

**Public Assessment Report**  
**for paediatric studies submitted in accordance**  
**with Article 46 of Regulation (EC) No1901/2006, as amended**

**Budesonide**

**CZ/W/0019/pdWS/001**

<b>Rapporteur:</b>	<b>Czech Republic</b>
<b>Finalisation procedure (day 120):</b>	<b>21.7.2016</b>
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## ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Entocort™
INN (or common name) of the active substance(s):	Budesonide
MAH:	AstraZeneca
Pharmaco-therapeutic group (ATC Code):	A07EA06
Pharmaceutical form(s) and strength(s):	Capsules

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## List of Abbreviations

AEs	Adverse events
BMI	Body Mass Index
CDAI	Crohn's Disease Activity Index
CRP	C- Reactive Protein
CSP	Clinical Study Protocol
CYP3A4	Cytochrome P450 3A4
D9421-C 9 m	Budesonide
DAEs	Discontinuation of investigational product due to adverse event
DHEAS	Dehydroepiandrosterone sulfate
EEA	European Economic Area
FAS	Full analysis set
FDA	Food and Drug Administration
GCS	Glucocorticosteroids
HPA-axis	Hypothalamic-pituitary-adrenal axis
HRQL	Health-related quality of life
IBDQ	Inflammatory Bowel Disease Questionnaire
IP	Investigational product
MAH	Market authorization holder
OAEs	Other significant adverse events (ie, significant AEs, other than SAEs and DAEs, which are program)
PCDAI	Paediatric Crohn's Disease Activity Index
PEO	Patient-reported outcome
PT	Preferred term
QOL	Quality of life
SAEs	Serious adverse events
SOC	System organ class
US	United States

## I. EXECUTIVE SUMMARY

This is a data submission for Entocort capsules in accordance with Article 46 of the Regulation (EC) No 1901/2006. The CZ is the rapporteur for this procedure.

The rapporteur concludes that based on the data provided as part of this European paediatric work-sharing procedure under Article 46, the benefit-risk balance of Entocort capsules remains unchanged for the paediatric population.

SmPC changes are proposed in sections 4.8 and 5.1 that reflect current knowledge about use of the Entocort in paediatric population.

## II. RECOMMENDATION

Based on the review of the submitted paediatric data, the rapporteur recommends the following updates in SmPC and PL for Entocort capsules:

### Summary of outcome:

- ☐ No change
- ☒ Change
- ☒ New study data: section 5.1
- ☒ New safety information: section 4.8
- ☐ Paediatric information clarified: <section(s) xxxx, xxxx>
- ☐ New indication: <section(s) xxxx, xxxx>

## SUMMARY OF PRODUCT CHARACTERISTICS

### Section 4.8 Undesirable effects

The proposed changes of section 4.8 are only applicable to products that are already licensed for the paediatric indication

*[This section should be amended to include the below wording]*

*[...]*

Paediatric population

Systemic and inhaled corticosteroids, including ENTOCORT <sup>TM</sup>, may cause a reduction of growth velocity in paediatric patients. No long-term studies have been performed in paediatric patients treated with ENTOCORT <sup>TM</sup> capsules. Based on the available data from short-term studies (see section 5.1), the overall observed safety profile of ENTOCORT <sup>TM</sup> in paediatric patients is consistent with the safety profile in adults.

[...]

## **Section 5.1 Pharmacodynamic properties**

*[This section should be amended to include the below wording]*

[...]

### **Paediatric population**

Study D9422C0001 was an open-label, uncontrolled study designed to evaluate Entocort in 108 pediatric patients (children and adolescents aged 5 to 17 years) diagnosed with mild to moderate Crohn's disease of the ileum and/or ascending colon. The median duration of treatment exposure of Entocort of 58 days (range: 5 days to 90 days). Patients were dosed with oral Entocort once daily according to bodyweight, patients weighing  $\leq 25$  kg received 6 mg once daily for 8 weeks; patients weighing  $>25$  kg received 9 mg once daily for 8 weeks. During the 8 weeks of treatment there was a reduction in the mean ( $\pm$ SD) PCDAI score from 19.1 ( $\pm 10.1$ ) to 9.1 ( $\pm 8.5$ ), indicating an improvement in disease activity; with an improvement in mean ( $\pm$ SD) IMPACT 3 score from 132.1 ( $\pm 18.8$ ) to 140.9 ( $\pm 16.9$ ). AEs were observed at a similar frequency and severity as seen in adults, and were mostly related to Crohn's disease, puberty and possible GCS related side effects.

Study D9422C00002 was an open-label, un-comparative study designed to evaluate Entocort 6 mg once daily as maintenance treatment in 50 pediatric patients (children and adolescents aged 5 to 17 years) with a diagnosis of mild to moderate Crohn's disease of the ileum and/or ascending colon who were in clinical remission (PCDAI  $\leq 10$ ). Treatment consisted of a 12-week maintenance treatment phase of 6 mg once daily, a 2-week taper phase to 3 mg once daily. The median duration of treatment exposure of Entocort was 98.5 days (range: 11 days to 135 days). Most patients remained in the clinical remission stage, as there were no major changes in the mean PCDAI composite score or IMPACT 3 score. Mean (SD) PCDAI was 4.85 (3.62) at baseline and 6.89 (8.08) after 12 weeks of maintenance treatment with Entocort 6 mg daily. At the same points in time the mean IMPACT3 score was 145.62 (12.43) and 146.98 (15.48), respectively. AEs were observed at a similar frequency and severity as seen in adults, and were mostly related to Crohn's disease, puberty and possible GCS related side effects.

## **III. INTRODUCTION**

In May 2015, the MAH has submitted completed paediatric studies for Entocort™ capsules, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Entocort™ capsules and that there is no consequential regulatory action needed.

## **IV. SCIENTIFIC DISCUSSION**

In this procedure the MAH presents results of studies D9422C00001, D9422C00002 and D9423C00001, in accordance with Article 46 requirements.

### **Product background**

Entocort is an oral formulation of the glucocorticoid budesonide that was first approved for the treatment of adults with mild-to-moderate Crohn's disease in Sweden in March 1995, and by the United States (US) Food and Drug Administration (FDA) in October 2001. As at 1 April 2015, Entocort is approved for the treatment of Crohn's disease in adults in 21 European Economic Area (EEA) states and it is approved for the treatment of paediatric patients aged  $\geq 8$  years in 14 of these countries.

Entocort capsules are indicated for the treatment of Crohn's disease in the ileum and/or the ascending colon. The recommended daily dose in mild to moderate active disease is 9 mg daily for up to eight weeks, and for long-term use, to prolong remission, the recommended dose is 6 mg daily. In mild to moderate active Crohn's disease in children 8 years and above with a body weight over 25 kg, the recommended daily dose in mild to moderate active disease is 9 mg daily for up to eight weeks.

Entocort is also available as an enema, tablet for rectal suspension 2 mg and indicated for adults for the treatment of active ulcerative colitis involving the rectum, the sigmoid and the descending colon. Entocort enema is not approved for paediatric use.

#### **IV.1 Non-clinical aspects**

Not applicable as no non-clinical studies have been submitted.

#### **IV.2 Clinical aspects**

##### **IV.2.1 Introduction**

The MAH submitted 3 final reports for:

##### **Study D9422C00001**

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 D9422C00002**

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 D9423C00001**

A multicenter, double-Blind, randomized, parallel-group, phase III study to assess efficacy and safety of D9421-C 9 mg versus mesalazine 3g in patients with active Crohn's disease in Japan.

#### **Assessor's comment**

*First two studies were of similar design and the primary objective of both studies was to evaluate safety of Entocort in paediatric subjects. These studies were conducted to fulfil the US FDA PREA commitment for Entocort.*

*The third study was conducted upon request for development for the new drug application of Entocort capsules as a treatment for mild to moderate active Crohn's disease, made by the Research and Development Division of the Health Policy Bureau, and the Pharmaceutical and Food Safety Bureau in Japan. This study was focused on efficacy as well as safety endpoints.*

##### **IV.2.2 Clinical studies**

##### **Study D9422C00001**



A multicentre, open-label, non-comparative study to evaluate the safety of Entocort™ EC for the treatment of Crohn's disease in paediatric subjects aged 5 to 17 years, inclusive.

### **Methods**

This study was a phase III, therapeutic confirmatory study, performed to fulfil the US FDA PREA commitment for Entocort.

### **Objectives**

The primary objective of this study was to investigate the safety of Entocort™ EC in a Paediatric population treated for mild to moderate Crohn's disease.

The secondary objectives were to characterize the disease activity in the trial population before and after treatment through the Paediatric Crohn's Disease Activity Index (PCDAI) and Patient Reported Outcomes: Quality of Life with Entocort™ EC treatment based on a subject questionnaire (IMPACT 3).

### **Study design**

This was a multicentre, open-label, non-comparative study to evaluate the safety of Entocort™ EC for the treatment of Crohn's disease in paediatric 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 PCDAI score were offered for immediate enrolment into an Entocort™ EC maintenance study (Study D9422C00002).

The study was conducted at 25 study centres across 5 countries: 12 centres in the United States, 5 centres in Poland, 4 centres in Italy, 1 centre in Germany and 3 centres in Canada

### **Study population /Sample size**

The subject population for this study were children and adolescents aged 5 to 17 years, inclusive, weighing  $\geq 15$  kg, with a diagnosis of 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.

Main **exclusion criteria** were:

- imidazole derivatives use (e.g., ketoconazole) within the 7 days prior to Visit 1. Anti-TNF monoclonal antibody (antibodies) and cyclosporine from 12 weeks prior to Visit 1. Oral prednisone 5 mg per day (or GCS equivalent) or higher within 7 days prior to Visit 1.
- evidence of severe active Crohn's disease and/or stricturing and prestenotic dilatation, clinical evidence of obstruction, perirectal abscess, perirectal disease with active draining fistulas, perforation, or any septic complications.
- any previous intestinal resection proximal to and including the ascending colon.
- initiation of azathioprine or 6-merkaptopurine less than 3 months prior to study start or during the treatment phase of the study was prohibited.
- diabetes, uncontrolled hypertension, liver function tests (transaminase and bilirubin) values  $>2$  times upper limit of their normal range, or a history of carcinoma (excluding basal or squamous carcinoma).
- Initiation of 5-aminosalicylates  $<2$  weeks prior to study start or during treatment phase of study was prohibited.
- Initiation of methotrexate  $<2$  weeks prior to study start or during treatment phase of study was prohibited.
- Initiation of antibiotics for Crohn's disease  $<2$  weeks prior to study start or during treatment phase of the study was prohibited.
- erythromycin and other macrolide antibiotics use within 7 days of study enrolment.
- morning cortisol level  $<150$  nmol/L (5.4  $\mu\text{g/dL}$ ) or DHEAS below normal range for age and gender.

**Sample size calculation:** 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.

## Treatments

The investigational product used in this study was Entocort™ EC in 3 mg capsules.

During the treatment phase of the study, subjects were dosed with oral Entocort™ EC once daily for 8 weeks (through Visit 4) according to body weight. Subjects weighing ≤ 25 kg received 6 mg (2 x 3 mg capsule) daily for 8 weeks. Subjects weighing >25 kg received 9 mg (3 x 3 mg capsule) daily for 8 weeks.

Each subject's weight at baseline determined how that subject was dosed for the duration of the study, regardless of any subsequent changes in weight during the course of the study.

During the tapering/follow-up period from Week 8 to Week 12 (Visit 4 to Visit 5), a subjects' dose was tapered. Subjects initially receiving the 9 mg dose tapered their dose to 6 mg (2 x 3 mg capsule) and subjects who initially received the 6 mg dose tapered to 3 mg (1 x 3 mg capsule) for two additional weeks of therapy. After two weeks at the tapered dosing, Entocort™ EC was discontinued and the subject followed up for a further 2 week period.

## Outcomes/endpoints (Table 1)

Priority	Objective		Variable	
	Type	Description	Description	Method of assessment and derivation
Primary	Safety	To investigate the safety of Entocort EC in a pediatric population treated for mild-to-moderate Crohn's disease	<ul style="list-style-type: none"> <li>• AEs (including AEs that occurred in subjects who took CYP3A4 inhibitors or inducers),</li> <li>• Clinical laboratory evaluations,</li> <li>• Vital signs and physical examination,</li> <li>• GCS-related side effects (presence of signs and symptoms listed in Section 4.3.3.4 of the CSP), HPA-axis measurement (serum cortisol and DHEAS)</li> </ul>	See CSP Sections 4.1 and 4.3
Secondary	Efficacy	To characterize the disease activity in the trial population before and after treatment through the PCDAI	Development in PCDAI total score over time	The calculation of PCDAI is described in Appendix C to the CSP
	PRO/QOL	To assess the QOL with Entocort EC treatment based on a subject questionnaire (IMPACT 3)	Development in IMPACT 3 scores over time	The calculation of the IMPACT 3 score is described in Appendix E to the CSP

AEs Adverse events; CSP Clinical study protocol; 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.

The PCDAI is a validated instrument used to assess disease activity in paediatric subjects. The following parameters were calculated: abdominal pain, stool pattern, general well-being rating, hematocrit, erythrocyte sedimentation rate, albumin levels, height and weight, abdominal mass, presence of perirectal disease, and extra-intestinal manifestations.

Each item in the PCDAI is numerically weighted. The PCDAI has a scoring range of approximately 0 to 100. A score of ≤ 10 is generally considered to represent inactive disease.

IMPACT 3 questionnaire is a validated instrument used to assess QOL for subjects with inflammatory bowel disease. It consists of 35 items categorized into the following 6 domains: bowel symptoms, systemic symptoms, emotional functioning, social functioning, body image, and treatment/interventions. The possible scores for IMPACT 3 ranged from 35 (the worst score) to 175 (indicating the best possible score with respect to QOL).

For subjects aged 9 years to 17 years, the questionnaire was self-administered. Subjects aged

8 years could complete this questionnaire with the help of a parent/guardian. Subjects aged 5 years to 7 years were not required to complete this questionnaire, as this tool has not been validated for that age group.

## Statistical Methods

There was no formal statistical analysis required for this study. Continuous variables have been summarized in terms of mean, standard deviation, median, minimum, and maximum and discrete variables are summarized in terms of frequency and percentage. All endpoints were measured at the end of the 8-week treatment period

Safety measures such as (AEs), GCS-related side effects, laboratory test results, and vital signs are listed and summarized descriptively with summaries including all subjects who received at least one dose of the IP. The serum cortisol and DHEAS measurement of the HPA-axis are summarized descriptively by visit. The change from baseline is also calculated and summarized.

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.

## Analysis sets

There were two analysis sets considered in this study; the safety set and the full analysis set (FAS).

The safety analysis set consisted of all subjects who took at least one dose of Entocort™ EC. The FAS included all subjects included in the safety analysis set who had a complete post-baseline data for PCDAI assessment (Table 2).

**Table 2: Analysis Set, All subjects (Study D9422C00001)**

	Number of subjects Entocort
Subjects enrolled	123
Subjects included in safety analysis set <sup>a</sup>	108
Subjects excluded from safety analysis set	15
Did not receive treatment	15
Subjects included in full analysis set <sup>b</sup>	105
Subjects excluded from full analysis set	18
Did not receive treatment	15
Insufficient data for efficacy endpoint	3

<sup>a</sup> The safety analysis set consist of all subjects who took at least one dose of Entocort.

<sup>b</sup> The full analysis set (FAS) includes all subjects included in the safety analysis set who had complete post baseline (Visit 4) data for Paediatric Crohns Disease Activity Index (PCDAI) assessment.

Source data derived from [Table 11.1.3](#).

## Results

### Recruitment/ Number analyzed

The first patient was enrolled to the study on 03rd November 2011. The last patient completed the study on 10th September 2014.

A total of 123 subjects were enrolled at 25 centres across the US (47 [38.2%] subjects), Poland (40 [32.5%] subjects), Canada (19 [15.4%] subjects), Italy (15 [12.2%] subjects), and Germany (2 [1.6%] subjects).

Of the 123 enrolled subjects, 108 (87.8%) received treatment with Entocort™ EC. There were 15 (12.2%) subjects who did not receive treatment; the most common reason for not receiving treatment was eligibility criteria not fulfilled (12 [9.8%] subjects).

A total of 17 (13.8%) subjects discontinued the study. The most common reasons for discontinuation of the study were due to AEs (8 [6.5%] subjects) and lack of efficacy (6 [4.9%] subjects). The majority (91 [74%]) of subjects completed the study. There was no impact on the interpretation of the study results due to the number of subjects who discontinued the study (Table 3).

**Table 3: Subject Disposition, All Subjects (Study D9422C00001)**

	Number(%) of subjects Entocort (N=123)
Subjects enrolled <sup>a</sup>	123
Subjects who received treatment	108 ( 87.8)
Subjects who did not receive treatment	15 ( 12.2)
Study discontinued due to withdrawal by subject	1 ( 0.8)
Study discontinued due to screen failure	12 ( 9.8)
Study discontinued due to adverse event	1 ( 0.8)
Study discontinued due to other	1 ( 0.8)
Subjects who completed study <sup>b</sup>	91 ( 74.0)
Subjects who discontinued study /withdrawn prematurely	17 ( 13.8)
Study discontinued due to withdrawal by subject	1 ( 0.8)
Study discontinued due to screen failure	1 ( 0.8)
Study discontinued due to lack of efficacy	6 ( 4.9)
Study discontinued due to dev. of study-spec. withdrawal criteria	1 ( 0.8)
Study discontinued due to adverse event	8 ( 6.5)

<sup>a</sup> Informed consent received.

<sup>b</sup> Subjects who completed follow-up visit or Visit 4 (Week 8) if opted for maintenance phase study.

N Number of subjects in treatment group.

Source data derived from Table 11.1.1.

## Baseline data

The demographics characteristics of the subjects were consistent with the study eligibility criteria. 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 male (57 [52.8%]) and female (51 [47.2%]) subjects. The majority of the subjects were White (100 [92.6%] subjects).

The baseline characteristics of the subjects were consistent with the study eligibility criteria. The mean height of subjects was 157.72 cm and the mean body weight was 48.09 kg (range 18.8 kg to 96.5 kg). The mean BMI of the subjects was 19.02 kg/m<sup>2</sup>.

There were 28/43 male subject and 36/49 subject who had Tanner stage more than 3. The maturity of the female subjects was same as the male subjects; the median Tanner stage was Stage 4. The mean PCDAI score was 19.1, indicating mild Crohn's disease at the study entry.

The mean duration from diagnosis of Crohn's disease was 1.08 years at baseline. The majority of subjects had Crohn's disease located in the ileum (94 [87%] subjects). A total of 63 (58.3%) subjects were detected with physical abnormalities at baseline (Visit 1). These abnormalities were commonly related to abdomen (30 [27.8%] subjects), skin (21 [19.4%] subjects), and genital/rectal region (20 [18.5%] subjects) reflecting Crohn's disease signs and symptoms (Table 4, Table 5)

**Table 4: Demographic Characteristics, Safety Analysis Set (Study D9422C00001)**

Demographic characteristic		Entocort (N=108)
Age (years)	n	108
	Mean	13.7
	SD	2.410
	Median	14
	Min	6
	Max	17
Age group (years) n (%)	≤ 8	5 ( 4.6)
	> 8	103 ( 95.4)
	Total	108 (100.0)
Sex n (%)	Male	57 ( 52.8)
	Female	51 ( 47.2)
	Total	108 (100.0)
Race n (%)	WHITE	100 ( 92.6)
	BLACK OR AFRICAN AMERICAN	4 ( 3.7)
	ASIAN	1 ( 0.9)
	OTHER	3 ( 2.8)
	Total	108 (100.0)
Ethnic group n (%)	Hispanic or Latino	13 ( 12.0)
	Not Hispanic or Latino	31 ( 28.7)
	Not reported	64 ( 59.3)
	Total	108 (100.0)

Max Maximum; Min Minimum; n Number of Subjects in analysis. N Number of Subjects in treatment group.

SD Standard deviation.

Source data derived from Table 11.1.4.

**Table 5: Subject Baseline Characteristics (Safety Analysis Set) (Study D9422C00001)**

Demographic characteristic		Entocort (N=108)
Height (cm)	n	107
	Mean	157.72
	SD	14.774
	Median	159.00
	Min	112.0
	Max	191.0
Weight (kg)	n	108
	Mean	48.09
	SD	15.356
	Median	47.25
	Min	18.8
	Max	96.5
Weight n (%)	≤ 25	5 ( 4.6)
	> 25	103 ( 95.4)
BMI (kg/m <sup>2</sup> )	n	107
	Mean	19.02
	SD	3.994
	Median	18.07
	Min	12.9
	Max	38.1
Location Crohn's disease		
Ascending Colon n (%)	No	57 ( 52.8)
	Yes	51 ( 47.2)
Ileum n (%)	No	14 ( 13.0)
	Yes	94 ( 87.0)
Time since first diagnosis of Crohn's disease (years)	n	108
	Mean	1.08
	SD	1.535
	Median	0.00
	Min	0.0
	Max	7.0

Baseline Visit 1 (Day 1).

Max Maximum; Min Minimum; n Number of subjects in analysis; N Number of subjects in treatment group;

SD Standard deviation.

Source data derived from [Table 11.1.5](#).

## Protocol deviation

A total of 40 (37%) subjects had at least one protocol deviation (Table 6). The most common protocol deviations were protocol required procedures not adhered to (27 [25%] subjects) and did not fulfil eligibility criteria (12 [11.1%] subjects).

These protocol deviations did not justify exclusion of the subjects from any of the analysis sets. Altogether, these protocol deviations did not raise concerns about the overall conduct of the study.

**Table 6: Protocol Deviations, Safety Analysis Set (Study D9422C00001)**



	Number (%) of subjects Entocort (N=108)
<b>Protocol deviation<sup>a</sup></b>	
<b>Number of subjects with at least 1 deviation</b>	40 ( 37.0)
Protocol-required procedure not adhered to	27 ( 25.0)
Did not fulfill eligibility criteria	12 ( 11.1)
Received incorrect investigational treatment/dose	5 ( 4.6)
Received prohibited concomitant medication	2 ( 1.9)
Deviations before the start of treatment and during treatment.	
Note that the same subject could have had more than 1 protocol deviation.	
↓ Number of subjects in treatment group.	

Restricted medication during treatment and taper phase:

There were 5 (4.6%) subjects who took restricted medications during the treatment phase (Table 7) and 4 (3.7%) subjects during the taper and follow-up phase of the study (Table 8).

**Table 7: Restricted Medications during Treatment Phase, Safety Analysis Set, (Study D9422C00001)**

ATC classification / Generic term	Number (%) of Subjects Entocort (N=108)
Number of Subjects with restricted concomitant medication	5 ( 4.6)
Glucocorticoids	2 ( 1.9)
Beclometasone dipropionate	1 ( 0.9)
Triamcinolone hexacetonide	1 ( 0.9)
Imidazole derivatives	1 ( 0.9)
Metronidazole	1 ( 0.9)
Macrolides	1 ( 0.9)
Azithromycin	1 ( 0.9)
Other immunosuppressants	2 ( 1.9)
Azathioprine	2 ( 1.9)

A subject could have one or more generic term reported under a given ATC text.

Includes medications that began prior to start of the study treatment but were ongoing after the start of the study treatment.

Treatment phase is from day of first dose till Visit 4.

ATC Anatomical therapeutic chemical classification.

Source data derived [Table 11.1.19](#).

**Table 8: Restricted Medications during taper/Follow-up Phase, Safety Analysis Set (Study D9422C00001)**

ATC classification / Generic term	Number (%) of Subjects Entocort (N=108)
Number of Subjects with restricted concomitant medication	4 ( 3.7)
IMIDAZOLE DERIVATIVES	2 ( 1.9)
METRONIDAZOLE	1 ( 0.9)
METRONIDAZOLE BENZOATE	1 ( 0.9)
OTHER IMMUNOSUPPRESSANTS	2 ( 1.9)
AZATHIOPRINE	1 ( 0.9)
METHOTREXATE	1 ( 0.9)

**Assessor's comments**

*There are discrepancies in the number of the subjects received restricted medication in the study report, document d9422c00001-12-2-02-protocol-deviations.pdf and document d9422c00001-12-2-04-demographic-and-baseline-characteristics.pdf. MAH is required to clarify the number of subjects who used restricted medication with particular attention to the type of restricted medication (i.e. glucocorticoids) for both treatment and taper/follow up period. (LoQ)*

Primary variable:

There were no primary efficacy variables in this study. Efficacy was a secondary objective.

**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 (Table 9). 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 were 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.



**Table 9: AEs, Most Common by Preferred Term, frequency of > 4%, Safety Analysis Set (Study D9422C00001)**

Preferred term	Number (%) of subjects <sup>a</sup>
	Entocort (N=108)
Subjects with any AE	79 ( 73.1)
Increased Appetite	17 ( 15.7)
Abdominal Pain	16 ( 14.8)
Acne	15 ( 13.9)
Irritability	14 ( 13.0)
Cushingoid	13 ( 12.0)
Crohn's Disease	11 ( 10.2)
Headache	9 ( 8.3)
Decreased Appetite	6 ( 5.6)
Insomnia	6 ( 5.6)
Nausea	6 ( 5.6)
Anaemia	5 ( 4.6)
Hirsutism	5 ( 4.6)
Vomiting	5 ( 4.6)

<sup>a</sup> Number (%) of subjects with at least 1 AE for a preferred term, sorted in decreasing frequency of PT. Includes adverse events with an onset date on or after the date of first dose and up to and including Week 12 ± 3 days after the date of first dose. Most common is defined as a total frequency of > 4% (in any treatment group). 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; GCS Glucocorticosteroids; MedDRA Medical dictionary for regulatory activities; N Number of subjects in treatment group; PT Preferred term. Source data derived from Table 11.3.2.4. MedDRA version 17.0.

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 (Table 10).

**Table 10: Possible Glucocorticosteroid (GSC) Side Effects by Examination Status, Safety Analysis Set (Study D9422C00001)**

GCS related side effects	Number of subjects in each visit Entocort (N=108)	Number (%) of subjects with side effects possibly related GCS at each visit
Subjects with any side effects possibly related GCS	108	72 ( 66.7)
Subjects with any side effects possibly related GCS at Visit 1	108	49 ( 45.4)
Subjects with any side effects possibly related GCS at Visit 4	106	65 ( 61.3)
Subjects with any side effects possibly related GCS at Visit 5	53	26 ( 49.1)

<sup>a</sup>percentage (%) of subjects reporting symptoms/signs following active questioning. <sup>b</sup>GCS Glucocorticosteroids. Source data derived from Table 11.3.6.2.

A total of 8 (7.4%) subjects reported 11 SAEs during the study (Table 11). These SAEs except for one 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.

**Table 11: SAEs by System Organ Class and Preferred Term, Safety Analysis Set (Study D9422C00001)**

System organ class / Preferred term	Number (%) of subjects <sup>a</sup>
	Entocort (N=108)
Subjects with any SAE	8 ( 7.4)
Gastrointestinal disorders	5 ( 4.6)
Crohn's Disease	4 ( 3.7)
Diarrhoea Haemorrhagic	1 ( 0.9)
Small Intestinal Obstruction	1 ( 0.9)
Metabolism and nutrition disorders	1 ( 0.9)
Hypokalaemia	1 ( 0.9)
Musculoskeletal and connective tissue disorders	1 ( 0.9)
Musculoskeletal Chest Pain	1 ( 0.9)
Skin and subcutaneous tissue disorders	1 ( 0.9)
Erythema Nodosum	1 ( 0.9)

<sup>a</sup> Number (%) of subjects with an SAE, sorted by international order for system organ class and alphabetically for preferred term.  
Subjects with multiple SAEs were counted once for each system organ class / preferred term.  
Includes adverse events with an onset date on or after the date of first dose and up to and including Week 12 ±3 days after the date of first dose.  
MedDRA Medical dictionary for regulatory activities; N Number of subjects in treatment group; SAE Serious adverse event.  
Source data derived from Table 11.3.4.1.  
MedDRA version 17.0.

There were 9 (8.3%) subjects who discontinued the IP due to AEs (Table 12). 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.

**Table 12: AEs leading to Discontinuation of IP, by System Organ Class and Preferred Term , Safety Analysis Set (Study D9422C00001)**

System organ class / Preferred term	Number (%) of subjects <sup>a</sup>
	Entocort (N=108)
Subjects with an AE leading to discontinuation <sup>b</sup>	9 ( 8.3)
Gastrointestinal disorders	6 ( 5.6)
Crohn's Disease	5 ( 4.6)
Abdominal Pain	1 ( 0.9)
Diarrhoea	1 ( 0.9)
Small Intestinal Obstruction	1 ( 0.9)
Musculoskeletal and connective tissue disorders	1 ( 0.9)
Fistula	1 ( 0.9)
Skin and subcutaneous tissue disorders	1 ( 0.9)
Hair Growth Abnormal	1 ( 0.9)
Vascular disorders	1 ( 0.9)
Pallor	1 ( 0.9)

<sup>a</sup> Number (%) of subjects with an AE leading to discontinuation of IP, sorted by international order for system organ class and by decreasing frequency for preferred term.  
<sup>b</sup> Action taken, Entocort EC permanently stopped.  
Subjects with multiple AEs leading to discontinuation were counted once for each system organ class/preferred term.  
Includes adverse events with an onset date on or after the date of first dose and up to and including Week 12 +/- 3 days  
AE Adverse event; IP Investigational product; MedDRA Medical dictionary for regulatory activities; N Number of subjects in treatment group.  
Source data derived from Table 11.3.5.1.  
MedDRA version 17.0.

### Assessor comments

Based on the submitted study and referring to Table 9 it seems that particular adverse reactions (i.e. acne; assessed by the investigators as related) appear more frequently in children in comparison with adults. The MA holder will be requested to compare safety profile of budesonide for children and adults and these findings possibly reflect in the section 4.8 of the SmPC.

The adrenal function was assessed by measurement of morning cortisol and DHEAS levels. The absolute and percentage change from baseline for cortisol levels and absolute change from baseline for DHEAS levels are presented in Table 13.

As expected, an adaptation of adrenal steroids (cortisol/ DHEAS) was seen after 8 weeks of treatment with Entocort™ EC.

**Table 13: Cortisol Levels, Absolute and % Change from Baseline (Safety Analysis Set), Dehydroepiandrosterone Sulphate (DHEAS), Absolute and Change from Baseline (Safety Analysis Set) (Study D9422C00001)**

Variable	SI-Unit	Visit	Result						% Change (Post-Baseline)-					
			n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Cortisol	nmol/L	Visit 1 (Day 1)	105	323.54	160.49	279.00	61.0	933.0						
		Visit 4 (Week 8)	103	185.07	169.54	160.00	14.0	897.0	103	-31.67	81.95	-50.00	-97.9	500.0
		Visit 5 (Week 12)	6	432.17	240.82	351.00	155.0	861.0	6	41.19	98.56	30.38	-57.2	228.6

Max..Maximum; Min Minimum; SD Standard deviation.

Source data derived from Table 11.3.7.12.

**Table 26 Dehydroepiandrosterone sulphate (DHEAS), absolute and change from baseline (Safety analysis set)**

Variable	SI-Unit	Visit	Result					Change (Post-Baseline)-						
			n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
Dehydroepiandr osterone Sulfate	umol/L	Visit 1 (Day 1)	104	2.47	1.875	0.2	1.85	8.8						
		Visit 4 (Week 8)	99	1.40	1.385	0.2	1.00	7.7	99	-1.08	1.289	-6.3	-0.90	2.9
		Visit 5 (Week 12)	6	1.77	1.429	0.2	1.45	4.4	6	-0.12	0.659	-1.1	0.00	0.8

Max..Maximum; Min Minimum; SD Standard deviation.

Source data derived from Table 11.3.7.10.

There were no AEs under this category as none of the subjects took CYP3A4 inhibitors or inducers during the study

None of the subjects had an AE with an outcome of death.

### Assessor comments

In the study report was mentioned, that there were no subjects receiving CYP3A4 inhibitors or inducers during the study. However, in the document "d9422c00001-12-2-04-demographic-and-baseline-characteristics.pdf." are disclosed patients, who received CYP3A4 inhibitors. MAH should discuss this discrepancy and evaluate the safety profile in the patients who received CYP3A4 inhibitors as concomitant medication.

## Secondary variables (efficacy endpoints):

### 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 Table 14.

**Table 14: PCDAI Score Distribution at Baseline and End of Treatment (Week8, FAS)  
(Study D9422C00001)**

Visit Number	n	Number(%) of subjects			
		PCDAI score ≤10	PCDAI score ≤20	PCDAI score ≤30	PCDAI score decrease of >12.5
Visit 1 (Day 1)	105	21(20.00)	73(69.52)	93(88.57)	
Visit 4 (Week 8)	105	76(72.38)	93(88.57)	103(98.10)	38(36.19)

Subjects with complete PCDAI scores were reported.

Baseline Visit 1 (Day 1).

FAS Full analysis set; n Number of subjects in analysis; PCDAI Pediatric Crohn's disease activity index.

Source data derived from Table 11.2.1.2.

### 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 (Table 15).

**Table 15: Impact 3 Total Score, Safety Analysis Set (Study D9422C00001)**

Visit	IMPACT3 score						Change from baseline					
	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
Visit 1 (Day 1)	107	132.07	18.769	63.0	134.00	167.0						
Visit 4 (Week 8)	103	140.86	16.910	88.0	141.00	171.0	103	7.85	13.290	-29.0	7.00	43.0

Baseline Visit 1 (Day 1).

Max Maximum; Min Minimum; n Number of subjects in analysis; SD Standard deviation.

Source data derived from Table 11.2.1.4.

### Assessor's comment

*Based on the provided demographic data, the population in this therapeutic confirmatory study was representative of the target population (i.e. paediatric).*

*The primary endpoint of this study was safety profile of Entocort in children aged 5 to 17 years. To our knowledge, the product is approved in EU for use in children from 8 years. As study was not designed to assess efficacy in children younger than 8 years, and there were only 5 subjects younger than 8 years, no conclusions on the efficacy in this aged group can be made.*

*As regards the safety, the MA holder is requested to clarify discrepancies in the use of the restricted medication, subjects took CYP3A4 inhibitors and evaluate safety profile of the product in children in comparison with adults and these findings reflect in the section 4.8 of the SmPC.*

*The MA holder is also requested to proposed changes in the section 5.1 to include the information about objectives and conclusions of the submitted study (LoQ).*

## Study D9422C00002

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 paediatric subjects aged 5 to 17 years.

### **Methods**

This study was a phase III, therapeutic confirmatory study, performed to fulfil the US FDA PREA commitment for Entocort.

### **Objectives**

The primary objective of this study was to investigate the safety of Entocort™ EC in a Paediatric population treated for mild to moderate Crohn's disease. The secondary objective was to characterize the disease activity in the trial population before and after treatment through the Paediatric Crohn's Disease Activity Index (PCDAI) and Patient Reported Outcomes: Quality of Life with Entocort™ EC treatment based on a subject questionnaire (IMPACT 3).

### **Study design**

This clinical study was a multi-centre, open-label, non-comparative study to evaluate the safety of Entocort™ EC when used as a maintenance treatment for Crohn's disease in paediatric subjects aged 5 to 17 years, inclusive.

The study consisted of screening and enrolment phase (Visit 1), 12-week maintenance treatment phase (Visit 2 to Visit 4), a 2-week taper phase, and a 2-week follow-up phase (Visit 5).

The study was conducted at 19 centres across 5 countries: 7 centres in the United States, 5 centres in Poland, 3 centres in Italy, 2 centres in Germany and 2 centres in Canada

### **Study population /Sample size**

The subject population for this study were children and adolescents aged 5 to 17 years, inclusive, weighing  $\geq 15$  kg, with a diagnosis of 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. Subjects could enter this study from the paediatric Entocort induction protocol (D9442C00001) but this was not mandatory. If subjects fulfilled the eligibility criteria as stated and were in Crohn's disease clinical remission, they could enter this study.

Other **inclusion criteria** were:

- PCDAI  $\leq 10$  (PCDAI  $\leq 10$  confirmed that the subject was in clinical remission.)

Main **exclusion criteria** were:

- imidazole derivatives use (e.g., ketoconazole) within the 7 days prior to Visit 1. Anti-TNF monoclonal antibody (antibodies) and cyclosporine from 12 weeks prior to Visit 1. Oral prednisone 5 mg per day (or GCS equivalent) or higher within 7 days prior to Visit 1.
- evidence of severe active Crohn's disease and/or stricturing and prestenotic dilatation, clinical evidence of obstruction, perirectal abscess, perirectal disease with active draining fistulas, perforation, or any septic complications.
- any previous intestinal resection proximal to and including the ascending colon.
- initiation of azathioprine or 6-merkaptopurine less than 3 months prior to study start or during the treatment phase of the study was prohibited.
- diabetes, uncontrolled hypertension, liver function tests (transaminase and bilirubin) values  $>2$  times upper limit of their normal range, or a history of carcinoma (excluding basal or squamous carcinoma).
- Initiation of 5-aminosalicylates  $<6$  weeks prior to study start or during treatment phase of study was prohibited.

- Initiation of methotrexate <2 weeks prior to study start or during treatment phase of study was prohibited.
- Initiation of antibiotics for Crohn's disease <2 weeks prior to study start or during treatment phase of the study was prohibited.
- erythromycin and other macrolide antibiotics use within 7 days of study enrolment.
- morning cortisol level <150 nmol/L (5.4 µg/dL) or DHEAS below normal range for age and gender.

Sample size calculation: No formal statistical analysis or hypothesis testing was planned, and as such, 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.

## Treatments

The investigational product used in this study was Entocort™ EC (budesonide) in 3 mg capsules. During the maintenance treatment phase of the study, subjects were dosed with oral Entocort™ EC once daily at 6 mg (2 x 3mg capsules) for 12 weeks (through Visit 4.) During the tapering/follow-up period from Week 12 to Week 16 (Visit 4 to Visit 5), a subjects' dose were tapered to 3 mg once daily (1 x 3mg capsule) for two weeks. After two weeks at the tapered dosing, Entocort™ EC were discontinued and the subject were followed for a further 2-week period, ending at Visit 5.

## Outcomes/endpoints (Table 16)

**Table 16: Study Objectives and Variable (study D9422C00002)**

Priority	Type	Objective	Variable	Method of assessment and derivation
		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.	<p>AEs (including AEs that occurred in subjects who took CYP3A4 inhibitors or inducers)</p> <p>Clinical laboratory evaluations</p> <p>Vital signs and physical examination</p> <p>GCS-related side effects (presence of signs and symptoms listed in Section 4.3.3.4 of the CSP) and HPA-axis measurement (serum cortisol and DHEAS).</p>	See CSP Section 4.1 and Section 4.3.
Secondary	Efficacy	To characterize the disease activity in the trial population before and after treatment through the PCDAI.	Development in PCDAI total score over time.	The calculation of the PCDAI is described in Appendix C of the CSP.
	PRO/QOL	PRO: QoL with Entocort™ EC treatment based on a subject questionnaire (IMPACT 3).	Development in IMPACT 3 score over time.	The calculation of the IMPACT 3 score is described in Appendix E of the CSP.

AEs Adverse events; CSP Clinical study protocol; 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.

## Statistical Methods

The statistical methods were the same as for study D9422C00001.

## Analysis sets

The safety analysis set consisted of all subjects who took at least one dose of Entocort™ EC. The FAS consisted of all subjects included in the safety analysis set who had a complete post-baseline (Visit 4) data for PCDAI assessment.



## Results

### Recruitment/ Number analysed

The first patient was enrolled to the study on 28th December 2011. The last patient completed the study on 13th February 2014.

A total of 55 subjects were enrolled at 19 centres 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) (Table 17).

**Table 17: Subject Disposition (All Subjects, Study D9422C00002)**

	Number(%) of subjects Entocort (N=55)
Subjects enrolled <sup>a</sup>	55
Subject who received treatment	50 ( 90.9)
Subject who did not received treatment	5 ( 9.1)
Study discontinued due to screen failure	5 ( 9.1)
Subjects who completed study <sup>b</sup>	41 ( 74.5)
Subject who discontinued study /withdrawn prematurely	9 ( 16.4)
Study discontinued due to adverse event	3 ( 5.5)
Study discontinued due to dev. of study-spec. withdrawal criteria	1 ( 1.8)
Study discontinued due to lack of efficacy	3 ( 5.5)
Study discontinued due to screen failure	1 ( 1.8)
Study discontinued due to other reason <sup>c</sup>	1 ( 1.8)

<sup>a</sup> Informed consent received.

<sup>b</sup> Includes subjects who completed treatment phase and follow-up phase.

Source: Table 11.1.1.

**Table 18: Analysis Set, All Subjects (study D9422C00002)**

	Number of subjects Entocort
<b>Subjects enrolled</b>	55
Subjects included in safety analysis set <sup>a</sup>	50
Subjects excluded from safety analysis set	5
Did not receive treatment	5
Subjects included in full analysis set <sup>b</sup>	49
Subjects excluded from full analysis set	6
Did not receive treatment	5
Insufficient data for efficacy endpoint	1

<sup>a</sup> The safety analysis set consisted of all subjects who took at least 1 dose of Entocort.

<sup>b</sup> The full analysis set included all subjects included in the safety analysis set who had complete post-baseline (Visit 4) data for Pediatric Crohn's Disease Activity Index assessment.

Source: Table 11.1.3.

## Baseline data

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). (Table 19)

**Table 19: Demographic Characteristics, Safety Analysis Set (Study D9422C00002)**

Demographic characteristic		Entocort (N=50)
Age (years)	N	50
	Mean	13.8
	SD	2.444
	Median	15
	Min	8
	Max	17
Age group (years) n (%)	≤ 8	2 ( 4.0)
	> 8	48 ( 96.0)
	Total	50 (100.0)
Sex n (%)	Male	30 ( 60.0)
	Female	20 ( 40.0)
	Total	50 (100.0)
Race n (%)	White	45 ( 90.0)
	Black or African American	2 ( 4.0)
	Other	3 ( 6.0)
	Total	50 (100.0)
Ethnic group n (%)	Hispanic or Latino	5 ( 10.0)
	Not Hispanic or Latino	13 ( 26.0)
	Not Applicable	32 ( 64.0)
	Total	50 (100.0)

n Number of subjects in analysis; N Number of subjects in treatment group.

SD Standard deviation.

Source: Table 11.1.4.

The baseline characteristics of the subjects were consistent with the study eligibility criteria. The mean height of subjects was 160.79 cm and the mean body weight was 49.64 kg (range: 23.5 kg to 84.5 kg). The mean BMI of the subjects was 18.77 kg/m<sup>2</sup>. 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 the study entry (Table 20).



**Table 20: Subject Baseline Characteristics, Safety Analysis Set (Study D9422C00002)**

Demographic characteristic		Entocort (N=50)
Height (cm)	n	50
	Mean	160.79
	SD	15.891
	Median	163.25
	Min	119.5
	Max	188.0
Weight (kg)	n	50
	Mean	49.64
	SD	14.626
	Median	48.85
	Min	23.5
	Max	84.5
BMI (kg/m <sup>3</sup> )	n	50
	Mean	18.77
	SD	2.893
	Median	18.26
	Min	13.2
	Max	25.8
Location Crohn's disease		
Ascending Colon	No	27 ( 54.0)
	Yes	23 ( 46.0)
Ileum	No	2 ( 4.0)
	Yes	48 ( 96.0)
Baseline diagnosis (years)	n	50
	Mean	1.48
	SD	1.619
	Median	1.00
	Min	0.0
	Max	6.0

n Number of subjects in analysis; N Number of subjects in treatment group. SD Standard deviation.

Baseline Visit 1 (Day 1).

Source: [Table 11.1.5](#).

The mean duration from diagnosis of Crohn's disease was 1.48 years at baseline. The majority of subjects had Crohn's disease located in the ileum (48 [96%] subjects). A total of 19 (38%) subjects were detected with physical abnormalities at baseline (Visit 1). These abnormalities were commonly related to skin (8 [16%] subjects), abdomen (6 [12%] subjects), and genital/rectal region (6 [12%] subjects) reflecting Crohn's disease signs and symptoms.

### Protocol deviation

A total of 17 (34%) subjects had at least 1 protocol deviation (Table 21). The most common protocol deviations were protocol-required procedure not adhered to (11 [22%] subjects) and received prohibited concomitant medications (9 [18%] subjects). These protocol deviations did not justify exclusion of the subjects from any of the analysis sets.

There were 2 (4%) subjects (E7805005 and E1004002) who did not fulfil eligibility criteria for study entry but were enrolled into the study.

Subject E7805005 had a total PCDAI score of 15; Subject E1004002 was enrolled in the study in an error due to a misunderstanding of site staff around the unit of measure for albumin, a component of the PCDAI scale. The recalculated overall PCDAI score was 17.5. Of the 2 subjects, 1 subject (E1004002) was excluded from the FAS as the subject did not have sufficient efficacy data for assessment at Visit 4.

**Table 21: Protocol Deviations, Safety Analysis Set (Study D9422C00002)**

Protocol deviation <sup>a</sup>	Number (%) of subjects Entocort (N=108)
Number of subjects with at least 1 deviation	40 ( 37.0)
Protocol-required procedure not adhered to	27 ( 25.0)
Did not fulfill eligibility criteria	12 ( 11.1)
Received incorrect investigational treatment/dose	5 ( 4.6)
Received prohibited concomitant medication	2 ( 1.9)

<sup>a</sup> Deviations before the start of treatment and during treatment.  
<sup>b</sup> Note that the same subject could have had more than 1 protocol deviation.  
<sup>c</sup> Number of subjects in treatment group.

Restricted medication during treatment and taper phase:

There were 7 (14%) subjects who took restricted medications during the treatment phase of the study. The restricted medications used were metronidazole (6 [12%] subjects), azathioprine (2 [4%] subjects), and infliximab (1 [2%] subject). The medications metronidazole and azathioprine were considered as restricted in Table 22 as these medications were started as the new therapy during the treatment period.

**Table 22: Restricted Medication during Treatment Phase, Safety Analysis Set (Study D9422C00002)**

ATC classification / Generic term	Number (%) of subjects Entocort (N=50)
Number of subjects with restricted concomitant medication	7 ( 14.0)
Imidazole derivatives	6 (12.0)
Metronidazole	3 ( 6.0)
Metronidazole benzoate	3 ( 6.0)
Other immunosuppressants	2 ( 4.0)
Azathioprine	2 ( 4.0)
Tumor necrosis factor alpha (tnf-a) inhibitors	1 ( 2.0)
Infliximab	1 ( 2.0)

<sup>a</sup> A subject could have 1 or more Generic term reported under a given ATC text.  
<sup>b</sup> Includes medications that began prior to start of study treatment but were ongoing after the start of study treatment.  
<sup>c</sup> Treatment phase is from day of first dose till Visit 4.  
<sup>d</sup> Source: Table 11.1.20.

There were 8 subjects (16%) subjects who took restricted medications during the taper/follow up phase of the study (Table 23).

**Table 23: Restricted Medication during Taper/Follow-up Phase, Safety Analysis Set (Study D9422C00002)**

ATC classification / Generic term	Number (%) of Subjects Entocort (N=50)
Number of subjects with restricted concomitant medication	8 ( 16.0)
Aminosalicylic acid and similar agents	1 ( 2.0)
Mesalazine	1 ( 2.0)
Benzimidazole derivatives	1 ( 2.0)
Mebendazole	1 ( 2.0)
Glucocorticoids	2 ( 4.0)
Prednisone	2 ( 4.0)
Imidazole derivatives	4 ( 8.0)
Metronidazole	2 ( 4.0)
Metronidazole benzoate	2 ( 4.0)
Other immunosuppressants	2 ( 4.0)
Azathioprine	2 ( 4.0)

**Primary variable**

The primary objective of this study was to investigate the safety of Entocort™ EC (budesonide) in a paediatric Crohn's disease population for maintenance of clinical remission.

**Safety results**

For subjects who crossed over from Study 1 (D9422C00001), any new AE, which occurred after Visit 4 of Study 1, was part of this study. On-going/resolved AEs before Visit 4 from Study 1 were not accounted in this study.

In total, 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.

A total of 37 (74%) subjects reported AEs in any category (Table 24). 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 SAEs and 3 (6%) subjects who reported DAEs. There were no OAEs identified in the study.

Most AEs were 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.

The majority of AEs were reported in the SOC Gastrointestinal disorders (25 [50%] subjects), Skin and subcutaneous tissue disorders (11 [22%] subjects), and Infections and infestations (11 [22%] subjects). The most common AEs reported by PT were: Abdominal pain (8 [16%] subjects), Crohn's disease (7 [14%] subjects), and acne (6 [12%] subjects).

**Table 24: AEs, Most Common by Preferred Term, Safety Analysis Set (Study D9422C00002)**

Preferred term	Number (%) of subjects <sup>[a]</sup>
	Entocort (N=50)
Subjects with any AE	37 ( 74.0)
Abdominal pain	8 ( 16.0)
Crohn's disease	7 ( 14.0)
Acne	6 ( 12.0)
Cushingoid	4 ( 8.0)
Increased appetite	4 ( 8.0)
Irritability	4 ( 8.0)
Mood swings	4 ( 8.0)
Arthralgia	3 ( 6.0)
Decreased appetite	3 ( 6.0)
Dyspepsia	3 ( 6.0)
Nasopharyngitis	3 ( 6.0)
Upper respiratory tract infection	3 ( 6.0)
Diarrhoea	2 ( 4.0)
Gastroenteritis	2 ( 4.0)
Gastroenteritis viral	2 ( 4.0)
Haematochezia	2 ( 4.0)
Headache	2 ( 4.0)
Hirsutism	2 ( 4.0)
Iron deficiency anaemia	2 ( 4.0)
Pain in extremity	2 ( 4.0)
Vomiting	2 ( 4.0)

Most common was defined as a total frequency of  $\geq 4\%$  (in any treatment group).

<sup>a</sup> Number (%) of subjects with AEs, sorted in decreasing frequency of PT.

Includes AEs with an onset date on or after the date of first dose and up to and including Week 16  $\pm$  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; GCS Glucocorticosteroids; MedDRA Medical dictionary regulatory activities; PT Preferred term.

MedDRA version 16.1.1.

Source: [Table 11.3.2.4](#).

There were no clinically relevant changes in possible GCS-related side effects over time in this study Table 25.

**Table 25: Possible Glucocorticosteroid (GCS) Side effects since Previous Visit, Safety Analysis Set (Study D9422C00002)**

GCS related side effects	Number of subjects in each visit	Number (%) of subjects with side effects possibly related GCS at each visit
Subjects with any side effects possibly related GCS	50	34 (68.0)
Subjects with any side effects possibly related GCS at Visit 1	50	30 (60.0)
Subjects with any side effects possibly related GCS at Visit 4	50	30 (60.0)
Subjects with any side effects possibly related GCS at Visit 5	45	21 (46.7)

Percentage (%) of subjects reporting symptoms/signs following active questioning.

Source: [Table 11.3.6.1.](#)

A total of 4 (8%) subjects reported 5 SAEs during the study (Table 26). All SAEs were reported in the SOC of Gastrointestinal disorders. Of the 4 subjects, 3 subjects had SAEs that were related to underlying Crohn's disease. The fourth subject had an SAE of gastrointestinal haemorrhage that was considered by the investigator to be related to ibuprofen. 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.

**Table 26: SAEs, by System Organ Class and Preferred Term, Safety Analysis Set (Study D9422C00002)**

System organ class / Preferred term	Number (%) of Subjects <sup>a</sup>
	Entocort (N=50)
Subjects with any SAE	4 ( 8.0)
Gastrointestinal disorders	4 ( 8.0)
Crohn's disease	3 ( 6.0)
Gastrointestinal haemorrhage	1 ( 2.0)
Ileal stenosis	1 ( 2.0)

<sup>a</sup> Number (%) of subjects with an SAE, sorted by international order for system organ class and alphabetically for preferred term.

Subjects with multiple SAEs were counted once for each system organ class/preferred term.

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.

MedDRA Medical dictionary regulatory activities; SAE Serious adverse event.

MedDRA version 16.1.

Source: [Table 11.3.4.1.](#)

There were 3 (6%) subjects who discontinued the IP due to AEs. All DAEs were reported in the SOC of Gastrointestinal disorder. The AEs reported were: Crohn's disease (2 [4%] subjects) and abdominal pain (1 [2%] subject). None of the DAEs were considered to be causally related to the IP by the investigator (Table 27).



**Table 27: AEs Leading to Discontinuation of IP, by System Organ Class and Preferred Term, Safety Analysis Set (Study D9422C00002)**

System organ class / Preferred term	Number (%) of Subjects <sup>a</sup> Entocort (N=50)
Subjects with an AE leading to discontinuation <sup>b</sup>	3 ( 6.0)
Gastrointestinal disorders	3 ( 6.0)
Crohn's disease	2 ( 4.0)
Abdominal pain	1 ( 2.0)

<sup>a</sup> Number (%) of subjects with an AE leading to discontinuation of IP, sorted by international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs leading to discontinuation were counted once for each system organ class/preferred term.

<sup>b</sup> Action taken, Entocort<sup>™</sup> permanently stopped.

Includes adverse events with an onset date on or after the date of first dose and up to and including Week 16 +/-3 days.

AE Adverse event; IP Investigational product; MedDRA Medical dictionary regulatory activities.

MedDRA version 16.1.

Source: Table 11.3.5.1.

### Assessor's comments

*As noted in the previous study, particular adverse reactions appear more frequently in children in comparison with adults (i.e. acne). The MA holder is requested to compare safety profile of budesonide for children and adults according to these observations and reflect these findings in the section 4.8 of the SmPC. (LoQ)*

The adrenal function was assessed by measurement of morning cortisol and DHEAS levels. The absolute and percentage change from baseline for cortisol levels and absolute change from baseline for DHEAS levels are presented in Table 28. 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.

**Table 28: Cortisol Levels, Absolute and % Change from Baseline; Dehydroepiandrosterone Suplhate (DHEAS) Absolute and Change from Baseline, Safety Analysis Set (Study D9422C00002)**

Variable	SI-Unit	Visit	n	Result					n	Change (Post-Baseline)				
				Mean	SD	Median	Min	Max		Mean	SD	Median	Min	Max
Cortisol	nmol/L	Visit 1 (Day 1)	51	147.08	141.88	116.00	14.0	621.0						
		Visit 4 (Week 12)	49	175.98	138.96	157.00	14.0	574.0	49	320.02	707.76	28.74	-97.7	3150.0
		Visit 5 (Week 16)	4	217.50	164.39	230.50	14.0	395.0	4	123.54	329.64	-13.67	-93.1	614.6

Source: Table 11.3.7.12.

**Table 27 Dehydroepiandrosterone sulphate (DHEAS), absolute and change from baseline (Safety analysis set)**

Variable	SI-Unit	Visit	n	Result					n	Change (Post-Baseline)				
				Mean	SD	Min	Median	Max		Mean	SD	Min	Median	Max
Dehydroepiandrosterone sulfate	umol/L	Visit 1 (Day 1)	49	1.31	0.957	0.2	1.10	3.8						
		Visit 4 (Week 12)	48	1.78	1.604	0.2	1.35	9.4	46	0.47	1.277	-2.4	0.30	6.9
		Visit 5 (Week 16)	4	1.35	1.207	0.5	0.90	3.1	4	0.10	0.356	-0.2	0.05	0.5

DHEAS Dehydroepiandrosterone sulphate.

Source: Table 11.3.7.10.

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

There were no AEs under this category as none of the subjects took CYP3A4 inhibitors or inducers during the study. None of the subjects had an AE with an outcome of death.

### Assessor's comments

*In the study report was mentioned, that there were no subjects receiving CYP3A4 inhibitors or inducers during the study. However, in the document "d9422c00002-12-2-04-demographic-and-baseline-characteristics.pdf" are disclosed patients, who received CYP3A4 inhibitors. MAH should discuss this discrepancy and evaluate the safety profile in the patients who received CYP3A4 inhibitors as concomitant medication.*

## Secondary variables

### Pediatric Crohn's disease activity index

There was no major change in the PCDAI composite score after 12 weeks treatment with 6 mg Entocort™ EC, indicating that most of the subjects remained in clinical remission (Table 29).

**Table 29: Descriptive Statistics for PCDAI Total Score over Time (FAS, Study D9422C00002)**

Visit	PCDAI score						Change from Baseline					
	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
Visit 1 (Day1)	49	4.85	3.623	0.0	5.00	15.0						
Visit 4 (Week 12)	49	6.89	8.077	0.0	5.00	30.0	49	2.04	7.010	-7.5	0.00	25.0

Subjects with complete PCDAI scores are reported.

Visit 1 is baseline.

FAS: Full analysis set; PCDAI: Pediatric Crohn's Disease Activity Index.

Source: [Table 11.2.1.1](#).

### Patient reported outcomes/quality of life: IMPACT 3

All subjects who received Entocort™ EC were ≥8 years of age and therefore were eligible for assessment of QOL using the IMPACT 3 questionnaire. There was no major change in the IMPACT 3 score after 12 weeks treatment with 6 mg Entocort™ EC, indicating that the subjects rated their QOL as high as that at baseline, when in clinical remission (Table 30).

**Table 30: IMPACT3 Total Score, Safety Analysis Set (Study D9422C00002)**

Visit	IMPACT3 score						Change from baseline					
	N	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max
Visit 1 (Day 1)	50	145.62	12.43	120.0	144.00	171.0						
Visit 4 (Week 12)	49	146.98	15.48	107.0	146.00	173.0	49	1.22	8.62	-17.0	0.00	22.0

Baseline Visit 1 (Day 1)

Source: [Table 11.2.1.5](#).

**Assessor's comment**

*This study was a continuation of the study D9422C00001.*

*Based on the provided demographic data, the population in this therapeutic confirmatory study was representative of the target population.*

*The primary endpoint of this study was safety profile of Entocort in children aged 5 to 17 years.*

*The product is in the EU approved for use in children from 8 years. As this study was not designed to assess efficacy in children younger than 8 years, and there were no subject younger than 8 years, no conclusions on the efficacy in this aged group can be made.*

*As regards the safety, the MA holder is requested to provide the number of patients who took CYP3A4 inhibitors and assess their safety profile. The MA holder should also evaluate the safety profile of the product in children in comparison with adults and these findings reflect in the section 4.8 of the SmPC. (LoQ)*

*The MA holder is also requested to proposed changes in the section 5.1 to include information concerning the objectives and conclusions of the submitted study.*

**Study D9423C00001**

A multicenter, Double-Blind, Randomized, Parallel-Group, Phase III Study to Assess Efficacy and Safety of D9421-C 9 mg Versus Mesalazine 3 g in Patients with Active Crohn's Disease in Japan

**Assessor's comment**

*This Phase III study was conducted upon request made by the Research and Development Division of the Health Policy Bureau and the Pharmaceutical and Food Safety Bureau for development for the new drug application of D9421-C as a treatment for mild to moderate active Crohn's disease affecting ileum, ileocecal region, and/or ascending colon in Japanese patients. Hence this study was not primarily targeted to paediatric patients.*

*In fact, only one paediatric patient ( $\leq 18$  years) was enrolled into this study and received budesonide.*

*Therefore this study has no additive value for the purpose of paediatric efficacy and safety profile of budesonide. In summary no SAE or unexpected AEs (only event of atopic dermatitis occurred in this subject) was observed in this paediatric patient.*

*However, as this study has been submitted by the MAH within this Art. 46 procedure, thorough description is provided below.*

**Methods****Objectives**

The objective of this study was to evaluate the clinical efficacy and safety of D9421-C 9 mg once daily compared to mesalazine 1 g three times a day.

**Study design**

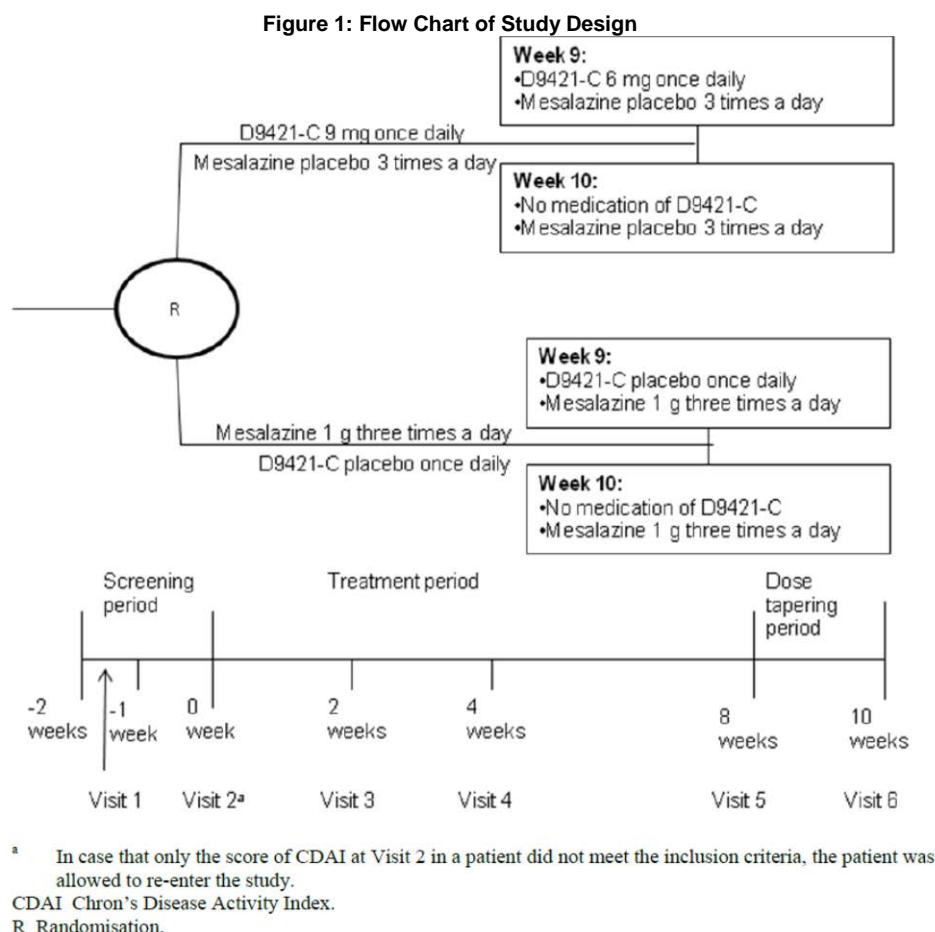
This was an 8-week treatment, multicenter, double-blind, randomized, parallel-group, Phase III study, to assess the efficacy and safety of D9421-C 9 mg compared to mesalazine 3 g over an 8-week treatment period, in patients with mild to moderate active Crohn's disease. Approximately, 110 patients were planned to be randomized in the study across 20 centers.

The study consisted of 3 periods: Screening period (Week -2 to Week -1), treatment period (Week 0 to Week 8), and dose tapering period (Week 9 to Week 10; to prevent withdrawal



symptoms in patients receiving budesonide). The patients were grouped according to whether they were concomitantly treated with azathioprine/mercaptopurine or not, and within each group, randomized to either D9421-C 9 mg or mesalazine 3 g in a ratio of 1:1. The blinding was maintained throughout the study.

Figure 1 shows the study design and the sequence of treatment periods.



### Study population /Sample size

Female or male subjects  $\geq 15$  years of age, diagnosed of Crohn's disease, verified by X-ray, endoscopy, or histology with main active disease of the ileal, ileocecal region, and/or ascending colon were included in the study. For randomisation in the study patients had to have mild to moderate active Crohn's disease, defined as CDAI score of 180 to 400 based on the patient's condition for 7 consecutive days prior to the Visit 2.

Sample size calculation: The non-inferiority was to be concluded when the lower limit of a 2-sided 90% CI of the difference in remission rates at Week 8 between D9421-C 9 mg and mesalazine 3 g was greater than or equal to  $-10\%$ . Based on the results of the Study D9421C00002 and overseas Phase III studies, 54 patients per treatment group were required to keep a 90% power or more with the lower limit of a 2-sided 90% CI of the difference in remission rates at Week 8 to be greater than or equal to  $-10\%$ . This was under the assumption that the remission rates at Week 8 are 28% for D9421-C 9 mg and 15% for mesalazine 3 g, respectively.

To ensure this number of evaluable patients, based on the estimate of 2% drop out from the FAS, a total of 110 patients (55 patients for each group) were planned to be randomised.

## Treatments

Patients were administered D9421-C 3 mg capsule or D9421-C placebo capsule, and mesalazine 250 mg tablet or mesalazine placebo tablet for 8 weeks. Combinations of the IP during the treatment period and dose tapering period for each treatment group are listed in Table 31.

Initial administration of D9421-C capsules and mesalazine tablets was done after confirmation of all eligibility criteria being met at Visit 2 (randomisation). As per the randomisation, the patients were instructed to take three D9421-C 3mg capsules (along with 4 mesalazine placebo tablets) or 4 mesalazine 250 mg tablets (along with 3 D9423-C placebo capsules), regardless of before or after food intake. The first dose was taken under the supervision of the study staff, who ensured that the patients had taken the IP.

After initial administration, patients were instructed to take the D9421-C capsules before breakfast and mesalazine tablets after meal, as detailed in Table 31.

Table 31: Combination of Study Drugs (Study D9423C00001)

Treatment		Combination of study drugs	
D9421-C 9 mg treatment group	Treatment period		Once daily before breakfast: D9421-C 3 mg capsule x 3 Three times a day after each meal: Mesalazine placebo tablet x 4
	Dose	Week 9	Once daily before breakfast: D9421-C 3 mg capsule x 2
	-tapering period		Three times a day after each meal: Mesalazine placebo tablet x 4
		Week 10	Once daily before breakfast: None Three times a day after each meal: Mesalazine placebo tablet x 4
Mesalazine 3 g treatment group	Treatment period		Once daily before breakfast: D9421-C placebo capsule x 3 Three times a day after each meal: Mesalazine 250 mg tablet x 4
	Dose	Week 9	Once daily before breakfast: D9421-C placebo capsule x 2
	-tapering period		Three times a day after each meal: Mesalazine 250 mg tablet x 4
		Week 10	Once daily before breakfast: None Three times a day after each meal: Mesalazine 250 mg tablet x 4

## Outcomes/endpoints

**Table 32: Subject Objectives and Variables (Study D9423C00001)**

Priority	Type	Objective	Variable	
		Description	Description	Method of assessment and derivation
Primary	Efficacy	To evaluate the clinical efficacy of D9421-C 9 mg once daily compared to mesalazine 1 g three times a day, in patients with mild to moderate active Crohn's disease affecting ileum, ileocecal region, and/or ascending colon (as defined by a score of 180 to 400 on the CDAI) by assessment of the remission after 8-week treatment defined by a CDAI score of $\leq 150$ .	Remission after 8-week treatment. CDAI score $\leq 150$ .	See CSP (see Appendix 12.1.1) Sections 11.1 and 12.2.1 and SAP Sections 3.1 and 4.2.1.
Secondary	Efficacy	To evaluate clinical efficacy of D9421-C 9 mg once daily compared to mesalazine 1 g three times a day in patients with mild to moderate active Crohn's disease affecting ileum, ileocecal region and/or ascending colon (as defined by a score of 180 to 400 on the CDAI).	<ul style="list-style-type: none"> <li>Remission after 2-week and 4-week treatment. CDAI score of <math>\leq 150</math></li> <li>Change in CDAI score after 2, 4, and 8 weeks treatment</li> <li>Time to first remission</li> <li>Clinical improvement defined by a remission ie, CDAI score of <math>\leq 150</math> or a decrease in CDAI score of at least 100 from Visit 2 after 2, 4, and 8 weeks treatment</li> <li>Clinical improvement defined by a remission ie, CDAI score of <math>\leq 150</math> or a decrease in CDAI score of at least 70 from Visit 2 after 2, 4, and 8 weeks treatment.</li> </ul>	See CSP Sections 11.1, 12.2.2.1 to 12.2.2.4 and SAP Sections 3.2 and 4.2.2.
Priority	Type	Objective	Variable	
		Description	Description	Method of assessment and derivation
Secondary	PRO	To evaluate the change in disease specific HRQL of D9421-C 9 mg once daily compared to mesalazine 1 g three times a day in patients with mild to moderate active Crohn's disease affecting ileum, ileocecal region and/or ascending colon (as defined by a score of 180 to 400 on the CDAI) by assessment of the IBDQ total score and all sub scores.	IBDQ total score and all sub-scores after 2, 4, and 8 weeks treatment.	See CSP Sections 11.3 and 12.2.2.5 and SAP Sections 3.3 and 4.2.3.
Secondary	Safety	To evaluate the overall safety of D9421-C 9 mg once daily compared to mesalazine 1 g three times a day to patients with mild to moderate active Crohn's disease affecting ileum, ileocecal region and/or ascending colon as defined by a score of 180 to 400 on the CDAI.	<ul style="list-style-type: none"> <li>AEs</li> <li>Laboratory variables (haematology, clinical chemistry [including serum DHEA-S], and urinalysis)</li> <li>Vital signs (pulse, blood pressure, and body temperature)</li> <li>Physical examination.</li> </ul>	See CSP Sections 11.2 and 12.2.2.6 and SAP Sections 3.4 and 4.2.4.

AE Adverse event; CDAI Crohn's Disease Activity Index; CSP Clinical Study Protocol; DHEA-S Dehydroepiandrosterone-sulphate; IBDQ Inflammatory Bowel Disease Questionnaire; HRQL Health-related quality of life; PRO Patient reported outcome; SAP Statistical Analysis Plan.

## Statistical Methods

In general, summary statistics (n, mean, standard deviation, median, minimum, and maximum) for continuous variables and counts and percentage for categorical variables are presented.

The non-inferiority margin for the research hypothesis was chosen on the basis of what would be a clinically relevant difference to be ruled out and was set at 10%. A normal 2-sided significance level of 10% was used for all efficacy analyses. The differences in the binary variable (remission and clinical improvement rates) between D9421-C 9 mg and mesalazine 3 g along with their 2-sided 90% confidence intervals (CIs) were calculated by the Newcombe-Wilson score method without continuity correction.

All subgroup and secondary efficacy parameter analyses were considered descriptive only and were not taken as formal testing. The safety data are presented using descriptive statistics only, without formal statistical analyses.

#### Analysis sets

##### Efficacy analysis set

Two analysis sets were defined for the purpose of analyses of the efficacy data:

- The FAS was the primary analysis set for efficacy and included all randomized patients who took the IP at least once and had data from the treatment period
- The PPS was a subset of patients in the FAS and included patients with no important protocol violations, deviations, or poor compliance with the conduct of the study.

##### Safety analysis set

All patients who received at least 1 dose of randomised IPs and for whom any post-dose data were available were included in the safety population.

## Results

### Recruitment/ Number analyzed

The first patient was enrolled to the study on 08 February 2012. The last patient completed the study on 08 September 2014.

In total, 123 patients were enrolled in the study. A total of 112 patients from 27 centres across Japan were randomized and received treatment (56 patients in the D9421-C 9 mg treatment group and 56 patients in the mesalazine 3 g group. FAS population). A total of 17 (15.2%) patients discontinued the treatment (6 [10.7%] and 11 [19.6%] patients in D9421-C 9 mg and mesalazine 3 g groups, respectively) and the reasons for discontinuation were patient decision and AEs.

Table 33: Subject Disposition, All Subjects (Study D9423C00001)

	Number(%) of subjects		
	D9421-C 9mg	Mesalazine 3g	Total
Subjects enrolled <sup>a</sup>			123
Subjects randomized	56	56	112
Subjects who were not randomized			11
Eligibility criteria not fulfilled			9
Adverse event			2
Subjects who received treatment	56 (100.0)	56 (100.0)	112 ( 100)
Subjects who completed study	50 ( 89.3)	45 ( 80.4)	95 (84.8)
Subjects who discontinued study	6 ( 10.7)	11 ( 19.6)	17 (15.2)
Subject decision	2 ( 3.6)	7 ( 12.5)	9 ( 8.0)
Adverse event	4 ( 7.1)	4 ( 7.1)	8 ( 7.1)

<sup>a</sup> Informed consent received.

Percentages are calculated based on number of patients randomised.

Table 34: Analysis Set (Study D9423C00001)

	Number of subjects		
	D9421-C 9 mg	Mesalazine 3 g	Total
Subjects randomized	56	56	112
Subjects included in safety analysis set	56	56	112
Subjects included in full analysis set	56	56	112
Subjects included in per-protocol analysis set	55	55	110
Subjects excluded from per-protocol analysis set	1	1	2
Received prohibited concomitant medication	1	1	2

Source: Table 11.1.3.

**Baseline data**

Randomization was stratified by the factor usage or non-usage of azathioprine/mercaptopurine and was well balanced (Table 35).

Table 35: Summary of Stratification Factors, Full analysis Set (Study D9423C00001)

Stratification factor	Number (%) of subjects		
	D9421-C 9mg (N=56)	Mesalazine 3g (N=56)	Total (N=112)
Received Azathioprine/Mercaptopurine			
Yes	14 ( 25.0)	14 ( 25.0)	28 ( 25.0)
No	42 ( 75.0)	42 ( 75.0)	84 ( 75.0)

Stratification factors as recorded at time of randomization.

Source: Table 11.1.7.

The mean age of the patients was 36.9 years and most of the patients had BMI <25 kg/m<sup>2</sup> (104 [92.9%] patients). A majority of the patients (73 [65.2%]) were ≥30 years old. A higher number of male patients (80 [71.4%]) were randomized in the study as compared with female patients (32 [28.6%]). All patients, except one were of Asian race. One patient was of Black or African American race.

The median duration of the disease was 6.5 years (range: 0 year to 40.7 years). The mean CDAI and mean total IBDQ scores were 259.1 and 154.5, respectively. A majority of the patients (87 [77.7%]) had CDAI score <300. There were 48 (42.9%) patients who did not use nutrition therapy or immune suppression therapy at baseline.

Overall, the treatment groups were well-balanced with respect to the demographic and baseline disease characteristics.



Table 36: Demographic Characteristics, Full analysis Set (Study D9423C00001)

		Number (%) of subjects		
Parameter		D9421-C 9mg (N=56)	Mesalazine 3g (N=56)	Total (N=112)
Age (years)	N	56	56	112
	Mean	38.1	35.8	36.9
	SD	13.43	10.71	12.15
	Median	35.5	34.0	34.5
	Min	16	19	16
	Max	77	64	77
Age group (years) n (%)	< 30 years	19 ( 33.9)	20 ( 35.7)	39 ( 34.8)
	≥30 years	37 ( 66.1)	36 ( 64.3)	73 ( 65.2)
	Total	56 (100.0)	56 (100.0)	112 (100.0)
Sex n(%)	Male	37 ( 66.1)	43 ( 76.8)	80 ( 71.4)
	Female	19 ( 33.9)	13 ( 23.2)	32 ( 28.6)
	Total	56 (100.0)	56 (100.0)	112 (100.0)
Race n(%)	Asian	56 (100.0)	55 ( 98.2)	111 ( 99.1)
	Black or African American	0 ( 0.0)	1 ( 1.8)	1 ( 0.9)
	Total	56 (100.0)	56 (100.0)	112 (100.0)
Ethnic group n (%)	Asian	0 ( 0.0)	2 ( 3.6)	2 ( 1.8)
	Japanese	56 (100.0)	53 ( 94.6)	109 ( 97.3)
	Other	0 ( 0.0)	1 ( 1.8)	1 ( 0.9)
	Total	56 (100.0)	56 (100.0)	112 (100.0)

Source: Table 11.1.5.1.

## Efficacy results

### Primary variable:

#### Remission after 8-week treatment (CDAI score $\leq 150$ )

Table 37 presents analysis results of remission rate (CDAI total score  $\leq 150$ ) at Week 8. Non-inferiority of D9421-C 9 mg to mesalazine 3 g after 8-week treatment was established as the lower limit of the 2-sided 90% CI of the difference in remission rates was greater than -10% (90% CI: -8.49, 18.94).

**Table 37: Analysis of Remission Rate (CDAI Total Score  $\leq 150$ ) at Week 8, Full analysis Set (Study D9423C00001)**

Treatment	N	Remission		Comparison between groups		
		n(%)	90% CI	Difference	90% CI	p-value <sup>a</sup>
D9421-C 9mg	56	17 ( 30.4)	(21.35,41.17)	5.4	(-8.49,18.94)	0.526
Mesalazine 3g	56	14 ( 25.0)	(16.79,35.52)			

<sup>a</sup> p-value calculated by using chi-square test.

90% CI calculated using the Newcombe-Wilson score method without continuity correction.

CDAI Crohn's Disease Activity Index; CI Confidence interval.

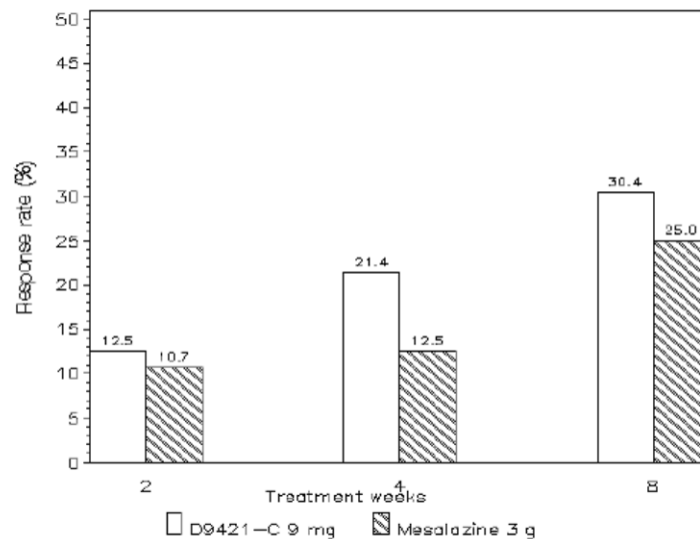
### Secondary variables:

#### Remission after 2-week and 4-week treatment

For D9421-C 9 mg group, the remission rates at Week 2 and Week 4 were 12.5% and 21.4%, respectively. For mesalazine 3 g group, the remission rates at Week 2 and Week 4 were 10.7% and 12.5% respectively. This implies that the remission rates were numerically higher at Week 2 and Week 4 for the D9421-C 9 mg group as compared with the mesalazine 3 g group.

Greater decrease from baseline in total CDAI score was observed at Week 2, Week 4, and Week 8 for D9421 C 9 mg as compared with mesalazine 3 g group (Figure 2).

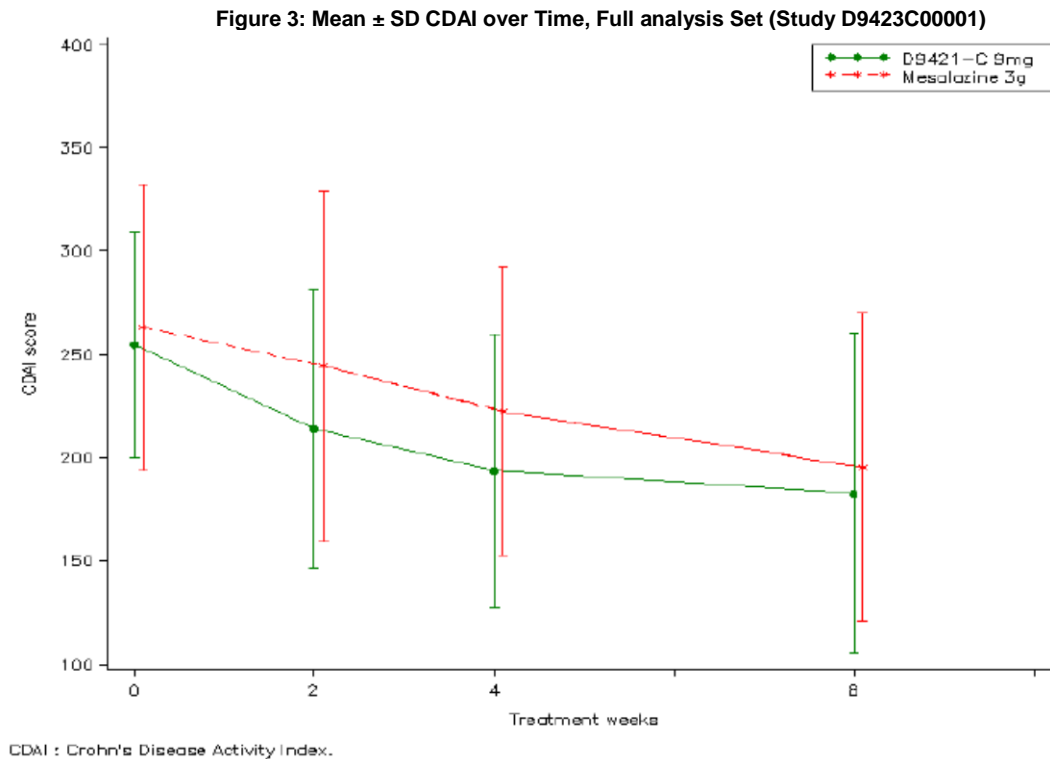
**Figure 2: Remission Rates (% with CDAI  $\leq 150$ ) over Time, Full analysis Set (Study D9423C00001)**



CDAI : Crohn's Disease Activity Index.

### Change in CDAI score

Greater decreases from baseline in total CDAI score was observed at Week 2, Week 4, and Week 8 in the D9421-C 9 mg group as compared with the mesalazine 3 g group (Figure 3).



### Time to first remission

The median time for first remission was not calculable for any of the treatment groups as remission was not observed for more than 50% of the patients. The cumulative remission rates increased over time in both the treatment groups; however, it was numerically higher in the D9421-C 9 mg group as compared with the mesalazine 3 g group.

### Clinical improvement

In the D9421 C 9 mg group, the clinical improvement rates (CDAI score of  $\leq 150$  or a decrease in CDAI score of at least 100 from baseline) were 25.0%, (Week 2), 33.9% (Week 4), and 42.9% (Week 8). In the mesalazine 3 g group, the clinical improvement rates were 17.9% (Week 2), 19.6% (Week 4), and 30.4% (Week 8).

In the D9421-C 9 mg group, the clinical improvement rates (CDAI score of  $\leq 150$  or a decrease in CDAI score of at least 70 from baseline) were 33.9% (Week 2), 39.3% (Week 4), and 48.2% (Week 8). In the mesalazine 3 g group, the clinical improvement rates were 19.6% (Week 2), 23.2% (Week 4), and 32.1% (Week 8).

This implies that the higher clinical improvement rates were observed at Week 2, Week 4, and Week 8 in the D9421-C 9 mg group as compared with mesalazine 3 g group.

### Patient reported outcomes - IBDQ



Increase in the IBDQ scores from baseline to all time points was observed in both the treatment groups; however, the improvement was numerically higher in D9421-C 9 mg group as compared with mesalazine 3 g group.

### Safety results

The mean duration of exposure in the D9421-C 9 mg group and the mesalazine 3g group was 61,2 days and 62,4 days, respectively.

The number of patients with any AE was similar in both the treatment groups (26 [46.4%] and 25 [44.6%] patients in the D9421-C 9 mg and mesalazine 3 g groups, respectively).

In total, 9 (16.1%) patients in the D9421-C 9 mg group and 5 (8.9%) patients in the mesalazine 3 g group had an AE that was causally related to the IP, as assessed by the investigator. Three (5.4%) and 1 (1.8%) patients in D9421-C 9 mg and mesalazine 3 g groups, respectively, had an SAE. None of the SAEs were considered to be causally related to the IP, as assessed by the investigator. The number of patients who discontinued the IP due to an AE was same in both, the treatment groups (4 [7.1%] patients in each treatment group).

**Table 38: Number (%) of Subjects who Had at Least 1 SAE by PT (Safety Analysis Set)**

Preferred term <sup>a</sup>	Number (%) of subjects	
	D9421-C 9mg (N=56)	Mesalazine 3g (N=56)
Subjects with any SAE	3 ( 5.4)	1 ( 1.8)
Ileus	1 ( 1.8)	1 ( 1.8)
Lower Gastrointestinal Haemorrhage	1 ( 1.8)	0 ( 0.0)
Pneumatosis Intestinalis	1 ( 1.8)	0 ( 0.0)

<sup>a</sup> Subjects with multiple SAEs are counted once for each PT.

PT Preferred term; SAE: Serious adverse event.

Source: Table 11.3.4.1.

The most commonly reported AE by the preferred term was nasopharyngitis (6 [10.7%] and 10 [17.9%] patients in the D9421-C 9 mg and mesalazine 3 g groups, respectively). One patient (1.8%) in the D9421-C 9 mg group had a possible glucocorticosteroid related AE (Dermatitis acneiform). This AE was of mild intensity; however, it was considered to be causally related to the IP as assessed by the investigator and the patient discontinued the study.

There were no clinically relevant trends observed in the 2 treatment groups related to laboratory values, physical examination, and vital signs, except C-reactive protein (CRP) and (DHEA-S). The patients in the D9421-C 9 mg group had lower CRP and lower DHEA-S values compared to the mesalazine 3 g group during the treatment period; however, the CRP and DHEA-S values returned towards baseline after the tapering period.

## **V. RAPPORTEUR'S CONCLUSION AT DAY 70 AND RECOMMENDATION**

The MAH Astra Zeneca has submitted paediatric data for Entocort capsules (budesonide) in accordance with Article 46 of the Paediatric Regulation.

Three studies were submitted by MAH and assessment has been done separately for each study.

Submitted studies D9422C00001 and D9422C00002 were performed to fulfil the US FDA PREA commitment for Entocort.

The primary endpoint of these two studies was safety profile of Entocort in children aged 5 to 17 years.

The product is in the EU approved for use in children from 8 years. As these two studies were not designed to assess efficacy in children younger than 8 years, and there were no (study D9422C00002) or very little number (5 subjects; study D9422C00001) of subject younger than 8 years, no conclusions on the efficacy in this age group can be made.

The primary endpoint of the submitted studies was safety in paediatric patients. The Rapporteur is of the opinion that basing on the submitted data safety profile of the Entocort capsules differs in children in comparison with adults.

The MA holder is requested to evaluate the safety profile of the product in the paediatric population in comparison with adults as some of the observed AEs (assessed as related to the study medication; i.e. acne) appear more frequently in the paediatric population than in adults and the current SmPC does not reflect this observation. The applicant is requested to propose changes in section 4.8 of the SmPC.

Furthermore, the MA holder is requested to proposed changes in section 5.1 of the SmPC to reflect obtained data from these two submitted studies. Objectives and conclusions of these two submitted studies should be stated in section 5.1 to provide more accurate information for the prescribers.

The study D9423C00001 was conducted upon request for development for the new drug application of Entocort capsules as a treatment for mild to moderate active Crohn's disease, made by the Research and Development Division of the Health Policy Bureau, and the Pharmaceutical and Food Safety Bureau in Japan.

Since the study had only one paediatric patient ( $\leq 18$  years), there is no additive value for the purpose of paediatric efficacy and safety profile of budesonide.

### **Overall conclusion**

There are some issues which need to be resolved. Therefore no final recommendation concerning the pdWS procedure under Art.46 can be given for the medicinal product Entocort capsules at this moment.

## ADDITIONAL CLARIFICATIONS REQUESTED

List of questions (LoQ):

1. Study D9422C00001: There are discrepancies in the number of the subjects who received restricted medication in the study report (document d9422c00001-12-2-02-protocol-deviations.pdf) and document d9422c00001-12-2-04-demographic-and-baseline-characteristics.pdf. MAH is required to clarify the number of subject who used restricted medication with particular attention to the type of restricted medication (i.e. glucocorticoids) for both treatment and taper/follow up period.
2. Based on the submitted studies D9422C00001 and D9422C00002 it seems, that particular adverse reactions (e.g. acne; assessed by the investigators as related to the study medication; please see Tables 21 and 24 in the study reports) appear more frequently in children in comparison with adults. The MA holder is therefore requested to compare safety profile of budesonide in paediatric population in comparison with adults. As the current wording of section 4.8 of the SmPC does not reflect this observation, the MAH is requested to propose changes in this section to reflect these findings.
3. In the study reports of the submitted studies D9422C00001 and D9422C00002 were mentioned, that there were no subjects receiving CYP3A4 inhibitors or inducers during the study. However, in the documents “d9422c00001-12-2-04-demographic-and-baseline-characteristics.pdf.” and “d9422c00002-12-2-04-demographic-and-baseline-characteristics.pdf.” are disclosed patients, who received CYP3A4 inhibitors. MAH should discuss this discrepancy and evaluate the safety profile in the patients who received CYP3A4 inhibitors as concomitant medication.
4. MAH is requested to proposed changes in the section 5.1. of the SmPC to implement information obtained from the submitted studies D9422C00001 and D9422C00002. Objectives and conclusions of these two studies should be stated in Section 5.1 of the SmPC to provide more accurate information for the prescribers.

### COMMENTS RECEIVED FROM OTHER MSs ON DAY 85

Supportive comments have been received from UK, DE and FR. The Rapporteur was informed that they do not have currently licensed paediatric indication; therefore this should be taken into account when proposing the final wording of the SmPC/PIL.

## VI. ASSESSMENT OF MAH'S RESPONSE

### Request 1

Study D9422C00001: There are discrepancies in the number of the subjects who received restricted medication in the study report (document d9422c00001-12-2-02-protocoldeviations.pdf) and document d9422c00001-12-2-04-demographic-and-baselinecharacteristics.pdf. MAH is required to clarify the number of subject who used restricted medication with particular attention to the type of restricted medication (i.e. glucocorticoids) for both treatment and taper/follow up period.

#### MAH's Response:

Appendix 12.2.2 lists all major protocol deviations, including intake of disallowed medication. These deviations were considered to have a potential to affect the study result and thereby the quality of the study. Only two cases of prohibited concomitant medication are mentioned:

- Patient E4101001 increased the dose of azathioprine treatment on day 22 of the treatment phase (25 to 50 mg daily)

- Patient E4103002 started treatment with azathioprine on day 1 of the treatment phase (100 mg daily)

Appendix 12.2.4 lists all concomitant medication that was recorded during the study (including the two cases mentioned in appendix 12.2.2). The intake of some of these medications was restricted, as described in section 3.6 of the CSP. Most of the restricted medications were allowed during the study if the restrictions were followed. Also, the investigator was allowed to use any medication that was considered necessary for the patient's safety and well-being.

The number of patients with intake of restricted medication during the treatment and follow-up phases of the study is given in Table 1.

**Table 1**                      **Restricted medication in Study D9422C00001**

Type of restricted medication	treatment phase	follow-up phase
Glucocorticoids	10	6
Methotrexate	0	4
Anti-TNF	1	2
6-mercaptopurine	1	1
Azathioprine	2	3
5-ASA	8	1
Antibiotics	11	9

Most of the intake of restricted medication during the treatment phase was related to exacerbation of Crohn's disease and premature discontinuation from the study. The reasons for the intake of these drugs are documented as adverse events, premature discontinuation from the study due to lack of therapeutic response etc. In such cases the effect of intake of these drugs on Crohn's disease was not reported and did therefore not distort the evaluation of the study results.

**Assessor comments:**

*The Applicant has clarified the discrepancies in the number of subjects receiving restricted medication. Since most of the intakes were related to the exacerbation of Crohn's disease, the reasons for using concomitant medication are acceptable.*

*The Applicant submitted the table with the number of patients who took restricted medication both during treatment and follow-up phase. It is noted that the number of patients who used restricted medication Metronidazol is missing in the table; however as the Applicant have not proposed any changes in the indications or targeted pediatric population for the Entocort based on the submitted studies, further clarification therefore does not seem to be necessary.*

*The Applicant's answer is considered sufficient. **Issue resolved.***

**Request 2**

Based on the submitted studies D9422C00001 and D9422C00002 it seems, that particular adverse reactions (e.g. acne; assessed by the investigators as related to the study medication; please see Tables 21 and 24 in the study reports) appear more frequently in children in comparison with adults. The MA holder is therefore requested to compare safety profile of budesonide in paediatric population in comparison with adults. As the current wording of section 4.8 of the SmPC does not reflect this observation, the MAH is requested to propose changes in this section to reflect these findings.

**MAH's Response:**

It is acknowledged that the frequency of some potential side effects of glucocorticoids (GCS) may be different in children compared with adults. It is also acknowledged that some signs/symptoms are more common in children than in adults irrespective of GCS treatment, e.g. acne. Therefore, when trying to establish if the likelihood of developing specific symptoms (e.g. acne) on exposure to Entocort is higher in children than in adults information on the prevalence of the symptoms after exposure is relevant, but also information on the prevalence of the symptoms in unexposed individuals (e.g. recordings at baseline). In the present studies a checklist was used in order to collect information on a set of predefined symptoms which may be potential adverse drug reactions.

As the patients in study D9422C00002 were already exposed to Entocort (or similar drugs) at study start they are not discussed here.

**Comparison of symptoms in children and adults exposed to Entocort**

A pooled analysis of 7 AZ sponsored studies (placebo controlled, randomised, double-blind, parallel group) on Entocort in adults with Crohn's disease, with in total 647 patients on Entocort and 316 on placebo, shows that some MedDRA preferred terms were observed more frequently in the present study than in the adult studies, e.g. increased appetite, abdominal pain and irritability, whereas other preferred terms were less frequently observed in the present study e.g. headache, insomnia and nausea. The frequency of acne was similar in the present study and in the adult studies. The overall safety profile in children is similar to the safety profile in adults, and thus it is the opinion of the MAH that the current wording of section 4.8 of the SmPC does not need to be changed.

**Comparison of symptoms in children before and after exposure to Entocort**

Another observation that is relevant when evaluating the extent of symptoms that may be adverse drug reactions, is comparing the prevalence of the symptoms before and after an 8-week treatment with Entocort. In Table 29 of study SD-008-3037 (see below) is seen that, although the frequency of acne is high (23) after treatment with budesonide, it is only slightly increased from baseline (18). It is reasonable to believe that the high prevalence of acne at baseline is related to puberty rather than to previous exposure to systemic steroids, since only one patient (5%) had documented GCS use before study start.

**Table 29.** Glucocorticosteroid (GCS) side effects by included term: Percentage (%) of patients reporting symptoms/signs

	<b>Prednisolone (n = 26)</b>		<b>Budesonide (n = 22)</b>	
	Baseline	Treatment	Baseline	Treatment
Moon face	0	60	0	23
Buffalo hump	0	4	0	0
Acne	8	36	18	23
Hirsutism	0	12	5	9
Skin striae	8	12	0	0
Bruising easily	0	4	0	5
Swollen ankles	0	4	0	0
Hair loss	0	12	0	5
Mood swings	12	12	14	18
Depression	12	12	9	9
Insomnia	8	20	0	23

In summary, the observed frequency of acne in study D9422C00001 in children is similar to what was observed in studies in adults. Although acne was frequently observed in children after exposure to Entocort in study SD-008-3037, the frequency was almost as high before exposure. These findings do not support the proposed higher likelihood of children developing acne on exposure to Entocort, compared with adults. Also for other symptoms where the observed frequency in our studies show numerical differences between children and adults, the available information is insufficient to provide guidance on differences in likelihood of developing the symptom on exposure to Entocort in children, compared with adults.

A paragraph in section 4.8 in the SmPC regarding safety profile in paediatric patients can be updated as follow:

Paediatric population

The observed safety profile of ENTOCORT™ in pediatric patients is consistent with its known safety profile in adults and no new safety concerns were identified Long-term studies have not been performed in pediatric patients treated with ENTOCORT™ capsules. Systemic and inhaled corticosteroids, including ENTOCORT™, may cause a reduction of growth velocity in pediatric patients. Children with Crohn's disease have a slightly higher systemic exposure and cortisol suppression than adults with Crohn's disease

**Assessor comments:**

*The Applicant has provided analyses of the differences in the frequencies of the potential side effects of glucocorticoids symptoms between children and adults. Although the Applicant conclude that some signs were observed more frequently in the present study than in the adult studies, (e.g. increased appetite, abdominal pain and irritability), the data is insufficient to provide adequate conclusion about the differences in the frequency of the particular symptoms.*

*The symptoms of acne were not seen more frequently in the paediatric population??? after the administration of the study medication. These findings are supported by the assessor.*

*The proposed wording of the section 4.8 regarding Paediatric population seems to adequately reflect the observations found and is endorsed by the Rapporteur.*

*The Applicant adequately responded the query. **Issue resolved.***

**Request 3**

In the study reports of the submitted studies D9422C00001 and D9422C00002 were mentioned, that there were no subjects receiving CYP3A4 inhibitors or inducers during the study. However, in the documents "d9422c00001-12-2-04-demographic-and-baselinecharacteristics. pdf." and "d9422c00002-12-2-04-demographic-and-baselinecharacteristics. pdf." are disclosed patients, who received CYP3A4 inhibitors. MAH should discuss this discrepancy and evaluate the safety profile in the patients who received CYP3A4 inhibitors as concomitant medication.

**MAH's Response:**

**Intake of cytochrome P 450 3A4 (CYP3A4) inhibitors/inducers in studies D9422C00001 and D9422C00002**

Drugs that significantly inhibit the enzyme CYP3A4 were not allowed in the studies since concomitant use of such drugs may significantly affect the exposure to the study drug (budesonide). Some strong inhibitors of CYP3A4 are specifically mentioned as prohibited in the study (ketoconazole, itraconazole, itraconazole, ritonavir, indinavir, saquinavir). None of these drugs were used in the studies. Also moderate inhibitors of CYP3A4 (e.g. erythromycin) were prohibited in the studies.

In D9422C00001-12-2.04 the medications that are indicated as "CYP3A4 inhibitors" include all drugs with any documentation of such effect, also drugs where the inhibition is weak and of doubtful clinical importance, e.g. proton pump inhibitors, histamine-2-receptor antagonists, several non-steroid anti-inflammatory drugs etc. None of the drugs that are indicated as "Yes" for "CYP3A4 inhibitors" are strong inhibitors. Only one case of moderate inhibitors (patient E1004014 took "Arithromycin" (=erythromycin) during 6 days for an incurrent urinary tract

infection. This patient recorded “increased appetite” 17 days after start of erythromycin. In study D9422C00002-12-2.04 only strong and moderate inhibitors were intended to be indicated as “CYP3A4 inhibitors”. No patient took any such medication during the study.

In summary only one patient in study D9422C00001 took a CYP3A4 inhibitor for 6 days.

This protocol deviation did not affect the interpretation of the results of the studies.

### **Discrepancy in reporting of intake of CYP3A4**

Unfortunately the programming of which medications should be indicated as “yes” in the column “CYP3A4” in appendix D9422C00001-12-2.04 was not revised as intended, only indicating drugs that are strong or moderate inhibitors of CYP3A4 (as was done in D9422C00002-12-2.04). In consequence, many instances of drugs that are weak inhibitors of CYP3A4, and where this interaction is of no clinical importance, were indicated as “yes”. The one case of intake of erythromycin was overseen and was therefore not mentioned in the body of the CSP for study D9422C00001.

In summary one case of intake of a drug that is a moderate inhibitor of CYP3A4 in study D9422C00001 occurred and this should have been mentioned in section 8.2.4 of the CSR, together with the above mentioned AE “increased appetite”.

### **Assessor comments:**

*The Applicant has adequately clarified the number of subjects receiving CYP3A4 inhibitors as concomitant medication and type of CYP3A4 inhibitors that need to be adequately monitored. Only one subject in study D9422C00001 took moderate CYP3A4 inhibitor erythromycin. Although this deviation was not mentioned in the body of the CSP of the study D9422C00001, this error is not expected to affect the result of the studies.*

*The Applicant's answer is considered sufficient. **Issue resolved.***

### **Request 4**

MAH is requested to proposed changes in the section 5.1. of the SmPC to implement information obtained from the submitted studies D9422C00001 and D9422C00002.

Objectives and conclusions of these two studies should be stated in Section 5.1 of the SmPC to provide more accurate information for the prescribers.

### **MAH's Response:**

The Sponsor proposes to update the SmPC with the following text describing the two additional studies:

Study D9422C00001 was an open-label, uncontrolled study, considered to include the actual age. The study evaluated Entocort in 108 pediatric patients (children and adolescents aged 5 to 17 years) diagnosed with mild to moderate Crohn's disease of the ileum and/or ascending colon. The median duration of treatment exposure of Entocort of 58 days (range: 5 days to 90 days). Patients were dosed with oral Entocort once daily according to bodyweight, patients weighing ≤25 kg received 6 mg once daily for 8 weeks; patients weighing >25 kg received 9 mg once daily for 8 weeks. During the 8 weeks of treatment there was a reduction in the mean (±SD) PCDAI score from 19.1 (±10.1) to 9.1 (±8.5), indicating an improvement in disease activity; with an improvement in mean (±SD) IMPACT 3 score from 132.1 (±18.8) to 140.9 (±16.9). Most AEs were related to Crohn's disease, puberty and possible GCS related side effects.

Study D9422C00002 was an open-label, un-comparative study, considered to include the actual age. The study evaluated Entocort 6 mg once daily as maintenance treatment in 50 pediatric patients (children and adolescents aged 5 to 17 years) with a diagnosis of mild to moderate Crohn's disease of the ileum and/or ascending colon who were in clinical remission. Treatment consisted of a 12-week maintenance treatment phase of 6 mg once daily, a 2-week taper phase to 3 mg once daily. The median duration of treatment exposure of Entocort was 98.5 days (range: 11 days to 135 days). Most patients remained in the clinical remission stage, as there were no major changes in the mean PCDAI composite score or IMPACT 3 score. Mean (SD)

PCDAI was 4.85 (3.62) at baseline and 6.89 (8.08) after 12 weeks of maintenance treatment with Entocort 6 mg daily. At the same points in time the mean IMPACT3 score was 145.62 (12.43) and 146.48 (15.98), respectively. Most of the AEs in the study were related to Crohn's disease, puberty, and possible GCS-related side effects.

**Assessor comments:**

*The proposed wording of the section 5.1 regarding experiences of use of Entocort by Paediatric population adequately reflects the relevant findings and is endorsed by the Rapporteur.*

*The Rapporteur proposes a minor change in the wording of the text as the current wording does not seem clear:*

*"... Study D9422C0001 was an open-label, uncontrolled study, ~~considered to include the actual age.~~ The study **designed to** evaluate Entocort in 108 pediatric patients (children and adolescents aged 5 to 17 years) diagnosed with mild to moderate Crohn's disease..."*

*"Study D9422C00002 was an open-label, un-comparative study, ~~considered to include the actual age.~~ The study **designed to** evaluate Entocort 6 mg once daily as maintenance treatment in 50 pediatric patients (children and adolescents aged 5 to 17 years) with a diagnosis of mild to moderate Crohn's disease..."*

*Furthermore, there is a small typo in the wording of the result of the IMPACT3 score in the study D9422C00002 and should be amended by the applicant as follows: "... At the same points in time the mean IMPACT3 score was 145.62 (12.43) and 146.498 (15.948), respectively..."*

**Issue partially resolved.**

**COMMENTS RECEIVED FROM OTHER MS**

Comments have been received from IE, NL and UK.

IE comments:

As there are currently no licensed paediatric indications in IE, it would be inappropriate to update section 4.8 of the SmPC, as this reflects the adult licensed use.

IE would like to review the final wording proposals from this procedure and consider whether it would be of benefit to prescribers to reflect this information in section 5.2 of the IE SmPC

NL comments:

Section 4.8:

The information 'Children with Crohn's disease have a slightly higher systemic exposure and cortisol suppression than adults with Crohn's disease' is already included in sections 5.1 and 5.2, which we consider more appropriate than section 4.8. Therefore we suggest to delete this from section 4.8. We suggest to restructure the paragraph as follows:

Paediatric population

Systemic and inhaled corticosteroids, including ENTOCORT™, may cause a reduction of growth velocity in pediatric patients. No long-term studies have been performed in paediatric patients treated with ENTOCORT™ capsules. Based on the available data from short-term studies (see section 5.1), the overall observed safety profile of ENTOCORT™ in pediatric patients is consistent with the safety profile in adults.

Section 5.1:

Study D9422C00002 was an open-label, un-comparative study designed to evaluate Entocort 6 mg once daily as maintenance treatment in 50 pediatric patients (children and adolescents aged 5 to 17 years) with a diagnosis of mild to moderate Crohn's disease of the ileum and/or ascending colon who were in clinical remission (PCDAI ≤10). Treatment consisted of a 12-week maintenance treatment phase of 6 mg once daily, a 2-week taper phase to 3 mg once daily. The



median duration of treatment exposure of Entocort was 98.5 days (range: 11 days to 135 days). Most patients remained in the clinical remission stage, as there were no major changes in the mean PCDAI composite score or IMPACT 3 score. Mean (SD) PCDAI was 4.85 (3.62) at baseline and 6.89 (8.08) after 12 weeks of maintenance treatment with Entocort 6 mg daily. At the same points in time the mean IMPACT3 score was 145.62 (12.43) and 146.98 (15.48), respectively. Most of the AEs in the study were related to Crohn's disease, puberty, and possible GCS-related side effects.

UK comments:

Section 4.8:

There is currently no licensed paediatric indication in the UK. It would be therefore inappropriate to add paediatric safety information to section 4.8 of the UK SmPC, as this section reflects the adult licensed use.

Section 5.1:

Study D9422C0001 was an open-label, uncontrolled study designed to evaluate Entocort in 108 pediatric patients (children and adolescents aged 5 to 17 years) diagnosed with mild to moderate Crohn's disease of the ileum and/or ascending colon. The median duration of treatment exposure of Entocort of 58 days (range: 5 days to 90 days). Patients were dosed with oral Entocort once daily according to bodyweight, patients weighing  $\leq 25$  kg received 6 mg once daily for 8 weeks; patients weighing  $>25$  kg received 9 mg once daily for 8 weeks. During the 8 weeks of treatment there was a reduction in the mean ( $\pm$ SD) PCDAI score from 19.1 ( $\pm 10.1$ ) to 9.1 ( $\pm 8.5$ ), indicating an improvement in disease activity; with an improvement in mean ( $\pm$ SD) IMPACT 3 score from 132.1 ( $\pm 18.8$ ) to 140.9 ( $\pm 16.9$ ). AEs were observed at a similar frequency and severity as seen in adults, and were mostly related to Crohn's disease, puberty and possible GCS related side effects.

Study D9422C00002 was an open-label, un-comparative study designed to evaluate Entocort 6 mg once daily as maintenance treatment in 50 pediatric patients (children and adolescents aged 5 to 17 years) with a diagnosis of mild to moderate Crohn's disease of the ileum and/or ascending colon who were in clinical remission. Treatment consisted of a 12-week maintenance treatment phase of 6 mg once daily, a 2-week taper phase to 3 mg once daily. The median duration of treatment exposure of Entocort was 98.5 days (range: 11 days to 135 days). Most patients remained in the clinical remission stage, as there were no major changes in the mean PCDAI composite score or IMPACT 3 score. Mean (SD) PCDAI was 4.85 (3.62) at baseline and 6.89 (8.08) after 12 weeks of maintenance treatment with Entocort 6 mg daily. At the same points in time the mean IMPACT3 score was 145.62 (12.43) and 146.98 (15.48), respectively. Most AEs were observed at a similar frequency and severity as seen in adults, and were mostly related to Crohn's disease, puberty and possible GCS related side effects.

**Assessor's comments:**

*The Rapporteur agrees with comments and proposed wording of the section 4.8 and 5.1 raised by CMS.*

*The proposed wording of the section 4.8 and 5.1 should be as follows:*

*The proposed changes of section 4.8 are only applicable to products that are already licensed for the paediatric indication  
[...]*

**Paediatric population**

*Systemic and inhaled corticosteroids, including ENTOCORT™, may cause a reduction of growth velocity in pediatric patients. No long-term studies have been performed in paediatric patients treated with ENTOCORT™ capsules. Based on the available data from short-term studies (see section 5.1), the overall observed safety profile of ENTOCORT™ in pediatric patients is consistent with the safety profile in adults.*

**Section 5.1 Pharmacodynamic properties**

*[This section should be amended to include the below wording]*

*[...]*

**Section 5.1:**

*Study D9422C0001 was an open-label, uncontrolled study designed to evaluate Entocort in 108 pediatric patients (children and adolescents aged 5 to 17 years) diagnosed with mild to moderate Crohn's disease of the ileum and/or ascending colon. The median duration of treatment exposure of Entocort of 58 days (range: 5 days to 90 days). Patients were dosed with oral Entocort once daily according to bodyweight, patients weighing ≤25 kg received 6 mg once daily for 8 weeks; patients weighing >25 kg received 9 mg once daily for 8 weeks. During the 8 weeks of treatment there was a reduction in the mean (±SD) PCDAI score from 19.1 (±10.1) to 9.1 (±8.5), indicating an improvement in disease activity; with an improvement in mean (±SD) IMPACT 3 score from 132.1 (±18.8) to 140.9 (±16.9). Most AEs were observed at a similar frequency and severity as seen in adults, and were mostly related to Crohn's disease, puberty and possible GCS related side effects.*

*Study D9422C00002 was an open-label, un-comparative study designed to evaluate Entocort 6 mg once daily as maintenance treatment in 50 pediatric patients (children and adolescents aged 5 to 17 years) with a diagnosis of mild to moderate Crohn's disease of the ileum and/or ascending colon who were in clinical remission (PCDAI ≤10). Treatment consisted of a 12-week maintenance treatment phase of 6 mg once daily, a 2-week taper phase to 3 mg once daily. The median duration of treatment exposure of Entocort was 98.5 days (range: 11 days to 135 days). Most patients remained in the clinical remission stage, as there were no major changes in the mean PCDAI composite score or IMPACT 3 score. Mean (SD) PCDAI was 4.85 (3.62) at baseline and 6.89 (8.08) after 12 weeks of maintenance treatment with Entocort 6 mg daily. At the same points in time the mean IMPACT3 score was 145.62 (12.43) and 146.98 (15.48), respectively. Most AEs were observed at a similar frequency and severity as seen in adults, and were mostly related to Crohn's disease, puberty and possible GCS related side effects.*

## VII. FINAL RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

### Overall conclusion

The MAH (Astra Zeneca) has adequately addressed the questions raised by the Rapporteur on Day 70. Based on the review of the submitted data, the Rapporteur proposes minor comments concerning the proposed wording of the section 4.8 and 5.1 of the SmPC. These should be addressed by the Applicant (for more detail please see above).

Following the finalisation of this procedure, the MAH should submit variations in all European countries where Entocort is currently registered.

### SmPC CHANGES

#### Section 4.8 Undesirable effects

*The proposed changes of section 4.8 are only applicable to products that are already licensed for the paediatric indication*

*This section should be amended to include the below wording]*

[...]

#### *Paediatric population*

*Systemic and inhaled corticosteroids, including ENTOCORT <sup>TM</sup>, may cause a reduction of growth velocity in paediatric patients. No long-term studies have been performed in paediatric patients treated with ENTOCORT <sup>TM</sup> capsules. Based on the available data from short-term studies (see section 5.1), the overall observed safety profile of ENTOCORT <sup>TM</sup> in paediatric patients is consistent with the safety profile in adults.*

[...]

#### Section 5.1 Pharmacodynamic properties

*[This section should be amended to include the below wording]*

[...]

#### *Paediatric population*

*Study D9422C0001 was an open-label, uncontrolled study designed to evaluate Entocort in 108 pediatric patients (children and adolescents aged 5 to 17 years) diagnosed with mild to moderate Crohn's disease of the ileum and/or ascending colon. The median duration of treatment exposure of Entocort of 58 days (range: 5 days to 90 days). Patients were dosed with oral Entocort once daily according to bodyweight, patients weighing ≤25 kg received 6 mg once daily for 8 weeks; patients weighing >25 kg received 9 mg once daily for 8 weeks. During the 8 weeks of treatment there was a reduction in the mean (±SD) PCDAI score from 19.1 (±10.1) to 9.1 (±8.5), indicating an improvement in disease activity; with an improvement in mean (±SD) IMPACT 3 score from 132.1 (±18.8) to 140.9 (±16.9). AEs were observed at a similar frequency and severity as seen in adults, and were mostly related to Crohn's disease, puberty and possible GCS related side effects.*

*Study D9422C00002 was an open-label, un-comparative study designed to evaluate Entocort 6 mg once daily as maintenance treatment in 50 pediatric patients (children and adolescents aged 5 to 17 years) with a diagnosis of mild to moderate Crohn's disease of the ileum and/or ascending colon who were in clinical remission (PCDAI  $\leq$ 10). Treatment consisted of a 12-week maintenance treatment phase of 6 mg once daily, a 2-week taper phase to 3 mg once daily. The median duration of treatment exposure of Entocort was 98.5 days (range: 11 days to 135 days). Most patients remained in the clinical remission stage, as there were no major changes in the mean PCDAI composite score or IMPACT 3 score. Mean (SD) PCDAI was 4.85 (3.62) at baseline and 6.89 (8.08) after 12 weeks of maintenance treatment with Entocort 6 mg daily. At the same points in time the mean IMPACT3 score was 145.62 (12.43) and 146.98 (15.48), respectively. AEs were observed at a similar frequency and severity as seen in adults, and were mostly related to Crohn's disease, puberty and possible GCS related side effects.*