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HEALTH TECHNOLOGY BRIEFING
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Risankiziumab for moderate to severe crohn's disease

NIHRIO ID	9706	**NICE ID**	10309
Developer/Company	AbbVie	**UKPS ID**	648129

Licensing and market availability plans	Currently in phase III clinical trials

SUMMARY

Risankizumab is in development as a treatment option for moderate to severe Crohn's disease (CD). CD is a type of inflammatory bowel disease which can affect any part of the digestive system. CD causes inflammation and ulceration, which affects food digestion, nutrient absorption, and waste elimination. Symptoms include abdominal pain, diarrhoea, weight loss and fatigue. There is no cure for CD so treatment options focus on managing and relieving symptoms. Patients may have periods of time when they are not suffering from symptoms (remission) or have flare-ups of symptoms (relapses). Additional treatments are required for CD as some patients don't respond to initial therapy.

Risankizumab is in development as a subcutaneous maintenance injection with intravenous induction for moderate to severe CD. It is a man-made protein that acts like antibodies within the human immune system. It specifically binds to a particular cytokine which prevents activation of the immune system which subsequently reduces inflammation. This drug is innovative as it binds to a novel target. If licensed, risankizumab will offer an additional treatment for patients with CD.

PROPOSED INDICATION

Treatment of patients with moderately to severely active Crohn's disease (CD).[1-3]

TECHNOLOGY

DESCRIPTION

Risankizumab (Skyrizi; BI-655066; ABBV066) is a humanised immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds with high affinity to the p19 subunit of human interleukin 23 (IL-23) cytokine without binding to IL-12 and inhibits its interaction with the IL-23 receptor complex. IL-23 is a cytokine that is involved in inflammatory and immune responses. By blocking IL-23 from binding to its receptor, risankizumab inhibits IL-23-dependent cell signalling and release of proinflammatory cytokines.[4] IL-23 plays a key part in the induction and function of immune cells, including T-helper 17 cells, innate lymphoid cells, γδ T-cells, and natural killer cells, which are responsible for tissue inflammation, destruction, and aberrant tissue repair that underlies the pathology of several immune-related disorders, including CD.[5]

Risankizumab is currently in phase III clinical trials. In these trials, risankizumab was administered as an intravenous induction dose of 600mg or 1200mg; with a maintenance dose of 180mg or 360mg.[1-3,6,7]

INNOVATION AND/OR ADVANTAGES

Risankizumab is the first biological therapy for CD that specifically targets the p19 subunit of IL-23. This selectivity prevents effects on the IL12 cytokine axis (via p40), which could potentially affect IL-12's role in tumour surveillance and in host defence against intracellular pathogens.[5,8]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Risankizumab has Marketing Authorisation in the EU/UK for moderate-to-severe plaque psoriasis.[4]

Risankizumab is currently in clinical development in phase II/III trials for several indications including plaque psoriasis in children, psoriatic arthritis and ulcerative colitis.[9]

Very common side effects (⩾ 1/10) include respiratory tract infection (viral, bacterial or unspecified), sinusitis (including acute), rhinitis, nasopharyngitis, pharyngitis (including viral) and tonsillitis.[4]

PATIENT GROUP

DISEASE BACKGROUND

Inflammatory bowel disease (IBD) is an umbrella term for describing long-term conditions that involve inflammation of the digestive system: ulcerative colitis (UC) and CD. These two conditions are separated in terms of the location of inflammation, with UC only affecting the colon (large intestine), whereas CD can affect any part of the digestive system.[10]

CD causes inflammation and ulceration, which affects food digestion, nutrient absorption, and waste elimination. CD most often develops in the ileum (the end of the small intestine) or the colon, and can produce inflamed patches with healthy gut in between. There is no cure for CD so treatment options focus on managing and relieving symptoms. Patients may have periods of time when they are not suffering from symptoms (remission), or have flare-ups of symptoms (relapses).[11]

Main symptoms of CD are abdominal pain, diarrhoea, weight loss and fatigue. Other symptoms include high temperatures and feverishness, mouth ulcers, anaemia (reduced red blood cells), generally feeling unwell, vomiting, joint pains, sore eyes, and patches of painful, red and swollen skin.[11,12] CD can sometimes cause other associated issues such as strictures (healing and scarring that narrows the tract), perforations (holes in the tract wall) and fistulas (a tunnel between the gut and skin/another organ).[11] Mild to moderate CD symptoms are characterised by diarrhoea and abdominal pain, whereas moderate to severe include intermitted vomiting, abdominal pain, >10% weight loss and abdominal mass without overt obstruction. Very severe CD includes persistent symptoms despite appropriate treatment, high fever, persistent vomiting and evidence of intestinal obstruction or abscesses.[13]

CD can occur in all age groups however it usually develops between the ages of 10 and 40 years old. CD is more common in urban areas, and in northern, developed countries such as Northern Europe, particularly amongst white people of European descent. CD is more common in smokers, and slightly more common in women than men.[14] The exact cause of CD is unknown but there are several factors that could contribute to its development, including: inheritance (people are more likely to get CD if a close family member has it), immune response issues, smoking, gut viruses, abnormal balance of gut bacteria, and stress.[11]

CLINICAL NEED AND BURDEN OF DISEASE

It is estimated that CD affects about one in every 650 people in the UK.[14] The annual cost for any patient with CD was estimated to be £6,156 (£1,800 for patients in remission; £10,513 for patients in relapse).[15]

In England, 2019-20, there were 139,303 finished consultant episodes (FCE) for patients with a primary diagnosis of CD (ICD-10 code K50) resulting in 90,148 FCE bed days and 114,365 day cases.[16]

In the UK, in 2017, the prevalence of CD was 400 per 100,000. CD has increased over the past two decades at a rate of 2-3% per annum and is predicted to reach a prevalence of 487.2 per 100,000 by 2025. CD is also associated with an increased risk of all-cause mortality.[17]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The aims of CD treatment are to achieve remission, maintain remission and control inflammation.[18] Options include steroids, liquid diet, antibiotics, immunosuppressants, anti-inflammatories, biological medicines and surgery.[18,19]

CURRENT TREATMENT OPTIONS

Pharmacological treatment options for CD are as follows:[18-20]

- Anti-inflammatories, such as sulfasalazine, mesalamine and olsalazine
- Steroids, such as prednisolone

- Immunosuppressants, such as azathioprine, mercaptopurine and methotrexate
- Biological medicines, such as adalimumab, infliximab, vedolizumab and ustekinumab
- Antibiotics, such as metronidazole and ciprofloxacin

PLACE OF TECHNOLOGY

If licensed, risankizumab will offer an additional treatment for patients with moderate to severe CD.

CLINICAL TRIAL INFORMATION

Trial	**FORTIFY;** NCT03105102; 2016-003191-50; A Multicenter, Randomized, Double-Blind, Placebo Controlled 52-Week Maintenance and an Open-Label Extension Study of the Efficacy and Safety of Risankizumab in Subjects With Crohn's Disease **Phase III** – active, not recruiting **Location(s):** 21 EU countries, UK, US, Canada, plus other countries **Primary completion date:** June 2026
Trial design	Randomised, parallel assignment, quadruple-blinded, placebo-controlled
Population	N=~1250; 16 to 80 years old; participants who have entered and completed Study M16-006 or Study M15-991 or other AbbVie risankizumab Crohn's disease study
Intervention(s)	Risankizumab 180 or 360 mg subcutaneous; administered every eight weeks.[6]
Comparator(s)	Matched placebo
Outcome(s)	• Sub-Study -1 and 2: Percentage of Participants with Crohn's Disease Activity Index (CDAI) Clinical Remission [Time Frame: Week 52] • Sub-Study 1 and 2: Percentage of Participants with Endoscopic Response [Time Frame: Week 52] • Sub-Study 3: Number of Participants with Adverse Events [Time Frame: Up to Week 220] • Sub-Study 4: Percentage of Participants with an Observer Rating of Successful Participant Self Administration [Time Frame: Up to Week 16] • Sub-Study 4: Percentage of Participants who had no Potential Hazards [Time Frame: Up to Week 16] • Sub-Study 4: Percentage of Participants Rating of Acceptability Using Self-Injection Assessment Questionnaire (SIAQ) at Weeks 0, 8, 16 [Time Frame: Up to Week 16] • Sub-Study 4: Percentage of Participants in CDAI Clinical Remission at Week 0, 16 [Time Frame: Up to Week 16] See trial record for full list of other outcomes
Results (efficacy)	Results from Sub-Study 1: • After one year, 47 percent of patients receiving risankizumab 360 mg achieved endoscopic response

	compared with 22 percent of patients in the induction-only control group (p<0.001). Significantly more patients receiving risankizumab 360 mg achieved clinical remission (CDAI; U.S. analysis plan), with 52 percent on risankizumab 360 mg achieving clinical remission versus 41 percent in the induction-only control group (p<0.01). Results also showed that 52 percent of patients receiving risankizumab 360 mg achieved clinical remission (SF/AP; per outside of the US (OUS) analysis plan) compared to 40 percent in the induction-only control group (p=0.004). In addition, 39 percent of patients receiving risankizumab 360 mg achieved endoscopic remission compared to 13 percent of patients in the induction-only control group (nominal p<0.001). Furthermore, 29 percent of risankizumab 360 mg-treated patients achieved deep remission compared to 10 percent in the induction-only control group (nominal p<0.001). Deep remission is a stringent endpoint defined by clinical remission (CDAI) and endoscopic remission, both measured in the same patient. • Risankizumab 180 mg met the co-primary endpoints in the U.S. analysis plan, but not in the OUS analysis plan. In this study, 47 percent of patients receiving risankizumab 180 mg achieved endoscopic response compared with 22 percent of patients in the induction-only control group (p<0.001 per U.S. analysis plan; nominal p<0.001 per OUS analysis plan). Furthermore, 55 percent of patients receiving risankizumab 180 mg achieved clinical remission (CDAI; U.S. analysis plan) compared to 41 percent of patients in the induction-only control group (p<0.01). Additionally, 46 percent of patients receiving risankizumab 180 mg achieved clinical remission (SF/AP; per OUS analysis plan) compared to 40 percent in the induction-only control group (nominal p=0.124). At one year, 30 percent of patients receiving risankizumab 180 mg achieved endoscopic remission compared to 13 percent of patients in the induction-only control group (nominal p<0.001). Results also showed that 25 percent of risankizumab 180 mg-treated patients achieved deep remission compared to 10 percent in the induction-only control group (nominal p<0.001).[6]
Results (safety)	Results from Sub-Study 1: • No new safety risks were observed. Serious adverse events (SAEs) occurred in 12.3 percent of patients in the risankizumab 180 mg group and 13.4 percent of patients in the risankizumab 360 mg group compared to 12.5 percent of patients in the induction-only control group. The most common adverse events (AEs) observed in the risankizumab treatment groups were exacerbation of Crohn's disease, nasopharyngitis and arthralgia. Rates of serious

	infections were 2.8 percent and 4.5 percent in those treated with risankizumab 180 mg or 360 mg, respectively, and 3.8 percent in the induction-only control group. The rates of AEs leading to discontinuation of the study drug were 1.7 percent and 3.4 percent of patients treated with risankizumab 180 mg and 360 mg, respectively, compared with 3.3 percent in the induction-only control group. There were two adjudicated major adverse cardiovascular events (MACE) reported at the time of database lock. One event occurred in the induction-only control arm and the other occurred in the risankizumab 360 mg arm. Both events were assessed by study investigators to be unrelated to the study drug and both patients had pre-existing risk factors. Both patients continued in the trial. There were no anaphylactic reaction events or deaths reported.[6]

Trial	**MOTIVATE;** NCT03104413; 2016-003190-17; A Multicenter, Randomized, Double-Blind, Placebo-Controlled Induction Study to Assess the Efficacy and Safety of Risankizumab in Subjects With Moderately to Severely Active Crohn's Disease Who Failed Prior Biologic Treatment **Phase III** - completed **Location(s):** 20 EU countries, UK, US, Canada, plus other countries **Study completion date:** May 2021
Trial design	Randomised, parallel assignment, double-blinded
Population	N = 618; 16-80 years old; Confirmed diagnosis of CD for at least 3 months; moderate-to-severe CD defined as CDAI 220 – 450, intolerance or inadequate response to prior biologic therapy plus assessment of stool frequency, abdominal pain score and Simple Endoscopic Score for CD.
Intervention(s)	Patients were randomised to receive either a 600mg or 1200mg risankizumab dose every 4 weeks for 12 weeks intravenously.[7]
Comparator(s)	Matched placebo
Outcome(s)	• Percentage of Participants with Crohn's Disease Activity Index (CDAI) Clinical Remission [Time Frame: Week 12] • Sub-Study 1 and 2 Percentage of Participants with Endoscopic Response [Time Frame: Week 12]. See trial record for full list of other outcomes
Results (efficacy)	Induction period 1 (week 12) results. • In terms of primary endpoints, 42 and 41 percent of patients treated with risankizumab 600 mg or 1200 mg achieved clinical remission (per CDAI) at week 12, respectively, versus 19 percent of patients receiving

	placebo (p<0.001). A significantly greater proportion of patients in MOTIVATE also achieved clinical remission (per PRO-2) (35 and 39 percent of risankizumab 600 mg or 1200 mg-treated patients, respectively, compared to 19 percent of patients receiving placebo; p=0.001 for 600 mg; p<0.001 for 1200 mg). In addition, 29 and 34 percent of patients receiving risankizumab 600 mg or 1200 mg achieved endoscopic response, respectively, versus 11 percent in the placebo group (p<0.001). • Multiplicity-adjusted key secondary endpoints showed significant clinical improvement observed as early as week 4. After 4 weeks of treatment 36 and 33 percent of patients receiving risankizumab 600 mg or 1200 mg achieved clinical response (per CDAI), respectively, compared to 21 percent in the placebo group (p=0.002 for 600 mg; p=0.012 for 1200 mg).[7]
Results (safety)	• Serious Adverse Events (SAEs) occurred in 4.9 percent of patients in the risankizumab 600 mg group and 4.4 percent of patients in the risankizumab 1200 mg group compared to 12.6 percent of patients in the placebo group. The most common AEs observed in the risankizumab treatment groups were headache, arthralgia and nasopharyngitis. Rates of serious infections were 0.5 and 1.0 percent in those treated with risankizumab 600 mg or 1200 mg, respectively, and 2.4 percent in patients who received placebo. The rates of AEs leading to discontinuation of the study drug were 1.0 and 2.4 percent of patients treated with risankizumab 600 mg or 1200 mg, respectively, compared with 8.2 percent on placebo. There was one death in the risankizumab 1200 mg group due to squamous cell carcinoma of the lung diagnosed on study day 8, which was assessed as unrelated to the study drug by the investigator. There were no adjudicated MACE or adjudicated anaphylactic reaction events reported.[7]

Trial	**ADVANCE;** NCT03105128; 2016-003123-32**;** A Multicenter, Randomized, Double-Blind, Placebo Controlled Induction Study of the Efficacy and Safety of Risankizumab in Subjects With Moderately to Severely Active Crohn's Disease **Phase III** - completed **Location(s):** 20 EU countries, UK, US, Canada, plus other countries **Study completion date:** April 2021
Trial design	Randomised, parallel assignment, double-blinded, placebo-controlled
Population	N = 931; 16 to 80 years old; confirmed diagnosis of moderate to severe CD; moderate-to-severe CD defined as CDAI 220 – 450, intolerance or inadequate response to prior biologic

	therapy plus assessment of stool frequency, abdominal pain score and Simple Endoscopic Score for CD.
Intervention(s)	Patients were randomised to receive either a 600mg or 1200mg risankizumab dose every 4 weeks for 12 weeks intravenously.[7]
Comparator(s)	Matched placebo
Outcome(s)	• Percentage of participants with Crohn's Disease Activity Index (CDAI) Clinical Remission [Time Frame: Week 12] • Sub-Study 1 and 2 percentage of participants with Endoscopic Response [Time Frame: Week 12]. See trial record for full list of other outcomes
Results (efficacy)	• A significantly greater proportion of patients treated with risankizumab 600 mg or 1200 mg achieved clinical remission per CDAI at week 12 (45 and 42 percent of patients, respectively, compared to 25 percent of patients receiving placebo; p<0.001). Similar results were seen with clinical remission per PRO-2 (43 and 41 percent, respectively, compared to 21 percent of patients receiving placebo; p<0.001). A significantly greater proportion of patients treated with either dose of risankizumab achieved endoscopic response at week 12 (40 and 32 percent of patients receiving risankizumab 600 mg or 1200 mg, respectively, versus 12 percent in the placebo group; p<0.001). • Multiplicity-adjusted key secondary endpoints showed significant clinical improvement observed as early as week 4. After 4 weeks of treatment, 41 and 37 percent of patients receiving risankizumab 600 mg or 1200 mg achieved clinical response (per CDAI) compared to 25 percent in the placebo group (p<0.001 for 600 mg; p=0.008 for 1200 mg).[7]
Results (safety)	• Serious adverse events (SAEs) occurred in 7.2 percent of patients in the risankizumab 600 mg group and 3.8 percent of patients in the risankizumab 1200 mg group compared to 15.1 percent of patients in the placebo group. The most common adverse events (AEs) observed in the risankizumab treatment groups were headache, nasopharyngitis and fatigue. Rates of serious infections were 0.8 and 0.5 percent in those treated with risankizumab 600 mg or 1200 mg, respectively, and 3.8 percent in patients who received placebo. The rates of AEs leading to discontinuation of the study drug were 2.4 and 1.9 percent of patients treated with risankizumab 600 mg or 1200 mg, respectively, compared with 7.5 percent on placebo. In ADVANCE, there were two deaths reported in the placebo group. There were no adjudicated major adverse cardiac events (MACE) or adjudicated anaphylactic reaction events reported.[7]

ESTIMATED COST

The cost of risankizumab 75mg/0.83ml solution is £3326.09.[21]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Ustekinumab for moderately to severely active Crohn's disease after previous treatment (TA456). July 2017.
- NICE technology appraisal. Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy (TA352). August 2015.
- NICE technology appraisal. Infliximab and adalimumab for the treatment of Crohn's disease (TA187). May 2010.
- NICE guideline. Crohn's disease: management (NG129). May 2019.
- NICE interventional procedure guidance. Extracorporeal photopheresis for Crohn's disease (IPG288). February 2009.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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

OTHER GUIDANCE

- Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. 2019.[22]
- NICE Clinical Knowledge Summary. Crohn's disease. January 2019.[23]
- ACG Clinical Guideline: Management of Crohn's Disease in Adults. 2018.[24]

ADDITIONAL INFORMATION

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