LAY SUMMARY
CLINICAL RESEARCH PROTOCOL
ACH UCP-301
EudraCT Number 2013-002952-34
IND Number 64,905

Who Sponsored the Study?
Atlantic Pharmaceuticals Ltd, Atlantic House, 10 Rose & Crown Walk, Saffron Walden,
Essex, CB10 1JH, United Kingdom.
Phone: +44 (0)1799 619 413
Email: info@atlantichc.com
Website: www.atlantic.com

Title of this Phase 3 Study:
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.

- In a Phase 3 study a new treatment is tested in many patients.
- In this study, researchers compared the test medicine (alicaforsen enema) to placebo (identical looking enema liquid but with no medicine in it).
- Randomising patients, by putting people (by chance) into 2 equal sized treatment groups, helps to reduce the differences between the groups, making the comparison between the groups fairer.
- This trial was also "double-blinded". This means that neither patients nor doctors knew who was given which treatment. This was done to make sure that the trial results were not influenced in any way.

There was also an optional open-label-access follow-on-phase available to patients in this study (except for patients in France, for whom the national regulatory agency declined this part of the study).

Alicaforsen enema is an investigational product designed to work in inflammatory bowel disease. In this study, the target was pouchitis.

As the sponsor for this study, we at Atlantic Pharmaceuticals Ltd feel it is important for you to know the results. When the study ended, we created a scientific report of all the data.
This is a short summary of that report.

General Information about the clinical trial:
Thank you for participating in the clinical study for the drug alicaforsen enema.

This study took place in Belgium, Canada, Switzerland, France, United Kingdom, Ireland, Israel, Italy, Netherland and the United States.

138 adult volunteers (patients) in 42 clinic locations took part in the double-blind phase of the study, and 65 of those patients then chose to take part in the open label access follow on phase.

When you left the study, other patients may have just been starting. The entire study, including the optional open label access follow on phase, took just over 3 years to complete. The study recruited its first patient in February 2016 and the last patient ended the double-blind phase in October 2018. The last open label access patient completed in March 2019.

The main purpose of the study was to investigate how good alicaforsen enema was at healing the area of inflammation in the gut called the 'pouch', and how good it was at reducing the patient's daily trips to the bathroom (stool frequency).
Patients were randomised to receive alicaforsen enema or placebo enema for a 6-week treatment period and then completed a 20-week follow-up period.

During the double-blind part of the study, each patient self-administered a 240 mg alicaforsen enema/placebo enema once daily for 42 days (6 weeks). Patients completed health questionnaires, and blood samples were also collected to test for concentrations of alicaforsen.

Patients received a telephone call at Week 1 to review compliance and safety.
Then returned to the study centre at Weeks 3, 6, and 10 for review of medications, assessment of pouchitis clinical symptoms and health status, recording of any adverse events (AEs), and completion of protocol required safety assessments.
In addition, the Pouchitis Disease Activity Index (PDAI) was assessed at these visits.

Follow-up visits were scheduled for Weeks 18 and 26.
After Week 26, patients then had the option to access open label alicaforsen enema (except patients in France, for whom the national regulatory agency declined this part of the study). 65 of 138 patients took up this option.

Again, each patient self-administered a 240 mg alicaforsen enema once daily for 42 days (6 weeks).

Safety and efficacy assessments were captured by the study doctors for the study.

Why was this study done?
This study was done to help patients with pouchitis. Pouchitis is a disease that causes pain and discomfort (inflammation) in the pouch.

A patient with a pouch has undergone a surgery where their entire colon (gut) was removed and then a piece of the small intestine is used to create a replacement gut (Ilea Pouch-Anal Anastomosis (IPAA)).

Pouchitis is a disease that is diverse in the way it presents. Some patients have continuous active disease, whilst some have infrequent episodes of the active disease.
Some patients respond to antibiotics, some are responsive to other medications, some don't respond to anything at all.
There is currently no approved medication specifically for pouchitis.

What Patients were included in this study?
This study included 138 adult men and women who had colon surgery (IPAA) and had a history of pouchitis with active disease.

Of the 138 patients, 58 were women and 80 were men, all aged between 19 and 70 years old.
To start the study, patients had to have active pouchitis based on clinical assessments such as endoscopic inflammation and patient reported bowel symptoms.

Patients also had to stop taking any antibiotics 2 weeks before starting the study.

What were the study results?
The study did not meet its primary goals:

1. There were no statistically significant improvements in endoscopic healing, or clinical symptoms or health-related quality of life indicators in patients with active antibiotic refractory pouchitis following treatment with alicaforsen enema once daily for 6 weeks compared with placebo enema.
   This outcome was not expected by the researchers.

2. However, there was a small trend seen in favour of alicaforsen for improvement in patient's stool frequency.

3. The concentrations of alicaforsen in the blood (pharmacokinetics) on Day 1 (Baseline) and Day 42 (Week 6) indicated that whole body exposure to alicaforsen is minimal when administered as an enema.
   This outcome was expected as alicaforsen is known to have low uptake in to the body when given as an enema.

4. Treatment with alicaforsen enema for 6 weeks was generally well tolerated; most adverse events were mild or moderate in their severity, and non-serious, and considered not related to study drug by the Investigator.

5. There were 8 serious adverse events during the whole study. None were found to be related to drug.

6. All adverse events, including the few that were serious resolved quickly and without any ongoing symptoms.

7. The number of laboratory test abnormalities and clinically significant changes in vital signs were low.

   These four safety outcomes were expected as alicaforsen is already known to be a relatively safe drug.

What side effects did patients have?
More than 10% of patients in the placebo group experienced abdominal pain.

More than 5%, but less than 10% of patients in the placebo group experienced:
- Anorectal discomfort (discomfort in area just inside anus)
- Pouchitis worsening
- Diarrhoea (liquid stools)

More than 5%, but less than 10% of patients in the alicaforsen group experienced:
- Nasopharyngitis (common cold)
- pouchitis worsening

Other adverse events were experience by less than 5% of either group.

What happens now?
Atlantic Pharmaceuticals Ltd has taken extensive advice from leading medical and regulatory professionals and the study endoscopy data has recently been reanalysed using new scientific methods.
Some positive results have been shown from this, and we are planning to hold discussions with the regulatory agencies to discuss a pathway to regulatory approval for alicaforsen use in pouchitis.

If you have any questions, please speak with the doctor or research staff at your study site.
A summary of scientific results will also be posted on the regulatory web portals www.clinicaltrials.gov and www.ema.europe.eu