mean numbers of viable fetuses), and/or increases in visceral and skeletal malformations in the 10, 20, and 30 mg/kg/day groups, 5 mg/kg/day was the NOAEL for embryo/fetal development. On Gestation Day 17, the AUC_{last} and C_{max} at the NOAEL of 5 mg/kg/day were 19,300 ng.h/mL and 1190 ng/mL, respectively.

Local Tolerance

Local tolerance was assessed by reviewing the digestive track changes in the GLP-compliant 28-day and 3-month toxicology studies in rats and dogs. No evidence of local gastrointestinal effects occurred in the rat at minimally lethal doses or lower. In the Beagle dog, at lethal exposures diarrhea (without histologic correlate) and esophageal and stomach erosions occurred. Emesis was noted in dogs at the HNSTD and the severely toxic dose levels.

Other toxicity studies

Ten specific impurities were identified in avapritinib drug substance.

In silico safety and *in vitro* genotoxicity assessments were conducted per ICH M7 (R1). The standard in silico structure activity relationship software programs DEREK and SARAH concluded three of the 10 impurities (C458/BLU133737, C613/BLU136700 and D147/ BLU136707) were negative, one was positive (C377/ BLU133735) and the genotoxic potential of 6 impurities (C402/ BLU110570, C614/ BLU110498, C827/ BLU112883, C358/ BLU133730, C359/ BLU133732, and C360/ BLU133733) could not be predicted by QSARs because they were negative for DEREK and equivocal for SARAH, or out of domain for both.

Three of the 10 impurities (C377, C402, and C614) were tested in the GLP-compliant bacterial reverse mutation assays and were demonstrated to be nonmutagenic.

Despite impurity BLU112316 level (0.55%) is above the qualification thresholds defined in ICH Q3A (0.15%), it is qualified up to 0.78% based on the 3-month rat toxicity study. BLU-112316 can be considered non genotoxic based on in vitro (Ames and micronucleus test) and in vivo (rat bone marrow and the liver comet assays) studies.

2.3.5. Ecotoxicity/environmental risk assessment

Summary of main study results

Substance (Avapritinib/Ayvakyt):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	3.6	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	3.6	not B
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surface\ water}$, default or refined (e.g. prevalence, literature)		0.0041 µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)

An environmental risk assessment report of avapritinib has been submitted.

The assessment of environmental risk of avapritinib was based in prevalence data. The predicted environmental concentration (PEC) for avapritinib is 0.0041 µg/L, which is below the trigger value of 0.01 µg/L as given by EMEA (2018). The assessment therefore does not proceed to Phase II – Tier A.

The logDow for avapritinib was determined experimentally using a shake flask method (OECD 107). The logDow value was determined to be 3.6.

2.3.6. Discussion on non-clinical aspects

The primary non-clinical pharmacodynamic data submitted as part of this application support a therapeutic rationale in the proposed indications.

Avapritinib showed broad inhibitory activity against a panel of GIST relevant KIT and PDGFRα mutant enzymes including the KIT exon 11, 17 and 18 mutants, and all PDGFRα exon 18 mutants tested. Avapritinib demonstrated lower binding affinity for the small group of highly related class III receptor tyrosine kinases to which KIT belongs as KIT wild type (K_d= 17 nM), PDGFRα wild type (K_d= 1 nM), PDGFRβ (K_d= 1 nM), CSF1R (K_d= 6 nM) and FLT3 (K_d= 31 nM), but all other 456 human kinases demonstrated K_d greater than 50 nM, demonstrating that avapritinib has limited potential for kinome activity outside of the related class III receptor tyrosine kinases.

In *in vivo* studies avapritinib produced significant antitumor activity, including partial regression at higher doses, in several KIT mutant driven tumours models, with inhibition of KIT mutant activity and downstream signaling markers (Erk and Akt phosphorylation).

Tumour regrowth was observed in the P815 xenograft model before treatment termination. Levels of KIT phosphorylation and genetic analysis of samples from these animals suggest that a secondary KIT exon 14 mutation (human equivalent of T670I) or KIT-independent alternate resistance mechanisms may be responsible for the increased tumour proliferation.

The Applicant was requested to analyse the levels of KIT phosphorylation in samples from P815 xenograft in which tumour regrowth was observed. The analysis showed avapritinib treatment inhibited KIT phosphorylation at more than 70%, which can be associated to antitumor efficacy, based on the PK/PD model. Additionally the genetic analysis of the samples showed the tumour with the lowest degree of KIT phosphorylation inhibition showed a heterozygous T669I mutation, equivalent to the human KIT T670I mutation in exon 14, for which avapritinib has shown a potency shift in a biochemical panel of KIT mutants and may represent an avapritinib resistance mutation. The rest of tumours (16/17) developed uncharacterized KIT mutations or no additional KIT mutations were detectable, suggesting that KIT-independent alternate resistance mechanisms may be responsible for the increased tumour proliferation in those samples. Data for patients with KIT D816Y mutation are limited to two patients with different progression of the disease after treatment with avapritinib. Therefore, no conclusion on the resistance to avapritinib can be reached based on clinical data.

Although inhibition of PDGFRα exon 18 mutants by avapritinib at low nM concentrations has been demonstrated, the effect of avapritinib in PDGFRα driven *in vivo* animal tumour models have not been examined. According to the ICH S9 Q&A document, the lack of *in vivo* characterization can be accepted if *in vitro* systems used for pharmacology studies of anti-tumour activity are demonstrated to generate relevant data. This is considered fulfilled in the non-clinical dossier for avapritinib. Furthermore, the clinical efficacy data for patients with identified PDGFRα D842V mutation are considered to provide proof of concept.

Adverse effects on cardiovascular or respiratory parameters have not been observed in non-clinical *in vitro* or *in vivo* studies. There were however findings in rat studies indicating an avapritinib induced increase in sensitivity to stimuli that are considered as potentially underlying indictors of preconvulsive activity.

Avapritinib demonstrated high oral bioavailability across preclinical species (77-81%). Avapritinib was not a human P-gp substrate and efflux transporters in gut are not expected to limit the oral bioavailability

of avapritinib. In addition, the plasma PK of avapritinib was not altered by pretreatment with pentagastrin or famotidine in dogs, suggesting that the use of gastric pH altering medications such as proton-pump inhibitor is not expected to change the absorption of avapritinib.

Plasma clearance of avapritinib was low in mouse and rat and moderate in dog and monkey. The apparent volume of distribution at steady state was moderate to high in all species, which is indicative of extensive tissue distribution.

Plasma protein binding is high (>99 %) across all species tested and given the small differences between dog and human, there is no need to compare free concentrations between these species. The 2-3 fold higher unbound fraction in rat plasma compared to human plasma may however be relevant to consider in calculation of exposure margins between rat and human.

Avapritinib was distributed widely to most tissues in rats, including the brain. This finding is of relevance to consider in relation to the serious avapritinib associated adverse CNS effects observed in dogs and patients. The distribution of [^{14}C]-avapritinib-related radioactivity in nonpigmented rats was the highest in the lung, adrenal gland, and liver, and was the lowest in uveal tract and adipose. Distribution to target organs for GIST and metastases (stomach wall, small intestine and large intestine) is confirmed. Avapritinib also showed a potential affinity to melanin-containing tissues such as skin and uveal tract in pigmented male Long Evans rats.

Avapritinib metabolism is mainly mediated by CYP3A4 and by CYP2C9 to a minor extent. *In vitro* metabolism of avapritinib in human, rat, and dog hepatocytes occurred via phase I metabolic pathways and was characterized by oxidation, N-demethylation, and oxidative deamination. There were no unique metabolites observed *in vitro* in human hepatocytes or liver microsomes. One of the major human metabolites (M690) was only detected at trace levels in rat and dog, but it is a water-soluble phase 2 conjugation hydroxyl glucuronide and therefore it is expected to pose minimal human safety risk. With respect to the other major human metabolite (M499), the exposure is a mixture of two pharmacologically active enantiomers, BLU111207 (R) and BLU111208 (S). The (S)- and (R)-enantiomers are 3.1- and 10.5-fold less potent against KIT D816V, respectively. Exposure to both enantiomers in rat and dog can be anticipated, but the relative exposure to the S- and R-form has not been determined. This is however not considered to have a significant impact on the calculation of exposure margins since the pharmacological activity of both enantiomers is lower than for the parent compound. Furthermore, the ratio avapritinib/M499 in dog plasma is lower than the ratio in human plasma. In conclusion, all important human avapritinib metabolites are considered qualified from a non-clinical point of view.

Pattern of excretion has only been investigated in rat. In the absence of toxicity to kidneys or renal function in either rat or dog, there are however no signals of species related differences. Consequently, the lack of an excretion study in dog is acceptable. Biliary excretion was the major route of elimination with a minor contribution by active gut secretion in rats.

There is no information available on excretion of avapritinib or metabolites into milk. Adequate information and warnings have been included in section 4.6 of the SmPC.

The adverse effects noted in rats and dogs were generally comparable (including metabolic perturbations, and inanition, reduced hematopoiesis and lymphopoiesis and effects in the gonads and adrenal gland) and likely pharmacologically driven. Key exceptions were that rats (and not dogs) manifested convulsions, potentially secondary to inhibition of Nav 1.2.

The potential for avapritinib to induce seizures in rats was monitorable with EEG and ameliorated with the anti-convulsive drug, diazepam. Despite the risk of convulsions in humans seem low, the risk management plan (RMP) describes two non-serious events of seizure and epilepsy reported in two patients and thus, related findings in rats are described in section 5.3 of the SmPC.

Repeat dose studies in dogs indicated haemorrhage and choroid plexus oedema in the brain at ≥ 0.4 times the human exposure at the clinical dose of 300 mg once daily. Rats manifested convulsions, which was potentially secondary to inhibition of Nav 1.2 at systemic exposures ≥8-fold higher than the exposure in patients at the clinical dose of 300 mg once daily. This effect was not seen in dogs. Since intracranial haemorrhage has been reported as a serious adverse event in patients receiving avapritinib, it is necessary to clarify the mechanism in order to determine potential risk factors and support risk minimisation measures. The applicant has not provided data indicating that the thrombocytosis seen in dogs is related to ICB. In patients with AdvSM, avapritinib-induced thrombocytopenia is considered as a major risk factor for ICB. A similar decrease in thrombocyte number is not detected in dogs. Changes in vascular integrity through altered pericyte function induced by inhibition of PDGFRB, is on the other hand, a more likely cause for brain haemorrhage in dogs than thrombocytosis. This is based on experience from other PDGFR inhibitors, and the observation that level of PDGFRB in mice brain decrease after avapritinib treatment. There are some obvious missing information that would help support this hypothesis, such as data about changes to the pericytes in CNS after avapritinib treatment, and the susceptibility of pericytes in different tissues/organs. This is information that can be acquired in in vivo studies, but based on the 3R's it is not recommended to do animal studies solely to investigate this issue. However, appropriate endpoints should be considered included if in vivo animal studies are initiated for other reasons.

All effects were reversible or reversing with three notable exceptions: effects in the lymphoid system (spleen and thymus), brain and the gonads.

Avapritinib was not genotoxic overall when tested in a panel of *in vitro* and *in vivo* genotoxicity studies.

Avapritinib reduced fetal viability and caused fetal malformations in a study in gravid rats. Adequate information about reproductive toxicity is included in the section 5.3 of the SmPC. Women of childbearing potential should be informed that avapritinib may cause foetal harm. The pregnancy status of women of reproductive potential should be verified prior to initiating avapritinib treatment. Women of childbearing potential should use effective contraception during treatment and for 1 month after the last dose of avapritinib. Patients should be advised to contact their healthcare professional immediately if they become pregnant, or if pregnancy is suspected, while taking avapritinib (see section 4.6 of the SmPC).

The absence of carcinogenicity studies is acceptable. Such studies are not required for a product for an advanced cancer indication.

Avapritinib demonstrated the potential for phototoxicity in vitro and in vivo. According to information in the RMP, treatment related grade 1 or 2 photosensitivity reactions were observed in 3% of patients included in trials with avapritinib. It is noted that due to the potential for phototoxicity identified in non-clinical studies, patients were advised to wear protecting clothing and sunscreen, and to avoid direct sun exposure. Taken together, a potential for phototoxicity has been established. An in vitro phototoxicity study in 3T3 mouse fibroblasts as well as a phototoxicity study in pigmented rats demonstrated that avapritinib has a slight potential for phototoxicity.

Nonclinical *in vitro* and *in vivo* studies could not establish a model or a mechanism for the memory impairment observed in patients.

Since the experimental value of logDow has been determined to be 3.6 for avapritinib, and this value is below the action limit of 4.5, a PBT assessment is not required. Based on log Dow value (3.6 at pH 7) and the PEC (0.0041µg/L) avapritinib is of no concern for the environment.

2.3.7. Conclusion on the non-clinical aspects

Avapritinib is approvable from the non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- ***Tabular overview of clinical studies***

Study Identifier/ Status	Number of Study Centers/Countries	Study Objective(s)	Study Design	Disease Population	Dose/Dosing Regimen	Number of Patients/ Subjects	Type of Report and Location in eCTD
BLU-285-0102 Complete	1 center/ 1 country	Effect of food on bioavailability and PK	Randomized, Single dose, crossover	Healthy Volunteers	Tablet: 2×100 mg fasted or after a high-fat meal	30	Clinical Study Report Module 5.3.1.1
BLU-285-0101 Complete	1 center/ 1 country	Relative bioavailability	Randomized, Single dose, crossover	Healthy Volunteers	Capsule: 2×100 mg Tablet: 1×200 mg	30	Clinical Study Report Module 5.3.1.2
BLU-285-0105 Complete	1 center/ 1 country	Bioequivalence between 400 mg and 100 mg tablets	Single dose, crossover	Healthy Volunteers	Tablet: 4×100 mg Tablet: 1×400 mg	62	Clinical Study Report Module 5.3.1.2
BLU-285-0104 Complete	1 center/ 1 country	PK in the presence and absence of itraconazole or rifampin	2-part, open-label; fixed sequence	Healthy Volunteers	avapritinib 200 mg with itraconazole or rifampin	Part 1: 20 Part 2: 20	Clinical Study Report Module 5.3.2.2
BLU-285-0103 Complete	1 center/ 1 country	Absorption, metabolism and elimination pathways of [^{14}C]avapritinib	Single dose	Healthy Volunteers	Tablet: 3×100 mg Capsule: 1× ~17 mg [14C]avapritinib (~100 µCi)	6	Clinical Study Report Module 5.3.3.1
BLU-285-1303 Ongoing	92 centers/ 17 countries	Efficacy, Safety, PK, and QOL	Phase 3, multi-center, open-label, randomized study of avapritinib vs regorafenib	Unresectable GIST, 3L and 4L	Arm A: avapritinib 300 mg PO QD Arm B: regorafenib 160 mg PO QD for 3 of every 4 weeks	460 (planned)	Study Protocol Module 5.3.5.1

Study Identifier/ Status	Number of Study Centers/Countries	Study Objective(s)	Study Design	Disease Population	Dose/Dosing Regimen	Number of Patients/ Subjects	Type of Report and Location in eCTD
BLU-285-1101 Part 1: complete Part 2: ongoing	17 centers/ 10 countries	Part 1: Safety and dose finding Part 2: Safety and efficacy	Dose escalation and expansion	Unresectable or metastatic GIST with or without a D842V mutation in PGDFRA	Part 1: dose-escalation Part 2: MTD of avapritinib 400 mg QD, changed to 300 mg QD (R2PD)	Part 1: 46 Part 2: 191	Clinical Study Report Module 5.3.5.2
BLU-285-2101 Part 1: complete Part 2: ongoing	11 centers/ 2 countries	Safety, dose finding, PK/PD, and QOL	Phase 1, single-arm, dose escalation	AdvSM	Part 1: dose-escalation Part 2. avapritinib 300 mg QD; and avapritinib 200mg QD	Part 1: 32 Part 2: ~55 planned	Study Protocol Module 5.3.5.2
BLU-285-1002 Complete	3 center/ 1 country	To characterize the natural history of disease in patients with PDGFRA D842-driven GIST who had been previously treated with a kinase inhibitor	Multicenter, retrospective, observational	Patients with PDGFRA D842-driven GIST who had previously treated with a kinase inhibitor	N/A	22	Clinical Study Report Module 5.3.5.4

Abbreviations: AdvSM = advanced systemic mastocytosis; GIST = gastrointestinal stromal tumor; MTD = maximum tolerated dose; PDGFRA = platelet-derived growth factor receptor alpha; PD = pharmacodynamics; PK = pharmacokinetics; L = line of therapy; PO = orally (by mouth); QD = once daily; QOL = quality of life; RP2D = recommended phase 2 dose

In addition to the listed studies, there is an ongoing Phase III study (Study BLU-285-1303, the VOYAGER study) where avapritinib is compared to regorafenib in patients with GIST who have progressed on imatinib and sunitinib.

2.4.2. Pharmacokinetics

Analytical Methods

Validated LC/MS-MS assays were used in all clinical studies for determining concentrations of avapritinib (BLU-285) and the constituent enantiomers BLU111207 and BLU111208 of the pharmacologically active metabolite M499 (BLU136707) in human plasma. All bioanalytical methods were validated successfully. The LTS does cover the maximum storage period for avapritinib, although the LTS of 558 days does not cover the maximum storage period of 765 days for the enantiomers. The applicant should provide in the Q1 2021 the LTS to cover the maximum storage period of 765 days for the enantiomers (See section on post authorization measures including recommendations).

The in-study validation shows acceptable calibration standards and QCs and the reasons for the re-analysis of samples are considered acceptable.

The incurred sample re-analysis was performed for BLU-285 in all clinical studies and for BLU111207 and BLU111208 in study BLU-285-1101. The ISR results were acceptable since at least 66.7% of the samples re-analysed were within the acceptance range (± 20%) for all analytes in all studies.

Absorption

- **Bioavailability**

Across the dose range of single doses of 30 to 400 mg in patients with GIST in Study BLU-285-1101, avapritinib was rapidly absorbed following oral administration in patients with GIST, with a median Tmax of 2.0 to 4.1 hours after single-dose administration.

After a single oral dose of approximately 310 mg (100 µCi) [14C]avapritinib in healthy subjects, the mean radioactive dose recovery was 88.2% (70.3% feces and 17.9% urine). Metabolic profiling of pooled fecal homogenates (representing > 90% of fecal excretion) indicated that 59.6% of the radioactive dose was recovered in feces (11.0% unchanged avapritinib). Subtracting the fecal excretion portion of avapritinib (11.0%) from the overall recovered dose (59.6%), and taking into account (adding) the excretion of unchanged avapritinib in urine (14.4%), suggests that at least 70% of the total administered dose of avapritinib is absorbed. This conservative estimate for the degree of absorption indicates that avapritinib exhibits moderate-to-high intestinal permeability.

- **Bioequivalence**

Table 8: Summary and Statistical Comparison of Avapritinib Pharmacokinetic Parameters After Administration of Avapritinib as 1 × 400 mg Tablet or 4 × 100 mg Tablets Under Fasted Conditions (Study BLU-285-0105)

Parameter	GeoMean (GeoMean %CV) [a]		Geometric Mean Ratio (%)	90% Confidence Interval (Lower-Upper)
	1 × 400 mg Avapritinib Tablet (Test)	4 × 100 mg Avapritinib Tablets (Reference)		
N	62	62	-	-
C_{max} (ng/mL)	418.8 (58.7)	397.5 (46.7)	105.34	93.25-119.00
T_{max} (h) [b]	4.001 (1.00-36.03)	3.650 (1.50-36.04)	-	-
AUC_{0-24} (h•ng/mL)	6531 (50.2)	6563 (40.0)	-	-
AUC_{0-t} (h•ng/mL)	22970 (44.6)	23680 (37.8)	97.00	90.01-104.53
$AUC_{0-\infty}$ (h•ng/mL)	23910 (45.8)	24710 (39.0)	96.86	89.77-104.52
$\%AUC_{extrap}$ (%)	4.021 (90.5)	4.132 (83.6)	-	-
$t_{1/2}$ (h)	54.661 (14.9298)	53.914 (14.6959)	-	-
CL/F (L/h)	16.73 (45.8)	16.19 (39.0)	-	-
V_z/F (L)	1274 (36.6)	1218 (28.7)	-	-

Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 hours postdose; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to time of last measurable concentration above the lower limit of quantitation; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time 0 to infinity; $\%AUC_{extrap}$ = percent of $AUC_{0-\infty}$ extrapolated; CL/F = apparent oral clearance; C_{max} = maximum plasma concentration; %CV = percent coefficient of variation; GeoMean = geometric mean; N = number of subjects in pharmacokinetic population; $t_{1/2}$ = apparent terminal elimination half-life; T_{max} = time of maximal plasma concentration; V_z/F = apparent volume of distribution.
[a] Median (minimum-maximum) for T_{max} and arithmetic mean (standard deviation) for $t_{1/2}$.
[b] Treatment difference: 0.507 h; p = 0.067 Wilcoxon signed-rank test.
Source: CSR BLU-285-0105, Table 11-2, Table 11-3, Table 11-4.

- **Influence of food**

Avapritinib Cmax and AUCinf were increased by 59% and 27%, respectively, in healthy subjects administered avapritinib after a high fat meal (approximately 909 calories, 58 grams carbohydrate, 56 grams fat and 43 grams protein) compared to the Cmax and AUCinf after overnight fasting.

Table 9: Summary and Statistical Comparison of Avapritinib Pharmacokinetic Parameters in Plasma After Administration of Avapritinib as 2 × 100 mg Tablets Under Fasted and Fed Conditions (Study BLU-285-0102)

Parameter	GeoMean (GeoMean %CV) [a]		Geometric Mean Ratio (%)	90% Confidence Interval (Lower-Upper)
	2 × 100 mg Avapritinib Tablets, Fed (Test)	2 × 100 mg Avapritinib Tablets, Fasted (Reference)		
N	30	30	-	-
C_{max} (ng/mL)	311.3 (19.6)	195.2 (42.9)	159.45	138.09-184.11
T_{max} (h) [b]	5.502 (2.00-10.00)	4.375 (2.00-24.16)	-	-
AUC_{0-24} (h•ng/mL)	4729 (19.6)	3527 (39.4)	-	-
AUC_{0-t} (h•ng/mL)	13890 (29.9)	10910 (37.7)	127.32	115.53-140.31
$AUC_{0-\infty}$ (h•ng/mL)	14030 (32.2)	10840 (36.9)	129.20	114.38-145.95
$\%AUC_{extrap}$ (%)	7.042 (74.8)	7.102 (100.6)	-	-
$t_{1/2}$ (h)	48.748 (12.7734)	49.532 (15.2472)	-	-
CL/F (L/h)	14.26 (32.2)	18.44 (36.9)	-	-
Vz/F (L)	970.2 (18.3)	1258 (37.9)	-	-
MRT (h)	62.866 (26.7)	65.079 (31.9)	-	-

Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 hours postdose; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to time of last measurable concentration above the lower limit of quantitation; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time 0 to infinity; $\%AUC_{extrap}$ = percent of $AUC_{0-\infty}$ extrapolated; CL/F = apparent total clearance; C_{max} = maximum plasma concentration; %CV = percent coefficient of variation; GeoMean = geometric mean; MRT = mean residence time; N = number of subjects in pharmacokinetic population; $t_{1/2}$ = apparent terminal elimination half-life; T_{max} = time of maximal plasma concentration; V_z/F = apparent volume of distribution.

[a] Median (minimum-maximum) for T_{max} and arithmetic mean (standard deviation) for $t_{1/2}$.

[b] Treatment difference: -0.374 h; p = 0.6225 Wilcoxon signed-rank test.

Source: CSR BLU-285-0102, Table 11-2, Table 11-3, and Table 11-4.

Distribution

Extensive in vitro plasma protein binding of avapritinib was observed in human plasma (98.8% at nominal concentrations of 1 and 10 µM). Plasma protein binding was comparable in human plasma from healthy volunteers and subjects with severe renal impairment. No concentration-dependence in binding was observed. Avapritinib was minimally associated with human red blood cells in vitro; the human blood-to-plasma ratio was 0.95. In patients with GIST, following a single 300 mg oral dose of avapritinib, the geometric mean apparent volume of distribution (Vz/F) of avapritinib was 17 L/kg, indicating extensive distribution into tissues from plasma.

Elimination

- **Excretion**

After single-dose administration of avapritinib across the dose range of 30 to 400 mg in patients with GIST, the mean t1/2 was long, ranging from 32 to 57 hours. The geometric mean CL/F ranged between 17.2 and 28.6 L/h after the single-dose administration of avapritinib and between 17.3 to 24.6 L/h after repeat-dose administration, indicating that avapritinib is a low clearance drug. Following oral administration of avapritinib 300 mg once daily, the steady state geometric mean apparent oral clearance (CL/F) was 19.5 L/h.

Following a single oral dose of approximately 310 mg (~100 µCi) [14C]avapritinib to healthy subjects, 70% of the radioactive dose was recovered in faeces and 18% excreted in urine. Unchanged avapritinib accounted for 11% and 0.23% of the administered radioactive dose excreted in faeces and urine, respectively (see section 5.2 of the SmPC).

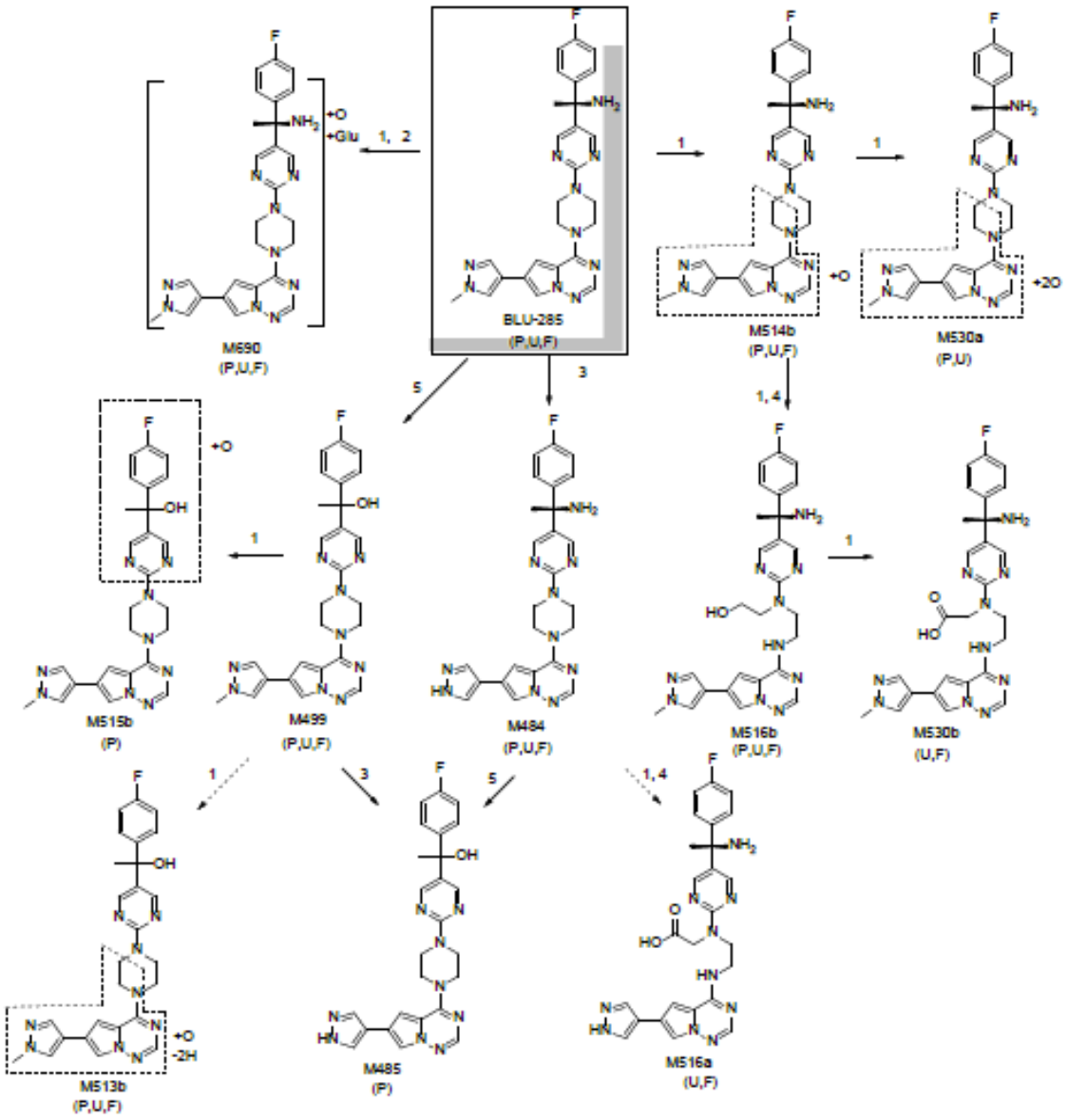
- **Metabolism**

Table 17: Percentage of Metabolites in Different Matrices Following Single Dose Oral Administration of ~310 mg (~100 µCi) [^{14}C]avapritinib to Healthy Male Subjects (Study BLU-285-0103)

Metabolite Identifier	Proposed Biotransformation	Mean % Radioactivity in Pooled Matrix		
		Plasma (0-24 h)	Urine (0-288 h) [a]	Feces (0-384 h) [b]
Avapritinib	Parent drug	49.4	1.40	17.5
UM1	-	-	12.4	22.3
M530a	Oxidation	Trace	40.8	-
M514b	Oxidation	Trace	7.71	Trace
M516a	Oxidation, *N*-dealkylation	-	Trace	2.72
M516b	Oxidation, *N*-dealkylation	Trace	24.6	8.52
M530b	Oxidation, *N*-dealkylation	-	Trace	16.8
M513b	Oxidative deamination, oxidation	Trace	0.86	12.4
M484	*N*-demethylation	Trace	Trace	Trace
M690	Oxidation, glucuronidation	34.8	1.40	10.8
M515	Oxidative deamination, oxidation	-	-	-
M485	Oxidative deamination, *N*-demethylation	Trace	-	-
M499	Oxidative deamination	14.1	-	1.61
UM3	-	-	-	1.75

Abbreviations = UM1 = Unknown 1; UM3 = Unknown 3.
[a] Pooled sample that represented > 90% of excreted radioactivity in urine (or about 14% of the administered dose).
[b] Pooled sample that represented > 90% of excreted radioactivity in feces (or about 60% of the administered dose).
Note: Retention times refer to high-performance liquid chromatography analyses.
Source: BLU-R7561, Table 8, Table 10, and Table 11.

Figure 25: Proposed Biotransformation Pathways of Avapritinib in Humans



Abbreviations: BLU-285 = avapritinib.
Note: See Table 17 for description of metabolites.
Source: BLU-R7561, Figure 10.

Pharmacokinetics of metabolites

Following administration of single oral doses of avapritinib ranging from 30 to 400 mg, BLU111207 and BLU111208 formation was rapid, with quantifiable concentrations at approximately 0.5 hours postdose. The median Tmax for BLU111207 and BLU111208 ranged from 3.0 to 24 hours and 3.0 to 16 hours postdose, respectively, across dose levels. The mean apparent terminal elimination half-life (t1/2) of BLU111207 and BLU111208 ranged from 36 to 65 hours and 37 to 90 hours postdose, respectively. Following repeat QD dosing of avapritinib 30 to 400 mg, the observed geometric mean accumulation ratio for BLU111207 and BLU111208 ranged from 3.1 to 14.3 and 4.4 to 15.7, respectively.

Table 11: Analysis of Dose Proportionality for BLU111207 and BLU111208 Pharmacokinetic Parameters Following Administration of Avapritinib 30 to 400 mg in Patients With GIST (Study BLU-285-1101)

Analyte	Cycle	Parameter	β_{est}	90% CI	Test Interval	Conclusion
BLU111207	C1D1	C_{max}	1.02	0.857–1.18	0.732 - 1.27	Proportional
		AUC_{0-24}	1.09	0.916–1.26	0.732 - 1.27	Proportional
	C1D15	$C_{max,ss}$	1.06	0.919–1.19	0.732 - 1.27	Proportional
		$AUC_{0-\tau,ss}$	1.03	0.801–1.25	0.732 - 1.27	Proportional
BLU111208	C1D1	C_{max}	1.01	0.857–1.16	0.732 - 1.27	Proportional
		AUC_{0-24}	1.09	0.926–1.26	0.732 - 1.27	Proportional
	C1D15	$C_{max,ss}$	1.00	0.868–1.12	0.732 - 1.27	Proportional
		$AUC_{0-\tau,ss}$	0.97	0.784–1.16	0.732 - 1.27	Proportional

Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 hours postdose; $AUC_{0-\tau,ss}$ = area under the plasma concentration-time curve over the dosing interval (τ = 24 hours) at steady state; β_{est} = proportionality constant; C1D1 = Cycle 1 Day 1; C1D15 = Cycle 1 Day 15; CI = confidence interval; C_{max} = maximum plasma concentration; $C_{max,ss}$ = maximum plasma concentration at steady state.
Source: NCA PK Report BLUE201803, Table 119, Table 120, Table 121, and Table 122.

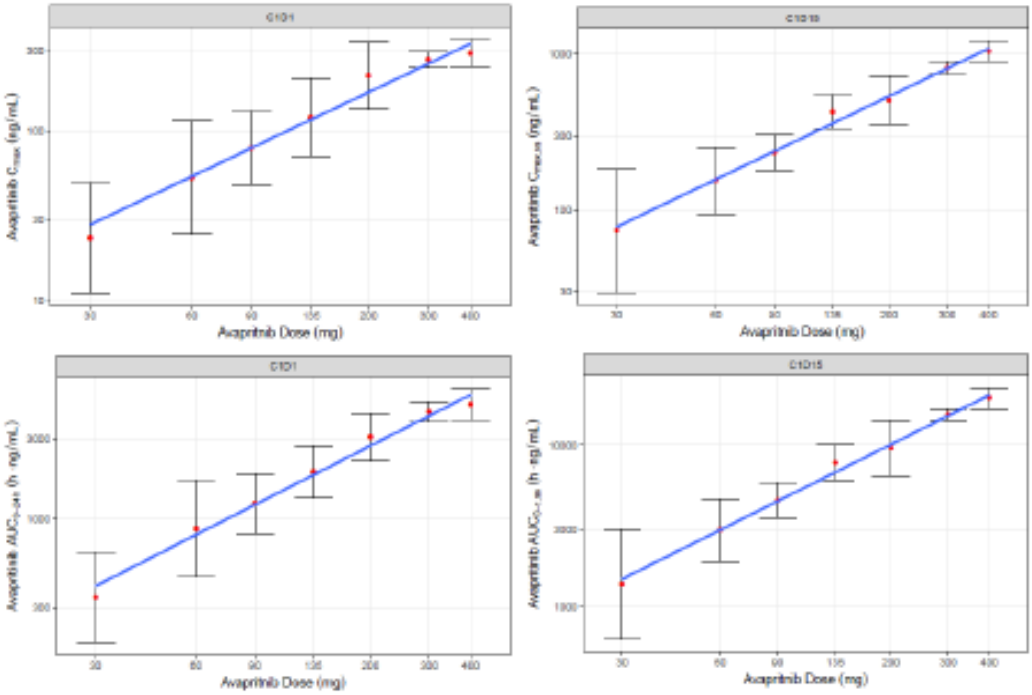
Table 12: Summary of BLU111207 and BLU111208 Metabolite to Parent Ratios Following Single and Repeat Dose Administration of Avapritinib 300 mg in Patients With GIST (Study BLU-285-1101)

	Cycle 1 Day 1				Cycle 1 Day 15			
		GeoMean AUC_{0-24} (h•ng/mL)				GeoMean $AUC_{0-\tau,ss}$ (h•ng/mL)		
Metabolite	N	Avapritinib	Metabolite	Metabolite to Parent Ratio (%)	N	Avapritinib	Metabolite	Metabolite to Parent Ratio (%)
BLU111207	27	4370	851	18.8	55	16000	5640	34.9
BLU111208	25	4390	1020	22.9	56	16100	6830	42.1

Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 hours postdose; $AUC_{0-\tau,ss}$ = area under the plasma concentration-time curve over the dosing interval (τ = 24 hours) at steady state
GeoMean = geometric mean; GIST = gastrointestinal stromal tumor; N = number of patients in the pharmacokinetic population with an observation.
Source: NCA PK Report BLUE201803, Table 7, Table 8, Table 11, and Table 12.

Dose proportionality and time dependencies

Figure 4: Dose Proportionality of Avapritinib Systemic Exposure Following Administration of Avapritinib in Patients With GIST (Study BLU-285-1101)



Abbreviations: $AUC_{0\text{-}24}$ = area under the plasma concentration-time curve from time 0 to 24 hours postdose; $AUC_{0\text{-}\tau,ss}$ = area under the plasma concentration-time curve over the dosing interval (τ = 24 hours) at steady state; C1D1 = Cycle 1 Day 1; C1D15 = Cycle 1 Day 15; $C_{max,ss}$ = maximum plasma concentration at steady state; C_{max} = maximum plasma concentration; GIST = gastrointestinal stromal tumor.
Note: Both axes are on a log scale. Red dot = geometric mean of exposure metric (C1D1: C_{max} or $AUC_{0\text{-}24h}$; C1D15: $C_{max,ss}$ or $AUC_{0\text{-}\tau,ss}$), error bars = 95% CI, blue line = line of best fit.
Source: NCA PK Report BLUE201803, Figure 6 and Figure 7.

Table 5: Analysis of Dose Proportionality for Avapritinib Pharmacokinetic Parameters Following Administration of Avapritinib 30 to 400 mg in Patients With GIST (Study BLU-285-1101)

Cycle	Parameter	β_{est}	90% CI	Test Interval	Conclusion
C1D1	C_{max}	0.95	0.825–1.08	0.732 - 1.27	Proportional
	$AUC_{0\text{-}24}$	1.00	0.892–1.11	0.732 - 1.27	Proportional
C1D15	$C_{max,ss}$	1.02	0.913–1.12	0.732 - 1.27	Proportional
	$AUC_{0\text{-}\tau,ss}$	1.01	0.915–1.11	0.732 - 1.27	Proportional

Abbreviations: $AUC_{0\text{-}24}$ = area under the plasma concentration-time curve from time 0 to 24 hours postdose; $AUC_{0\text{-}\tau,ss}$ = area under the plasma concentration-time curve over the dosing interval (τ = 24 hours) at steady state; β_{est} = proportionality constant; C1D1 = Cycle 1 Day 1; C1D15 = Cycle 1 Day 15; CI = confidence interval; C_{max} = maximum plasma concentration; $C_{max,ss}$ = maximum plasma concentration at steady state.
Source: NCA PK Report BLUE201803, Tables 117 and Table 118.

Table 3: Summary of Avapritinib Pharmacokinetics on Cycle 1 Day 1 Following Single-dose Administration of Avapritinib in Patients With GIST (Study BLU-285-1101)

Parameter (Units)	Statistic	Avapritinib Dose						
		30 mg	60 mg	90 mg	135 mg	200 mg	300 mg	400 mg
C_{max} (ng/mL)	N	6	5	6	6	6	113	50
	Mean (SD)	28.8 (19.4)	62.3 (39.0)	86.5 (35.5)	132 (52.8)	229 (88.7)	305 (153)	343 (181)
	GeoMean (%CV)	23.4 (82.2)	53.2 (68.7)	79.4 (50.3)	121 (53.8)	213 (45.6)	264 (62.1)	288 (72.9)
T_{max} (h)	N	6	5	6	6	6	113	50
	Median (Min – Max)	4.1 (3.9 – 8.0)	4.0 (2.0 – 8.1)	2.0 (2.0 – 23.8)	4.0 (2.0 – 8.0)	3.0 (2.0 – 8.0)	4.0 (1.0 – 23.5)	4.0 (2.0 – 24.0)
C_{24} (ng/mL)	N	6	5	6	6	6	36	19
	Mean (SD)	14.0 (7.46)	34.6 (13.0)	44.2 (7.6)	70.3 (18.7)	98.8 (19.1)	134 (49.4)	185 (80.2)
	GeoMean (%CV)	12.6 (53.5)	32.8 (37.6)	43.6 (17.1)	68.1 (29.2)	97.3 (19.8)	124 (44.6)	166 (55.1)
AUC_{0-24} (h•ng/mL)	N	6	5	6	6	6	36	19
	Mean (SD)	399 (214)	993 (546)	1310 (467)	1980 (553)	3170 (918)	4510 (1760)	5310 (2080)
	GeoMean (%CV)	348 (64.8)	883 (57.6)	1240 (40.1)	1900 (34.1)	3060 (31.8)	4140 (47.4)	4840 (50.3)
CL/F (L/h)	N	3	4	5	6	6	23	8
	Mean (SD)	18.7 (9.9)	19.2 (6.6)	19.6 (7.0)	22.9 (6.6)	23.3 (8.6)	31.5 (15.2)	29.9 (20.1)
	GeoMean (%CV)	17.2 (52.3)	18.5 (32.7)	18.4 (44.0)	22.2 (29.6)	22.0 (38.6)	28.6 (46.4)	24.6 (77.6)
V_z/F (L)	N	3	4	5	6	6	23	8
	Mean (SD)	1270 (491)	1310 (772)	1320 (353)	1410 (513)	1320 (314)	1310 (676)	1340 (597)
	GeoMean (%CV)	1200 (44.3)	1150 (64.9)	1270 (34.1)	1350 (31.1)	1290 (22.3)	1200 (43.3)	1240 (42.1)
$t_{1/2}$ (h)	N	3	4	5	6	6	23	8
	Mean (SD)	51.0 (20.9)	47.8 (28.5)	56.7 (38.4)	43.8 (13.1)	43.6 (16.8)	32.1 (15.6)	43.5 (28.4)
	GeoMean (%CV)	48.5 (39.4)	43.0 (53.1)	47.7 (73.1)	42.1 (31.4)	40.8 (43.2)	29.0 (48.1)	35.1 (84.2)

Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 hours postdose; C_{24} = plasma concentration at 24 hours postdose; CL/F = apparent oral clearance, unadjusted for bioavailability; C_{max} = maximum plasma concentration; %CV = percent coefficient of variation; GeoMean = geometric mean; GIST = gastrointestinal stromal tumor; Max = maximum; Min = minimum; N = number of patients in the pharmacokinetic population with an observation; SD = standard deviation; $t_{1/2}$ = terminal elimination half-life; T_{max} = time of maximum plasma concentration; V_z/F = apparent volume of distribution during the terminal phase after oral administration.

Note: The difference in the N (number of observations), if any, across the pharmacokinetic parameters in a given cohort is due to insufficient data to estimate the particular pharmacokinetic parameter.

Source: NCA PK Report BLUE201803, Table 3.

Table 4: Summary of Avapritinib Pharmacokinetics on Cycle 1 Day 15 Following Repeat-dose Administration of Avapritinib at Steady State in Patients With GIST (Study BLU-285-1101)

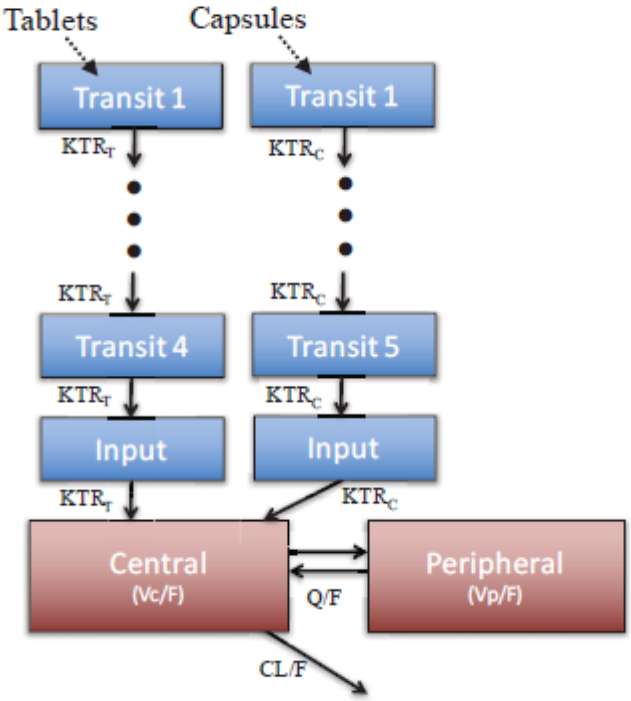
Parameter (Units)	Statistic	Avapritinib Dose						
		30 mg	60 mg	90 mg	135 mg	200 mg	300 mg	400 mg
$C_{max,ss}$ (ng/mL)	N	6	6	6	6	6	110	38
	Mean (SD)	91.7 (50.6)	169 (79.0)	239 (62.4)	435 (115)	526 (161)	905 (402)	1140 (469)
	GeoMean (%CV)	73.5 (106)	154 (50.0)	233 (25.4)	424 (23.9)	503 (34.7)	813 (52.2)	1040 (47.8)
T_{max} (h)	N	6	6	6	6	6	110	38
	Median (Min – Max)	3.0 (2.0 – 7.9)	7.9 (4.0 – 8.0)	4.0 (2.1 – 4.5)	2.0 (2.0 – 4.0)	4.0 (2.0 –8.0)	4.0 (0.0 – 8.2)	4.0 (0.5 – 8.0)
$C_{24,ss}$ (ng/mL)	N	6	6	6	6	6	110	38
	Mean (SD)	58.9 (35.3)	112 (51.2)	161 (44.6)	283 (90.6)	334 (118)	593 (263)	760 (343)
	GeoMean (%CV)	48.3 (89.1)	102 (49.9)	156 (31.7)	272 (30.5)	313 (43.2)	535 (50.1)	688 (49.2)
$AUC_{0-\tau,ss}$ (h*ng/mL)	N	6	6	6	6	6	110	38
	Mean (SD)	1660 (992)	3210 (1360)	4660 (1080)	8030 (2160)	10100 (3270)	16900 (7230)	21300 (9250)
	GeoMean (%CV)	1370 (86.4)	2980 (44.7)	4560 (24.2)	7820 (24.9)	9550 (38.5)	15400 (48.3)	19400 (46.7)
CL_{ss}/F (L/h)	N	6	6	6	6	6	110	38
	Mean (SD)	28.4 (25.4)	21.7 (8.7)	20.2 (4.9)	17.7 (4.0)	22.3 (9.43)	21.8 (12.0)	22.8 (11.7)
	GeoMean (%CV)	21.9 (86.4)	20.2 (44.7)	19.8 (24.2)	17.3 (24.9)	21.0 (38.5)	19.5 (48.3)	20.6 (46.7)
Accumul-ation Ratio	N	6	5	6	6	6	34	15
	Mean (SD)	4.47 (2.10)	4.24 (2.48)	4.02 (1.65)	4.38 (1.78)	3.24 (0.95)	3.82 (1.26)	5.03 (2.13)
	GeoMean (%CV)	3.94 (66.8)	3.66 (67.6)	3.68 (51.3)	4.12 (38.0)	3.12 (31.4)	3.63 (32.5)	4.58 (49.5)

Abbreviations: $AUC_{0-\tau,ss}$ = area under the plasma concentration-time curve over the dosing interval (τ = 24 hours) at steady state; $C_{24,ss}$ = plasma concentration at 24 hours postdose at steady state; CL_{ss}/F = apparent oral clearance at steady state, unadjusted for bioavailability; $C_{max,ss}$ = maximum plasma concentration at steady state; %CV = percent coefficient of variation; GeoMean = geometric mean; GIST = gastrointestinal stromal tumor; Max = maximum; Min = minimum; N = number of patients in the pharmacokinetic population with an observation; SD = standard deviation; T_{max} = time of maximal plasma concentration.
Note: The difference in the N (number of observations), if any, across the pharmacokinetic parameters in a given cohort is due to insufficient data to estimate the particular pharmacokinetic parameter.
Source: NCA PK Report BLUE201803, Table 4.

Pharmacokinetics in target population

Base Population PK model in healthy volunteers

Schematic of the Base Population PK Model



KTR_T – absorption transit rate constant for tablets; KTR_C – absorption transit rate constant for capsules; V_c/F – apparent volume of distribution for the central compartment; Q/F – apparent inter-compartmental clearance; CL/F – apparent oral clearance; V_p/F – apparent volume of distribution for the peripheral compartment.

Base Population PK model in GIST patients

Data from 3 Phase 1 studies in healthy volunteers and 1 Phase 1 study in patients with GIST were included in the creation of the final dataset.

Parameter Estimates for the Base Population PK Model

Parameter Name	Estimated Value (%RSE)
Apparent Clearance (CL/F, L/h)	16.8 (4.1)
Apparent Central Volume of Distribution (V_c/F, L)	1070 (4.4)
Apparent Peripheral Volume of Distribution (V_p/F, L)	209 (10.0)
Apparent Inter-compartmental Clearance (Q/F, L/h)	9.74 (23.2)
Rate of Transit Absorption for Tablets (KTR_T, 1/h)	3.27 (2.9)
Rate of Transit Absorption for Capsules (KTR_C, 1/h)	3.92 (5.4)
Between Subject Variability for CL/F (%)	49.1 (7.0)
Between Subject Variability for V_c/F (%)	48 (8.4)
Correlation between CL/F-V_c/F (%)	79.2 (8.5)
Between Subject Variability for Rate of Transit Absorption (%)	22.5 (18.5)
Between-occasion Variability for Bioavailability (%)	29.2 (8.4)
Between-occasion Variability for Rate of Transit Absorption (%)	27.3 (8.8)
Residual Unexplained Variability for Study BLU-285-0101/BLU-285-0102 (Proportional) (%)	16.9 (6.4)
Residual Unexplained Variability for Study BLU-285-0105 (Proportional) (%)	18.4 (4.6)

RSE = relative standard error.

Covariate analysis

Lean body weight (LBW) was included as a covariate on Vc/F. The expression in the final population PK model is shown below:

$$V_c/F = 1020 \cdot (LBW/56.8)^{0.37}$$

where 0.37 was the estimated covariate effect of LBW on CL/F (note that the median LBW in the analysis population was 56.8 kg).

Concomitant PPI use was included as a covariate on F, as shown below:

$$F = GISTF \cdot PPIF$$

where GISTF was the covariate effect of being a GIST patient on F (see Section 3.5.1.3), and PPIF is the estimated covariate effect of concomitant PPI use, where it is 1 if there was no concomitant PPI use (0 to less than 5 consecutive days of PPI use prior to the PK sample), and 0.769 if there was equal or more than 5 consecutive days of PPI use prior to the PK sample.

Patient population was included as a covariate on F, as shown in Equation 2, where GISTF was set to 1 for healthy volunteers, and estimated to be 0.846 for patients with GIST.

Formulation of avapritinib was included as a covariate on KTR, as shown in the equation below:

$$KTR = 3.2 \text{ (if Tablets) or } 3.73 \text{ (if Capsules)}$$

where KTR was dependent upon formulation i.e. tablets or capsules.

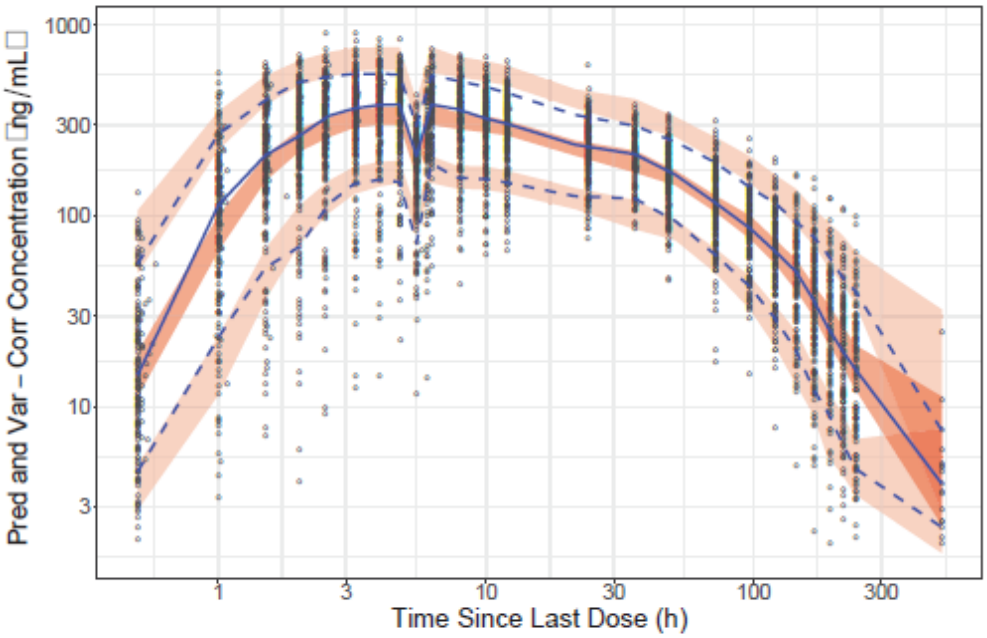
Evaluation of the final Population PK model

Parameter Estimates for the Final Population PK Model

Parameter Name	Estimated Value (%RSE)
Apparent Clearance (CL/F, L/h)	16.1 (3.4)
Apparent Central Volume of Distribution (V_c/F, L)	1020 (2.5)
Covariate Effect of LBW on V_c/F	0.37 (30.8)
Apparent Peripheral Volume of Distribution (V_p/F, L)	226 (8.5)
Apparent Inter-compartmental Clearance (Q/F, L/h)	12.2 (17.9)
Rate of Transit Absorption for Tablets (KTR_T, 1/h)	3.2 (1.3)
Rate of Transit Absorption for Capsules (KTR_C, 1/h)	3.73 (2.6)
Relative Bioavailability for GIST Patients (Fold)	0.846 (3.6)
Covariate Effect of PPI Comedication on F	0.769 (4.4)
Between Subject Variability for CL/F (%)	44.2 (5.1)
Between Subject Variability for V_c/F (%)	46.6 (6.6)
Correlation between CL/F-V_c/F (%)	69.4 (7.3)
Between Subject Variability for Rate of Transit Absorption (%)	26.9 (15.6)
Between-occasion Variability for Bioavailability (%)	24.6 (5.5)
Between-occasion Variability for Rate of Transit Absorption (%)	30.6 (9.4)
Residual Unexplained Variability for Study BLU-285-0101/BLU-285-0102 (Proportional) (%)	17 (6.4)
Residual Unexplained Variability for Study BLU-285-0105 (Proportional) (%)	18.4 (4.5)
Residual Unexplained Variability for Study BLU-285-1101 (Proportional) (%)	26.3 (4.0)

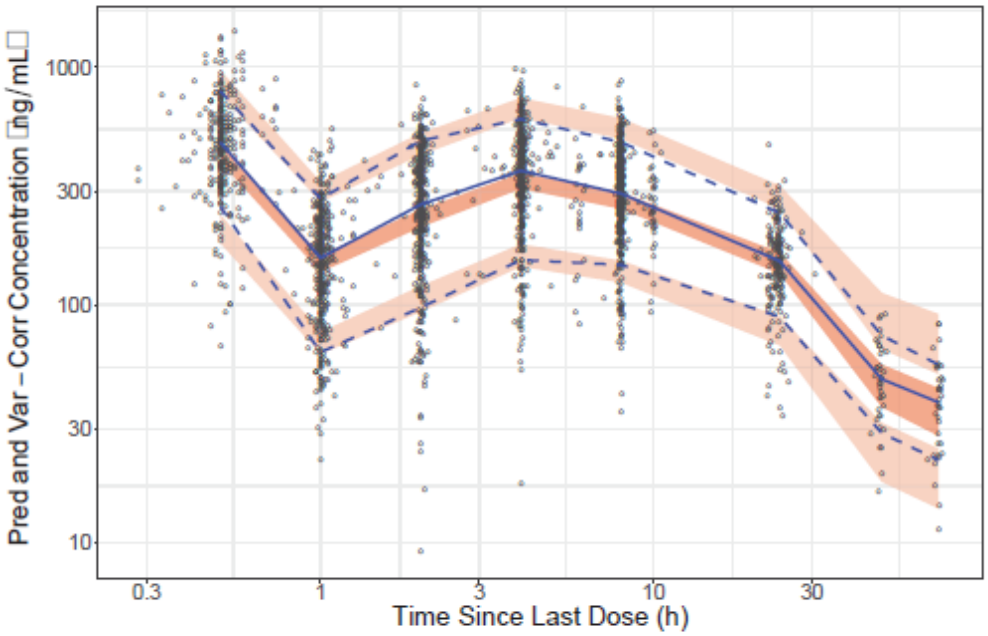
RSE = relative standard error.

pvcVPC for the Final Population PK Model (Healthy Volunteers)



Open circles = individual observed, dashed blue lines = observed 10th & 90th percentiles of the observed data, solid blue line = observed median concentration, shaded red area = 95% prediction interval around the model predicted 10th, 50th, & 90th percentile. Note: Log-log scale is used.

pvcVPC for the Final Population PK Model (Patients with GIST)



Open circles = individual observed, dashed blue lines = observed 10th & 90th percentiles of the observed data, solid blue line = observed median concentration, shaded red area = 95% prediction interval around the model predicted 10th, 50th, & 90th percentile. Note: Log-log scale is used.

Tumour kinetic model

Study*	Study Description	Initial Dose‡	Sampling Time
BLU-285-1101	Phase 1, open-label, first-in-human study to evaluate the safety, tolerability, PK, PD, and anti-tumor activity of avapritinib in patients with gastrointestinal stromal tumors (GIST)	30 mg (n=3) 60 mg (n=3) 90 mg (n=4) 135 mg (n=4) 200 mg (n=3) 300 mg (n=28) 400 mg (n=10)	**PK:** **Dose-Escalation (Part 1)** Lead-in: Predose, 0.5, 1, 2, 4, 8, 10, 24, 48, 72 h C1D15: Predose, 0.5, 1, 2, 4, 8 h C2-4: Predose **Dose-Expansion (Part 2)** *Intensive Sampling Schedule* C1: Predose, 0.5, 1, 2, 4, 8, 24 h C1D15: Predose, 0.5, 1, 2, 4, 8 h C2-4: Predose *Sparse Sampling Schedule* C1D15: Predose, 1, 4, 6-8 h C2-4: Predose **Tumor:** Tumor data were collected at baseline and then every 8 weeks until disease progression or death

* Only GIST patients with PDGFRα D842V mutation positive (n=55) were included in the tumor model development.
‡ One patient who received avapritinib 600 mg was not included in the analysis.

Tumour growth model development

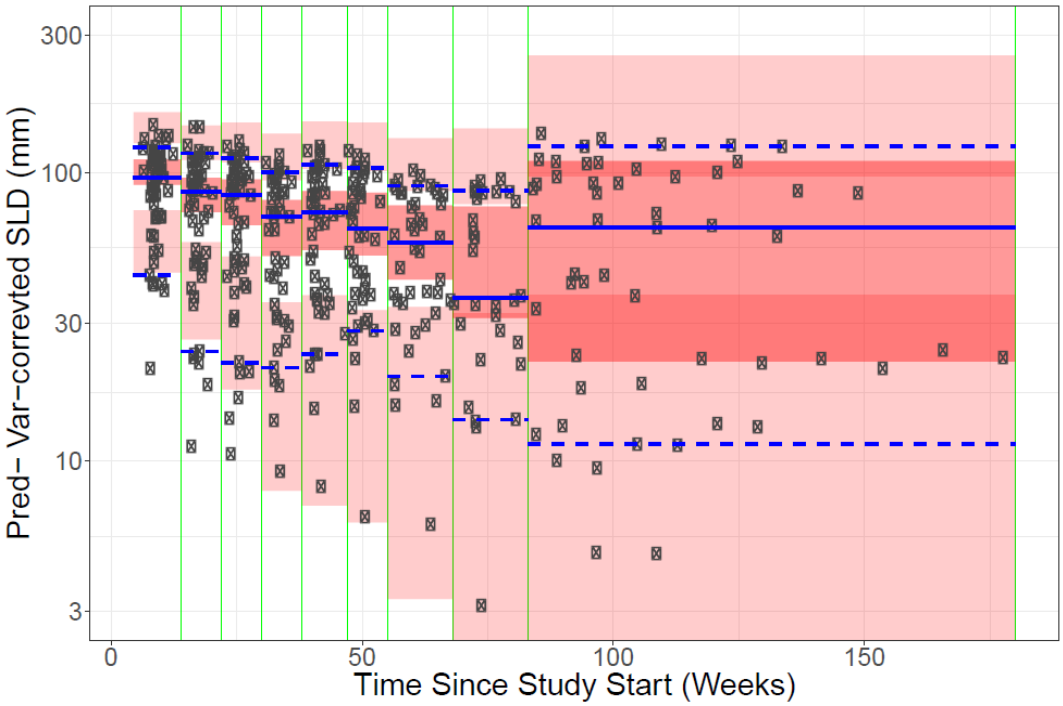
Tumor size was modeled using the SLD of all target lesions, with data measured across study BLU-285-1101 at baseline (before start the treatment), and thereafter every 6 – 8 weeks during treatment. The TGI model was used to describe tumor growth and is shown by the following differential equation

$$\frac{dSLD}{dt} = k_{growth} \cdot SLD(t) - k_{kill} \cdot Exposure \cdot e^{-\lambda \cdot t} \cdot SLD(t)$$

where SLD(t) is the tumor SLD at time t. The TGI model assumes that, in the absence of treatment, tumor SLD increases exponentially according to a disease-specific first-order growth rate constant (k_{growth}). Drug-related tumor shrinkage is accounted for by drug exposure and a drug-specific kill rate constant (k_{kill}). A decrease in drug effect is described by a time-dependent mono-exponential function, the resistance rate (λ) parameter. The parameter is assumed to start at the start of treatment and to be independent of the dosing schedule and drug exposure.

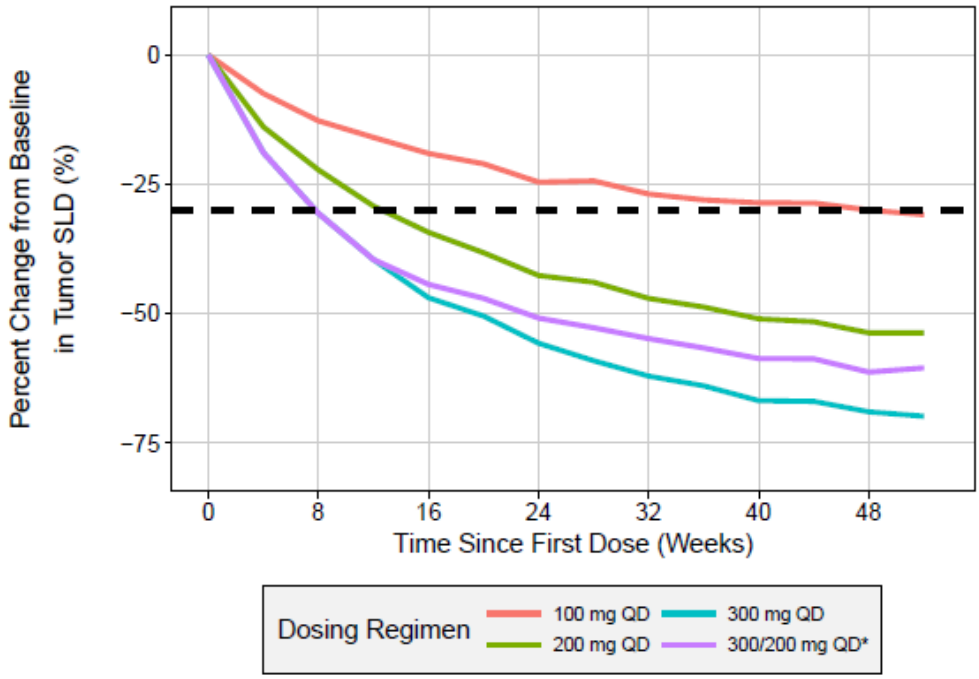
Parameter Name	Estimated Value (%RSE)	95% CI‡
Growth Rate Constant (k_{growth}, $week^{-1}$)	0.00147 (23.9)	0.00090 – 0.00192
Tumor Kill Rate Constant (k_{kill}, $mg^{-1} \cdot L \cdot h^{-1} \cdot week^{-1}$)	0.00338 (22.0)	0.00245 – 0.00447
Resistance Rate Constant (λ, $^{-1}$)	0.0286 (18.4)	0.0177 – 0.0381
Between Subject Variability for k_{growth} (%)	78.4 (6.6)	63.5 – 91.0
Between Subject Variability for k_{kill} (%)	76.2 (13.2)	61.3 – 100.0
Between Subject Variability for λ (%)	95.4 (25.5)	69.8 – 148.7
Residual Unexplained Variability (%)	12.9 (4.3)	12.0 – 14.2

‡ = Derived from sampling importance resampling (SIR).
RSE = relative standard error, CI = confidence interval.

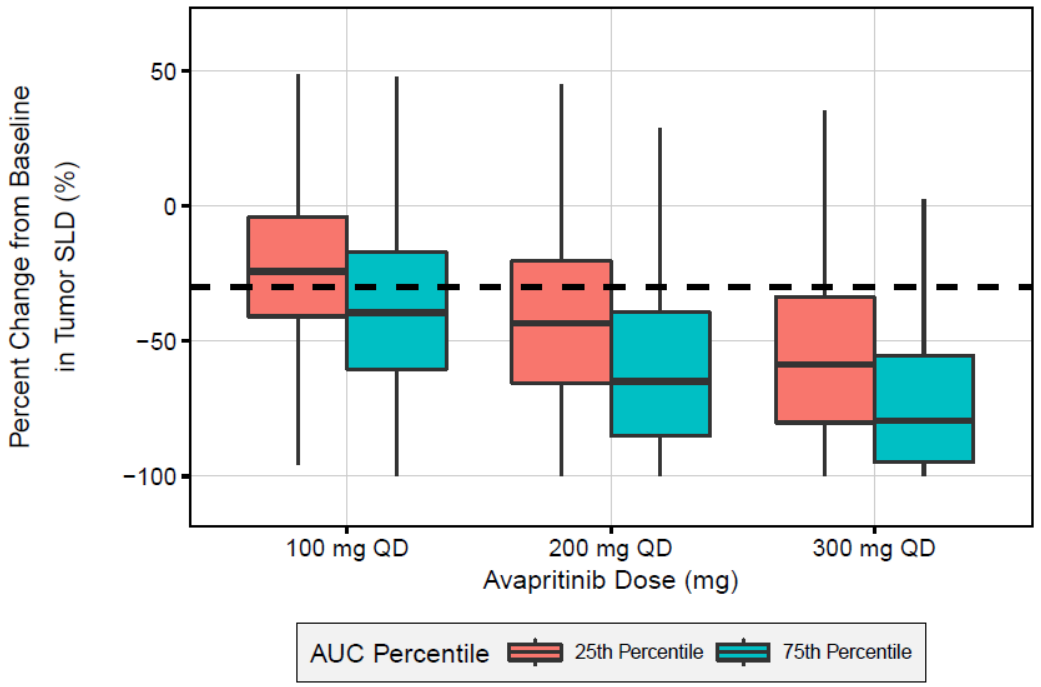


Open circles = individual observed, dashed blue lines = observed 10th & 90th percentiles, solid blue line = observed median, shaded red area = 95% confidence intervals, green lines = bin limits

Exposure-response simulations



Solid lines represent median tumor SLD profile from 1000-simulated patients, black dashed lines represent a reduction in tumor SLD of 30%. * = avapritinib dosing regimen with a dose reduction (300 mg QD for 3 months followed by 200 mg QD).



The thick solid black lines represent the median of simulated tumor SLD, the hinges (top and bottom of the boxes) represent the 25th and 75th percentiles (i.e. IQR), the top and bottom whiskers extents to the largest and smallest values that are within 1.5 * IQR of the hinges respectively. The black dashed line represents a reduction in tumor SLD of 30%.

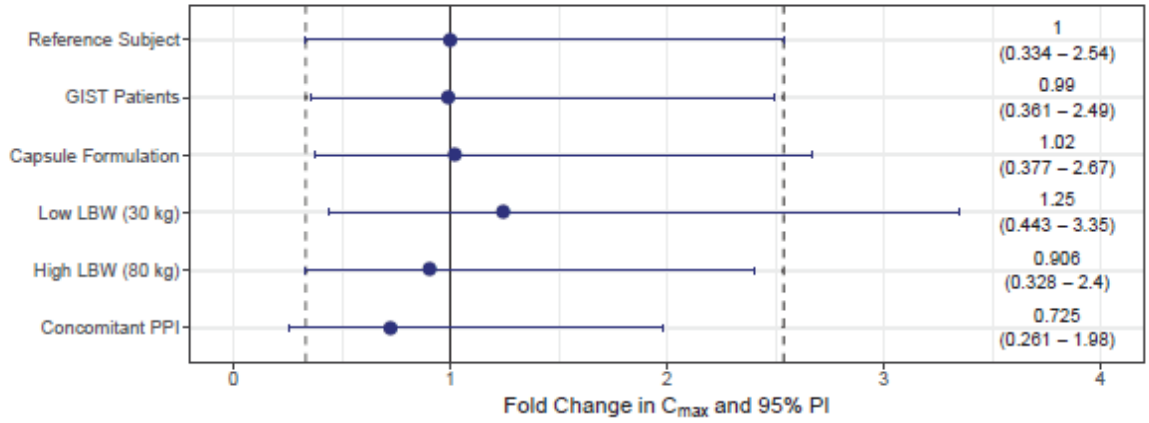
Table 3. Simulated percentage of patients with tumour response per RECIST criteria. Source: 202002 modelling report, Table 7

Dosing Regimen	Complete Response (%)		Partial Response (%)		Progression Disease (%)		Stable Disease (%)	
	Week 8	Week 16	Week 8	Week 16	Week 8	Week 16	Week 8	Week 16
100 mg	0.1	0.2	18.2	31.5	19.3	26.3	62.4	42.0
200 mg	0.2	1.2	34.8	56.4	10.1	13.0	54.9	29.4
300 mg	0.8	3.2	51.2	71.2	5.8	7.9	42.2	17.7
300 mg/200 mg‡	0.8	2.8	51.2	68.7	5.8	8.0	42.2	20.5

‡ 300 mg QD for 3 months and then titrated down to 200 mg QD.

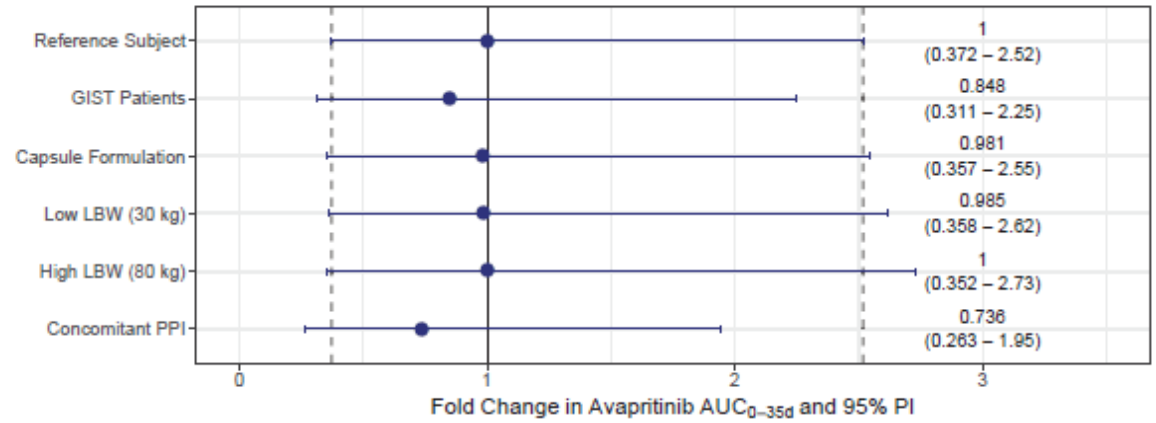
Special populations

Figure 27: Model Predicted Effect of Covariates on Fold Change in C_{max}



The solid black line represents no impact of the covariate with the reference subject referring to a healthy volunteer with median lean body weight (56.8 kg) receiving a single 300 mg dose of avapritinib (as tablet formulation) in a fasted condition. Dashed black lines represent the 95% PI (2.5^{th} to 97.5^{th} percentiles of the simulations) of the reference subject. The blue dots and error bars represent the median and 95% PI of the covariate effect based on 1000 simulated subjects within each group.

Figure 25: Model Predicted Effect of Covariates on Fold Change in AUC_{0-35d}



The solid black line represents no impact of the covariate with the reference subject referring to a healthy volunteer with median lean body weight (56.8 kg) receiving a single 300 mg dose of avapritinib (as tablet formulation) in a fasted condition. Dashed black lines represent the 95% PI (2.5^{th} to 97.5^{th} percentiles of the simulations) of the reference subject. The blue dots and error bars represent the median and 95% PI of the covariate effect based on 1000 simulated subjects within each group.

- **Impaired renal function**

Based on a population pharmacokinetic analysis, avapritinib exposures were similar among 88 subjects with mild renal impairment (CLcr 60-89 mL/min), 24 subjects with moderate renal impairment (CLcr 30-59 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 PK of avapritinib in patients with severe renal impairment (CLcr 15 to 29 mL/min) or end-stage renal disease (CLcr < 15 mL/min) has not been studied.

- **Impaired hepatic function**

Based on a population pharmacokinetic analysis, avapritinib exposures were similar between 53 subjects with mild hepatic impairment (total bilirubin within upper limit of normal [ULN] and AST > ULN or total bilirubin >1 to 1.5 times ULN and any AST), 6 subjects with moderate hepatic impairment (total bilirubin >1.5 to 3.0 times ULN and any AST), and 284 subjects with normal hepatic function

(total bilirubin and AST within ULN). The PK of avapritinib in patients with severe (total bilirubin > 3.0 × ULN and any AST) hepatic impairment has not been studied.

- **Gender**

PopPK modelling showed that gender did not influence avapritinib PK.

- **Race**

PopPK modelling showed that race did not influence avapritinib PK.

- **Weight**

The median value of the 95% PI in patients with low lean body weight (30 kg) showed a 25% increase in Cmax, suggesting that half of the patients with low lean body weight will show exposure changes greater than ±30%. Nevertheless, considering that %CV in Cmax and AUC was 52.2 and 48.3% in patients receiving avapritinib 300 mg QD, its impact in patients with low lean body weight might be of minor relevance.

- **Elderly**

PopPK modelling showed that age did not influence avapritinib PK.

- **Children**

No clinical study with avapritinib has been conducted in children. The PK of alpelisib in children is unknown.

Pharmacokinetic interaction studies

- **In vitro**

Effect of Avapritinib on the Pharmacokinetics of CYP450 substrates

In vitro studies with recombinant human CYP450 enzymes demonstrated that avapritinib Phase I metabolism is predominantly mediated by CYP3A4, and to a minor extent by CYP2C9

CYP Isoform	X720776	
	Clint (µL/min/pmol rCYP)	Individual CYP to the Overall Metabolism (Fm,cyp) (%)
1A2	0.00	0.00
2B6	0.00	0.00
2C8	0.00	0.00
2C9	0.05	15.14
2C19	0.00	0.00
2D6	0.00	0.00
3A4	0.19	84.86

The potential of avapritinib to inhibit the major CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) in vitro in human liver microsomes was evaluated. Avapritinib inhibited CYP1A2, CYP2B6, CYP2C8, and CYP2C19 with IC50 values ≥ 28 µM. IC50 values for inhibition of CYP2C9 and CYP3A4/5 in vitro were 15.2 µM (inhibition constant [Ki] = 11.9 µM), 29.9 µM (testosterone 6β-hydroxylation), and 21.6 µM (midazolam 1'-hydroxylation). The R1 values for CYP2C9

and CYP3A4 inhibition and R1, gut value for CYP3A4 inhibition for avapritinib are either at or above the threshold for a potential clinical drug-drug interaction (R1 ≥ 1.02 and R1,gut >11).

Avapritinib was not a time-dependent inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 catalyzed activities in vitro; however, avapritinib demonstrated time-dependent inhibition of CYP3A4 activity with a maximal inactivation rate constant (Kinact)and the inhibitor concentration causing half-maximal inactivation [KI] of 0.0301 min-1 and 12.3 µM, respectively. The estimated R2 value is above the threshold for a potential drug-drug interaction (≥ 1.25).

Effect of Avapritinib on the Pharmacokinetics of Transporter substrates

In vitro, avapritinib (0.03 to 10 µM) did not significantly inhibit human organic anion transporting polypeptide 1B1 (OATP1B1), human organic anion transporting polypeptide 1B3 (OATP1B3), organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3), organic cation transporter 1 (OCT1) or organic cation transporter 2 (OCT2), hence the likelihood of drug-drug interactions at clinically relevant concentrations is considered to be low. In vitro IC50 values for inhibition of P-gp, BCRP, bile salt export pump (BSEP), multidrug and toxin extrusion protein 1 (MATE1), and multidrug toxin and extrusion protein 2-K (MATE2-K) by avapritinib were 0.696, 3.67, 2.59, 0.825, and 0.128 µM, respectively. Estimated intestinal luminal concentration of drug (Igut)/IC50 values for P-gp and BCRP and maximal unbound plasma concentration of drug (Imax,u)/IC50 values for MATE1 and MATE2-K exceeded the regulatory threshold of > 10 and > 0.02, respectively. Avapritinib may have the potential for drug-drug interactions with P-gp, BCRP, MATE1, and MATE2-K substrates.

Table 8: Summary of Transporter Inhibition by Avapritinib

Transporter	System[a]	Probe Substrate	Avapritinib Concentration Range (µM)	IC_{50} (µM)
OAT1	Transfected MDCK II	p-aminohippurate	0.03 – 10	>10
OAT3	Transfected MDCK II	Estrone-3-sulfate	0.03 – 10	>10
OCT1	Transfected MDCK II	1-methyl-4-phenylpyridinium	0.03 – 10	>10
OCT2	Transfected MDCK II	Metformin	0.03 – 10	>10
OATP1B1	Transfected MDCK II	Estadiol-17β-D-glucuronide	0.03 – 10	>10
OATP1B3	Transfected MDCK II	CCK-8[b]	0.03 – 10	>10
MATE1	Transfected MDCK II	Metformin	0.03 – 10	0.825
MATE2-K	Transfected MDCK II	Metformin	0.003 – 1	0.128
BCRP	Transfected MDCK II	Prazosin	0.3 – 100	3.67
P-gp	MDCK-MDR1	Quinidine	0.25 – 10	0.696
BSEP	Sf9 membrane vesicles	Taurocholate	0.3 – 100	2.59

[a] Transfected cells except for BSEP

[b] CCK-8 = L-aspartyl-L-tyrosyl-L-methionylglycyl-L-tryptophyl-L-methionyl-L-aspartyl-L-phenylalaninamide hydrogen sulfate ester

- **In silico**

Effect of CYP3A4 inhibitors/inducers on the Pharmacokinetics of Avapritinib

Table 27: Summary of Predicted Geometric Mean C_{max} and AUC ratios for Avapritinib in the Absence and Presence of CYP3A Inhibitors and Inducers in Patients with GIST Following Single (300 mg) and Repeat (300 mg QD for 15 days) Oral Dosing of Avapritinib

	Geometric Mean Ratio			
	Single Dose (300 mg)		Repeat Dose (300 mg QD for 15 days)	
Perpetrator	C_{max}	AUC	C_{max}	AUC
Itraconazole (strong CYP3A inhibitor)	1.24	4.79	3.85	7.45
Ketoconazole (strong CYP3A inhibitor)	1.24	3.52	3.09	3.90
Fluconazole (moderate CYP3A inhibitor)	1.18	2.92	2.39	1.67
Cimetidine (weak CYP3A inhibitor)	1.05	1.19	1.16	1.10
Efavirenz (moderate CYP3A inducer)	0.69	0.31	0.45	0.23

Abbreviations: AUC = area under the plasma concentration-time curve; C_{max} = maximum observed concentration; CYP3A = cytochrome P450 3A; GIST = gastrointestinal stromal tumor; QD = once daily.
Source: PBPK DDI Report, Table 1.

Effect of Gastric Acid Reducing Agents on the Pharmacokinetics of Avapritinib

The established PBPK model adequately simulated the plasma concentration-time profiles of avapritinib after a single oral dose of 200 mg in healthy subjects in the fasted state, and avapritinib exposure metrics were within 1.1-fold of observed data. The simulated effect of food on the PK of a single oral dose of 200 mg avapritinib in healthy subjects was also consistent with the observed data: the AUC ratio (fed to fast) was 1.26 (predicted) versus 1.28 (observed); the Cmax ratio (fed to fast) was 1.59 (predicted) versus 1.51 (observed), respectively. The model was then qualified using PK profiles from patients with GIST. The PBPK model was able to recover the plasma concentration-time profiles and exposure levels of avapritinib after a single and repeat oral dose of 300 or 400 mg QD in patients with GIST in the fasted state, and were within 1.25-fold of observed data, thus validating the accuracy of the model.

The most common PPI taken by patients with GIST in Study BLU-285-1101 was omeprazole, which has been shown to be associated with elevated gastric pH values of 3.6 to 4.5 (Miner et al, 2003; Dodd et al, 2019). Hence, the verified PBPK model was subsequently applied to assess the impact of increase in gastric pH (range: 3.5 to 4.8) on the PK/fraction absorbed of avapritinib via manipulation of system parameters. The model predicted a 1.23- to 2.16-fold change in fraction absorbed of avapritinib as a consequence of elevating gastric pH. The discrepancy in the results of the sensitivity analysis versus results of the population PK and NCA PK analyses may be partially explained by the elevated gastric pH associated with gastric/intestinal cancer. A significant increase in mean gastric pH values from 2.9 in healthy subjects (n = 165) to 6.6 in patients with gastric/intestinal cancer (n = 89) has been reported (Lu et al, 2010). Thus, patients with cancer may have smaller PPI effects, compared to healthy subjects, due to an elevated gastric pH.

- **In vivo**

Effect of CYP3A4 inhibitors on the Pharmacokinetics of Avapritinib

Avapritinib Phase I metabolism is predominantly mediated by CYP3A4, so strong CYP3A inhibitors may affect the plasma exposure of avapritinib. In a clinical drug-drug interaction study, coadministration of

itraconazole (200 mg twice daily on Day 1 followed by 200 mg QD for 13 days), a strong CYP3A inhibitor, with a single 200 mg dose of avapritinib increased avapritinib Cmax by 1.4-fold and AUC0-∞ by 4.2-fold, relative to a 200 mg dose of avapritinib administered alone.

The concomitant use of strong CYP3A inhibitors, including grapefruit or grapefruit juice, with avapritinib should be avoided.

Effect of CYP3A4 inducers on the Pharmacokinetics of Avapritinib

Avapritinib Phase I metabolism is predominantly mediated by CYP3A4, so CYP3A inducers may affect the plasma exposure of avapritinib. In a clinical drug-drug interaction study, coadministration of rifampin (600 mg QD for 18 days), a strong CYP3A inducer, with a single 400 mg dose of avapritinib decreased avapritinib Cmax by 74% and AUC0-∞ by 92%, relative to a 400 mg dose of avapritinib administered alone.

The concomitant use of strong and moderate CYP3A inducers, including St. John's Wort, should be avoided.

Effect of Gastric Acid Reducing Agents on the Pharmacokinetics of Avapritinib

Coadministration of avapritinib with drugs that elevate the gastric pH was not evaluated in a clinical drug-drug interaction study. However, altered avapritinib absorption that is clinically significant or relevant was not observed in patients with GIST in Study BLU-285-1101. Seventy seven out of 221 patients (34.8%) had concomitant PPI use for ≥ 5 consecutive days during the analysis period. The effect of concomitant PPI use, as defined by the event level classification system, was determined to be 0.736 (95% PI, 0.263 to 1.95) for AUC and 0.725 (95% PI, 0.261 to 1.98) for Cmax. Overall, the magnitude of the effect on avapritinib AUC and Cmax was minor (< 0.5-fold change) and is not considered clinically relevant when taking into consideration the observed interindividual variability in steady state PK in patients receiving 300 mg QD (%CV for Cmax and AUC of 52.2% and 48.3%, respectively). A significant increase in mean gastric pH values from 2.9 in healthy subjects (n = 165) to 6.6 in patients with gastric/intestinal cancer (n = 89) has been reported (Lu et al, 2010). Thus, cancer patients may have smaller PPI effects, compared to healthy subjects, due to an elevated gastric pH.

2.4.3. Pharmacodynamics

Mechanism of action

Avapritinib has been developed as a type 1 kinase inhibitor to selectively inhibit oncogenic KIT and PDGFRα mutants by targeting the kinase active conformation. In particular, the potential of avapritinib to inhibit KIT and PDGFRα mutants resistant to tyrosine kinase inhibitors already approved for treatment of GIST has been investigated.

Nearly 80% of GIST patients have a primary activating mutation in KIT exon 9 or 11. These tumours initially respond well to imatinib therapy, but secondary resistance mutations in the KIT may develop and result in relapse. Secondary KIT resistance mutations include mutations in KIT exon 17 (mutations at the D816 position, among others) and are found with increasing frequency after imatinib and second-line sunitinib treatment (Heinrich et al., 2008; Antonescu et al., 2005; Leigl et al., 2008). In the 10-15% of GIST driven by PDGFRα, the most common mutations occur in exon 18, particularly the D842V substitution in exon 18 (Corless et al., 2005; Cassier et al., 2012). This mutation is structurally similar to the KIT exon 17 D816V mutant and is found in 5% of unresectable or metastatic GIST

patients (Cassier et al., 2012). Furthermore, PDGFRα D842V mutant GIST is insensitive to imatinib and all other agents approved for GIST (Cassier et al., 2012).

Primary and Secondary pharmacology

Primary pharmacology

In the E-R analyses for Study BLU-285-1101, the relationship of a number of PK exposure variables (Steady state [C1D15] Cmax, C24 & AUC0−τ) to efficacy and safety endpoints was examined. Due to multiple dose adjustments during treatment, systemic exposure at steady state (C1D15) was not considered to truly represent the individual patient avapritinib exposure prior to an adverse event (AE) or measure of efficacy. Subsequently, a model predicted average plasma concentration (Cave) was derived from the start of treatment until the first occurrence of an event of interest as detailed below. Avapritinib cumulative area under the plasma concentration-time curve (AUCcum) and Cave were required for each patient at each day of study participation.

The model predicted Cave for efficacy (progression-free survival [PFS], duration of response [DOR] and overall response rate [ORR]) was calculated as AUCcum,event/duration of event/24 h. The model predicted Cave used in the safety analysis was calculated as AUCcum,AE/treatment duration/24 h. Treatment duration was defined as the number of days between the first dose of avapritinib and the first occurrence of the AE of interest. If the patient did not experience the AE of interest throughout the study, the treatment duration was defined as the number of days of study participation. For change from baseline hemoglobin and bilirubin, treatment duration was defined as the number of days between the first dose of avapritinib and the final hemoglobin or bilirubin observation.

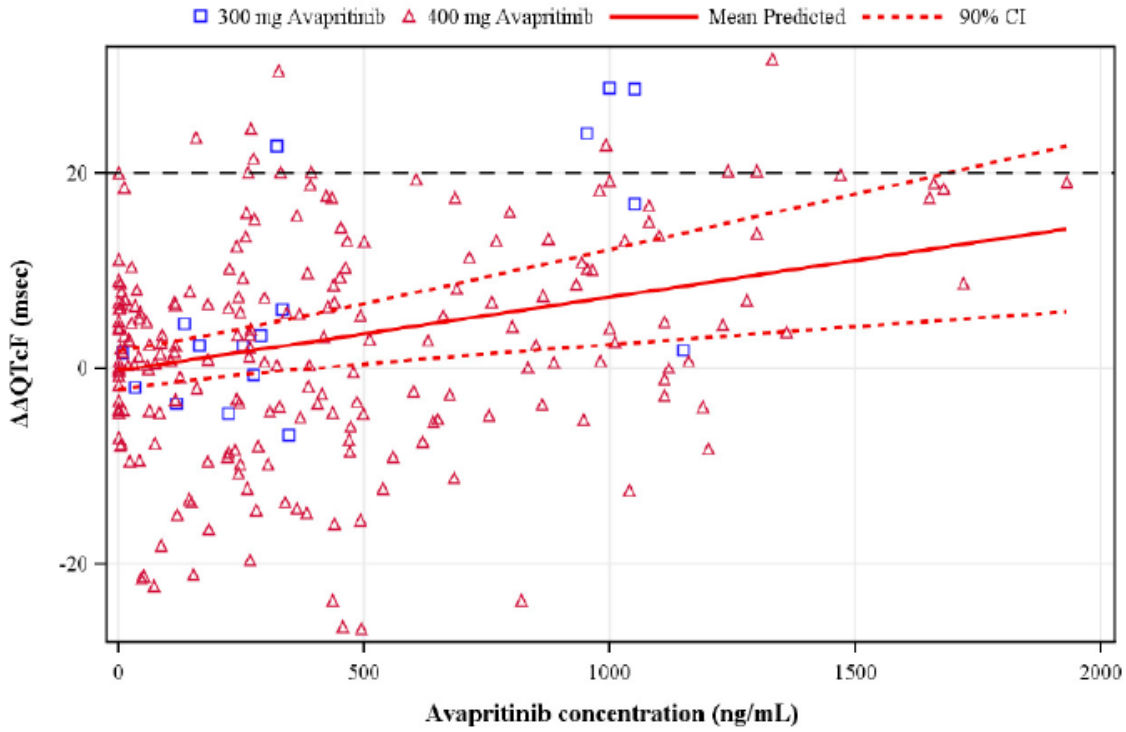
Secondary pharmacology

Avapritinib had a small effect on the QTc interval at steady state plasma concentrations after administration at doses of 300/400 mg QD. The mean baseline QTcF (on Day 1) was 411.9 ms. On Day 15 (steady state), the mean change from baseline in QTcF (ΔQTcF) was 7.0 ms at the predose time point, and above 5 ms at all postdose time points except 4 hours postdose (4.6 ms) (Figure 7). The largest mean ΔQTcF was observed at 1 hour (9.9 ms) and 8 hours (9.5 ms) postdose. Only 3 patients had a ΔQTcF of > 30 ms, and no patients had a ΔQTcF of > 60 ms (BLU-285-1101, Cardiac Safety Report, Section 5.3). No patients had a QTcF of > 450 ms.

The observed mean plasma concentrations were similar for the 300 and 400 mg QD treatments (BLU-285-1101, Cardiac Safety Report). For the combined data from both dose levels (ie, at clinical doses of 300/400 mg QD), mean plasma concentrations of avapritinib at steady state (Day 15) were substantially higher than on Day 1 (Figure 7), with the more than 3-fold accumulation observed on Day 15 being consistent with the long half-life of avapritinib (Section 2.1.1). On Day 15, the peak mean

plasma concentration was observed at 4 hours postdose.

Figure 8: Scatter Plot of Observed Avapritinib Concentrations in Plasma Versus Placebo-adjusted ΔQTcF (Study BLU-285-1101)



Abbreviations: CI = confidence interval; ΔQTcF = mean change from baseline in the QTc corrected for heart rate by the Fridericia method.
Note: The solid red line with dashed red lines denotes the model-predicted mean ΔQTcF with 90% CI. The blue squares and red triangles denote the pairs of observed avapritinib plasma concentrations and observed ΔQTcF by subjects for the 300 mg and 400 mg doses of avapritinib, respectively.
Source: BLU-285-1101, Cardiac Safety Report, Figure 7.2.5.

This analysis confirmed observations in a by-time point analysis, with a very shallow but statistically significant positive slope (0.007 ms per ng/mL [90% CI: 0.003, 0.012]) and a small, statistically nonsignificant intercept (-0.2 ms [90% CI: -2.26, 1.89]) (BLU-285-1101, Cardiac Safety Report). The predicted ΔQTcF effect using this model was 6.55 ms (90% CI: 1.80, 11.29) at the steady state geometric mean Cmax of avapritinib (899 ng/mL). A mean QT effect (ΔQTcF) exceeding 20 ms can be excluded at avapritinib plasma concentrations up to 1645 ng/mL.

Avapritinib at clinical doses of 300/400 mg QD had no effect on cardiac conduction (pulse rate and QRS intervals). Mean change from baseline pulse rate varied between -2.8 and 1.5 ms on Day 1 and between -3.8 and 0.5 ms on Day 15 (BLU-285-1101 Cardiac Safety Report, Section 5.4). Mean change from baseline QRS (ΔQRS) varied between -1.3 and 0.2 ms across all time points on both study days. There were no pulse rate or QRS outliers.

In conclusion, avapritinib administered at clinical doses of 300/400 mg QD resulted in a small increase in QTc that was not clinically relevant. The estimated mean ΔQTcF was 6.55 ms (90% CI: 1.80 to 11.29 ms) at the observed steady state geometric mean avapritinib Cmax of 899 ng/mL. A QT effect (ΔQTcF) exceeding 20 ms can be excluded at avapritinib plasma concentrations up to 1645 ng/mL. No effect on heart rate or cardiac conduction was observed.

Relation between plasma concentration and effect

Exposure-efficacy analysis

- **Overall Response Rate**

Overall, the ORR was > 80% in patients with PDGFRA D842V mutation. Therefore, interpretation of the E-R relationship is challenging because the majority of patients are in the partial response (PR) group (n = 43, Figure below).

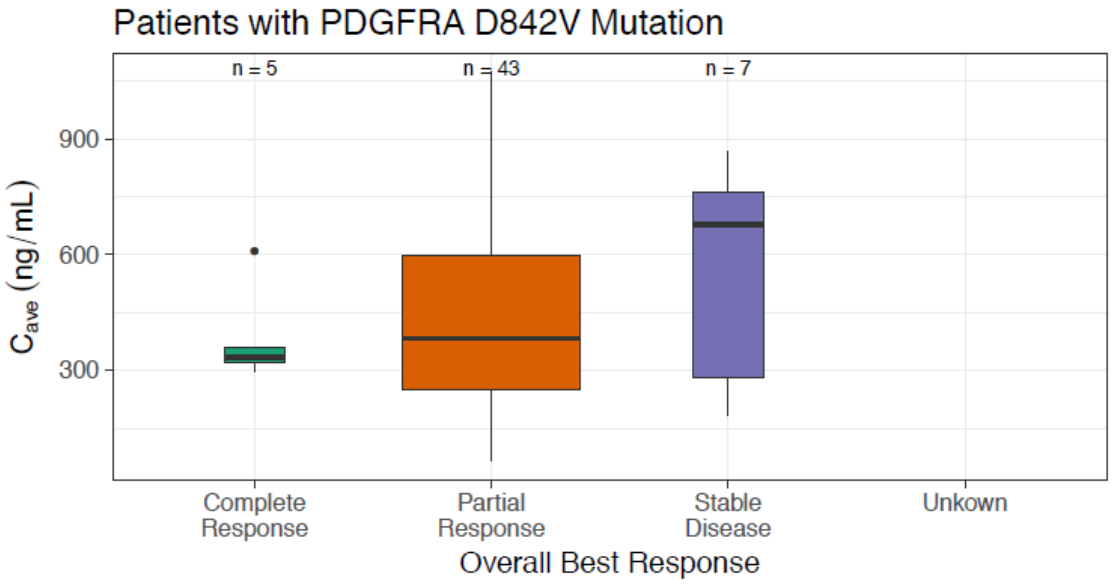


Figure above. Best overall response vs C_{ave}

- **Progression Free Survival**

No significant relationship in median PFS (p-value > 0.05, log-rank test) was evident in the PDGFRA D842V mutation or 4L+ non-D842V patient subpopulation by age, BSA, sex, prior number of unique TKIs, race, region, and baseline tumor size (plots not shown). A trend of shorter PFS with higher ECOG performance was evident (Figure 27 in the 201802I E-R report), although subject numbers are low and these results should be interpreted with caution.

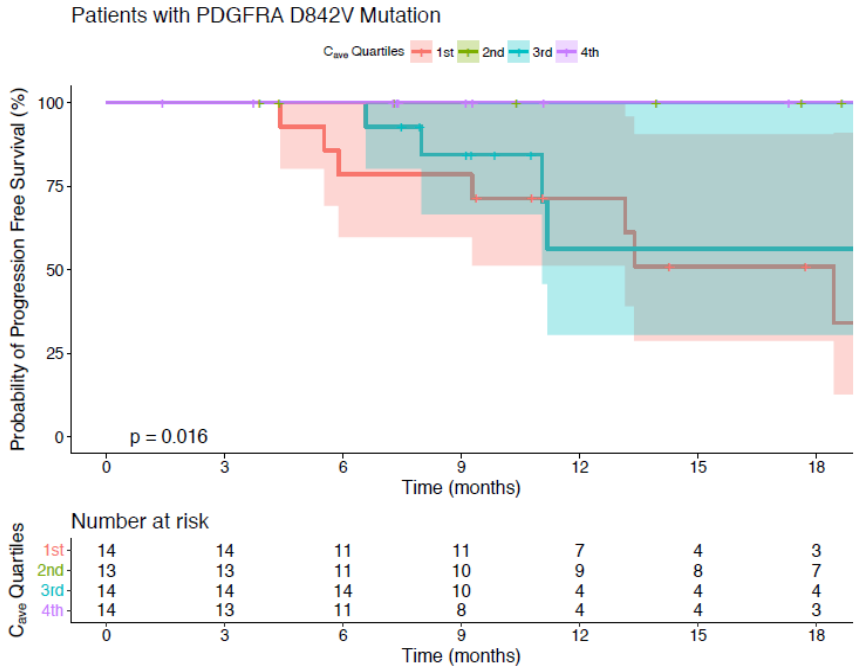


Figure 2. Progression-free survival by quartiles of avapritinb C_{ave}. Source: 201802I E-R report, Figure 10

Duration of Response

Kaplan-Meier curves of DOR by quartiles of Cave and analysis subpopulation are displayed in *Figure 2*. As the DOR analysis was restricted to a subset of patients with confirmed CR or PR, patient numbers were limited. A possible difference in DOR was observed between the 1st and 2nd quartile of C_{ave} to the 3rd and 4th quartile of C_{ave} in the patients with PDGFRA D842V mutation, however should be interpreted with caution due to limited subject numbers.

Kaplan-Meier curves of DOR for patients with PDGFRA D842V mutation stratified by covariates were explored. No significant relationship in DOR was evident by BSA, age group, sex, prior number of unique TKIs, race, region, or baseline tumor size. A significant trend was evident in DOR was evident when stratifying by baseline ECOG performance status, although subject numbers are low and these results should be interpreted with caution.

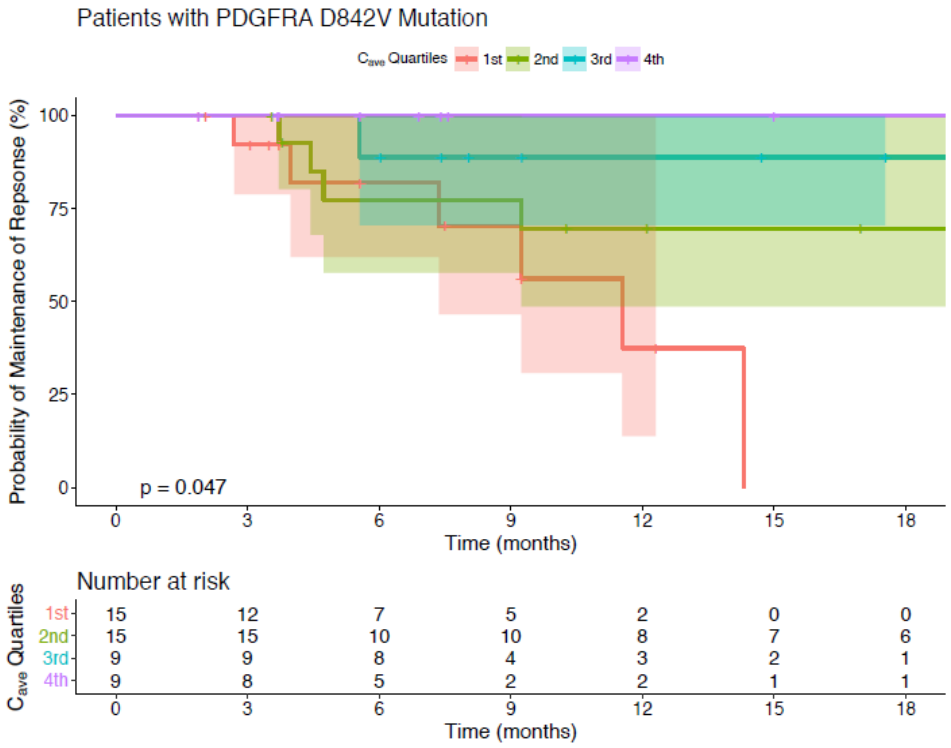


Figure 3. Duration of response by quartiles of C_{ave}. Source: 201802I E-R report, Figure 11

Exposure-safety analysis

Boxplots of C_{ave} vs grade 3 or 4 AEs, all grade memory impairment, all cognitive effects, grade 2 or higher oedema and intracranial haemorrhage is shown in *Figure 3*.

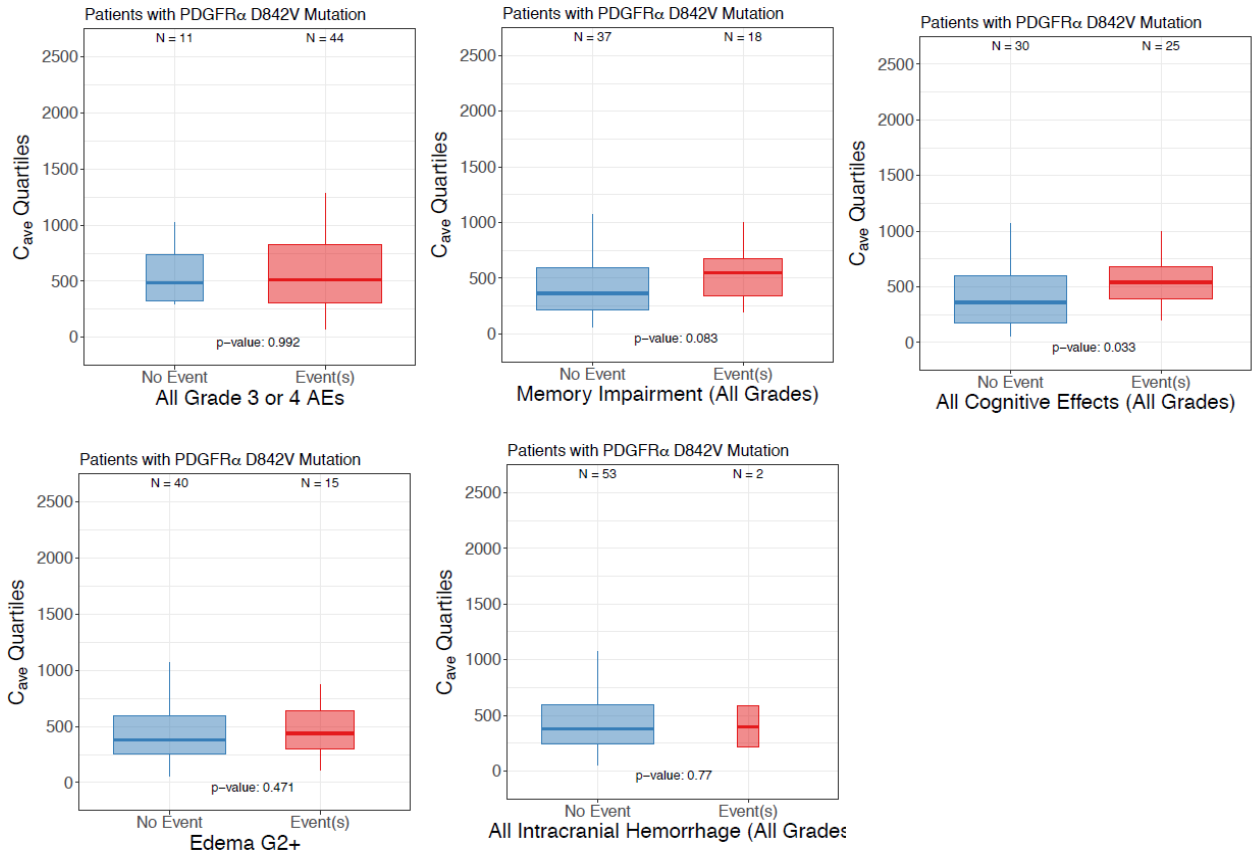


Figure 4. Boxplots of C_{ave} vs safety outcomes. Source: 201802I E-R report, Figures 13, 15, 17, 19 and 21

Kaplan-Meier plot of time to grade 3 or 4 AEs is shown in *Figure 4*. Time to memory impairment (all grades) and oedema (grade 2 or higher) showed similar pattern as *Figure 4*, and are not shown here.

A Kaplan-Meier curve of time to first cognitive effect AE (all grades) by quartiles of C_{ave} is shown in *Figure 5*.

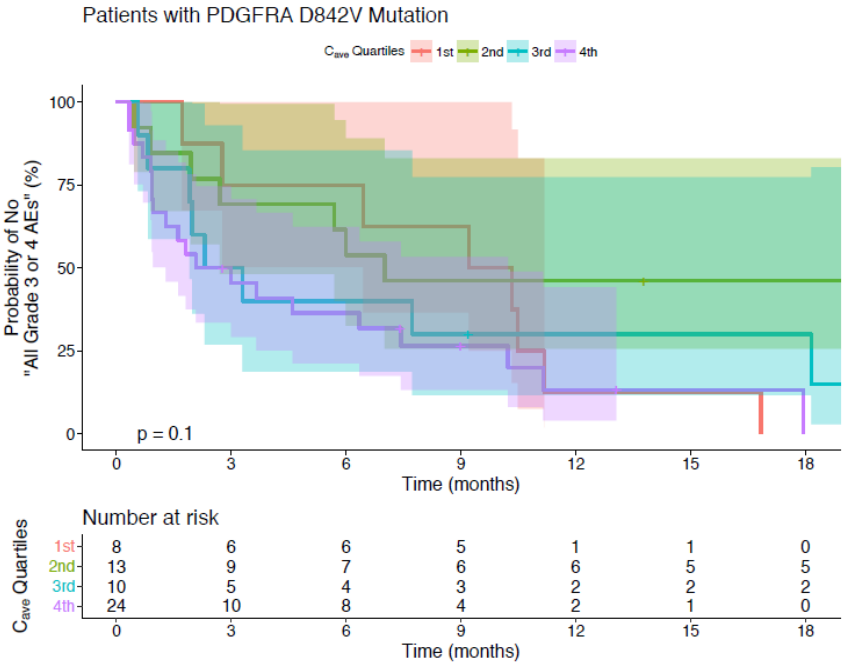


Figure 5. Time to grade 3 or 4 AEs by quartiles of C_{ave}. Source: 201802I E-R report, Figure 14

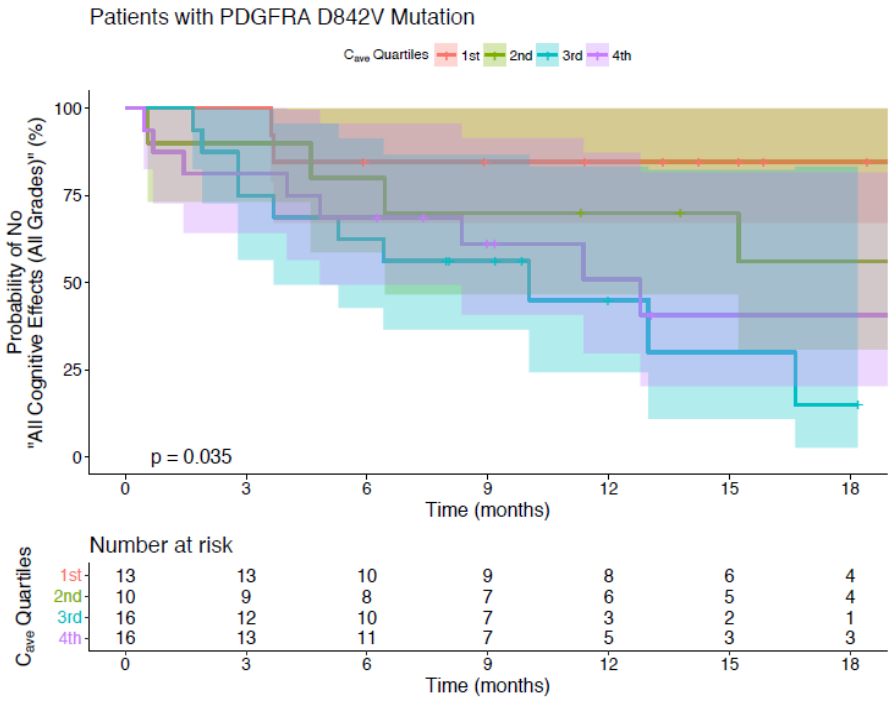


Figure 6. Time to all cognitive effects by quartiles of C_{ave}. Source: 201802I E-R report, Figure 18.

Scatterplots showing the relationship between C_{ave} and change in bilirubin and haemoglobin is shown in *Figure 6*.

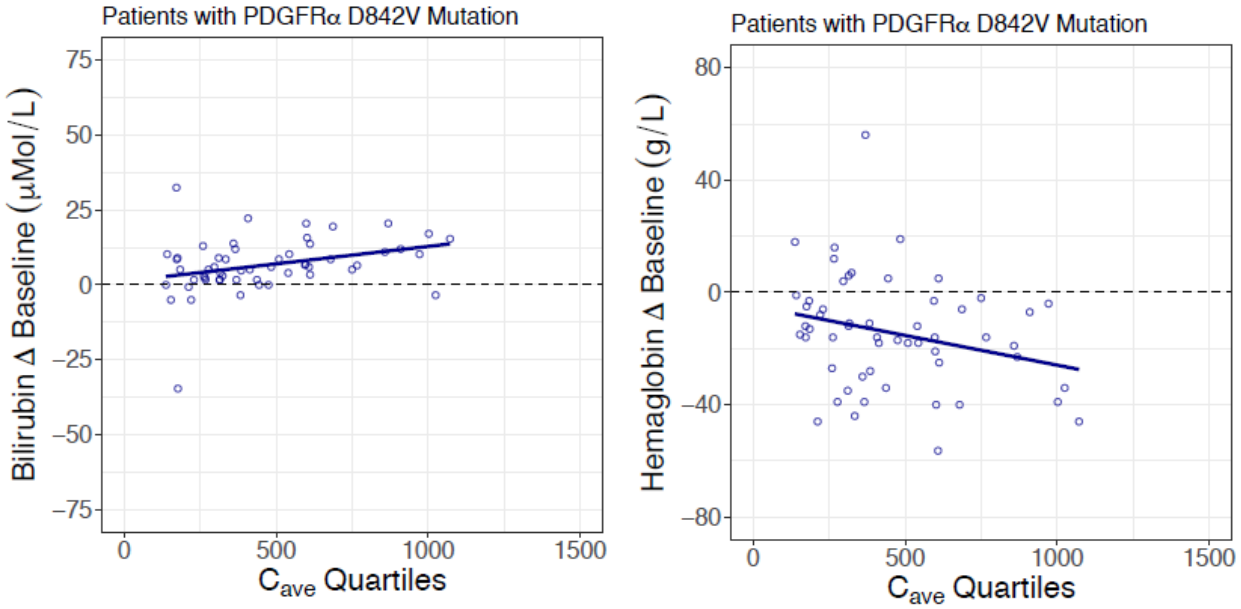
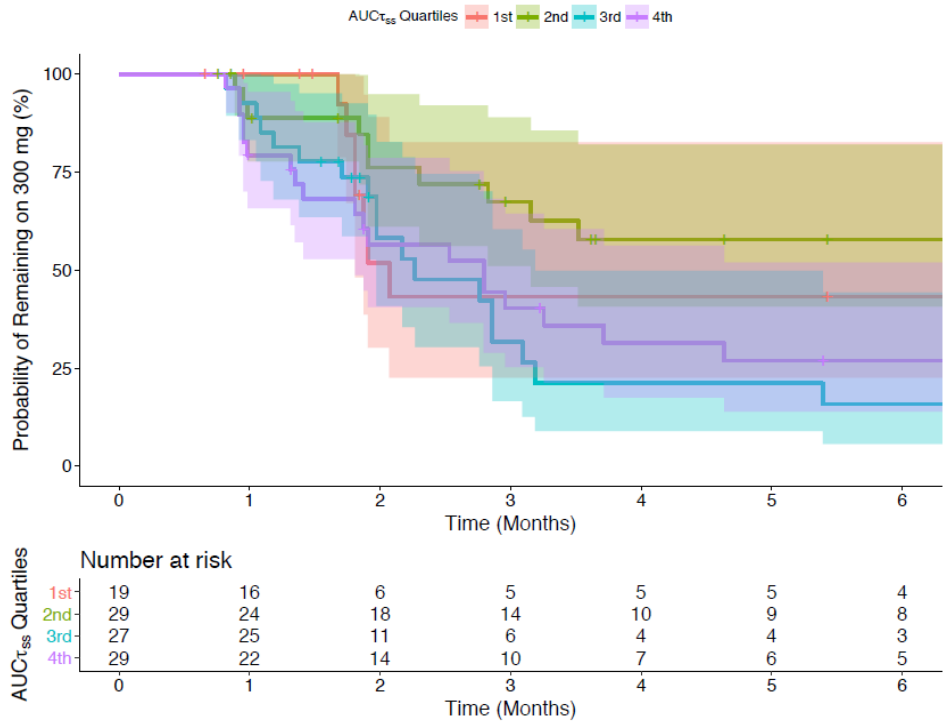


Figure 7. Changes in bilirubin and haemoglobin according to C_{ave}

Kaplan-Meier curves were created to explore the relationship between time to dose interruptions/reductions and exposure on Day 15 (Figure 7). The analysis was conducted in patients pooled from the D842V negative and positive populations initiating therapy with 300 mg doses.



Solid line represent the Kaplan-Meir curves, shaded areas represent 95% CI. An event correlates with either a dose interruption or a dose change. If no dose change occurs the data are right censored at the time of the last recorded dose. Note: plot is truncated at 6 months.

Figure 8. Time to dose interruption for patients starting with 300 mg doses. Source: 201802I E-R report, Figure 9

- **Grade 3 or 4 Adverse Events**

Kaplan-Meier curves of time to first Grade 3 or 4 AE by quartiles of Cave, stratified by analysis population, are shown in Figure 13. A clear trend was observed in both subpopulations, with a median time to a Grade 3 or 4 AE of approximately 10 months for the 1st quartile of Cave and approximately 2 to 3 months for the 4th quartile of Cave. The empiric probabilities of Grade 3 or 4 AEs by quartiles of Cave at 3, 6, and 9 months, stratified by analysis population, are presented in Table 13.

Differences in time to event between the subpopulations were observed for Eastern Cooperative Oncology Group (ECOG) performance status, race, region, and sex; however, none of the differences appeared to be clinically relevant or the sample size was too low to be confident in an interpretation of the results. There was no significant relationship ($p > 0.05$, log-rank test) between time to first Grade 3 or 4 AE and BSA, age groups, race, prior number of unique tyrosine kinase inhibitors (TKIs), and baseline tumor size in either subpopulation.

- **All Cognitive Effects**

Boxplots of all cognitive effect AEs (all grades) versus Cave stratified by analysis populations are shown in Figure 14. A trend was evident between an increased Cave and the occurrence of a cognitive effect AE at any stage throughout the study. The trend was greater in the 4L+ subpopulation. No clear trends were evident between steady state (C1D15) exposure metrics and the occurrence of a cognitive effect AE in either subpopulation.

Kaplan-Meier curves of time to first cognitive effect AE (all grades) by quartiles of Cave, stratified by PDGFRA exon 18 mutation and 4L+ subpopulations, are shown in Figure 15. A clear trend was evident in the 4L+ subpopulation, with a median time to a cognitive effect AE of approximately 4 to 5 months for the 3rd and 4th quartiles of exposure compared to approximately15 months for the 2nd quartile of exposure, with few patients in the 1st quartile of Cave experience a cognitive effect. The relationship

for the time to first cognitive effect AE was less clear in the PDGFRA exon 18 mutation subpopulation. The empiric probabilities of all cognitive effects AE (all grades) by quartiles of Cave at 3, 6, and 9 months, stratified by analysis population, are presented in Table 14.

- **Edema**

Kaplan-Meier curves of time to first Grade 2 or higher edema AE by quartiles of Cave, stratified by PDGFRA exon 18 mutation and 4L+ subpopulations, are shown in Figure 17. A trend was apparent in the 4L+ subpopulation, with a faster onset of any Grade 2 or higher edema AE associated with a higher avapritinib Cave. However, no relationship was present in the PDGFRA exon 18 mutation subpopulation. The empiric probabilities of grouped edema AE (Grade 2+) by quartiles of Cave at 3, 6, and 9 months, stratified by analysis population, are presented in Table 15.

Full details of the exposure-response analyses of Grade 2 or higher edema events by predefined covariates are available in E-R Report BLUE201802 Section 10.3.1. Kaplan-Meier curves of time to the first Grade 2 or higher edema AE by region showed a significant relationship in the 4L+ subpopulation. Patients from Europe appeared to have a faster time to a Grade 2 or higher edema AE compared with patients from the US or Asia. However, the effect may be in part due to differences in average avapritinib exposure. Additionally, in the PDGFRA exon 18 mutation subpopulation, a significant relationship was present between time to the first Grade 2 or higher edema AE by baseline ECOG performance status. Patients with a baseline ECOG performance status of 0 appeared to have a faster onset than patients with a baseline ECOG performance status of 1. The effect appeared to be largely independent of avapritinib exposure.

- **Hemoglobin and Bilirubin**

In both subpopulations, a possible trend was apparent with an increase in change from baseline bilirubin as Cave increased. Additionally, a change from baseline was apparent at lower Cave, indicating the possibility of disease progression and liver involvement rather than an avapritinib exposure effect.

2.4.4. Discussion on clinical pharmacology

Avapritinib has been characterized using in vitro and in vivo data from several clinical trials. The methodology applied to characterize the pharmacokinetics and interactions through non-compartmental analysis and population approach is mainly endorsed.

Absorption

The information given in the SmPC describes only the time to reach Cmax and should be updated to reflect that the absolute bioavailability has not been determined.

Formulation bridge and food effect

Two biopharmaceutical studies have been performed in healthy individuals: A 6% to 10% lower exposure (C_{max}, AUC_{0-24}, AUC_{0-72}) was observed for the 200 mg tablet compared to the 2 x 100 mg capsules in study **BLU-285-0101**. The AUC parameters were contained within the acceptance limits of 0.8-1.25, however C_{max} was not (90%CI: 78.5-102.7). Bioequivalence between the 100 mg and 400 mg tablet strengths was demonstrated in study **BLU-285-0105**. A strength-based biowaiver was confirmed at pH 4.5 for the additional 200 and 300 mg tablets intended for marketing.

In the food-effect study, **BLU-285-0102**, samples were reanalysed due to uncertainty regarding the terminal slopes of the time-concentration profiles, which is an obvious PK reason. Furthermore the applicant states that the geometric means of AUC_{0-24h} (n=30) is similar to AUC_{0-inf} (n=23). Firstly,

$AUC_{0\text{-}24h}$ was, in contrast to $AUC_{0\text{-}T}$ and $AUC_{0\text{-}inf}$, not a primary endpoint of the food effect study. Secondly, it is not possible to assess the impact of omitting 23% of the patients without doing a sensitivity analysis. The geometric mean ratio of the 30 individual values was 126%, showing that $AUC_{0\text{-}inf}$ increases by 26% in fed vs fasted conditions.

Elimination

The PK of the pharmacologically active metabolites BLU111207 and BLU111208 and the have been studied in GIST patients and pharmacokinetic data have been provided. The Applicant intends to evaluate the pharmacological activity for M690 in Q2 2020. In case the pharmacological activity index is greater than 20%, steady-state concentrations will be collected in patients, which seems acceptable.

The potential impact of polymorphisms on CYP2C9 has not been further explored. The applicant argues that clinically relevant effects are not expected as the relative contribution of 2C9 to overall metabolism is minor at approximately 15%. CYP2C9 polymorphisms are likely to be one of the sources of intra-individual variability for avapritinib. However, as a single contributor to variability, the impact on the exposure levels of avapritinib is not expected to be major. The SmPC text has been updated with percentage per metabolizing pathway.

The potential impact of genetic polymorphisms in CYP3A5 was investigated in an in vitro study (Report 2001071). The study design and conduct is considered adequate for the purpose; using CYP3A5 cDNA expressed enzymes and human liver microsomes (HLM) of various CYP3A5 genotypes (CYP3A5*1*1, *1*3, *3*3) to understand their contribution to the metabolism of avapritinib. The study results show a negligent contribution of the CYP3A5 genotypes to the metabolism of avapritinib and support that clinical relevant effects would not be expected for CYP3A5 as single contributor to variability on exposure. The SmPC section 5.2 has been updated to reflect that CYP3A5 also metabolizes avapritinib.

Overall, the polymorphisms discussed above are not expected to majorly impact the exposure levels of avapritinib as single contributors to variability. However, genetic polymorphisms are likely to contribute to the inter-individual variability of avapritinib. The relative impact of the various polymorphisms have not been investigated and can accordingly not be used longside the other source of variability for avapritinib PK to inform an individualized dosing algorithm. This should be reflected in the EPAR in order to allow both a reflection of the current knowledge and the gaps in knowledge as well as inform potentially personalized dosing algorithms or TDM studies.

The applicant should provide in the Q1 2021 the LTS to cover the maximum storage period of 765 days for the enantiomers (See section on post authorization measures including recommendations).

To better understand the metabolizing pathways leading to glucuronidation for avapritinib an in vitro study (BLU-R8399) was conducted. The study design and conduct is considered adequate for the explorative purpose. The study indicates that the CYP3A4 formed metabolite M514 is further converted to the glucuronide and could also be the precursor to a carbocation intermediate which can undergo reaction with water to form M499. The applicant argues that the results indicate that any downward-regulation of glucuronidation rate of M514 to M690 due the genetic polymorphism will shift the metabolism toward the formation of M499 (no activity) and major impact on exposure levels are not expected from UGT polymorphisms as single source of variability. The relative percentage that is metabolized per pathway has not been determined. Further, M690 is a major metabolite and the pharmacokinetic and pharmacological properties of M690 is largely unknown. The applicant conducted *in vitro* studies of avapritinib hydroxylamine (M514) with human rUGTs that suggested that the formation of the glucuronide M690 is catalyzed mainly by UGT1A3, but also UGT1A4 and UGT2B7 to a lesser extent.

Population pharmacokinetic models

Model building and evaluation

A population PK model for avapritinib following oral administration was developed using data from 4 Phase 1 studies consisting of both healthy volunteers and patients with GIST. The PK of avapritinib was best described by a two compartment model, with absorption described using 4 or 5 transit compartments, depending upon formulation of tablets or capsules, respectively. LBW on Vc/F, capsule formulation on transit time, GIST patients and concomitant PPI administration on bioavailability were identified as the main significant covariates. The final population PK model seems able to describe the observed data.

Intra-patient variability (between-occasion variability) in apparent oral clearance (CL/F) and volume of the central compartment (V_C/F) was unknown based on the figures presented. The applicant provided intra-individual %CV for CL/F and V_C/F, which ranged from 1.2% to 37.9% with a median of 8.9%.

Pharmacokinetics in target population

Avapritinib demonstrated proportional pharmacokinetics in both HV and the target population. The population-PK analysis shows decreased BA in patients compared to HV and differences in CL between ethnic groups. The effect of intrinsic factors affecting the PK of avapritinib has been sparsely investigated.

PK/PD model of tumour dynamics

The applicant has presented a tumour dynamics model in patients with GIST. Simulations show that increasing doses may lead to median reduction in absolute (mm) and relative (%) tumour diameters. However, the distributions of change in tumour size are to a large extent overlapping between the 100 mg, 200 mg and 300 mg doses.

Renal impairment

Dedicated clinical study investigating the impact of renal impairment have not been conducted. Based on a population pharmacokinetic analysis, no dose adjustment is recommended for patients with mild and moderate renal impairment [creatinine clearance (CLcr) 30-89 mL/min estimated by Cockcroft-Gault]. Avapritinib has not been studied in patients with severe renal impairment (CLcr 15-29 mL/min) or end-stage renal disease (CLcr <15 mL/min), therefore its use in patients with severe renal impairment or end-stage renal disease cannot be recommended (see sections 4.2 and 5.2 of the SmPC).

Impaired hepatic function

As hepatic elimination is a major route of excretion for avapritinib, hepatic impairment may result in increased plasma avapritinib concentrations. Based on a population pharmacokinetic analysis, no dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin within upper limit of normal [ULN] and aspartate aminotransferase (AST) > ULN or total bilirubin greater than 1 to 1.5 times ULN and any AST) and moderate hepatic impairment (total bilirubin >1.5 to 3.0 times ULN and any AST). Avapritinib has not been studied in subjects with severe (Child-Pugh class C) hepatic impairment and therefore its use in patients with severe hepatic impairment cannot be recommended (see sections 4.2 and 5.2 of the SmPC). A dedicated study in hepatic impairment will be conducted to evaluate the pharmacokinetics of avapritinib in hepatically impaired subjects and the results will become available in Q1 2024 (see section on Post Authorization Measures and RMP).

Population pharmacokinetic analyses indicate that age, race, sex, body weight, and albumin concentration have no clinically meaningful effect on the pharmacokinetics of avapritinib. No dose adjustment is recommended for patients aged 65 years and above.

Interactions

In vitro

There are some limitations in the conducted in vitro studies.

Estimation of intestinal luminal concentration (Igut), maximal unbound plasma concentration (Imax,u) and maximal unbound hepatic inlet concentration (Iu,inlet,max) is poorly described. Additional information was requested from the applicant at D120. For instance, the applicant concluded that the R1 value for CYP2C9 inhibition by avapritinib is either at or above the threshold for a potential clinical drug-drug interaction (R1 ≥ 1.02), whereas the assessors found the R1 value to be below the threshold. This was clarified (R<1) along with several aspects on the interaction potential of avapritinib.

In vivo

Victim:

The conducted clinical DDI study investigated the effect of CYP3A/p-gp inhibition and induction, however at different dose levels than intended for clinical use. The effect of a strong inhibitor was investigated at a lower dose (200 mg) and the effect of a strong inducer was investigated at a higher dose (400mg). The applicant has discussed this deviation from Guideline requirements and has built a PBPK model to estimate the effect of strong inhibitors and inducers at 300mg, estimate the interaction at steady state vs single dose as well as to estimate the effect of concomitant use of moderate inducers and inhibitors. The SmPC has been updated to include a recommendation of avoiding the concomitant use of avapritinib with strong and moderate CYP3A inhibitors/inducers or in case moderate CYP3A inhibitors use cannot be avoided, to reduce the starting dose of avapritinib to 100 mg orally once daily.

Perpetrator:

In vitro data demonstrate that avapritinib may have the potential for DDIs with P-gp, BCRP, MATE1 and MATE2-K substrates. The Applicant recognized the value of glucose monitoring to prevent any hypoglycemic event in patients. (SmPC section 5.2).

The combined inhibition and induction of CYP3A4 by avapritinib is difficult to interpret based on the in vitro data alone. The Applicant has planned to conduct a post-authorization DDI study to assess the effect of concomitant inhibition and induction of CYP3A4 by avapritinib. Results will be expcted in Q2 2024 (refer to post authorization measures section).

Dose

The applicant states that "vigilant dose modification is important for improvement/resolution to improve tolerability" is needed. Of 28 patients initiating therapy with 300 mg dose, only 5 patients (18%) could maintain the dose without interruption or dose reduction. It is worrisome that 80% of patients have to develop toxicities for the dosing to be reduced. The current strategy of starting at 300 mg, wait for toxicity, and then reduce the dose, is not considered optimal.

Avapritinib has a large interpatient PK variability, with an 8-10 fold range in the exposure following 300 mg doses. The applicant has simulated if this affects the efficacy in patients receiving 100 mg, 200 mg and 300 mg doses. For each dose level (100 mg, 200 mg and 300 mg), the 75th percentile had a higher probability of tumour response compared to the 25th percentile. However, the 75th percentile receiving 200 mg had higher efficacy than the 25th percentile receiving 300 mg. This finding supports that the efficacy of avapritinib can be improved by prospectively adjusting the dose according to exposure (therapeutic drug monitoring, TDM).

On the other hand, there are confirmed relationships between higher avapritinib exposure and cognitive effects, increased bilirubin and decreased haemoglobin (*Figure 3*, *Figure 5* and *Figure 6*). It

also seems to be a relationship between steady-state exposure at day 15 and time to dose interruption or reduction of the 300 mg dose (Figure 7). All patients in the quartile with the lowest exposure withstood the 300 mg dose for 2 months, while patients in the 2nd to 4th quartile had to start reducing doses after 1 month, supporting that there is a relationship between higher exposure and adverse events leading to dose reductions. This finding, taken together with the fact that there is a high proportion patients with objective response, but no apparent exposure-efficacy relationship for the investigated dose, supports that individualised dosing according to exposure may reduce the risk of adverse events, while maintaining optimal efficacy. At this stage, a prospective clinical trial to test a TDM regimen in the small patient population with the D842V mutation seems unfeasible. The applicant was requested to, but has not provided substantial information for clinicians to explore the use of TDM in individual patients.

QTc effect analysis

Avapritinib had an effect on the QTc interval at steady state plasma concentrations, following once daily administration of 300 or 400 mg. On Day 15 (steady state), the mean ΔQTcF was 7.0 msec (90% CI 2.84 – 11.14) at the predose time point. The largest mean ΔQTcF was observed at 1 hour and 8 hours postdose: 9.9 (90% CI 5.72 – 14.03) and 9.5 (90% CI 5.30 – 13.62) msec, respectively. Three patients had a ΔQTcF > 30 msec, and no patients had a ΔQTcF > 60 msec. No patients had a QTcF > 450 msec. Flat T-waves were observed in 5 subjects at a total of 8 time points.

The relationship between ΔQTcF and concentration of avapritinib was investigated by linear mixed-effects modelling. The concentration-QTc analysis confirmed the observations in the by-time point analysis with a shallow, statistically significant positive slope. The predicted ΔQTcF effect using this model was 6.55 msec (90% CI: 1.80 to 11.29) at the steady state geometric mean Cmax of avapritinib (899 ng/mL). The estimated worst-case (concomitant use of a strong CYP3A4 inhibitor and a high fat meal) Cmax (582.4 ng/mL) is actually lower than the observed mean steady-state Cmax after 300 mg dosing (905 ng/mL; refer to clinical PK data), and is therefore not considered to be a reasonable worst-case scenario. Considering that PK data show large variability in C_{max} at steady-state, it is expected that a proportion of patients treated with avapritinib will reach C_{max} concentrations with associated predicted ΔQTcF > 20 ms (within the 90% CI). The applicant has included a warning in the SmPC section 4.4 on the QT-prolonging potential of avapritinib.

2.4.5. Conclusions on clinical pharmacology

The applicant has committed to perform a clinical CYP3A drug-drug interaction study of avapritinib and midazolam, and a study to evaluate the PK of avapritinib in hepatically impaired subjects.

From the presented data, it cannot be excluded that patients would benefit from a lower starting dose, and it is possible that prospective individualised dosing (TDM) would lead to fewer adverse events while maintaining efficacy. However, from a clinical pharmacology perspective, avapritinib is approvable.

2.5. Clinical efficacy

Dose response study(ies)

Study BLU-285-1101 Part 1

A formal dose-finding study has not been conducted. The dose intended for marketing was selected based on the MTD from Part 1 of the phase 1 study (NAVIGATOR), an ongoing Phase 1, first-in-human,

open-label study to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics and efficacy of avapritinib, administered orally, in adult patients with unresectable GIST or other relapsed or refractory solid tumors. The study design consists of a dose escalation part (Part 1), which is now complete, and an ongoing dose expansion (Part 2).

The primary objectives of Part 1 were to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of avapritinib and to determine initial safety and tolerability.

The primary endpoints were:

- MTD and RP2D of avapritinib
- Overall safety profile of avapritinib, as assessed by the type, frequency, severity, timing, and relationship to study drug of any AEs, serious adverse events (SAEs), and changes in vital signs, ECGs, and safety laboratory tests

The dose escalation part of the study was designed to allow enrollment of patients with unresectable or metastatic GIST or other relapsed or refractory solid tumors; however, no patients with relapsed or refractory solid tumors were enrolled.
Patients with GIST must have had disease that progressed after treatment with imatinib and at least 1 of the following: sunitinib, regorafenib, sorafenib, dasatinib, pazopanib, or an experimental kinase inhibitor agent, or disease with a D842V mutation in the PDGFRA gene.
A standard 3+3 dose escalation design was employed. The first cohort of patients received avapritinib at a starting dose of 30 mg QD. The dose escalation increment for the first escalation step was to be a maximum of 100%. However, if ≥1 patient treated at the starting dose level had a ≥Grade 2 non-hematologic AE or a ≥ Grade 3 hematologic AE that was not clearly attributable to a cause other than avapritinib, then the maximum dose escalation increment for the first escalation step was to be 50%. All subsequent dose escalation increments were to be maximum of 50%.
Three patients were to be enrolled initially in each cohort and an additional 3 patients (for a total of 6) were to be enrolled should the cohort require expansion due to a DLT.
After the current escalation cohort was full, up to 3 additional patients, all with diagnosis of GIST, could have been enrolled into an enrichment cohort at a lower dose that was reviewed at a dose escalation meeting, and did not exceed the MTD.

Dose-Limiting Toxicity

Toxicities were graded and documented according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. Dose-limiting toxicity was defined as any treatment-emergent AE of Grade ≥ 3 occurring during C1 and not clearly attributable to a cause other than avapritinib.

Maximum Tolerated Dose

The MTD was defined as the highest dose level at which ≤1 patient experienced DLTs in Cycle 1 during Part 1 of the study. At least 6 patients must have been treated at this dose in order to determine that it was the MTD.

Selection of Dose for Expansion Part of the Study

A total of 43 patients were initially treated with avapritinib 400 mg QD (MTD) in Part 2 of the study. However, emerging data at the time suggested a trend toward higher incidence of Grade 3 neurologic AEs and more dose reductions at 400 mg QD after multiple cycles of treatment. Based on these factors, as well as the observed exposure levels and efficacy of avapritinib at 300 mg, 300 mg QD was selected as the RP2D and starting dose for further enrollment. Per protocol, if avapritinib was tolerated at 300

mg QD for 2 consecutive cycles and specific safety and response criteria were met, then Investigators could subsequently increase the patient's dose to the MTD of 400 mg QD.

Dose modifications

The majority of patients needed dose modifications during the expansion part of the study, especially in the patients with D842V mutation (table below). In the groups of patients initiating therapy with 300 mg and 400 mg, 20% and 22% of the patients permanently discontinued therapy due to adverse events. Of 84 patients starting on 300 mg QD, seven 4L+ patients increased the dose from 300 mg to 400 mg. None of the D842V patients increased the dose from 300 mg to 400 mg.

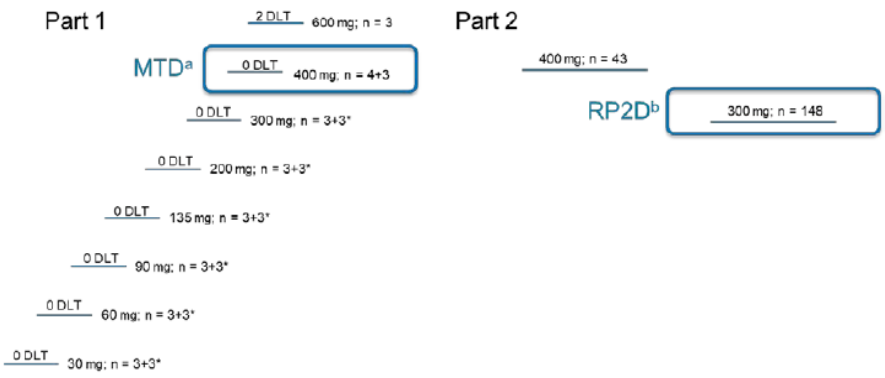
Table 4. Dose interruptions and reductions in the D842V and 4L+ populations according to avapritinib starting dose. Source BLU-285-1101

			<300 mg n=17	300 mg n=28	400 mg n=10	300 mg or 400 mg n=38
D842V patients						
	Dose interruptions, n (%)					
		≥1	15 (88)	23 (82)	8 (80)	31 (82)
	Dose reductions, n (%)					
		≥1	10 (59)	17 (61)	7 (70)	24 (63)
	Dose intensity, , median (range)					
		mg/day	153 (99-270)	223 (74-300)	204 (64-400)	220 (64-400)
			<300 mg n=16	300 mg n=84	400 mg n=37	300 mg or 400 mg n=121
4L+ patients*						
	Dose interruptions, n (%)					
		≥1	10 (62)	53 (63)	23 (62)	76 (63)
	Dose reductions, n (%)					
		≥1	6 (37)	38 (45)	23 (62)	61 (50)
	Dose intensity, median (range)					
		mg/day	145 (29-270)	267 (113-372)	313 (177-400)	282 (113-400)

*Including 8 patients harbouring the PDGFRA D842V mutation. Dose modifications in the 4L+ non-D842V population was not found in the submitted data.

Efficacy analyses presented below therefore focus on the 300 mg and 400 mg dose levels.

Figure 7: Schematic of Part 1 Dose Escalation (3+3 Design)



Abbreviations: DLT=dose-limiting toxicity; MTD=maximum tolerated dose; RP2D=recommended Phase 2 dose
[a] MTD determined based on Cycle 1 DLT. Note Patient 07-1601-005 received <21 doses of study drug during Cycle 1 and did not experience DLT and thus, was not evaluable per protocol
[b] RP2D chosen to optimize tolerability and anti-tumor activity
*additional accrual of patients after dose level declared tolerable
Source: Table 14.3.12.4 and Listing 16.1

Main study

Study BLU-285-1101

Methods

An open-label, multicenter study of avapritinib in adult patients with unresectable or metastatic GIST or other relapsed or refractory solid tumours. The study was initiated as a Phase 1, FIH study but was expanded with registrational intent in advanced GIST based on initial efficacy data. The study included a dose escalation part (Part 1) to determine the MTD and/or RP2D; and an expansion part (Part 2) to further evaluate the safety and tolerability, and to assess the clinical efficacy of avapritinib at the MTD/RP2D.

Study Participants

Main Inclusion criteria

2. For Part 1: Histologically- or cytologically-confirmed diagnosis of unresectable GIST or another advanced solid tumour. Patients with unresectable GIST must have had disease that had progressed following imatinib and at least 1 of the following: sunitinib, regorafenib, sorafenib, dasatinib, pazopanib or an experimental kinase inhibitor agent, or disease with a D842 mutation in PDGFRA. Patients with an advanced solid tumour other than GIST must have had relapsed or refractory disease without an available effective therapy.

    • At daily doses <100 mg, patients could have had the diagnosis of either GIST or a relapsed or refractory solid tumour.

    • At daily doses ≥100 mg, at least 2 patients in a cohort (4 patients if the cohort was expanded) must have had the diagnosis of GIST.

3. For Part 2:

    • Group 1: Patients must have had a confirmed diagnosis of unresectable GIST that had progressed following imatinib and at least 1 of the following: sunitinib, regorafenib, sorafenib, dasatinib, pazopanib, or an experimental kinase inhibitor agent, and the patient did not have a D842V mutation in PDGFRA.

    • Group 2: Patients must have had a confirmed diagnosis of unresectable GIST with a D842V mutation in PDGFRA. The PDGFRA mutation should have been identified by local or central assessment, either in an archival tissue sample or a new tumour biopsy obtained prior to treatment with avapritinib.

    • Group 3: Patients must have had a confirmed diagnosis of unresectable GIST that had progressed and/or patients must have had experienced intolerance to imatinib and not have received additional kinase inhibitor therapy. Patients must not have had a known D842V mutation in PDGFRA.

    • Groups 1, 2, and 3: At least 1 measurable lesion defined by the modified Response Evaluation Criteria in Solid Tumours (mRECIST) version 1.1 for patients with GIST.

    • Groups 1 and 2: A tumour sample (archival tissue or a new tumour biopsy) had been submitted for mutational testing.

4. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2

Main Exclusion Criteria

1. Patient had any of the following within 14 days prior to the first dose of study drug:

a. Alanine aminotransferase (ALT) and aspartate aminotransferase >3×upper limit of normal (ULN) if no hepatic metastases were present; >5×ULN if hepatic metastases were present.

b. Total bilirubin >1.5×ULN; >3×ULN with direct bilirubin >1.5×ULN in the presence of Gilbert's Disease.

c. Estimated (Cockcroft-Gault formula) or measured creatinine clearance <40 mL/min.

d. Platelet count <90×109/L.

e. Absolute neutrophil count (ANC) <1.0×109/L.

f. Hemoglobin <9 g/dL. Transfusion and erythropoietin may have been used to reach at least 9 g/dL, but must have been administered at least 2 weeks prior to the first dose of study drug.

2. Patient received an anti-cancer drug less than 5 half-lives or 14 days (whichever was shorter) prior to the first dose of study drug.

3. Patient had received neutrophil growth factor support within 14 days of the first dose of study drug.

4. Group 3: Patients known to be KIT wild type.

5. Patient required therapy with a concomitant medication that was a strong inhibitor or strong inducer of cytochrome P450 (CYP) 3A4.

6. Patient had a major surgical procedure (minor surgical procedures such as central venous catheter placement, tumour needle biopsy, and feeding tube placement were not considered major surgical procedures) within 14 days of the first dose of study drug.

8. Patient had a QT interval corrected using Fridericia's formula (QTcF) >450 ms.

9. Patient had a history of a seizure disorder (eg, epilepsy) or requirement for anti-seizure medication.

10. Patient had a history of a cerebrovascular accident or transient ischemic attacks within 1 year prior to the first dose of study drug.

11. Patient had a known risk of intracranial bleeding, such as a brain aneurysm or history of subdural or subarachnoid bleeding.

12. Patient had a primary brain malignancy or metastases to the brain.

13. Patient had clinically significant, uncontrolled, cardiovascular disease, including congestive heart failure Grades II, III or IV according to the New York Heart Association classification, myocardial infarction, or unstable angina within the previous 6 months, or poorly controlled hypertension.

Treatments

Avapritinib was to be administered PO QD, in the morning, on Days 1 to 28 in 28-day cycles. Patients in Part 1 were also to be administered a single dose of avapritinib on Day -3 as part of the PK lead-in phase. Dosing was to be continuous, with no inter-cycle rest periods.

A temporary discontinuation (up to 2 weeks) in avapritinib dosing was allowed for patients who required an interruption (eg, for surgery or other procedure) during the treatment period. Avapritinib was to be discontinued 48 hours before the procedure and resumed 48 hours after the procedure was completed.

Objectives

The **primary objectives** were:

- To determine the ORR by mRECIST version 1.1 criteria at the MTD/RP2D of avapritinib in patients with GIST who had a D842V mutation in PDGFRA.
- To determine the ORR by mRECIST version 1.1 criteria at the MTD/RP2D of avapritinib in patients with GIST that had progressed following treatment with imatinib and at least 1 other kinase inhibitor, and who are not known to have a D842V mutation in PDGFRA.
- To determine the ORR by mRECIST version 1.1 criteria at the MTD/R2PD of avapritinib in patients with GIST who had progressed or who experienced intolerance to imatinib, including in the adjuvant setting, and who had not received additional kinase inhibitor therapy and did not have a known D842V mutation in PDGRA.
- To determine the safety and tolerability of avapritinib.

Outcomes/endpoints

The **primary endpoints** were:

- ORR, defined as the rate of centrally confirmed CR or PR by mRECIST version 1.1

Overall safety profile of avapritinib, as assessed by the type, frequency, severity, timing, and relationship to study drug of any AEs, SAEs, and changes in vital signs, ECGs, and safety laboratory tests.

The **secondary endpoints** were:

- PK parameters of avapritinib
- DOR, PFS, and CBR, as per mRECIST version 1.1
- Response rate as defined by Choi Criteria
- PFS on last prior anti-cancer therapy
- KIT, PDGFRA, and other cancer relevant mutations present in tumor tissue at baseline and EOT
- Change from baseline in the levels of KIT, PDGFRA, and other cancer relevant mutant allele fractions in peripheral blood

Exploratory Endpoints were:

- OS
- Correlation of baseline KIT, PDGFRA, and other cancer relevant mutation status with antineoplastic activity.
- Correlation of KIT, PDGFRA, and other cancer relevant mutant allele fractions in ctDNA with antineoplastic activity.
- Levels of exploratory blood and tumor markers.

Time to response was not specified in the protocol as an exploratory endpoint but was included in the statistical analysis plan (SAP) as it was considered to be helpful in the interpretation of study results.

Sample size

Sample size calculations were carried out separately for three groups and were based on exact binomial tests of ORR with 90% power and assuming a 2-sided Type I error of 0.05 for each separate group. An ORR with a lower bound of the 95% confidence interval above the 'Null ORR' was considered clinically meaningful and to exceed expected ORR with available therapies.

Amendment 6 (14th Feb 2017) changed the number of patients in Group 2 from "approximately 15" to 50, when the primary objective changed from safety to ORR.

Amendment 7 (01 Sept 2017) changed the sample size of Group 1 from 50 to 100 based on observed PFS of 9.3 months and 8% response rate.

The sample size for Group 2 was changed from 50 to 31 in Amendment 8 (28th Feb. 2018) where Table 2, section 1.4 of the protocol already presents an ORR of 71% (95% CI: 52% - 86%) based on 31 PDGFRα D842V patients with ≥ 1 radiographic assessment.

Blinding (masking)

N/A

Statistical methods

The study data were analyzed and reported based on all patients' data from the Part 1 dose escalation, and the combined Part 1 and Part 2 data by mutation type and/or line of therapy and dose levels.

All primary analyses were conducted and presented by starting daily dose, grouped as '300 mg', '400 mg', and '300/400 mg' for the Safety Population and/or its subpopulations.

Analysis Populations

The following analysis populations were defined for the presentation of efficacy and safety data:

- Safety Population: All patients who received at least 1 dose of study drug. This was the primary population for efficacy and safety analyses unless otherwise specified. Patients were analyzed based on the dose they received on Day 1.

Selected analyses were conducted on subpopulations of safety population based on lines of TKI therapy and GIST mutation types, which were determined in the order of QIAGEN, Sysmex or PGDx, and local assays when available. These patients can be identified by currently available validated and standardised laboratory tests as well as commercially available IVD's.

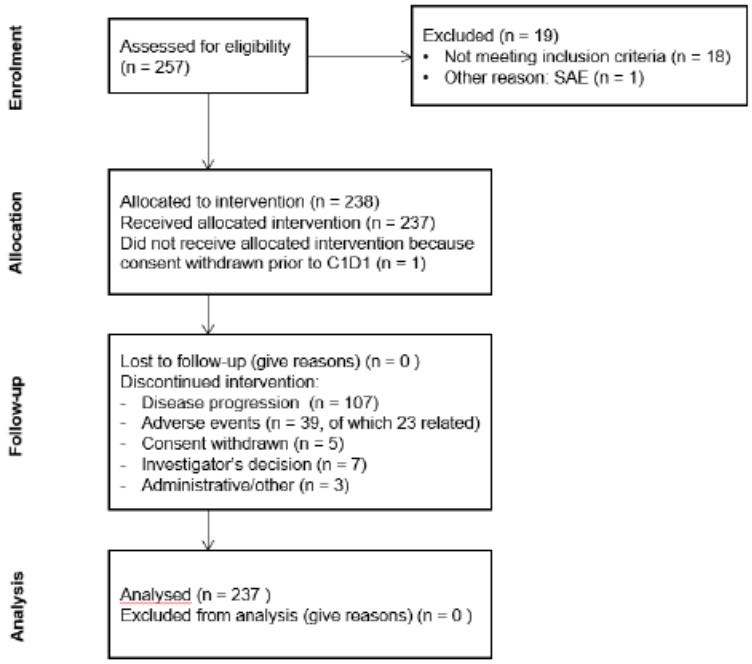
- Fourth-line or later (4L+): all patients regardless of mutation type, who received 3 or more prior lines of TKI
  - Non-D842V 4L+: non-PDGFRA D842V 4L+ patients
- Exon 18: PDGFRA exon 18 patients
  - D842V: PDGFRA D842V patients
  - QIAGEN D842V: PDGFRA D842V patients determined by the QIAGEN assay

Results

Participant flow

A comprehensive description of the progress of study BLU-285-1101 is provided in the figure below.

CONSORT flow diagram of study BLU-285-1101



Data cut-off date: 16-11-2018

Table 18: Overall Demographic and Baseline Characteristics (Safety Population)

Parameter	Avapritinib Starting Dose (QD)				All Doses[c] (N=237)
	<300 mg[a] (N=30)	300 mg (N=154)	400 mg (N=50)	300/400 mg[b] (N=204)	
Age (years), n	30	154	50	204	237
Mean (StdDev)	60.4 (9.46)	59.8 (11.30)	58.7 (10.39)	59.5 (11.06)	59.5 (11.03)
Median	60.5	62.0	60.5	62.0	62.0
Min, Max	41, 77	29, 90	35, 85	29, 90	25, 90
Age Group, n (%)					
<65 years	20 (66.7)	91 (59.1)	31 (62.0)	122 (59.8)	144 (60.8)
≥65 years	10 (33.3)	63 (40.9)	19 (38.0)	82 (40.2)	93 (39.2)
Sex, n (%)					
Female	11 (36.7)	60 (39.0)	20 (40.0)	80 (39.2)	92 (38.8)
Male	19 (63.3)	94 (61.0)	30 (60.0)	124 (60.8)	145 (61.2)
Race, n (%)					
American Indian or Alaska Native	0	1 (<1)	1 (2.0)	2 (<1)	2 (<1)
Asian	0	21 (13.6)	0	21 (10.3)	21 (8.9)
Black or African American	2 (6.7)	7 (4.5)	1 (2.0)	8 (3.9)	10 (4.2)
White	24 (80.0)	106 (68.8)	40 (80.0)	146 (71.6)	173 (73.0)
Unknown	4 (13.3)	14 (9.1)	8 (16.0)	22 (10.8)	26 (11.0)
Other	0	5 (3.2)	0	5 (2.5)	5 (2.1)
Ethnicity, n (%)					
Hispanic or Latino	0	5 (3.2)	1 (2.0)	6 (2.9)	6 (2.5)
Not Hispanic or Latino	24 (80.0)	132 (85.7)	40 (80.0)	172 (84.3)	199 (84.0)
Not Reported	3 (10.0)	10 (6.5)	4 (8.0)	14 (6.9)	17 (7.2)
Unknown	3 (10.0)	7 (4.5)	5 (10.0)	12 (5.9)	15 (6.3)
Region, n (%)					
US	14 (46.7)	71 (46.1)	21 (42.0)	92 (45.1)	108 (45.6)
Europe	16 (53.3)	66 (42.9)	29 (58.0)	95 (46.6)	112 (47.3)
Asia	0	17 (11.0)	0	17 (8.3)	17 (7.2)
Weight (kg), n	30	154	50	204	237
Mean (StdDev)	83.31 (20.740)	75.74 (20.988)	76.98 (21.199)	76.04 (20.994)	77.04 (21.045)
Median	79.80	73.70	75.60	74.10	75.00

Parameter	Avapritinib Starting Dose (QD)				All Doses[c] (N=237)
	<300 mg[a] (N=30)	300 mg (N=154)	400 mg (N=50)	300/400 mg[b] (N=204)	
Min, Max	46.1, 131.1	42.0, 156.3	39.5, 125.3	39.5, 156.3	39.5, 156.3
BMI (kg/m^2), n	27	139	46	185	215
Mean (StdDev)	26.83 (5.872)	25.77 (6.443)	26.23 (5.935)	25.88 (6.308)	26.02 (6.221)
Median	26.26	24.03	25.83	24.62	25.06
Min, Max	18.0, 41.1	15.6, 55.6	15.3, 42.0	15.3, 55.6	15.3, 55.6
ECOG Performance Status, n (%)					
0	15 (50.0)	58 (37.7)	19 (38.0)	77 (37.7)	93 (39.2)
1	14 (46.7)	91 (59.1)	29 (58.0)	120 (58.8)	136 (57.4)
2	1 (3.3)	5 (3.2)	2 (4.0)	7 (3.4)	8 (3.4)

Abbreviations: BMI=body mass index; ECOG=Eastern Cooperative Oncology Group; Max=maximum; Min=minimum; StdDev=standard deviation; QD=once daily; US=United States.

[a] Includes patients who received avapritinib at starting dose levels of 30 mg, 60 mg, 90 mg, 135 mg, or 200 mg

[b] Includes patients who received a starting dose of either 300 mg or 400 mg avapritinib

[c] Includes 3 patients who received 600 mg avapritinib

Source: Table 14.1.4.1

For the 121 patients in the 4L+ population who received a 300 or 400 mg starting dose, the primary tumor site of GIST was stomach (34 patients, 28%) and small intestine (34 patients, 28%) at the time of study entry. At study entry, the largest target lesion was > 5 cm for 65%. Metastatic disease was reported in 119 patients (98%), primarily to the liver (65%); 88% of patients had prior surgical resection.

Of them, 91% (110 patients) of the 4L+ population had KIT mutations, primarily at exon 11 (61%) and exon 17 (46%) and 9% (11 patients) had PDGFRA mutations at exon 18. Of the 11 patients with PDGFRA mutations at exon 18, 8 had PDGFRA D842V mutations and 3 had PDGFRA non-D842V mutations.

A total of 40 (33%) and 81 (67%) patients received 3 or ≥ 4 lines of prior TKI therapy. The median number of prior TKI therapies was 4 (range 3 to 11) indicating patients in the 4L+ population have exhausted all available treatment options with a clinical trial or palliative care remaining the only options.

Very few patients in the 4L+ population had objective response reported with their last prior TKI therapy; the best response to last prior TKI therapy was PD in 44 (36%), SD in 43 (36%), PR in 4 (3%), and CR in 1 (< 1%) patient.

In the population of patients with a PDGFRA D842V mutation(n=38), the demographic and baseline characteristics were: most patients were male (25 patients, 66%), white (25 patients, 66%), and < 65 years of age (22 patients; 58%). The median age was 64 years and ranged from 29 to 90 years. Most patients (36 patients, 95%) had an ECOG performance status of 0 or 1 at baseline. Overall, 22 (58%) patients were treated at study sites in Europe, 11 (29%) patients were treated at study sites in the US, and 5 (13%) patients were treated at study sites in Asia.

Baseline disease characteristics of the 38 patients with PDGFRA D842V mutations are summarized in Table 16.

Table 16: Overall Baseline Disease Characteristics (Safety Population: PDGFRA D842V Patients)

Parameter	Avapritinib Starting Dose (QD)		
	300 mg (N=28)	400 mg (N=10)	300 mg/ 400 mg[a] (N=38)
Primary Tumor Site of GIST, n (%)			
Stomach	21 (75.0)	8 (80.0)	29 (76.3)
Duodenum	0	1 (10.0)	1 (2.6)
Jejunum or Ileum	1 (3.6)	0	1 (2.6)
Rectum	1 (3.6)	0	1 (2.6)
Omentum	1 (3.6)	1 (10.0)	2 (5.3)
Colon	1 (3.1)	0	1 (2.6)
Peritoneum	3 (10.7)	0	3 (7.9)
Other	0	0	0
Largest Target Lesion Size, n (%)			
≤ 5 cm	13 (46.4)	4 (40.0)	17 (44.7)
> 5 to ≤ 10 cm	9 (32.1)	4 (40.0)	13 (34.2)
> 10 cm	6 (21.4)	2 (20.0)	8 (21.1)
Metastatic Disease, n (%)			
Yes	27 (96.4)	10 (100)	37 (97.4)
No	1 (3.6)	0	1 (2.6)
Site of Metastatic Disease, n (%)			
Abdomen	1 (3.6)	1 (10.0)	2 (5.3)
Adrenals	1 (3.6)	0	1 (2.6)
Bone	1 (3.6)	0	1 (2.6)
Colorectal	0	1 (10.0)	1 (2.6)
Liver	13 (46.4)	6 (60.0)	19 (50.0)
Lymph Nodes	1 (3.6)	1 (10.0)	2 (5.3)
Pancreas	1 (3.6)	0	1 (2.6)
Peritoneum	17 (60.7)	3 (30.0)	20 (52.6)
Other	5 (17.9)	3 (30.0)	8 (21.1)
Prior Surgical Resection, n (%)			
Yes	25 (89.3)	9 (90.0)	34 (89.5)
No	3 (10.7)	1 (10.0)	4 (10.5)

Abbreviations: GIST = gastrointestinal stromal tumor; QD = once daily.
[a] Includes patients who received a starting dose of either 300 mg or 400 mg avapritinib.

For the 38 patients with PDGFRA D842V mutations population, the primary tumor site of GIST was most commonly reported as the stomach (76%); the largest target lesion was > 5 cm for 55% of patients. Metastatic disease was reported in 37 patients (97%) primarily to the peritoneum (53%) and liver (50%); 90% of patients had prior surgical resection.

Prior TKI therapies received by the PDGFRA D842V mutations population who received starting doses of 300 or 400 mg avapritinib for the underlying malignancy are summarized in Table 17.

Table 17: Prior Tyrosine Kinase Inhibitor Therapy (Safety Population: PDGFRA D842V Patients)

Parameter	Avapritinib Starting Dose (QD)		
	300 mg (N=28)	400 mg (N=10)	300 mg/ 400 mg[a] (N=38)
Number of Prior Lines of TKI			
Mean (StdDev)	1.7 (1.42)	1.5 (0.97)	1.6 (1.30)
Median	1.0	1.0	1.0
Min, Max	0, 5	0, 3	0, 5
Number of Prior Lines TKI, n (%)			
0	4 (14.3)	1 (10.0)	5 (13.2)
1	13 (46.4)	5 (50.0)	18 (47.4)
2	5 (17.9)	2 (20.0)	7 (18.4)
3	2 (7.1)	2 (20.0)	4 (10.5)
4+	4 (14.3)	0	4 (10.5)
Best Response to Last Prior TKI, n (%)			
Complete Response (CR)	0	0	0
Partial Response (PR)	0	0	0
Stable Disease (SD)	6 (21.4)	2 (20.0)	8 (21.1)
Progressive Disease (PD)	11 (39.3)	2 (20.0)	13 (34.2)
Not Evaluable (NE)	6 (21.4)	2 (20.0)	8 (21.1)
Missing	5 (17.9)	4 (40.0)	9 (23.7)
Prior Regorafenib, n (%)			
Yes	4 (14.3)	2 (20.0)	6 (15.8)
No	24 (85.7)	8 (80.0)	32 (84.2)

Abbreviations: max = maximum; min = minimum; QD = once daily; StdDev = standard deviation; TKI = tyrosine kinase inhibitor.
Notes: Prior therapies are coded using World Health Organization Drug Dictionary, enhanced March 2017. Prior therapy is defined as all treatment that started and ended on or before first dose date of avapritinib. If a patient had multiple occurrences of a medication, the patient was presented only once in the respective patient count.
[a] Includes patients who received a starting dose of either 300 mg or 400 mg avapritinib.
Source: CSR BLU-285-1101, Table 14.1.10.1.2

A total of 18 (47%), 7 (18%), 4 (11%), and 4 (14%) patients received 1, 2, 3, or ⩾ 4 lines of prior TKI therapy; 5 (13%) of 38 patients received no prior lines of TKI therapy. The median number of prior TKI therapies was 1 (range 0 to 5) for the PDGFRA D842V mutant patients.

Numbers analysed

Table 4: Analysis Populations in Study BLU-285-1101

Safety Population[a]	Avapritinib Starting Dose (QD)		
	300 mg[b] N	400 mg[c] N	300 mg/400 mg[d] N
4L+	84	37	121
Non-D842V 4L+	78	35	113
PDGFRA D842V	28	10	38
PDGFRA exon 18, non-D842V	4	1	5

Abbreviations: L = line of therapy; QD = once daily.
[a] All patients who received at least 1 dose of study drug.
[b] 300 mg is the recommended starting dose.
[c] 400 mg was determined to be the maximum tolerated dose.
[d] Includes patients who received a starting dose of either 300 mg or 400 mg avapritinib.
Source: CSR BLU-285-1101, Table 14.1.1.1

Outcomes and estimation

4L + population

The indication in 4L+ population was withdrawn by the applicant during the procedure. Therefore, this section is focused in the population of patients with a PDGFRA D842V mutation.

PDGFRA D842V patients

Efficacy data from 38 patients with unresectable or metastatic PDGFRA D842V-mutant GIST treated at 300 mg/400 mg QD were updated serval times during the procedure. The most current results for ORR and OS, confirming the data below, were provided with a cut-off date of 17 April 2020 (data snapshot). Median follow-up time was 26 months.

Primary endpoint:

The **ORR** was 95% (n=38; 95% CI: 82.3, 99.4).

Table 1: Comparison of Efficacy in Patients with PDGFRA D842V-Mutant GIST at 300/400 mg Starting Dose per Central Radiology Review by mRECIST v1.1

	Efficacy 300/400mg Data as of 16 November 2018		Efficacy 300/400 mg Update as of 17 January 2020	
Confirmed Best Response*	N=38 n (%)	95% CI (%)	N=38 n (%)	95% CI (%)
ORR	34 (89.5)	(75.2, 97.1)	36 (94.7)	(82.3, 99.4)
CR	3 (7.9)		5 (13.2)	
PR	31 (81.6)		31 (81.6)	
SD	4 (10.5)		2 (5.3)	
PD	0		0	
DCR (CR+PR+SD)	38 (100)	(90.7, 100.0)	38 (100)	(90.7, 100.0)
CBR^	37 (97.4)	(86.2, 99.9)	37 (97.4)	(86.2, 99.9)
DOR Median (months)	NE	-	22.1	(14.1, -)

Abbreviations: CI, confidence interval; CR, complete response; CBR, clinical benefit rate; DCR, disease control rate; DOR, duration of response; n/N, number of patients; GIST, gastrointestinal stromal tumors; NE, not estimated; ORR, overall response rate; PDGFRA, platelet-derived growth factor alpha; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease

Secondary endpoints:

Median **PFS** and duration of response (**DOR**) had been reached at the time of the 17 January 2020 snapshot and were 24 months (95% CI: 18.4, NE) and 22.1 months (95% CI: 14.1, NE), respectively.

Exploratory endpoint (OS):

Based on the most recent snapshot date, **median OS** has not been reached, but OS rate was estimated to be 88.6% (95% CI: 78.0, 99.1) at 18 months, and 70.6 % (95% CI: 55.2,86.0) at 24 and 36 months.

Ancillary analyses

ORR per Choi criteria

N/A

Assessment of PDGFRA D842V mutation status

In partnership with Blueprint, QIAGEN is developing an in vitro diagnostic (IVD) device, therascreen PDGFRα Polymerase Chain Reaction Kit, to detect the D842V single point mutation in the PDGFRα gene in DNA extracted from formalin-fixed paraffin-embedded GIST tumor tissue. Banked tumor samples from dose escalation and expansion patients were used to support development of this IVD. Patient samples were tested locally, and local results were used to assign patients to the appropriate expansion group. Samples were also tested retrospectively at a central laboratory, MolecularMD, as part of the development of the QIAGEN assay, see BLU-285-1101 CSR. The development of the QIAGEN assay is ongoing and CE marking is planned for the EU.

These patients can be identified by currently available laboratory tests as well as commercially available IVD's. The applicant is partnering with QIAGEN to develop a CE marked IVD. In line with current practice in the EU and prescribing information precedents, the proposed prescribing information indicates the need to test for mutational status with a validated test without mentioning any specific tests as several suitable tests are commercially available in the EU.

During Part 1, KIT mutations in tumor tissue was evaluated using KIT Plasma-Seq assay (Sysmex, Hamburg, Germany), PDGFRA mutations were evaluated using OncoBEAM™ PDGFRA assay (Sysmex, Hamburg, Germany).

In Part 2, a next generation sequencing panel was used to detect KIT, PDGFRA, and other cancer relevant mutations. Tumor tissue for both KIT and PDGFRA patients was evaluated using the CancerSELECT™ 125 assay PGDx, Baltimore, MD).

Summary of main efficacy results

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table: Summary of efficacy for trial BLU-285-1101:

Title: A Phase 1 Study of BLU-285 in Patients with Gastrointestinal Stromal Tumours (GIST) and other Relapsed and Refractory Solid Tumours.			
Study identifier	BLU-285-1101 EudraCT Number: 2015-001660-18		
Design	Phase 1, open-label, first-in-human (FIH) dose-escalation study (Part 1) which was expanded to evaluate efficacy and safety of avapritinib in patients with unresectable GIST (Part 2).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		ongoing, patients may continue to receive avapritinib until precluded by toxicity, noncompliance, withdrawal of consent, physician decision, progressive disease, death, or closure of the study by the Sponsor not applicable not applicable
Hypothesis	To evaluate the safety, tolerability, PK, PD and preliminary antineoplastic activity of avapritinib, administered orally (PO), in adult patients with unresectable GIST (Part 1). The study was further expanded to include approximately 185 number of patients to evaluate efficacy and safety of 3 populations (Part 2). The final pivotal analyses were performed on two populations: the 4L+ and PDGFRA D842V GIST populations.		
Treatment groups	**PDGFRA D842V mutation population**: comprised of GIST patients with this mutation		Oral dose of avapritinib 300 mg or 400 mg starting QD N=38
Endpoints and definitions	Primary endpoint: Overall Response Rate	mRECIST 1.1 ORR	The primary efficacy endpoint of ORR was defined as the proportion of patients with a confirmed best response of CR or PR, where CR or PR had to be confirmed at a subsequent assessment without intervening progression. The primary analysis of ORR was conducted by central radiology per mRECIST v1.1. Overall response rate was estimated using frequency, percentage, and 2-sided 95% CIs based on the exact binomial distribution (Clopper-Pearson) for the safety population.
	Secondary endpoint: Duration of Response	DOR	Duration of response was defined as the time from first documented response (CR/PR) to the date of first documented disease progression or death due to any cause, whichever occurred first.
	Secondary endpoint: Disease Control Rate	DCR	Disease control rate was defined as the proportion of patients with a confirmed CR,PR, or SD lasting for 4 cycles (16 weeks). The response was assessed per mRECIST v1.1 by central radiology and Investigator. Disease Control rate was estimated using frequency, percentage, and two-sided 95% CI based on the exact binomial distribution.

	Secondary endpoint: Overall Response Rate by Choi Criteria	Choi ORR	Overall response rate per Choi response criteria (Choi et al, 2007) was estimated using frequency, percentage, and two-sided 95% CI based on the exact binomial distribution (Clopper-Pearson).
	Explorator y endpoint: Overall Survival	OS	Overall survival was defined as the time from the start of treatment to the date of death. Patients who died before or on the data cutoff date were considered to have had an OS event. Patients who did not have death recorded prior to or on the cutoff date were censored at the last date known live.
Database lock	data cut-off date for PDGFRA D842V patients: 17-04-2020		

Results and Analysis

Analysis description	**Primary Analysis: mRECISTv1.1 ORR**	
Analysis population and time point description	The Safety Population includes all patients who have received at least 1 dose of study drug. The Safety Population will be the primary population for efficacy and safety analysis unless otherwise specified. Patients will be analysed based on the dose they receive on Day 1.	
Descriptive statistics and	Treatment group	PDGFRA D842V
	Number of subject	38
	mRECIST v1.1 ORR1, (%) (95% CI) **CR** **PR**	95 (82.3-99.4) 13 82
Effect estimate per comparison	Not Applicable. Single arm study.	
Analysis description	Secondary analyses: **DOR (months), DCR, ORR (Choi), ≥ 12 Months OS rate by K-M**	
Analysis population and time point description	other: safety population The Safety Population includes all patients who have received at least 1 dose of study drug. The Safety Population will be the primary population for efficacy and safety analysis unless otherwise specified. Patients will be analysed based on the dose they receive on Day 1.	
	DOR (months); median (CI)	22.1 (14.1, NE)
	DCR, n (%)	38 (100)[1]
	ORR (Choi criteria), (%) (95% CI)	97 (86.2, 99.9)[2]
	≥ 18 Months OS rate by K-M, (%), (95% CI)	88 (88.6 – 99.1)

[1] Reached at a previous data cut-off date: 17-01-2020 (responses to D120 LoQ)
[2] From the original data, no update is available.

Effect estimate per comparison	Not Applicable. Single arm study.

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

The proposed indication in this application are supported solely by the results of NAVIGATOR Study (BLU-285-1101). The Applicant has provided the table below, showing side-by-side the results in PDGRFA D842V patients from their study, the supportive study BLU-285-1002 and others from literature. Taking into account all the inherent limitations of indirect comparisons, the data presented is merely informative.

Table 25: Comparison of Treatment Response for PDGFRA D842V GIST Patients – Natural History versus Study BLU-285-1101

	Cassier	Yoo	Farag	BLU-285-1002	BLU-285-1101 (300/400 mg QD)
N	32	9	17[a]	22	38
ORR – 1L (95% CI)	0/32 (0%) (0.0, 10.9)	0/9 (0%) (0.0, 33.6)	2/17 (11.8%) (1.5, 36.4)	1/22 (4.5%) (0.1, 22.8)	5/5 (100%) (47.8, 100.0)
ORR - 2L (95% CI)	Not reported	0/8 (0%) (0.0, 36.9)	Not reported	0/19 (0%) (0.0, 17.7)	17/18 (94.4%) (72.7, 99.9)
ORR – 3L (95% CI)	Not reported	Not reported	Not reported	0/16 (0%) (0.0, 20.6)	6/7 (85.7) (42.1, 99.6)
ORR – any line (95% CI)	Not reported	0/9 (0%) (0.0, 33.6)	Not reported	2/22 (9.1%)[b] (1.1, 29.2)	34/38 (89.5%) (75.2, 97.1)

Abbreviations: CI = confidence interval; GIST = gastrointestinal stromal tumor; L = line of therapy; ORR = overall response rate; PD = progressive disease; PFS = progression free survival; TTP = time to tumor progression; QD = once daily.

[a] One patient without measurable disease at baseline is included because they were used in the overall evaluation of clinical activity (TTP and PD).

Clinical studies in special populations

N/A

Supportive study(ies)

Study (BLU-285-1002): A Retrospective Natural History Study of Patients with PDGFRA D842 Mutant Gastrointestinal Stromal Tumor (GIST) Previously Treated with a Kinase Inhibitor.

Retrospective data were collected from 22 patients at 3 study centers. To prevent bias in the collection of information, case selection was based on a sequential, look-back approach. In particular, information regarding any treatment outcomes was not to be used for selection purposes. The intention-to-treat (ITT) and FPT populations included all 22 (100%) patients for whom data were collected. The SPT population, a subset of the ITT population, was comprised of 19 (86%) patients who received second-line TKI treatment. The TPT population, also a subset of the ITT population, was comprised of 16 (73%) patients who received third-line TKI treatment. Of note, most patients (73%) included in this study were in the TPT population suggesting many GIST patients are not genotyped prior to treatment with approved inhibitors in the US (NCCN, 2018).

The demography and baseline characteristics of patients enrolled were consistent with that expected for patients with unresectable or metastatic GIST and the main study; most patients with data available

were male (68%), white (95%), and not Hispanic or Latino (100%). The median age at the time of diagnosis was 57 years and ages ranged from 31 years to 72 years.

Per inclusion criteria, all patients included had a confirmed PDGFRA D842 mutation. The mutation in all patients was D842V. The primary tumor location in most patients (68%) was the stomach. Overall the patients studied had high disease burden with poor prognostic features. More than half of the patients (65%) had a primary tumor size > 10 cm; 96% of patients had prior surgical resection. A total of 3 (14%), 3 (14%), 5 (23%), and 11 (50%) patients received 1, 2, 3, or ≥ 4 lines of prior TKI therapy, respectively.

The efficacy analysis across the first-line treatment, second-line treatment, and third-line treatment populations was based principally on best overall response/ORR, DOR, and PFS with OS investigated as a secondary efficacy endpoint.

The ORR, as calculated for all patients who received first-line treatment, was 4.5% (95% CI: 0.1, 22.8). No response was observed for the second-line or third-line treatment (ORR 0%).

Overall, across all lines of treatment, including those beyond third-line that were not included in the FPT, SPT, and TPT population analyses, 2 patients had a CR or PR. One patient achieved CR for 11.9 months after a partial omental resection and first-line treatment with imatinib. The other patient had an unconfirmed PR for less than a month (0.6 months) in duration during fourth-line treatment with crenolanib.

The median PFS was 5.6 months (95% CI: 3.1, 16.2) after initiating first-line treatment, 2.6 months (95% CI: 1.4, 5.9) after initiating second-line treatment, and 5.6 months (95% CI: 2.1, 11.5) after initiating third-line treatment. Figure 13 presents the Kaplan-Meier curve of PFS by line of prior therapy.

The median OS was 44.5 months (95% CI: 20.4, 69.6) after initiating first-line treatment, 28.1 months (95% CI: 12.6, 56.7) after initiating second-line treatment, and 25.5 months (95% CI: 10.5, 55.0) after initiating third-line treatment.

D180 Update

The Applicant has provided an efficacy update from study BLU-285-1101 (the main clinical study included in the original submission), as well as topline results from the phase III, randomized, active controlled (vs. regorafenib) study BLU-285-1303, and preliminary results from study BLU-285-1105 (a phase I/II, open label, single arm study in Chinese patients).

Topline Results from Study BLU-285-1303 (VOYAGER)

Study BLU-285-1303 (VOYAGER) is a global, open-label, randomized, Phase 3 trial designed to evaluate the efficacy and safety of avapritinib versus regorafenib in patients with ≥3L GIST. Patients were randomized 1:1 to receive either avapritinib (300 mg QD dosing) or regorafenib (160 mg QD dosing for 3 out of every 4 weeks). The primary efficacy endpoint was PFS by blinded, independent central radiology review, based on mRECIST v1.1 criteria for GIST. Patients were allowed to enroll regardless of their PDGFRA-D842V mutation status, the mutation status being a pre-specified stratification factor. Overall, a total of 13 patients with a PDGFRA-D842V mutation were included, 7 in the avapritinib group and 6 in the regorafenib group.

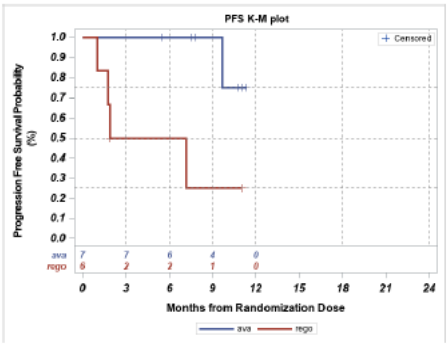
Based on the data from the 09 March 2020 DCO date, the study did not meet the primary endpoint in the ITT population (≥3L GIST patients). However, there was a statistically significant difference in PFS observed in the subset of patients with PDGFRA D842V mutations between the avapritinib and regorafenib arms (see Table 5 and Figure 1).

Table 5: Summary of Progression Free Survival in Study BLU-285-1303 – ITT Population, by PDGFRA D842V Mutation

	PDGFRA D842V Mutation Present		PDGFRA D842V Mutation Absent	
	Patients Randomized to Avapritinib N=7	Patients Randomized to Regorafenib N=6	Patients Randomized to Avapritinib N=233	Patients Randomized to Regorafenib N=230
Number of Events (%)	1 (14.3)	4 (66.7)	153 (65.7)	141 (61.3)
Median PFS (months)	NE	4.5	3.9	5.6
95% CI	(9.7, NE)	(1.7, NE)	(3.7, 5.5)	(3.8, 7.2)
HR (95% CI)	0.000 (0, -)		1.338 (1.063, 1.685)	
Log rank Test p-value	0.035		0.012	

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NE, not estimated; PDGFRA, platelet-derived growth factor receptor alpha; PFS, progression free survival.
Data cut-off date: 09 March 2020.

Figure 1: Progression Free Survival Kaplan-Meier Plot in Study BLU-285-1303 – ITT Population, PDGFRA D842V Mutation Present



Abbreviations: K-M, Kaplan-Meier; PDGFRA, platelet-derived growth factor receptor alpha; PFS, progression free survival.
Data cut-off date: 09 March 2020.

Among the patients with the D842V mutation, ORR (secondary endpoint) in the avapritinib group is 42.9%, all of which were partial responses (i.e., 0% complete responses). None of the patients in the regorafenib group responded (0% ORR).

Among avapritinib-treated patients, 1 patient had PD after ~10 months, but continued on avapritinib post-progression, 3 patients had PR and 3 patients had SD. Two of the 6 regorafenib-treated patients crossed-over to avapritinib after centrally confirmed PD as per protocol. One of them achieved a CR, whereas the other did not have a disease assessment before DCO.

Table 6: Summary of Overall Response Rate in Study BLU-285-1303 – ITT Population, by PDGFRA D842V Mutation

	PDGFRA D842V Mutation Present		PDGFRA D842V Mutation Absent	
Best Response*	Patients Randomized to Avapritinib N=7 n (%)	Patients Randomized to Regorafenib N=6 n (%)	Patients Randomized to Avapritinib N=233 n (%)	Patients Randomized to Regorafenib N=230 n (%)
ORR	3 (42.9)	0	38 (16.3)	17 (7.4)
95% CI	9.9, 81.6	0, 45.9	11.8, 21.7	4.4, 11.6
CR	0	0	0	0
PR	3 (42.9)	0	38 (16.3)	17 (7.4)
SD	4 (57.1)	3 (50)	109 (46.8)	156 (67.8)
PD	0	1 (16.7)	67 (28.8)	48 (20.9)
UNK	0	2 (33.3)[a]	18 (7.7)[b]	9 (3.9)[b]
DCR (CR, PR or SD for at least 4 cycles)	100.0	33.3	39.9	46.5
95% CI	59.0, 100.0	4.3, 77.7	33.6, 46.5	39.9, 53.2
DOR Median (months)	NE	NA	6.8	9.4

Abbreviations: CI, confidence interval CR, complete responses; DCR, disease control rate; DOR, duration of responses; n/N, number of patients; NA, not available; NE, not estimated; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; UNK, unknown
[a] Died before first on study disease assessment.
[b] No post-baseline disease assessment.
Data cut-off date: 09 March 2020.

- **Study BLU-285-1105**

Study BLU-285-1105 is an open-label, multicenter, Phase 1/2 study designed to evaluate the safety, PK and clinical efficacy of avapritinib in Chinese patients with unresectable or metastatic GIST. The study consists of a dose escalation part (Phase 1) and dose expansion (Phase 2) part. The Phase 1 portion was a modified 3+3 dose escalation design with a starting dose of 200 mg QD, escalating to 300 mg QD. The lower starting dose was used to assess for differences in tolerability in the Chinese population. As no dose limiting toxicities were observed, the Phase 2 portion of the study enrolled patients at the recommended Phase 2 (RP2D) dose of 300 mg QD.

The Phase 2 portion of the study began enrolling in December 2019 and a cohort of 25 patients with PDGFRA D842V mutations regardless of previous lines of therapy is expected to be complete with data available in Q4 2022.

Eight patients with unresectable or metastatic PDGFRA D842V-mutant GIST have been enrolled into the study (Phase 1 and Phase 2), all receiving a starting dose of 300 mg QD. At the time of the DCO date of 31 March 2020, 5 out of 8 patients had an objective response (62.5%), all of them as a PR.

Discussion on clinical efficacy

Dose-response

No formal Phase II dose-ranging studies have been conducted. The dose finding was conducted with a 3+3 dose escalation based on dose-limiting toxicities in the first treatment cycle (28 days). The optimal biologically active dose, i.e. the dose level where an increase in dose does not further improve effect outcomes, is not known. The MTD was initially set to 400 mg QD due to dose-limiting toxicities seen at 600 mg QD. However, after initiation of the study extension, the recommended starting dose was subsequently reduced to 300 mg QD. This reduction was not predefined in the study protocol. Of the patients with GIST harbouring the PDGFRA D842V mutation, 34 of 38 patients (90%) had a partial

or complete response even though 82% had dose interruptions and 63% had dose reductions due to adverse events. It was not investigated if lower initial doses can lead to similar efficacy with a lower risk of dose limiting adverse events.

Avapritinib is given as a flat dose to all patients even though it has a high pharmacokinetic variability. The population pharmacokinetic model showed that the apparent oral clearance had inter-patient variability of 44%, and there is an eight to ten-fold difference in exposure (AUC_{0-T}) at steady state between individual patients. There are known covariates affecting avapritinib exposure (PPI treatment, concomitant food intake, CYP3A inhibitors and -inducers) and several not yet investigated covariates that may affect the variability (e.g. CYP2C9 and CYP3A5-genotypes, UGT-genotypes and liver transporters).

Design and conduct of clinical studies

The Applicant initially applied for a Conditional Marketing Approval (CMA) based on a single "pivotal" study (study BLU-285-1101, NAVIGATOR) for the intended indication:

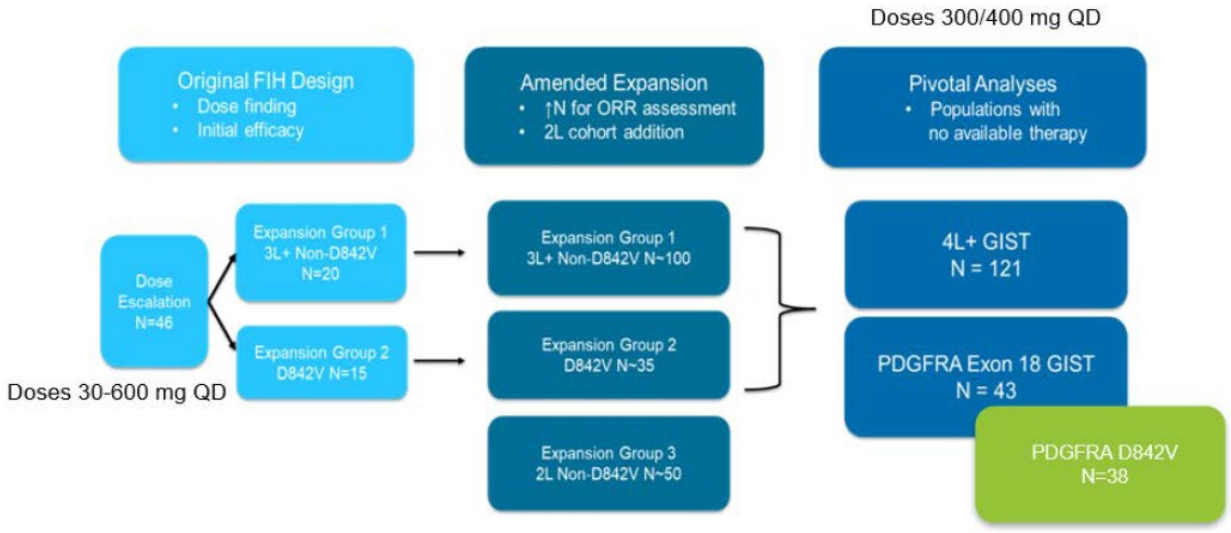
> "treatment of adult patients with unresectable or metastatic GIST who have been treated with at least 3 prior lines of therapy.
> And
> "treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation, regardless of prior therapy."

During the procedure, the applicant notified the withdrawal of the 4L indication from this MAA. As a result, the study population are 38 patients carrying the PDGFRA D842 mutation.

The NAVIGATOR study is an ongoing Phase 1, first-in-human, dose-escalation, expansion, open-label study to evaluate the safety, tolerability, PK, PD and efficacy of avapritinib in adults with unresectable GIST. At the time of the MAA submission, efficacy data have been provided with a DCO date of 16 November 2018. Additional follow-ups were provided during the procedure with a DCO date: 17 January 2020 (+14 months), and data snapshot cut-off: 17 April 2020 (+4 months).
The study design consisted of two parts: a dose escalation part (Part 1, completed), and a dose expansion part (Part 2, ongoing). The open-label, uncontrolled design of the NAVIGATOR study, along with the reduced sample size, pose relevant limitations to the interpretation of the results.

Following the results from Part 1, the initial study design was modified to increase the sample size in part 2 and to add the central assessment of ORR (by mRECIST v1.1) as a primary objective of Part 2. As a result, there are 3 expansion groups in cohort 3: the original expansion groups 1 (+3L non PDGFRA D842V patients) and 2 (PDGFRA D842V patients, regardless of prior therapy) and a new group, expansion group 3 (+2L non PDGFRA D842V patients).

Figure 4: Study Schematics Reflecting Changes in Study Design



Abbreviations: FIH = first in human; GIST = gastrointestinal stromal tumor; L = line of therapy; ORR = overall response rate.

The population included in the study is composed mainly by two different patient subsets:

- GIST patients who had received 3L+ of prior therapies (4L+ GIST population, n=121);
- GIST patients carrying the PDGFRA D842V mutation, regardless of number of prior therapies (n=38).

Five extra patients had PDGFRA exon 18 mutations different from D842V.

Efficacy results have been presented for the 300mg and 400mg doses separately and by pooling both together. This approach is considered acceptable.

Key eligibility criteria for part 2 included age ≥ 18 years, unresectable GIST, progressing following imatinib and at least 1 subsequent treatment, ECOG 0-2. Patients with D842 mutation in PDGFRA were allowed to enrol regardless of prior therapy. Patients with known brain metastasis, and relevant CNS, cardiovascular disorders or other relevant comorbidity were excluded.

The primary efficacy endpoint was ORR (CR+PR), by central radiology per mRECIST v1.1. Key secondary efficacy endpoints were DOR, PFS, and CBR, as per mRECIST v1.1; OS was included as an exploratory efficacy endpoint.

Overall, the selection of primary endpoint is in line with phase 1 development. In the context of a CMA in a setting where there are no alternative treatments with proven clinical benefit, this endpoint selection could be considered acceptable.

Regarding the patients carrying the PDGFRA D842V mutation (n=38), their demographics and disease characteristics were similar to those of the overall 4L+ population in terms of age, race, gender, ECOG performance status, and presence of metastatic disease at the time of study entry. The median number of treatment lines received, was 1 (range 0-5), with only 15.8% of patients having been exposed to regorafenib in the subgroup of patients with the PDGFRA D842V mutation. Five patients were TKi-naïve.

An additional phase III study (**BLU-285-1303**) is currently ongoing. This is a global, open-label, randomized (1:1), Phase 3 trial designed to evaluate the efficacy and safety of avapritinib versus regorafenib in patients with ≥3L disease. Patients were randomized 1:1 to receive either avapritinib (300 mg QD dosing) or regorafenib (160 mg QD dosing for 3 out of every 4 weeks). Patients are allowed to enroll regardless of their PDGFRA-D842V mutation status, although the mutation status was a pre-specified stratification factor. The primary efficacy endpoint was PFS as assessed by blinded, independent central radiology review, based on mRECIST v1.1 criteria for GIST. Per the design of the trial, patients with PDGFRA D842V-mutant GIST were eligible, but given the rarity of this mutation, only 13 patients

(~3%) were randomized. The PDGFRA D842V mutation status was a stratification factor, thus patients were evenly distributed between the 2 treatment arms.

This study did not meet the primary endpoint of an improvement in PFS for avapritinib versus regorafenib in the general patient population (ITT) with third- or fourth-line GIST. Available PFS results in the subset of patients with the PDGFRA D842V mutation, although immature, are presented as supportive to the benefit-risk balance in the target patient population with PDGFRA D842V mutated GIST.

Efficacy data and additional analyses

Results in the population of patients with the PDGFRA D842V mutation

BLU-285-1101 (NAVIGATOR) study

At the time of the most recent DCO available (data snapshot: 17 April 2020), median follow up time was 26 months. The results show an outstanding efficacy with an ORR of 95% (95% CI: 82.3, 99.4), a DOR of 22.1 months (95% CI: 14.1, NE) and a median PFS of 24 months (95% CI: 18.4, NE), while the median OS has not been reached yet (36-months OS rate is 70.6% [95% CI: 55.2, 86.0]).

ORR results in the patients with the **PDGFRA D842V** mutation, are outstanding in this patient population. Data on patients naïve to TKIs appear consistent with that of the overall D842V-mutant group, but is even more limited (n=5). However, it is agreed that in the D842V mutant GIST patient population, ORR results are unprecedented and results would not be expected to be of a lesser magnitude in the 1L setting, and the benefit is considered to be demonstrated regardless of the line of treatment. In addition, the reported durable responses compare favourably with that reported from the literature for other TKIs in the target population. Overall, the reported results in the population with the PDGFRA D842V mutation are considered relevant in the context of a patient population with limited treatment options and poor responses to approved TKI agents. This benefit is considered clinically meaningful.

BLU-285-1303 (VOYAGER) study

The topline results in the subset of patients with PDGFRA D842V mutations (DCO date: 09 March 2020) show an ORR (secondary endpoint) in the avapritinib group of 42.9% (all partial responses), while none of the patients in the regorafenib group responded (0% ORR). The magnitude of these results is smaller than those reported in study BLU-285-1101 (NAVIGATOR), and the reason behind it remains unclear. Several factors could have played a role in the differences observed, such as the small sample size and different therapy settings in terms of prior TKI treatments across all studies, since most patients from BLU-285-1101 were either TKI naïve or had received 1 prior TKI (13.2% and 47.4%, respectively), while patients in study BLU-285-1303 are at a later stage of the disease (≥3L).

Regarding median PFS in the patients with the PDGFRA D842V mutation , there was a statistically significant difference, with a not estimable median PFS in the subset of patients with PDGFRA D842V mutations who were randomized to avapritinib (95% CI: 9.7, NE) compared to 4.5 months in patients receiving regorafenib (95% CI: 1.7, NE).

Results from study *BLU-285-1105*, although limited (n=8), are considered supportive of the benefit-risk of avapritinib in the target patient population: 5 patients achieved a PR (62.5% ORR) and 3 had a SD. All of the mutant GIST patients in this study received a starting dose of 300 mg avapritinib QD.

Overall, the reported results in the patients with the PDGFRA D842V mutation are considered relevant in the context of a patient population with limited treatment options and poor responses to approved TKI agents.

Additional expert consultation

N/A

Assessment of paediatric data on clinical efficacy

N/A

Additional efficacy data needed in the context of a conditional MA

In order to provide comprehensive efficacy and safety data and being able to address remaining uncertainties needed to support the switching from conditional to normal marketing authorisation, the following SOBs are proposed:

• Study BLU-285-1101: Final CSR by 2H 2021

• Study BLU-285-1303: Final CSR by 1H 2021

Final CSRs from the ongoing studies BLU-285-1101 and BLU-285-1303 will include all available data on the safety and efficacy of avapritinib in patients with PDGFRA D842V-mutant GIST (n=51). Study results in the 2L+ GIST patients demonstrate an equivalent median duration of exposure to avapritinib as those in the 1L setting (23.2 months in both populations), indicating that safety and efficacy are similar despite prior line of treatment, and are therefore considered relevant when assessing avapritinib in the 1L disease setting.

• Study BLU-285-1406: this is a newly proposed observational study to assess long-term safety and efficacy in treatment naïve patients with unresectable or metastatic PDGFRA D842V-mutant GIST. Final study report to be provided by December 2027. Draft protocol: to be submitted at the latest 2 months after EC Decision. Enrollment update to be provided within each PSUR cycle. Annual interim reports will be provided within the annual renewal as of the second annual renewal.

This proposed study will be set up to collect long-term (minimum 2 years) safety and efficacy data in approximately 50 GIST patients in the 1L disease setting harbouring the PDGFRA D842V mutation.

Conclusions on the clinical efficacy

Avapritinib has shown an outstanding and durable ORR in patients expressing the PDGFRA D842V mutation regardless of prior line of therapy, which is unprecedented in a population subset that traditionally is unresponsive to TKI therapy. Even acknowledging the limitations associated to the low number of patients treated, the clinical benefit of this treatment in the intended target population has been shown.

2.6. Clinical safety

Patient exposure

The primary evidence of safety for the registration of avapritinib is Study BLU-285-1101, an ongoing Phase 1, open-label study designed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and efficacy of avapritinib administered orally (PO), which enrolled a total of 237

patients with unresectable or metastatic GIST. Additional safety data for avapritinib from an ongoing Phase 3 study in patients with advanced GIST (Study BLU-285-1303) and an ongoing Phase 1 study in patients with AdvSM (Study BLU-285-2101) are provided. Safety data from these 3 studies were pooled for analysis. Data are presented as of 16 November 2018, the data cutoff date for this marketing application. An updated safety database with a cut-off date 9th March 2020 has been submitted during the procedure and is presented at the end of this section.

Table 1: Completed and Ongoing Clinical Studies with Avapritinib Included in the Pooled Safety Set

	Study Number		
	BLU-285-1101	**BLU-285-1303[a]**	**BLU-285-2101**
Status	Ongoing (dose escalation complete; expansion ongoing)	Ongoing	Ongoing (dose escalation complete; expansion ongoing)
Phase	1	3	1
Number of Countries with Centers Enrolling Patients	9	17	2
Study Design and Objectives	Multicenter, open-label, dose escalation with expansion at the MTD or RP2D Primary: dose escalation - MTD, RP2D, safety and tolerability; expansion – ORR, safety and tolerability Secondary: PK, clinical activity	Multicenter, open-label, randomized with comparator (regorafenib) and crossover option Primary: progression-free survival Secondary: PK, QoL, safety and tolerability, clinical activity	Multicenter, open-label, dose escalation with expansion Primary: MTD, RP2D, safety and tolerability Secondary: PK, pharmacodynamics, QoL, clinical activity
Study Population	Dose escalation: patients with unresectable GIST (PD after imatinib + 1 other TKI or disease with PDGFRA D842 mutation) or advanced solid tumor other than GIST relapsed or refractory to treatment Expansion: patients with unresectable GIST who had PD after imatinib + 1 other TKI and did not have PDGFRA D842 mutation; patients with unresectable GIST who had PDGFRA D842 mutation; or patients with unresectable GIST who had PD and/or were intolerant to imatinib and did not have PDGFRA D842 mutation	Patients with metastatic and/or unresectable GIST with PD, inadequate clinical benefit, or intolerance to imatinib and 1 or 2 other TKIs	Patients with AdvSM and other relapsed or refractory myeloid malignancies
Study Drug Dose(s) and Regimen(s)	Dose escalation: avapritinib PO at 30, 60, 90, 135, 200, 300, 400, 600 mg QD on Days 1 to 28 of each 28-day cycle Expansion: avapritinib PO at 300 mg (RP2D) or 400 mg (MTD) QD	Avapritinib: 300 mg PO QD on Days 1 to 28 of each 28-day cycle; may escalate to 400 mg QD after 2 consecutive cycles Regorafenib: 160 mg PO QD on Days 1 to 21 of each 28-day cycle	Dose escalation: avapritinib PO at 30, 60, 100, 130, 200, 300, 400 mg QD on Days 1 to 28 of each 28-day cycle Expansion: avapritinib PO at 300 mg (Cohort 1) or 200 mg (Cohort 2) QD
Treatment Duration	Until toxicity, noncompliance, withdrawal of consent, physician decision, PD, death, or closure of study by Sponsor	Until toxicity, noncompliance, pregnancy, withdrawal of consent, physician decision, PD, death, or closure of study by Sponsor	Until toxicity, noncompliance, withdrawal of consent, physician decision, PD, death, or closure of study by Sponsor
Number of Patients	Planned: 235 (dose escalation up to 50; expansion up to 185) Dosed: 237 (46 dose escalation; 191 expansion) Discontinued treatment: 161 Continuing treatment: 76	Planned: 460 (230 avapritinib; 230 regorafenib) Dosed with avapritinib: 30 Discontinued treatment: 13 Continuing treatment: 17	Planned: 80 (dose escalation up to 25; expansion up to 55) Dosed: 68 (32 dose escalation; 36 expansion) Discontinued treatment: 17 Continuing treatment: 51
Demographics	145 M/92 F 25-90 years (median 62.0 years) White: 73.0%; Asian: 8.9%; Black: 4.2%; Other/Unknown: 13.9%	20 M/10 F 37-91 years (median 62.0 years) White: 50.0%; Asian: 26.7%; Black: 3.3%; Other/Unknown: 20.0%	35 M/33 F 34-83 years (median 64 years) White: 85.3%; Asian: 2.9%; Black: 1.5%; Other/Unknown: 10.3%
Analysis Cutoff Date for CSR	16 November 2018	No CSR available; protocol provided (Protocol BLU-285-1303)	No CSR available; protocol provided (Protocol BLU-285-2101)
Analysis Cutoff Date for Integrated Safety Analyses: 16 November 2018			
Analysis Cutoff Date for Late-breaking Safety Information: 28 February 2019			

Abbreviations: AdvSM = advanced systemic mastocytosis; CSR = clinical study report; F = female; GIST = gastrointestinal stromal tumor; M = male; MTD = maximum tolerated dose; ORR = objective response rate; PD = progressive disease; PK = pharmacokinetics; PO = orally; QD = once daily; QoL = quality of life; RP2D = recommended Phase 2 dose; TKI = tyrosine kinase inhibitor.

[a] Only data from patients assigned to Arm A and treated with avapritinib are included in the ISS pooled analysis; patients in Arm B who received regorafenib only or those who crossed over from Arm B (regorafenib) to Arm A are excluded from the pooled ISS analysis.

The Safety Population includes all patients who received at least 1 dose of avapritinib. All analyses are based on the Safety Population, and/or its subgroups, unless otherwise specified. Discussion of results

focuses on patients with GIST whose starting dose of avapritinib was 300/400 mg, unless otherwise specified.

A total of 335 patients with GIST or AdvSM across all doses were included in the Safety Population. Among the patients with GIST, 234 patients received a starting dose of 300/400 mg avapritinib.

Studies BLU-285-1101 and BLU-285-1303 contributed 237 and 30 patients with GIST, respectively, and Study BLU-285-2101 contributed 68 patients with AdvSM to the Safety Population. Studies BLU-285-1101 and BLU-285-2101 contributed 44 and 31 patients, respectively, to the DD Population.

As of the data cutoff date, 83 (35.5%) of these patients continued to receive avapritinib.

A total of 151 (64.5%) of the 234 patients had discontinued treatment. The primary reason for discontinuation of treatment was disease progression (41.9%), followed by AE (15.4%). As of the data cutoff date, 94/234 GIST patients exposed to 300/400mg (40.2%) had discontinued from the study. The primary reason for study discontinuation was death (30.8%), followed by withdrawal by subject (6.0%).

The majority of patients with GIST (234/ 267, 87.6%) received a starting dose of 300/400 mg of avapritinib. The median duration of treatment for these patients was 17.5 weeks (range: 0.1, 107.1 weeks), with 61/234 (26.1%) and 33/234 (14.1%) having been exposed to avapritinib for >24 to ≤48 weeks and >48 weeks, respectively. The median relative dose intensity was 90%, indicating good overall compliance with dosing.

For patients whose starting dose was 400 mg, the median relative dose intensity was 73% compared with 94% for patients whose starting dose was 300 mg.

A majority of patients (63.7%) had at least 1 dose interruption or missed dose due to an AE, and nearly half (47.0%) had at least 1 dose reduction due to an AE.

Demographics and disease baseline characteristics have been extensively presented in the Efficacy Section. From the safety point of view, it is relevant to note that up to 107 (40.1%) of patients with GIST were older than 65 years old, and that 96 (36.0%) of patients with GIST had received 4 or more prior lines of TKIs. Among the patients with GIST whose starting dose was 300/400 mg, 96.2% had at least 1 ongoing medical condition at baseline (GI disorders (66.7%) and Vascular Disorders (55.1%), the most frequent), and 98.7% took at least 1 concomitant medication, including paracetamol, furosemide, ondansetron red blood cells, etc.

Adverse events

- An overall summary of the AEs reported for patients in the Safety Population is provided in Table 8

Table 8: Summary of Adverse Events (Safety Population)

Patients with any:	GIST					AdvSM	GIST + AdvSM
	<300 mg N=30 n (%)	300 mg N=184 n (%)	400 mg N=50 n (%)	300/400 mg N=234 n (%)	All Doses N=267 n (%)	All Doses N=68 n (%)	All Doses N=335 n (%)
AE	30 (100)	181 (98.4)	49 (98.0)	230 (98.3)	263 (98.5)	68 (100)	331 (98.8)
Grade ≥3 AE	21 (70.0)	123 (66.8)	41 (82.0)	164 (70.1)	188 (70.4)	60 (88.2)	248 (74.0)
Treatment-related AE	30 (100)	174 (94.6)	47 (94.0)	221 (94.4)	254 (95.1)	65 (95.6)	319 (95.2)
Grade ≥3 treatment-related AE	14 (46.7)	89 (48.4)	27 (54.0)	116 (49.6)	133 (49.8)	46 (67.6)	179 (53.4)
SAE	20 (66.7)	87 (47.3)	27 (54.0)	114 (48.7)	137 (51.3)	35 (51.5)	172 (51.3)
Treatment-related SAE	8 (26.7)	39 (21.2)	8 (16.0)	47 (20.1)	58 (21.7)	17 (25.0)	75 (22.4)
AE leading discontinuation from study drug	8 (26.7)	35 (19.0)	11 (22.0)	46 (19.7)	54 (20.2)	11 (16.2)	65 (19.4)
Treatment-related AE leading discontinuation from study drug	6 (20.0)	16 (8.7)	5 (10.0)	21 (9.0)	27 (10.1)	5 (7.4)	32 (9.6)
AE leading to dose interruption	21 (70.0)	118 (64.1)	34 (68.0)	152 (65.0)	176 (65.9)	47 (69.1)	223 (66.6)
AE leading to dose reduction	13 (43.3)	75 (40.8)	33 (66.0)	108 (46.2)	123 (46.1)	43 (63.2)	166 (49.6)
DLT	0	0	0	0	2 (<1)	3 (4.4)	5 (1.5)
AE leading to death	6 (20.0)	19 (10.3)	8 (16.0)	27 (11.5)	33 (12.4)	4 (5.9)	37 (11.0)
Treatment-related AE leading to death	0	0	0	0	0	0	0
AESI of cognitive effects	10 (33.3)	65 (35.3)	24 (48.0)	89 (38.0)	101 (37.8)	21 (30.9)	122 (36.4)
AESI of intracranial bleeding	1 (3.3)	2 (1.1)	0	2 (<1)	3 (1.1)	7 (10.3)	10 (3.0)
Treatment-related AESI of cognitive effects	10 (33.3)	65 (35.3)	21 (42.0)	86 (36.8)	98 (36.7)	18 (26.5)	116 (34.6)
Treatment-related AESI of intracranial bleeding	1 (3.3)	1 (<1)	0	1 (<1)	2 (<1)	4 (5.9)	6 (1.8)
Serious AESI of cognitive effects	2 (6.7)	4 (2.2)	2 (4.0)	6 (2.6)	8 (3.0)	3 (4.4)	11 (3.3)
Serious AESI of intracranial bleeding	1 (3.3)	1 (<1)	0	1 (<1)	2 (<1)	4 (5.9)	6 (1.8)
AESI of cognitive effects leading to discontinuation from study drug	2 (6.7)	1 (<1)	3 (6.0)	4 (1.7)	6 (2.2)	2 (2.9)	8 (2.4)
AESI of intracranial bleeding leading to discontinuation from study drug	1 (3.3)	1 (<1)	0	1 (<1)	2 (<1)	1 (1.5)	3 (<1)

Abbreviations: AdvSM = advanced systemic mastocytosis; AE = adverse event; AESI = adverse event of special interest; DLT = dose-limiting toxicity; GIST = gastrointestinal stromal tumor; SAE = serious adverse event.
Notes: Percentages are based on the number of patients in the Safety Population in each column.
Patients with GIST who received a starting dose of 600 mg are included in the GIST All Doses and GIST + AdvSM All Doses columns.
If a patient experienced more than 1 event in a given category, that patient was counted only once.
Source: Table 18.1.1.3.1.1. Data cutoff date: 16 November 2018.

- Common Adverse Events: a summary of AEs by PT reported in ≥10% of all 335 patients in the Safety Population is provided in Table 9.

Table 9: Adverse Events Reported in at Least 10% of Patients Overall by Preferred Term, Indication, and Dose Level (Safety Population)

Preferred Term	GIST					AdvSM	GIST + AdvSM
	<300 mg N=30 n (%)	300 mg N=184 n (%)	400 mg N=50 n (%)	300/400 mg N=234 n (%)	All Doses N=267 n (%)	All Doses N=68 n (%)	All Doses N=335 n (%)
Patients with any adverse event	30 (100)	181 (98.4)	49 (98.0)	230 (98.3)	263 (98.5)	68 (100)	331 (98.8)
Nausea	16 (53.3)	107 (58.2)	38 (76.0)	145 (62.0)	164 (61.4)	25 (36.8)	189 (56.4)
Fatigue	22 (73.3)	90 (48.9)	34 (68.0)	124 (53.0)	148 (55.4)	25 (36.8)	173 (51.6)
Anaemia	14 (46.7)	85 (46.2)	26 (52.0)	111 (47.4)	126 (47.2)	36 (52.9)	162 (48.4)
Periorbital oedema	15 (50.0)	62 (33.7)	26 (52.0)	88 (37.6)	104 (39.0)	50 (73.5)	154 (46.0)
Diarrhoea	15 (50.0)	59 (32.1)	19 (38.0)	78 (33.3)	96 (36.0)	24 (35.3)	120 (35.8)
Vomiting	14 (46.7)	56 (30.4)	27 (54.0)	83 (35.5)	99 (37.1)	20 (29.4)	119 (35.5)
Decreased appetite	11 (36.7)	62 (33.7)	21 (42.0)	83 (35.5)	97 (36.3)	11 (16.2)	108 (32.2)
Oedema peripheral	15 (50.0)	47 (25.5)	18 (36.0)	65 (27.8)	80 (30.0)	23 (33.8)	103 (30.7)
Lacrimation increased	11 (36.7)	50 (27.2)	21 (42.0)	71 (30.3)	83 (31.1)	7 (10.3)	90 (26.9)
Memory impairment	7 (23.3)	43 (23.4)	19 (38.0)	62 (26.5)	70 (26.2)	13 (19.1)	83 (24.8)
Hair colour changes	11 (36.7)	29 (15.8)	14 (28.0)	43 (18.4)	55 (20.6)	20 (29.4)	75 (22.4)
Constipation	10 (33.3)	39 (21.2)	12 (24.0)	51 (21.8)	62 (23.2)	10 (14.7)	72 (21.5)
Abdominal pain	8 (26.7)	38 (20.7)	10 (20.0)	48 (20.5)	57 (21.3)	13 (19.1)	70 (20.9)
Face oedema	3 (10.0)	43 (23.4)	14 (28.0)	57 (24.4)	62 (23.2)	7 (10.3)	69 (20.6)
Dizziness	6 (20.0)	24 (13.0)	21 (42.0)	45 (19.2)	53 (19.9)	13 (19.1)	66 (19.7)
Blood bilirubin increased	4 (13.3)	38 (20.7)	11 (22.0)	49 (20.9)	55 (20.6)	9 (13.2)	64 (19.1)
Headache	6 (20.0)	30 (16.3)	10 (20.0)	40 (17.1)	48 (18.0)	10 (14.7)	58 (17.3)
Dysgeusia	5 (16.7)	28 (15.2)	5 (10.0)	33 (14.1)	40 (15.0)	11 (16.2)	51 (15.2)
Dyspnoea	4 (13.3)	25 (13.6)	12 (24.0)	37 (15.8)	42 (15.7)	8 (11.8)	50 (14.9)
Hypokalaemia	5 (16.7)	27 (14.7)	7 (14.0)	34 (14.5)	40 (15.0)	9 (13.2)	49 (14.6)
Dyspepsia	8 (26.7)	27 (14.7)	7 (14.0)	34 (14.5)	43 (16.1)	4 (5.9)	47 (14.0)
Hypophosphataemia	5 (16.7)	22 (12.0)	8 (16.0)	30 (12.8)	36 (13.5)	8 (11.8)	44 (13.1)
Insomnia	7 (23.3)	20 (10.9)	6 (12.0)	26 (11.1)	34 (12.7)	8 (11.8)	42 (12.5)
Rash	5 (16.7)	17 (9.2)	10 (20.0)	27 (11.5)	33 (12.4)	9 (13.2)	42 (12.5)
Alopecia	4 (13.3)	18 (9.8)	10 (20.0)	28 (12.0)	33 (12.4)	8 (11.8)	41 (12.2)
Cough	10 (33.3)	14 (7.6)	7 (14.0)	21 (9.0)	33 (12.4)	7 (10.3)	40 (11.9)
Pleural effusion	4 (13.3)	21 (11.4)	5 (10.0)	26 (11.1)	31 (11.6)	7 (10.3)	38 (11.3)
Weight decreased	7 (23.3)	22 (12.0)	5 (10.0)	27 (11.5)	35 (13.1)	3 (4.4)	38 (11.3)
Aspartate aminotransferase increased	2 (6.7)	20 (10.9)	10 (20.0)	30 (12.8)	32 (12.0)	4 (5.9)	36 (10.7)
Cognitive disorder	2 (6.7)	23 (12.5)	3 (6.0)	26 (11.1)	29 (10.9)	7 (10.3)	36 (10.7)
Pyrexia	1 (3.3)	21 (11.4)	9 (18.0)	30 (12.8)	31 (11.6)	4 (5.9)	35 (10.4)

Abbreviations: AdvSM = advanced systemic mastocytosis; GIST = gastrointestinal stromal tumor.
Notes: Percentages are based on the number of patients in the Safety Population in each column.
Patients with GIST who received a starting dose of 600 mg are included in the GIST All Doses and GIST + AdvSM All Doses columns.
If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term.
Source: Table 18.1.1.3.2.1. Data cutoff date: 16 November 2018.

- Adverse events by severity

Table 10: Grade 3 or Higher Adverse Events Reported in at Least 2% of Patients Overall by Preferred Term, Indication, and Dose Level (Safety Population)

	GIST					AdvSM	GIST + AdvSM
Preferred Term	<300 mg N=30 n (%)	300 mg N=184 n (%)	400 mg N=50 n (%)	300/400 mg N=234 n (%)	All Doses N=267 n (%)	All Doses N=68 n (%)	All Doses N=335 n (%)
Patients with any Grade ≥3 adverse event	21 (70.0)	123 (66.8)	41 (82.0)	164 (70.1)	188 (70.4)	60 (88.2)	248 (74.0)
Anaemia	7 (23.3)	43 (23.4)	17 (34.0)	60 (25.6)	68 (25.5)	18 (26.5)	86 (25.7)
Fatigue	1 (3.3)	8 (4.3)	8 (16.0)	16 (6.8)	17 (6.4)	5 (7.4)	22 (6.6)
Hypophosphataemia	2 (6.7)	6 (3.3)	3 (6.0)	9 (3.8)	12 (4.5)	5 (7.4)	17 (5.1)
Abdominal pain	2 (6.7)	12 (6.5)	1 (2.0)	13 (5.6)	15 (5.6)	1 (1.5)	16 (4.8)
Disease progression	2 (6.7)	8 (4.3)	4 (8.0)	12 (5.1)	14 (5.2)	2 (2.9)	16 (4.8)
Blood bilirubin increased	0	9 (4.9)	1 (2.0)	10 (4.3)	11 (4.1)	2 (2.9)	13 (3.9)
Neutropenia	1 (3.3)	3 (1.6)	1 (2.0)	4 (1.7)	6 (2.2)	7 (10.3)	13 (3.9)
Thrombocytopenia	0	0	0	0	0	13 (19.1)	13 (3.9)
Diarrhoea	1 (3.3)	7 (3.8)	3 (6.0)	10 (4.3)	11 (4.1)	1 (1.5)	12 (3.6)
Nausea	2 (6.7)	3 (1.6)	3 (6.0)	6 (2.6)	8 (3.0)	3 (4.4)	11 (3.3)
Hypertension	0	5 (2.7)	2 (4.0)	7 (3.0)	7 (2.6)	3 (4.4)	10 (3.0)
Decreased appetite	3 (10.0)	3 (1.6)	3 (6.0)	6 (2.6)	9 (3.4)	0	9 (2.7)
Hypokalaemia	0	4 (2.2)	2 (4.0)	6 (2.6)	7 (2.6)	2 (2.9)	9 (2.7)
Neutrophil count decreased	1 (3.3)	6 (3.3)	1 (2.0)	7 (3.0)	8 (3.0)	1 (1.5)	9 (2.7)
Ascites	1 (3.3)	4 (2.2)	2 (4.0)	6 (2.6)	7 (2.6)	1 (1.5)	8 (2.4)
Hyponatraemia	0	5 (2.7)	1 (2.0)	6 (2.6)	6 (2.2)	2 (2.9)	8 (2.4)
Pneumonia	0	4 (2.2)	0	4 (1.7)	4 (1.5)	4 (5.9)	8 (2.4)
Dyspnoea	1 (3.3)	4 (2.2)	2 (4.0)	6 (2.6)	7 (2.6)	0	7 (2.1)
General physical health deterioration	1 (3.3)	4 (2.2)	2 (4.0)	6 (2.6)	7 (2.6)	0	7 (2.1)
Pleural effusion	1 (3.3)	3 (1.6)	2 (4.0)	5 (2.1)	6 (2.2)	1 (1.5)	7 (2.1)
Upper gastrointestinal haemorrhage	3 (10.0)	3 (1.6)	0	3 (1.3)	6 (2.2)	1 (1.5)	7 (2.1)
Vomiting	1 (3.3)	3 (1.6)	1 (2.0)	4 (1.7)	5 (1.9)	2 (2.9)	7 (2.1)

Abbreviations: AdvSM = advanced systemic mastocytosis; GIST = gastrointestinal stromal tumor.
Notes: Percentages are based on the number of patients in the Safety Population in each column.
Patients with GIST who received a starting dose of 600 mg are included in the GIST All Doses and GIST + AdvSM All Doses columns.
If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term.
Source: Table 18.1.1.3.4.1. Data cutoff date: 16 November 2018.

- Treatment-related adverse events

Table 11: Treatment-Related Adverse Events Reported in at Least 10% of Patients Overall by Preferred Term, Indication, and Dose Level (Safety Population)

	GIST					AdvSM	GIST + AdvSM
Preferred Term	<300 mg N=30 n (%)	300 mg N=184 n (%)	400 mg N=50 n (%)	300/400 mg N=234 n (%)	All Doses N=267 n (%)	All Doses N=68 n (%)	All Doses N=335 n (%)
Patients with any treatment-related adverse event	30 (100)	174 (94.6)	47 (94.0)	221 (94.4)	254 (95.1)	65 (95.6)	319 (95.2)
Nausea	14 (46.7)	99 (53.8)	35 (70.0)	134 (57.3)	151 (56.6)	21 (30.9)	172 (51.3)
Periorbital oedema	15 (50.0)	61 (33.2)	26 (52.0)	87 (37.2)	103 (38.6)	48 (70.6)	151 (45.1)
Fatigue	19 (63.3)	74 (40.2)	31 (62.0)	105 (44.9)	126 (47.2)	19 (27.9)	145 (43.3)
Anaemia	11 (36.7)	67 (36.4)	15 (30.0)	82 (35.0)	94 (35.2)	26 (38.2)	120 (35.8)
Vomiting	11 (36.7)	47 (25.5)	23 (46.0)	70 (29.9)	83 (31.1)	14 (20.6)	97 (29.0)
Diarrhoea	12 (40.0)	52 (28.3)	15 (30.0)	67 (28.6)	81 (30.3)	14 (20.6)	95 (28.4)
Oedema peripheral	10 (33.3)	41 (22.3)	16 (32.0)	57 (24.4)	67 (25.1)	19 (27.9)	86 (25.7)
Lacrimation increased	9 (30.0)	48 (26.1)	18 (36.0)	66 (28.2)	76 (28.5)	6 (8.8)	82 (24.5)
Memory impairment	7 (23.3)	43 (23.4)	18 (36.0)	61 (26.1)	69 (25.8)	13 (19.1)	82 (24.5)
Decreased appetite	7 (23.3)	47 (25.5)	17 (34.0)	64 (27.4)	74 (27.7)	5 (7.4)	79 (23.6)
Hair colour changes	11 (36.7)	28 (15.2)	14 (28.0)	42 (17.9)	54 (20.2)	20 (29.4)	74 (22.1)
Face oedema	3 (10.0)	43 (23.4)	13 (26.0)	56 (23.9)	61 (22.8)	5 (7.4)	66 (19.7)
Blood bilirubin increased	3 (10.0)	33 (17.9)	10 (20.0)	43 (18.4)	48 (18.0)	6 (8.8)	54 (16.1)
Dysgeusia	5 (16.7)	27 (14.7)	5 (10.0)	32 (13.7)	39 (14.6)	8 (11.8)	47 (14.0)
Dizziness	2 (6.7)	15 (8.2)	14 (28.0)	29 (12.4)	32 (12.0)	7 (10.3)	39 (11.6)
Hypophosphataemia	5 (16.7)	18 (9.8)	8 (16.0)	26 (11.1)	32 (12.0)	5 (7.4)	37 (11.0)
Cognitive disorder	2 (6.7)	23 (12.5)	3 (6.0)	26 (11.1)	29 (10.9)	7 (10.3)	36 (10.7)
Alopecia	4 (13.3)	14 (7.6)	9 (18.0)	23 (9.8)	28 (10.5)	7 (10.3)	35 (10.4)

Abbreviations: AdvSM = advanced systemic mastocytosis; GIST = gastrointestinal stromal tumor.
Notes: Percentages are based on the number of patients in the Safety Population in each column.
Patients with GIST who received a starting dose of 600 mg are included in the GIST All Doses and GIST + AdvSM All Doses columns.
If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term.
Source: Table 18.1.1.3.5.1. Data cutoff date: 16 November 2018.

The safety database includes a total of 585 patients with GIST (all doses), of which 550 patients received avapritinib at a starting dose of 300 mg or 400 mg. This includes 250 patients in study BLU-285-1101, 239 patients in study BLU-285-1303 who received treatment with avapritinib, and 96 patients who received regorafenib in study BLU-285-1303 and then crossed over to receive avapritinib treatment due to disease progression on the regorafenib control treatment.

The most frequently reported adverse reactions of any Grade during treatment with Ayvakyt were nausea (45%), fatigue (40%), anaemia (39%), periorbital oedema (33%), face oedema (27%), hyperbilirubinaemia (28%), diarrhoea (26%), vomiting (24%), oedema peripheral (23%), lacrimation increased (22%), decreased appetite (21%) and memory impairment (20%).

Serious adverse reactions occurred in 23% of patients receiving avapritinib. The most common serious adverse reactions during treatment with avapritinib were anaemia (6%), and pleural effusion (1%).

The most common adverse reactions leading to permanent treatment discontinuation were fatigue, encephalopathy and intracranial haemorrhage (< 1% each). Adverse reactions leading to a dose reduction included anaemia, fatigue, neutrophil count decreased, blood bilirubin increased, memory impairment, cognitive disorder, periorbital oedema, nausea and face oedema.

Serious adverse events and deaths

- **Deaths**

Table 12 provides a summary of AEs leading to death for all patients in the Safety Population.

Table 12: Adverse Events Leading to Death (Safety Population)

	GIST					AdvSM	GIST + AdvSM
Preferred Term	<300 mg N=30 n (%)	300 mg N=184 n (%)	400 mg N=50 n (%)	300/400 mg N=234 n (%)	All Doses N=267 n (%)	All Doses N=68 n (%)	All Doses N=335 n (%)
Patients with any adverse event leading to death	6 (20.0)	19 (10.3)	8 (16.0)	27 (11.5)	33 (12.4)	4 (5.9)[a]	37 (11.0)
Disease progression	2 (6.7)	8 (4.3)	4 (8.0)	12 (5.1)	14 (5.2)	1 (1.5)	15 (4.5)
General physical health deterioration	1 (3.3)	4 (2.2)	1 (2.0)	5 (2.1)	6 (2.2)	0	6 (1.8)
Sepsis	0	2 (1.1)	1 (2.0)	3 (1.3)	3 (1.1)	0	3 (<1)
Tumour haemorrhage	0	1 (<1)	1 (2.0)	2 (<1)	2 (<1)	0	2 (<1)
Acute myeloid leukaemia	0	0	0	0	0	1 (1.5)	1 (<1)
Cardiac failure	0	1 (<1)	0	1 (<1)	1 (<1)	0	1 (<1)
Gastric haemorrhage	0	0	0	0	0	1 (1.5)	1 (<1)
Hepatic failure	1 (3.3)	0	0	0	1 (<1)	0	1 (<1)
Hyperbilirubinaemia	1 (3.3)	0	0	0	1 (<1)	0	1 (<1)
Metastatic neoplasm	1 (3.3)	0	0	0	1 (<1)	0	1 (<1)
Multi-organ failure	0	1 (<1)	0	1 (<1)	1 (<1)	0	1 (<1)
Neoplasm progression	0	1 (<1)	0	1 (<1)	1 (<1)	0	1 (<1)
Pleural effusion	0	1 (<1)	0	1 (<1)	1 (<1)	0	1 (<1)
Respiratory failure	0	0	1 (2.0)	1 (<1)	1 (<1)	0	1 (<1)
Staphylococcal sepsis	0	0	0	0	0	1 (1.5)	1 (<1)

Abbreviations: AdvSM = advanced systemic mastocytosis; GIST = gastrointestinal stromal tumor.
Notes: Percentages are based on the number of patients in the Safety Population in each column.
Patients with GIST who received a starting dose of 600 mg are included in the GIST All Doses and GIST + AdvSM All Doses columns.
If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term.
[a] One patient with AdvSM (Patient BLU-285-2101-04-2002-002) experienced an adverse event of disease progression that led to death more than 30 days after the last dose of avapritinib. This death is, therefore, not considered "on treatment" and is not included in Table 13.
Source: Table 18.1.1.3.2.3. Data cutoff date: 16 November 2018.

--Patients with GIST

Of the 27 patients who experienced on-treatment death, over half (15 of 27) of the deaths occurred at least 7 days after the last dose of avapritinib (range: 7, 30 days). For the majority of patients (20 of 27), the cause of these on-treatment deaths was assessed by the Investigator as progressive disease.

- **Other serious adverse events**

Table 14: Serious Adverse Events Reported in at Least 1% of Patients Overall by Preferred Term, Indication, and Dose Level (Safety Population)

	GIST					AdvSM	GIST + AdvSM
Preferred Term	**<300 mg N=30 n (%)**	**300 mg N=184 n (%)**	**400 mg N=50 n (%)**	**300/400 mg N=234 n (%)**	**All Doses N=267 n (%)**	**All Doses N=68 n (%)**	**All Doses N=335 n (%)**
Patients with any serious adverse event	20 (66.7)	87 (47.3)	27 (54.0)	114 (48.7)	137 (51.3)	35 (51.5)	172 (51.3)
Anaemia	2 (6.7)	15 (8.2)	5 (10.0)	20 (8.5)	23 (8.6)	6 (8.8)	29 (8.7)
Disease progression	2 (6.7)	8 (4.3)	4 (8.0)	12 (5.1)	14 (5.2)	1 (1.5)	15 (4.5)
Pleural effusion	1 (3.3)	4 (2.2)	2 (4.0)	6 (2.6)	7 (2.6)	3 (4.4)	10 (3.0)
Abdominal pain	2 (6.7)	6 (3.3)	1 (2.0)	7 (3.0)	9 (3.4)	0	9 (2.7)
Upper gastrointestinal haemorrhage	4 (13.3)	3 (1.6)	1 (2.0)	4 (1.7)	8 (3.0)	1 (1.5)	9 (2.7)
Acute kidney injury	1 (3.3)	4 (2.2)	1 (2.0)	5 (2.1)	6 (2.2)	1 (1.5)	7 (2.1)
General physical health deterioration	1 (3.3)	4 (2.2)	2 (4.0)	6 (2.6)	7 (2.6)	0	7 (2.1)
Pneumonia	0	3 (1.6)	0	3 (1.3)	3 (1.1)	4 (5.9)	7 (2.1)
Vomiting	1 (3.3)	3 (1.6)	1 (2.0)	4 (1.7)	5 (1.9)	2 (2.9)	7 (2.1)
Gastrointestinal haemorrhage	3 (10.0)	0	1 (2.0)	1 (<1)	4 (1.5)	2 (2.9)	6 (1.8)
Confusional state	1 (3.3)	1 (<1)	2 (4.0)	3 (1.3)	4 (1.5)	1 (1.5)	5 (1.5)
Sepsis	0	3 (1.6)	2 (4.0)	5 (2.1)	5 (1.9)	0	5 (1.5)
Ascites	0	1 (<1)	1 (2.0)	2 (<1)	2 (<1)	2 (2.9)	4 (1.2)
Gastric haemorrhage	0	1 (<1)	1 (2.0)	2 (<1)	2 (<1)	2 (2.9)	4 (1.2)
Pyrexia	0	2 (1.1)	0	2 (<1)	2 (<1)	2 (2.9)	4 (1.2)
Tumour haemorrhage	1 (3.3)	2 (1.1)	1 (2.0)	3 (1.3)	4 (1.5)	0	4 (1.2)

Abbreviations: AdvSM = advanced systemic mastocytosis; GIST = gastrointestinal stromal tumor.
Notes: Percentages are based on the number of patients in the Safety Population in each column.
Patients with GIST who received a starting dose of 600 mg are included in the GIST All Doses and GIST + AdvSM All Doses columns.
If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term.
Source: Table 18.1.1.3.3.1. Data cutoff date: 16 November 2018.

--Patients with GIST

A total of 20.1% of patients experienced SAEs that were considered treatment-related. Treatment-related SAEs experienced by ≥1% of patients were anaemia (4.3%), pleural effusion (1.7%), and acute kidney injury (1.3%). The incidence of these most commonly reported treatment-related SAEs was generally similar between patients whose starting dose was 300 mg and those whose starting dose was 400 mg with the exception of anaemia, although the difference was small (5.4% vs 0%). Most of these commonly reported SAEs and treatment-related SAEs are consistent with inhibition of KIT and PDGFRA, oral kinase inhibitors in general, and the underlying disease.

- Other significant adverse events: Adverse Events Leading to Study Drug Discontinuation

A total of 19.7% of patients with GIST discontinued study drug due to an AE, which appeared to be predominantly related to the patients' underlying disease. The most commonly (≥1%) reported AEs leading to study drug discontinuation by PT were disease progression (3.0%), general physical health deterioration (1.7%), and abdominal pain, acute kidney injury, anaemia, fatigue, and sepsis (1.3%).

For these patients, 9.0% discontinued study drug due to an AE that was considered treatment-related. The following treatment-related AEs led to study drug discontinuation in >1 patient: fatigue (1.7%) and confusional state, encephalopathy, nausea, and vomiting (<1% each)

- Other significant adverse events: Adverse Events Leading to Dose Modification

A total of 65.0% of patients experienced AEs leading to dose interruption. The most commonly (≥5%) reported AEs leading to dose interruption by PT were anaemia (10.3%), fatigue (9.8%), nausea (7.7%), vomiting (5.6%), and blood bilirubin increased (5.1%).

The incidence of AEs leading to dose interruption was similar for patients whose starting dose was 300 mg compared with those whose starting dose was 400 mg except for the PT of fatigue (7.1% vs 20.0%).

A total of 46.2% of patients experienced AEs leading to dose reduction. The most commonly (≥5%) reported AEs leading to dose reduction by PT were fatigue (9.8%) and anaemia (5.6%).

The incidence of AEs leading to dose reduction was lower for patients whose starting dose was 300 mg (40.8%) than for those whose starting dose was 400 mg (66.0%). For most AEs leading to dose reduction by PT, the incidence was similar between the 2 dose groups with the exception of fatigue (5.4% vs 26.0%).

- **Adverse Events of Special Interest**

The AESIs identified for the avapritinib clinical development program include cognitive effects and intracranial bleeding. The PTs for the AESI of cognitive effects include memory impairment, cognitive disorder, confusional state, and encephalopathy. The PTs for the AESI of intracranial bleeding include haemorrhage intracranial, cerebral haemorrhage, and subdural haematoma.

Table 19: Adverse Events of Special Interest by Category, Preferred Term, Indication, and Dose Level (Safety Population)

	GIST					AdvSM	GIST + AdvSM
AESI Category Preferred Term	<300 mg N=30 n (%)	300 mg N=184 n (%)	400 mg N=50 n (%)	300/400 mg N=234 n (%)	All Doses N=267 n (%)	All Doses N=68 n (%)	All Doses N=335 n (%)
Cognitive effects	10 (33.3)	65 (35.3)	24 (48.0)	89 (38.0)	101 (37.8)	21 (30.9)	122 (36.4)
Memory impairment	7 (23.3)	43 (23.4)	19 (38.0)	62 (26.5)	70 (26.2)	13 (19.1)	83 (24.8)
Cognitive disorder	2 (6.7)	23 (12.5)	3 (6.0)	26 (11.1)	29 (10.9)	7 (10.3)	36 (10.7)
Confusional state	1 (3.3)	11 (6.0)	5 (10.0)	16 (6.8)	17 (6.4)	5 (7.4)	22 (6.6)
Encephalopathy	0	1 (<1)	2 (4.0)	3 (1.3)	3 (1.1)	2 (2.9)	5 (1.5)
Intracranial bleeding	1 (3.3)	2 (1.1)	0	2 (<1)	3 (1.1)	7 (10.3)	10 (3.0)
Subdural haematoma	0	1 (<1)	0	1 (<1)	1 (<1)	4 (5.9)	5 (1.5)
Haemorrhage intracranial	0	1 (<1)	0	1 (<1)	1 (<1)	3 (4.4)	4 (1.2)
Cerebral haemorrhage	1 (3.3)	0	0	0	1 (<1)	0	1 (<1)

Abbreviations: AdvSM = advanced systemic mastocytosis; AESI = adverse event of special interest; GIST = gastrointestinal stromal tumor.
Notes: Percentages are based on the number of patients in the Safety Population in each column.
Patients with GIST who received a starting dose of 600 mg are included in the GIST All Doses and GIST + AdvSM All Doses columns.
If a patient experienced more than 1 event within a given AESI category or preferred term, that patient was counted only once for that category or term.
Source: Table 18.1.1.3.13.1. Data cutoff date: 16 November 2018.

Table 20: Serious Adverse Events of Special Interest by Category, Preferred Term, Indication, and Dose Level (Safety Population)

AESI Category Preferred Term	GIST					AdvSM	GIST + AdvSM
	<300 mg N=30 n (%)	300 mg N=184 n (%)	400 mg N=50 n (%)	300/400 mg N=234 n (%)	All Doses N=267 n (%)	All Doses N=68 n (%)	All Doses N=335 n (%)
Cognitive effects	2 (6.7)	4 (2.2)	2 (4.0)	6 (2.6)	8 (3.0)	3 (4.4)	11 (3.3)
Confusional state	1 (3.3)	1 (<1)	2 (4.0)	3 (1.3)	4 (1.5)	1 (1.5)	5 (1.5)
Cognitive disorder	1 (3.3)	2 (1.1)	0	2 (<1)	3 (1.1)	0	3 (<1)
Encephalopathy	0	1 (<1)	0	1 (<1)	1 (<1)	2 (2.9)	3 (<1)
Memory impairment	0	0	0	0	0	0	0
Intracranial bleeding	1 (3.3)	1 (<1)	0	1 (<1)	2 (<1)	4 (5.9)	6 (1.8)
Haemorrhage intracranial	0	1 (<1)	0	1 (<1)	1 (<1)	2 (2.9)	3 (<1)
Subdural haematoma	0	0	0	0	0	2 (2.9)	2 (<1)
Cerebral haemorrhage	1 (3.3)	0	0	0	1 (<1)	0	1 (<1)

Abbreviations: AdvSM = advanced systemic mastocytosis; AESI = adverse event of special interest; GIST = gastrointestinal stromal tumor.
Notes: Percentages are based on the number of patients in the Safety Population in each column.
Patients with GIST who received a starting dose of 600 mg are included in the GIST All Doses and GIST + AdvSM All Doses columns.
If a patient experienced more than 1 event within a given AESI category or preferred term, that patient was counted only once for that category or term.
Source: Table 18.1.1.3.14.1. Data cutoff date: 16 November 2018.

Cognitive disorders

Overall, 36% of patients who received treatment with avapritinib experienced cognitive effects, including 38% of patients with GIST and 31% of patients with AdvSM. The majority of the events in both indications were nonserious. Most patients (25% of patients with GIST and 19% of patients with AdvSM) experienced Grade 1 (mild) cognitive effects, which according to the CTCAE definition did not interfere with ADLs. Approximately 13% of patients with GIST and 12% of patients with AdvSM experienced Grade 2 or Grade 3 cognitive effects, which according to the CTCAE definition had clinical relevance (eg, interfered with ADLs or self-care). No patients reported Grade 4 or Grade 5 cognitive effects. The most frequently reported cognitive effect was memory impairment reported in 20% of patients with GIST and 19% of patients with AdvSM. The other cognitive effect terms were reported at a lower incidence and included cognitive disorder (12% and 10% in patients with GIST and AdvSM, respectively), confusional state (5% and 7% in patients with GIST and AdvSM, respectively) and encephalopathy (<1% and 3% in patients with GIST and AdvSM, respectively).

Overall, 3% of patients reported serious events of cognitive effects, including 3% of patients with GIST and 4% of patients with AdvSM. The majority of the serious cognitive effects in both indications were Grade 3 (73%) and assessed as related to study drug (82%). Slightly less than half of the serious events resolved or resolved with sequelae.

Confounders were present in 10 of the 11 patients who experienced serious events and included a history of psychiatric conditions or insomnia, psychiatric or opioid concomitant medication use, polypharmacy, poor sleep hygiene, concurrent illness/infection/dehydration, and cognitive symptoms occurring in the setting of disease progression leading to imminent death.

The majority of patients with cognitive effects continued dosing with avapritinib with only 2% of patients overall experiencing cognitive effects leading to permanent discontinuation of study treatment (2% and 3% of patients with GIST and AdvSM, respectively). This observation implies that the cognitive effects appeared to be tolerated by the physicians and patients as the benefit/risk profile of continued treatment with avapritinib was positive.

Additional variables identified that may have a potential impact on cognitive effects included age (≥65 years) and medical history of cognitive effects. Thirty-five percent of patients with GIST and 53% of patients with AdvSM had a medical history of events within the SOC of Psychiatric Disorders (eg,

insomnia, anxiety, and depression). Patients in North America also had a higher incidence of cognitive effects compared with patients in Europe or RoW; however, this observation may be influenced by reporting bias. Logistic regression modeling showed a significant effect for maximum dose of avapritinib on the odds ratio of cognitive effects of Grade ≥2: the odds of patients with a maximum dose of ≤300 mg experiencing a Grade ≥2 cognitive effect were reduced by a multiplier of 33% compared with patients with a maximum dose of >300 mg.

An analysis of time to onset and improvement of cognitive effects in patients with GIST was performed. Of the 234 patients with GIST whose starting dose was 300/400 mg, 89 patients experienced cognitive effects of any grade. In the patients who had an event, the median time to onset was 9 weeks. Kaplan-Meier analyses of time to onset of these events demonstrated that if patients have not experienced a cognitive effect over the initial 7 to 8 months of treatment, they are unlikely to experience an event. Of the 234 patients with GIST whose starting dose was 300/400 mg, 29 patients experienced Grade ≥2 cognitive effects. The median time to improvement to Grade ≤1 for these patients was 13 weeks. Because cognitive effects of Grade ≤1 do not affect ADLs or self-care, improvement to Grade ≤1 is clinically important to patients. Additional data on long-term outcome and additional risk factors are needed to further understand the long-term impact of cognitive effects associated with avapritinib.

Nonclinical mechanistic studies could not clearly identify the underlying mechanism for cognitive effects (ie, memory impairment). Review of brain imaging results during the clinical studies did not reveal any anatomical changes associated with cognitive effect symptoms.

The Applicant proposes that patients should be informed about potential cognitive effects, and the dose of avapritinib should be interrupted and reduced according to the severity of the events. The SmPC includes dose-adjustment recommendations (Section 4.2.) and a precautionary statement in Section 4.4. to manage this AE.

Intracranial Bleeding

Overall, 3.0% of the 335 patients who received treatment with avapritinib for the indications of GIST and AdvSM experienced events of intracranial bleeding (Table 19). Three patients with GIST (1.1%) experienced subdural haematoma, haemorrhage intracranial, and cerebral haemorrhage (1 patient each), and 10.3% of patients with AdvSM (7 patients) experienced subdural haematoma (5.9%) and haemorrhage intracranial (4.4%).

Six patients (1.8%) reported serious events of intracranial bleeding (2 patients with GIST and 4 patients with AdvSM), and 3 patients (<1%) experienced intracranial bleeding events leading to permanent discontinuation of study treatment (2 patients with GIST and 1 patient with AdvSM) (Table 20). In addition to the serious AESIs of intracranial bleeding discussed in this section, 2 additional events were reported after the data cutoff date of 16 November 2018;

Thus, in the avapritinib clinical trials, so far 12 events of intracranial bleeding have been reported, 5 in the GIST population and 7 in the Advanced Systemic Mastocytosis (AdvSM) population of which nine were considered related to treatment with avapritinib.

Serious adverse reactions of intracranial haemorrhage were reported in patients with unresectable or metastatic GIST receiving avapritinib. The exact mechanism is unknown. However, some risk factors were identified. Therefore, a precautionary statement has been included in the SmPC in order to minimise the risk, which recommends particular caution in patients with risk factors such as severe thrombocytopenia, and in patients with increased risk of intracranial haemorrhage such as those with a vascular aneurysm or a history of intracranial haemorrhage within the prior year, a history of a cerebrovascular accident or transient ischaemic attack. In addition, a recommendation to seek medical advice to patients who experience clinically relevant neurological signs and symptoms (e.g. severe headache, vision problems, somnolence, or focal weakness) during treatment with Ayvakyt, to perform

brain MRI or CT at the discretion of the physician based on severity and the clinical presentation, and to permanently discontinue treatment for patients with observed intracranial haemorrhage during treatment with avapritinib, regardless of Grade are now included (Section 4.4, 4.2, and 4.8).

In addition, appropriate information is now included in the SmPC concerning other relevant risks identified or potential for avapritinib treatment, including the risk for hemarraghic events other than IC bleedings, cognitive events, fluid retention (e.g. including facial, peripheral, and pleural effusion), GI disorders, photosensitivity reactions, the risk for prolonging QT effects, as well as relevant DDI with CYP3A inhibitors /inducers, and liver enzyme and bilirubin elevations, which require particular monitoring.

- Late-breaking safety data

Between database cutoff (16 November 2018) and the late-breaking data cutoff (28 February 2019) deaths and treatment-related SAEs were reported for patients participating in ongoing studies (BLU-285-1101, BLU-285-1303, and BLU-285-2101). A total of 4 deaths (6 fatal events) and 31 treatment-related SAEs (in 18 patients) have been reported. One of these deaths was considered to be related to avapritinib treatment. There were 4 serious AESIs reported during the late-breaking period, 2 intracranial bleedings and 2 cognitive effects, all of which occurred in patients with GIST, and related to avapritinib (discussed above).

- Analysis of Adverse Events by Organ System or Syndrome

An analysis of AEs was performed for those SOCs that included any PT (all grades) experienced by ≥ 10% of all patients in the Safety Population (Table 27). The results of this analysis are presented in the subsections that follow in order of descending frequency.

Table 27: Adverse Events Reported in at Least 10% of Patients Overall by System Organ Class, Preferred Term, Indication, and Dose Level (Safety Population)

	GIST					AdvSM	GIST + AdvSM
System Organ Class Preferred Term	<300 mg N=30 n (%)	300 mg N=184 n (%)	400 mg N=50 n (%)	300/400 mg N=234 n (%)	All Doses N=267 n (%)	All Doses N=68 n (%)	All Doses N=335 n (%)
Patients with any adverse event	30 (100)	181 (98.4)	49 (98.0)	230 (98.3)	263 (98.5)	68 (100)	331 (98.8)
Gastrointestinal disorders	28 (93.3)	161 (87.5)	46 (92.0)	207 (88.5)	238 (89.1)	59 (86.8)	297 (88.7)
Nausea	16 (53.3)	107 (58.2)	38 (76.0)	145 (62.0)	164 (61.4)	25 (36.8)	189 (56.4)
Diarrhoea	15 (50.0)	59 (32.1)	19 (38.0)	78 (33.3)	96 (36.0)	24 (35.3)	120 (35.8)
Vomiting	14 (46.7)	56 (30.4)	27 (54.0)	83 (35.5)	99 (37.1)	20 (29.4)	119 (35.5)
Constipation	10 (33.3)	39 (21.2)	12 (24.0)	51 (21.8)	62 (23.2)	10 (14.7)	72 (21.5)
Abdominal pain	8 (26.7)	38 (20.7)	10 (20.0)	48 (20.5)	57 (21.3)	13 (19.1)	70 (20.9)
Dyspepsia	8 (26.7)	27 (14.7)	7 (14.0)	34 (14.5)	43 (16.1)	4 (5.9)	47 (14.0)
General disorders and administration site conditions	26 (86.7)	146 (79.3)	46 (92.0)	192 (82.1)	221 (82.8)	49 (72.1)	270 (80.6)
Fatigue	22 (73.3)	90 (48.9)	34 (68.0)	124 (53.0)	148 (55.4)	25 (36.8)	173 (51.6)
Oedema peripheral	15 (50.0)	47 (25.5)	18 (36.0)	65 (27.8)	80 (30.0)	23 (33.8)	103 (30.7)
Face oedema	3 (10.0)	43 (23.4)	14 (28.0)	57 (24.4)	62 (23.2)	7 (10.3)	69 (20.6)
Pyrexia	1 (3.3)	21 (11.4)	9 (18.0)	30 (12.8)	31 (11.6)	4 (5.9)	35 (10.4)
Nervous system disorders	21 (70.0)	119 (64.7)	33 (66.0)	152 (65.0)	176 (65.9)	46 (67.6)	222 (66.3)
Memory impairment	7 (23.3)	43 (23.4)	19 (38.0)	62 (26.5)	70 (26.2)	13 (19.1)	83 (24.8)
Dizziness	6 (20.0)	24 (13.0)	21 (42.0)	45 (19.2)	53 (19.9)	13 (19.1)	66 (19.7)
Headache	6 (20.0)	30 (16.3)	10 (20.0)	40 (17.1)	48 (18.0)	10 (14.7)	58 (17.3)

Dysgeusia	5 (16.7)	28 (15.2)	5 (10.0)	33 (14.1)	40 (15.0)	11 (16.2)	51 (15.2)
Cognitive disorder	2 (6.7)	23 (12.5)	3 (6.0)	26 (11.1)	29 (10.9)	7 (10.3)	36 (10.7)
Eye disorders	22 (73.3)	107 (58.2)	36 (72.0)	143 (61.1)	166 (62.2)	52 (76.5)	218 (65.1)
Periorbital oedema	15 (50.0)	62 (33.7)	26 (52.0)	88 (37.6)	104 (39.0)	50 (73.5)	154 (46.0)
Lacrimation increased	11 (36.7)	50 (27.2)	21 (42.0)	71 (30.3)	83 (31.1)	7 (10.3)	90 (26.9)
Metabolism and nutrition disorders	23 (76.7)	101 (54.9)	34 (68.0)	135 (57.7)	161 (60.3)	30 (44.1)	191 (57.0)
Decreased appetite	11 (36.7)	62 (33.7)	21 (42.0)	83 (35.5)	97 (36.3)	11 (16.2)	108 (32.2)
Hypokalaemia	5 (16.7)	27 (14.7)	7 (14.0)	34 (14.5)	40 (15.0)	9 (13.2)	49 (14.6)
Hypophosphataemia	5 (16.7)	22 (12.0)	8 (16.0)	30 (12.8)	36 (13.5)	8 (11.8)	44 (13.1)
Blood and lymphatic system disorders	16 (53.3)	93 (50.5)	28 (56.0)	121 (51.7)	139 (52.1)	50 (73.5)	189 (56.4)
Anaemia	14 (46.7)	85 (46.2)	26 (52.0)	111 (47.4)	126 (47.2)	36 (52.9)	162 (48.4)
Skin and subcutaneous tissue disorders	23 (76.7)	80 (43.5)	30 (60.0)	110 (47.0)	136 (50.9)	44 (64.7)	180 (53.7)
Hair colour changes	11 (36.7)	29 (15.8)	14 (28.0)	43 (18.4)	55 (20.6)	20 (29.4)	75 (22.4)
Rash	5 (16.7)	17 (9.2)	10 (20.0)	27 (11.5)	33 (12.4)	9 (13.2)	42 (12.5)
Alopecia	4 (13.3)	18 (9.8)	10 (20.0)	28 (12.0)	33 (12.4)	8 (11.8)	41 (12.2)
Investigations	14 (46.7)	97 (52.7)	24 (48.0)	121 (51.7)	137 (51.3)	35 (51.5)	172 (51.3)
Blood bilirubin increased	4 (13.3)	38 (20.7)	11 (22.0)	49 (20.9)	55 (20.6)	9 (13.2)	64 (19.1)
Weight decreased	7 (23.3)	22 (12.0)	5 (10.0)	27 (11.5)	35 (13.1)	3 (4.4)	38 (11.3)

Table 27: Adverse Events Reported in at Least 10% of Patients Overall by System Organ Class, Preferred Term, Indication, and Dose Level (Safety Population) (Continued)

	GIST					AdvSM	GIST + AdvSM
System Organ Class Preferred Term	<300 mg N=30 n (%)	300 mg N=184 n (%)	400 mg N=50 n (%)	300/400 mg N=234 n (%)	All Doses N=267 n (%)	All Doses N=68 n (%)	All Doses N=335 n (%)
Aspartate aminotransferase increased	2 (6.7)	20 (10.9)	10 (20.0)	30 (12.8)	32 (12.0)	4 (5.9)	36 (10.7)
Respiratory, thoracic and mediastinal disorders	16 (53.3)	73 (39.7)	26 (52.0)	99 (42.3)	117 (43.8)	42 (61.8)	159 (47.5)
Dyspnoea	4 (13.3)	25 (13.6)	12 (24.0)	37 (15.8)	42 (15.7)	8 (11.8)	50 (14.9)
Cough	10 (33.3)	14 (7.6)	7 (14.0)	21 (9.0)	33 (12.4)	7 (10.3)	40 (11.9)
Pleural effusion	4 (13.3)	21 (11.4)	5 (10.0)	26 (11.1)	31 (11.6)	7 (10.3)	38 (11.3)
Psychiatric disorders	13 (43.3)	49 (26.6)	26 (52.0)	75 (32.1)	90 (33.7)	17 (25.0)	107 (31.9)
Insomnia	7 (23.3)	20 (10.9)	6 (12.0)	26 (11.1)	34 (12.7)	8 (11.8)	42 (12.5)

Abbreviations: AdvSM = advanced systemic mastocytosis; GIST = gastrointestinal stromal tumor.
Notes: Percentages are based on the number of patients in the Safety Population in each column.
Patients with GIST who received a starting dose of 600 mg are included in the GIST All Doses and GIST + AdvSM All Doses columns.
If a patient experienced more than 1 event within a given system organ class or preferred term, that patient was counted only once for that class or term.
Source: Table 18.1.1.3.2.2. Data cutoff date: 16 November 2018.

By Organ System or Syndrome, GI disorders SOC were the most commonly reported AEs (89.1%), among all GIST patients, followed by general disorders and administration site conditions (82.2%), and nervous system disorders (65.9%).

The most common treatment-related GI AEs (≥10%) among patients with GIST 300/400mg were nausea (57.3%), vomiting (29.9%), and diarrhoea (28.6%). The majority of GI disorders were Grade 1 or 2 in severity; Grade ≥3 GI AEs were reported in 22.6% of patients. Serious AEs were experienced by 14.5% of patients, including GI haemorrhages. Most AEs in this SOC did not result in dose modification. Of the 234 patients, 8.5% had a dose reduction (primarily due to AEs of nausea) and 22.6% had dose interruptions.

Among the 234 patients with GIST whose starting dose was 300/400 mg, 82.1% had at least 1 AE within the General Disorders and Administration Site Conditions SOC. The most common AEs (≥10%) within this SOC were fatigue (53.0%), oedema peripheral (27.8%), face oedema (24.4%), and pyrexia (12.8%). The majority of general disorders AEs were Grade 1 or 2 in severity; Grade ≥3 AEs were

reported in 17.5% of patients, primarily reports of fatigue (6.8%), disease progression (5.1%), and general physical health deterioration (2.6%). Serious AEs were experienced by 10.7% of patients.

Treatment-related respiratory AEs were reported in 19.2% of patients; the majority of respiratory disorders were Grade 1 or 2 in severity; Grade ≥3 AEs were reported in 6.8% of patients, primarily reports of dyspnoea (2.6%) and pleural effusion (2.1%). Pleural effusion is an expected toxicity that is likely related to inhibition of wild-type KIT/PDGFRA in patients with advanced GIST.

Laboratory findings

- Serum Chemistry

Shifts in selected serum chemistry parameters from Grade ≤2 at baseline to Grade ≥3 at the worst value on treatment are summarized in Table 28 for patients with GIST whose starting dose was 300/400 mg, patients with AdvSM, and the overall population.

Table 28: Proportion of Patients with Shifts in Selected Serum Chemistry Parameters from Grade ≤2 at Baseline to Grade ≥3 at Worst Value on Study (Safety Population)

	GIST			AdvSM	GIST + AdvSM
Parameter	300 mg N=184 n/N (%)	400 mg N=50 n/N (%)	300/400 mg N=234 n/N (%)	All Doses N=68 n/N (%)	All Doses N=335 n/N (%)
ALT increased	1/184 (<1)	0/50 (0)	1/234 (<1)	2/68 (2.9)	3/335 (<1)
AST increased	1/184 (<1)	2/50 (4.0)	3/234 (1.3)	2/68 (2.9)	5/335 (1.5)
ALP increased	1/184 (<1)	1/50 (2.0)	2/234 (<1)	6/68 (8.8)	9/335 (2.7)
Bilirubin increased	13/184 (7.1)	6/50 (12.0)	19/234 (8.1)	6/68 (8.8)	29/335 (8.7)
Potassium decreased	11/184 (6.0)	2/50 (4.0)	13/234 (5.6)	2/68 (2.9)	18/335 (5.4)

Abbreviations: AdvSM = advanced systemic mastocytosis; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GIST = gastrointestinal stromal tumor.
Notes: Patients with GIST who received a starting dose of 600 mg are included in the GIST All Doses and GIST + AdvSM All Doses columns.
Baseline value was defined as the last observation before the first dose of study drug.
Source: Table 18.1.1.4.1.3. Data cutoff date: 16 November 2018.

Table 29: Adverse Events Associated with Serum Chemistry Laboratory Abnormalities Most Commonly Reported (≥10% for Any Grade or ≥2% for Grade ≥3) Overall by Preferred Term, Indication, and Dose Level (Safety Population)

	GIST					AdvSM	GIST + AdvSM
Preferred Term	<300 mg N=30 n (%)	300 mg N=184 n (%)	400 mg N=50 n (%)	300/400 mg N=234 n (%)	All Doses N=267 n (%)	All Doses N=68 n (%)	All Doses N=335 n (%)
Any Grade							
Blood bilirubin increased	4 (13.3)	38 (20.7)	11 (22.0)	49 (20.9)	55 (20.6)	9 (13.2)	64 (19.1)
Hypokalaemia	5 (16.7)	27 (14.7)	7 (14.0)	34 (14.5)	40 (15.0)	9 (13.2)	49 (14.6)
Hypophosphataemia	5 (16.7)	22 (12.0)	8 (16.0)	30 (12.8)	36 (13.5)	8 (11.8)	44 (13.1)
Aspartate aminotransferase increased	2 (6.7)	20 (10.9)	10 (20.0)	30 (12.8)	32 (12.0)	4 (5.9)	36 (10.7)
Grade ≥3							
Hypophosphataemia	2 (6.7)	6 (3.3)	3 (6.0)	9 (3.8)	12 (4.5)	5 (7.4)	17 (5.1)
Blood bilirubin increased	0	9 (4.9)	1 (2.0)	10 (4.3)	11 (4.1)	2 (2.9)	13 (3.9)
Hypokalaemia	0	4 (2.2)	2 (4.0)	6 (2.6)	7 (2.6)	2 (2.9)	9 (2.7)
Hyponatraemia	0	5 (2.7)	1 (2.0)	6 (2.6)	6 (2.2)	2 (2.9)	8 (2.4)

Abbreviations: AdvSM = advanced systemic mastocytosis; GIST = gastrointestinal stromal tumor.
Notes: Percentages are based on the number of patients in the Safety Population in each column.
Patients with GIST who received a starting dose of 600 mg are included in the GIST All Doses and GIST + AdvSM All Doses columns.
If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term.
Source: Table 18.1.1.3.2.1 and Table 18.1.1.3.4.1. Data cutoff date: 16 November 2018.

In patients with GIST, there were no shifts in laboratory values from any grade at baseline to Grade 4 for any of these selected serum chemistry parameters except for decreased potassium. Mean values of ALT initially decreased from baseline at Week 1, increased from baseline from Weeks 2 through 12, and then generally stabilized near or below baseline thereafter. Mean values of AST increased slightly from baseline at Week 1, increased more notably at Weeks 2 through 8, and, remained above baseline thereafter, although generally lower than Weeks 2 through 8. Mean values of total bilirubin initially showed a small decrease at Week 1, increased notably at Weeks 2 through 12, and generally decreased and remained below 20 µmol/L after Week 24. Increased bilirubin was generally not associated with transaminase or alkaline phosphatase elevation, and there were no cases that met Hy's law criteria. The increases in total bilirubin were consistent with avapritinib's known inhibition of hepatic BSEP. Mean values of potassium increased very slightly at Week 1 and then decreased at Week 2 and remained below baseline, although never less than 3.5 mmol/L, thereafter. The decreases in potassium levels may be related to diarrhea and vomiting, which are commonly reported for patients with GIST.

- Hematology

Shift analyses from baseline to worst value on treatment based on the NCI CTCAE were conducted for hematology parameters; Shifts in selected hematology parameters from Grade ≤2 at baseline to Grade ≥3 at the worst value on treatment are summarized in Table 30 for patients with GIST whose starting dose was 300/400 mg, patients with AdvSM, and the overall population.

Table 30: Proportion of Patients with Shifts in Selected Hematology Parameters from Grade ≤2 at Baseline to Grade ≥3 at Worst Value on Study (Safety Population)

	GIST			AdvSM	GIST + AdvSM
Parameter	300 mg N=184 n/N (%)	400 mg N=50 n/N (%)	300/400 mg N=234 n/N (%)	All Doses N=68 n/N (%)	All Doses N=335 n/N (%)
Platelets decreased	1/184 (<1)	0/50 (0)	1/234 (<1)	19/68 (27.9)	20/335 (6.0)
Hgb decreased	41/184 (22.3)	16/50 (32.0)	57/234 (24.4)	23/68 (33.8)	88/335 (26.3)
Neutrophils decreased	12/184 (6.5)	1/50 (2.0)	13/234 (5.6)	11/68 (16.2)	28/335 (8.4)
Leukocytes decreased	8/184 (4.3)	2/50 (4.0)	10/234 (4.3)	8/68 (11.8)	20/335 (6.0)

Abbreviations: AdvSM = advanced systemic mastocytosis; GIST = gastrointestinal stromal tumor; Hgb = hemoglobin.
Notes: Patients with GIST who received a starting dose of 600 mg are included in the GIST All Doses and GIST + AdvSM All Doses columns.
Baseline value was defined as the last observation before the first dose of study drug.
Source: Table 18.1.1.4.2.3. Data cutoff date: 16 November 2018.

Table 31: Adverse Events Associated with Hematology Laboratory Abnormalities Most Commonly Reported (≥10% for Any Grade or ≥2% for Grade ≥3) Overall by Preferred Term, Indication, and Dose Level (Safety Population)

	GIST					AdvSM	GIST + AdvSM
Preferred Term	<300 mg N=30 n (%)	300 mg N=184 n (%)	400 mg N=50 n (%)	300/400 mg N=234 n (%)	All Doses N=267 n (%)	All Doses N=68 n (%)	All Doses N=335 n (%)
Any Grade							
Anaemia	14 (46.7)	85 (46.2)	26 (52.0)	111 (47.4)	126 (47.2)	36 (52.9)	162 (48.4)
Grade ≥3							
Anaemia	7 (23.3)	43 (23.4)	17 (34.0)	60 (25.6)	68 (25.5)	18 (26.5)	86 (25.7)
Neutropenia	1 (3.3)	3 (1.6)	1 (2.0)	4 (1.7)	6 (2.2)	7 (10.3)	13 (3.9)
Thrombocytopenia	0	0	0	0	0	13 (19.1)	13 (3.9)
Neutrophil count decreased	1 (3.3)	6 (3.3)	1 (2.0)	7 (3.0)	8 (3.0)	1 (1.5)	9 (2.7)

Abbreviations: AdvSM = advanced systemic mastocytosis; GIST = gastrointestinal stromal tumor.
Notes: Percentages are based on the number of patients in the Safety Population in each column.
Patients with GIST who received a starting dose of 600 mg are included in the GIST All Doses and GIST + AdvSM All Doses columns.
If a patient experienced more than 1 event within a given preferred term, that patient was counted only once for that term.
Source: Table 18.1.1.3.2.1 and Table 18.1.1.3.4.1. Data cutoff date: 16 November 2018.

--Patients with GIST

As shown in Table 30, 24.4% of patients had decreased hemoglobin values that shifted from Grade ≤2 at baseline to Grade ≥3 on study. For decreased neutrophil and leukocyte counts, 5.6% and 4.3% of

patients, respectively, had values that shifted from Grade ≤2 at baseline to Grade ≥3 on study. Only 1 patient had decreased platelet counts that shifted from Grade ≤2 at baseline to Grade ≥3 on study. There were no shifts in laboratory values from any grade at baseline to Grade 4 for any of these selected hematology parameters except for decreased neutrophil count. One patient had decreased neutrophil counts that shifted from Grade 2 at baseline to Grade 4 as the worst value on study.

Consistent with the known effects of KIT inhibition on hematopoiesis, avapritinib treatment led to decreases in hemoglobin, neutrophil count (and subsequently leukocyte count), and platelet count. Mean hemoglobin values decreased from Weeks 2 through 16 and generally stabilized after Week 20. Mean neutrophil counts decreased notably at Week 2, continued to decrease slightly through Week 12, and generally stabilized after Week 16. Mean leukocyte counts followed a pattern similar to neutrophil counts. Mean platelet counts increased markedly at Week 1, decreased to near baseline and then below baseline at Weeks 2 through Week 12 and generally stabilized after Week 16.

- Vital signs and physical findings, and other observations related to safety

There were no relevant changes in mean systolic blood pressure and mean diastolic blood pressure from baseline at week 52.

--CV findings

Cardiovascular and vital sign assessments of avapritinib have been conducted in a hERG assay in vitro and, subsequently, in vivo in dogs implanted with radiotelemetry and administered single PO doses of avapritinib in a Good Laboratory Practice-compliant cardiopulmonary safety pharmacology study and ECG assessments in the 28-day and 3-month oral toxicity studies in dogs. There were no observations of QT prolongation or other negative cardiovascular signals.

In addition, an analysis of continuous ECG (Holter) data from the expansion part (Part 2) of Study BLU-285-1101 was performed to satisfy the requirement for a definitive QT assessment of avapritinib:

A total of 27 patients at selected sites participated in continuous ECG (Holter) monitoring in Study BLU-285-1101. Avapritinib had a small effect on the QTc at steady-state plasma concentrations, after QD administration of 300 or 400 mg:

On C1D15 (steady state), the mean ΔQTcF was 7.0 msec (90% CI: 2.84, 11.14) at the time point before dosing, and above 5 msec at all time points after dosing, except at 4 hours after dosing (4.6 msec; 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 msec, respectively (90% CIs: 5.72, 14.03 and 5.30, 13.62, respectively). Three patients had a ΔQTcF >30 msec, and no patients had a ΔQTcF >60 msec. No patients had a QTcF >450 msec.

In the concentration-QTc analysis of data, a linear model was used to establish the relationship between plasma concentrations of avapritinib and ΔQTcF. The predicted ΔQTcF effect using this model was 6.55 msec (90% CI: 1.80 to 11.29) at the steady-state geometric mean maximum observed concentration of avapritinib (899 ng/mL) for the pooled 300/400 mg doses. A QT effect (ΔQTcF) exceeding 20 msec can be excluded at avapritinib plasma concentrations up to 1645 ng/mL. No effect on heart rate or cardiac conduction (PR, RR, and QRS intervals) was observed.

In addition, 3.9% of patients overall reported events within the SMQ Torsade de pointes/QT prolongation (3.0% and 7.4% of patients with GIST and AdvSM, respectively), including events of electrocardiogram QT prolonged, ventricular arrhythmia, and syncope. The majority of events were nonserious, Grade 1 or 2, resolved, and assessed as not related to study drug. Events of pericardial effusion were reported for 2 patients with GIST. For Patient BLU-285-1101-05-2001-005, a patient with GIST whose starting dose was <300 mg, the event of pericardial effusion was Grade 4, serious, and considered to be related to avapritinib; the event led to study drug interruption.

Table 32: Adverse Events Within the SMQ Torsade de Pointes/QT Prolongation (Safety Population)

Preferred Term	GIST					AdvSM	GIST + AdvSM
	<300 mg N=30 n (%)	300 mg N=184 n (%)	400 mg N=50 n (%)	300/400 mg N=234 n (%)	All Doses N=267 n (%)	All Doses N=68 n (%)	All Doses N=335 n (%)
Patients with any AE within the SMQ	2 (6.7)	5 (2.7)	0	5 (2.1)	8 (3.0)	5 (7.4)	13 (3.9)
Electrocardiogram QT prolonged	0	3 (1.6)	0	3 (1.3)	3 (1.1)	4 (5.9)	7 (2.1)
Syncope	2 (6.7)	0	0	0	3 (1.1)	1 (1.5)	4 (1.2)
Ventricular arrhythmia	0	3 (1.6)	0	3 (1.3)	3 (1.1)	0	3 (<1)

Abbreviations: AE = adverse event; AdvSM = advanced systemic mastocytosis; GIST = gastrointestinal stromal tumor; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standardised MedDRA query.
Notes: Percentages are based on the number of patients in the Safety Population in each column.
Patients with GIST who received a starting dose of 600 mg are included in the GIST All Doses and GIST + AdvSM All Doses columns.
If a patient experienced more than 1 event within a given SMQ category or preferred term, that patient was counted only once for that category or term.
Source: Data on file. Data cutoff date: 16 November 2018.

Safety in special populations

In NAVIGATOR and VOYAGER (N=550), 39% of patients were 65 years of age and older, and 9% were 75 years of age and older. Compared with younger patients (<65), more patients ≥65 years old had reported adverse reactions that led to dose reductions (55% versus 45%) and dose discontinuation (18% versus 4%). The types of adverse reactions reported were similar regardless of age. Older patients reported more Grade 3 or higher adverse reactions compared to younger patients (63% versus 50%).

Table 27: Safety Profile of Avapritinib in Elderly Patients

MedDRA Terms	Age <65 N = 194 n (%)	Age 65-74 N = 109 n (%)	Age 75-84 N = 26 n (%)	Age ≥85 N = 3 n (%)
Total AEs	190 (97.9)	109 (100)	26 (100)	3 (100)
Serious AEs – Total*	108 (55.7)	91 (83.5)	30 (100)	3 (100)
• Fatal*	19 (9.8)	15 (13.8)	5 (19.2)	0
• Hospitalization/prolong existing hospitalization*	74 (38.1)	61 (56.0)	18 (69.2)	2 (66.7)
• Life-threatening*	3 (1.5)	9 (8.3)	4 (15.4)	0
• Disability/incapacity*	1 (0.5)	1 (0.9)	0	0
• Other (medically significant)*	11 (5.7)	5 (4.6)	3 (11.5)	1 (33.3)
AE leading to Treatment Discontinuation	18 (9.3)	29 (26.6)	8 (30.8)	1 (33.3)
SOC Psychiatric disorders	59 (30.4)	39 (35.8)	6 (23.1)	1 (33.3)

MedDRA Terms	Age <65 N = 194 n (%)	Age 65-74 N = 109 n (%)	Age 75-84 N = 26 n (%)	Age ≥85 N = 3 n (%)
SOC Nervous system disorders	120 (61.9)	73 (67.0)	18 (69.2)	1 (33.3)
SOC Injury, poisoning and procedural complications	27 (13.9)	18 (16.5)	4 (15.4)	1 (33.3)
SOC Cardiac disorders	12 (6.2)	12 (11.0)	5 (19.2)	1 (33.3)
SOC Vascular disorders	38 (19.6)	27 (24.8)	7 (26.9)	0
PT Cerebrovascular disorder	0	0	0	0
SOC Infections and infestations	78 (40.2)	54 (49.5)	10 (38.5)	2 (66.7)
PT Anticholinergic syndrome	0	0	0	0
PT Quality of life decreased	0	0	0	0
Sum of PTs of postural hypotension, **falls**, black outs, **syncope**, **dizziness**, **ataxia**, fractures	45 (23.2)	28 (25.7)	3 (11.5)	0

Abbreviations: AE, adverse event; MedDRA, medical dictionary for regulatory activities; n/N, number of patients; PT, preferred term, SOC, system organ class.
* Data on SAEs and serious criteria were obtained from the safety database which had a higher number of patients with SAEs compared to the clinical database at the time of the data cut-off date. Percentages are estimated.

In general, the types of AEs reported was similar between patients ≥65 years in all age categories and patients <65 years with the exception of events within the Cardiac disorders SOC which had a higher incidence in patients ≥65 years (6% vs 11%, 19%, 33%) and increased with increasing age. The SmPC includes relevant available information on the elderly population.

In general, no relevant differences, or a clear trend in a particular direction, were observed in the AE profiles by gender, race, region, prior lines of TKIs, prior distinct TKIs, total duration of prior TKIs. With caution, given the limitations of the safety database, it is noted that patients who had received 4+ prior distinct TKIs (49.1%) were more likely to experience AESIs of cognitive effects than were patients who had received 2 (36.0%), 3 (33.8%), or 1 TKI(s) (30.2%); Similarly, patients who had received 3 or 4+ prior lines of TKI therapy were more likely to experience treatment-related Grade ≥3 AEs and SAEs, predominantly events of anaemia.

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

Drugs That May Increase Avapritinib Plasma Concentrations

CYP3A Inhibitors

In vitro studies demonstrated that avapritinib Phase I metabolism is predominantly mediated by cytochrome P450 (CYP) 3A4, and to a minor extent by CYP2C9.

In a crossover clinical DDI study in healthy subjects (N=20), coadministration of 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 Cmax by 1.4-fold and area under the plasma concentration-time curve (AUC) by 4.2-fold, relative to a 200 mg dose of avapritinib administered alone, and may result in increased adverse reactions. Based on physiologically-based pharmacokinetic (PBPK) modelling and simulation, the increase in avapritinib AUC in patients with GIST treated with 300 mg QD is estimated to be 7.5-fold and 3.9-fold at steady state with concomitant used of strong CYP3A inhibitors itraconazole and

ketoconazole, respectively. PBPK modelling and simulation predicted a 1.7-fold and 1.1-fold increase in avapritinib AUC from concomitantly used moderate (fluconazole) or mild (cimetidine) CYP3A inhibitors. The Applicant proposes that concomitant use of strong CYP3A inhibitors with avapritinib should be avoided as a risk minimisation measure (Section 4.5 SmPC), which appears insufficient considering the relevance of the DDI.

Drugs That May Decrease Avapritinib Plasma Concentrations

CYP3A Inducers

In a crossover clinical DDI study in healthy subjects (N=20), coadministration of rifampin (600 mg QD for 18 days) with a single 400 mg dose of avapritinib on Day 9 decreased avapritinib Cmax by 74% and AUC by 92%, relative to a 400 mg dose of avapritinib administered alone, and may result in decreased efficacy. Based on PBPK modeling and simulation, the decrease in avapritinib AUC in patients with GIST treated with 300 mg QD is estimated to be 77% at steady state with concomitant use of a moderate CYP3A inducer (efavirenz). The Applicant proposes that concomitant use of strong and moderate CYP3A inducers should be avoided, which appears of little clinical value.

Given the clinical relevance of these DDIs, and consistent with prior decisions for other TKIs, the Applicant has been requested to review current information in the SmPC and include appropriate information to warm prescribing physicians on this risk, including appropriate risk minimisation measures in Sections 4.4 and 4.5. The possibility to provide recommendations for dose adjustments in any situation is discussed.

Drugs That May Have Their Plasma Concentrations Altered/Affected by Avapritinib

Sensitive CYP3A Substrates

Avapritinib is a direct and time-dependent inhibitor and an inducer of CYP3A in vitro. Caution should be exercised with concomitant use of sensitive CYP3A substrates because their plasma concentrations may be altered.

CYP2C9 Substrates

Avapritinib is a direct inhibitor of CYP2C9 in vitro. Therefore, avapritinib may have the potential to increase plasma concentrations of drugs that are substrates of CYP2C9. Caution should be exercised with coadministration of avapritinib with CYP2C9 substrates.

Transporter Substrates

In vitro, avapritinib is an inhibitor of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), BSEP, multidrug and toxin extrusion protein 1 (MATE1) and 2-K (MATE2-K). Estimated intestinal luminal concentration (Igut)/half-maximal inhibitory concentration (IC50) values for P-gp and BCRP and maximal unbound plasma concentration (Imax,u)/IC50 values for MATE1 and MATE2-K exceeded the regulatory thresholds of $\geq$10 and $\geq$0.02, respectively. Avapritinib may have the potential for PK drug interactions with P-gp, BCRP, MATE1, and MATE2-K substrates. However, clinical studies to investigate the potential for transporter-mediated DDIs have not been pursued.

Avapritinib is an inhibitor of P-gp, BCRP, MATE1, MATE2-K, and BSEP in vitro. Therefore, avapritinib has the potential to alter concentrations of co-administered substrates of these transporters.

At the same time, avapritinib is an in vitro inducer of CYP3A, inhibitor of CYP2C9, and inhibitor of P-glypoprotein (and other transporters). These DDIs have not been investigated in vivo, and thus, its clinical relevance is uncertain. 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.

In vitro studies indicated that avapritinib is an inducer of CYP3A. Therefore, avapritinib may have the potential to decrease plasma concentrations of co-administered medicinal products that are substrates of CYP3A.

Caution should be exercised with co-administration of avapritinib with narrow therapeutic index CYP3A substrates as their plasma concentrations may be altered.

Discontinuation due to AES

Patients with GIST

A total of 19.7% of patients discontinued study drug due to an AE, which appeared to be predominantly related to the patients' underlying disease. The most commonly (≥1%) reported AEs leading to study drug discontinuation by PT were disease progression (3.0%), general physical health deterioration (1.7%), and abdominal pain, acute kidney injury, anaemia, fatigue, and sepsis (1.3%).

For these patients, 9.0% discontinued study drug due to an AE that was considered treatment-related. The following treatment-related AEs led to study drug discontinuation in >1 patient: fatigue (1.7%) and confusional state, encephalopathy, nausea, and vomiting (<1% each).

Post marketing experience

There is no marketing experience to report for avapritinib.

During the procedure, two updates of the safety database were provided, one at D120 with the 8th July 2019 as new data cut-off and a second one as of cut-off date 9th March 2020. Information in the SmPC correspond with the most updated data cut-off point presented as follows:

Update of the Safety database with cut-off date 9th March 2020

The safety profile of avapritinib has been characterized in 585 patients with GIST. This includes 250 patients in study **BLU-285-1101** who received treatment with avapritinib, and 473 patients in study **BLU-285-1303** who received study treatment, including 239 patients who received avapritinib and 234 patients who received regorafenib. Of note, 96 patients who received regorafenib in study BLU-285-1303 crossed over to receive avapritinib treatment due to disease progression on the regorafenib control treatment. This provides an additional 8 months of follow-up for study BLU-285-1101 and an additional 6 months of follow-up for study BLU-285-1303 compared to the safety data presented in the Applicant's responses to the D120 LoQ. The median treatment duration is 23.2 months both in 1L and 2L+ GIST patients included in study BLU-285-1101 and 8.9 months in the GIST patients included in study BLU-285-1303.

Safety data from study **BLU-285-1101** showed that all patients except for one (>99%) reported any AEs, where 80% were ≥G3 (13% fatal G5 AEs), 65% reported SAEs and 27% experienced AEs that led to permanent discontinuation. The most common AEs leading to death were disease progression (15/32), general physical health deterioration (6/32), sepsis (3/32), and tumor haemorrhage (2/32). Cognitive effects were reported by 46% (115/250) of the patients, most cases were mild-moderate AEs (90% G1-2 AEs, 10% G3 AEs), with a median time to onset of 8.3 weeks and median treatment duration was 12.4 months in patients who experienced cognitive effects (n=115), and 3.8 months in those patients (54%; n=135) who did *not* experience cognitive effects. Intracranial haemorrhages were reported by 3% (7/250) of the patients. No fatal cognitive or IC bleeding events were reported. As expected, the safety data in the subset of 56 GIST patients with mutation PDGFRA D842V showed consistent results to the overall study population: 100% experienced AEs, 80% (45/56) ≥G3 AEs, 57% (32/56) SAEs, 21% (12/56) AEs that lead to permanent treatment discontinuation.

The safety analysis from **BLU-285-1303** is consistent with the safety results reported from BLU-285-1101 and no new safety signals were identified. Overall, 99% of the patients reported any AEs in the avapritinib treatment arm, including 75% ≥G3 AEs (4% G5 AEs), 41% SAEs, and 13% AEs that lead to treatment discontinuation. The safety profile in this study is similar to that observed in the phase 1 study. The figures for regorafenib were: 100% AEs, 70% ≥G3 AEs (5% G5AEs), 36% SAEs, and 11% AEs that lead to discontinuation, which are comparable to the safety profile observed for the avapritinib treatment arm. Consistent with the overall trend of a slightly less severe safety profile observed in the phase 3 trial, cognitive effects were reported by 26% of the patients, 95% G1-2 AEs and 5% G3 AEs, and intracranial bleedings were reported in 1% of the patients. No fatal cognitive or IC bleeding events were reported.

Preliminary safety data from a total of 50 unresectable or metastatic GIST patients enrolled in study **BLU-285-1105** (in Chinese patients) with the DCO of 31 March 2020, where 8 patients had PDGFRA D842V mutations, were largely consistent with those reported in the other avapritinib studies BLU-285-1101 and BLU-285-1303, and also for other TKIs. Overall, 98% of the patients reported ≥1AE, 38% G1-2 AEs, 46% G3 AEs and 14% G5 AEs, SAEs were reported by 28% of the patients. No IC bleeding events were observed and only 1 cognitive effect (2%) was reported. Although no observations of ICBs and the very low number of cognitive effects in this study are fortunate, these results should be interpreted with caution as they are only preliminary, and the studied patient population had received the study treatment for a short duration of time at the DCO.

2.6.1. Discussion on clinical safety

The safety profile of avapritinib has been characterized in 585 patients with GIST. This includes 250 patients in study **BLU-285-1101** who received treatment with avapritinib, and 473 patients in study **BLU-285-1303** who received study treatment, including 239 patients who received avapritinib and 234 patients who received regorafenib. In total, 96 patients who received regorafenib in study BLU-285-1303 crossed over to receive avapritinib treatment due to disease progression on the regorafenib control treatment. The median treatment duration is 23.2 months both in 1L and second-line and beyond (2L+) GIST patients included in study BLU-285-1101 and 8.9 months in the GIST patients included in study BLU-285-1303.

Safety data from study **BLU-285-1101** showed that all patients except for one **(>99%) reported any AEs**, where **80% were ≥G3** (**13% fatal G5 AEs**), **65% reported SAEs** and **27% led to permanent discontinuation**. The most common AEs leading to death were disease progression (15/32), general physical health deterioration (6/32), sepsis (3/32), and tumor haemorrhage (2/32). **Cognitive effects were reported by 46%** (115/250) of the patients, most cases were mild-moderate AEs (90% G1-2 AEs, 10% G3 AEs), with a median time to onset of 8.3 weeks and median treatment duration was 12.4 months in patients who experienced cognitive effects (n=115), and 3.8 months in those patients (54%; n=135) who did *not* experience cognitive effects. **Intracranial haemorrhages were reported by 3%** (7/250) of the patients. No fatal cognitive or IC bleeding events were reported. As expected, the safety data in the subset of 56 GIST patients with mutation PDGFRA D842V showed consistent results to the overall study population: 100% experienced AEs, 80% (45/56) ≥G3 AEs, 57% (32/56) SAEs, 21% (12/56) experienced AEs that lead to permanent treatment discontinuation.

The safety analysis from the ongoing phase 3 study **BLU-285-1303,** that compares avapritinib vs regorafenib in GIST patients >2L, is consistent with the safety results reported from BLU-285-1101 and no new safety signals were identified. Overall, **99% of the patients reported any AEs in the avapritinib treatment arm, including 75% ≥G3 AEs (4% G5 AEs), 41% SAEs, and 13% AEs that lead to treatment discontinuation**. The safety profile in this study is similar to that observed in the phase 1 study. The figures for regorafenib were: 100% AEs, 70% ≥G3 AEs (5% G5AEs), 36% SAEs,

and 11% AEs that lead to discontinuation, which are comparable to the safety profile observed for the avapritinib treatment arm. Consistent with the overall trend of a slightly less severe safety profile observed in the phase 3 trial, **cognitive effects were reported by 26%** of the patients, 95% G1-2 AEs and 5% G3 AEs, and **intracranial bleedings were reported in 1%** of the patients. No fatal cognitive or IC bleeding events were reported. The Applicant argues that early recognition and management of cognitive effects as a consequence of more careful attention to instructions for dose modification of cognitive effects might explain the lower incidence. Although this argumentation may be true, it is noticed that the treatment duration in the -1303 study compared to the -1101 study is considerably shorter, see above.

Preliminary safety data from a total of 50 unresectable or metastatic GIST patients enrolled in study **BLU-285-1105** (in Chinese patients) with the DCO of 31 March 2020, where 8 patients had PDGFRA D842V mutations, were largely consistent with those reported in the other avapritinib studies BLU-285-1101 and BLU-285-1303, and also for other TKIs.

The safety profile observed in studies BLU-285-1101 and BLU-285-1303 showed that almost all patients reported AEs, and the most commonly reported AEs were largely consistent with that reported for other TKIs. The distribution of AEs by severity appear similar between the studies and across treatment arms. Based on the pooled analysis of studies BLU-285-1101 and BLU-285-1303 (as now included in section 4.8 of the SmPC), the most frequently reported treatment related AEs of any grade during treatment with avapritinib were nausea (45%), fatigue (40%), anaemia (39%), periorbital oedema (33%), hyperbilirubinaemia (27%), face oedema (27%), diarrhoea (26%), vomiting (24%), blood bilirubin increased (24%), oedema peripheral (23%), lacrimation increased (22%), and decreased appetite (21%) and memory impairment (20%). Among these, anaemia, abdominal pain, sepsis, physical health deterioration, and GI haemorrhages were commonly reported as SAEs during avapritinib treatment, some leading to permanent discontinuation or even had a fatal outcome.

In summary, avapritinib presents substantial toxicity, as shown by the high incidence of severe, including life-threatening and fatal, adverse events. The safety profile is consistent with that seen for other TKIs, with significant gastrointestinal and hematological toxicities. Haemorrhages, including IC bleedings, and cognitive effects are AEs of particular concern. The update of safety data provided is somewhat reassuring given that the frequency of G5 AEs, SAEs, and AEs leading to treatment discontinuation tended to be lower in the controlled phase 3 trial than those initially reported in the phase 1 study, and similar to the frequencies observed in the regorafenib control arm. Similarly, less AESIs of cognitive effects and intracranial bleeding were reported in the phase 3 trial. Thus, it can be argued that to some extent the toxicity is manageable with appropriate risk minimization measures, including lower starting dose and restrictions for dose escalation, closer monitoring of AEs, and careful selection of candidates to treatment. However, long-term follow-up is still needed to properly characterise the safety profile of avapritinib, particularly for patients in the 1L disease setting.

There are no data from the use of avapritinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 2.3.4. Toxicology). Avapritinib is not recommended during pregnancy and in women of childbearing potential not using contraception.

If avapritinib is used during pregnancy or if the patient becomes pregnant while taking avapritinib, the patient should be advised of the potential risk to the foetus.

It is unknown whether avapritinib/ metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with avapritinib and for 2 weeks following the final dose (see section 4.6 of the SmPC).

Avapritinib may cause adverse reactions such as cognitive effects that may influence the ability to drive and use machines. Patients should be made aware of the potential for adverse effects that affect their

ability to concentrate and react. Patients who experience these adverse effects should take special care when driving a car or operating machinery (see section 4.7 of the SmPC).

The observed higher incidence of SAEs, including fatal events, and AEs leading to treatment discontinuation in the elderly population is considered relevant information for prescribing physicians and has been appropriately reflected in Section 4.8 of the SmPC. I

Additional safety data needed in the context of a conditional MA

In the context of a CMA additional safety data will be provided as SOBs:

• **Study BLU-285-1101**: Final CSR by 2H 2021

• **Study BLU-285-1303**: Final CSR by 1H 2021

Final CSRs from studies BLU-285-1101 and BLU-285-1303 will include all available data on the safety and efficacy of avapritinib in patients with PDGFRA D842V-mutant GIST (n = 51).

• **Study BLU-285-1406:** *A new observational long-term safety and efficacy study in treatment naïve patients with unresectable or metastatic PDGFRA D842V-mutant GIST*. Final study report to be provided by December 2027. This proposed study will be set up to collect long-term (minimum 2 years) safety and efficacy data in approximately 50 GIST patients in the 1L disease setting harbouring the PDGFRA D842V mutation.

2.6.2. Conclusions on clinical safety

The safety database includes a total of 585 patients with GIST (all doses), of which 550 patients received avapritinib at a starting dose of 300 mg or 400 mg. This includes 250 patients in study BLU-285-1101, 239 patients in study BLU-285-1303 who received treatment with avapritinib and 96 patients who received regorafenib in study BLU-285-1303 and then crossed over to receive avapritinib treatment due to disease progression on the regorafenib control treatment.

Based on the totality of the evidence available, it is concluded that avapritinib presents substantial toxicity, as shown by the high incidence of severe, including life-threatening and fatal adverse events. The safety profile is nevertheless consistent with that seen for other TKIs, with significant gastrointestinal and haematological toxicities. Haemorrhages, including IC bleedings, and cognitive effects are AEs of particular concern. The most updated data provided are somewhat reassuring given that the frequency of G5 AEs, SAEs, and AEs leading to treatment discontinuation tended to be lower to those initially reported in the phase 1 study, and similar to the frequencies observed in the regorafenib control arm. Similarly, less AESIs of cognitive effects and intracranial bleeding were reported in the phase 3 trial. Thus, it can be argued that to some extent the toxicity is manageable with appropriate risk minimization measures, including lower starting dose and restrictions for dose escalation, closer monitoring of AEs, and careful selection of candidates to treatment.

Nevertheless, although considered acceptable in view of the high efficacy shown, and overall manageable, the substantial toxicity of avapritinib requires an adequate selection and close monitoring of patients. To this aim, information in sections 4.2, 4.4 and 4.8 of the SmPC has been notably extended in order to provide accurate and useful information for the prescribing physician.

Finally, long-term follow-up is still needed as uncertainties still remain on the safety profile of avapritinib, particularly in patients treated in the 1L GIST disease setting. In order to address remaining uncertainties, the Applicant has committed to provide additional evidence on safety (and efficacy) during the post-marketing. In particular, final study results of the two ongoing studies will be

provided as SOB of the proposed CMA.

-In order to further confirm the safety and efficacy of avapritinib in the treatment of adult patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation, the MAH will submit the results of study **BLU-285-1303 (efficacy data of the PDGFRA D842V-mutant population and safety data from the overall safety population), an ongoing open-label, randomized, Phase 3 study** of avapritinib vs regorafenib in patients with locally advanced unresectable or metastatic GIST. Although this study is not restricted to patients harbouring the mutation, these patients will be included and will provide additional evidence of efficacy and safety in this subset of patients, plus controlled efficacy and safety data vs regorafenib, which will allow contextualising the study results.

-In order to further confirm the safety and efficacy of avapritinib in the treatment of adult patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation, the MAH should submit the results of study **BLU-285-1101, an ongoing single-arm, open-label multiple-cohort Phase 1 study in patients with GIST** and other relapsed and refractory solid tumours. This study will provide additional longer term efficacy and safety data in the target population.

-**Non-interventional post-authorisation safety study (PASS):** In order to further confirm the safety and efficacy of avapritinib in the treatment of adult patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation, the MAH will submit the results of an observational long-term safety and efficacy study in patients with unresectable or metastatic PDGFRA D842V-mutant GIST.

2.7. Risk Management Plan

Safety concerns

Summary of Safety Concerns updated RMP v0.4, signed off 14 July 2020

Summary of Safety Concerns	
Important identified risks	Intracranial haemorrhage (e.g. haemorrhage intracranial, cerebral haemorrhage, and subdural haematoma) Cognitive effects (e.g. memory impairment, cognitive disorders, confusional state, and encephalopathy) Drug-drug interactions with moderate or strong CYP3A inhibitors or inducers
Important potential risks	Cardiac toxicity, including QT prolongation Embryofoetal toxicity
Missing information	Use in patients with severe hepatic impairment Drug-drug interactions with CYP3A substrates

Pharmacovigilance plan

Ongoing and Planned Additional Pharmacovigilance Activities

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 2 – imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Study BLU-285-1406 "Observational study evaluating safety and efficacy of avapritinib in the first-line treatment of patients with Platelet derived Growth Factor Alpha D842V mutated gastrointestinal stromal tumor" Planned	Primary objective: – To evaluate long-term safety Secondary objective: – To evaluate long-term efficacy	– Intracranial haemorrhage (e.g. haemorrhage intracranial, cerebral haemorrhage, and subdural haematoma) – Cognitive effects (e.g. memory impairment, cognitive disorders, confusional state, and encephalopathy) – 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	– Protocol submission	– 2 months after the European Commission Decision
			– Interim reports	– Annually within the annual renewal (starting with the second annual renewal)
			– Final clinical study report	– December 2027
Category 3 – required additional pharmacovigilance activities				
"A Study to Evaluate the Pharmacokinetics of Avapritinib in Hepatically Impaired Subjects" Planned	– To characterise the pharmacokinetics of avapritinib in patients with hepatic impairment	– Use in patients with severe hepatic impairment	– Final protocol	– Q3 2020
			– Study completion	– Q3 2023
			– Final clinical study report	– March 2024

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
DDI study "Clinical drug-drug interaction study of avapritinib with a CYP3A substrate" Planned	– To investigate net effect of CYP3A inhibition and induction by avapritinib on midazolam pharmacokinetics in patients	– Drug-drug interactions with CYP3A substrates	– Final protocol	– December 2020
			– Study completion	– December 2023
			– Final clinical study report	– May 2024

Risk minimisation measures

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

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Intracranial haemorrhage (e.g. haemorrhage intracranial, cerebral haemorrhage, and subdural haematoma)	Routine risk minimisation measures: – SmPC sections 4.2, 4.4 and 4.8 – PL sections 2 and 4 Recommendation to perform brain imaging by magnetic resonance imaging or computed tomography 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 temporarily stop treatment and contact treating physician if symptoms such as severe headache, vision problems, severe sleepiness, or severe weakness on one side of your body (signs of bleeding in your brain) occur is included in PL section 2. Restricted prescription medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting: – Follow-up questionnaire Additional pharmacovigilance activities: – Study BLU-285-1406 (final study report: December 2027) This risk will be evaluated in Study BLU-285-1406. Two PAES studies (BLU-285-1101 and BLU-285-1303) will provide further information.
Cognitive effects (e.g. memory impairment, cognitive disorders,	Routine risk minimisation measures: – SmPC sections 4.2, 4.4, 4.7 and 4.8	Routine pharmacovigilance activities beyond signal

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
confusional state, and encephalopathy)	– PL sections 2 and 4 Recommendations for dose modification in case of Grade 1-Grade 3 events is included in SmPC section 4.2 . Recommendation to permanently discontinue therapy if Grade 4 cognitive effects occur is included in SmPC section 4.2. Restricted prescription medicine Additional risk minimisation measures: None	detection and adverse reactions reporting: – Follow-up questionnaire Additional pharmacovigilance activities: – Study BLU-285-1406 (final study report: December 2027) This risk will be evaluated in Study BLU-285-1406. Two PAES studies (BLU-285-1101 and BLU-285-1303) will provide further information.
Drug-drug interactions with moderate or strong CYP3A inhibitors or inducers	Routine risk minimisation measures: – SmPC sections 4.2, 4.4, 4.5, and 5.2 – PL section 2 If concomitant use with a moderate CYP3A inhibitor cannot be avoided, the starting dose of avapritinib should be reduced from 300 mg orally once daily to 100 mg orally once daily as stated in SmPC section 4.2. Restricted prescription medicine Additional risk minimisation measures: None	Additional pharmacovigilance activities: – Study BLU-285-1406 (final study report: December 2027) This risk will be evaluated in Study BLU-285-1406. Two PAES studies (BLU-285-1101 and BLU-285-1303) will provide further information.
Cardiac toxicity, including QT prolongation	Routine risk minimisation measures: – SmPC sections 4.4, 4.8 and 5.1 – PL sections 2 and 4 Restricted prescription medicine Additional risk minimisation measures: None	Additional pharmacovigilance activities: – Study BLU-285-1406 (final study report: December 2027) This risk will be evaluated in Study BLU-285-1406. Two PAES studies (BLU-285-1101 and BLU-285-1303) will provide further information.
Embryofoetal toxicity	Routine risk minimisation measures: – SmPC sections 4.6 and 5.3 – PL section 2 Recommendation for use of effective contraception during and after treatment in SmPC section 4.6 and PL section 2. Restricted prescription medicine Additional risk minimisation measures: None	Additional pharmacovigilance activities: – Study BLU-285-1406 (final study report: December 2027) This risk will be evaluated in Study BLU-285-1406. Two PAES studies (BLU-285-1101 and BLU-285-1303) will provide further information.
Use in patients with severe hepatic impairment	Routine risk minimisation measures: – SmPC sections 4.2 and 5.2 Restricted prescription medicine Additional risk minimisation measures: None	Additional pharmacovigilance activities: – Study BLU-285-1406 (final study report: December 2027) – A Study to Evaluate the Pharmacokinetics of Avapritinib in Hepatically

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		Impaired Subjects (final study report: March 2024) This missing information will be evaluated in studies outlined above. Two PAES studies (BLU-285-1101 and BLU-285-1303) will provide further information.
Drug-drug interaction with CYP3A substrates	Routine risk minimisation measures: – SmPC sections 4.5 and 5.2 – PL section 2 Restricted prescription medicine Additional risk minimisation measures: None	Additional pharmacovigilance activities: – Study BLU-285-1406 (final study report: December 2027) – DDI study (final study report: May 2024) This missing information will be evaluated in studies outlined above. Two PAES studies (BLU-285-1101 and BLU-285-1303) will provide further information.

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 09.01.2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The CHMP, based on the available data, considers avapritinib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Avapritinib Blueprint Medicines (avapritinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The following indication is being sought:

Treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation.

Gastrointestinal stromal tumour is a rare sarcoma that arises from the interstitial cells of Cajal and occurs throughout the GI tract.

The indication in 4L+ GIST population was withdrawn by the applicant during the procedure.

3.1.2. Available therapies and unmet medical need

Chemotherapy and radiation therapy are ineffective in the population with GIST harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation, so the current treatment scheme involves sequential administration of the TKIs imatinib, sunitinib, and regorafenib. In the general GIST population, ORR and median PFS decrease with each subsequent TKI, from 60% ORR and median PFS of 18-24 months (Demetri et al, 2002; Blanke et al, 2008) with imatinib down to 5-7% ORR and median PFS of 5-6 months with sutinib and regorafenib (Demetri et al, 2006; Demetri et al, 2013). Once the patient continues to progress while on regorafenib, the options are TKI re-challenge, best supportive or inclusion in a clinical trial (Casali et al, 2018; ESMO, 2018; NCCN, 2018).

The GIST patients carrying the PDGFRA D842V mutation are described as refractory to TKI treatment (Heinrich et al, 2003a; Cassier et al, 2012). In studies conducted in 1L patients, the ORR ranged from 0-12%, with median PFS of only 3 to 5 months, OS of approximately 15 months (Cassier et al, 2012; Yoo et al, 2016). Therefore, patients with PDGFRA D842V mutated GIST represent an unmet medical need that avapritinib attempts to fulfil.

3.1.3. Main clinical studies

The Applicant provided one single pivotal study (NAVIGATOR study) to support the claimed indication. This is an on-going Phase 1, first-in-human, dose-escalation, expansion, open-label study to evaluate the safety, tolerability, PK, PD and efficacy of avapritinib in adults with unresectable GIST. The population included in the initial proposed indication is composed by two different patient subsets:

- GIST patients who had received 3L+ of prior therapies (4L+ population, n=121);
- GIST patients carrying the PDGFRA D842V mutation, regardless of number of prior therapies (n=38).

Study BLU-285-1303 (VOYAGER) is a global, open-label, randomized, Phase 3 trial designed to evaluate the efficacy and safety of avapritinib versus regorafenib in patients with ≥3L GIST. Patients were randomized 1:1 to receive either avapritinib (300 mg QD dosing) or regorafenib (160 mg QD dosing for 3 out of every 4 weeks).

During the procedure, the Applicant withdrew the 4L+ indication from this MAA.

3.2. Favourable effects

In the **PDGFRA D842V mutated GIST population** (n=38), initial ORR was 90% (95% CI: 75.2%, 97.1%), while median DOR, PFS and median OS were not reached (PFS rate at 18 months of 71%). The most recent data (snapshot DCO date: 17-04-2020) is consistent with the previously submitted one and confirm a high and durable response : ORR of 95% (95% CI: 82.3, 99.4), median PFS of 24 months (95% CI: 18.4, NE), and a DOR of 22.1 months (95% CI: 14.1, NE), while the median OS has not been reached yet (36-months OS rate is 70.6% (95% CI: 55.2, 86.0).

Among the patients with the PDGFRA D842V mutation from the ongoing, controlled, phase III study BLU-285-1301 (VOYAGER), ORR in the avapritinib group is 42.9% (all partial responses) while none of the patients in the regorafenib group responded (0% ORR). Regarding median PFS in the population with the PDGFRA D842V mutation, there was a statistically significant difference, with a non estimable median PFS in patients with PDGFRA D842V mutations randomized to avapritinib (95% CI: 9.7, NE) compared to 4.5 months in patients receiving regorafenib (95% CI: 1.7, NE).

3.3. Uncertainties and limitations about favourable effects

Results from the phase III study (VOYAGER) are of a smaller magnitude than those reported in study BLU-285-1101 (NAVIGATOR). Several factors could have played a role in the differences observed, such as the small sample size across, shorter duration of follow-up and different therapy settings in terms of prior TKI treatments, since most patients from BLU-285-1101 were either TKI naïve or had received 1 prior TKI (13.2% and 47.4%, respectively), while patients in study BLU-285-1301 are at a later stage of the disease (≥3L).

3.4. Unfavourable effects

The safety database includes a total of 585 patients with GIST (all doses), of which 550 patients received avapritinib at a starting dose of 300 mg or 400 mg. This includes 250 patients in study **BLU-285-1101** who received treatment with avapritinib, and 473 patients in study **BLU-285-1303** who received study treatment, including 239 patients who received avapritinib and 234 patients who received regorafenib. In total, 96 patients who received regorafenib in study BLU-285-1303 crossed over to receive avapritinib treatment due to disease progression on the regorafenib control treatment. The median treatment duration is 23.2 months both in 1L and second-line and beyond (2L+) GIST patients included in study BLU-285-1101 and 8.9 months in the GIST patients included in study BLU-285-1303 (patients with the D842V mutation).

Safety data from study **BLU-285-1101** showed that all patients except for one **(>99%) reported any AEs**, where **80% were ≥G3** (**13% fatal G5 AEs**), **65% reported SAEs** and **27% led to permanent discontinuation**.

The most common AEs leading to death were disease progression (15/32), general physical health deterioration (6/32), sepsis (3/32), and tumor haemorrhage (2/32). **Cognitive effects were reported by 46%** (115/250) of the patients, most cases were mild-moderate AEs (90% G1-2 AEs, 10% G3 AEs), with a median time to onset of 8.3 weeks and median treatment duration was 12.4 months in patients who experienced cognitive effects (n=115), and 3.8 months in those patients (54%; n=135) who did *not* experience cognitive effects. **Intracranial haemorrhages were reported by 3%** (7/250) of the patients. No fatal cognitive or IC bleeding events were reported. As expected, the safety data in the subset of 56 GIST patients with mutation PDGFRA D842V showed consistent results to the overall study population: 100% experienced AEs, 80% (45/56) ≥G3 AEs, 57% (32/56) SAEs, 21% (12/56) AEs that lead to permanent treatment discontinuation.

The safety analysis from the ongoing phase 3 study **BLU-285-1303,** that compares avapritinib vs regorafenib in GIST patients >2L, is consistent with the safety results reported from BLU-285-1101 and no new safety signals were identified. Overall, **99% of the patients reported any AEs in the avapritinib treatment arm, including 75% ≥G3 AEs (4% G5 AEs), 41% SAEs, and 13% AEs that lead to treatment discontinuation**.

Based on the pooled analysis of studies BLU-285-1101 and BLU-285-1303 (as now included in section 4.8 of the SmPC), the most frequently reported treatment related AEs of any grade during treatment with avapritinib were nausea (45%), fatigue (40%), anaemia (39,6%), periorbital oedema (33%), hyperbilirubinaemia (27%), face oedema (27%), diarrhoea (26%), vomiting (24%), blood bilirubin increased (24%), oedema peripheral (23%), lacrimation increased (22%), decreased appetite (21%) and memory impairment (20%). Among these, anaemia, abdominal pain, sepsis, physical health deterioration, and GI haemorrhages were commonly reported as SAEs during avapritinib treatment, some leading to permanent discontinuation or even had a fatal outcome.

3.5. Uncertainties and limitations about unfavourable effects

The main limitations of the safety database are related to difficulties in establishing a causal relationship with avapritinib for key adverse events in the context of non-controlled studies and of a severe underlying condition. In addition, the limited exposure data, raise important uncertainties on the actual safety profile of avapritinib. The new information presented, which includes preliminary comparative (vs regorafenib) safety data from the ongoing phase 3 trial, alleviates to some extent the concerns given that the overall incidence of AEs, SAEs, >G3 AEs, and AEs leading to discontinuation tended to be lower in the phase 3 trial and comparable to those seen in the regorafenib treatment arm.

There are uncertainties about the mechanism behind the IC bleeding serious risk, possible risk factors, and the potential relation between avapritinib and bleedings in various locations with focus on potential underlying patterns and mechanisms. Although uncertainties still remain, the new data submitted showed lower incidences and severity of these AEs, which is somewhat reassuring and may indicate that appropriate risk minimisation measures including lower starting dose and restrictions for dose escalation may be implemented to reduce the risk. Interruption of treatment with or without dose reduction may be considered to manage adverse reactions based on severity and clinical presentation (section 4.2 of the SmPC).

Therefore, information in the SmPC has been substantially extended to provide an accurate and helpful information to physicians. In addition, to address remaining uncertainties, the Applicant has committed to further assess these risks within the agreed SOBs.

However, long-term safety data are still limited, which is an important uncertainty in particular for patients treated in first line due to longer exposure to the drug. This uncertainty will be further evaluated in the context of the agreed SOBs.

There are remaining uncertainties related to the appropriateness and usefulness of the risk minimisation measures proposed to manage some key adverse events, including cognitive disorders, GI events, and fluid retention. However, based on current knowledge, the SmPC has been updated to include appropiate precautionary statements concerning the most relevant risks and where possible, appropriate risk minimization measures, including lower starting dose and restrictions for dose escalation, closer monitoring of AEs, and careful selection of candidates to treatment.

The actual risk for QT prolongation and arrhythmias during avapritinib treatment is uncertain, given that a dedicated QT study has not been conducted, patients with risk factors were systematically excluded from study participation, results of the ECG substudy have not been presented according to ICH

requirements, and simulations conducted do not cover exposures that could be found in clinical practice (e.g. concomitant use with strong CYP3A4 inhibitors). This risk has been included as an important potential safety risk in the Safety Specifications and the studies agreed as SOBs will provide additional data to better characterise the risk. The SmPC has also been updated to include accurate and useful information to the prescribing physicians.

3.6. Effects Table

Effects Table for Avapritinib in GIST Study **BLU-285-1101** and **Study BLU-285-1303** (DCO for efficacy: 17-04-2020, DCO date for safety: 9th March 2020).

Effect	Short Description	Unit	Treatment AVAPRITINIB		Uncertainties/ Strength of evidence	References
Favourable Effects						
					- -	
PDGFRA D842V mutated GIST population in Study 1101 (n=38)	ORR DOR mPFS mOS	% Months Months Months	95 (95% CI: 82.3, 99.4) 22.1 (95% CI: 14.1, NE) 24 (95% CI: 18.4, NE) not reached (36-months OS rate is 70.6% (95% CI: 55.2, 86.0).			
PDGFRA D842V mutated GIST population in Study 1303 (n=13)	ORR mPFS	% Months	Avapritinib (n = 7) 43 NE (95% CI; 9.7, NE)	Regorafenib (n=6) 0 4.5 (95% CI; 1.7, NE)	This data is preliminary and limited as the study is ongoing	
Unfavourable Effects (Adverse reactions observed in patients at a 300/400mg starting dose)						
			All AEs	Treatment-related AEs		
General Safety profile	AE overall ≥G3 AEs SAEs AEs leading to death AE leading to treatment discontinuation AE leading to dose reductions AE leading to dose interruptions		98.4% 75.1% 49.8% 8.0% 18.0% 51.8% 70.7%	93.8% 55.5% 23.1% 0.4%* 10.9% 48.7% 62%	**Includes reports of disease progression*	
GI AEs	Overall G≥3 SAE Nausea Vomiting (2 PTs)		61.5% 5.5% 3.1% 45.1% 24.2%		SAEs includes GI hemorrhages	

	Diarrhoea Abdominal pain (5 PTs)		26.4% 10.9%		
Cytopenias	Overall G≥3 SAE Anaemia G≥3/SAE Neutropenia G≥3/SAE		44.5% 27.1% 6.4% 20.0%/6.2% 8.9%/0.2%		
Fluid retention	Oedema peripheral Face oedema Periorbital oedema Pleural effusion - Overall - G≥3 - SAEs		22.5% 26.5% 32.9% 6% 0.9% 1.1%		
Fatigue/ Asthenia	Overall G≥3 SAEs		45.1% 6.5% 0.9%		
Cognitive effects	Overall Grade ≥3 SAE Memory impairment Cog. Disorders Conf. state Encephalopathy		33.1% 2.2% 1.3% 20.2% 11.8% 4.7% 0.9%	Not all resolved, half ongoing (2 at the time of patient´s death) or resolved with sequalae	
Haemorrhages	Overall Grade ≥3 SAE Intracranial haemorrhage -Overall -Grade ≥3 -SAE		3.8% 2.0% 2.0% 1.6% 1.1% 1.5%		

Abbreviations: Conf. state = confusional state

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

GIST is a rare disorder and the proportion of patients expressing the PDGFRA D842V mutation is even smaller. It is acknowledged that the presence of the D842V mutation seems to provide resistance or very little response to TKI (Farag et al., JCO 2016 34:15_suppl, 11011-11011). Furthermore, even though data is mainly focused on imatinib and to a lesser extent on sunitinib (Hirota et al. Gastroenterology 2003), the D842V mutant GIST do not show any actionable recurrent molecular events of therapeutic significance (Indio et al. Int J Mol Sci. 2018).

Overall, the efficacy of avapritinib is currently based on results from a total of 59 patients (from the NAVIGATOR, VOYAGER and BLU-285-1105 studies). The pivotal evidence supporting this application is a single arm trial (NAVIGATOR) with ORR as primary endpoint in a limited sample size (n=38). ORR

results in the population with the **PDGFRA D842V** mutation, are unprecedented in this patient population, with 36 (94.7%) out of 38 patients achieving an ORR (81.6% PR), with a median DOR of 22 months and median PFS of 24 months (median OS not yet reached). Data on patients naïve to TKIs appear consistent with that of the overall D842V-mutant group, but is even more limited (n=5). However, it is agreed that in the D842V mutant GIST patient population ORR results are unprecedented and results would not be expected to be of a lesser magnitude in the 1L setting, and the benefit is considered to be demonstrated regardless of the line of treatment.

Supportive data from the phase III, controlled study and the phase I study in Chinese patients also show favourable and clinically relevant results, although of smaller magnitude.

- The available data support the benefit of avapritinib in the intended target population.

In addition, the impressive result in term of durable responses compares favourably with that reported from the literature for other TKIs in the target population. Overall, the reported results in the population with the PDGFRA D842V are considered relevant in the context of a patient population with limited treatment options and poor responses to approved TKI agents. This benefit is considered clinically meaningful.

The safety database has been substantially extended throughout the procedure, and the safety profile of avapritinib has now been characterized based on 585 patients with GIST. As of the last DCO, 9th March 2020, the median treatment duration is 23.2 months both in 1L and 2L and beyond (2L+) GIST patients included in study BLU-285-1101 and 8.9 months in the GIST patients included in study BLU-285-1303, which provides some preliminary comparative safety data. The safety profile is largely consistent with that reported for other TKIs. Based on the pooled analysis of studies BLU-285-1101 and BLU-285-1303, the most frequently reported treatment related AEs of any grade during treatment with avapritinib were nausea (45%), fatigue (40%), anaemia (39%), periorbital oedema (33%), hyperbilirubinaemia (27%), face oedema (27%), diarrhoea (26%), vomiting (24%), blood bilirubin increased (24%), oedema peripheral (23%), lacrimation increased (22%), and decreased appetite (21%) and memory impairment (20%). Among these, anaemia, abdominal pain, sepsis, physical health deterioration, and GI haemorrhages were commonly reported as SAEs during avapritinib treatment, some leading to permanent discontinuation or even had a fatal outcome.

For avapritinib, intracranial bleedings and GI/tumour haemorrhages have been reported, which remain as AEs of important concern. Cognitive disorders were very frequently reported, ranging from mild memory impairment events (mostly) to severe encephalopathy (few cases). Finally, as for other TKIs, reduced appetite and laboratory changes including hypokalaemia, hypophosphatemia, hyperbilirubinemia and ALT increases have been reported and monitoring activities have been proposed.

Avapritinib presents substantial toxicity, as shown by the high incidence of severe, including life-threatening and fatal adverse events. The safety profile is nevertheless consistent with that seen for other TKIs, with significant gastrointestinal and haematological toxicities. Haemorrhages, including IC bleedings, and cognitive effects are AEs of particular concern. The most updated data provided are somewhat reassuring given that the frequency of G5 AEs, SAEs, and AEs leading to treatment discontinuation tended to be lower to those initially reported in the phase 1 study, and similar to the frequencies observed in the regorafenib control arm. Similarly, less AESIs of cognitive effects and intracranial bleeding were reported in the phase 3 trial. Thus, it can be argued that to some extent the toxicity is manageable with appropriate risk minimization measures, including lower starting dose and restrictions for dose escalation, closer monitoring of AEs, and careful selection of candidates to treatment as described in the SmPC.

Finally, longer-term follow-up is still needed as uncertainties still remain on the safety profile of avapritinib, particularly in patients treated in the 1L GIST disease setting.

3.7.2. Balance of benefits and risks

In view of the substantial, although manageable, toxicity of avapritinib, adequate patient selection and surveillance are important. In addition, this safety profile should be considered within the context of the substantial efficacy shown, with high and durable responses, which are unprecedented in a patient population resistant to traditional TKI therapy. Therefore, the CHMP consider the benefit-risk balance of avapritinib in patients with unresectable or metastatic PDGFRA D842V-mutant GIST to be positive.

Conditional marketing authorisation

As comprehensive clinical data on the safety and efficacy of the medicinal product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.
The product falls within the scope of Regulation (EC) No 507/2006 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease and is designated as an orphan medicinal product.
Results in the population with the PDGFRA D842V mutation

1) *Positive Risk Benefit Profile:* the Applicant has presented high and durable tumour responses in a small sample size (n=38), which represent an unprecedented clinical activity in this patient population regardless of prior line of therapy. Preliminary results from the controlled, randomized phase 3 VOYAGER study (n=13) show supportive ORR data (42.9% vs. 0%, for avapritinib and regorafenib, respectively) and statistically significant differences in terms of median PFS in favour of avapritinib (NE vs 4.5 months, respectively).
   It is acknowledged that GIST is a rare disorder and the proportion of patients expressing the PDGFRA D842V mutation is even smaller. Nevertheless, the available data continue to support the outstanding benefit of avapritinib in the intended target population. This requirement has been met.

2) *Likelihood that Comprehensive Clinical Data will be Provided:*

   In order to provide comprehensive efficacy and safety data and to address remaining uncertainties needed to support the switching from conditional to normal marketing authorisation, the following SOBs are proposed:

   • Study BLU-285-1101: Final CSR by 2H 2021. This study is currently ongoing and recruitment has been completed, with a total of 38 patients with the PDGFRA D842V mutation being included. The Applicant has committed to provide the final CSR by 2021.

   • Study BLU-285-1303: Final CSR by 1H 2021. The Applicant included approximately 3% (n=13) of patients with the PDGFRA D842V mutationin the VOYAGER study. Mutation status is a stratification factor, so patients have been evenly balanced between both treatment groups. This study is also currently ongoing and the Applicant has committed to provide the final CSR by 2021.

   • Study BLU-285-1406: A new observational long-term safety and efficacy study in treatment naïve patients with unresectable or metastatic PDGFRA D842V-mutant GIST. Final study report to be provided by December 2027. Draft protocol: to be submitted at the latest 2 months after EC Decision. Enrolment update to be provided within each PSUR cycle. Annual interim reports will be provided within the annual renewal as of the second annual renewal.

   Final CSRs from studies BLU-285-1101 and BLU-285-1303 will include all available data on the safety and efficacy of avapritinib in patients with PDGFRA D842V-mutant GIST (n=51). The final study results in the 2L+ GIST patients demonstrate an equivalent median duration of exposure

to avapritinib as those in the 1L setting (23.2 months in both populations), indicating that safety and efficacy are similar despite prior line of treatment, and are therefore considered relevant when assessing avapritinib in the 1L disease setting. The newly proposed study BLU-285-1406 will contribute with long-term (minimum 2 years) safety and efficacy data in approximately 50 GIST patients in the 1L disease setting harbouring the PDGFRA D842V mutation. Overall, the proposed SOBs will contribute to obtaining comprehensive clinical data in approximately 100 patients with PDGFRA D842V-mutant GIST. It appears likely that the Applicant will be able to be provide these data and feasibility will not be an issue.

3) *Unmet Need Fulfilled:* this requirement could be considered fulfilled since the activity of currently used treatments is almost negligible in GIST patients with the D842V mutation.
4) *Benefit to Public Health of Immediate Availability Outweighs Risk that Additional Data are Still Required:* The outstanding activity shown in the context of a population with an unmet medical need renders the limited evidence acceptable to grant approval. In addition, the positive B/R balance has been demonstrated in the intended indication. Therefore, this requirement has been met.

3.8. Conclusions

The overall B/R of Avapritinib Blueprint Medicines is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus the benefit-risk balance of Ayvakyt is favourable in the following indication:

Ayvakyt is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
In order to further confirm the safety and efficacy of avapritinib in the treatment of adult patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation, the MAH should submit the results of study BLU-285-1303 (efficacy data of the PDGFRA D842V-mutant population and safety data from the overall safety population), an ongoing open-label, randomized, Phase 3 study of avapritinib vs regorafenib in patients with locally advanced unresectable or metastatic GIST.	Due date: June 2021
In order to further confirm the safety and efficacy of avapritinib in the treatment of adult patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation, the MAH should submit the results of study BLU-285-1101, an ongoing single-arm, open-label multiple-cohort Phase 1 study in patients with GIST and other relapsed and refractory solid tumours.	Due date: December 2021
Non-interventional post-authorisation safety study (PASS): In order to further confirm the safety and efficacy of avapritinib in the treatment of adult patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation, the MAH should submit the results of an observational safety and efficacy study in patients with unresectable or metastatic PDGFRA D842V-mutant GIST.	Due date: December 2027

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that avapritinib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.