Alicaforsen is intended to be used as second line therapy for the treatment of pouchitis refractory to, or contra-indicated for, antibiotic therapy. If licensed, it will offer a treatment option for patients with pouchitis, for whom there are currently no approved effective therapies. Alicaforsen is administered by retention enema, and may also achieve topical drug delivery to the affected area while minimising systemic bioavailability. Alicaforsen is a first-generation phosphorothioate-modified antisense oligodeoxynucleotide for the down regulation of intercellular adhesion molecule 1 (ICAM-1) messenger RNA levels by RNase H-mediated degradation. Several studies have reported increased ICAM-1 expression within inflamed gut mucosa as well as increased serum concentrations of soluble ICAM-1 in pouchitis and experimental colitis.

The prevalence of ulcerative colitis (UC) in the UK is estimated to be 243 per 100,000 (equating to 136,264 people in England and Wales), with an annual incidence of 10 per 100,000. Approximately 30% of patients with UC eventually require colectomy, usually restorative proctocolectomy with ileal pouch-anal anastomosis. Pouchitis is the most common long-term complication after restorative proctocolectomy for UC, affecting up to 60% of patients and accounts for 10% of pouch failures. The quality of life for patients with pouchitis is adversely affected by their symptoms (e.g. diarrhoea, abdominal pain, and perianal or pelvic discomfort) and their poor functional status.

Second line treatment options for chronic pouchitis include mesalazine, anti-TNF therapies e.g. infliximab, probiotics, butyrate suppositories, bismuth carbomer enemas, budesonide, corticosteroids, short-chain fatty acids or further surgery. Alicaforsen has completed a phase II single arm clinical trial to test its effect on change in Pouchitis Disease Activity Index.
**TARGET GROUP**

- Pouchitis: active flares in; after ileal pouch-anal anastomosis for ulcerative colitis (UC); refractory to, or contra-indicated for antibiotic therapy – second line.

**TECHNOLOGY**

**DESCRIPTION**

Alicaforsen (AP1007; AP 1431; AP-1451; ISIS-1570; ISIS-2302; ISIS-3082; ISIS-8005) is a first-generation phosphorothioate-modified antisense oligodeoxynucleotide for the down regulation of intercellular adhesion molecule 1 (ICAM-1) messenger RNA levels by RNase H-mediated degradation\(^1\). ICAM-1 is an inducible transmembrane glycoprotein which serves multiple functions in the inflammatory process\(^1\). Induction of ICAM-1 expression occurs in many cell types, including colonic epithelial cells, in response to pro-inflammatory cytokines and mediators\(^1\). Several studies have reported increased ICAM-1 expression within inflamed gut mucosa as well as increased serum concentrations of soluble ICAM-1 in pouchitis and experimental colitis\(^2,3\). Alicaforsen is intended for the treatment of active flares of pouchitis after restorative proctocolectomy with ileal pouch-anal anastomosis for UC. It is administered by 60ml retention enema as a hydroxypropyl-methylcellulose formulation at 4mg/ml daily for 6 weeks\(^1,3\).

Alicaforsen is also in phase II clinical trials for UC affecting the distal colon and rectum.

**INNOVATION and/or ADVANTAGES**

If licensed, alicaforsen will offer a treatment option for patients with pouchitis, for whom there are currently no approved therapies. Alicaforsen is administered by retention enema, so may also achieve topical drug delivery to the affected area while minimising systemic bioavailability.

**DEVELOPER**

Atlantic Pharmaceuticals.

**AVAILABILITY, LAUNCH OR MARKETING**

Alicaforsen is a designated orphan drug in the EU and USA.

It is currently in phase III clinical trials.

**PATIENT GROUP**

**BACKGROUND**

Pouchitis is an idiopathic inflammatory condition that may occur in the ileal pouch formed after restorative proctocolectomy with ileal pouch-anal anastomosis\(^4\). This is well established as the procedure of choice for most patients requiring surgery for UC\(^5\) and involves the
removal of the colon and rectum with construction of a pouch (made from a loop of ileum) to serve in place of the rectum\(^4\). Although the aetiology and pathogenesis of pouchitis are not known, it is speculated that alterations in the microbial environment of the ileal pouch and host immune response may play a role in its development\(^6\). Pouchitis occurs more frequently in patients with primary sclerosing cholangitis, preoperative extraintestinal manifestations, and in patients who have never smoked\(^7\). Clinical symptoms of pouchitis include increased stool frequency, rectal bleeding, abdominal cramping, faecal urgency and tenesmus, incontinence and fever\(^4\).

**NHS or GOVERNMENT PRIORITY AREA**

None identified.

**CLINICAL NEED and BURDEN OF DISEASE**

The prevalence of UC in the UK is estimated to be 243 per 100,000 (equating to 136,264 people in England and Wales), with an annual incidence of 10 per 100,000\(^8\). Acute severe colitis has a mortality rate of up to 2%\(^9\); 166 deaths from UC were registered in England and Wales during 2011 (ICD-10 K51)\(^9\). UC can present at any age but the incidence has a bimodal age distribution, with peaks between the ages of 15 and 25 years and between 55 and 65 years\(^8\).

Approximately 30% of patients with UC eventually require colectomy\(^10\), usually restorative proctocolectomy with ileal pouch-anal anastomosis\(^5,10\). Some degree of inflammation in the newly formed ileal pouch develops in about 50% of cases\(^b\). Pouchitis is diagnosed when histologically proven acute inflammation is associated with symptoms of frequency, urgency and liquid stool in the presence of endoscopic evidence of inflammation\(^b\). Pouchitis is the most common long-term complication after restorative proctocolectomy for UC, and accounts for 10% of pouch failures\(^11\). The incidence of a first episode of pouchitis at 1, 5 and 10 years post operatively is approximately 15%, 33% and 45%, respectively\(^3\). Two-thirds of pouchitis cases recur and manifest either as acute relapsing pouchitis (three quarters of the recurrent population) or chronic, unremitting pouchitis (one quarter of the recurrent population)\(^3\). Expert opinion state that the prevalence of chronic persisting pouchitis is around 5%\(^a\). Half of the chronic, unremitting population will eventually require further surgical treatment\(^3\). Resection of the pouch can be associated with long term morbidity e.g. small bowel obstruction\(^7\). The use of recurrent antibiotic therapy for chronic recurrent pouchitis is also associated with significant side effects\(^b\). The quality of life for patients with pouchitis is adversely affected by their symptoms (e.g. diarrhoea, abdominal pain, and perianal or pelvic discomfort) and their poor functional status\(^6\).

In 2011-12, there were 289 hospital admissions in total for proctocolectomy and anastomosis of ileum to anus and creation of pouch however further qualified (HFQ) (OPCS4 H04.2) and anastomosis of ileum to anus and creation of pouch HFQ (OPCS4 G72.5) in England and Wales, resulting in 2,843 bed days and 290 finished consultant episodes\(^12\).

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\(^a\) Expert personal communications.
PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance


Other Guidance

- Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 3: special situations. 201313.
- Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. 201214.
- Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. 201215.
- The Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults. 20128,16.
- Clinical guidelines for the management of pouchitis. 200918.

EXISTING COMPARATORS and TREATMENTS

Antibiotics are the mainstay treatment for pouchitis19 and the use of metronidazole or ciprofloxacin are recommended by current guidelines for first line treatment17. However patients with chronic unremitting pouchitis may not respond to antibioticsb. Other first line treatments include aminosalicylates and corticosteroids (to control or reduce the inflammation)3.

Second line treatment options for chronic pouchitis (not licensed for this indication) include16:

- mesalazine-containing preparations (oral or enema formulation)19
- further antibiotics i.e. low dose metronidazole or ciprofloxacin17,19
- anti-TNF therapies e.g. infliximab17,19,20,c
- probiotics19 e.g. VSL#3 probiotic food supplement17 (as maintenance treatment)c
- butyrate suppositories19
- bismuth carborner enemas19
- budesonide17,21
- corticosteroids19
- short-chain fatty acids17

Some people with pouchitis will require surgical treatment of the pouch3.

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b Expert personal communication.
EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>ISIS 2302-CS23; alicaforsen; pouchitis; chronic; unremitting; phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Isis Pharmaceuticals.</td>
</tr>
<tr>
<td>Status</td>
<td>Published.</td>
</tr>
<tr>
<td>Source of information</td>
<td>Publication⁵, manufacturer.</td>
</tr>
<tr>
<td>Location</td>
<td>USA.</td>
</tr>
<tr>
<td>Design</td>
<td>Non-randomised, single arm.</td>
</tr>
<tr>
<td>Participants</td>
<td>n=12; aged ≥18 years; unremitting pouchitis⁶; chronic; failed alternative therapies; Pouchitis Disease Activity Index (PDAI) score ≥7; ≥2 weeks since last antibiotic therapy.</td>
</tr>
<tr>
<td>Schedule</td>
<td>Received alicaforsen 60ml retention enema at 4mg/ml nightly for 6 weeks.</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Active treatment for 6 weeks, follow-up at weeks 10 and 18. Subjects had the option of 9-month extended follow-up period after the week 18 visit. During this time, a 3-week re-treatment of alicaforsen enema was permitted if the subject relapsed (defined as a PDAI score = 7), but only if 3 months had elapsed since last alicaforsen enema. A maximum of 2 re-treatment courses were allowed during the extended follow-up period.</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Change in PDAI at week 6.</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>Change in PDAI at week 10; safety.</td>
</tr>
<tr>
<td>Key results</td>
<td>Mean reduction in PDAI score, -4.59 (p=0.001) at week 6; mean reduction in PDAI endoscopy sub-score, -2.17 at week 3 (p=0.0039) and -2.67 at week 6 (p=0.0005); mean reduction in PDAI clinical symptom sub-score, -1.42 at week 3 (p=0.0156) and -1.5 at week 6 (p=0.0117); mean reduction in PDAI histology sub-score, -0.4 at week 6 (p=0.05); 83% achieved a PDAI mucosal appearance score of 0 or 1 at endoscopy at week 6; 42% had a decrease in PDAI histology sub-score of -1 at week 6 (p&gt;0.05); 58% were in remission (PDAI &lt;7), with a mean reduction in PDAI score of -6 at week 6. Decrease in PDAI scores, 39% at week 6 and 42% at week 10; proportion of subjects with clinical remission, 16.7% at week 6 and 41.7% at week 10; proportion of subjects with clinical improvement, 33.3% at week 6 and 25.0% at week 10.</td>
</tr>
<tr>
<td>Adverse effects (AEs)</td>
<td>No serious AEs reported. 105 AEs: mild or moderate AEs, 89/105; severe non-serious AEs, 14/105 related to the disease.</td>
</tr>
</tbody>
</table>

ESTIMATED COST and IMPACT

COST

The reported costs (including consultation and administration) of selected second line treatments for recurrent pouchitis are as follows⁶⁰:

<table>
<thead>
<tr>
<th>Drug</th>
<th>6-month cost</th>
<th>Annual cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alicaforsen</td>
<td>£7,884</td>
<td>£15,242</td>
</tr>
<tr>
<td>Infliximab (not licensed for indication)</td>
<td>£9,968</td>
<td>£15,764</td>
</tr>
<tr>
<td>Surgery</td>
<td>£14,291</td>
<td>£15,833</td>
</tr>
</tbody>
</table>

⁵ Chronic unremitting pouchitis defined as intolerance of or no response to treatment with antibiotics, mesalazine, or steroid enemas for at least 4 weeks.
**IMPACT - SPECULATIVE**

**Impact on Patients and Carers**
- Reduced mortality/increased length of survival
- No impact identified

**Impact on Services**
- Increased use of existing services
- Decreased use of existing services
- Need for new services

**Impact on Costs**
- Increased drug treatment costs
- Other reduction in costs: alicaforsen will be self-administered.

**Other Issues**
- Clinical uncertainty or other research question identified: the patient group eligible for treatment (i.e. chronic refractory pouchitis) and their previous medical approach needs to be defined carefully. Efficacy needs to be assessed clinically (PDAI score), endoscopically and histologically to allow objective measures of response. Long term follow-up data for the completed trial is required to assess medium and long term outcomes.

**REFERENCES**


2. van Deventer SJH, Tami JA and Wedel MK. A randomised, controlled, double blind, escalating dose study of alicaforsen enema in active ulcerative colitis. Gut 2004;53(11);1646-1651.


