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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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PROTOCOL SYNOPSIS

Title	A Randomised, Double-Blind, Placebo-Controlled, Multi-Centre Trial of the Safety and Efficacy of Topical Alicaforsen Enema in Subjects with Active, Chronic, Antibiotic Refractory Primary Idiopathic Pouchitis
Study Phase	Phase III
Indication	Treatment of Chronic, Antibiotic Refractory Pouchitis
Study Population	Subjects with pouchitis refractory to antibiotics
Locations	This study will be conducted at sites in North America and Europe, including Israel.
Treatment Groups	a) Alicaforsen 240mg enema, administered nightly, for 6 weeks. b) Matching placebo enema, administered nightly, for 6 weeks.
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 randomised 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. Subjects will be contacted by telephone during Week 1 to ensure adequate compliance with study treatment, to ensure concomitant medications are being used at levels consistent with those prior to randomisation, and to inquire about any adverse events. Subjects may receive certain permitted medications as per Entry Criteria, which must remain at stable doses throughout the trial. Introduction of any new medication for pouchitis, or a dose change to an existing concomitant medication for pouchitis, other than those detailed in the protocol, will not be permitted. Introduction of any new medication, or escalation of dose of current therapy, primarily for the treatment of pouchitis before Week 10

	will be determined as “rescue” intervention. Once rescued, a subject will complete an early termination visit and will be considered a treatment failure. Surgical procedures targeted to pouchitis before Week 10 will also be considered as “rescue” interventions. Clinical symptoms associated with pouchitis will be recorded daily by the subject in an electronic diary card and elements recorded in the eCRF up to Week 10. Subjects will undergo endoscopic examination of their pouch (during Screening, and at Weeks 6 and 10). Subjects may receive an additional endoscopic examination later during the study if clinically indicated. Indications for repeated endoscopy might include confirmation of sustained response to treatment, or recurrent disease (following initially successful response). The purpose of the additional endoscopy is to document duration of effect and / or time-to-next-flare, hence the timing of any additional endoscopic procedure will vary from subject to subject. For this reason, this procedure will be undertaken at the investigator’s discretion following discussion with the Sponsor’s Medical Monitor. Where technically feasible, each endoscopy will provide at least one biopsy sample for histopathology. To assess Quality of Life, subjects will complete: the EQ-5D, the Cleveland Global Quality of Life score [CGQL] and the Work Productivity Activity Impairment index [WPAI]. These assessments will be made during the treatment period, and the follow-up phase of the study. Bloods for routine assessment, including haematology and biochemistry will be taken. Bloods will also be taken for biomarkers, including CRP. In addition, stool samples will be collected to evaluate faecal calprotectin levels. Blood samples for routine haematology and biochemistry, as well as faecal calprotectin, will be collected during the screening period and results should be available to the investigator at the Baseline visit. Following the Baseline visit the investigator will be blinded to CRP, WBC, and lab faecal calprotectin levels (which will be collected again at Weeks 3 and 6, and for calprotectin specifically

	during the follow-up period of the trial). Additional blood samples will be collected for pharmacokinetic determinations. Any subjects who withdraw consent to participate in the study after receiving study medication, for any reason, will be asked to complete the Early Discontinuation Visit. The overall study design is described by a study flowchart at the end of the protocol synopsis section.
Number of Subjects	This study will randomise 138 subjects. 69 subjects will receive 240 mg alicaforsen enema, once nightly; 69 subjects will receive matching placebo enema.
Estimated Study Duration	A subject's participation in this study will last for up to 29 weeks (including the ≤3 week screening phase, 6 week treatment phase and 20 week follow up phase).
Summary of Subject Eligibility Criteria	**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. Inclusion criteria removed 7. Overall PDAI score > 7 8. <u>Must have Chronic Antibiotic Refractory Pouchitis</u> 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. **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 (t½) of the agent (whichever is longer) **It is acceptable to recruit subjects who remain on optimised, 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 which precludes evaluation of the pouch and terminal ileum. 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 malignancy, except

	for basal cell carcinoma or non-metastatic squamous cell carcinoma of the skin and ductal carcinoma in situ breast cancer. Subjects who have a history of malignancy with ≥5 years since completion of curative therapy, without recurrence, may be screened. 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 (including coagulation disorders), 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.
Concomitant Medications	During the course of their participation in the study, all subjects will be required to remain on stable doses of their existing concomitant medications for pouchitis, neither increasing nor decreasing the dose. Introduction of a new medication for pouchitis, or an increase in the dose of an existing pouchitis medication, should be avoided throughout the study. This will be regarded as "rescue" intervention if it occurs prior to Week 10 and lead to the early termination of the subject. Loperamide and other anti-diarrhoeal medication should

	also be maintained at a stable dose where possible.
Drugs, Drug Dosages and Formulations	Alicaforsen enema will be administered at a dose of 240mg of alicaforsen per 60ml enema. Applications will be made once daily, at night time. Study drug will be produced in a hydroxypropyl methylcellulose enema formulation, and will be provided for the trial in sealed, plastic enema bottles. This may be lubricated with petroleum jelly as required.
Control Groups	Placebo will be provided in matching bottles and consist of hydroxypropylmethylcellulose base plus methyl and propyl parabens preservatives.
Route of Administration	Study medication will be administered by the subject, at bedtime, while the subject is lying down. Subjects will be instructed to remain in this position until they no longer have the urge to evacuate the enema. The enema should be retained for as long as possible, ideally until the following morning.
Procedures	At each study visit, some or all of the following procedures will be conducted: Medical history taken (including smoking history), physical examination, vital signs, bodyweight, blood samples for, haematology, biochemistry and CRP. Urine samples will be collected for urinalysis. A serum pregnancy test will be performed. Stool samples for faecal calprotectin will be collected. The PDAI score will also be calculated. Subjects will complete the EQ-5D, the CGQL quality of life questionnaire, and a health outcome questionnaire (WPAI). Electronic diary cards will be utilised daily to record subjects' symptoms (bowel frequency, degree of urgency, incontinence, abdominal pain/cramps, rectal bleeding). In addition, they will confirm administration of study

	medication and record enema retention time. The subjects will complete the diary daily from Screening until Week 10. Study bottles (unused) will be collected for assessment of compliance at each visit and subjects re-educated about administration if compliance is low. Please see Schedule of Events at the end of this synopsis for additional details.
Co-Primary Endpoint	**Co-Primary Endpoints:** 1. Proportion of subjects with endoscopic remission; defined as absence of friability and ulceration, represented by a score of $\leq$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 $\leq$1 at Week 10.
Secondary Endpoints	**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.
Tertiary and Exploratory Endpoints	**Tertiary Endpoints** 1. Time to first use of "rescue" intervention 2. Proportion of subjects who achieve histological response; response = PDAI subscore 1 (for subjects with baseline score >1), or ≥2 point reduction; remission = PDAI subscore 0 for subjects who had a baseline subscore above 0. 3. Proportion of subjects achieving endoscopic response, as defined by improvement of ≥1 point on the endoscopic component of the modified MAYO score, by the central reader; Week 10 4. Change from baseline in PDAI score, at Week 6 and Week 10 5. Change from baseline in PDAI clinical symptoms score (at Weeks 6 and 10) 6. Proportion of subjects who achieve overall PDAI <3 at both Week 6 and Week 10 7. Change from baseline in PDAI endoscopy score; at Week 6 and Week 10 8. Change from baseline in Quality of Life measured by the EQ-5D at Week 6 and Week 10 9. Mean change from baseline in CGQL at Week 10 10. Proportion of subjects who achieve post surgery stool frequency at both Week 6 and Week 10 11. Time to clinical "remission" (defined as achieving post surgery stool frequency) 12. Change from baseline in faecal incontinence episodes

	Exploratory Endpoints: 1. Change from baseline in work productivity and activity as measured by the WPAI 2. Change from baseline in histology score on D'Haens scale 3. Change from baseline in inflammatory markers including CRP, WBC, calprotectin
Safety and Pharmacokinetics	**Safety Endpoints:** The safety analysis will be conducted in all randomised subjects receiving at least a part of one dose 1. The number and proportion of subjects with AEs; (worsening of pouchitis will also be evaluated separately) 2. Assessment of clinical laboratory parameters 3. Assessment of vital signs **Pharmacokinetic Endpoints:** Systemic absorption of alicaforsen will be determined from plasma samples. Full plasma profiles will be determined in a cohort of approximately 12 separately consenting subjects. In order to obtain 12 alicaforsen profiles, a total of 24 subjects will be separately consented and bled. The blood samples obtained from subjects randomised to placebo will not be analysed. Profiles will be determined at Weeks 0 (baseline) and 6. Samples will be taken at the following time-points: pre-dose, 10, 20, 30min, 1, 2, 3, 4, 6, 12 and 24h. In addition, single bleeds will be taken from all other consenting subjects, prior to enema administration, at Weeks 0, 3 and 6.
Statistical Considerations	Assuming 50% of subjects on alicaforsen and 20% on placebo meet the co-primary end-point a 1:1 design will require 69 subjects per treatment group, 138 in total to show a significant difference using a Z-test with continuity correction and pooled variance. This assumes a two-sided 5% statistical significance level and 90% power (PASS 13 Power Analysis and Sample Size Software (2014). NCSS, LLC. Kaysville, Utah, USA,

	ncss.com/software/pass).
Open Label Access after Week 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. Safety and efficacy data will be collected in accordance with regulatory requirements pertaining to open label access to unlicensed medications. This provision of open-label access to alicaforsen through this clinical trial will continue until the subject no longer derives benefit, or until alicaforsen receives marketing authorisation for use in Pouchitis, or development is discontinued, whichever is sooner. Procedures: For each OLA alicaforsen treatment course, the following procedures will be conducted: Collection of changes in medical history or adverse events since last study visit, physical examination to ascertain changes since last study visit, vital signs, blood samples for haematology and biochemistry. Urine samples for urinalysis. A serum pregnancy test will be performed. Please see Schedule of Events for additional details 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: 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; Drugs, Dosages and Formulations: Alicaforsen enema will be administered at a dose of 240mg of alicaforsen per 60ml enema. Applications will be made once daily, at night time in the same regimen as the double-blind phase of the study. OLA alicaforsen will be produced in a hydroxypropyl methylcellulose enema formulation, and will be provided in sealed, plastic enema bottles.
Sponsor	This study is sponsored by Atlantic Pharmaceuticals Ltd. Atlantic Pharmaceuticals Ltd is responsible for all operational aspects of this study.