Clinical Study Report Synopsis

Drug Substance	Entocort™ EC[1]
Study Code	D9422C00001
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A Multicenter, Open-Label, Non-Comparative Study to Evaluate the Safety of Entocort™ EC for the Treatment of Crohn's Disease in Pediatric Subjects Aged 5 to 17 Years, Inclusive

Study dates:	First subject enrolled: 03 November 2011
	Last subject last visit: 10 September 2014
Phase of development:	Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

This document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

[1] Entocort™ EC is a trademark of the AstraZeneca group of companies.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The primary and secondary objectives and the outcome variables are presented in Table S1.

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Safety	To investigate the safety of Entocort EC in a pediatric population treated for mild-to-moderate Crohn's disease	• AEs (including AEs that occurred in subjects who took CYP3A4 inhibitors or inducers), • Clinical laboratory evaluations, • Vital signs, and physical examination, • GCS-related side effects, HPA-axis measurement (serum cortisol and DHEAS)
Secondary	Efficacy	To characterize the disease activity in the trial population before and after treatment through the pediatric Crohn's Disease Activity Index (PCDAI)	Development in PCDAI total score over time
	PRO/QOL	To assess the QOL with Entocort EC treatment based on a subject questionnaire (IMPACT 3)	Development in IMPACT 3 scores over time

AEs Adverse events; CYP3A4 Cytochrome P450 3A4; DHEAS Dehydroepiandrosterone sulfate; GCS Glucocorticosteroids; HPA-axis Hypothalamic-pituitary-adrenal axis; PCDAI Pediatric Crohn's Disease Activity Index; PRO Patient-reported outcome; QOL Quality of life.

Study design

This was a multicenter, open-label, non-comparative study to evaluate the safety of Entocort EC for the treatment of Crohn's disease in pediatric subjects aged 5 to 17 years. The study consisted of an 8-week treatment phase, a 2-week taper phase, and a 2-week follow-up phase. Subjects who were considered in remission at the end of the 8-week treatment phase per their Pediatric Crohn's Disease Activity Index (PCDAI) score were offered for immediate enrollment into an Entocort EC maintenance study.

Target subject population and sample size

The subject population for this study were children and adolescents aged 5 years to 17 years, inclusive, diagnosed with mild-to-moderate Crohn's disease of the ileum and/or ascending colon confirmed by endoscopic and/or radiographic evidence, and/or evidence of mucosal erosions and/or histology.

No formal sample size calculation was performed. The planned number of 110 subjects in the study was expected to provide adequate safety and tolerability data to address the primary objective.

Investigational product and comparator: Dosage, mode of administration, and batch numbers

The investigational product (IP) used in this study was Entocort EC in 3 mg capsules. Eleven batches of Entocort EC were used in this study; individual batch numbers and further information are included in the Clinical Study Report. During the treatment phase, subjects were dosed with oral Entocort EC once daily (qd) for 8 weeks (through Visit 4), according to body weight. Subjects weighing ≤25 kg received 6 mg (2x3 mg capsule) qd for 8 weeks. Subjects weighing >25 kg received 9 mg (3x3 mg capsule) qd for 8 weeks.

During the tapering and follow-up phases from Week 8 to Week 12 (Visit 4 to Visit 5), a subjects' dose was tapered for 2 weeks and then IP was discontinued and the subject was followed-up for 2 weeks. Subjects initially receiving the 9 mg qd dose had their dose tapered to 6 mg (2x3 mg capsule) qd and subjects who initially received the 6 mg qd dose had their dose tapered to 3 mg (1x3 mg capsule) qd.

Duration of treatment

This open-label study consisted of, an 8-week treatment phase with a 2-week taper phase, and a 2-week follow-up phase, a total of 12 weeks.

Subjects who participated in the subsequent maintenance study were not required to undergo the 2-week taper phase in this induction study.

Statistical methods

No formal statistical analyses or hypothesis tests were performed on any of the data from this study. Data are listed and summarized descriptively according to body weight at baseline.

Safety measures such as adverse events (AEs), glucocorticosteroid (GCS)-related side effects, hypothalamic-pituitary-adrenal-axis measurement, laboratory test results, and vital signs are listed and summarized descriptively using safety analysis set, with summaries including all subjects who received at least 1 dose of the IP.

Descriptive statistics summarize the PCDAI and IMPACT 3 scores at baseline and after 8 weeks of therapy, as well as the change in the scores from baseline using full analysis set.

All endpoints were measured at the end of the 8-week treatment phase.

Subject population

The population included in the study is representative of the target population i.e. children and adolescents aged 5 years to 17 years, with a diagnosis of mild-to-moderate Crohn's disease of the ileum and/or ascending colon.

A total of 123 subjects were enrolled in the study and 108 (87.8%) subjects received treatment with Entocort EC. A total of 17 (13.8%) subjects discontinued the study. The most common reasons for discontinuation of study were AEs (8 [6.5%] subjects) and lack of efficacy (6 [4.9%] subjects). There was no impact on the interpretation of study results due to the number of subjects who discontinued the study.

The mean age of subjects was 13.7 years (range 6 years to 17 years). The majority of subjects (103 [95.4%] subjects) were of age >8 years. There was similar number of males (57 [52.8%]) and females (51 [47.2%]) subjects. The demographics characteristics of the subjects were consistent with the study eligibility criteria.

Summary of efficacy results

Pediatric Crohn's disease activity index

A reduction (improvement) of the mean total PCDAI score was seen after 8 weeks of treatment with Entocort EC.

Patient reported outcomes/quality of life: IMPACT 3

There was an increase (improvement) in mean IMPACT 3 total score in subjects after 8 weeks of treatment with Entocort EC.

Summary of safety results

In total, 108 subjects received Entocort EC with a median duration of treatment exposure of 58 days (range: 5 days to 90 days). This duration of treatment exposure was considered to be sufficient for evaluation of safety of Entocort EC.

A total of 79 (73.1%) subjects reported AEs in any category. Of these, 39 (36.1%) subjects had AEs that were considered causally related to the IP as assessed by the investigator. Of the possibly related AEs, more than 75% were pre-specified potentially GCS side effects. None of the subjects had AE with an outcome of death. There were 8 (7.4%) subjects who reported serious adverse events (SAEs) and 9 (8.3%) subjects who reported discontinuation of the IP due to an AE (DAEs). There were no other significant adverse events (OAEs) identified in the study.

The majority of AEs were reported in the system organ class (SOC) of Gastrointestinal disorders (41 [38%] subjects), Skin and subcutaneous tissue disorders (29 [26.9%] subjects), and Metabolism and nutrition disorders (25 [23.1%]), and Infections and infestations (20 [18.5%] subjects). The most common AEs reported by preferred term were: Increased

appetite (17 [15.7%] subjects), abdominal pain (16 [14.8%] subjects), and acne (15 [13.9%] subjects).

Most AEs are related to Crohn´s disease, puberty, and possible GCS-related side effects. New or aggravated possible GCS-related signs and symptoms were reported following an active questioning according to a checklist and are included in the AE tables. This means that the frequencies of the corresponding AEs are higher than in a study with only standard reporting of AEs.

The proportion of subjects with any side effect possibly related to GCS increased from 45% at baseline to 60% during 8 weeks of treatment with Entocort EC.

A total of 8 (7.4%) subjects reported 11 SAEs during the study. These SAEs except for 1 were not related to the IP as assessed by the investigator. The majority of SAEs were reported in the SOC of Gastrointestinal disorders. Of the 8 subjects, 4 subjects had SAEs that were related to underlying Crohn's disease.

There were 9 (8.3%) subjects who discontinued the IP due to AEs. Six subjects had DAEs reported in the SOC of Gastrointestinal disorder. The DAEs except for 1 were not related to the IP as assessed by the investigator.

There were no clinically relevant safety findings noted in clinical laboratory parameters (haematology, clinical chemistry, and urinalysis), vital signs, and physical findings. As expected, an adaptation of adrenal steroids (cortisol/dehydroepiandrosterone sulfate [DHEAS]) was seen after 8 weeks of treatment with Entocort EC.