CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212608Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	212608
PDUFA Goal Date	February 14, 2020
OSE RCM #	2019-1280; 2019-1282
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Team Leader	Elizabeth Everhart, MSN, RN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	November 26, 2019
Subject	Review to determine if a REMS is necessary
Established Name	avapritinib
Trade Name	Ayvakit
Name of Applicant	Blueprint Medicines Corporation
Therapeutic Class	Kinase Inhibitor
Formulation(s)	100 mg, 200 mg or 300 mg Tablets
Dosing Regimen	The recommended dosage is 300 mg orally once daily on an empty stomach, at least one hour before and two hours after a meal

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity avapritinib (Ayvakit) is necessary to ensure the benefits outweigh its risks. Blueprint Medicines Corporation submitted a New Drug Application (NDA) 212608 for avapritinib with the proposed indication for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumor (GIST) who:

- have a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, (b) (4) the PDGFRA D842V mutation, regardless of prior therapy
- (b) (4)

About 80 percent of cases of GIST are associated with a mutation in the KIT gene, and about 10 percent of cases are associated with a mutation in the *PDGFRA* gene. Although surgery is the therapeutic modality of choice, it does not routinely cure GIST. The current treatment paradigm for advanced GIST involves sequential administration of the tyrosine kinase inhibitors (TKIs) imatinib, sunitinib, and regorafenib. Primary resistance due to mutation in the PDGFRA activation loop (exon 18), particularly the D842V mutation occurs in 5-6% of patients with advanced GIST. The D842V mutation is insensitive to imatinib and other approved agents. Primary and acquired KIT and PDGFRA resistance mutations appear closely linked with therapeutic failure in advanced GIST. The presence of mutations in specific regions of the KIT and PDGFRA genes are correlated with response (or lack of response) to specific TKIs. Novel treatments targeting primary oncogenic and secondary resistance- KIT and PDGFRA mutations are needed to improve outcomes for patients with advanced GIST. In the clinical trial, avapritinib appeared efficacious in both its primary and secondary outcomes. Based on the efficacy and safety information currently available, the clinical reviewers stated that avapritinib shows clinically meaningful benefit to GIST patients harboring PDGFRA genetic alterations and recommends approval of avapritinib for the indication as treatment of adult patients with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation including PDGFRA D842V mutations.

DRISK and Division of Oncology Products II (DOP II) have determined that if approved, a REMS is not necessary to ensure the benefits of avapritinib outweigh its risks. The most concerning adverse reactions observed with the use of avapritinib are intracranial hemorrhage, cognitive effects, and embryo-fetal toxicity. If avapritinib is approved, labeling, including Warnings and Precautions and Dosage and Administration sections will be used to communicate the safety issues and management of toxicities associated with avapritinib. Labeling instructs prescribers to withhold avapritinib and then resume at the same dose or at a reduced dose upon improvement, or permanently discontinue avapritinib based on the severity of the risks for intracranial hemorrhage and central nervous systems effects. Information will also be included in section 17, Patient Counseling Information, and in the PPI to inform patients and to increase the prominence of this information and promote its mitigation.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) avapritinib (Ayvakit) is necessary to ensure the benefits outweigh its risks. (b) (4) submitted a New Drug Application (NDA) 212608 for avapritinib with the proposed indication for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumor (GIST) who have a platelet-derived growth factor receptor alpha (PDGFRA) exon 18

mutation, (b) (4) the PDGFRA D842V mutation, regardless of prior therapy (b) (4) .[1] The applicant did not submit a REMS with this application but proposed Prescribing Information that includes Warnings and Precautions, as well as information to be included in section 17, Patient Counseling Information, and a Patient Package Insert (patient labeling or PPI).

2 Background

2.1 PRODUCT INFORMATION

Avapritinib is a NME NDA type 505(b)(1) pathway application.[a] It is a kinase inhibitor proposed for the indication of treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumor (GIST) who have a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, (b) (4) the PDGFRA D842V mutation, regardless of prior therapy (b) (4) (b) (4) Avapritinib is a Type 1 kinase inhibitor that binds to the active conformation and inhibits a broad range of V-Kit Hardy-Zuckerman 4 Feline Sarcoma Viral Oncogene Homolog (KIT) and PDGFRA mutant kinases. Constitutive activation of KIT and PDGFRA receptor tyrosine kinases have been implicated in the pathogenesis of a number of malignancies and rare hematologic diseases. In in vitro biochemical assays, avapritinib inhibited the activity of KIT exon 11, 11/17 and 17 mutants (d557-558, V560G, V560G/D816V, V560G/N822K, D816E, D816F, D816H, D816I, D816V, D816Y, D820E, D820Y and Y823D) and PDGFRA exon 18 mutants (D842V, D842I and D842Y), sparing activity on a range of other kinases including VEGFR2. In in vitro cultured cells and in vivo tumor models, avapritinib demonstrated potent on-target inhibition of KIT exon 17 mutant signaling, inhibition of cellular proliferation and apoptotic induction in KIT exon 17 mutant cell lines (b) (4) Avapritinib is prepared as 100 mg, 200 mg or 300 mg tablets. The recommended dose of avapritinib is 300 mg orally once daily on an empty stomach, at least one hour before and two hours after a meal until disease progression or unacceptable toxicity.[b] Avapritinib was granted orphan drug designation on January 6, 2016, fast track designation on October 4, 2016 and breakthrough therapy designation on June 1, 2017. Avapritinib is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for avapritinib (NDA 212608) relevant to this review:

- 06/09/2015: Investigation New Drug (IND) IND 125379 submission for avapritinib (BLU-285) was received.
- 01/06/2016: Orphan Drug designation granted
- 10/04/2016: Fast track designation granted
- 06/01/2017: Breakthrough therapy designation granted
- 06/14/2019: NDA 212608 submission for avapritinib with the proposed indication for the treatment of adult patients with unresectable or metastatic GIST who have a PDGFRA exon 18

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

mutation, (b) (4) the PDGFRA D842V mutation, regardless of prior therapy (b) (4) received.

- 09/26/2019: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for avapritinib.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Gastrointestinal stromal tumor (GIST) is a type of tumor that occurs in the gastrointestinal tract, most commonly in the stomach or small intestine. The tumors are thought to grow from specialized cells found in the gastrointestinal tract called interstitial cells of Cajal (ICCs) or precursors to these cells. GISTs are usually found in adults between ages 40 and 70; rarely, children and young adults develop these tumors. Approximately 5,000 new cases of GIST are diagnosed in the United States each year.[c,2] GISTs represent the most common mesenchymal neoplasms of the GIT. With an annual incidence of 11-14 per 10^6, they form 0.1%-3.0% of gastrointestinal malignant tumors.[d] After the discovery of gain-of-function mutations in the c-KIT proto-oncogene in 1998 that these tumors were reliably distinguished from other histopathological subtypes of mesenchymal tumors.[3] The tumors can be malignant or benign. Affected individuals with no family history of GIST typically have only one tumor (called a sporadic GIST). People with a family history of GISTs (called familial GISTs) often have multiple tumors and additional signs or symptoms, including noncancerous overgrowth (hyperplasia) of other cells in the gastrointestinal tract and patches of dark skin on various areas of the body. Genetic changes in one of several genes are involved in the formation of GISTs. About 80 percent of GIST cases are associated with a mutation in the KIT gene, and about 10 percent of cases are associated with a mutation in the *PDGFRA* gene. Mutations in the *KIT* and *PDGFRA* genes are associated with both familial and sporadic GISTs. A small number of affected individuals have mutations in other genes.[2]

3.2 Description of Current Treatment Options

Surgery is the primary treatment of choice in localized or potentially resectable GIST.[3,4] As chemotherapy and radiation are ineffective, the current treatment paradigm for advanced GIST involves sequential administration of the tyrosine kinase inhibitors (TKIs) imatinib[5], sunitinib[6], and regorafenib[7].[8] Although surgery is the therapeutic modality of choice, it does not routinely cure GIST. Complete resection is possible in approximately 85% of patients and 50% patients will develop recurrence or metastasis following complete resection. The 5-year survival rate is approximately 50%, while the median time to recurrence after resection of primary high-risk GIST is 2 years. First-line treatment with imatinib is effective with a 60% response rate and median progression free survival (PFS) of 18 to 24 months. Subsequent treatment with sunitinib and regorafenib is markedly less effective with a response rate of 5% to 7%, and a median PFS of 5-6 months. Once patients experience progressive disease (PD)

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

following treatment with imatinib, sunitinib, and regorafenib, no agents are effective; therefore, the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology guidelines recommend a clinical trial or palliative care for fourth-line patients.[4,8] Primary resistance due to mutation in the PDGFRA activation loop (exon 18), particularly the D842V mutation occurs in 5-6% of patients with advanced GIST. The D842V mutation is insensitive to imatinib and other approved agents.[9] Primary and acquired KIT and PDGFRA resistance mutations appear closely linked with therapeutic failure in advanced GIST. The presence of mutations in specific regions of the KIT and PDGFRA genes are correlated with response (or lack of response) to specific TKIs.[4]

Despite the fact that patients with metastatic GIST clearly benefit from imatinib and may derive some benefit with other available TKIs, the advantage is limited to patients with KIT-mutant GIST; there remains a clear medical need for the treatment of advanced. KIT-driven GIST represents most cases and these patients typically have disease progression through 3 lines of therapy. The prognosis for patients receiving fourth-line treatment and beyond is poor and there are no approved or effective agents in this setting. Novel treatments targeting primary oncogenic and secondary resistance- KIT and PDGFRA mutations are needed to improve outcomes for patients with advanced GIST.

4 Benefit Assessment

The Clinical reviewer determined that the efficacy of avapritinib was demonstrated in a multi-center, single-arm, open-label clinical trial (NAVIGATOR; NCT02508532). Eligible patients were required to have a confirmed diagnosis of GIST and an ECOG performance status (PS) of 0 to 2. Patients received avapritinib 300 mg or 400 mg orally once daily until disease progression or unacceptable toxicity. The recommended dose was determined to be 300 mg once daily. The major efficacy outcome measure was overall response rate (ORR) based on disease assessment by independent radiological review using modified RECIST v1.1 criteria, in which lymph nodes and bone lesions were not target lesions and progressively growing new tumor nodules within a pre-existing tumor mass was progression. An additional efficacy outcome measure was duration of response (DOR). The efficacy was also evaluated in patients harboring PDGFRA exon 18 mutations, including D842V regardless of line of therapy and patients with unresectable or metastatic GIST previously treated with at least 3 prior lines of TKIs (4L+) regardless of mutation.

(b) (4) The following section is a summary of relevant efficacy information to date for avapritinib. The assessment of efficacy was based on a total of 43 patients, including 38 patients with PDGFRA D842V mutations. The median duration of follow up for patients with PDGFRA D842 genetic alterations was 10.6 months (range: 0.3 to 24.9 months). Efficacy results in patients with GIST harboring PDGFRA D842V mutations enrolled in NAVIGATOR are summarized in Table 5.[1,10,e]

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

Table 5. Efficacy Results for Patients with GIST Harboring PDGFRA D842V Mutations in NAVIGATOR[1,10,e]

Efficacy Parameter	PDGFRA exon 18* N = 43	PDGFRA D842V N = 38
Overall Response Rate (95% CI)	84% (69%, 93%)	89% (75%, 97%)
Complete Response	7%	8%
Partial Response	77%	82%
Duration of Response	n=36	n=34
Median in months (range)	NR (1.9+, 20.3+)	NR (1.9+, 20.3+)

Abbreviations: CI=confidence interval; NR=not reached; NE=not estimable
*Exon 18 mutations other than D842V included in this population are: deletion of D842_H845 (n=3); D842Y (n=1); and deletion of D842_H845 with insertion of V (n=1).

5 Risk Assessment & Safe-Use Conditions

(b) (4) The following section is a summary of relevant safety information to date for avapritinib. The safety analysis of avapritinib primarily focuses in 335 patients who were exposed to avapritinib at either 300 mg or 400 mg once daily with unresectable or metastatic GIST enrolled in NAVIGATOR (NCT02508532), a multi-center, single-arm, open-label clinical trial and VOYAGER (NCT03465722), an open-label, randomized trial. Among patients receiving avapritinib, 49% were exposed for 6 months or longer and 23% exposed for greater than 1 year.[1]

The most common adverse reactions (incidence ≥20%) noted were are edema (65%), nausea (57%), fatigue (45%), anemia (35%), vomiting (30%), diarrhea (29%), increased lacrimation (28%), decreased appetite (27%), memory impairment (26%), and hyperbilirubinemia (24%).[1]

Deaths
A total of 11.5% of patients experienced AEs leading to death. All of the AEs leading to death were considered not related to study drug, and most were related to the patients' underlying disease.[10,11]

Serious Adverse Events (SAE)
The most common serious adverse reactions occurring in ≥2% patients who received avapritinib were anemia (9%), abdominal pain (3%), pleural effusion (3%), sepsis (3%), gastrointestinal hemorrhage (2%), acute kidney injury (2%) and sepsis (2%). Permanent discontinuation due to adverse reactions occurred in 7% of patients who received avapritinib. Most frequent adverse reactions requiring permanent discontinuation were fatigue, confusional state, and encephalopathy (< 1% each). A total of 65% of patients experienced AEs leading to dose interruption. The most commonly (≥5%) reported AEs leading to dose interruption by PT were anemia (10.3%), fatigue (9.8%), nausea (7.7%), vomiting (5.6%), and blood bilirubin increased (5.1%). Dose reduction due to an adverse reaction occurred in 46% of patients

who received avapritinib. The most commonly (≥5%) reported AEs leading to dose reduction by preferred term (PT) were fatigue (9.8%) and anemia (5.6%).[1,10,11]

If approved, labeling will include the following risks in the Warnings and Precautions section.

5.1 INTRACRANIAL HEMORRHAGE

There were 3% of intracranial hemorrhage reported in 335 patients who received avapritinib including 1% of the 267 patients with GIST. Severe (Grade 3 or 4) intracranial hemorrhage (e.g. subdural hematoma, intracranial hemorrhage, and cerebral hemorrhage) occurred in 1.2% of the 335 patients and in 0.7% of the 267 patients with GIST. Labeling instructs to withhold avapritinib and then resume at a reduced dose upon resolution, or permanently discontinue avapritinib based on severity. The risk of intracranial hemorrhage will likely be communicated in the Warnings and Precautions section of the label. Monitoring and dosage modifications for toxicities to address the safety issues with avapritinib will likely be included in the Dosage and Administration section of the label. Patient Counseling Information, section 17 and PPI instructs the patient to tell the healthcare provider if they develop any symptoms such as severe headache, vision problems, severe sleepiness, severe weakness on one side of their body.[1] Additionally, the applicant will be required to conduct a post-marketing requirement (PMR) study to fully characterize the risk of intracranial hemorrhage.[12]

5.2 CENTRAL NERVOUS SYSTEM EFFECTS (CNS)

CNS include effects on cognition, sleep, mood, speech, mental status, and hallucinations. A broad spectrum of CNS adverse reactions have been reported in patients receiving avapritinib. Cognitive effects occurred in 41% of 335 patients who received avapritinib, 3.3% of these were severe (Grade 3 or 4). Of patients with cognitive effects 90% had events of memory impairment, cognitive disorder, confusional state, and encephalopathy. Among patients who experienced these four events at Grade 2 or worse severity (impacting activities of daily living) the median time to improvement to Grade 1 or complete resolution was 13 weeks. Sleep disorders occurred 15% of patients; 0.3% of these events were severe. Mood effects occurred in 13% of patients; 1.5% of these events were severe. Speech effects occurred in 6% of patients; none of these events were severe. Mental status changes occurred in 4% of patients; 1.5% of these events were severe. Hallucinations occurred in 2.1% of patients; none of these events were severe. The median time to onset of the first CNS adverse reaction was 7.9 weeks (range <1 day to 22.6 months). Overall, 3.6% of patients required permanent discontinuation of avapritinib for a CNS adverse reaction; 13% required dosage interruption and 9% required dose reduction. Labeling instructs prescribers to withhold avapritinib and then resume at the same dose or at a reduced dose upon improvement, or permanently discontinue avapritinib based on severity. The risk of cognitive effects will likely be communicated in the Warnings and Precautions section of the label. Monitoring and dosage modifications for toxicities to address the safety issues with avapritinib will likely be included in the Dosage and Administration section of the label.[1] Additionally, the applicant will be required to conduct a PMR study to fully characterize the risk of cognitive effects.[12]

5.3 EMBRYO-FETAL TOXICITY

Similar to other kinase inhibitors, based on its mechanism of action and findings from animal data, avapritinib can cause fetal harm when administered to a pregnant woman. In an embryo-fetal development study, administration of avapritinib to pregnant rats during the period of organogenesis was teratogenic and embryotoxic at exposures approximately 2.7 times the human exposure based on

area under the curve (AUC) at the 300 mg dose. Besides being communicated in the Warnings and Precautions section of the label, recommended guidance to use effective contraception for females of reproductive potential during treatment with avapritinib for (b) (4) after the last dose will be communicated in the Use in Specific Populations section of the label.[1]

6 Expected Postmarket Use

The proposed indication is for the treatment of adult patients with unresectable or metastatic GIST who have a PDGFRA exon 18 mutation, (b) (4) the PDGFRA D842V mutation, regardless of prior therapy (b) (4) Oncologists are the likely prescribers of avapritinib in both inpatient and outpatient settings and with the recommendations provided in labeling are expected to be able to the manage the risks of intracranial hemorrhage, cognitive effects and embryo-fetal toxicity.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for avapritinib beyond routine pharmacovigilance and labeling. The applicant proposed a PI that includes Warnings and Precautions to address the risks of intracranial hemorrhage, cognitive effects and embryo-fetal toxicity.

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for avapritinib, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing population. The likely prescribers for avapritinib will be oncologists and the risks identified are risks that these providers have likely encountered in their practice experience.

Avapritinib is a kinase inhibitor proposed for indication as treatment of adult patients with unresectable or metastatic GIST who:

- have a PDGFRA exon 18 mutation, (b) (4) the PDGFRA D842V mutation, regardless of prior therapy
- (b) (4) (b) (4)

At the time of this writing, labeling negotiations were still ongoing with the Applicant. Based on the efficacy and safety information currently available, the clinical reviewers stated that avapritinib shows clinically meaningful benefit to GIST patients harboring PDGFRA genetic alteration, and recommends approval of avapritinib for the indication as treatment of adult patients with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation including PDGFRA D842V mutations.[f,10]

[f] Labeling negotiations were ongoing at the time of completion of this review. Indication statement is likely to be updated and significant changes to the proposed label likely to be made by FDA prior to negotiations.

(b) (4)

Genetic changes in one of several genes are involved in the formation of GISTs. About 80 percent of GIST cases are associated with a mutation in the KIT gene, and about 10 percent of cases are associated with a mutation in the *PDGFRA* gene. Although surgery is the therapeutic modality of choice, it does not routinely cure GIST. The current treatment paradigm for advanced GIST involves sequential administration of the TKIs, imatinib, sunitinib, and regorafenib. Primary resistance due to mutation in the PDGFRA activation loop (exon 18), particularly the D842V mutation occurs in 5-6% of patients with advanced GIST. The D842V mutation is insensitive to imatinib and other approved agents. Primary and acquired KIT and PDGFRA resistance mutations appear closely linked with therapeutic failure in advanced GIST. The presence of mutations in specific regions of the KIT and PDGFRA genes are correlated with response (or lack of response) to specific TKIs. Novel treatments targeting primary oncogenic and secondary resistance- KIT and PDGFRA mutations are needed to improve outcomes for patients with advanced GIST. Avapritinib appeared efficacious in both its primary and secondary outcomes and its risks can be communicated and managed through labeling.

DRISK and DHP have determined that if approved, a REMS is not necessary to ensure the benefits of avapritinib outweigh its risks. The most concerning adverse reactions observed with the use of avapritinib are intracranial hemorrhage, cognitive effects, and embryo-fetal toxicity. If avapritinib is approved, labeling, including Warnings and Precautions and Dosage and Administration section will be used to communicate the safety issues and management of toxicities associated with avapritinib. Labeling instructs prescribers to withhold avapritinib and then resume at the same dose or at a reduced dose upon improvement, or permanently discontinue avapritinib based on the severity of the risks for intracranial hemorrhage and central nervous systems effects. Information will also be included in section 17, Patient Counseling Information, and in the PPI to inform patients and to increase the prominence of this information and promote its mitigation. At this time, none of these risks will receive a boxed warning in the label. Additionally, the applicant will be required to conduct a post-marketing commitment (PMC) study to develop a companion diagnostic to identify the patients for whom this drug will ultimately be indicated and PMR studies to fully characterize the risks of intracranial hemorrhage and cognitive effects.

9 Conclusion & Recommendations

If approved, DRISK has determined that a REMS is not necessary to ensure the benefits outweigh the risks of avapritinib. The management of the risks associated with avapritinib treatment will be communicated through labeling. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 References

(b) (4)

[2] U.S. National Library of Medicine. Genetics Home Reference. Your Guide to understanding Genetic Conditions: Gastrointestinal Stromal Tumor. https://ghr.nlm.nih.gov/condition/gastrointestinal-stromal-tumor. Accessed September 25, 2019.

[3] Rammohan A, Sathyanesan J, Rajendran K, et al. A gist of gastrointestinal stromal tumors: A review. *World journal of gastrointestinal oncology.* 2013;5(6):102-112.

[4] NCCN. National Comprehensive Cancer Network. Soft Tissue Sarcoma (Version 2. 2018) [Online]. Available at: https://jnccn.org/abstract/journals/jnccn/16/5/article-p536.xml. Accessed September 25, 2019.

(b) (4)

[8] Casali PG, Abecassis N, Aro HT, et al. Gastrointestinal stromal tumours: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology.* 2018;29(Suppl 4):iv267.

[9] Cassier PA, Fumagalli E, Rutkowski P, et al. Outcome of patients with platelet-derived growth factor receptor alpha-mutated gastrointestinal stromal tumors in the tyrosine kinase inhibitor era. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2012;18(16):4458-4464.

[10] Osgood C. Mid-Cycle Meeting dated September 16, 2019.

[11] Blueprint Medicines Corporation. Summary of Clinical Safety of avapritinib, dated June 14, 2019.

[12] Mid-Cycle Communication Agenda, darrted on September 24, 2019.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TILL OLICKAL
11/26/2019 02:47:53 PM

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I concur.

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