POST-AUTHORISATION SAFETY STUDY (PASS) PROTOCOL

STUDY TITLE

Observational study evaluating the long-term safety and efficacy of avapritinib in the first-line treatment of patients with platelet-derived growth factor receptor alpha (PDGFRA) D842V-mutated gastrointestinal stromal tumour (GIST)

Study Product:	Avapritinib (AYVAKYT®/AYVAKIT®)
Protocol Number:	BLU-285-1406
Study Phase:	Phase IV
Short Title:	Observational safety and efficacy study of avapritinib in first-line PDGFRA D842V GIST
Protocol Version:	Version 5.0
Protocol Date:	24 January 2023

PASS INFORMATION

Title	Observational study evaluating the long-term safety and efficacy of avapritinib in the first-line treatment of patients with platelet-derived growth factor receptor alpha (PDGFRA) D842V-mutated gastrointestinal stromal tumour (GIST)
Protocol version identifier	5.0
Date of last version of protocol	24 January 2023
EU PAS register number	EUPAS41969
Active substance	avapritinib - L01EX18
Medicinal product	AYVAKYT®/AYVAKIT®
Product reference	EU/1/20/1473/001-005
Procedure number	EMEA/H/C/PSA/S/0092
Marketing authorisation holder(s)	Blueprint Medicines Corporation 45 Sidney Street Cambridge, MA 02139 USA Blueprint Medicines (Netherlands) B.V. Gustav Mahlerplein 2 1082 MA Amsterdam The Netherlands
Joint PASS	No
Research question and objectives	The overall objective of this study is to collect long-term safety and efficacy data for avapritinib in first-line patients with PDGFRA D842V-mutated GIST
Country(-ies) of study	Patients will be included from multiple sites worldwide
Authors	PPD Blueprint Medicines PPD Blueprint Medicines

MARKETING AUTHORISATION HOLDER(S)

Marketing Authorisation Holder(s)	Blueprint Medicines (Netherlands) B.V. Gustav Mahlerplein 2 1082 MA Amsterdam The Netherlands
MAH contact person	PPD Blueprint Medicines

PROTOCOL APPROVAL PAGE

Protocol Title: Observational study evaluating the long-term safety and efficacy of avapritinib in the first-line treatment of patients with platelet-derived growth factor receptor alpha (PDGFRA) D842V mutated gastrointestinal stromal tumour (GIST)

Protocol Number: BLU-285-1406

Protocol Number: Version 5.0

Protocol Date: 24 January 2023

This study protocol was subject to critical review and has been approved by Blueprint Medicines. The information contained in this protocol is consistent with the current risk-benefit evaluation of the investigational product.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

PPD

Date

INVESTIGATOR SIGNATURE PAGE

Protocol Title: Observational study evaluating the long-term safety and efficacy of avapritinib in the first-line treatment of patients with platelet-derived growth factor receptor alpha (PDGFRA) D842V-mutated gastrointestinal stromal tumour (GIST).

Protocol Number: BLU-285-1406

- I, the undersigned, have reviewed this protocol (and amendments), including annexures, and I will conduct the study as described in compliance with this protocol (and amendments).
- After the protocol has been approved by the independent ethics committee (IEC)/institutional review board (IRB), I will not modify this protocol without obtaining prior approval of Blueprint Medicines and of the IEC/IRB. I will submit the protocol amendments and/or any informed consent form/assent form modifications to Blueprint Medicines and the IEC/IRB, and approval will be obtained before any amendments are implemented.
- I ensure that source documents and study records that include all pertinent observations on each of the site's study patients will follow good document practices where required, e.g., will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study with regard to the patients' state of health will be regarded as confidential. No patients' personal identifying information will be disclosed. All patients will be identified by assigned numbers on all case report forms or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the patient before disclosure of patient information to a third party.
- Information developed in this clinical study may be disclosed by Blueprint Medicines to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

<Investigator Name>

<Title>

<Institution>

_____

Investigator Signature

_____

Date (DD-Mmm-YYYY)

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMA	Conditional marketing authorization
CR	Complete response
CUP	Compassionate Use Program
DCO	Data cutoff
DoR	Duration of response
DoT	Duration of treatment
EAP	Expanded Access Program
eCRF	Electronic case report form
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EMA	European Medicines Agency
EP	Enrolled population
GIST	Gastrointestinal stromal tumour
HCP	Healthcare provider
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IRB	Institutional review board
KIT	v-Kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	Modified Response Evaluation Criteria in Solid Tumours
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Overall response rate
OS	Overall survival
PDGFRA	Platelet-derived growth factor receptor alpha
PD	Progressive disease
PFS	Progression-free survival

PO	Oral
PR	Partial response
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred term
RMP	Risk management plan
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
SP	Safety population
TKI	Tyrosine kinase inhibitor
UK	United Kingdom
US	United States
WHO	World Health Organization

3. RESPONSIBLE PARTIES

Principal Investigator	PPD Blueprint Medicines PPD
Statistical Lead	PPD Blueprint Medicines PPD
Drug Safety & Pharmacovigilance Lead	PPD Blueprint Medicines PPD
Qualified Person Responsible for Pharmacovigilance (QPPV)	PPD PrimeVigilance Ltd. PPD

Contact details of all Investigators participating in the study will be kept in a stand-alone document referenced in Annex 1.

4. ABSTRACT

Title of study	Observational study evaluating the long-term safety and efficacy of avapritinib in the first-line treatment of patients with platelet-derived growth factor alpha (PDGFRA) D842V-mutated gastrointestinal stromal tumour (GIST) Version 5.0, 24 January 2023, PPD and PPD, Blueprint Medicines
Rationale and background	Gastrointestinal stromal tumours (GISTs) are rare, yet the most common mesenchymal tumours occurring in the gastrointestinal tract with an incidence of 10-15 per million people per year. (Søreide et al. 2016) About 90% of patients with GIST have a tumour that is dependent on mutations in the receptor tyrosine kinase protein v-Kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT) (75-80%) or the highly related receptor tyrosine kinase protein platelet-derived growth factor receptor alpha (PDGFRA) (10-15%), most commonly a substitution of valine for aspartic acid at amino acid 842 (D842V). (Corless et al. 2011) The dependence of GIST on mutated receptor tyrosine kinases led to the exploration of tyrosine kinase inhibitors (TKIs) for the systemic treatment of this rare malignancy. However, the PDGFRA D842V mutation causes primary resistance to conventional TKIs (Gounder et al. 2011) with low overall response rates (ORRs) found in first-line patients with PDGFRA D842V-mutant GIST (ORR 0-12%; Cassier et al. 2012; Farag et al. 2017; Yoo et al. 2016; BLU-285-1002 study report). Avapritinib (also known as BLU-285) is a potent and selective oral inhibitor of PDGFRA D842V and showed clinical activity in patients with unresectable or metastatic PDGFRA D842V-mutant GIST regardless of line of therapy. The ORR in patients with PDGFRA D842V-mutant was 95% in study BLU-285-1101 (100% in first-line patients; data cut off [DCO] 17 April 2020). The safety profile of avapritinib has been well characterised in patients with GIST and adverse events associated with avapritinib treatment can be managed with adherence to product labeling. As of 09 March 2020, the safety database included 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 the Phase I study BLU-285-1101 who received treatment with avapritinib, and 473 patients in the Phase III study BLU-285-1303 that compares avapritinib versus regorafenib in patients with GIST beyond second-line, including 239 patients who received avapritinib and 96 patients who received regorafenib and then crossed over to receive avapritinib treatment upon disease progression. Safety data from the study BLU-285-1101 (DCO 9 March 2020) showed that all patients except for one (>99%) reported adverse events (AEs), where 80% of patients reported an AE ≥ Grade 3 (13% fatal Grade 5 AEs), 65% reported serious AEs (SAEs) and 27% led to permanent discontinuation. The safety analysis from the study 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 in the avapritinib treatment arm reported AEs, where 75% of patients reported ≥ Grade 3 AEs (4% Grade 5 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, 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%). 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%). A total of 19.7% of patients with GIST discontinued avapritinib 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 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). During clinical development, two AEs of Special Interest (AESIs) were identified: intracranial bleeding and cognitive effects. Although the mechanism for these events is unclear, intracranial bleeding and cognitive effects have been reported with imatinib and other TKIs. (Feki et al. 2015; Shaw et al. 2017; Song et al. 2004) Intracranial bleeding (e.g., subdural haematoma, intracranial haemorrhage, cerebral haemorrhage) occurred in 9 (1.6%) of the 550 patients with GIST who received avapritinib at starting doses of either 300 or 400 mg once daily. Intracranial bleeding was reported by 3% (7/250) of the patients in BLU-285-1101: 3 patients had a subdural haematoma (Grade 1, Grade 2 or Grade 3), 2 patients had an intracranial haemorrhage (Grade 1 or Grade 3) and 2 patients had a cerebral haemorrhage (Grade 3 or Grade 4). Consistent with the overall trend of a slightly less severe safety profile observed in the Phase III trial, intracranial bleeding was reported in 1% in BLU-285-1303: 2 patients with Grade 4 intracranial haemorrhage and 1 patient with both a Grade 4 subdural haematoma and a Grade 4 intracranial haemorrhage. No fatal intracranial bleeding events were reported in either study. The mechanism by which avapritinib may cause events of intracranial bleeding are uncertain. Risk factors for intracranial bleeding include severe thrombocytopenia, vascular aneurysm, a history of intracranial haemorrhage within the prior year, and a history of a cerebrovascular accident or transient ischaemic attack. Appropriate risk minimisation measures including lower starting dose and restrictions for dose escalation might reduce the risk. It is recommended that avapritinib be permanently discontinued in patients with an observed intracranial bleeding event of any severity grade during treatment. Cognitive effects occurred in 182 (33%) of the 550 patients with GIST who received avapritinib at starting doses of either 300 or 400 mg once daily. Most cognitive effects were Grade 1 (89%), with Grade ≥2 occurring in 11%

	of 550 patients. Memory impairment occurred in 20% of patients, <1% of these events were Grade 3. Cognitive disorder occurred in 12% of patients; <1% of these events were Grade 3. Confusional state occurred in 5% of patients; <1% of these events were Grade 3. Encephalopathy occurred in <1% of patients; <1% of these events were Grade 3. SAEs of cognitive effects were reported for 7 of the 550 (1.3%) patients. Overall, 1.3% of patients required permanent discontinuation of avapritinib for a cognitive effect. Cognitive effects were reported by 46% of the patients in BLU-285-1101 and most cases were mild-moderate AEs (90% Grade 1-2 AEs, 10% Grade 3 AEs). Consistent with the overall trend of a slightly less severe safety profile observed in the Phase III trial, cognitive effects were reported by 26% of the patients in BLU-285-1303, 95% Grade 1-2 AEs and 5% Grade 3 AEs. The 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 in the Phase III trial as AESIs of cognitive effects were higher in the 400 mg starting dose group compared to the 300 mg group in BLU-285-1101 (48% vs 39%). However, the median treatment duration for patients receiving avapritinib (any dose) in the Phase III trial was also considerably shorter (8.9 months) than in the Phase I trial (23.2 months). No fatal cognitive events were reported in either study. In the clinical development program, the probability of experiencing a cognitive effect increased over the first 7 to 8 months of treatment and then reached a plateau. Non-clinical mechanistic studies could not clearly identify the underlying mechanism for cognitive effects (i.e., memory impairment). Clinical factors associated with an increased likelihood of experiencing Grade ≥2 cognitive effects include a medical history of cognitive effects, prior regorafenib use and age ≥65 years. Brain imaging studies of patients experiencing cognitive effect symptoms during the clinical studies did not reveal any associated anatomical changes. Cardiac toxicity, including QT prolongation, is considered a safety concern for avapritinib and is classified as an important potential risk in the EU risk management plan (RMP). While non-clinical studies did not show any effects of avapritinib on the cardiovascular system, in clinical Study BLU-285-1101, a small increase in the QTc interval (6.55 ms; 90% CI: 1.80 to 11.29 at 300/400 mg QD clinical dose) that was not clinically relevant was observed in a subset of GIST patients. In addition, the slope of the avapritinib concentration-QTc relationship was very shallow: 0.007 ms per ng/mL (90% CI: 0.003 to 0.012), with a small, non-statistically significant intercept of -0.2 ms (90% CI: -2.26 to 1.89). However, considering the existing potential of mainly multi-target TKIs to cause QT prolongation (Porta-Sanchez et al. 2017) and cardiac toxicity (Orphanos et al. 2009; Chen et al. 2016; Lee et al. 2018; Porta-Sanchez et al. 2017) cardiac toxicity, including QT prolongation is considered an important potential risk associated with avapritinib warranting further evaluation in the post authorisation setting. Therefore, cardiac toxicity, including QT prolongation and associated symptoms such as cardiac arrest, sudden cardiac death, syncope or ventricular arrhythmia are to be closely monitored during the course of this study. In study BLU-285-1101, 56 patients carried the PDGFRA D842V mutation of whom 17 patients received an avapritinib starting dose <300 mg and 1 patient a starting dose of 600 mg. A total of 38 patients were treated

	with an avapritinib starting dose of 300 or 400 mg including 28 patients at a starting dose of 300 mg and 10 patients at a starting dose of 400 mg. Of the 56 patients with PDGFRA D842V-mutated GIST, avapritinib was received first-line by 11 patients, second-line by 21 patients, third-line by 10 patients, fourth-line by 6 patients and after at least 4 previous lines of treatment by 8 patients. Of the 11 patients with PDGFRA D842V-mutated GIST receiving first-line avapritinib, 6 received an avapritinib starting dose <300 mg, 4 patients a starting dose of 300 mg and 1 patient a starting dose of 400 mg. As expected, the safety data in the subset of 56 patients with PDGFRA D842V-mutated GIST in study BLU-285-1101 showed consistent results to the overall study population in the safety analysis based on data from the 9 March 2020 DCO date: 100% experienced AEs, 80% (45/56) ≥Grade 3 AEs, 57% (32/56) SAEs and 21% (12/56) AEs that lead to permanent treatment discontinuation. Only 11 of the 56 patients with PDGFRA D842V-mutant GIST received first-line avapritinib in study BLU-285-1101 and safety data are limited, which is an important uncertainty for patients treated in first-line due to longer exposure to the drug. Avapritinib is approved in the United States (US) for the treatment of adults with unresectable or metastatic GIST harbouring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations. On 24 September 2020, the European Commission granted conditional marketing authorization (CMA) for avapritinib as monotherapy for GIST harbouring the PDGFRA D842V mutation. To address the Specific Obligation of the CMA in Europe and to provide further evidence of the positive benefit-risk profile of first-line treatment with avapritinib in patients with metastatic and unresectable GIST harbouring mutations in PDGFRA D842V, this study aims to collect long-term safety and efficacy data in the first-line population. This study is designated as a Post-Authorisation Safety Study (PASS).
Research question and objectives	The overall objective is to collect long-term safety and efficacy data for avapritinib in first-line patients with PDGFRA D842V-mutated GIST. <u>Primary objective:</u> • To describe types, severity and rates of AEs, SAEs, AEs leading to discontinuation or decreased dosing of avapritinib, AESIs, and deaths. <u>Secondary objective:</u> • To evaluate efficacy in terms of disease response to treatment, progression-free survival (PFS) and overall survival (OS) as well as duration of treatment and duration of response.
Study design	This is a multinational, open-label, observational PASS that will evaluate the long-term safety and efficacy of avapritinib in first-line or following ≤4 months of imatinib treatment in at least 50 patients with PDGFRA D842V-mutated GIST. Three patient populations are planned to be enrolled: • Patients with PDGFRA D842V-mutated GIST who are scheduled to receive avapritinib in the first-line (or have received imatinib for ≤4 months)

	• Patients with PDGFRA D842V-mutated GIST who are already receiving treatment with avapritinib (in the first-line or following ≤4 months of imatinib treatment) • Patients with PDGFRA D842V-mutated GIST who previously received treatment with avapritinib in the first line or following ≤4 months of imatinib treatment and have discontinued treatment In addition to evaluating safety and efficacy of first-line avapritinib treatment, patients who were initially treated with imatinib for ≤4 months are also being included in this study to allow for practical, real-world, clinical experience with use of avapritinib in the PDGFRA D842V-mutated GIST population setting and increase the feasibility of study completion in this ultra-rare patient population. Informed consent will be obtained from all patients according to the regulatory and legal country-specific requirements of the participating site before enrolment in this study. Patients who were scheduled to receive avapritinib prior to enrolment will initiate treatment after enrolment in this study based on the locally approved product label prescribing information. If a patient was already receiving avapritinib prior to enrolment, they will continue treatment at the same dose after enrolment. The dose level may be adjusted based on the locally approved product label prescribing information. Investigators must refer to the local prescribing information for contraindications, warnings and precautions as well as use in specific populations. As this study is observational, the decision to treat patients with avapritinib will be independent from the decision to enrol patients into the study. Baseline and follow-up assessments will be in accordance with local standard medical care. Both prospective and retrospective data collection will be performed in this study. All patients who will initiate or continue treatment with avapritinib after enrolment will have prospective data collection for 24 months on the study. For patients who have received avapritinib prior to enrolment in this study, retrospective data will also be collected (if data are available). Retrospective data collection will be performed at the participating investigator site through extraction of available data from the patient's medical records. Patients will have standard of care visits at least once per month during the first 3 months of avapritinib treatment where practical and every 2-3 months thereafter in accordance with local treatment guidelines. Standard of care evaluations will be conducted via telehealth or in person (at study center or local clinic) in accordance with local standards. Tumour response and disease progression will be assessed either in accordance with mRECIST 1.1 when feasible or local standard practice. In addition, patients will be requested to contact the study center for AE reporting, evaluation, and medical intervention (when needed), whenever feasible. All efforts will be made to ensure that the retrospective data of patients who discontinued avapritinib treatment previously are of good quality and provide sufficient information on the variables required.

	The total study duration is estimated to be 5 years including an enrolment period of approximately 3 years and a follow-up period of at least 24 months for the collection of safety and efficacy data
Population	***Inclusion Criteria:*** A patient who meets **all** of the following criteria is eligible for inclusion: • Written informed consent • Male or female, ≥ 18 years of age at the start of avapritinib treatment • Histologically or cytologically-confirmed diagnosis of unresectable or metastatic GIST harbouring the D842V mutation in the PDGFRA gene • Is scheduled to receive, previously received, or currently receiving first-line treatment with avapritinib consistent with the approved labelling for unresectable or metastatic GIST. Note: Patients who were treated with imatinib for ≤4 months prior to initiation of avapritinib treatment are also eligible. • For patients who received avapritinib treatment and discontinued prior to enrolment in this study, their retrospective data must be available • No concomitant treatment with other anticancer therapy ***Exclusion Criteria:*** A patient who meets the following criterion is not eligible for inclusion: • Concurrent enrolment in an interventional clinical trial involving either an investigational medicinal product or medical device

Variables	• Demographic data and relevant medical history at baseline
	• Avapritinib treatment data including the setting (e.g. trial, CUP, EAP, or routine care)
	• Treatment efficacy data during the study period
	  ○ Overall survival
	  ○ PFS
	  ○ Duration of treatment (DoT)
	  ○ Tumour response according to investigator's evaluation
	  ○ Duration of response (DoR)
	• Safety data during the study period
	  ○ Date, type, severity, relationship to avapritinib and action taken for all AEs that occur during and/or up to 30 days after administration of avapritinib, including AEs leading to discontinuation or decreased dosing of avapritinib

Data sources	For patients who initiate or continue to receive avapritinib in this study, data will be collected prospectively for 24 months following enrolment. For patients who have already received avapritinib prior to enrolment, retrospective data will also be collected (if data are available). Retrospective data collection will be performed at the participating investigator site through extraction of available data from the patient's medical records. Data will include: relevant baseline data at the time of the first dose of avapritinib and safety data from the time of the first dose of avapritinib to the end of follow-up, i.e. at least 24 months, until study discontinuation for any reason, or 30 days after the last dose of avapritinib; whichever comes first. In addition,

	data will include efficacy data (i.e. treatment response) between the first dose of avapritinib and the end of follow-up, i.e. at least 24 months, until initiation of second-line treatment or until study discontinuation for any reason; whichever comes first. Survival is an exception and will be ascertained for all patients until study closure, which will occur when the last patient enrolled has been followed for at least 24 months or withdraws from the study for any reason.
Study size	A sample size of at least 50 patients with PDGFRA D842V-mutated GIST is planned for this study. It is estimated that this number will be adequate to provide sufficient safety information in this ultra-rare patient population. If additional patients are available in a timely manner, more patients will be enrolled. The sample size calculation is presented as follows: 'For patients with the PDGFRA D842V mutation, a sample size of 31 patients will allow testing the null hypothesis of ORR ≤ 10% versus the alternative hypothesis of ORR ≥ 35% using Fisher's exact test with 90% power assuming a 2-sided type I error rate of 0.05.'
Data analysis	Analysis populations: Two analysis populations will be defined: • Enrolled Population (EP) - All patients who signed informed consent • Safety Population (SP) - All patients enrolled in the study who met the eligibility criteria and received at least one dose of avapritinib. The SP will be the primary analysis population for the efficacy and safety analyses. Statistical Methods: Continuous variables will be described (distribution) by their mean, standard deviation, median, extreme values (minimum and maximum) and the number of missing data. Categorical variables will be described using frequency counts and percentages. Time-to-event data will be summarized by Kaplan-Meier (KM) estimates. Data analysis: The following analyses will be performed for the primary endpoint: • Number, proportions and incidence rate of patients experiencing an AE during the study period (i.e., from the first dose of avapritinib until the end of follow-up): by SOC (System Organ Class) and PT (Preferred Term) terms (MedDRA classification), severity, seriousness and relationship to avapritinib, including the description of types, severity and rates of AEs leading to discontinuation or decreased dosing of avapritinib. • Number and proportions of patients with dose reductions or interruptions, or discontinuing avapritinib treatment due to an AE during the study period: overall and by comorbidity, including the description of types, severity and rates of AEs leading to discontinuation or decreased dosing of avapritinib. The following analyses will be performed for the secondary endpoints: • OS, PFS, DoR and DoT during the study period using the Kaplan-Meier (KM) method • OS rates at select timepoints

	• ORR during the study period with 95% CI based on the exact binomial distribution An interim analysis is planned for an interim study report (data lock point in November 2025, submission interim report in February 2025). Details of the interim analysis will be described in the Statistical Analysis Plan (SAP).
Milestones	This study is projected to begin enrolment in Q4 2022 and the study will end in August 2026. An interim study report is planned to be completed in February 2025 and the final study report in Q1 2027.

5. AMENDMENTS AND UPDATES

Version 5.0, 24 January 2023

General Changes

- Revised date and version throughout

Section 9.2.4 Study Enrollment

- Based on the feedback from the EMA, a new section was added to describe the recruitment of investigating sites and patients in the study protocol.

Section 9.9.4 Site Selection Bias

- Based on the feedback from the EMA, this section was updated to include the following text: "*No sites will be prospectively excluded for reasons related to selection bias.*"

Version 4.0, 16 November 2022

General Changes

- Revised date and version throughout
- Formatting and other minor changes and clarifications

Section 9.3 Variables

- Included "*Setting (e.g. trial, CUP, EAP or routine care)*" under the collection of avapritinib treatment details.

Section 9.7.2 Statistical Methods

The protocol language has been updated with the following text in italics related to stratification by treatment setting.

- The primary endpoint for the study will be to describe AEs during the study period for the SP. Analyses will be conducted for the SP overall and *stratified by treatment setting at the first dose of* avapritinib *and 300 mg dose*, Eastern Cooperative Oncology Group (ECOG) performance status and country; feasibility requirements will be described in the SAP.
- Secondary endpoints will be described using the SP. Analyses will be conducted for the SP overall and avapritinib dose 300 mg, *and may be stratified by treatment setting at the first dose of avapritinib (i.e. study BLU-285-1101, CUP/EAP, and routine care),* Eastern Cooperative Oncology Group (ECOG) performance status and by country if feasible; feasibility requirements will be described in the SAP.

Section 9.9.2 Information bias

The following text was added:

Also, if the data collected from the retrospectively enrolled patients is of poor quality or insufficient, the number of newly enrolled patients will be increased, if feasible.

Section 9.9.3 Effect Modifiers

The following text in italics was added:

Effect modification occurs when the effects of a treatment vary by presence/level of another factor (effect modifier). Stratified outcome analyses or analyses restricted to a selection of the study population will be conducted when deemed necessary and feasible, *such as when population characteristics and results differ greatly between patients receiving their first dose in a controlled trial setting (i.e. enrolled in BLU-285-1101), a semi-real world setting (i.e. enrolled in a CUP or*

EAP and likely unable or ineligible to participate in BLU-285-1101) or real-world setting (i.e. receiving commercially available avapritinib as part of routine clinical care).

Section 9.9.4 Site Selection Bias

This section was updated to include the following language:

Investigators that previously participated in trials of patients with GIST, prescribing physicians, and other clinicians with expertise in GIST clinical studies were approached for participation in this study. Each identified site was sent a confidentiality agreement and then study information. For those sites interested, a feasibility questionnaire was also sent for completion. Qualified sites with the intended patient population were selected for the study. After the feasibility assessment for sites to be included in this study, site selection bias will be reduced by taking a representative sample of sites when feasible given the number of sites per country.

Version 3.0, 08 August 2022

General Changes

- Revised date and version throughout
- Updated Table of Contents and ENCePP checklist in alignment with section revisions
- Formatting, typographical changes and other minor clarifications

PASS Information

- Added EU PAS register number
- Updated product reference number and author names
- Updated the MAH contact person and protocol authors
- Change in geographic region for the study from EU and US to global

Section 6 - Milestones

- Study start date was updated to Q4 2022 based on delays in site identification and the time needed to negotiate contracts with participating sites and obtain required IRB/IEC approvals.

Section 9 – Research Methods

- Clarified the language relating to prospective and retrospective patients and removed specific references to patients enrolling from the CUP or EAP program. The protocol language has been amended to include the following three groups of patients:
    - *Patients with PDGFRA D842V-mutated GIST who are scheduled to receive avapritinib in the first line (or have received imatinib for ≤4 months)*
    - *Patients with PDGFRA D842V-mutated GIST who are already receiving treatment with avapritinib (in the first-line or following ≤4 months of imatinib treatment):*
    - *Patients with PDGFRA D842V-mutated GIST who previously received treatment with avapritinib in the first line or following ≤4 months of imatinib treatment and have discontinued treatment*
- Added inclusion of patients who receive imatinib treatment for ≤4 months prior to initiation of avapritinib
- Language was added to allow for telehealth visits.

Section 10 – Protection of Human Subjects

- Modified text to align with Blueprint standard procedures
- Language was added to allow for remote consenting by phone or mail when a patient is unable to meet with the investigator in person due to logistical or other reasons

Version 2.0, 22 March 2021

General Changes

- Revised date and version throughout
- Updated Table of Contents and ENCePP checklist in alignment with section revisions
- Formatting, typographical changes and other minor clarifications
- Added Annex 3 - Derivation of Child-Pugh Classification Score

PASS Information

- Updated text regarding Active substance, Medicinal product and Procedure number based on information presented in the PRAC-Rapporteur assessment report

Abstract

- To address requests from the EMA-PRAC assessment report (PAR):
  - Updated the presented background data on the number of patients receiving first-line avapritinib as part of study BLU-285-1101 to match the numbers presented in the study design section and to include additional information on cardiac toxicity.
  - Added AEs leading to decreased dosing of avapritinib to the Research Question and Objectives and the Variables sections.
  - Added the following in italic to the Study Design and Population sections:
    - '...from approximately 26 patients who *meet the eligibility criteria and* already received *first-line* avapritinib during their participation in study BLU-285-1101 or an avapritinib compassionate use program (CUP) or early access program (EAP).
    - *'Should the number of retrospectively enrolled patients, who meet these criteria, be less than the expected 26 patients, the number of prospectively enrolled patients in this study will be increased to ensure availability of adequate data from 50 patients.'*
    - *'All efforts will be made to ensure that the data of retrospectively enrolled patients are of good quality and provide sufficient information on the variables required.'*
  - Added the sample size calculation to the Study Size section
  - Added the following in italic to the Data Analysis section:
    - 'Number and proportions of patients with dose reductions or interruptions, or discontinuing avapritinib treatment due to an AE during the study period*: overall and by comorbidity, including the description of types, severity and rates of AEs leading to decreased dosing of avapritinib.'*
    - '*An interim analysis is planned for an interim study report (data lock point in August 2024, submission interim report in February 2025). Details of the interim analysis will be described in the Statistical Analysis Plan (SAP).*'
  - Changed the text to the following in the Milestones section: '*This study is projected to begin enrolment in August 2021 and the study will end in August 2026. An interim study report is planned to be completed in February 2025 and the final study report in Q1 2027.*'

Section 6 - Milestones

- The planned dates for milestones have been amended in the Milestones section based on a request from the EMA-PRAC assessment report (PAR).

Section 7 - Rationale and Background

- To address requests from the EMA-PRAC assessment report (PAR):
  - Updated the presented background data on the number of patients receiving first-line avapritinib as part of study BLU-285-1101 to match the numbers presented in the study design section and to include additional information on cardiac toxicity.
  - Added the following in italic: '...from approximately 26 patients who *meet the eligibility criteria and* already received *first-line* avapritinib....

Section 8.1 – Primary objective

- Added AEs leading to decreased dosing of avapritinib based on a request from the EMA-PRAC assessment report (PAR).

Section 9 – Research Methods

- Based on a request from the EMA-PRAC assessment report (PAR):
  - Added the following in italic to the Study Design, Setting and Data sources sections based on a request from the EMA-PRAC assessment report (PAR):
    - '...from approximately 26 patients who *meet the eligibility criteria and* already received *first-line* avapritinib ...'.
    - *'Should the number of retrospectively enrolled patients, who meet these criteria, be less than the expected 26 patients, the number of prospectively enrolled patients in this study will be increased to ensure availability of adequate data from 50 patients.*'
  - Added the following in italic in addition to the above to the Setting section: *'All efforts will be made to ensure that the data of retrospectively enrolled patients are of good quality and provide sufficient information on the variables required.'*
  - Added that dates of dose modifications are being captured in section 9.3.
  - The following in italic is added under safety variables in section 9.3: 'Action taken including *description of types, severity and rates of AEs leading to avapritinib dose reductions, interruptions or discontinuations as well as medication* used for AE treatment (coded according to the WHO Drug Dictionary)'.
  - The Data Collection Plan Table was moved from section 9.4 to section 9.3
  - Added the sample size calculation to section 9.5 and that '*It is estimated that this number will be adequate to provide sufficient safety information in this very rare patient population. If additional patients are available in a timely manner, more patients will be enrolled*.'
  - The interim analysis and corresponding data lock point are mentioned in section 9.6
  - In section 9.7 the interim report and the first data lock point in August 2024 are added as well as that correction of inconsistencies or errors will be described in the SAP
  - In section 9.7.4:
    - Added the following in italic: 'Number and proportions of patients with dose reductions or interruptions, or discontinuing avapritinib treatment due to an AE during the study period will be determined: *overall and by comorbidity, including the description of types, severity and rates of AEs leading to discontinuation or decreased dosing of avapritinib.*
    - Clarifications are added to how the sum of person-months at risk is derived when analysing the incidence of specific AEs to clarify that patients who experience another AE earlier in time will not be censored.
    - The following in italic is added regarding specific AEs: Cardiac toxicity, including QT prolongation *and related symptoms (e.g. cardiac arrest, sudden cardiac death, syncope, ventricular arrhythmia)*
    - The following in italics is added regarding severe hepatic impairment: *Any off-label* use in patients with severe hepatic impairment *(Child-Pugh class C, i.e. ≥10 points, Annex 3)*
    - CYP3A was changed to CYP3A4
  - Text on data verification and monitoring was moved from section 9.6 to section 9.8.
  - In section 9.9.2 the following has been added: 'Also, if the data collected from the retrospectively enrolled patients is of poor quality or insufficient, the number of newly enrolled patients will be increased, if feasible.'
  - In section 9.10.1 the following in italic has been added: 'If clarification or follow-up is needed regarding a potential ADR or medical information question reported during the

study conduct, *patients may be contacted only by medical staff of the site involved in this PASS*.'

Section 12 – Plans for dissemination and communicating study results

- The interim report is mentioned now in this section.

6. MILESTONES

Milestone	Planned Date
Start of data collection	By Q4 2022
End of data collection	August 2026
Study progress report 1	August 2022
Study progress report 2	August 2023
Study progress report 3	August 2024
Study progress report 4	August 2025
Interim report 1	February 2025
Final report of study results	By Q1 2027

7. RATIONALE AND BACKGROUND

7.1. Background

Gastrointestinal stromal tumours (GISTs) are rare, yet the most common mesenchymal tumours occurring in the gastrointestinal tract with an incidence of 10-15 per million people per year. (Søreide et al. 2016) About 90% of patients with GIST have a tumour that is dependent on mutations in the receptor tyrosine kinase protein KIT (75-80%) or the highly related receptor tyrosine kinase protein PDGFRA (10-15%), most commonly a substitution of valine for aspartic acid at amino acid 842 (D842V). (Corless et al. 2011)

Surgical resection is the only available curative treatment for primary, localised, and resectable GIST, yet 40% to 50% of patients will experience recurrent or metastatic disease during follow-up. (Rutkowski et al. 2016) The dependence of GIST on mutated receptor tyrosine kinases led to the exploration of tyrosine kinase inhibitors (TKIs) for the systemic treatment of this rare malignancy. However, the PDGFRA D842V mutation causes primary resistance to conventional TKIs (Gounder et al. 2011) with low ORRs found in PDGFRA D842V-mutant GIST first-line patients (ORR 0-12%; Cassier et al. 2012; Farag et al. 2017; Yoo et al. 2016; BLU-285-1002 study report).

Avapritinib (also known as BLU-285, BLU112317 and X720776) is a potent and selective oral inhibitor of PDGFRA D842V and showed clinical activity in patients with unresectable or metastatic PDGFRA D842V-mutant GIST regardless of line of therapy. The ORR in patients with PDGFRA D842V-mutant was 95% in study BLU-285-1101 (100% in first-line patients; DCO 17 April 2020).

The safety profile of avapritinib has been well characterised in patients with GIST and adverse events associated with avapritinib treatment can be managed with adherence to product labeling. As of 09 March 2020, the safety database included 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 the Phase I study BLU-285-1101 who received treatment with avapritinib, and 473 patients in the Phase III study BLU-285-1303 that compared avapritinib versus regorafenib in patients with GIST beyond second line, including 239 patients who received avapritinib and 96 patients who received regorafenib and then crossed over to receive avapritinib treatment upon disease progression. Safety data from study BLU-285-1101 (DCO 09 March 2020) showed that all patients except for one (>99%) reported adverse events (AEs), where 80% of patients reported an AE ≥ Grade 3 (13% fatal Grade 5 AEs), 65% reported serious AEs (SAEs) and 27% reported AEs that led to permanent discontinuation of study drug. The safety analysis from the study BLU-285-1303 was consistent with the safety results reported from BLU-285-1101 and no new safety signals were identified. Overall, 99% of the patients in the avapritinib treatment arm reported any AEs, where 75% of patients reported ≥ Grade 3 AEs (4% Grade 5 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, 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%). 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%). A total of 19.7% of patients with GIST discontinued avapritinib 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 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).

During clinical development, two AESIs were identified: intracranial bleeding and cognitive effects. Although the mechanism for these events is unclear, intracranial bleeding and cognitive effects have been reported with imatinib and other TKIs. (Feki et al. 2015; Shaw et al. 2017; Song et al. 2004)

Intracranial bleeding (e.g., subdural haematoma, intracranial haemorrhage) occurred in 9 (1.6%) of the 550 patients with GIST who received avapritinib at starting doses of either 300 or 400 mg once daily. Intracranial bleeding was reported by 3% (7/250) of all patients in BLU-285-1101: 3 patients had a subdural haematoma (Grade 1, Grade 2 or Grade 3), 2 patients had an intracranial haemorrhage (Grade 1 or Grade 3) and 2 patients had a cerebral haemorrhage (Grade 3 or Grade 4). Consistent with the overall trend of a slightly less severe safety profile observed in the Phase III trial, intracranial bleeding was reported in 1% of all patients who received any dose of avapritinib in BLU-285-1303: 2 patients with Grade 4 intracranial haemorrhage and 1 patient with both a Grade 4 subdural haematoma and a Grade 4 intracranial haemorrhage. No fatal intracranial bleeding events were reported in either study. The mechanism by which avapritinib may cause events of intracranial bleeding are uncertain. Risk factors for intracranial bleeding include severe thrombocytopenia (platelet count <50,000/µl), vascular aneurysm, a history of intracranial haemorrhage within the prior year, and a history of a cerebrovascular accident or transient ischaemic attack. Appropriate risk minimisation measures including lower starting dose and restrictions for dose escalation might reduce the risk. It is recommended that avapritinib be permanently discontinued in patients with an observed intracranial bleeding event of any severity grade during treatment.

Cognitive effects occurred in 182 (33%) of the 550 patients with GIST who received avapritinib at starting doses of either 300 or 400 mg once daily. Most cognitive effects were Grade 1 (89%), with Grade ≥2 occurring in 11% of 550 patients. Memory impairment occurred in 20% of patients, <1% of these events were Grade 3. Cognitive disorder occurred in 12% of patients; <1% of these events were Grade 3. Confusional state occurred in 5% of patients; <1% of these events were Grade 3. Encephalopathy occurred in <1% of patients; <1% of these events were Grade 3. SAEs of cognitive effects were reported for 7 of the 550 (1.3%) patients. Overall, 1.3% of patients required permanent discontinuation of avapritinib for a cognitive effect. Cognitive effects were reported by 46% of the patients in BLU-285-1101, most cases were mild-moderate AEs (90% Grade 1-2 AEs, 10% Grade 3 AEs). Consistent with the overall trend of a slightly less severe safety profile observed in the Phase III trial, cognitive effects were reported by 26% of the patients in BLU-285-1303, 95% Grade 1-2 AEs and 5% Grade 3 AEs. The 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 in the Phase III trial as

AESIs of cognitive effects were higher in the 400 mg starting dose group compared to the 300 mg group in BLU-285-1101 (48% vs 39%). However, the median treatment duration for patients receiving avapritinib (any dose) in the Phase III trial was also considerably shorter (8.9 months) than in the Phase I trial (23.2 months). No fatal cognitive events were reported in either study. In the clinical development program, the probability of experiencing a cognitive effect increased over the first 7 to 8 months of treatment and then reached a plateau. Non-clinical mechanistic studies could not clearly identify the underlying mechanism for cognitive effects (i.e., memory impairment). Clinical factors associated with an increased likelihood of experiencing Grade ≥2 cognitive effects include a medical history of cognitive effects, prior regorafenib use and age ≥65 years. Brain imaging studies of patients experiencing cognitive effect symptoms during the clinical studies did not reveal any associated anatomical changes.

Cardiac toxicity, including QT prolongation, is considered a safety concern for avapritinib and is classified as an important potential risk in the EU RMP. While non-clinical studies did not show any effects of avapritinib on the cardiovascular system, in clinical Study BLU-285-1101, a small increase in the QTc interval (6.55 ms; 90% CI: 1.80 to 11.296 at 300/400 mg QD clinical dose) that was not clinically relevant was observed in a subset of GIST patients. In addition, the slope of the avapritinib concentration-QTc relationship was very shallow: 0.007 ms per ng/mL (90% CI: 0.003 to 0.012), with a small, non-statistically significant intercept of -0.2 ms (90% CI: -2.26 to 1.89). However, considering the existing potential of mainly multi-target TKIs to cause QT prolongation (Porta-Sanchez et al. 2017) and cardiac toxicity (Orphanos et al. 2009; Chen et al. 2016; Lee et al. 2018; Porta-Sanchez et al. 2017) cardiac toxicity, including QT prolongation is considered an important potential risk associated with avapritinib warranting further evaluation in the post authorisation setting. Therefore, cardiac toxicity, including QT prolongation and associated symptoms such as cardiac arrest, sudden cardiac death, syncope or ventricular arrhythmia are to be closely monitored during the course of this study.

In study BLU-285-1101, 56 patients carried the PDGFRA D842V mutation of whom 17 patients received an avapritinib starting dose <300 mg and 1 patient a starting dose of 600 mg. A total of 38 patients were treated with an avapritinib starting dose of 300 or 400 mg including 28 patients at a starting dose of 300 mg and 10 patients at a starting dose of 400 mg. Of the 56 patients with PDGFRA D842V-mutated GIST, avapritinib was received first-line by 11 patients, second-line by 21 patients, third-line by 10 patients, fourth-line by 6 patients and after at least 4 previous lines of treatment by 8 patients. Of the 11 patients with PDGFRA D842V-mutated GIST receiving first-line avapritinib, 6 received an avapritinib starting dose <300 mg, 4 patients a starting dose of 300 mg and 1 patient a starting dose of 400 mg.

As expected, the safety data in the subset of 56 patients with PDGFRA D842V-mutated GIST in study BLU-285-1101 showed consistent results to the overall study population in the safety analysis based on data from the 09 March 2020 DCO date: 100% experienced AEs, 80% (45/56) ≥Grade 3 AEs, 57% (32/56) SAEs and 21% (12/56) AEs that lead to permanent treatment discontinuation. Only 11 of the 56 patients with PDGFRA D842V-mutant GIST received first-line avapritinib in study BLU-285-1101 and long-term safety data are limited, which is an important uncertainty for patients treated in first-line due to longer exposure to the drug.

7.2. Rationale

Avapritinib is approved in the US for the treatment of adults with unresectable or metastatic GIST harbouring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations. On 24 September 2020, the European Commission granted a CMA for avapritinib as monotherapy for GIST harbouring the PDGFRA D842V mutation. The approval status of avapritinib in different regions and indications is provided in Annex 4.

To address the Specific Obligation of the CMA in Europe and to provide further evidence of the positive benefit-risk profile of first-line treatment with avapritinib in patients with metastatic and unresectable GIST harbouring mutations in PDGFRA D842V, this non-interventional post-authorisation safety study (PASS) aims to collect long-term safety and efficacy data in the first-line population. Data from at least 50 patients with PDGFRA D842V-mutated GIST who receive avapritinib in the first-line or following ≤4 months of imatinib treatment will be evaluated from sites worldwide. Real-world biomarker testing practices and treatment landscape for metastatic or unresectable GIST patients suggest a significant percentage of patients do not receive complete biomarker testing for KIT and PDGFRA prior to first-line treatment initiation. Given this, the inclusion criteria of this study also allows for enrolment of patients with PDGFRA D842V-mutated GIST who were treated with standard of care imatinib for ≤4 months prior to initiation of avapritinib. Patients will be evaluated for AEs and efficacy outcomes (i.e. survival and tumour response). This data will provide important information on the safety and efficacy of avapritinib in this ultra-rare patient population.

8. RESEARCH QUESTION AND OBJECTIVES

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

8.1. Primary Objective

To describe types, severity and rates of AEs, SAEs, AEs leading to discontinuation or decreased dosing of avapritinib, AESIs, and deaths.

This PASS has been implemented following a commitment to the EMA to address the Specific Obligation of the CMA in Europe to provide additional safety data for patients with PDGFRA D842V-mutated GIST on first-line avapritinib treatment.

8.2. Secondary Objectives

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

9. RESEARCH METHODS

9.1. Study design

This is a multinational, open-label, observational PASS that will evaluate the long-term safety and efficacy of avapritinib in the first line or following ≤4 months of imatinib treatment in at least 50 patients with PDGFRA D842V-mutated GIST. Three patient populations are planned to be enrolled:

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

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

Informed consent will be obtained from all patients according to the regulatory and legal country-specific requirements of the participating site before enrolment in this study.

Patients who were scheduled to receive avapritinib prior to enrolment will initiate treatment after enrolment in this study based on the locally approved product label prescribing information. If a patient was already receiving avapritinib prior to enrolment, they will continue treatment at the same dose after enrolment. The dose level may be adjusted based on the locally approved product label prescribing information. Investigators must refer to the local prescribing information for contraindications, warnings and precautions as well as use in specific populations. As this study is observational, the decision to treat patients with avapritinib will be independent from the decision to enrol patients into the study.

Baseline and follow-up assessments will be in accordance with local standard medical care. Both prospective and retrospective data collection will be performed in this study. All patients who will initiate or continue treatment with avapritinib after enrolment will have prospective data collection for 24 months on the study. For patients who have received avapritinib prior to enrolment in this study, retrospective data may also be collected (if data are available). Retrospective data collection will be performed at the participating investigator site through extraction of available data from the patient's medical records. The data collection plan is provided in Table 1.

9.2. Setting

9.2.1. Inclusion criteria

A patient who meets all of the following criteria is eligible for inclusion:

- Written informed consent.
- Male or female, ≥ 18 years of age at the start of avapritinib treatment
- Histologically or cytologically-confirmed diagnosis of unresectable or metastatic GIST harbouring the D842V mutation in the PDGFRA gene
- Is scheduled to receive, previously received, or currently receiving first-line treatment with avapritinib consistent with the approved labelling for unresectable or metastatic GIST. Note: Patients who were treated with imatinib for ≤4 months prior to initiation of avapritinib treatment are also eligible.
- For patients who received avapritinib treatment and discontinued prior to enrolment in this study, their retrospective data must be available
- No concomitant treatment with other anticancer therapy

9.2.2. Exclusion criteria

A patient who meets the following criterion is not eligible for inclusion:

- Concurrent enrolment in an interventional clinical trial involving either an investigational medicinal product or medical device

9.2.3. Study duration

The estimated enrolment period is approximately 3 years.

It is planned to follow patients for at least 24 months for efficacy and safety events, though this may be extended based on new insights during the study period. OS is an exception and will be ascertained for all patients until study closure, which will occur when the last patient enrolled has been followed for at least 24 months or withdraws from the study for any reason.

The total study duration will therefore be the estimated 3-year enrolment period plus at least 24 months follow-up, so at least 5 years.

9.2.4. Study Enrollment

Investigators who previously participated in trials of patients with GIST, prescribing physicians, and other clinicians with expertise in GIST clinical studies will be approached for participation in this study. Each identified site will be sent a confidentiality agreement and then study information. For those sites interested, a feasibility questionnaire will be sent for completion. Qualified sites with the intended patient population will be selected for the study. To facilitate enrollment into the study, the Sponsor will offer sites additional support as needed within the confines of local regulations and guidelines.

9.3. Variables

The data collection plan is outlined in Table 1. Data will be collected prospectively for patients who initiate or continue to receive treatment with avapritinib. Retrospective data collection will be performed when available. All efforts will be made to ensure that the retrospective data of

patients who discontinued avapritinib treatment previously are of good quality and provide sufficient information on the variables required.

Data of interest include the following:

Demographic data and relevant medical history at the time of the first avapritinib dose:

- Age
- Sex
- Height
- Weight
- Race/ethnicity (in accordance with the local regulations)
- ECOG performance status GIST diagnosis (before the first avapritinib dose according to local standard procedures)
  - Date of diagnosis
  - Primary tumor site (e.g. stomach, duodenum, rectum, small intestine)
  - Largest lesion size (≤10 cm or > 10 cm)
  - Resectable (yes / no)
  - PDGFRA mutation status
  - Metastatic (yes / no)
  - Location of metastatic site(s)
- Relevant medical and surgical history including comorbidities and previous cancer diagnoses
- Prior imatinib therapy (yes / no)
- Duration of prior imatinib therapy
- Best response to prior imatinib therapy (CR, PR, SD, progressive disease, NE)
- Concomitant medications, with a special focus on CYP3A4 inhibitors/inducers to address the drug-drug interaction risk

The Medical Dictionary for Regulatory Activities (MedDRA) will be used for coding concomitant diseases, and the World Health Organization (WHO) Drug Dictionary for medications.

Avapritinib treatment details from the time of the first dose until 30 days after the last dose:

- Date of treatment initiation
- Primary reason for treatment initiation
- Setting (e.g. trial, CUP, EAP or routine care)
- Treatment schedule (e.g. qd, bid)

- Avapritinib treatment information: dose and dose modifications including date(s)
- Reason for dose modification
- Date of discontinuation or interruption
- Primary reason for discontinuation or interruption
- Reason for initiating further lines of treatment

Efficacy variables:

Efficacy data are of interest when collected prospectively or available from previous data collection efforts during standard of care visits at each site between the time of the first dose of avapritinib and the end of follow-up, ie, at least 24 months, until initiation of another treatment for GIST or until study discontinuation for any reason; whichever comes first. Survival is an exception and will be ascertained for all patients until study closure, which will occur when the last patient enrolled has been followed for at least 24 months or withdraws from the study for any reason.

The following efficacy data will be of interest:

- Date and details of tumour response and disease progression evaluations in accordance with mRECIST 1.1 when feasible or with local standard practice by the investigator

Safety variables:

All AEs that occur or have occurred during and/or up to 30 days after administration of avapritinib regardless of a causal relationship to avapritinib.

The following data will be collected for any AE (serious or non-serious):

- Date of event
- Event (all coded according to the same MedDRA version)
- Severity of event (classified using the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 5.0)
- Relationship to avapritinib
- Outcome (resolved, continuing, etc.)
- Action taken including description of types, severity and rates of AEs leading to avapritinib dose reductions, interruptions or discontinuations as well as medication used for AE treatment (coded according to the WHO Drug Dictionary)

Table 1: Data Collection Plan

Prospective Data Collection and Extraction of Available Retrospective Data				
Variables	**Baseline Period[a]**	**Standard of Care Visits[b]**	**Safety Follow-Up (Final Standard of Care Visit +30 days for all non-fatal AEs or study closure for deaths)[c]**	**Survival Follow-up (every 6 months**

				until study closure)
Informed Consent[d]	X			
Patient Eligibility	X			
Demographics	X			
Medical and Surgical History	X			
Prior Imatinib Therapy (yes/no)	X			
Concomitant Medications[e]	X	X	X	
Avapritinib Treatment Details	X	X		
Disease Progression Evaluation by Investigator		X		
Objective Response Evaluations by Investigator		X		
Telephone contact				X[f]
All AEs/SAEs	X	X	X	

Abbreviations: AE = adverse event; SAE = serious adverse event.
[a] The baseline period includes the time up to and including the first avapritinib dose
[b] Standard of care visits will be performed via telehealth or as in-person visits (study center or local clinic) in accordance with local standards. Data will be collected at least once per month during the first 3 months of avapritinib treatment where practical and every 2-3 months thereafter in accordance with local treatment guidelines.
[c] Study closure will occur when the last patient enrolled has been followed for at least 24 months or withdraws from the study for any reason
[d] According to the regulatory and legal country-specific requirements of the participating site. For those patients that have discontinued avapritinib treatment and/or were lost to follow-up and consent cannot be obtained, the Investigator will consult their IRB/IEC for guidance on accessing these patients' data retrospectively.
[e] Information regarding concomitant medication (including over-the-counter medications) will include, when available: drug name, indication for treatment, route, and duration of drug administration, with a special focus on CYP3A4 inhibitors/inducers to address the drug-drug interaction risk
[f] Patients will be followed for overall survival every 6 months until study closure. This follow-up can be completed via telephone.

9.4. Data Sources

For patients who initiate or continue to receive avapritinib in this study, data will be collected prospectively for 24 months following enrolment. For patients who have already received avapritinib prior to enrolment, retrospective data will also be collected (if available). Retrospective data collection will be performed at the participating investigator site through extraction of available data from the patient's medical records as per local law and regulations. Data will include: relevant baseline data at the time of the first dose of avapritinib and safety data from the time of the first dose of avapritinib to the end of follow-up, i.e. at least 24 months, until study discontinuation for any reason, or 30 days after the last dose of avapritinib; whichever comes first. In addition, data will include efficacy data (i.e. treatment response) between the first dose of avapritinib and the end of follow-up, i.e. at least 24 months, until initiation of second-line treatment or until study discontinuation for any reason; whichever comes first (see Table 1). Survival is an exception and will be ascertained for all patients until study closure, which will

occur when the last patient enrolled has been followed for at least 24 months, or withdraws from the study for any reason.

9.5. Study size

At least 50 patients are planned to be enrolled in this study. It is estimated that this number will be adequate to provide sufficient safety information in this ultra-rare patient population. If additional patients are available in a timely manner, more patients will be enrolled.

The sample size calculation is presented as follows: 'For patients with the PDGFRA D842V mutation, a sample size of 31 patients will allow testing the null hypothesis of ORR ≤ 10% versus the alternative hypothesis of ORR ≥ 35% using Fisher's exact test with 90% power assuming a 2-sided type I error rate of 0.05.'

9.6. Data management

All information outlined in Section 9.3 will either be recorded prospectively in an eCRF or extracted from patients' medical records for retrospective data collection, if data are available before the start of the study. Data collection will be completed in a suitable software platform for the creation and delivery of data collection, data analysis, and data reporting. Data collected will be stored at secure servers ensuring compliance with local or national regulations. Database lock is anticipated in August 2024 for an interim analysis and on the date the study is closed. Additional details regarding data collection and validation procedures will be detailed in a data management plan.

9.7. Data Analysis

The statistical analysis plan (SAP) provides further information to that discussed below (e.g. on handling missing data, correction of inconsistencies or errors, and differences in outcome definitions). The final analysis will conform to the analysis specifications provided in the SAP.

9.7.1. Analysis Populations

9.7.1.1. Enrolled Population (EP)

The enrolled population will consist of all patients who signed an informed consent.

9.7.1.2. Safety Population (SP)

The SP will include all patients enrolled in the study who met the eligibility criteria and received at least one dose of avapritinib. The SP will be the primary analysis population for the efficacy and safety analyses.

9.7.2. Statistical Methods

Descriptive analysis:

Demographic and other baseline characteristics collected before or at the time of the first avapritinib dose will be summarised for the SP. Continuous variables will be described (distribution) by their mean, standard deviation, median, extreme values (minimum and maximum) and the number of missing data. Categorical variables will be described using

frequency counts and percentages. Time-to-event data will be summarized by Kaplan-Meier (KM) estimates.

Analysis of the primary endpoint:

The primary endpoint for the study will be to describe AEs during the study period for the SP. Analyses will be conducted for the SP overall and stratified by treatment setting at the first dose of avapritinib and 300 mg dose, Eastern Cooperative Oncology Group (ECOG) performance status and country; feasibility requirements will be described in the SAP.

The study period for the safety analyses is defined as the time from the first dose of avapritinib to the end of follow-up, i.e. at least 24 months, until study discontinuation for any reason, or 30 days after the last dose of avapritinib; whichever comes first.

The following analyses will be performed:

- Number and proportions of patients experiencing an AE during the study period (i.e., from the first dose of avapritinib until the end of follow-up): by SOC (System Organ Class) and PT (Preferred Term) (MedDRA classification), severity, seriousness and relationship to avapritinib, including the description of types, severity and rates of AEs leading to discontinuation or decreased dosing of avapritinib.
- Number and proportions of patients with dose reductions or interruptions, or discontinuing avapritinib treatment due to an AE during the study period: overall and by comorbidity, including the description of types, severity and rates of AEs leading to discontinuation or decreased dosing of avapritinib.
- Incidence rate of patients experiencing an AE, overall and by SOC and PT terms
  - Defined as the number of patients with at least one (specific) AE during follow-up divided by the sum of person-months at risk in the study.
  - The sum of person-months at risk in the study when calculating the overall incidence is defined as the duration of follow-up for patients without AEs plus the duration of follow-up until the date of the first AE for patients with an AE.
  - The sum of person-months at risk in the study when calculating the incidence for specific AEs is defined as the duration of follow-up for patients without the specific AE plus the duration of follow-up from baseline until the date of the first specific AE for patients with a specific AE, i.e. patients who experience another AE earlier in time will not be censored

Specific safety concerns that will be reported, include but are not limited to:

- Intracranial bleeding (e.g. cerebral haematoma, cerebral haemorrhage, haemorrhage intracranial, subdural haematoma)
- Cognitive effects (e.g. agitation, amnesia, cognitive disorder, confusional state, delirium, dementia, disorientation, encephalopathy, hallucination, memory impairment, mental impairment, mental status changes, mood altered, personality change, psychotic disorder, somnolence, speech disorder)
- Drug-drug interactions with moderate or strong CYP3A4 inhibitors or inducers

- Cardiac toxicity (e.g. electrocardiogram QT interval abnormal, electrocardiogram QT prolonged long QT syndrome, long QT syndrome congenital, torsade de pointes, ventricular tachycardia, cardiac arrest, cardiac death, cardiac fibrillation, cardio-respiratory arrest, electrocardiogram repolarisation abnormality, electrocardiogram U wave inversion, electrocardiogram u wave present, electrocardiogram U-wave abnormality, loss of consciousness, multiple organ dysfunction syndrome, subacute kidney injury, sudden cardiac death, sudden death, syncope, ventricular arrhythmia, ventricular fibrillation, ventricular flutter, and ventricular tachyarrhythmia)
- Embryofoetal toxicity
- Any off-label use in patients with severe hepatic impairment (Child-Pugh class C, i.e. ≥10 points, Annex 3)
- Drug-drug interactions with CYP3A4 substrates

Analysis of the secondary endpoints:

Secondary endpoints will be described using the SP. Analyses will be conducted for the SP overall and avapritinib dose 300 mg, and may be stratified by treatment setting at the first dose of avapritinib (i.e. study BLU-285-1101, CUP/EAP, and routine care), Eastern Cooperative Oncology Group (ECOG) performance status and by country if feasible; feasibility requirements will be described in the SAP.

The study period for the efficacy analyses is defined as the time from the first dose of avapritinib to the end of follow-up at 24 months, until initiation of second-line treatment or until study discontinuation for any reason; whichever comes first. Survival is an exception and will be ascertained for all patients until study closure, which will occur when the last patient enrolled has been followed for at least 24 months or withdraws from the study for any reason. The analyses to be performed will be:

- Median, 95% CIs and 25th and 75th percentiles using the Kaplan-Meier (KM) method for:
  - OS
  - PFS
  - DoR
  - DoT
- OS rates at select timepoints
- ORR during the study period with 95% CI based on the exact binomial distribution

The following definitions will be used for the above outcomes:

- OS is defined as the time in months from the start of avapritinib treatment to the date of death due to any cause.
- PFS is defined as the time in months from the start of avapritinib treatment to the date of the first documented disease progression by a responsible physician according to mRECIST 1.1 criteria or local standard practice, or death.

- DoT is defined as the time from the date of the first to the date of the last avapritinib dose.
- DoR is defined as the time from the date of the first documented disease response to the date of disease progression.
- ORR is defined as the proportion of patients with a best response during the study period of complete response (CR) or partial response (PR) evaluated by a responsible physician based on mRECIST v1.1 criteria if feasible or to local standard practice.

An interim analysis is planned for an interim study report (data lock point in August 2024, submission interim report in February 2025). Details of the interim analysis will be described in the SAP.

9.8. Quality Control

Syneos Health and Blueprint Medicines are responsible for following standard operating procedures (SOPs) to ensure data quality and integrity, including archiving of statistical programs, appropriate documentation of data cleaning and validity for created variables, and description of available data. All sites will be trained on the protocol, study logistics, and the electronic data capture (EDC) system. Investigators will be reminded of the processes and importance of reporting all AEs, SAEs, AESIs and other information.

The investigator is responsible for entering data in a timely manner and verifying that data are accurate and correct by physically or electronically signing the eCRF. The investigator must permit study-related monitoring, audits, institutional review board (IRB) review, and regulatory agency inspections and provide direct access to source data documents. On-line logic checks will be built into the EDC system as much as possible, so that missing or illogical data are not submitted. In the event that inconsistent data persist, queries may be issued electronically to the clinical study centre and answered electronically by that study centre's personnel.

9.9. Limitations of the Research Methods

9.9.1. Selection Bias

For patients who will be newly enrolled into this study, inviting consecutive patients at each site will reduce selection bias. In addition, AE rates obtained from this study will be compared with expected rates from the pooled analysis of AEs for all lines from the BLU-285-1101 and BLU-285-1303 trials. Survivor bias will be avoided (i.e. outcome ascertainment only for those who make it to the start of this study) by including patients who discontinued avapritinib treatment before enrolment in this study.

9.9.2. Information bias

Relying on investigators to fill out the assessment forms might induce the presence of missing data, which can result in bias. Entry of prospectively collected data in eCRFs will minimise missing or incorrect data by having automated queries. Clear instructions and engagement with the study staff with appropriate training will minimise the amount of missing data.

This study will collect both retrospective and prospective data. The retrospective data maybe of lesser quality than the prospective data that will be collected from enrolment, with more missing data and fewer details. It is therefore important to determine the impact of this in sensitivity analyses, and include rules about how missing data will be handled in the SAP. Also, if the data collected from the retrospectively enrolled patients is of poor quality or insufficient, the number of newly enrolled patients will be increased, if feasible.

9.9.3. Effect modifiers

Effect modification occurs when the effects of a treatment vary by presence/level of another factor (effect modifier). Stratified outcome analyses or analyses restricted to a selection of the study population will be conducted when deemed necessary and feasible, such as when population characteristics and results differ greatly between patients receiving their first dose in a controlled trial setting (i.e. enrolled in BLU-285-1101), a semi-real world setting (i.e. enrolled in a CUP or EAP and likely unable or ineligible to participate in BLU-285-1101) or real-world setting (i.e. receiving commercially available avapritinib as part of routine clinical care).

9.9.4. Site Selection Bias

After the feasibility assessment for sites to be included in this study, site selection bias will be reduced by taking a representative sample of sites when feasible given the number of sites per country. No sites will be prospectively excluded for reasons related to selection bias.

9.9.5. Patients Lost to Follow-up or With no Follow-up Data

Because the follow-up duration will be at least 24 months, the proportion of discontinued patients might be significant. As standard of care visits are assumed to take place every 2-3 months at least, this is expected to reduce loss to follow-up. Patients lost to follow-up will be compared with regard to baseline characteristics to patients with complete follow-up. Also, baseline characteristics will be compared between patients with no follow-up data (i.e. the EP) and the SP.

9.10. Other Aspects

9.10.1. Confidentiality

The information in this and related documents is confidential and may not be disclosed, unless such disclosure is required by federal or other laws or regulations. In any event, persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.

Data generated as a result of this study are to be available for inspection on request of Blueprint Medicines' representative, ethics committees, or local regulatory agency, as required. Study data will be reported in aggregate and de-identified. Data will be stored in a secure database and shall be treated in compliance with all local applicable laws and regulations. Patients will not be contacted regarding assessments. If clarification or follow-up is needed regarding a potential ADR or medical information question reported during the study conduct, patients may be contacted, only by medical staff of the site involved in this PASS.

9.10.2. Protocol Amendment

Any amendment to the protocol will be created by Blueprint Medicines. Substantial amendments to the study protocol will be submitted to the Pharmacovigilance Risk Assessment Committee (PRAC) and independent ethics committees (IECs), in accordance with GVP Module VIII Addendum I.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Participant Information and Consent

The Investigator at each study center will ensure that the patient or his/her legally authorised representative is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that their participation is voluntary and that they are free to discontinue from the study at any time. The patient must be given the opportunity to ask questions and allowed time to consider the information provided.

Patients or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center. Remote consent by phone or mail may be considered where a patient is unable to meet with the investigator in person due to logistical or other reasons. For those patients that have discontinued avapritinib treatment and/or were lost to follow-up and consent cannot be obtained, the Investigator will consult their IRB/IEC for guidance on accessing these patients' data retrospectively.

The patient's signed and dated informed consent must be obtained before conducting any study-related procedures. The Investigator must maintain the original, signed consent form which includes the signature of the authorised person obtaining the informed consent. A copy of the signed form must be given to the patient.

The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s). The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

10.2. Participant Withdrawal

Participation in this study is voluntary and patients may withdraw from the study at any time without prejudice. If the patient withdraws or is withdrawn, the reason will be collected in the eCRF. The ICF will explain that in case of withdrawal, all study data collected before withdrawal will be kept in the study database.

The Sponsor reserves the right, at any time, to discontinue enrolment of additional patients into the study, at any site; or to discontinue the study, for medical or administrative reasons.

10.3. Data Protection

Each patient will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.4. Independent Ethics Committee

It is the responsibility of Blueprint Medicines and the investigators to have prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., ICFs), if applicable, from the IEC.

10.5. Ethical conduct of the study

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (version 2008) and applicable legal and regulatory requirements and related guidances, especially Directive 2001/83/EC, Regulation (EC) No 726/2004 (REG) and Commission Implementing Regulation (EU) No 520/2012 (IR) as detailed in Good Pharmacovigilance Practices (GVP) Modules V, VI and VIII. For scientific purpose, value, and rigor the study will follow generally accepted research practices described in the EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, the ENCePP check-list for study protocol, Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), and Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association.

This study has been registered in the EU-PAS Register (EUPAS41969).

The study will be submitted and supervised by the PRAC. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained.

10.6. Record Retention

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 25 years or according to applicable regulatory requirement(s). If the Investigator wishes to withdraw from the responsibility of keeping the study records, Sponsor must be notified promptly in writing of such potential custodial change. The notification must include the name, contact information, new location of records, and any other pertinent information. Sponsor must approve such transfer in writing, which will not be unreasonably withheld, before Investigator is released of any obligations regarding such records. Custody must be transferred to a person willing to accept the responsibility.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Definitions

11.1.1. Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

11.1.2. Serious Adverse Event (SAE)

An SAE is an adverse event which results in death, is life threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect. Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.
All intracranial bleeding events should be considered serious regardless of severity.

11.1.3. Adverse Drug Reaction (ADR)

An ADR is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside of the terms of the marketing authorisation or from occupational exposure. Conditions of use outside of the marketing authorisation include off label use, overdose, abuse and medication errors.

A serious adverse drug reaction meets both the definition of a SAE and an ADR.

11.1.4. Adverse Event of Special Interest (AESI)

An AESI is an adverse event of scientific and medical concern specific to the product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to

characterise and understand it. AESIs selected for this study include cognitive effects and intracranial bleeding.

11.2. Adverse Event Severity

The investigator will use the following definitions to rate the severity of each recorded event. Severity and seriousness need to be independently assessed by the investigator for each event recorded on the CRF. Severity of events will be classified using NCI CTCAE Version 5.0 (see Table 2; of note a Semi-colon indicates 'or' within the description of the grade).

Table 2: Severity rating adverse events

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL).
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.[a]

[a] Death is not appropriate for some AEs and therefore not an option.

11.3. Relationship

The relationship of avapritinib to an AE will be determined by the investigator. Investigators should use their knowledge of the patient, the circumstances surrounding the event, the temporal sequence between the event and the use of avapritinib, and an evaluation of any potential alternative causes to determine whether an AE is considered to be related to avapritinib. The investigator will use the following definitions to assess the relationship of the AE to the use of the product:

Not Related: There is evidence against a reasonable causal relationship between the use of avapritinib and the occurrence of the event, either due to lack of temporal relationship, or lack of biological plausibility, or to the existence of more plausible alternative explanations for the occurrence of the event of concern such as underlying or concurrent illness.

Related: There is evidence in favour of a reasonable causal relationship between the use of avapritinib and the occurrence of the event due to plausible temporal relationship (the event occurred within a reasonable time after drug administration) and also biological plausibility, despite the potential existence of alternative explanations for the occurrence of the event of concern such as the event could not be reasonably explained by known characteristics including concomitant therapies and/or the AE abated after discontinuing the study drug.

11.4. Adverse Event Reporting

All adverse events should be collected in accordance with Section 9.3 in Electronic Data Capture System (EDC).

All adverse events should be followed until they are resolved, or the Investigator assesses them as chronic or stable, the patient's participation in the study ends.

For all adverse events that will be collected and reported in this study, the investigator will assess seriousness and causality. The investigator or representative must make an accurate and adequate report within 1 business day or no later than 3 calendar days for SAEs and AESIs that occur during the study preferably by email (globalsaeinbox@blueprintmedicines.com). For non-serious ADRs, these events should be reported within 30 calendar days by preferably e-mail (globalsaeinbox@blueprintmedicines.com). To secure the reporting process and in parallel to notification to the investigator, Syneos Health will email to Blueprint Medicines (globalsaeinbox@blueprintmedicines.com) a copy of every serious SAE/ fatal outcome collected from patients during follow-up. This additional reporting process should not be considered as a substitute for the investigator responsibilities described above (i.e. seriousness/ causality assessment, medical confirmation with event treating HCP, expedited reporting to Blueprint Medicines). After receipt of the initial report, the information will be reviewed, and the investigator can be contacted to request additional information or for data clarification. If required, a follow-up report must be prepared and sent to Blueprint Medicines (globalsaeinbox@blueprintmedicines.com).

Copies of each report will be kept in the site's study files, and adequate documentation will be provided to Blueprint Medicine, including documentation of IRB/IEC notification, as applicable.

Blueprint Medicine and/or a designated party, assumes responsibility for appropriate case processing, medical review, causality assessment, MedDRA coding, case narrative writing, expedited and aggregated reporting to regulatory authorities of valid cases of SAE/AESI/ADRs. In case of a safety concern identified during the study, Blueprint Medicines will inform the PRAC and regulatory authority.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Blueprint Medicines and/or a designated party will prepare annual progress reports as detailed in Section 6. In addition, data may be summarised periodically for presentation at professional conferences and sessions, as appropriate.

Blueprint Medicines and/or a designated party will submit an interim study report, summarizing the safety and efficacy results 3 years after study's start, and a final study report to the appropriate regulatory authorities. The final study report will be sent no later than 1 year after study completion or termination by Blueprint Medicines as detailed in Section 6. Study status and results will be communicated to the PRAC as required by applicable regulation and guidelines and detailed in GVP Module VIII.

Blueprint Medicines is responsible for presentations and/or publications. For studies that are fully or partially conducted by investigators who are not employees of the Marketing Authorisation Holder, the Marketing Authorisation Holder and the investigator should agree in advance a publication policy allowing the principal investigator to independently prepare publications based on the study results irrespective of data ownership. The Marketing Authorisation Holder should be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication.

In order to allow national competent authorities to review in advance the results and interpretations to be published, the Marketing Authorisation Holder will communicate to the Agency the final manuscript of the article within two weeks after first acceptance for publication.

13. REFERENCES

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ANNEXURES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Contact details of all Investigators participating in the study will be kept in a stand-alone document.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

Observational study evaluating the long-term safety and efficacy of avapritinib in the first-line treatment of patients with platelet-derived growth factor receptor alpha (PDGFRA) D842V-mutated gastrointestinal stromal tumour (GIST)

EU PAS Register® number: EUPAS41969
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	10.5
1.1.6 Final report of study results.	☒	☐	☐	6

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	8
	2.1.2 The objective(s) of the study?	☒	☐	☐	8
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1/9.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.1
4.2	Is the planned study population defined in terms of:				

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.1 Study time period	☒	☐	☐	9.2.3
4.2.2 Age and sex	☒	☐	☐	9.2.1
4.2.3 Country of origin	☒	☐	☐	9.2
4.2.4 Disease/indication	☒	☐	☐	9.2.1
4.2.5 Duration of follow-up	☒	☐	☐	9.2.3
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2/9.4

Comments:

Patients will be included from multiple sites worldwide.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Duration of treatment is an outcome in this study. Exposure will be stratified according to setting (source – see 9.4).

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8/9.7
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3/9.7

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.9

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.1/9.2/ 9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.1/9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.1/9.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7/9.9
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7

Comments:

At least 50 patients are planned for the study. The sample size is not based on a statistical power consideration but it is estimated that this number will be adequate to provide sufficient safety information in this ultra-rare patient population, considering already available data.

Rules about how missing data will be handled, correction of inconsistencies or errors, and outcome misclassification will be set in the SAP as indicated in 9.7 and 9.9.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	12

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.2.3

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.3

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	9.10.2

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: PPD

Date: 24/January/2023

Signature: PPD

ANNEX 3. ADDITIONAL INFORMATION

Derivation of Child-Pugh Classification Score [1]

Parameter	1 Point	2 Points	3 Points
Serum albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
Total serum bilirubin (mg/dL)	<2.0	2.0 to 3.0	>3.0
Prothrombin time (sec prolonged) or international normalised ratio (ratio)	<4 <1.70	4 to 6 1.70 to 2.30	>6 >2.30
Ascites	Absent	Slight	Moderate or Subject on medication(s) to control ascites
Hepatic encephalopathy (see Table 2)	None	Grade 1 or 2	Grade 3 or 4 or subject receiving medication(s) to prevent encephalopathy

[1] Adapted from FDA Guidance for Industry. Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (FDA 2003).

ANNEX 4. APPROVAL STATUS OF AVAPRITINIB

Country/ Region	Indication
MAH: Blueprint Medicines	
US	Treatment of adults with unresectable or metastatic GIST harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations
	Treatment of adult patients with advanced systemic mastocytosis (AdvSM). AdvSM includes patients with aggressive systemic mastocytosis (ASM, systemic mastocytosis with an associated hematological neoplasm (SM-AHN) and mast cell leukemia (MCL)
EU	Monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumors (GIST) harboring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation
	Monotherapy for the treatment of adult patients with advanced systemic mastocytosis: aggressive systemic mastocytosis (ASM, systemic mastocytosis with an associated hematological neoplasm (SM-AHN) or mast cell leukemia (MCL), after at least one systemic therapy
UK	Monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumors (GIST) harboring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation
MAH: Cstone	
China	Treatment of adults with unresectable or metastatic GIST harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations
Taiwan	For treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumor harboring a platelet-derived growth factor receptor alpha (PDGFRA) D842V mutations
Hong Kong	Treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a PDGFRA D842V mutation