Clinical Study Report Synopsis

Drug Substance	Entocort™[1] EC
Study Code	D9422C00002
Edition Number	1
EudraCT Number	2011-003742-40

A Multicenter, Open label, Non-Comparative Study to Evaluate the Safety of Entocort™ EC as a Maintenance Treatment for Crohn's Disease in Pediatric Subjects Aged 5 to 17 Years, Inclusive

Study dates: First subject enrolled: 28 December 2011
Last subject last visit: 13 February 2014

Phase of development: Therapeutic confirmatory (III)

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

[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 (budesonide) in a pediatric mild to moderate Crohn's disease population for maintenance of clinical remission.	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 (presence of signs and symptoms), and HPA-axis measurement (serum cortisol and DHEAS).
Secondary	Efficacy	To characterize the disease activity through the PCDAI.	Development in PCDAI total score over time.
	PRO/ HRQOL	To assess QOL utilising a patient reported outcome (PRO) questionnaire (IMPACT 3).	Development in IMPACT 3 score over time.

Abbreviations: AE Adverse events; CYP3A4 Cytochrome P450 3A4; DHEAS Dehydroepiandrosterone sulfate; GCS Glucocorticosteroids; HPA-axis Hypothalamic-pituitary-adrenal axis; HRQOL Health-related quality of life; PCDAI Paediatric Crohn's disease activity index; PRO Patient-reported outcome; QOL Quality of life.

Study design

This clinical trial was a multi-center, open-label, non-comparative study to evaluate the safety of Entocort™ EC when used as a maintenance treatment for Crohn's disease in pediatric subjects aged 5 years to 17 years, inclusive. The study consisted of enrolment (Visit 1), 12-week maintenance treatment phase (Visit 2 to Visit 4); 2-week taper phase, and 2-week follow-up phase (Visit 5).

Target subject population and sample size

The subject population for this study was children and adolescents aged 5 years to 17 years, inclusive, with a diagnosis of mild to moderate Crohn's disease of the ileum and/or ascending colon that was in clinical remission. The diagnosis was confirmed by endoscopic and/or radiographic evidence, and/or evidence of mucosal erosions and/or histology and had a Paediatric Crohn's Disease Activity Index (PCDAI) score of ≤10 (PCDAI ≤10 confirmed that the subject was in clinical remission.).

No formal sample size calculation was performed. The planned number of 50 subjects in the study was expected to provide adequate safety and tolerability data to address the primary objective.

Investigational product and comparators: dosage, mode of administration, and batch numbers

The investigational product (IP) used in this study was Entocort™ EC in 3 mg capsules. The batch numbers were: 12-001064AZ/12-001169AZ/MPCP1100137-CA, 11-002572AZ/11-003399AZ/MPCP1100190-DE1, 11-001326AZ/11-002191AZ/MPCP1100137-IT, 11-001326AZ/11-002181AZ/MPCP1100137-PL, 12-001169AZ/12-001345AZ/MPCP1100137-PL , 11-000956AZ/11-001623AZ/MPBT1100078-US, and 13-000200AZ/13-000272AZ/MPBT1100078-US.

During the treatment phase, subjects were dosed with oral Entocort™ EC 6 mg once daily (qd) for 12 weeks (Visit 4). During the taper/follow-up phase from Week 12 to Week 16 (Visit 4 to Visit 5), subjects' dose was tapered to 3 mg qd (1x3 mg capsule) for 2 weeks. After 2 weeks at the tapered dosing, Entocort™ EC was discontinued and the subjects' were followed up for a further 2-week period, ending at Visit 5.

Duration of treatment

This open label study consisted of a 12-week maintenance treatment phase, a 2-week taper phase, and a 2-week follow-up phase.

Statistical methods

No formal statistical analyses or hypothesis tests were performed on any of the data from this study. Safety measures such as adverse events (AEs) including Glucocorticosteroids (GCS)-related side effects, hypothalamic-pituitary-adrenal axis (HPA-axis) measurement, laboratory test results, and vital signs are listed and summarized descriptively, with summaries including all subjects who received at least 1 dose of study treatment. Descriptive statistics was used to summarize the PCDAI and IMPACT 3 scores at baseline and after 12 weeks of therapy, as well as the change in the scores from baseline. All endpoints were measured at the end of the 12-week treatment period.

Subject population

A total of 55 subjects were enrolled at 19 centers across US (19 [34.5%]) subjects), Europe (27 [49.1%] subjects), and Canada (9 [16.4%] subjects). The majority of the subjects (43 subjects) enrolled in this study had entered into this study after completion of Study 1; this was in accordance with the CSP plan.

Of the 55 enrolled subjects, 50 (90.9%) subjects received and 5 (9.1%) subjects did not receive Entocort™ EC. The reason for not receiving Entocort™ EC was eligibility criteria not fulfilled for all 5 subjects. A total of 9 (16.4%) subjects discontinued the study. The most common reasons for discontinuation of study were AEs (3 [5.5%] subjects) and lack of efficacy (3 [5.5%] subjects). The majority (41 [74.5%]) of subjects completed the study.

The demographics characteristics of the subjects were consistent with the study eligibility criteria. The mean age of subjects was 13.8 years (range 8 years to 17 years). The majority of subjects (48 [96%] subjects) were of age >8 years. There was slightly higher number of males (30 [60%] subjects) than females (20 [40%] subjects). The majority of the subjects were white (45 [90%] subjects). The baseline characteristics of the subjects were consistent with the study eligibility criteria. There were 9/15 male subjects and 14/19 female subjects who had Tanner Stage ≥3. Female subjects were slightly more mature than male subjects; the median Tanner stage was Stage 4 for female subjects and Stage 3 for male subjects. The mean PCDAI score was 5.1, indicating that Crohn's disease was in the clinical remission stage at study entry.

Summary of efficacy results

Pediatric Crohn's disease activity index

After 12 weeks of treatment with Entocort™ EC, there was no major change in the mean PCDAI composite score, indicating that most of the subjects remained in the clinical remission stage.

Patient reported outcomes/quality of life

After 12 weeks of treatment with Entocort™ EC, subjects rated their quality of life as high as that at the baseline, when they were in the clinical remission stage. There was no major change in the mean total or individual domain score of IMPACT 3 scale.

Summary of safety results

A total of 50 subjects received Entocort™ EC with a median duration of treatment exposure of 98.5 days (range: 11 days to 135 days). This duration of treatment exposure was considered to be sufficient for evaluation of safety of Entocort™ EC 6 mg qd.

All the AEs reported during the treatment, taper, and follow up phases are reported collectively in this section. When looking at the frequency of AEs in this study, it should be noted that new or aggravated possible GCS-related signs and symptoms reported following active questioning according to a checklist have been included in the AE tables. This means that the frequencies of the corresponding AEs are higher than in a study with standard unsolicited reporting of AEs.

A total of 37 (74%) subjects reported AEs in any category (Table S2.). Of these, 10 (20%) subjects had AEs that were considered causally related to the IP by the investigator. Of the possibly related AEs, more than 80% were pre-specified potentially GCS side effects. None of the subjects had AE with an outcome of death. There were 4 (8%) subjects who reported serious adverse event (SAEs) and 3 (6%) subjects who reported AEs leading to discontinuation of the investigational product (DAEs). There were no OAEs reported in the study.

Table S2 AEs in any category for Entocort (Safety analysis set)

AE category	Number (%) of Subjects[a] Entocort (N=50)
Any AE	37 (74.0)
Any AE with outcome = death	0 (0.0)
Any SAE (including events with outcome = death)	4 (8.0)
Any AE leading to discontinuation of IP	3 (6.0)
Any AE causality related to the IP[b]	10 (20.0)
Any other significant AE[c]	0 (0.0)

[a] Subjects with multiple events in the same category were counted only once in that category. Subjects with events in more than one category were counted once in each of those categories.
[b] As assessed by the investigator.
[c] Significant AEs, other than SAEs, and those AEs leading to discontinuation of investigational product, which were of particular clinical importance were identified and classified as Other Significant AEs (OAEs). Includes adverse events with an onset date on or after the date of first dose and up to and including week 16 ±3 days after the date of first dose.
Please note that new or aggravated possible GCS-related signs and symptoms identified following active questioning according to a checklist have been included in the AE tables. This means that the frequencies of the corresponding AEs are higher than in a study with standard reporting of AEs.
AE Adverse event; SAE Serious adverse event; IP Investigational product.

Most of the AEs in the study were related to Crohn´s disease, puberty, and possible GCS-related side effects. The most common AEs reported by preferred term (PT) were: Abdominal pain (8 [16%] subjects), Crohn's disease (7 [14%] subjects), and acne (6 [12%] subjects). At each clinic visit, the subjects were evaluated for presence of 16 different signs and symptoms, associated with GCS treatment. There were no clinical relevant changes in possible GCS-related side effects over time. None of the subjects took CYP3A4 inhibitors or inducers during the study.

A total of 4 (8%) subjects reported 5 SAEs during the study. All SAEs were reported in the System organ class (SOC) of Gastrointestinal disorders. The SAEs reported were Crohn's disease (3 [6%] subjects), gastrointestinal haemorrhage (1 [2%] subject), and Ileal stenosis (1 [2%] subject). None of the SAEs were considered to be causally related to the IP by the investigator.

There were 3 (6%) subjects who discontinued the IP due to AEs. All DAEs were reported in the SOC of Gastrointestinal disorder. The DAEs reported were: Crohn's disease (2 [4%] subjects) and abdominal pain (1 [2%] subjects). None of the DAEs were considered as causally related to the IP by the investigator.

During the study, the mean value of serum cortisol increased, which is consistent with a reduced steroid dose compared to baseline. The changes in mean DHEAS value indicate unchanged or reduced adrenal suppression over time.

There were no clinically relevant safety findings noted in clinical laboratory parameters (haematology, clinical chemistry, and urinalysis), vital signs, and physical findings.