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Newcastle University

Health Technology Briefing
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Etrasimod for treating moderately to severely active ulcerative colitis

Company/Developer	Arena Pharmaceuticals Inc.

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 11429	NICE ID: 10656	UKPS ID: 661090

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Etrasimod is in clinical development for the treatment of moderately to severely active ulcerative colitis. Ulcerative colitis is one of two major types of inflammatory bowel disease (IBD). It is a long-term immune-mediated inflammatory disorder where the colon and rectum become inflamed and small ulcers can develop on the colon's lining, which can cause rectal bleeding and recurring diarrhoea. The main aims of treatment are to reduce symptoms, known as inducing remission, and maintaining remission. Current ulcerative colitis treatment options have relatively low remission rates and/or are associated with loss of response over time and possible adverse side effects. In addition, despite the advent of novel treatments, 10-15% of patients still require a colectomy (surgical removal of all or part of the colon). Therefore, there is a significant unmet need to develop new medicinal products for ulcerative colitis that are more effective and are associated with fewer adverse effects.

Etrasimod, administered orally, is a highly selective sphingosine 1-phosphate (S1P) receptor modulator. S1P is involved in the regulation of multiple physiologic and pathophysiologic processes and S1P receptor modulators have been explored as therapies for immune-mediated diseases as they can be used to modulate immune responses. It is thought that because etrasimod is more selective than other S1P receptor modulators, such as fingolimod, it may show fewer adverse effects. If licenced, etrasimod would offer an additional treatment option for those with moderately to severely active ulcerative colitis.

Proposed Indication

For treating moderately to severely active ulcerative colitis.[1]

Technology

Description

Etrasimod (APD334) is a highly selective sphingosine 1-phosphate $S1P_1$, $S1P_4$, and $S1P_5$ receptor modulator. S1P is involved in the regulation of multiple physiologic and pathophysiologic processes and S1P receptor modulators have been explored as therapies for immune-mediated diseases.[2] The function of each receptor is highly dependent on the cell type on which it is expressed. $S1P_1$ expression on lymphocytes plays a key role in lymphocyte trafficking by regulating lymphocyte egress from lymphoid organs, $S1P_4$ may play a role in dendritic cell trafficking and function, and $S1P_5$ has been implicated in regulation of natural killer cell trafficking.[1] A key role of S1P in innate and adaptive immunity is regulation of lymphocyte trafficking, T helper 17 cell polarization, dendritic cell differentiation, and natural killer cell migration.[2,3] Upon binding to S1P, synthetic modulators including etrasimod, induce and sustain receptor internalization.[3] Loss of cell surface–expressed S1P prevents cells from migrating along S1P gradients and results in retention of lymphocytes within lymphoid tissue and subsequent reduction of lymphocyte accumulation in peripheral tissues.[2,4] This results in modulation of immune responses.[4]

Etrasimod is currently in phase III clinical development for the treatment of moderately to severely active ulcerative colitis.[1,5] In the phase III clinical trials (NCT03945188 and NCT03950232), participants receive a 2mg etrasimod tablet taken orally once daily.[1,5]

Key Innovation

Current ulcerative colitis treatment options have relatively low remission rates and/or are associated with loss of response over time and possible adverse side effects.[6] In addition, despite the advent of novel treatments, 10-15% of patients still require a colectomy.[6] Therefore there is a significant unmet need to develop new medicinal products for ulcerative colitis.[6] Etrasimod is a once daily oral, highly selective sphingosine 1-phosphate $S1P_1$, $S1P_4$, and $S1P_5$ receptor modulator. There are currently no S1P receptor modulators recommended by the National Institute for Health and Care Excellence (NICE) for the treatment of moderately to severely active ulcerative colitis.[7] More selective S1P receptor modulators in clinical development have demonstrated improved clinical safety profiles compared with fingolimod, a non-selective S1P receptor modulator. In this regard, the receptor-binding profile of etrasimod should theoretically avoid some of the adverse effects with fingolimod associated with modulation of these receptors, while simultaneously decreasing intestinal inflammation.[2,8]

Regulatory & Development Status

Etrasimod does not currently have Marketing Authorisation in the EU/UK for any indication.

Etrasimod is currently in phase II/III clinical trials for the treatment of:[9,10]

- Crohn's disease
- Atopic dermatitis
- Eosinophilic esophagitis
- Alopecia areata

Patient Group

Disease Area and Clinical Need

Ulcerative colitis is one of two major types of inflammatory bowel disease (IBD), the other condition being Crohn's disease.[11] It is a long-term condition where the colon and rectum become inflamed and small ulcers can develop on the colon's lining, which can bleed and produce pus. Some people may go for weeks or months with very mild symptoms, or none at all, known as remission, followed by periods where the symptoms are particularly troublesome, known as flare-ups or relapses.[12] Symptoms of active disease or relapse include bloody diarrhoea, an urgent need to defecate, tiredness and abdominal pain. [12,13] The exact cause of ulcerative colitis is unknown, although it's thought to be the result of a problem with the immune system. Many experts believe ulcerative colitis is the result of an autoimmune condition whereby the immune system mistakes bacteria in the colon which aids digestion, for a harmful infection. This causes the immune system to attack healthy tissue and leads to the colon and rectum becoming inflamed.[14] It is also believed that inherited genes are a factor in the development of ulcerative colitis, and certain environmental factors such as viral and bacterial infection, air pollution, medication and diet may be potential triggers.[11,14]

Ulcerative colitis is the most common type of IBD.[13] It is estimated that ulcerative colitis affects about one in every 420 people in the UK and that around 146,000 people in England have ulcerative colitis, of whom about 52% have moderate to severe disease.[15,16] It can develop at any age, but peak incidence is between the ages of 15 and 25 years, with a second, smaller peak between 55 and 65 years.[16] According to hospital episode statistics for England in 2020-21 there were a total of 109,967 finished consultant episodes (FCEs) where ulcerative colitis (ICD-10 code K51) was recorded as primary diagnosis, which resulted in 98,926 admissions and 88,128 day cases.[17]

Recommended Treatment Options

The main aims of treatment are to reduce symptoms, known as inducing remission, and maintain remission. This usually involves taking various types of medicine, although surgery may sometimes be an option.[18] First-line treatment usually involves a topical or oral aminosalicylate, or an oral corticosteroid.[18,19]

In the UK, NICE currently recommends the following treatment options for moderate to severe ulcerative colitis when conventional therapy or a biological agent cannot be tolerated, or the disease has responded inadequately or lost response to treatment:[7]

- Ustekinumab
- Tofacitinib
- Vedolizumab
- Infliximab, adalimumab, golimumab

Clinical Trial Information

Trial	NCT02447302; 2015-001942-28; A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multi-Center Study to Investigate the Safety and Efficacy of APD334 in Patients With Moderately to Severely Active Ulcerative Colitis	NCT02536404; Extension Study of APD334-003 in Patients With Moderately to Severely Active Ulcerative Colitis **Phase II** - Completed **Locations:** 12 EU countries, UK, USA, Canada and other countries

	Phase II - Completed **Locations:** 12 EU countries, UK, USA, Canada and other countries **Study completion date:** February 2018	**Study completion date:** November 2018
Trial Design	Randomised, placebo-controlled, parallel assignment, triple-blind (Participant, Care Provider, Investigator)	Single group assignment, open label
Population	N=156; Subjects with moderately to severely active ulcerative colitis; aged 18 to 80 years old.	N=118; Subjects who completed study NCT02447302; subjects with moderately to severely active ulcerative colitis; aged 18 to 80 years old.
Intervention(s)	Etrasimod (oral tablet)	Etrasimod (oral tablet)
Comparator(s)	Placebo (oral tablet)	Placebo (oral tablet)
Outcome(s)	Primary outcome: Change from baseline in adapted Mayo Score (MCS) at week 12 [Time frame: Baseline and week 12] See trial record for full list of other outcomes	Primary outcome: Number of participants with treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (SAEs) [Time frame: Up to week 48 (up to 30 days following discontinuation of the study drug)] See trial record for full list of other outcomes
Results (efficacy)	See trial record	See trial record
Results (safety)	See trial record	See trial record

Trial	**ELEVATE UC 12,** NCT03996369, 2018-003986-33**;** A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 12-Week Study to Assess the Efficacy and Safety of Etrasimod in Subjects With Moderately to Severely Active Ulcerative Colitis **Phase III** – Completed **Locations:** 18 EU countries, UK, USA, Canada and other countries **Study completion date:** December 2021
Trial Design	Randomised, placebo-controlled, parallel assignment, triple-blind (Participant, Care Provider, Investigator)
Population	N=354; Subjects diagnosed with ulcerative colitis; aged 16 to 80 years old.
Intervention(s)	Etrasimod 2mg (oral tablet)
Comparator(s)	Placebo (oral tablet)

Outcome(s)	Primary outcome: Proportion of participants achieving clinical remission assessed by Mayo component sub-scores [Time frame: week 12] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**ELEVATE UC 52, NCT03945188; 2018-003985-15;** A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Assess the Efficacy and Safety of Etrasimod in Subjects With Moderately to Severely Active Ulcerative Colitis **Phase III** – Active, not recruiting **Locations:** 19 EU countries, UK, USA, Canada and other countries **Primary completion date:** January 2022	**ELEVATE UC OLE, NCT03950232; 2018-003987-29;** An Open-Label Extension Study of Etrasimod in Subjects With Moderately to Severely Active Ulcerative Colitis **Phase III** - Recruiting **Locations:** 19 EU countries, UK, USA, Canada and other countries **Primary completion date:** August 2027
Trial Design	Randomised, parallel assignment, double-blind (Participant, Investigator), placebo-controlled	Single group assignment, open label
Population	N=433; Subjects diagnosed with ulcerative colitis; aged 16 to 80 years old.	N=912; Subjects who were previously enrolled in NCT03945188, NCT04607837 or NCT03996369; subjects diagnosis of ulcerative colitis; aged 16 to 80 years old.
Intervention(s)	Etrasimod 2mg (oral tablet)	Etrasimod 2mg (oral tablet)
Comparator(s)	Placebo (oral tablet)	No comparator
Outcome(s)	Primary outcomes: • Proportion of participants achieving clinical remission assessed by mayo component sub-scores [Time frame: week 12] • Proportion of participants achieving clinical remission assessed by Mayo component sub-scores [Time Frame: Week 52] See trial record for full list of other outcomes	Primary outcome: Number and severity of safety measures [Time frame: Up to approximately 5 years] Safety as assessed by the evaluation of adverse events See trial record for full list of other outcomes

Results (efficacy)	-	-
Results (safety)	-	-

Trial	**GLADIATOR UC; NCT04607837; 2020-003507-34;** A Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Assess the Efficacy and Safety of Etrasimod in Subjects With Moderately Active Ulcerative Colitis **Phase II** - Recruiting **Locations:** 10 EU countries, USA, Canada and other countries **Primary completion date:** May 2023
Trial Design	Randomised, parallel assignment, double-blind (Participant, Investigator), placebo-controlled
Population	N=162; Subjects with moderately active ulcerative colitis; aged 18 to 80 years old.
Intervention(s)	Etrasimod 2mg (oral tablet)
Comparator(s)	Placebo (oral tablet)
Outcome(s)	Primary outcome: Proportion of participants achieving clinical remission as assessed by total MCS [Time frame: Week 12] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of etrasimod was confidential at the time of producing this briefing.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Mirikizumab for previously treated moderately to severely active ulcerative colitis (GID-TA10872). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Upadacitinib for treating moderately to severely active ulcerative colitis (GID-TA10866). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Etrolizumab for treating moderately to severely active ulcerative colitis (GID-TA10717). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Ozanimod for treating moderately to severely active ulcerative colitis (GID-TA10732). Expected September 2022.
- NICE technology appraisal in development. Filgotinib for treating moderately to severely active ulcerative colitis (GID-TA10600). Expected June 2022.
- NICE technology appraisal. Ustekinumab for treating moderately to severely active ulcerative colitis (TA633). June 2020.
- NICE technology appraisal. Tofacitinib for moderately to severely active ulcerative colitis (TA547). November 2018.

- NICE technology appraisal. Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (TA329). February 2015.
- NICE technology appraisal. Infliximab for acute exacerbations of ulcerative colitis (TA163). December 2008.
- NICE guideline. Ulcerative colitis: management (NG130). May 2019.
- NICE quality standard. Inflammatory bowel disease (QS81). February 2015.
- NICE evidence summary. Remsima (infliximab biosimilar) for subcutaneous injection for managing Crohn's disease and ulcerative colitis (ES35). February 2021.

NHS England (Policy/Commissioning) Guidance

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

Other Guidance

- European Crohn's and Colitis Organisation (ECCO). ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment. 2021.[20]
- NICE Clinical Knowledge Summary. Ulcerative Colitis. 2020.[21]
- British Society of Gastroenterology. BSG consensus guidelines on the management of Inflammatory Bowel Disease in adults. 2019.[22]

Additional Information

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