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HEALTH TECHNOLOGY BRIEFING
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Budesonide for Ulcerative Proctitis

NIHRIO ID	28349	**NICE ID**	10320
Developer/Company	Dr Falk Pharma UK Ltd	**UKPS ID**	654145

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

SUMMARY

Budesonide is in clinical development for ulcerative proctitis. Ulcerative proctitis is a mild form of ulcerative colitis, a chronic inflammatory bowel disease (IBD) consisting of small ulcers that develop on the colon's lining, which can cause rectal bleeding and recurring diarrhoea. About a quarter of the patients that are diagnosed with ulcerative colitis may also have ulcerative proctitis. Ulcerative proctitis first occurs when there is inflammation that begins in the last part of the large bowel. The main symptoms of ulcerative proctitis are blood in the stool and diarrhoea (most common symptom).

Budesonide is a second-generation corticosteroid that will be administered as a suppository. The mechanism of action of budesonide has not been completely understood however, it appears to decrease inflammation. Rectal therapy also provides higher drug concentrations at the site of inflammation. If licenced, budesonide may offer an additional treatment option for patients with ulcerative proctitis.

PROPOSED INDICATION

For the treatment of ulcerative proctitis in adults.[1]

TECHNOLOGY

DESCRIPTION

Budesonide (Budenofalk) is a second-generation corticosteroid that allows local, selective treatment of the gastrointestinal tract and the liver.[2] The exact mechanism of action of budesonide in the treatment of ulcerative colitis/procto-sigmoiditis is not fully understood.[3] However, it appears to exert potent anti-inflammatory effects at the site of inflammation by high-affinity binding to the intracellular glucocorticoid receptor. Extensive (90%) pre-systemic metabolism within the mucosa of the small intestine and the liver results in low systemic availability.[2]

Budesonide is in clinical development for ulcerative proctitis. In the phase III clinical trial (2016-001921-15) patients are given 4mg budesonide suppository once-daily.[1] Budesonide has also completed another phase III clinical trial (2012-003362-41), where it compares different dosages of the budesonide suppository versus a mesalazine suppository versus a combination therapy of budesonide/mesalazine suppositories in patients with acute ulcerative proctitis.[4]

INNOVATION AND/OR ADVANTAGES

When given orally, budesonide is absorbed at the proximal part of the intestine, leading to low drug concentrations at the site of colonic inflammation.[5] This means that it will not be available for ulcerative proctitis. Rectal administration circumvents these drawbacks and is recommended as a first line therapy for ulcerative proctitis.[5,6]

In addition, patients may prefer suppositories to enemas; thus, budesonide suppositories combine the preferred mode of drug delivery for proctitis together with budesonide's favourable safety profile.[5,7] This is due to budesonide having a lower systemic bioavailability, and therefore less toxicity, than conventional corticosteroids.[8]

All 4 treatments in the clinical trial 2012-003362-41 were well tolerated and similar to gold standard mesalazine therapy. Although relatively few patients in the budesonide groups presented decreased cortisol levels, no clinical sequelae was observed, and their cortisol levels remained within normal limits, thus verifying budesonide's excellent safety profile as reported in numerous studies in conjunction with oral and rectal preparations with adverse event rates similar to those of placebo.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Budesonide is currently not licensed as a suppository for any indication. It is licensed in various other routes of administration for the treatment of:[9]

- Prophylaxis of asthma
- Allergic rhinitis
- Nasal polyps
- Prophylaxis and treatment of allergic and vasomotor rhinitis
- Crohn's disease affecting the ileum or ascending colon
- Autoimmune hepatitis
- Ulcerative colitis affecting sigmoid colon and rectum
- Microscopic colitis
- Ulcerative colitis involving rectal and recto-sigmoid disease
- Eosinophilic oesophagitis

PATIENT GROUP

DISEASE BACKGROUND

Ulcerative proctitis is a mild form of ulcerative colitis, a chronic inflammatory bowel disease (IBD) consisting of fine ulcerations in the inner mucosal lining of the large intestine that do not penetrate the bowel muscle wall. In this form of colitis, the inflammation begins at the rectum, and spreads no more than about 20 cm (7-8″) into the colon. About 25-30% of those diagnosed with ulcerative colitis might have ulcerative proctitis.[10]

The presenting symptoms of ulcerative proctitis all relate to the rectum. Blood in the stool occurs in almost everyone with the disease. Diarrhoea is a common symptom, although constipation can also develop as the body struggles to maintain normal bowel function.[10]

The cause of ulcerative proctitis is undetermined but there is considerable research evidence to suggest that interactions between environmental factors, intestinal flora, immune dysregulation, and genetic predisposition are responsible. It is unclear why the inflammation is limited to the rectum. There is a slightly increased risk for those who have a family member with the condition.[10]

Although there is a range of treatments to help ease symptoms and induce remission, there is no cure. A diagnosis of ulcerative proctitis can occur at any point throughout life, with a high occurrence in young children and then again around 40-50 years of age. Progression of this disease to ulcerative colitis, extending farther up the bowel to involve the sigmoid colon, occurs in about 30-50% of those with ulcerative proctitis.[10]

The condition can develop at any age but is most often diagnosed in people aged from 15 to 25 years old. It's also more common in white people of European descent, especially those descended from Ashkenazi Jewish communities, and black people.[11]

CLINICAL NEED AND BURDEN OF DISEASE

In 2017, it is estimated around 570 per 100 000 people living in the UK have ulcerative colitis.[12] Based on the 2019 mid-year estimate of the UK population, this amounts to around 379,528 people.[12,13] As it is estimated that 25%-30% of patients diagnosed with ulcerative colitis have ulcerative proctitis; thus, it is predicted that approximately 94,882-113,859 patients are also diagnosed with ulcerative proctitis.[10,12,13]

According to hospital episode statistics for England in 2019-20 there were a total of 8,719 finished consultant episodes for ulcerative (chronic) proctitis (ICD-10 code K51.2) recorded as primary diagnosis of which 7,831 were recorded as admissions with a total of 7,007 day cases.[14]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

As previously mentioned, there is no cure for ulcerative proctitis; however, there are several treatments to help ease symptoms and induce remission.[10] 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.[15,16]

CURRENT TREATMENT OPTIONS

The treatment of ulcerative proctitis is multi-faceted; it includes managing symptoms along with following therapies targeted to reduce the underlying inflammation.[10]

In the UK, NICE currently recommends the following treatment options for mild to moderate ulcerative proctitis:[17]

- To induce remission in people with a mild-to-moderate first presentation or inflammatory exacerbation of proctitis, a topical aminosalicylate is recommended as first-line treatment.
- If remission is not achieved within 4 weeks, an oral aminosalicylate may be added.
- For people who decline a topical aminosalicylate, an oral aminosalicylate as first-line treatment may be given
- If further treatment is needed, a time-limited course of a topical or an oral corticosteroid may be given.
- For people who cannot tolerate aminosalicylates, a time-limited course of a topical or an oral corticosteroid may be given.
- For people who decline a topical aminosalicylate and if remission is not achieved within 4 weeks, a time-limited course of a topical or an oral corticosteroid may be given.

PLACE OF TECHNOLOGY

If licenced, budesonide will offer an additional treatment for patients diagnosed with ulcerative proctitis.[1]

CLINICAL TRIAL INFORMATION

Trial	**2016-001921-15;** Randomised, double-blind, double-dummy, multicentre study to compare the efficacy and safety of once daily novel 4 mg budesonide suppository versus once daily 2 mg budesonide foam in patients with acute ulcerative proctitis. **Phase III** - completed **Location(s):** Germany, Hungary, Latvia, Poland, Russia, Slovakia and Ukraine **Actual study completion date:** March 2020
Trial design	Controlled, randomized, parallel assignment, double-blind, double dummy.
Population	N = 576, adults between 18 and 75 years of age; patients with mildly to moderately active ulcerative proctitis
Intervention(s)	Daily 4 mg budesonide suppository
Comparator(s)	Daily 2 mg budesonide foam
Outcome(s)	After 8 weeks of treatment: • Rate of clinical remission • Rate of mucosal healing
Results (efficacy)	-
Results (safety)	-

Trial	**2012-003362-41;** Randomized, double-blind, multicentre study to compare the efficacy and safety of two different dosages of a novel budesonide suppository versus a mesalazine suppository versus a combination therapy of budesonide/mesalazine suppositories in patients with acute ulcerative proctitis **Phase III** - completed **Location(s):** Germany, Russia, Slovakia and Ukraine **Actual study completion date:** July 2015
Trial design	Controlled, randomized, parallel assignment, double-blind, double dummy.
Population	N = 337, adults between 18 and 75 years of age; patients with active ulcerative proctitis
Intervention(s)	• Daily budesonide 2mg suppository (morning) with daily mesalazine placebo suppository (evening) • Daily budesonide 4mg suppository (morning) with daily mesalazine placebo suppository (evening)

	• Daily budesonide 2mg suppository (morning) with daily mesalazine 1g suppository (evening)
Comparator(s)	• Daily budesonide placebo suppository (morning) with daily mesalazine 1g suppository (evening)
Outcome(s)	Time to resolution of clinical symptoms (defined as the first day of 3 consecutive days with a score of 0 for "rectal bleeding" and "stool frequency"). Analysed by descriptive statistics using the Kaplan-Meier estimator, 50% percentile estimates [days]. [Timeframe 8 weeks]
Results (efficacy)	Patients in the 1 g MES treatment group resolved fastest from clinical symptoms, with slightly longer times in the 4 mg BUS and the combined 2 mg BUS and 1 g MES group. The longest time to clinical remission was observed under therapy with 2 mg BUS. However, only the 1 g MES and combined groups showed significantly faster resolution of clinical symptoms than the 2 mg BUS group (2 mg BUS vs 1 g MES, P = .041; 2 mg BUS vs 2 mg BUS and 1 g MES, P = .031; log-rank test). In contrast, we found no significant treatment differences with the 4 mg BUS monotherapy in comparison with any of the other treatments or with combined treatment in comparison with the 1 g MES standard therapy.[5]
Results (safety)	In total, 164 adverse events (AEs) occurred in 96 (28.5%) patients (Table 4). The wide majority of AEs were of mild severity; no severe AE was reported. Only 7 patients (2.1%) prematurely discontinued the trial because of an AE, 4 of them because of worsening UC, 1 because to AEs considered to be budesonide-related (preferred terms abdominal pain and pyrexia), and 2 patients because of other AEs showing no association with the trial medication. No serious AEs or deaths were reported.[5]

ESTIMATED COST

The cost of budesonide suppository is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Infliximab for acute exacerbations of ulcerative colitis. (TA163). December 2008
- NICE guidance. Ulcerative colitis: management. (NG130). May 2019.
- NICE quality standard. Inflammatory bowel disease (QS81). February 2015.
- NICE diagnostic guidance. Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel (DG11). October 2013.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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

OTHER GUIDANCE

- British Society of Gastroenterology. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. 2019.[16]
- European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA). ECCOEFCCA Patient Guidelines on Ulcerative Colitis (UC). 2014.[18]

ADDITIONAL INFORMATION

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