CLINICAL REVIEW

Application Type	sNDA
Application Number	021324
Priority or Standard	Standard
Received Date(s)	30 June 2015
PDUFA Goal Date	29 April 2016
Division / Office	DGIEP / ODE 3
Reviewer Name	Marjorie Dannis, M.D.
Review Completion Date	30 March 2016
Established Name	Budesonide
Trade Name	Entocort EC
Therapeutic Class	Glucocorticoid
Applicant	AstraZeneca LP
Formulation(s)	Oral Capsule
Dosing Regimen	9 mg orally daily for up to 8 weeks
Indication(s)	The treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon
Intended Population(s)	Pediatric patients 8 years of age and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From the clinical standpoint, the submitted clinical data are adequate to support the recommendation of US marketing approval for Entocort for " the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon in patients 8 years of age and older. This submission was in response to the PMRs as stated below. Both of the PMRs have been fulfilled.[1]

- PMR 1027 – 1: deferred pediatric study under PREA for the treatment* of mild to moderate active Crohn's disease involving the ileum and/or ascending colon in pediatric patients ages 5 to 17 years
- PMR 1224 – 3: deferred study under PREA for the maintenance of remission in Crohn's disease in pediatric patients ages birth to 17 years of age

1.2 Risk Benefit Assessment

Review of the current application reveals that the benefit of treatment with Entocort for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon in patients 8 years of age and older outweighs the risk of Entocort. Entocort is a product with a known safety profile approved for adults for the same (treatment) indication. It is recognized that CD is similar (although not identical) in adults and children. The pivotal study shows that the product is efficacious. The totality of the safety data from the pivotal trial and the two supportive safety trials provide an acceptable safety profile for a pediatric patient population ages 8 and older who have mild to moderate active Crohn's disease involving the ileum and/or the ascending colon.

[1] Although Entocort will not be indicated for maintenance treatment, a clinical study was performed and was included as part of the safety analysis. The pediatric use section of labeling will include relevant information regarding this study.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable

1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable

2 Introduction and Regulatory Background

2.1 Product Information

Entocort™ EC capsules are formulated to allow slow release of budesonide in the small intestine and ascending colon. Budesonide is a glucocorticoid used for the anti-inflammatory treatment of diseases in the gastrointestinal and respiratory tracts. According to the Sponsor, budesonide has a high topical glucocorticoid activity and a substantial first-pass metabolism. Budesonide formulations are approved for the treatment of Crohn's disease, ulcerative colitis, chronic obstructive pulmonary disease, asthma, rhinitis, and nasal polyps. Not all indications are approved in all countries.

2.2 Currently Available Treatments for Proposed Indications

Currently, there are no FDA approved treatments available for the proposed indication:

"Treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon in patients (b) (4) *years and older"*

2.3 Availability of Proposed Active Ingredient in the United States

This product is currently licensed and marketed in the United States for:

"Treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon in adults" ***and*** *"Maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or the ascending colon for up to 3 months in adults".*

In addition, budesonide is widely commercially available in both the United States and other countries. It has several formulations including an inhalation powder, nebulized suspension, and metered dose inhaler for the treatment of chronic asthma; an aerosol nasal spray suspension for the localized treatment of allergic rhinitis; and for the treatment of ulcerative colitis as extended release tablets and most recently as a rectal foam.

2.4 Important Safety Issues with Consideration to Related Drugs

Budesonide is a synthetic glucocorticoid. Side effects typical of systemic glucocorticoids include adrenal suppression, sleep and mood disturbance, acne, striae, hirsutism, proximal myopathy, glucose intolerance, hypertension, narrow angle glaucoma, cataracts, bone loss, aseptic necrosis and reduced growth velocity. These side effects are generally dependent on dose, treatment time, concomitant and previous glucocorticoids intake, and individual sensitivity.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Relevant Clinical Pre-submission Regulatory Background	
Date	**Action**
October 2001	Entocort approved for induction of remission in adults
October 2002	• AstraZeneca (AZ) submitted revised pediatric plan • Included completed PK study (#44), completed efficacy study (#37) and proposed safety study (#310)
January 2003	• Formal Written Request (induction) sent to AZ
April 2003	• Agency "finds the [October 2002] plan acceptable"
November 2003	• AZ informed Agency that (b) (4) • However, the planned study (#310), as agreed in the communication dated April 10, 2003, would be conducted
April 2005	• Adult approval for maintenance of clinical remission of 6 mg for mild/moderate Crohn's disease (up to 3 months) • In approval letter, deferral of pediatric studies (for maintenance) for ages 0-17 until September 2007
October 2005	• (b) (4) •
December 2005	•

Relevant Clinical Pre-submission Regulatory Background	
Date	**Action**
February 2006	(b) (4)
May 2007	AZ submits revised induction protocol, Study D9421C00001(Study 1), with justification for the use of prednisone as historical control
February 2009	• Agency and PERC accept use of proposed historical control induction Study 1 • Agency and PERC request PK and HPA axis assessments (morning plasma cortisol and ACTH stimulation test)
May 2009	• AZ does not agree to add PK to Study 1 says they already did it in previous PK study (#44) • .AZ claims that "provocative HPA axis testing with …. ACTH was reported by investigators to be a significant impediment to study enrollment secondary to the relative invasiveness of this test" • AZ decides to measure dehydroepiandrosterone sulphate (DHEAS) at baseline and end of therapy
August 2011	Final pediatric protocols for Study 1 and Study 2 (maintenance) submitted
December 2012	Deferral Extension requests for Study 1 and Study 2
June 2013	Deferral Extension granted for PMR 1027-1 and PMR 1224-2
May- July 2013	• Agency requests ACTH stimulation tests on patients with normal baseline AM cortisol levels • Agency requests that patients with abnormal ACTH stim tests be folllowed monthly to determine when adrenal function returns to normal • Agency requests that HPA axis effects (by ACTH stim test) must be evaluated in a sufficient number of patients 6-11 and 12-17 • Agency requests for entry, cortisol levels should be normal before and after ACTH stim test
December 2013	"In summary, AZ believes that at this stage of study recruitment, to amend the protocols to include a test that is invasive would be nearly impossible. In addition, the current protocols already include assessment of adrenal function by morning cortisol and DHEAS a baseline and at the end of treatment"
October 2014	Deferral Extension requested for Study 1 and Study 2
December 2014	Deferral Extension is granted for PMR 1027-1 and PMR 1224-2
June 2015	Two efficacy supplements submitted to fulfill outstanding PMRs

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of reasonable quality. The electronic application was acceptable.

3.2 Compliance with Good Clinical Practices

The Sponsor certified that all of the studies contained in the NDA submission were performed in compliance with guidelines for Good Clinical Practice (GCP) and were conducted under the supervision of an IRB, or IEC equivalent, with adequate informed consent procedures.

3.3 Financial Disclosures

In the submission, the Sponsor provided a signed copy of FDA Form 3454 certifying that they have not entered into any financial arrangement with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Budesonide, the active ingredient of ENTOCORT EC capsules, is a synthetic corticosteroid. Budesonide is designated chemically as (RS)-11β, 16α, 17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is C25H34O6 and its molecular weight is 430.5.

Entocort EC is formulated as hard gelatin capsules filled with enteric-coated granules that dissolve at pH greater than 5.5. Each capsule for oral administration contains 3 mg of micronized budesonide with the following inactive ingredients: ethylcellulose, acetyltributyl citrate, methacrylic acid copolymer type C, triethyl citrate, antifoam M, polysorbate 80, talc, and sugar spheres. The capsule shells have the following inactive ingredients: gelatin, iron oxide, and titanium dioxide.

The CMC Review was unavailable at the time of writing this Clinical Review; therefore, when available, refer to the CMC review for further details regarding CMC issues

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

No animal pharmacology/toxicology data was submitted as part of this supplemental BLA.

4.4 Clinical Pharmacology

According to the Clinical Pharmacology Review by Insook Kim, dated March 25, 2016: "The Division of Clinical Pharmacology 3 has reviewed the application and found it acceptable from a clinical pharmacology perspective provided a mutual agreement on the labeling can be reached."
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4.4.1 Mechanism of Action[2]

Budesonide has a high glucocorticoid effect and a weak mineralocorticoid effect, and the affinity of budesonide to glucocorticoid receptors, which reflects the intrinsic potency of the drug, is about 200-fold that of cortisol and 15-fold that of prednisolone.

4.4.2 Pharmacodynamics[3].

Treatment with glucocorticoids, including ENTOCORT EC is associated with a suppression of endogenous cortisol concentrations and an impairment of the hypothalamus-pituitary-adrenal (HPA) axis function. There was a positive correlation between the percent (%) reduction of AUC_{0-24} of plasma cortisol and systemic exposure to budesonide both in pediatric and adult patients.

4.4.3 Pharmacokinetics[4]

Absorption

Following administration of ENTOCORT EC, the time to peak concentration varies in individual patients between 30 and 600 minutes. Mean oral bioavailability of budesonide ranges from 9% to 21% both in patients and in healthy subjects, demonstrating a high first-pass elimination of the drug.

Budesonide pharmacokinetics is dose-proportional following repeated administration in the dose range of 3 to 15 mg. No accumulation of budesonide was observed following repeated dosing.

[2] From FDA proposed Entocort EC label currently being negotiated
[3] From FDA proposed Entocort EC label currently being negotiated
[4] From FDA proposed Entocort EC label currently being negotiated

Following oral administration of 9 mg for five days of ENTOCORT EC capsules in healthy subjects, the mean peak plasma concentration and the steady state area under the plasma concentration time curve for budesonide were 5.3 ± 1.8 nmol/L and 37.0 ±14.6 nmol•hr/L, respectively.

Following administration of 9 mg ENTOCORT EC once daily in patients with active Crohns' Disease, the mean peak plasma concentration and AUC was 4.0 ±2.1 nmol/L and 35.0 ±19.8 nmol•h/L, respectively.

Concomitant high-fat meal delayed the time to peak concentration of budesonide from ENTOCORT EC by 2.3 hours but no significantly affected AUC in healthy subjects.

Distribution

The mean volume of distribution (V_{ss}) of budesonide varies between 2.2 and 3.9 L/kg in healthy subjects and in patients. Plasma protein binding is estimated to be 85% to 90% in the concentration range 1 to 230 nmol/L, independent of gender. The erythrocyte/plasma partition ratio at clinically relevant concentrations is about 0.8.

Elimination

Budesonide has a plasma clearance, 0.9 to 1.8 L/min in healthy adults. Mean plasma clearance after intravenous administration of budesonide in patients with Crohn's disease was 1.0 L/min. These plasma clearance values approach the estimated liver blood flow, and, accordingly, suggest that budesonide is a high hepatic clearance drug. The plasma elimination half-life, after administration of intravenous doses ranges between 2 and 3.6 hours, and does not differ between healthy adults and patients with Crohn's disease.

Metabolism

Following absorption, budesonide is subject to high first pass metabolism (80% to 90%). *In vitro* experiments in human liver microsomes demonstrate that budesonide is rapidly and extensively biotransformed, mainly by CYP3A4, to its 2 major metabolites, 6β-hydroxy budesonide and 16α-hydroxy prednisolone. The corticosteroid activity of these metabolites is negligible (less than 1/100) in relation to that of the parent compound. *In vivo* investigations with intravenous doses in healthy subjects are in agreement with the *in vitro* findings.

Excretion

Budesonide is excreted in urine and feces in the form of metabolites. After oral as well as intravenous administration of micronized [^{3}H]-budesonide, approximately 60% of the recovered radioactivity is found in urine. The major metabolites, including 6β-hydroxy budesonide and 16α-

hydroxy prednisolone, are mainly renally excreted, intact or in conjugated forms. No unchanged budesonide is detected in urine.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1: Induction and Maintenance Studies

	Induction		Maintenance
	Study 37* (n=48)	**Study 1# (n=108)**	**Study 2** (n=55)**
Design	R, DB, AC	Open-label, non-comparative safety	Open-label, non-comparative safety
Treatment duration	8 weeks	8 weeks	12 weeks
Age range	8-16	6-17	5-17
Entocort Dose	9 mg QD 8 wks followed by 6 mg QD 4 wks	• > 25 kg: 9 mg QD 8 wks / taper at 6 mg QD 2 wks • ≤ 25 kg: 6 mg QD 8 wks / taper at 3 mg QD 2 wks	6 mg QD for 12 wks
Primary Efficacy Endpoint	**CDAI**	**None**	**None**
Other Endpoints		Descriptive PCDAI	Descriptive PCDAI before/after treatment
HPA axis evaluations	ACTH stimulation	AM cortisol and DHEA levels[5]	AM cortisol and DHEA levels

* Study 37= Study SD-008-CR-3037

Study 1= Study D9422C00001

** Study 2= Study D9422C00002

[5] AM cortisol and DHEA levels have no clinical significance so are not discussed in this review

5.2 Review Strategy

This submission contains data relevant for induction and maintenance; however, the review will focus on induction. Within the induction indication, pivotal study 37 was reviewed in detail. The details of the pivotal study design and conduct are contained in Section 5. Study results are discussed in Sections 6 (efficacy) and 7 (safety).

Study 1 was open label non-comparative induction safety study and thus primarily safety will be assessed. Further details of Study 1 will be discussed when relevant.[6]

Study 2 was an open label non-comparative maintenance safety study and thus primarily safety will be assessed.[7] Further details of Study 2 will be discussed when relevant.[8]

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5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Protocol Summary

Title
Study SD-008-3037[9]
A Multicenter, Randomized, Double-blind, Double-dummy, Active controlled Study to evaluate the efficacy of budesonide compared with prednisolone in children with active CD with respect to remission after 8 weeks of treatment.

Study Centers and Study Period
This study was conducted from April 24, 1998 to December 22, 2000 in 6 centers in Belgium, 3 centers in Germany, 2 centers in France, 2 centers in the Netherlands, 3 centers in Spain, 1 center in Sweden, 1 centers in Switzerland, and 4 centers in the United Kingdom. The study was terminated prematurely due to increasingly poor recruitment rate.

[6] More detailed information on Study 1 can be found Appendix B
[7] Of note, the Sponsor acknowledged that within the scientific community there is a strong recommendation not to use corticosteroids as a maintenance therapy and thus did not seek a maintenance indication
[8] More detailed information on Study 2 can be found Appendix C
[9] Study 37

Study Objectives

The primary objective of the study was to evaluate the efficacy of budesonide compared with prednisolone in children with active CD with respect to remission after 8 weeks of treatment.
A secondary objective was safety measured as adrenal function, morning plasma cortisol levels and frequency of possible glucocorticoid side effects.

Study Design

This was a randomized, double-blind, double-dummy, active-controlled multicenter study that enrolled pediatric subjects aged 6 to 16 years with active Crohn's disease (defined as CDAI score ≥200) involving the ileum and/or ascending colon. A total of 120 children with active CD were planned to be randomized in the study. Thirty-six centers in Belgium, France, Germany, the Netherlands, Spain, Sweden, Switzerland and the United Kingdom participated, and each center was expected to recruit approximately 6 patients.

Children aged 6-16 years with active CD (CDAI>200) affecting the ileum and/or ascending colon were randomly allocated to receive either budesonide capsules (9 mg orally once daily during 8 weeks followed by 6 mg orally once daily during 4 weeks) or prednisolone tablets (orally once daily according to the dosing scheme in Table 2 below) during 12 weeks. The primary variable was remission defined as a CDAI ≤ 150 units.

Table 2: Prednisolone Dosing Scheme

Week	1-4	5	6	7	8	9	10	11	12
Body weight	Prednisolone dose (mg)								
≤25 kg	20	17.5	15	12.5	10	7.5	5	2.5	2.5
>25 - ≤30 kg	25	20	15	12.5	10	7.5	5	2.5	2.5
>30 - ≤35 kg	30	25	20	15	12.5	10	7.5	5	2.5
>35 - ≤40 kg	35	30	25	20	15	10	7.5	5	2.5
>40 kg	40	35	30	25	20	15	10	5	2.5

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The randomization was stratified to ensure that 50% of the patients that were included were pre-pubertal as defined by Tanner stage ≤ II.

During the study, the patients visited the clinic six times. The procedures that were performed during the clinic visits are shown in Table 3. After a four- to seven-day run-in period, the patient was randomized at Visit 2 to receive either budesonide capsules or

prednisolone tablets to be taken once daily in the mornings. After the randomization, the patient came to the clinic for visits after 2, 4, 8 and 12 weeks.

Efficacy Measurements
Study procedures were performed as summarized in the study schematic presented in Table 3 below.

Table 3: Study Assessments

Assessment Weeks (days)	Visit 1 4 days (+3)	Visit 2 0	Visit 3 2(±2)	Visit 4 4 (±2)	Visit 5 8 (±2)	Visit 6 12 (±2)
Clinical assessments:						
Inclusion/exclusion criteria fulfilled	X	X				
Patient characteristics and medical history	X					
Physical examination	X					X
(Ileo)colonoscopy[1)]	X					
Rigid/flexible sigmoidoscopy or colonoscopy[2)]	X					
CDAI and PCDAI calculations		X	X	X	X	X
Investigator's global evaluation		X	X	X	X	X
Height and weight measurements		X[3)]	X	X	X	X
Blood pressure and pulse rate	X		X	X	X	X
Check for possible GCS side effects		X	X	X	X	X
Check for adverse events		X	X	X	X	X
Laboratory assessments:						
Blood sample for clinical chemistry and hematology	X		X	X	X	X
Short ACTH-test		X			X	
Morning P-cortisol			X	X		X
Stool sample	X					
U-pregnancy test[4)]	X					X
Others:						
Informed consent	X					
Dispense diary cards	X	X	X	X	X	
Return diary cards		X	X	X	X	X
Dispense study drugs		X	X	X	X	
Return of unused study drugs			X	X	X	X

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In this study, The Crohn's Disease Activity Index (CDAI) was utilized as the primary tool to measure disease activity. The Pediatric Crohn's Disease Activity Index (PCDAI) was also utilized; however only as a secondary endpoint. Tables 4 and 5 below describe the details of both indices.

Table 4: CDAI Assessments and Score Calculation

			Factor	Subtotal
1. Number of liquid or very soft stools (Record the frequency per day)	___+___+___+___+___+___+___ + ___ Days: 1 2 3 4 5 6 7 Sum	X	2	
2. Abdominal pain rating: 0 = none, 1 = mild, 2 = moderate, 3 = severe	___+___+___+___+___+___+___ + ___ Days: 1 2 3 4 5 6 7 Sum	X	5	
3. General well-being: 0 = generally well, 1 = slightly underpar, 2 = poor, 3 = very poor, 4 = terrible	___+___+___+___+___+___+___ + ___ Days: 1 2 3 4 5 6 7 Sum	X	7	
4. Number of 6 listed categories the subject now has: Check all items that apply: □ Arthritis/arthralgia □ Iritis/uveitis □ Erythema nodosum/ pyoderma gangrenosum/ aphthous stomatitis □ Fissure, abscess and/or anal fistula (draining/non-draining) □ Other cutaneous fistula (draining/ non-draining) fistula □ Fever over 100°F (37.8°C) during past week	_____ Record "0" if no categories checked	X	20	
5. Taking Lomotil/Imodium/Loperamide /opiates for diarrhea 0 = no, 1 = yes	_____	X	30	
6. Abdominal mass 0 = none, 2 = questionable, 5 = defined	_____	X	10	
7. Hematocrit:[a] _____	Male: (47 – hematocrit) = Female: (42 – hematocrit) = Subtotal ____ If hematocrit > normal, enter "0"	X	6	
8. Body weight: __ __ __ . __ (kg) Ideal weight for height[b] __ __ __ . __ (kg)	100 × [1 – (Body wt/Ideal wt)] = Percent below ideal weight: _____ If body wt > ideal wt, enter "0"	X	1	
			Total	

a. Hematocrit values should be rounded to a whole number prior to completing the calculation in box 7 of the CDAI. Numbers that fall between the range of 0.1 to 0.4 must be rounded down. Numbers that fall between the range of 0.5 to 0.9 must be rounded up.

b. Ideal weight is obtained from CDC growth charts. The subtotal of box 8 should be rounded to a whole number. Numbers that fall between the range of 0.1 to 0.4 must be rounded down. Numbers that fall between the range of 0.5 to 0.9 must be rounded up.

Table 5: PCDAI Assessments and Score Calculation

1. Abdominal pain rating			**Score**
- None		= 0 p	
- Mild - Brief, does not interfere with activities		= 5 p	
- Moderate/severe-Daily, longer lasting, affects activities, nocturnal		= 10 p	
2. Stools (per day)			
- 0 – 1 liquid stools, no blood		= 0 p	
- Up to 2 semi-formed with small blood, or 2 – 5 liquid		= 5 p	
- Gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea		= 10 p	
3. Patient Functioning, General Well-Being			
- No limitation of activities, well		= 0 p	
- Occasional difficulty in maintaining age appropriate activities, below par		= 5 p	
- Frequent limitation of activity, very poor		= 10 p	
LABORATORY			**Score**
4. HCT: Male and female ≤ 10 years: ≥ 33 = 0 p; 28 – 32 = 2.5 p; < 28 = 5 p	Male 11 – 14 years: ≥ 35 = 0 p; 30 – 34 = 2.5 p; < 30 = 5 p		
Female 11 – 19 years: ≥ 34 = 0 p; 29 – 33 = 2.5 p; < 29 = 5 p	Male 15 – 19 years: ≥ 37 = 0 p; 32 – 36 = 2.5 p; < 32 = 5 p		
5. ESR (mm/hr)	< 20 = 0 p; 20 – 50 = 2.5 p; > 50 = 5 p		
6. Albumin (g/dL)	≥ 3.5 = 0 p; 3.1 – 3.4 = 5 p; ≤ 3.0 = 10 p		
EXAMINATION			**Score**
7. Weight - Weight gain or voluntary weight stable/loss		= 0 p	
- Involuntary weight stable, weight loss 1% – 9%		= 5 p	
- Weight loss ≥ 10%		= 10 p	

Of note, at this time, DGIEP is exploring other tools which could better quantify disease activity. However, the PCDAI and CDAI have been used to help determine efficacy in previous registration trials.

Study Population

Key Inclusion Criteria

Each patient had to meet the following criteria to be eligible for the study:

- Were 6-16 years old and had not passed their 17th birthday (50% of the patients being pre-pubertal; Tanner stage ≤II).

- Had a diagnosis of CD verified by small bowel follow-through/enteroclysis and colonoscopy. Another alternative to verify CD was by histology examination of operative specimens.
- Had an extent of CD limited to the ileum, ileo-ceacal region and/or ascending colon apart from scattered apthous ulcers elsewhere as judged by the clinician and supported by an ileo-colonoscopy within 6 months prior to or at Visit 1.
- Had active CD defined by a CDAI ≥200 units at Visit 2

Key Exclusion Criteria

Patients who met any of the following criteria were excluded from the study

- Had > 50 cm resected of the small bowel or any resection of the proximal colon extending beyond the mid-transverse colon.
- Had an ileostomy, pouch or colostomy.
- Had active CD of the distal colon verified with an investigation of at least the most distal 25 cm using either rigid or flexible sigmoidoscopy/colonoscopy anytime during the 8 weeks prior to or at Visit 1.
- Had a body weight < 20 kg.
- Had signs of septic complications, abscess, mechanical obstruction, perforation or an active fistula (with the exception of chronic asymptomatic anorectal fistula).
- Were candidates for immediate surgery or were unlikely to complete the study due to a poor general condition.
- Were scheduled to undergo in-patient major surgery during the study.
- Had active peptic ulcer disease.
- Had hepatic, renal, respiratory, cardiovascular, endocrine, neurologic, psychiatric or other diseases judged by the investigator as clinically relevant for the purpose of the study.
- Had uncontrolled diabetes mellitus.
- Were on total parenteral nutrition or chemically defined, nutritionally complete, amino acid-based, polymeric peptide-based or modular diets 7 days before Visit 1.
- Had a history of carcinoma (excluding basal and squamous cell skin carcinoma) within the last five years.
- Had been exposed (including immunization) to live viruses (e.g. chicken pox, measles, polio) or tuberculosis within the last 90 days prior to Visit 1.
- Had previously been enrolled in this study or had been enrolled in any other investigational drug study within 30 days prior to Visit 1.

Exclusion criteria at Visit 2

- Had laboratory values or abnormalities in pulse, blood pressure or at physical examination as judged by the investigator as clinically relevant for the purpose of the study.
- Had enteric pathogens, Clostridium difficile toxin, ova or parasites in stools at Visit 1.
- Had received any glucocorticoid within 30 days prior to Visit 2, except for eye drops and low potency steroid ointments, e.g. hydrocortisone derivatives.
- Had been treated with sulfasalazine, olsalazine, mesalazine, balsalazide, metronidazole, ciprofloxacin, cholestyramine or other drugs for treatment of CD within 7 days prior to

Visit 2. These drugs were allowed if the dose had been kept constant more than 30 days prior to Visit 2 and the dose was planned to be kept constant during the study period.

- Had received azathioprine, cyclosporin or other immunosuppressive drugs within 90 days prior to Visit 2.
- Had received ketoconazole within 7 days prior to Visit 2.

Study Treatments

A double-dummy technique was used to ensure blindness of the study. All patients took active drug, either budesonide (b) (4) capsules or prednisolone tablets, as well as placebo capsules and tablets. The placebo capsules and tablets were identical in appearance to the active drugs. The medication was to be taken once daily in the morning before breakfast together with at least one glass of water.
Patients in the budesonide group received 9 mg (3x3 mg) for eight weeks, followed by 6 mg (2x3 mg) budesonide (b) (4) capsules for four weeks.
Patients in the prednisolone group received study drug according to a weight based scheme (See Table 2 above):

Concomitant Therapy

A list of medications that were prohibited during the study as well as any restrictions associated with those drugs are listed below in Table 6.

Table 6: Concomitant Therapy

Medication	Restrictions
Glucocorticosteroids	*Prohibited and not allowed 30 days prior to Visit 2 (except for eye drops and low potency steroid ointments, e.g. hydrocortisone derivatives)*
Sulfasalazine, olsalazine, mesalazine (5-ASA), balsalazide, metronidazole, ciprofloxacine, cholestyramine or other drugs for treatment of CD	*Prohibited and not allowed 7 days prior to Visit 2, unless the dose was kept constant during the 30 days prior to Visit 2 and the dose was kept constant during the study period.*
Azathioprine, cyclosporin or other immunosuppressive drugs	*Prohibited and not allowed 90 days prior to Visit 2 and during the study.*
Ketokonazole	*Prohibited and not allowed 7 days prior to Visit 2 and during the study.*

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Study Visits and Procedures

The study visits and related safety assessments are summarized in Table 3 above.

Study Endpoints

Primary Variables

The primary variable was remission rate defined as a CDAI of 150 or lower. The primary analysis was based on the intention to treat approach and used the last value extended principle from Visit 3 onwards, whenever data was missing. The primary evaluation was made after 8 weeks of treatment.

Major Secondary Variables

- percentage improved, where improvement is defined as CDAI < 150 units or a decrease in CDAI of 70 units from the baseline
- quantitative changes in CDAI
- quantitative changes in PCDAI

CDAI

The CDAI was calculated at Visits 2-6. The CDAI was calculated on the basis of signs and symptoms, clinical examination and the patient's hematocrit value (modified for the children with a hematocrit cut off of 41%). Signs and symptoms were recorded by the patient in a diary card including the number of liquid or very soft stools, abdominal pain rating (none, mild, moderate, severe) and general well-being (generally well, slightly below par, poor, very poor and terrible), intake of loperamide or other opiates, and temperature if feeling feverish. Data from the seven days preceding each visit were used for calculation of the CDAI unit. If data from all seven days preceding the visits were not available, the CDAI were calculated on data from at least four days.
At all clinic visits the investigator asked if the patient had experienced any complications (arthritis/arthralgia, iritis/uveitis, erythema, nodosum/pyoderma gangrenosum/aphthous stomatitis, anal fissure, fistula or abscess, other fistula). The investigator also examined the patient's abdomen for any abdominal mass. The patient's weight was measured. The standard weight was calculated by each center and they used their own growth standards and growth charts. Actual height was plotted in a growth chart. The corresponding weight was taken from the growth chart and this weight was defined as the standard weight and expressed in kilograms

PCDAI

The PCDAI was calculated at Visits 2-6. The PCDAI is calculated on the basis of disease history, laboratory values and physical examination. The disease history includes abdominal pain rating, stool pattern and general well-being. Laboratory values include hematocrit, erythrocyte sedimentation rate and albumin levels. The physical examination includes measurements for weight and height velocity, abdominal mass, perirectal disease and presence of extra-intestinal manifestations. Data from the seven days preceding each visit were used for calculation of the PCDAI. If data from all seven days preceding the visit were not available, the PCDAI was calculated on data from at least four days.

6 Review of Efficacy

6.1 Indication

The Sponsor proposed to expand the current treatment indication in adult CD patients to pediatric CD patients. The proposed indication statement is the following:

"ENTOCORT EC is a corticosteroid indicated for treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon, in patients (b) (4) years and older."

6.1.1 Methods

Section 5.3 contains a discussion of the pivotal study protocol. Section 6 contains the study results as well as a discussion of the efficacy issues that arose during the review of this application.

The efficacy of budesonide for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon, in patients 8 years and older, was partially extrapolated from the adult induction trials. Thus, to establish efficacy in the pediatric population (in addition to PK study), one randomized, double-blind induction trial was performed. In these adult studies,[10] CDAI ≤ 150 after 8 weeks of treatment was also used as the primary endpoint.

Efficacy Discussion
This pivotal study was originally designed to evaluate the efficacy of Entocort compared with prednisolone in children with active CD with respect to remission after 8 weeks of treatment. However, according to the Sponsor, there were difficulties with the recruitment of patients, so the study was prematurely terminated. The study did show a numerical difference (55% vs. (b) (4) % in remission rates between Entocort and prednisolone, respectively).
Although the disease process and disease progression in CD are not exactly equivalent between adult and pediatric patients, it has generally been accepted that they are similar enough that we may use adult efficacy data to extrapolate the results from pediatric trials. The adult pivotal trials had similar primary endpoints of CDAI < 150 after 8 weeks of treatment; the results are presented below in Table 7. Depicted in red are the relevant results. Although cross-study comparisons are very challenging, the percentage for the Entocort treatment group of 55 seen in the pediatric study, appears to be comparable to the percentages of 48-69 seen in the adult studies.

[10] The registration trials

Table 7: Adult Efficacy Results: CDAI ≤l 150 After 8 weeks of Treatment

Clinical Study	ENTOCORT EC 9 mg Daily	ENTOCORT EC 4.5 mg Twice Daily	Comparator**	Placebo	Prednisolone
1	62/91 (69%)*		37/83 (45%)		
2		31/61 (51%)#		13/64 (20%)	
3	38/79 (48%)	41/78 (53%)		13/40 (33%)	
4	35/58 (60%)	25/60 (42%)			35/58 (60%)
5	45/86 (52%)				56/85 (65%)

*p=0.0004 compared to comparator.

#p=0.001 compared to placebo.

**This drug is not approved for the treatment of Crohn's disease in the United States.

6.1.2 Demographics and Baseline Disease Activity

Demographic characteristics at baseline for all subjects randomized are provided below in Table 8. Of the 48 patients randomized, 33 (69%) were males and 15 (31%) were females. Their average age was 13 (range 8-16) years. All but four were Caucasians. In general (with exceptions as noted in green) these demographic characteristics were similar between the treatment groups.

Table 2: Key Demographics and Baseline Characteristics

Demographic Subgroup	Prednisolone n=26	Budesonide n=22	All n=48
Sex (n,%)			
Male	18 (69)	17 (77)	33 (69)
Female	8 (31)	7 (32)	15 (31)
Age (years)			
mean	13	13	13
Min, Max	8, 16	8, 16	8, 16
< 8 years	0	0	0
≥8 years	26	22	48
Height (cm)			
mean	156	155	156
Min, Max	128, 177	135, 186	128, 186
Weight (kg)			
mean	40	40	40
Min, Max	(22, 57)	(26, 58)	(22, 58)
≤ 25 kg	3	0	3
> 25 kg	23	22	45
Baseline value CDAI (range)	268 (145-411)	239 (182-307)	255 (145-411)
Ileum			
no	1	2	3
yes	25	20	45
Caecum			
no	7	13	20
yes	18	9	27

Adapted from CSR, Table 12 pg 50

6.1.3 Subject Disposition

A total of 56 patients were enrolled at 22 centers in 8 countries: Belgium, France, Germany, the Netherlands, Spain, Sweden, Switzerland, and the United Kingdom. Of these, 48 were randomized at Visit 2. The first patient entered the study on April 24, 1998 and the last patient finished the study on December 22, 2000. Thirty patients completed the study with most of the discontinuations secondary to worsening of disease (in both treatment groups). See Table 9 below.

Table 9: Patient Disposition

	Prednisolone	Budesonide	All
Enrolled patients			56
- Not randomized			8
- Eligibility criteria not fulfilled			8
Randomized	26	22	48
Discontinued	10	8	18
- disease under study deteriorated	8	6	14
- disease under study did not improve	0	1	1
- eligibility criteria not fulfilled	2	1	3
Completers	16	14	30

From CSR, Table 8 pg 45

6.1.4 Analysis of Primary Endpoint

The primary efficacy endpoint was remission where remission was defined as a CDAI of 150 or lower. The primary analysis of CDAI was the analysis of proportions of patients in remission after eight weeks (Visit 5). The results were:

- 55% (95% [CI]: 32%, 77%) of subjects in budesonide group vs.
- (b) (4)% (95%CI: (b) (4)%, (b) (4)%) of subjects in prednisolone group

However, there was no statistical power to determine whether budesonide or prednisolone was more effective (p=(b) (4)).

(b) (4)

[11] a change generally considered clinically relevant

(b) (4)

(b) (4)

(b) (4)

6.1.6 Other Endpoints

The clinically relevant efficacy endpoints are discussed above and below in Section 6..

6.1.7 Subpopulations

No subpopulation analyses were performed.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Results from the pharmacokinetic/pharmacodynamic study (SD-008-3044) showed that systemic exposure and cortisol suppression after oral administration of 9 mg budesonide were only slightly higher in pediatric subjects than in adults with active Crohn's disease. Moreover, in the active-controlled study (Study 37), the proportion of subjects in clinical remission after treatment with budesonide daily was similar to that previously seen in adult subjects, and there was no correlation between age or weight and reduction in plasma cortisol, or an increased frequency of adverse events in smaller subjects.

In Study 1, according to the Sponsor, a daily dose of 9 mg was selected for subjects weighing >25 kg based on data from previous pediatric clinical studies. For pediatric subjects weighing 15 to 25 kg, the dose of budesonide was reduced to 6 mg daily.[12] However, PK blood samples were not collected during the efficacy and safety studies in pediatric patients

[12] The Sponsor does not provide a data driven rationale for the 6 mg dose.

According to Clinical Pharmacology Review dated March 25, 2016 by Insook Kim, Ph.D.,

"The pharmacokinetics was studied in pediatric patients (mean age 12; 9-14 years old) and compared with that in adult patients (mean age 33; 21-52 years old) in the same study. After 9 mg once daily dosing of budesonide for 7 days, the median time to peak plasma concentration was 5 hours in pediatric patients and 4 hours in adult patients. The mean Cmax and AUC0-24 for budesonide were higher in pediatric patients by 41% and 21%, respectively compared to those in adult patients. The distribution of AUC0-24 values was largely overlapped between pediatric patients and adult patients while the interpretation of the results is limited by a small sample size and a high intersubject variability in both age groups. The PK of budesonide in pediatrics patients was studied after administration of 9 mg but not after 6 mg dose, (b) (4) .

"The efficacy for the induction of remission was assessed with one dose level, i.e. 9 mg once daily. The PK blood samples were not collected during the efficacy and safety studies in pediatric patients. As such the dose-response or concentration-response relationship for the induction of remission was not assessed in pediatric patients. The efficacy of 6 mg in patients < 25 kg was not studied for the induction of remission" For complete information, see the Clinical Pharmacology Review.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable because this submission applies to short-term treatment

6.1.10 Additional Efficacy Issues/Analyses

Study 37

The mean daily score for the stool frequency and abdominal pain components of the CDAI are shown below at Baseline and Week 8.

Time	Mean Daily Score	
	Stool Frequency	Abdominal Pain
Baseline	1.49	1.49
Week 8	0.96	0.54

Above is taken from the Response to Information Request dated 3/16/16

Both the stool frequency and abdominal pain mean daily scores decreased from Baseline to Week 8.

Study 1
Study 1 was an open-label, non-comparative induction safety study of 8 weeks duration with weight based treatment. Subjects with weight > 25 kg received Entocort 9 mg a day and those weight ≤ 25 kg received Entocort 6 mg a day. Although this was primarily a safety study, (b) (4)

(b) (4)

Age/Weight Distribution

Age
The Sponsor proposed the following indication:

"Entocort is indicated for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon in patients (b) (4) years of age and older ."

(b) (4)

Weight
The Sponsor proposed the following weight-tiered dosing regimen:
(b) (4)

[13] In Study 1, there was one patient who was age 6.

(b) (4)

(b) (4)

7 Review of Safety

7.1 Methods

The safety of budesonide in pediatric subjects with CD was determined using the totality of data from four clinical studies:

- Study SD-008-3044 compared the pharmacokinetics of budesonide and its effects on cortisol secretion in pediatric and adult subjects with active Crohn's disease following administration of Entocort 9 mg/day for 7 days[15]

[14] DGIEP has been focusing on these two components of the PCDAI
[15] This was a very small, short duration PK Study which only included 8 pediatric patients thus safety will be included

- Study 37 was a randomized, double-blind study that compared Entocort with prednisolone in the treatment of 48 pediatric subjects with active Crohn's disease.

- Study 1 evaluated the safety and tolerability of Entocort in 108 pediatric subjects aged 5 to 17 years with active disease.[16]

- Study 2 evaluated the safety and tolerability of Entocort as maintenance treatment in 50 pediatric subjects aged 5 to 17 years who were in clinical remission.[17]

The focus of this safety review will be on the one randomized, double-blind study (Study 37) and the combination of data from the two open-label, non-comparative safety studies in pediatric (Study 1 and Study 2). Due to differences in study designs, these will be reviewed separately.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data were reviewed from the four studies as described above.

7.1.2 Categorization of Adverse Events

Adverse events (AEs) were classified by the Sponsor using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Adverse event incidence data were included from Study 37, Study 1 and Study 2. See Section 7.1 for a description of how pooled data is presented in this review.

7.2 Adequacy of Safety Assessments

The safety assessments performed were adequate. Safety variables included AEs, clinical laboratory evaluations (hematology, clinical chemistry), vital signs, and physical examination parameters. AEs of special interest such as any possible glucocorticoid (GC) related AEs were collected by active questioning[18]. Patients who were given at least one dose of the study medication were included in the safety analysis population.

only if relevant. See Appendix B for further information
[16] See Appendix B for further information
[17] See Appendix C for further information

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Entocort EC 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. As of 1 March 2015, Entocort is approved for the treatment of Crohn's disease in adults in 39 countries, including the United States (US), and it is approved for the treatment of pediatric patients aged ≥8 years in 17 countries.

Study 1 and Study 2

Exposure to Entocort in studies 1 and 2 is summarized below in Table 13. In Study 1, 108 subjects received Entocort for a median (range) of 58.0 (5 to 90) days, and the corresponding values for the 50 subjects in Study 2 were 98.5 (11 to 135) days. The difference in exposure between the two studies is in keeping with the longer treatment phase of Study 2 (12 weeks versus 8 weeks).

Table 13: Duration of exposure in studies 1 and 2

Duration of exposure (days)	D9422C00001 N=108	D9422C00002 N=50
Mean	60.8	94.0
Standard deviation	16.37	18.47
Median	58.0	98.5
Minimum	5	11
Maximum	90	135
Total treatment days	6565	4702

Source: study D9422C00001 CSR, Section 8.1 and Table 19, and study D9422C00002 CSR, Section 8.1 and Table 22.

The demographic and baseline characteristics of subjects in studies 1 and 2 were generally very similar, with the exception of the longer mean duration of Crohn's disease in study 2 subjects (1.48 vs. 1.08 years) This is not unexpected considering that 43 of the 50 subjects (86%) in

[18] In Studies 1 and 2

study 2 had previously participated in study 1. In both studies, subjects mean age was approximately 13 years, and >95% of subjects were aged >8 years. There were slightly more males than females and the majority of subjects (≥90%) were white. See Table 14 below.

.

Table 14: Demographic and baseline characteristics of subjects in studies 1 and 2

Demographic Subgroup	**Study 1 n=108**	**Study 2 N=50**
Sex (n,%)		
Male	57 (53)	30 (60)
Female	51 (47)	20 (40)
Age (years)		
Mean (SD)	13.7 (2.41)	13.8 (2,44)
Median (Min, Max)	14 (6, 17)	15 (8, 17)
Age Group (n,%)		
≤ 8 years	5 (4.6)	2 (4)
>8 years	103 (95.4)	48 (96)
Race (n,%)		
Caucasian	100 (92.6)	45 (90)
Black	4 (3.7)	2 (4)
Other	4 (3.7)	3 (6)
Weight (kg)		
mean	48.1(15.36)	49.6(14.6)
Min, Max	(18.8, 95.5)	(23.5, 84.5)

Adapted from SCS Table 4 pgs 21-22

Study 37
In Study 37, 22 subjects received Entocort for a median (range) of 82 (10 to 90) days and a mean of 66 days. The total exposure to Entocort was 1449 days. The corresponding values for the 26 subjects in the prednisolone group were median (range) of 83 (3 to 89) days, a mean of 66 days and a total exposure of 1706 days.

The demographic characteristics for Study 37 are listed in Section 6.1.2.

7.2.2 Explorations for Dose Response

There was one randomized, controlled, double-blind study, in which only one induction dose was studied (9 mg). This was not adequate to explore dose response.

7.2.3 Special Animal and/or In Vitro Testing

No new non-clinical data were submitted in support of this sNDA.

7.2.4 Routine Clinical Testing

Routine clinical testing as described in Section 7.2 was included as part of the safety assessments. See Section 5.3.1 for detailed information on study visits and procedures.

7.2.5 Metabolic, Clearance, and Interaction Workup

For more information see Section 4.4 above and the Clinical Pharmacology Review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adverse events related to suppression of the HPA axis are of special interest when evaluating glucocorticoid (GC) treatment, especially in pediatric subjects. Thus, subjects in studies 1 and 2 were evaluated for the presence of 16 signs and symptoms associated with GC treatment at each study visit. At each study visit, the following 16 possible GCS-related signs and symptoms were collected by active questioning and scored (0=none, 1=mild, 2=moderate, 3=severe): moon face, buffalo hump, acne, hirsutism, skin striae, easy-to-bruise, swelling of the ankles, mood swings, irritability, depression, psychosis, memory disturbance, concentration disturbance, insomnia, hair loss, and alteration of appetite.

GC-related adverse events in Study 1 versus historical controls

In 2006, it was agreed between the FDA and the Sponsor that a pediatric study would be conducted without an active control group and that the GC-related safety of Entocort during *induction of remission* would be assessed in conjunction with GC-related safety data derived from the published literature (i.e. historical controls).[19]

For (descriptive) comparison purposes only, the highest and lowest rates of occurrence of GC-related AE reported for conventional GC treatment in the 5 published studies are presented in Table 15 below, together with the corresponding frequencies of GC related AEs that were collected by active questioning during Entocort treatment in study 1 (and additionally as reported for Entocort in Escher 2004 (Study 37)).

The frequencies of all GC-related AEs reported for Entocort in study 1 were lower than the corresponding low values for the conventional GCS historical controls. Furthermore, with the exception of easy-to- bruise, mood swings, depression, and insomnia, the reported frequencies of GC-related AEs for Entocort in the Escher 2004 publication (Study 37) were also lower than the corresponding low values for the GC historical controls.

Thus, based on this comparison with historical control data from study1 subjects treated with prednisone, prednisolone or methylprednisolone, it appears that Entocort has a more favorable safety profile with regard to GC-related AEs. However, the limitations of using historical control data and the methodology that was used to make such comparisons ***severely limit the interpretation of these results.***

[19] Due to great enrollment challenges FDA accepted this study design.

Table 15: Ranges of AEs reported for historical controls compared with AEs reported in study

	Historical controls (conventional GCS) Ranges of GCS-related AEs[a]		Entocort EC Escher 2004[b] N=22	Entocort EC Study D9422C00001 N=108
	Low value	High value		
GCS-related AEs	20/26 (77%)[c]	20/26 (77%)[c]	11 (50%)	72 (66.7%)
Moon face	15/26 (58%)	10/14 (71%)	5 (23%)	0
Buffalo hump	1/26 (4%)[c]	1/26 (4%)[c]	0	0
Acne	7/26 (27%)	7/15 (47%)	1 (4%)	15 (13.9%)
Hirsutism	3/26 (12%)	4/14 (29%)	2 (9%)	5 (4.6%)
Skin striae	1/26 (4%)	4/15 (27%)	0	2 (1.9%)
Easy-to-bruise	1/26 (4%)[c]	1/26 (4%)[c]	1 (4%)	0
Swelling of the ankles	1/26 (4%)[c]	1/26 (4%)[c]	0	0
Mood swings	2/26 (8%)[c]	2/26 (8%)[c]	3 (14%)	3 (2.8%)
Irritability	NR	NR	NR	0
Depression	1/26 (4%)	5/58 (9%)	2 (9%)	2 (1.9%)
Psychosis	NR	NR	NR	0
Memory	NR	NR	NR	0
Concentration	NR	NR	NR	0
Insomnia	1/14 (7%)	4/26 (15%)	5 (23%)	6 (5.6%)
Hair loss	3/26 (12%)[c]	3/26 (12%)[c]	1 (4%)	2 (1.9%)[d]
Alteration in appetite	NR	NR	NR	23 (21.3%)
PCDAI at baseline, mean (SD)	28.9 (5.3)	45 (10.7)	39.0 (10.7)	19.1 (9.98)

[a] Reported ranges are the lowest and highest values for each of the AEs reported for conventional GCS treatment in Table 11.
[b] AstraZeneca study SD-008-3037.
[c] AE reported in only 1 publication. Therefore, the AE is presented in the table as both low and high values.
[d] Reported as alopecia.

AE Adverse event; GCS Glucocorticosteroid; NR Not reported; PCDAI Pediatric Crohn's Disease Activity Index; SD Standard deviation.

Sources of study D9422C00001 data: study D9422C00001 CSR, Tables 11.1.6, 11.3.2.2, and 11.3.6.2.

From SCS pg 36 Table 12

In addition, morning serum cortisol and dehydroepiandrosterone sulfate (DHEAS) levels were measured in both studies 1 and 2. However, in clinical practice morning serum cortisol and dehydroepiandrosterone sulfate (DHEAS) levels are **NOT** reliable indicators of possible HPA-axis suppression. The Sponsor was advised to perform ACTH stimulation tests since this is the accepted measure of HPA- axis function; however, ACTH stimulation tests were NOT performed in studies 1 and 2.

Study 37
After 8 weeks of treatment the proportion of patients with abnormal function measured by the ACTH test was 63% in the entocort group vs 89% in the prednisolone group (P=0.07)

Thus, it appears that using this particular analysis, the HPA axis was suppressed more in response to prednisolone than Entocort.

See Clinical Pharmacology Review by Insook Kim Ph.D., dated March 25, 2016, for further details.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in studies 1 and 2 or Study 37.

7.3.2 Nonfatal Serious Adverse Events

Study 1 and Study 2

Serious AEs were reported in 8 (7.4%) subjects (11 events) in study 1 and 4 (8%) subjects (5 events) in study 2. In study 1, the SAEs were related to the underlying Crohn's disease in 4 (3.7%) subjects. In addition, diarrhea hemorrhagic, small intestinal obstruction [2 events]), hypokalemia, musculoskeletal chest pain, and erythema nodosum were each reported in 1 (0.9%) subject. The SAEs of diarrhea hemorrhagic and small intestinal obstruction could be complications of the underlying disease.

In study 2, the SAEs were related to the underlying Crohn's disease in 3 (6%) subjects Furthermore, gastrointestinal hemorrhage and ileal stenosis were each reported in 1 (2%) subject. Both of these SAEs could be complications of the underlying disease.

Study 37

In total, 13 SAEs (10 in the prednisolone group and 3 in the budesonide group) were reported during the study .All SAEs in the Entocort group were related to Crohn's disease.

7.3.3 Dropouts and/or Discontinuations

Study 1 and Study 2

Adverse events leading to discontinuation of study treatment were reported in 9 (8.3%) subjects (11 events) in study 01 and 3 (6%) subjects in study 2 (3 events).

In study 1, 5 (4.6%) subjects discontinued study treatment because of the underlying Crohn's disease. In addition, abdominal pain, diarrhea, small intestinal obstruction, fistula, abnormal hair growth, and pallor were also reported as AEs leading to discontinuation from study treatment, each in 1 (0.9%) subject. The AEs of abdominal pain, diarrhea, small intestinal obstruction, and fistula could be secondary to the underlying disease or complications of the underlying disease..

In study 2, 2 (4%) subjects discontinued study treatment because of the underlying Crohn's disease and 1 (2%) subject discontinued because of abdominal pain (also could be considered secondary to the underlying disease).

Study 37

In total, 14 Discontinuations due to Adverse Events (DAEs) (8 in the prednisolone group and 6 in the budesonide group) were reported during the study; all were classified as "DAE: disease under study deteriorated".

7.3.4 Significant Adverse Events

There were no other significant AEs in Study 1, Study 2 or Study 37.

7.3.5 Submission Specific Primary Safety Concerns

Study 1 and Study 2

As noted in Section 7.2.6, AEs related to suppression of the HPA axis are of special interest when evaluating the safety profile of a GC treatment, especially in pediatric patients. Reporting of any of the possible GCS-related AEs at baseline and the other study visits is summarized below in Table 16. In study 1, the proportion of subjects with

any possible GC-related AEs increased from 45.4% at baseline to 61.3% at the end of the treatment phase (Visit 4). In contrast, the proportion of subjects with any possible GC-related AEs was 60% at both baseline and the end of the treatment phase in study 2. This is not unexpected considering that 86% of the subjects in study 2 had been treated with Entocort previously in study 1.

Table 16: Possible GCS-related AEs by examination status

GCS-related AEs	Number (%) of subjects	
	Study D9422C00001 N=108	Study D9422C00002 N=50
Subjects with any possible GCS-related AEs	72 (66.7)	34 (68.0)
Subjects with any possible GCS-related AEs at baseline (Visit 1)	49 (45.4)	30 (60.0)
Subjects with any possible GCS-related AEs at the end of the treatment phase (Visit 4)[a]	65 (61.3)	30 (60.0)
Subjects with any possible GCS-related AEs at the end of follow-up (Visit 5)[b]	26 (49.1)	21 (46.7)

[a] Week 8 in study D9422C00001 (N=106) and Week 12 in study D9422C00002 (N=50).
[b] Week 12 in study D9422C00001 (N=53) and Week 16 in study D9422C00002 (N=45). In study D9422C00001, only the subjects who did not continue to study D9422C00002 attended Visit 5.
AE Adverse event; GCS Glucocorticosteroid.
Source: study D9422C00001 CSR, Section 8.2.3 and Table 11.3.6.2, and study D9422C00002 CSR, Section 8.2.3 and Table 11.3.6.1.

From CSC Table 8 pg 27

Study 37

Signs of possible GCS-associated side effects
At each visit, the patients were evaluated for 11 possible GCS-associated side effects. The percentage of patients in each treatment group reporting any of the symptoms or signs at baseline and treatment are presented below in Table 17. According to this table, it appears that there was a higher frequency of glucocorticoid associated side effects in some prednisolone treated patients in comparison with patients treated with Entocort. This difference was particularly obvious for moon face and acne. However, due to the small number of patients in the study, it is difficult to draw definitive conclusions from this data.

Table 17: Glucocorticoid (GCS) side effects by included term: Percentage (%) of patients reporting symptoms/signs

	Prednisolone (n = 26)		Budesonide (n = 22)	
	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

From CSC Table 29 pg 61

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study 1 and Study 2

In both studies, most of the reported AEs were related to Crohn's disease and puberty and were possible GC-related AEs (the latter were obtained by active questioning). The most commonly reported AEs were in the SOCs Gastrointestinal disorders and Skin and subcutaneous disorders, and the most common AEs by PT were abdominal pain, increased appetite, acne, Crohn's disease, irritability, and Cushingoid. Given the known side effect profile of glucocorticoids, almost all these AEs would be expected.

In study 1, AEs in the SOCs Gastrointestinal disorders, Skin and subcutaneous disorders, and Metabolism and nutrition disorders were reported in 41 (38%), 29 (27%), and 25 (23%) subjects, respectively. Adverse events by PT reported in ≥4% of subjects are listed in Appendix D Table 1. The most frequently reported AEs were increased

appetite (17 [16%] subjects), abdominal pain (16 [15%] subjects), and acne (15 [14%] subjects).

In study 2, AEs in the SOCs Gastrointestinal disorders, Skin and subcutaneous disorders, and Infections and infestations were reported in 25 (50%), 11 (22%), and 11 (22%) subjects, respectively. Adverse events by PT reported in ≥4% of subjects are listed in Appendix D Table 2. The most frequently reported AEs were abdominal pain (8 [16%] subjects), Crohn's disease (7 [14%] subjects), and acne (6 [12%] subjects).

Study 37

The most frequently reported AEs are presented in decreasing order in Table 18 below. When looking at the AEs on a preferred term level, the most frequent AE is Cushing Syndrome (Medicamentosa) as might be expected in this study. Due to the small number of patients in the study, it is difficult to draw conclusions from this data; however, most of the AEs could be attributed to the underlying disease or consistent with typical childhood illnesses.

Table 18: Most frequently reported Adverse Events (preferred term):

Preferred term	Prednisolone (n = 26)	Budesonide (n = 22)	p-value*
Cushing syndrome (Med)**	22 (85%)	14 (64%)	0.0944
Crohn's disease aggravated	4 (15%)	5 (23%)	0.5161
Abdominal pain	6 (23%)	3 (14%)	0.4037
Headache	4 (15%)	4 (18%)	0.7956
ESR increased	1 (4%)	5 (23%)	0.0487
Vomiting	3 (12%)	3 (14%)	0.8267
Anemia hypochromic	3 (12%)	1 (5%)	0.3824
Diarrhea	3 (12%)	1 (5%)	0.3824
Myalgia	2 (8%)	2 (9%)	0.8613
Fever	2 (8%)	1 (5%)	0.6536
Fatigue	0	3 (14%)	0.0518
Pharyngitis	1 (4%)	2 (9%)	0.4545
Nausea	2 (8%)	1 (5%)	0.6536
Anorexia	1 (4%)	2 (9%)	0.4545

*The test is a chi-square test.
** From active questioning

CSR pg 59 Table 28

7.4.2 Laboratory Findings

Study 1 and Study 2

In studies 1 and 2, there were no clinically relevant changes I hematology, clinical chemistry, or urinalysis parameters, and no subjects met Hy's Law criteria.

Study 37

There were no changes in mean laboratory values indicating any influence by the investigational products. Individual laboratory values and treatment emergent changes generally showed small changes that were not considered clinically relevant.

7.4.3 Vital Signs

Study 1 and Study 2

No clinically significant differences between baseline and end of the treatment were observed in vital signs variables

Study 37
There were no changes in mean variables indicating any influence on pulse rate, blood pressure or physical findings, by the investigational products. Individual values and treatment emergent changes generally showed small changes that were not considered clinically relevant.

7.4.4 Electrocardiograms (ECGs)

Entocort is an approved product with no known effects on ECG findings. ECG data were not obtained.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies or clinical trials were submitted in support of this application.

7.4.6 Immunogenicity

No clinical or adverse event data regarding immunogenicity was provided in this application.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was no trend of higher incidence of AEs with increasing budesonide dose; however, Study 37(the DB, R, C study) only explored one dose (9 mg qD).

7.5.2 Time Dependency for Adverse Events

No particular explorations for time dependency of adverse events were conducted.

7.5.3 Drug-Demographic Interactions

No particular explorations for drug-demographic safety interactions were conducted.

7.5.4 Drug-Disease Interactions

No particular explorations for drug-disease interactions were conducted.

7.5.5 Drug-Drug Interactions

No drug-drug interactions were explored in this supplement. However, according to the current Prescribing Information, it is recommended that a reduction in the dose of oral budesonide should be considered when it is administered concomitantly with an inhibitor of CYP3A4 activity, such as ketoconazole, to avoid an increase in the systemic exposure to budesonide. For the same reason, it is recommended that ingestion of grapefruit or grapefruit juice should be avoided in connection with budesonide administration.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The Sponsor did not provide any clinical or adverse event data regarding human carcinogenicity in this application.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies of budesonide in pregnant women. Therefore, it is recommended that budesonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Budesonide is secreted in human milk. Since there are no data from controlled trials on the use of Entocort by nursing mothers or their infants, and because of the potential for serious adverse reactions in nursing infants from Entocort, a decision should be made whether to discontinue nursing or to discontinue Entocort, taking into account the clinical importance of Entocort to the mother. Edits to this section in the Prescribing Information are currently being negotiated with the Sponsor.

7.6.3 Pediatrics and Assessment of Effects on Growth

There were no assessments of the effects of Entocort on growth in this application.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There are no pertinent data derived from pediatric subjects regarding these to report in this application. According to the Sponsor, "reports of acute toxicity and/or death following overdosage of GCs are rare. The potential for acute toxic effects following overdose of budesonide is low and acute overdose, even with high doses, is not expected to cause any clinical problems.

8 Postmarket Experience

Patient exposure to Entocort has been calculated by (b) (4) . Exposure since launch is estimated to be (b) (4) treatment days. Entocort was first approved for use in pediatric patients with Crohn's disease in Finland in December 2003, and it is currently approved for this indication in 17 countries.
The Sponsor global safety database contains all AE reports from post-marketing use since the first approval of Entocort for use in pediatric patients with Crohn's disease..
No new or unexpected safety signals have emerged from the global safety database.

9 Appendices

9.1 Literature Review/References

See individual references noted throughout this review.

9.2 Labeling Recommendations

At the time of this review, the labeling was being negotiated with the Sponsor. However, due to insufficient efficacy data for pediatric patients with age < 8 or weight < 25 kg, Entocort should only be labeled for patients with age ≥ 8 and weight > 25 kg.

9.3 Advisory Committee Meeting

No Advisory Committee meeting was convened for this application.

Appendix A

Table 1: Weight Based Prednisolone Dosing Regimen

	Weight (kg)				
Week	≤25	>25-≤30	>30-≤35	>35-≤40	>40
1-4	2x10 mg	2x10 mg + 5 mg	3x10 mg	3x10 mg + 5 mg	4x10 mg
5	10 mg+5 mg+ 2.5 mg	2x10 mg	2x10 mg + 5 mg	3x10 mg	3x10 mg + 5 mg
6	10 mg + 5 mg	10 mg + 5 mg	2x10 mg	2x10 mg + 5 mg	3x10 mg
7	10 mg + 2.5 mg	10 mg + 2.5 mg	10 + 5 mg	2x10 mg	2x10 mg + 5 mg
8	10 mg	10 mg	10 mg + 2.5 mg	10 mg + 5 mg	2x10 mg
9	5 mg + 2.5 mg	5 mg + 2.5 mg	10 mg	10 mg	10 mg + 5 mg
10	5 mg	5 mg	5 mg + 2.5 mg	5 mg + 2.5 mg	10 mg
11	2.5 mg	2.5 mg	5 mg	5 mg	5 mg
12	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg

Appendix B

Study SD-008-3044

The objectives of study SD-008-3044 were to compare the systemic availability of budesonide and suppression of cortisol secretion in pediatric and adult subjects with active Crohn's disease following administration of Entocort EC. Eight children aged 9 to 14 years and 6 adults aged 21 to 52 years with mild-to-moderate active Crohn's disease were administered Entocort EC 9 mg daily for 7 days.

There were no serious adverse events (SAEs), discontinuations due to AEs, or clinically important changes in laboratory values reported during the study. The only AE reported during Entocort EC treatment in the 8 pediatric subjects was a case of respiratory infection. Plasma cortisol (measured as area under the plasma concentration versus time curve) decreased by 64% and 50% in pediatric and adult subjects, respectively, after 7 days of Entocort EC administration

Study 1:

Study design

This was a multicenter, open-label, non-comparative study to evaluate the safety of Entocort EC for the treatment of Crohn's disease in pediatric subjects aged 5 to 17 years. The study consisted of an 8-week treatment phase, a 2-week taper phase, and a 2-week follow-up phase. Subjects who were considered in remission at the end of the 8-week treatment phase per their Pediatric Crohn's Disease Activity Index score (defined by PCDAI≤ 10) were offered for immediate enrollment into an Entocort EC maintenance study.

Target subject population and sample size

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

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

Dosage,

During the treatment phase, subjects were dosed with oral Entocort once daily for 8 weeks (through Visit 4), according to body weight. Subjects weighing ≤25 kg received 6 mg (2x3 mg capsule) qd for 8 weeks. Subjects weighing >25 kg received 9 mg (3x3 mg capsule) qd for 8 weeks.

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

dose tapered to 6 mg (2x3 mg capsule) qd and subjects who initially received the 6 mg qd dose had their dose tapered to 3 mg (1x3 mg capsule) qd.

Duration of treatment
This open-label study consisted of, an 8-week treatment phase with a 2-week taper phase, and a 2-week follow-up phase, a total of 12 weeks.
No formal statistical analyses or hypothesis tests were performed on any of the data from this study.
Safety measures such as adverse events (AEs), glucocorticoid (GC)-related side effects, hypothalamic-pituitary-adrenal-axis measurement, laboratory test results, and vital signs were collected.

Descriptive statistics summarize the PCDAI and IMPACT 3 scores at baseline and after 8 weeks of therapy, as well as the change in the scores from baseline using full analysis. All endpoints were measured at the end of the 8-week treatment phase.

Subject population
The population included in the study is representative of the target population i.e. children and adolescents aged 5 years to 17 years, with a diagnosis of mild-to-moderate Crohn's disease of the ileum and/or ascending colon.
A total of 123 subjects were enrolled in the study and 108 (87.8%) subjects received treatment with Entocort. A total of 17 (13.8%) subjects discontinued the study. The most common reasons for discontinuation of study were AEs (8 [6.5%] subjects) and lack of efficacy (6 [4.9%] subjects). There was no impact on the interpretation of study results due to the number of subjects who discontinued the study.
The mean age of subjects was 13.7 years (range 6 years to 17 years). The majority of subjects (103 [95.4%] subjects) were of age >8 years. There was similar number of males (57 [52.8%]) and females (51 [47.2%]) subjects. The demographics characteristics of the subjects were consistent with the study eligibility criteria.

Summary of efficacy results

(b) (4)

[redacted]

Conclusions
- The population included in this study was representative of the target population, i.e., children and adolescents aged 5 years to17 years, with mild-to-moderate Crohn's disease of the ileum and/or the ascending colon.

- Treatment with Entocort EC was generally well tolerated in children and adolescents aged 5 years to 17 years, with mild-to-moderate Crohn's disease of the ileum and/or ascending colon.
- (b) (4)
-

Appendix C

Study 2 (n=55)

- Open-label, non-comparative safety study (for maintenance of remission)
- Entry criteria- ages 5-17 with active CD in remission defined by PCDAI ≤ 10
- Entocort 6 mg QD for 12 weeks
- PCDAI before/after treatment

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Appendix D

Table 1: Adverse events reported in ≥4% of subjects in study 1 (Safety analysis set)

Preferred term	Number (%) of subjects N=108
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)
Anemia	5 (4.6)
Hirsutism	5 (4.6)
Vomiting	5 (4.6)

AE Adverse event.
Source: study D9422C00001 CSR, Section 8.2.2 and Table 21.

From SCS page 24 Table 6

Table 2: Adverse events reported in ≥4% of subjects in study 2 (Safety analysis set)

Preferred term	Number (%) of subjects N=50
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)
Diarrhea	2 (4.0)
Gastroenteritis	2 (4.0)
Gastroenteritis viral	2 (4.0)
Hematochezia	2 (4.0)
Headache	2 (4.0)
Hirsutism	2 (4.0)
Iron deficiency anemia	2 (4.0)
Pain in extremity	2 (4.0)
Vomiting	2 (4.0)

AE Adverse event.
Source: study D9422C00002 CSR, Section 8.2.2 and Table 24.

:From SCS page 24 Table 7

Appendix E

(b) (4)

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/s/

MARJORIE F DANNIS
04/11/2016

ANIL K RAJPAL
04/11/2016
I concur with Dr. Dannis.