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HEALTH TECHNOLOGY BRIEFING FEBRUARY 2020

Avapritinib for advanced systemic mastocytosis

NIHRIO ID	26588	**NICE ID**	10141
Developer/Company	Blueprint Medicines Corp	**UKPS ID**	N/A

Licensing and market availability plans	Currently in phase II clinical trials.

SUMMARY

Avapritinib is in clinical development for the treatment of advanced systemic mastocytosis (SM) in adults. SM is a condition where mast cells grow uncontrollably and accumulate in body organs/tissues such as the skin, internal organs, lymph nodes and bones. Mast cells are immune cells that release inflammatory mediators that are important in the body's allergic responses. When mast cells are present in large numbers there is a high release of these mediators leading to symptoms such as itching, fever, abdominal pain, nausea and vomiting. In advanced SM, mast cells collect in such high quantities that they lead to organ damage and dysfunction, bone fractures and anaemia.

Avapritinib, formulated for oral administration, works by selectively blocking the active form of the KIT protein kinase. More than 90% of SM cases are due to a KIT D816V mutation that results in KIT being constantly active. In its active state, KIT triggers a series of downstream signals resulting in the accumulation of mast cells and uncontrolled release of inflammatory mediators. By blocking KIT, avapritinib will reduce the accumulation and uncontrolled activation of mast cells. If licenced, avapritinib will offer an additional treatment option for patients with advanced SM.

PROPOSED INDICATION

Treatment of patients aged 18 years and over with advanced systemic mastocytosis (SM).[1]

TECHNOLOGY

DESCRIPTION

Avapritinib (BLU-265) is a highly potent and selective type I kinase inhibitor developed to specifically target the activation conformation of KIT by conferring potent inhibition of KIT D816V.[2] KIT is a transmembrane type III tyrosine kinase receptor that is frequently mutated at exon 11 or 17, resulting in the receptor becoming constitutively active in a variety of cancers. Mutations in exon 17 (D816V), which encodes the activation loop of the kinase, shift the conformational equilibrium of the kinase to the active state.[2] By blocking the action of these tyrosine kinase enzymes which are found on the surface of mast cells, avapritinib is expected to control the proliferation and activation of mast cells, thereby slowing down the progression of mastocytosis, thus reducing disease symptoms and organ involvement.[3]

Avapritinib is in clinical development for the treatment of patients with advanced SM in 2 clinical studies. In the phase I dose-escalation EXPLORER study (NCT02561988) patients receive avapritinib doses by oral administration once daily ranging from 30-400mg.[4,a] In the phase II PATHFINDER study (NCT03580655, EudraCT 2017-004836-13), participants receive by oral administration a dose of avapritinib once daily in 28 day cycles.[1,a]

INNOVATION AND/OR ADVANTAGES

Several approved tyrosine kinase inhibitors (TKIs), such as imatinib and nilotinib, have activity against wild-type KIT but lack potent activity against D816V mutated KIT, the primary genetic driver in majority of advanced SM patients.

Midostaurin, a broad spectrum TKI with activity against KITD816V, has a shown 28.3% overall response rate and median progression free survival (PFS) was 14.1 months. However, treatment discontinuation due to adverse events (AEs) occurred in 9.2% of patients and 31% of patients required dose modification due to toxicity.[5] Midostaurin is currently the only drug specifically approved in the EU and USA for advanced SM. While this agent improves the prognosis of advanced SM patients and provides proof of principle for targeting KITD816V as a driver mutation, most responses are partial and/or not sustained, indicating that more potent and/or specific inhibitors are required.[6]

Avapritinib is a potent inhibitor of KIT D816V and compared to other TKIs including, midostaurin, is more selective.[6] Avapritinib inhibits KIT D816V 150-fold more potently than several other important kinases suggesting that off-target inhibition in vivo would be unlikely.[7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Avapritinib does not currently have marketing authorisation in the EU/UK for any indication.

Avapritinib is approved in the USA for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a PDGFRA exon 18 mutation, including

[a] Information provided by BluePrint Medicines Corp

PDGFRA D842V mutations and is under EMA review for the treatment of advanced gastrointestinal stromal tumours (GIST) harbouring PDGFRA D842V mutation.[8]

Avapritinib is also in phase II development for the treatment of indolent and smoldering forms of non-advanced SM.[9]

PATIENT GROUP

DISEASE BACKGROUND

Mastocytosis is a rare disease caused by an excess number of mast cells accumulating in various body tissues. There are two main types of mastocytosis; cutaneous mastocytosis and systemic mastocytosis (SM).[10] In SM, mast cells are found not only in the skin but also in bones, joints, lymph nodes, liver, spleen and gastrointestinal tract.[11] Based on the sites of organ involvement and extent of organ dysfunction, five subtypes of SM are distinguished according to the WHO.[6,12] The mildest forms of SM are the indolent and smoldering types (non-advanced SM).[12]

Advanced SM is a term collectively used to refer to the three most aggressive forms of SM, which are: aggressive SM, SM with associated hematologic neoplasm and mast cell leukaemia.[6] In advanced SM, mast cells collect in such high quantities that they lead to organ damage and dysfunction, bone fractures and anaemia.[13] Individuals with milder forms of the condition generally have a near normal life expectancy whilst those with the more severe forms typically survive a few months or a few years after diagnosis.[12]

Mast cells have an important role in inflammatory responses as they can be activated to release a wide variety of inflammatory mediators, such as histamine, by many different antigens including allergens, pathogens and physiological mediators. The release of these inflammatory mediators from activated mast cells leads to a host of symptoms.[14,15] Skin reactions include pruritus, extreme flushing under emotional or physical stress and urticarial (hives). Gastrointestinal symptoms include diarrhoea, abdominal pain or cramping, nausea or vomiting and heartburn. Cardiovascular symptoms include dizziness, palpitations, anaphylaxis with hypotension and syncopal events. Many patients have bone and muscle pain as well as neuropsychiatric disturbances such as memory impairment, anxiety and depression.[6,16] Nearly half of individuals with systemic mastocytosis will experience severe, often unpredictable allergic reactions, including life-threatening episodes of anaphylaxis (anaphylactic shock).[12,17]

The uncontrolled growth, accumulation and activation of mast cells is caused in many people by a KIT mutation. KITD816V is the most common mutation in SM occurring in about 90% of patients.[13] KIT is a class III tyrosine kinase transmembrane receptor encoded by the KIT gene. Activation of the KIT receptor, results in downstream intracellular signal transduction pathways to increase cell proliferation, differentiation, survival, cytokine production, chemotaxis and adhesion. In mastocytosis, mast cells accumulate slowly over time due to constitutive KIT activity and are easily triggered to degranulate leading to the typical symptoms of mastocytosis.[6]

CLINICAL NEED AND BURDEN OF DISEASE

SM mainly affects adults, with an estimated prevalence in England around 1 in 150,000 people.[18] It preferentially affects Caucasians and there is no sex predominance.[19] The prevalence of advanced SM is even less common given that majority of patients with systemic disease have indolent SM.[20,21]

In 2018-19, there were 248 finished consultant episodes (FCE) for histiocytic and mast cell tumours of uncertain and unknown behaviour (ICD-10 code D47.2), which resulted in 361 bed days.[22]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The treatment of mastocytosis depends on the type, the symptoms of the disease, extent of disease and the person's overall health. In many cases, this involves a multidisciplinary team working together to create the patient's overall treatment plan.[23] Patients should be counselled about the signs and symptoms of mast cell activation.[24]

The three different subtypes of advanced SM differ substantially from each other in terms of course and prognosis so it is important to establish the correct final diagnosis before establishing a treatment plan.[25]

There is no cure for mastocytosis, treatment aims to relieve symptoms and to control mast cell expansion.[10,25]

CURRENT TREATMENT OPTIONS

Midostaurin is approved by the EMA as a monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL).[26]

Nearly all other medicines used to treat mastocytosis are unlicensed. This means the manufacturers haven't applied for a license for their medicine to be used to treat mastocytosis. Many physicians will use an unlicensed medicine if they think it will be effective and the benefits of treatment outweigh any associated risk.[27]

PLACE OF TECHNOLOGY

If licensed avapritinib will offer an additional treatment option for patients aged 18 years and older with advanced systemic mastocytosis.

CLINICAL TRIAL INFORMATION

Trial	**Pathfinder;** NCT03580655, Eudra CT 2017-004836-13, BLU-285-2202; Study to evaluate the efficacy and safety of avapritinib (BLU-285), a selective KIT mutation-targeted tyrosine kinase inhibitor, in patients with advanced systemic mastocytosis **Phase II** **Locations:** 8 EU countries (incl UK), USA, Canada and Denmark
Trial design	Open label, single arm study
Population	N=103 (planned); adults aged 18 years and older; diagnosis of aggressive SM, SM with an associated hematologic

	neoplasm or mast cell leukaemia based on WHO diagnostic criteria
Intervention(s)	Avapritinib (oral formulation)
Comparator(s)	No Comparator
Outcome(s)	• The primary objective was to determine objective response rate (ORR) (CR/CRh + PR + CI) based IWG-MRT-ECNM consensus response criteria in patients with advanced SM treated with avapritinib and enrolled in Cohort 1 on modified [Time frame: 10 months] • The key secondary objective par patients in cohorts 1 and 2 is to assess mean change from baseline in advanced SM SAF TSS.[b]
Results (efficacy)	-
Results (safety)	-

Trial	**Explorer;** NCT02561988, BLU-285-2101; Study of BLU-285 in patients with advanced systemic mastocytosis and relapsed or refractory myeloid malignancies Phase I **Locations:** UK and USA
Trial design	Open label, single arm study
Population	N=80; adults aged 18 years and older; diagnosis based on WHO diagnostic criteria of: aggressive SM, SM with an associated hematologic neoplasm mast cell leukaemia or histologically - or cytologically - confirmed myeloid malignancy that is relapsed or refractory to standard treatments.
Intervention(s)	Avapritinib (oral formulation)
Comparator(s)	No Comparator
Outcome(s)	• Maximum tolerated dose of avapritinib [Time Frame: During cycle 1 (28 days) of treatment] • Number of patients with adverse and serious adverse events and changes in physical findings, vital signs, clinical laboratory results and ECG findings [Time Frame: Approximately 24 months] • Recommended phase 2 dose of avapritinib [Time frame: Approximately 24 months] • Secondary and exploratory objectives include assessing anti-neoplastic activity as measured by changes in serum tryptase, spleen size, mast cell burden, *KIT* D816V mutation allele fraction (MAF) and ORR by centrally adjudicated modified IWG-MRT-ECNM criteria. • Additional objectives included assessing duration of response (DOR), OS, and changes in PROs and QoL measures from baseline
Results (efficacy)	
Results (safety)	

[b] Information provided by BluePrint Medicines Corp

ESTIMATED COST

The estimated cost of avapritinib is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Midostaurin for treating advanced systemic mastocytosis (TA10503). Expected publication date 11 November 2020.
- NICE technology appraisal guidance in development. Mastocytosis (systemic) – masitinib (GID-TA10019). Expected publication date to be confirmed.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard contract for specialised allergy services (All ages). B09/S/b

OTHER GUIDANCE

- National Comprehensive Cancer Network (NCCN). Systemic Mastocytosis, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. 2019.[24]

ADDITIONAL INFORMATION

Blueprint Medicines Corp did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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