

**NIHR Innovation Observatory  
Evidence Briefing: January 2018****Crenolanib for advanced or metastatic  
gastrointestinal stromal tumours (GISTs) with the  
D842V mutation in the PDGFRA gene**

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**LAY SUMMARY**

Gastrointestinal stromal tumours (GISTs) are abnormal growths that develop in the digestive tract from the tissues that support the movements of the gut. Some GISTs are non-cancerous (benign) and some are cancerous (malignant). A benign behaving tumour can start to act like a cancerous tumour if untreated. The majority of GISTs arise in the stomach and the small bowel but can spread to other parts of the body when it becomes advanced or metastatic. GISTs frequently contain mutations (changes) in a receptor called platelet-derived growth factor receptor alpha (PDGFRA). This mutation may occur in one specific spot of the gene called a D842V mutation. This mutation is thought to cause the cancer cells to keep on growing and dividing.

GISTs with D842V mutation in PDGFRA are usually resistant to the currently available targeted cancer drugs. Crenolanib is a medicine that specifically blocks the PDGFRA pathway involved in the production of blood vessels that supply the cancer cells, thereby preventing the cancer cells from growing and multiplying. It is being developed for the treatment of advanced or metastatic GISTs with D842V mutation in the PDGFRA gene. This drug is given by mouth. If licensed, crenolanib will offer an additional treatment option for this patient group, particularly those that do not respond to other treatments.

*This briefing reflects the evidence available at the time of writing. A version of the briefing was sent to the company for a factual accuracy check. The company was available to provide comment. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.*

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## TARGET GROUP

Gastrointestinal stromal tumours (advanced or metastatic with D842V mutation in the PDGFRA gene).

## TECHNOLOGY

### DESCRIPTION

Crenolanib is an orally bioavailable, selective tyrosine kinase inhibitor (TKI) with nanomolar potencies against platelet-derived growth factor receptor alpha (PDGFRA) and PDGFR beta and the FMS-related tyrosine kinase 3 (FLT3). Crenolanib binds to and inhibits PDGFR isoforms, which result in the inhibition of PDGFR-related signal transduction pathways thereby leading to inhibition of tumour angiogenesis and tumour cell proliferation.<sup>1, 2</sup>

In the ongoing phase III clinical trial (The CrenoGIST Study - NCT02847429), subjects with advanced or metastatic Gastrointestinal stromal tumours (GIST) with a D842V mutation in the PDGFRA gene will receive crenolanib 100 mg orally 3 times daily in combination with best supportive care.<sup>3</sup>

Crenolanib does not currently have Marketing Authorisation in the EU for any indication.

Crenolanib is in phase III stage of development for the treatment of:

- Newly Diagnosed Acute Myeloid Leukemia (AML)<sup>4</sup>
- Relapse/Refractory AML<sup>5</sup>

Crenolanib is in phase II stage of development for the treatment of recurrent/refractory Glioblastoma Multiforme (GBM).<sup>6</sup>

Crenolanib is in phase I stage of development for the treatment of Advanced Esophagogastric Adenocarcinoma.<sup>7</sup>

## INNOVATION and/or ADVANTAGES

The most common PDGFR alpha (PDGFRA) mutation associated with GIST, D842V, is strongly resistant to inhibition by imatinib or sunitinib (PDGFRA TKIs).<sup>8</sup> In preclinical models of cell lines with the D842V mutation in the PDGFRA gene, crenolanib blocked phosphorylation of PDGFRA at nanomolar concentrations, suggesting that it may provide a clinical benefit to patients with D842V mutant gastrointestinal stromal tumours (GIST). In addition, crenolanib was also active in inhibiting phosphorylation of cell lines with two point mutations (double mutants) PDGFRA V561D + D842V and PDGFRA T674I + D842V.<sup>1</sup>

The drug development company, Arog Pharmaceuticals Inc. indicates that:

- Crenolanib has shown benefit in PDGFRA-mutant GIST.
- Patients who progress after treatment with prior TKIs may still remain sensitive to crenolanib.
- Crenolanib has favourable pharmacokinetics and does not accumulate with repeated dosing.<sup>9</sup>

If licensed, crenolanib will offer an additional treatment option for patients with advanced or metastatic GIST with a D842V mutation in the PDGFRA gene.

## DEVELOPER

Arog Pharmaceuticals, Inc.

## AVAILABILITY, LAUNCH or MARKETING

Crenolanib was awarded a Fast Track designation by the US Food and Drug Administration FDA in 2016 for the treatment of patients with unresectable or metastatic GIST harbouring PDGFRA D842V mutation.<sup>10</sup>

## PATIENT GROUP

### BACKGROUND

Gastrointestinal stromal tumours (GISTs) is a type of soft tissue sarcoma that develops in the gastrointestinal tract (digestive tract) from the tissues that support connective tissue controlling the movements of the gut. GISTs can be non-cancerous (benign) or cancerous (malignant). In general, the larger the GIST, the more likely it is to be cancerous. However, if left untreated, a benign tumour can become cancerous.<sup>11, 12</sup>

Although GISTs can occur along the length of the GI tract, the majority arise in the stomach (60–70%), small bowel (25–35%), colon and rectum (5%) and, to a lesser extent, the oesophagus.<sup>13</sup> Most GISTs are sporadic (not inherited) and have no clear cause. In rare cases, though, they have been found in several members of the same family. These family members have inherited a gene mutation that can lead to GISTs.<sup>14</sup>

GISTs frequently contain oncogenic mutations in one of two receptor tyrosine kinases: KIT or PDGFRA (platelet-derived growth factor receptor alpha). These mutations lead to constitutive activation of cell pathways leading to spontaneous proliferation and uncontrolled growth of tumour cells.<sup>15</sup> In about 5-10% of GIST cases, PDGFRA is mutated.<sup>16</sup> Over 60% of these mutations<sup>16</sup> occur in one specific spot in exon 18 of the gene and are called a D842V mutation (PDGFRA mutation, exon 18, D842V)<sup>17</sup> which causes the cancer cells to make PDGFRA protein in excess. This mutation in PDGFRA makes the cancer cells always growing and dividing.<sup>18</sup>

The symptoms of an advanced GIST include abdominal pain or discomfort, feeling of fullness after only a little food is eaten, being sick, blood in the stools or vomit, a painless lump in the abdomen, feeling very tired, trouble or pain when swallowing, anaemia, fever and sweating at night, and weight loss.<sup>11, 12, 19</sup>

Generally, sarcomas are divided into four stages:<sup>12</sup>

- Stage 1: small and localised.
- Stage 2 and 3: spread into surrounding structures.
- Stage 4: spread to other parts of the body (this is known as secondary or metastatic cancer).

The size, growth rate and location of the tumour often influence prognosis. Without treatment, GISTs progress and will eventually metastasize. Prognosis depends on whether the tumour can be resected, which is the primary treatment for GISTs. Only 50% of GISTs are resectable at presentation. Conventional cytotoxic chemotherapy and radiotherapy are ineffective in treating advanced or metastatic GISTs. Similarly, surgery to treat advanced or metastatic GISTs is not recommended unless there is an immediate clinical need, such as to remove an obstructing tumour.<sup>20</sup>

## CLINICAL NEED and BURDEN OF DISEASE

Estimates of GIST incidence vary widely, from 4 to 40 cases per million population, which corresponds to between 200 and 2000 new cases per year in England and Wales.<sup>13</sup> Approximately 900 people are newly diagnosed with GIST in the UK each year.<sup>20</sup> Recent epidemiological data from Sweden suggests that the incidence of GIST is in the region of 15 per million per year. Approximately half of new cases of GIST are likely to be metastatic and/or unresectable on first presentation. Although GIST can occur at any age, the mean age of presentation is between 50 and 70 years.<sup>13</sup> PDGFRA is mutated in 5%–10% of GISTs, the PDGFRA D842V mutation accounting for about 60% of all PDGFRA mutations known in GISTs.<sup>16</sup>

According to the American Cancer Society, the overall relative 5-year survival rate of people diagnosed with a malignant GIST between 2003 and 2009 was estimated to be about 76%. The 5-year relative survival if the tumour had grown into nearby structures (or spread to nearby lymph nodes), or spread to distant parts of the body when it was first diagnosed was 74% or 48% respectively.<sup>21</sup> Data from 21st Century Mortality dataset, England & Wales 2001–16 shows that there were 422 registered death for ICD 10 code: D37.<sup>22</sup>

The population likely to be eligible to receive crenolanib could not be estimated from available published sources.

### PATIENT PATHWAY

### RELEVANT GUIDANCE

### NICE GUIDANCE

- NICE technology appraisal in development. Regorafenib for treating advanced gastrointestinal stromal tumours (ID1056). Expected publication date: 15 November 2017
- NICE technology appraisal. Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours (TA488). November 2017
- NICE technology appraisal. Imatinib for the adjuvant treatment of gastrointestinal stromal tumours (TA326). November 2014.
- NICE technology appraisal. Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours (TA209). November 2010.
- NICE technology appraisal. Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours (TA86). October 2004 (Last updated: November 2010)
- NICE technology appraisal. Sunitinib for the treatment of gastrointestinal stromal tumours (TA179). September 2009.
- NICE technology appraisal. Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma (TA169). March 2009
- NICE quality standard. Sarcoma (QS78). January 2015
- NICE interventional procedure guidance. Laparoscopic gastrectomy for cancer (IPG269). July 2008

### NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: soft tissue sarcoma (adult). B12/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B12/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

## OTHER GUIDANCE

- British Sarcoma Group (BSG). UK clinical practice guidelines for the management of gastrointestinal stromal tumours (GIST). 2017.<sup>23</sup>
- The European Society for Medical Oncology (ESMO) / European Sarcoma Network Working Group. Gastrointestinal Stromal Tumours: ESMO Clinical Practice Guidelines. 2014.<sup>24</sup>
- The ESMO / European Sarcoma Network Working Group. Gastrointestinal stromal tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2012.<sup>25</sup>
- NHS Wales. National Standards for Sarcoma Services 2009.<sup>26</sup>

## CURRENT TREATMENT OPTIONS

No current treatment options specifically for GISTs with D842V PDGFRA mutation were identified. Generally, the main treatments for GISTs are surgery and targeted cancer drugs. It is less likely that the surgery can completely remove large tumours. For large tumours that have spread to nearby organs, the patient might need to take targeted therapy (Imatinib) first. This can often shrink the tumour, which can make it easier to remove with surgery.<sup>11, 27</sup>

The types of targeted cancer drugs used to treat GISTs include:

- **Imatinib (Glivec).**  
Imatinib is recommended by the National Institute for Health and Care Excellence (NICE) as an option as adjuvant treatment for up to 3 years for adults who are at high risk of relapse after surgery for KIT (CD117)-positive GISTs.<sup>28</sup> Also, imatinib treatment at 400 mg/day is recommended as first-line management of people with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic GISTs.<sup>13</sup> Imatinib at 600 or 800 mg/day is not recommended for people with unresectable and/or metastatic GISTs whose disease has progressed after treatment with 400 mg/day imatinib. People who are currently receiving 600 or 800 mg/day imatinib for unresectable and/or metastatic GISTs should have the option to continue therapy until they and their clinicians consider it appropriate to stop.<sup>20</sup>
- **Sunitinib (Sutent)**  
Sunitinib is recommended by NICE as a treatment option for people with unresectable and/or metastatic malignant gastrointestinal stromal tumours if:
  - Imatinib treatment has failed because of resistance or intolerance, and
  - The drug cost of sunitinib (excluding any related costs) for the first treatment cycle will be met by the manufacturer.<sup>29</sup>
- **Regorafenib (Stivarga)**  
Regorafenib is recommended as an option for treating unresectable or metastatic GISTs whose disease has progressed on, or who are intolerant to, prior treatment with imatinib and sunitinib, only if:
  - Their Eastern Cooperative Oncology Group (ECOG) performance status is 0 to 1 and
  - The company provides regorafenib with the discount agreed in the patient access scheme.

When using ECOG performance status, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect ECOG performance status and make any adjustments they consider appropriate.<sup>30</sup>

## EFFICACY and SAFETY

<b>Trial</b>	<b>The CrenoGIST Study, NCT02847429; crenolanib vs placebo; phase III</b>
<b>Sponsor</b>	Arog Pharmaceuticals, Inc.
<b>Status</b>	Ongoing, recruiting.
<b>Source of Information</b>	Trial registry, <sup>3</sup> poster. <sup>31</sup>
<b>Location</b>	EU (incl. UK) and USA
<b>Design</b>	Randomized, Double-Blind, Placebo-Controlled, Parallel Assignment, Multicentre.
<b>Participants</b>	n=120 (planned); aged 18 years and older; males and females; GIST; D842V mutation in the PDGFRA gene; advanced or metastatic; measurable disease as per modified Response Evaluation Criteria In Solid Tumors (RECIST) 1.1; female subjects with reproductive potential must have negative serum or urine pregnancy test; Eastern Cooperative Oncology Group (ECOG) performance status of $\leq 2$ .
<b>Schedule</b>	Randomised in a 2:1 ratio to crenolanib 100 mg orally 3 times daily; or matching placebo orally 3 times daily; both in combination with best supportive care.
<b>Follow-up</b>	Active treatment period: not reported. Follow-up: up to 3 years.
<b>Primary Outcomes</b>	Progression-free survival (PFS) will be measured from the date of randomisation to the date of the first objective radiological disease progression according to centralised committee assessment using modified RECIST version 1.1 or death. [ Time Frame: 3 years ]
<b>Secondary Outcomes</b>	Overall survival (OS) will be measured from the date of randomization to the date of death from any cause. OS will be estimated using the Kaplan-Meier method. [ Time Frame: 3 years]
<b>Key Results</b>	-
<b>Adverse effects (AEs)</b>	-
<b>Expected reporting date</b>	Study completion date reported as August 2019.

<b>Trial</b>	<b>NCT01243346; crenolanib; phase II.</b>
<b>Sponsor</b>	Arog Pharmaceuticals, Inc.
<b>Status</b>	Study complete but unpublished.
<b>Source of Information</b>	Abstract, <sup>32</sup> trial registry <sup>1</sup>
<b>Location</b>	USA
<b>Design</b>	Non-randomised, Single Group Assignment, Open Label
<b>Participants</b>	n=20; aged 18 years and older; males or females; any racial or ethnic group; histologically or cytologically confirmed GIST with a D842-related mutation or deletion on the PDGFRA gene; life expectancy of greater than 12 weeks; normal liver function, defined as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 2.5x$ upper limit of normal (ULN), and Total Bilirubin $\leq$

	2x ULN; total creatinine $\leq$ 1.5x ULN; ECOG Performance Status 0 – 2; measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as $>20$ mm with conventional techniques or as $>10$ mm with spiral computerised tomography (CT) scan; patients must have recovered from any prior therapy and completed the minimum of, either 5 half-lives of prior therapy or 2 weeks must have elapsed since prior treatment.
<b>Schedule</b>	Participants were given crenolanib 200mg Once a day (QD), 340mg (QD), 140mg orally twice daily (BID), or 72 mg/m <sup>2</sup> (TID)
<b>Follow-up</b>	Active treatment period: not reported. Follow-up: 1.5 years.
<b>Primary Outcomes</b>	Overall response rate [ Time Frame: 1.5 years ]
<b>Secondary Outcomes</b>	Progression free survival rate [ Time Frame: 6 months ] Obtain toxicity information [ Time Frame: 1 year] Pharmacokinetic/Pharmacodynamic (PKPD) analysis [ Time Frame: 1 year ]
<b>Key Results</b>	20 patients (12 males, 8 females, median age 61) were enrolled. 16/20 had progressed after prior imatinib (15), sunitinib (7), dasatinib (5), sorafenib (4), nilotinib (2), and regorafenib (2). 16/20 patients had undergone prior partial (14) or total (2) gastrectomy. Only 4 out of 20 patients were Fluorodeoxyglucose (FDG)-avid by a baseline positron emission tomography (PET) scan (PDGFR GIST is typically PET negative). Crenolanib was administered at 200mg Once a day (QD) to the first 9 patients. 4/9 patients were subsequently escalated to 340mg QD. Pharmacokinetics (PK) demonstrated half-life ( $t_{1/2}$ ) of 8.6 hours, suggesting a Twice a day (BID) or Three times a day (TID) schedule would be more optimal to maintain adequate trough crenolanib levels. The next 7 patients were given crenolanib on a 140 BID schedule. 4/7 patients were escalated to an individualized body surface area (BSA) dosing of 73.3 mg/m <sup>2</sup> /TID. 4 additional patients were also treated at the 72 mg/m <sup>2</sup> /TID schedule. 2/16 patients achieved a partial response (PR) while 3/16 patients achieved Stable Disease (SD); clinical benefit rate was 31% (5/16 patients). 7 patients stayed on crenolanib for over 6 months and 1 patient each for 1 year and 2 years. <sup>32</sup>
<b>Adverse effects (AEs)</b>	Grade 3/4 AEs included reversible Liver Function Test (LFTs) elevations (3 patients) and anaemia (3 patients). 1 patient each with pre-existing ascites and pleural effusion developed worsening fluid accumulation in the context of disease progression. Despite prior gastrectomy, crenolanib reached clinically relevant concentration. <sup>32</sup>
<b>Expected reporting date</b>	-

## ESTIMATED COST and IMPACT

### COST

The cost of crenolanib is not yet known.

## IMPACT – SPECULATIVE

### IMPACT ON PATIENTS AND CARERS

- |  |   |
|--|---|
| <input checked="" type="checkbox"/> Reduced mortality/increased length of survival | <input type="checkbox"/> Reduced symptoms or disability |
| <input type="checkbox"/> Other   | <input type="checkbox"/> No impact identified           |

### IMPACT ON HEALTH and SOCIAL CARE SERVICES

- |   |   |
|---|---|
| <input type="checkbox"/> Increased use of existing services   | <input type="checkbox"/> Decreased use of existing services |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services              |
| <input type="checkbox"/> Other                                | <input checked="" type="checkbox"/> None identified         |

### IMPACT ON COSTS and OTHER RESOURCE USE

- |  |   |
|--|---|
| <input checked="" type="checkbox"/> Increased drug treatment costs | <input type="checkbox"/> Reduced drug treatment costs |
| <input type="checkbox"/> Other increase in costs                   | <input type="checkbox"/> Other reduction in costs     |
| <input type="checkbox"/> Other                                     | <input type="checkbox"/> None identified              |

### OTHER ISSUES

- |   |   |
|---|---|
| <input type="checkbox"/> Clinical uncertainty or other research question identified | <input checked="" type="checkbox"/> None identified |
|---|---|

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