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HEALTH TECHNOLOGY BRIEFING
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Ozanimod for moderate to severe ulcerative colitis

NIHRIO ID	8531	**NICE ID**	9682
Developer/Company	Celgene Ltd	**UKPS ID**	646081

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

SUMMARY

Ozanimod is currently in clinical development for adult patients with moderate to severe ulcerative colitis (UC). Ulcerative colitis is a long-term condition where the colon and rectum (parts of the bowel), become inflamed. Small ulcers can develop on the colon's lining, which can cause rectal bleeding and recurring diarrhoea. The symptoms of ulcerative colitis often follow a pattern where individuals with the condition have periods of no symptoms or mild symptoms (remission) followed by periods where their symptoms are particularly troublesome (flare-ups or relapses).

Ozanimod, administered orally, is a new sphingosine 1-phosphate (S1P) receptor modulator. Treatment with S1P modulators is believed to work by interfering with signalling pathways that contribute to tissue inflammation. If licensed, ozanimod will offer an additional treatment option for adult patients with moderate to severe UC who have had an inadequate response, lost response to, or were intolerant to conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist. In one phase II clinical trial, ozanimod at a daily dose of 1mg resulted in a slightly higher rate of clinical remission of ulcerative colitis than placebo.

PROPOSED INDICATION

Treatment for adult patients with moderate to severe ulcerative colitis (UC) who have had an inadequate response, lost response to, or were intolerant to conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.[1a]

TECHNOLOGY

DESCRIPTION

Ozanimod (Zeposia[2], RPC1063) is a potent sphingosine-1-phosphate receptor-1 (S1P1) and receptor-5 (S1P5) agonist with autoimmune disease-modifying activity. Sphingosine1-phosphate (S1P) receptors mediate multiple events including lymphocyte trafficking, cardiac function, and endothelial barrier integrity.[3] Ozanimod binds to special locations (or receptors) on the surface of the lymphocytes, called sphingosine-1-phosphate receptors (S1P-R). This causes a larger proportion of lymphocytes to be retained in the lymph glands. The number of activated lymphocytes reaching the brain is decreased, resulting in reduced immune attack on nerve cells in the brain and spinal cord.[2] Pharmacological activation of $S1P_{R1}$ results in selective and reversible sequestration of C-C chemokine receptor type 7 $(CCR7)^{+}$ lymphocyte subsets in peripheral lymphoid tissue. This sequestration prevents migration of autoreactive lymphocytes to areas of inflammation. Agonism of $S1P_{R1}$ has recently been shown to modulate IFN alpha (IFNα) signaling, a critical inflammatory driver in autoimmune diseases.[4]

Ozanimod is currently in clinical development for adult patients with moderate to severe UC who have had inadequate response, lost response to, or were intolerant to conventional therapy or a TNFα antagonist. In the phase III clinical trials (NCT02435992; NCT02531126), 1mg of ozanimod is administered orally to patients once daily during induction and maintenance period and compared to a placebo.[1,5]

INNOVATION AND/OR ADVANTAGES

Ozanimod is a new oral selective S1P1 and S1P5 receptor modulator that is under investigation for the treatment of UC. The S1P receptor family consists of widely expressed receptors (S1P1 through S1P5) that are implicated in regulating multiple immunological and cardiovascular functions such as cell proliferation and migration, immune cell tracking, angiogenesis and the epithelial barrier. Targeting S1P receptors for inflammatory conditions was successful in several clinical trials.[6]

Ozanimod is currently in clinical development for the treatment of moderate to severe ulcerative colitis. In phase II (TOUCHSTONE, NCT01647516) and phase III (NCT02435992, NCT02531126) clinical trials, participants received a daily dose of 1mg of ozanimod orally.[1,5,7] According to results from the phase II clinical trial, ozanimod resulted in a slightly higher rate of clinical remission of ulcerative colitis than placebo.[7,8]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Ozanimod has Marketing Authorisation in the EU for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features.[2]

[a] Information provided by Celgene Ltd on UK PharmaScan

The most common side effects associated with treatment with ozanimod are nasopharyngitis (inflammation of the nose and throat), which may affect more than 1 in 10 people, and increased levels of liver enzymes (a sign of liver problems), which may affect up to1 in 10 people; around 1 person in 100 had to stop treatment during the studies because of serious increases in liver enzyme levels.[2]

Ozanimod is currently in phase II/III clinical development for Crohn's disease, multiple sclerosis and COVID-19.[9]

PATIENT GROUP

DISEASE BACKGROUND

Ulcerative colitis (UC), one of the two main forms of Inflammatory Bowel Disease (IBD), is a chronic, relapsing-remitting, non-infectious inflammatory disease of the gastrointestinal tract that causes inflammation and ulceration of the inner lining of the colon and rectum.[10,11] It is characterized by diffuse, continuous, superficial inflammation of the large bowel limited to the intestinal mucosa, and usually affects the rectum with a variable length of the colon involved proximally.[11] The exact pathophysiology of UC is unknown but it is thought to be multifactorial involving epithelial barrier defects, dysregulated immune responses and environmental factors in genetically susceptible people.[12] UC tends to run in families with 8-14% of patients with the disease having a family history of IBDs and first degree relatives have four times the risk of developing the disease.[12]

The main symptoms of UC are recurring diarrhoea which may contain blood, mucus or pus, abdominal cramping and frequently needing to empty bowels. Patients may also experience extreme tiredness, loss of appetite and weight loss.[13] Extra-intestinal manifestations such as arthritis, mouth ulcers, uveitis and primary sclerosing cholangitis may also be present during a flare-up of UC.[13,14] These extra-intestinal manifestations can have a severe impact on the patient's quality of life with significant mental health problems, including depression. Patients can develop professional and social constraints that interfere with their work and recreational activities. [15]

The severity of the symptoms will depend on how much of the rectum and colon is inflamed and how severe the inflammation is.[13] Severity is classified as mild, moderate or severe by using the Truelove and Witts' severity index, which assesses bowel movements, heart rate, erythrocyte sedimentation rate and the presence of melaena, pyrexia or anaemia.[16] Patients often follow a remission then relapse cycle where they go for weeks or months experiencing none or very mild symptoms (remission) before they experience a flare-up where their symptoms are particularly troublesome (relapse).[13]

UC is a lifelong disease associated with significant morbidity, and the potential for social and psychological sequelae particularly if poorly controlled.[17]

CLINICAL NEED AND BURDEN OF DISEASE

It is estimated that 1 in every 420 people living in the UK is affected by UC which amounts to around 146,000 people with a diagnosis UC has an incidence of 10 per 100,000 annually and a prevalence of 242 per 100,000.[17]

The condition can develop at any age, but is most often diagnosed in people aged from 15 to 25 and between 55 and 65 years.[17] It affects both men and women equally. UC is more

common in white people of European descent, especially those of Ashkenazi Jewish descent, and black people.[10,13] Although UC usually has a mild to moderate course, approximately 20%-25% of patients suffer at least one severe acute attack, requiring hospitalisation.[6] An estimated 30-60% of people with UC will have at least one relapse per year, with 80% of these classified as mild to moderate and 20% classified as severe.[18]

According to hospital episode statistics for England in 2018-19 there were a total of 103,050 finished consultant episodes for ulcerative colitis (ICD-10 code K51) recorded as primary diagnosis of which 91,021 were recorded as admissions with a total of 79,830 day cases.[19]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There are no curative therapies for inflammatory and autoimmune diseases like UC.[13] The British Society of Gastroenterology (BSG) guideline states that people with IBD should be cared for by a defined multidisciplinary team including gastroenterologists, colorectal surgeons, nurse specialists, a dietitian, pharmacist, and gastrointestinal radiologist. This should allow for early initiation of appropriate therapy and ongoing assessment of disease progress and any adverse effects of treatment.[20,21]

For those with moderate to severe UC, most treatment options are pharmacological. Colectomy (with the creation of either an ileostomy or an ileo-anal pouch) is a surgical treatment option for some patients, to improve the quality of life in chronic or treatment-refractory active disease or to treat cancer or pre-cancerous changes.[22]

CURRENT TREATMENT OPTIONS

Treatment for UC depends on how severe the condition is and how often your symptoms flare-up.[13] In the UK, NICE currently recommends the following treatment options for moderate to severe UC:[23]

Tofacitinib

- Tofacitinib is recommended, within its marketing authorisation, as an option for treating moderately to severely active ulcerative colitis in adults when conventional therapy or a biological agent cannot be tolerated or the disease has responded inadequately or lost response to treatment. It is recommended only if the company provides tofacitinib with the discount agreed in the commercial arrangement.

Vedolizumab

- Vedolizumab is recommended, within its marketing authorisation, as an option for treating moderately to severely active ulcerative colitis in adults only if the company provides vedolizumab with the discount agreed in the patient access scheme.
- Vedolizumab should be given until it stops working or surgery is needed. At 12 months after the start of treatment, people should be reassessed to see whether treatment should continue. Treatment should only continue if there is clear evidence of ongoing clinical benefit. For people in complete remission at 12 months, consider stopping vedolizumab, then resuming treatment if there is a relapse. People who continue vedolizumab should be reassessed at least every 12 months to see whether continued treatment is justified.

Infliximab, adalimumab and golimumab

- Infliximab, adalimumab and golimumab are recommended, within their marketing authorisations, as options for treating moderately to severely active ulcerative colitis in adults whose disease has responded inadequately to conventional therapy including

corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies.

- Golimumab is recommended only if the company provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, as agreed in the patient access scheme.
- The choice of treatment between infliximab, adalimumab or golimumab should be made on an individual basis after discussion between the responsible clinician and the patient about the advantages and disadvantages of the treatments available. This should take into consideration therapeutic need and whether or not the patient is likely to adhere to treatment. If more than 1 treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage and price per dose).
- Infliximab is recommended, within its marketing authorisation, as an option for treating severely active ulcerative colitis in children and young people aged 6–17 years whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies.
- Infliximab, adalimumab or golimumab should be given as a planned course of treatment until treatment fails (including the need for surgery) or until 12 months after starting treatment, whichever is shorter. Specialists should then discuss the risks and benefits of continued treatment with the patient, and their parent or carer if appropriate.
- They should continue treatment only if there is clear evidence of response as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. People who continue treatment should be reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate.
- They should consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People whose disease relapses after treatment is stopped should have the option to start treatment again.

Budesonide multimatrix

- NICE has published an evidence summary on the use of budesonide multimatrix for the treatment of UC.

PLACE OF TECHNOLOGY

If licensed, ozanimod will offer an additional treatment option for adult patients with moderate to severe UC who have had an inadequate response, lost response to, or were intolerant to conventional therapy or a TNFα antagonist.

CLINICAL TRIAL SUMMARY INFORMATION

Trial	NCT02435992, **RPC01-3101,** EudraCT: 2015-000319-41; A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Oral RPC1063 as Induction and Maintenance Therapy for Moderate to Severe Ulcerative Colitis **Phase III** **Location(s):** EU (incl UK), USA, Canada and other countries	NCT02531126, **RPC01-3102,** EudraCT: 2015-001600-64, WHO UTN: U1111-1218-0284; A Phase 3, Multicenter, Open-Label Extension Trial of Oral RPC1063 as Therapy for Moderate to Severe Ulcerative Colitis **Phase III extension** **Location(s):** EU (incl UK), USA, Canada and other countries
Trial design	Randomized, parallel assignment, quadruple-blinded	Single group assignment, open label
Population	N=1,012 (actual); adults aged 18 to 75 years (at screening for Cohort 1	N=890 (estimated); adults aged 18 to 75 years with (at screening for

	and 2), male or female adolescent patients aged 12 to <18 (at screening) with a body weight greater than or equal to 45kg with: • UC confirmed on endoscopy, • Moderately to severely active UC (May score 6-12), • Currently receiving treatment with aminosalisylate, prednisone, or budesonide, and • Can be receiving azathioprine, mercaptopurine, or methotrexate, but treatment will be stopped prior to randomization.	Cohort 1 and 2), male or female adolescent patients aged 12 to <18 (at screening) with a body weight greater than or equal to 45kg with (Cohort 3): • UC confirmed on endoscopy, moderately to severely active UC (May score 6-12), • Currently receiving treatment with aminosalisylate, prednisone, or budesonide, and • Can be receiving azathioprine, mercaptopurine, or methotrexate, but treatment will be stopped prior to randomization.
Intervention(s)	1mg of ozanimod daily oral administration during Induction and maintenance periods	1mg of ozanimod
Comparator(s)	Matched placebo - daily oral administration during Induction and Maintenance periods	No comparator
Outcome(s)	Primary outcomes: • Clinical Remission assessed by Mayo component sub-scores {Time frame: Week 10] – Induction Period • Clinical remission assessed by Mayo component sub-scores [Time frame: Weeks 52] – Maintenance Period	Primary outcomes: • Evaluate the long-term safety of ozanimod for the treatment of all patients with moderate to severe UC [Time frame: Up to 6 years] • Evaluate the long-term efficacy of ozanimod for the treatment of adult patients with moderate to severe UC [Time frame: Up to 6 years]
Results (efficacy)	-	-
Results (safety)	-	-

ESTIMATED COST

The cost of ozanimod is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal proposed. Filgotinib for treating moderately to severely active ulcerative colitis (ID3736). Expected date of issue to be confirmed.

- NICE technology appraisal in development. Ustekinumab for treating moderately to severely active ulcerative colitis (ID1511). Expected date of issue to be confirmed.
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- NICE technology appraisal. Adalimumab for the treatment of moderate to severe ulcerative colitis (TA262). July 2012.
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- NICE quality standard. Inflammatory bowel disease (QS81). February 2015.
- NICE diagnostics guidance. Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel (DG11). October 2013.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Colorectal: Complex Inflammatory Bowel Disease (Adult). A08/S/c.

OTHER GUIDANCE

- British Society of Gastroenterology. Consensus guidelines on the management of inflammatory bowel diseases in adults. 2019. [21]
- European Federation of Crohn's and Ulcerative Colitis Association (EFCCA). ECCO-EFCCA Patient Guidelines on Ulcerative Colitis (UC). 2014. [24]

ADDITIONAL INFORMATION

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