A Randomised, Double-Blind, Placebo-Controlled Trial of the Safety and Efficacy of Topical Alicaforsen Enema in Subjects with Active, Chronic, Antibiotic Refractory Primary Idiopathic Pouchitis

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Primary Objective : To determine the effect of alicaforsen enema on endoscopic healing and symptoms associated with pouchitis in those subjects with active antibiotic refractory pouchitis Secondary Objectives : 1. To determine the ability of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON46082

Source
ToetsingOnline

Brief title
ACH UCP-301

Condition

- Gastrointestinal inflammatory conditions
- Gastrointestinal therapeutic procedures

Synonym
inflammation of the ileal pouch

Research involving
Human

Sponsors and support

Primary sponsor: Atlantic Pharmaceuticals Ltd
Source(s) of monetary or material Support: Atlantic Pharmaceuticals Ltd

Intervention

Keyword: Alicaforsen, pouchitis

Outcome measures

Primary outcome

Co-Primary Endpoints :

1. Proportion of subjects with endoscopic remission; defined as absence of friability and ulceration, represented by a score of <1 (endoscopy component of a modified MAYO score) at Week 10.

Note : the area within 1 cm of the pouch suture line will not be included in the endoscopic evaluation.

2. Proportion of subjects with a stool frequency represented by a MAYO subscore of *1 at Week 10.

Secondary outcome

Secondary Endpoints:

1. Percentage change in stool frequency from baseline compared to placebo; Week 6 and Week 10.

2. Change in urgency score from baseline compared to placebo; Week 6.

3. Change in rectal bleeding score from baseline compared to placebo; Week 6.

4. Proportion of subjects who achieve overall PDAI <5 at both Week 6 and Week 10.

5. Mean change from baseline in CGQL at Week 6.

6. Proportion of subjects by Week 26, who have not received additional

treatment for pouchitis flares, since commencing study.

Study description

Background summary

Surgical treatment of ulcerative colitis usually involves removal of the entire colon (proctocolectomy). Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) has become a part of standard surgical treatment for subjects with ulcerative colitis (UC). IPAA is a surgical procedure creating a reservoir (pouch) from the last part of the small intestine. The pouch is then connected to the anus and serves as a reservoir for the storage of stool. Despite advances in medical therapy, approximately 30% of subjects with UC eventually require an IPAA. Pouchitis, a nonspecific inflammatory condition at the pouch, is the most common long-term complication in subjects with IPAA which significantly affects subjects* quality of life. While the majority of subjects with pouchitis respond favorably to antibiotic therapy.

Study objective

Primary Objective : To determine the effect of alicaforsen enema on endoscopic healing and symptoms associated with pouchitis in those subjects with active antibiotic refractory pouchitis

Secondary Objectives :
1. To determine the ability of alicaforsen enema to improve the clinical symptoms associated with antibiotic refractory pouchitis
2. To determine the effect of alicaforsen enema on health related quality of life.
3. To evaluate duration of effect following cessation of therapy

Tertiary and Exploratory Objectives :
1. To determine the effect of alicaforsen enema on reducing pouchitis *rescue* intervention;
2. To determine the effect of alicaforsen enema on histological inflammation
3. To determine the effect of alicaforsen enema on health outcome
4. To determine the effects of alicaforsen enema on changes in biological markers; including CRP, WBC, and faecal calprotectin.

Safety Objectives : To evaluate the safety and tolerability of alicaforsen

enema, in subjects with chronic or recurrent acute antibiotic refractory pouchitis.

Pharmacokinetic Objectives : To determine the systemic exposure of subjects to parent compound following single and repeated once-daily doses of alicaforsen.

Study design

A Phase III, multi-centre, double-blind, randomized, controlled trial in subjects with chronic antibiotic refractory pouchitis.
Subjects will undertake a * 3 week screening period to provide baseline data and be assessed for eligibility. At the Baseline visit (Day 1) eligible subjects will be randomised on a 1:1 basis to either a) 240 mg alicaforsen enema or b) matching placebo.
Study drug will be administered once nightly (on going to bed) up to and including week 6.
Following the Day 1 Visit, subjects will return to the clinic for safety and efficacy assessments at Week 3, 6, 10, 18 and 26.

Provision will be made for subjects who meet appropriate criteria to receive open-label access (OLA) to alicaforsen after they have completed Week 26 of the double-blind phase of the study. In the OLA, alicaforsen treatment course isTopical alicaforsen 240mg enema (in 60 mls) for a 6-week treatment period.

Intervention

Patients will be randomised to 1 of 2 groups. Enema will be applied once daily.
Group 1 : Topical alicaforsen 240mg enema (in 60 ml) for the 6 week treatment period
Group 2 : Placebo enema throughout the 6-week treatment period

Study burden and risks

The study includes administration of the study drug once nightly (on going to bed) during 6 weeks. As with all drugs, the patients may experience adverse events, although Alicaforsen is generally safe and well-tolerated.
The frequent non-serious adverse events are abdominal pain, viral gastroenteritis, aggravated Ulcerative Colitis, nausea, fatigue, common cold, sinusitis, upper respiratory tract infection, joint pain, headache.
Rare adverse events include mild-moderate proctalgia (rectal pain) and mild itching. pneumonia and anemia were observed but pneumonia was thought to be possibly related to the study drug and it is not known if the anemia was related.
Mild local irritation associated with use of the enema may be experienced.
Allergy symptoms cannot be excluded.
Rare risks associated with endoscopy and biopsy include: perforation, or a tear

through the lining of the pouch, bleeding from a biopsy site.
Patients need to record symptoms and confirmation of study drug administration daily in a diary and fill in questionnaires.
Bloods, urine and stool samples will be taken. Some discomfort may result of these tests.
But patients who are taking the study drug may have an improvement of the disease.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

DOUBLE-BLIND PHASE INCLUSION CRITERIA:
1. Written informed consent;
2. Male or female subjects, *18 years of age who have undergone an IPAA for UC

3. History of pouchitis
Documented evidence of active pouchitis, based on endoscopy, symptoms and histopathology, as follows:
4. Endoscopic score *2 on the endoscopic component of a modified MAYO score (where friability is scored as *2)
Note: the area within 1 cm of the pouch staple, or pouch suture line, is not considered evaluable
5. Symptomatic disease (stool frequency): Subjects must demonstrate increased stool frequency compared to what is considered *normal* after their IPAA operation (*baseline*). Stool frequency must be an absolute value of * 6 stools per day, and * 3 stools per day above the post-IPAA *baseline*.
Note: The measurement of stool frequency will be a 7-day average rounded to the nearest integer. The most recent 7 days of data will be used to calculate the average.
6. Histology: evidence of disease (Score * 2 on PDAI)
7. Overall PDAI score > 7
8. Must have Chronic Antibiotic Refractory Pouchitis
Chronic Antibiotic Refractory Pouchitis is defined as remaining in active disease despite antibiotic therapy for at least 2 continuous weeks. There is no requirement for antibiotic use to be current, or within a defined time-window. Antibiotics must be stopped 4 weeks before the Randomisation Visit, which is effectively 2 weeks before the Screening Visit. As a minimum the antibiotic regime will comprise ciprofloxacin 1g/day, or metronidazole 15 * 20 mg/kg/day. Subjects must have been in active disease for a minimum of 4 weeks at the point of randomisation.;4.1.1 OPEN LABEL ACCESS INCLUSION CRITERIA
1. Written informed consent;
2. Previous participation to Week 26 of double blind phase
3. Demonstrated compliance with previous alicaforsen/blinded treatment
4. Current evidence of active disease, based on clinical symptoms

Exclusion criteria

DOUBLE-BLIND FASE EXCLUSION CRITERIA:
1. Lack of effective contraception
Women of childbearing potential may not participate unless they are surgically sterile or are using adequate contraception.
The following contraceptive methods are acceptable: hormonal (eg oral, injection, transdermal patch, implant, cervical ring), barrier (eg condom or diaphragm with spermicidal agent), intrauterine system or intrauterine device. If hormonal contraceptives are used by female subjects they must be established for 6 weeks before the first administration of test product. Male sterilization is considered an acceptable form of contraception if the appropriate post-vasectomy documentation (absence of sperm) is provided in the subject*s medical notes. Sexual abstinence is considered acceptable if this is in line with the preferred and usual lifestyle of the subject; periodic abstinence (eg calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
Male subjects with female partners of child-bearing potential and female subjects who are

neither surgically sterilized nor post-menopausal (defined as no menses for one year or an FSH value > 40 IU/L) will be required to use effective contraception throughout the study and for 30 days after.
2. Women who are pregnant or breastfeeding;
3. History of allergy or adverse event to oligonucleotides including alicaforsen, hydroxymethylcellulose, methyl or propylparabens.
Stable use of concomitant medications for pouchitis is generally permitted, doses of concomitant medication, where taken, should be optimised in accordance with local/national practice guidelines, and dose levels and types of baseline medications for pouchitis will be documented and any changes during the study will be recorded. Changes in use of medications for pouchitis and high doses of oral steroids are not permitted. It is particularly important to maintain stable medication through to measurement of the primary end-point at Week 10. Criteria which would lead to exclusion of subjects from the study are described below:
4. Changes in dose to strong analgesia, such as opioid containing compounds within 4 weeks of
the Screening Visit.
5. History of regular NSAID use.
6. Oral 5-aminosalicylate (5-ASA) compounds; exclude subjects who have discontinued or changed doses of oral 5-ASA within 4 weeks of the Screening Visit.
7. Oral budesonide > 6.0 mg / day is not permitted; exclude subjects who have received budesonide for < 6 weeks, or who have changed doses of budesonide within 4 weeks of the Screening Visit.
8. Oral steroids other than budesonide; exclude subjects who exceed a daily dose of 15 mg prednisolone or equivalent, who have received oral steroids for < 6 weeks, or who have changed dose within 4 weeks of the Screening Visit.
9. Use of rectal compounds is not permitted; these agents must be discontinued at the Screening Visit.
10. Immunosuppressant therapy (azathioprine, 6-mercaptopurine, methotrexate, cyclosporin); exclude subjects who have received treatment for < 12 weeks, or who have changed doses within 8 weeks of the Screening Visit.
11. Biological agents: Anti-tumour necrosis factor (anti * TNF) therapy and / or vedolizumab; are not permitted within 8 weeks of the Screening Visit.
12. Previous use of alicaforsen is permitted: treatment course must have completed at least 12 weeks prior to the Screening Visit (Alicaforsen pre-treated subjects may not contribute to the primary efficacy analysis).
13. All other agents targeted to pouchitis, including experimental agents, must have been discontinued at least 8 weeks prior to the Screening Visit, or for a period equivalent to 5 half-lives (t*) of the agent (whichever is longer)
It is acceptable to recruit subjects who remain on optimized, stable doses of oral 5-ASA, oral steroids (below the doses stipulated above) and immunosuppressants.
It is acceptable to recruit subjects who terminated treatment with oral 5-ASA or oral steroids 4 weeks before the Screening Visit, or immunosuppressants 8 weeks before the Screening Visit.
Note: Analgesic use should remain stable throughout the trial where possible. Paracetamol is the analgesic of choice.
Note: VSL3 treatment (and other probiotic treatments) will be permitted as long as

maintained stable for 4 weeks prior to the Screening Visit, and maintained at a stable dose throughout the trial
Also excluded are subjects with:-
14. Anastomotic stricture
15. Unable to undertake endoscopic evaluation
16. Faecal incontinence due to anal sphincter dysfunction
17. Infections to cytomegalovirus or Clostridium Difficile
18. Faecal transplantation within 12 weeks of screening
19. Intestinal malabsorption
20. Pancreatic maldigestion
21. Suspected irritable pouch syndrome
22. Cuffitis (inflammation of the anal mucosa). Subjects with active antibiotic refractory pouchitis as the predominant condition, but who also have cuffitis, may be enrolled
23. Crohn*s disease of the pouch, defined as either:
a) complex perianal or pouch fistula and/or
b) extensive pre-pouch ileitis with deep ulceration
24. Subjects with a history of neoplastic disease except for basal cell carcinoma or non-metastatic squamous cell carcinoma of the skin
25. Subjects who are receiving or have received nasogastric/nasoenteric bottle feeding, an elemental diet, or total parenteral nutrition within the 2 weeks prior to Day 1
26. Subjects with a history of clinically significant and/or persistent haematologic, renal, hepatic,
metabolic, psychiatric, CNS, pulmonary or cardiovascular disease; which in the investigators opinion, would exclude entry into the study
27. Subjects with any laboratory tests considered clinically significant at screening
28. Subjects who may be unavailable for the duration of the trial, likely to be noncompliant with the protocol, or who are felt to be unsuitable by the Investigator for any other reason including, for example, inability to retain an enema formulation
29. Pelvic sepsis should be excluded as a differential diagnosis, within 12 months of randomisation.;OPEN LABEL ACCESS EXCLUSION CRITERIA
1. Lack of effective contraception
2. Women who are pregnant or breastfeeding;
3. History of allergy or adverse event to hydroxymethylcellulose, methyl or propylparabens.
4. Concurrent use of experimental agents
5. Subjects with any laboratory tests considered clinically significant
6. Subjects who may be unavailable for the duration of the treatment course, likely to be noncompliant, or who are felt to be unsuitable by the Investigator for any other reason

Study design

Design

Study phase: 3

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-06-2016
Enrollment:	8
Type:	Actual

Ethics review

Approved WMO Date:	17-11-2015
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-05-2016
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-06-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-06-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	02-08-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-08-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-08-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-10-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-11-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-12-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-03-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2013-002952-34-NL
ClinicalTrials.gov	NCT02525523
CCMO	NL55296.000.15