OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	**NDA 21-324/S-012**
Submission Date(s)	June 30, 2015
Brand Name	Entercort EC capsule
Generic Name	Budesonide
Reviewer	Insook Kim, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Gastroenterology and Inborn Errors Products
Sponsor	Elan Pharma International
Submission Type;	Pediatric Efficacy Supplement
Formulation; Strengths;	Oral capsule contains enteric-coated granules, 3 mg
Proposed Regimen	Pediatric patients (5 to 17 years) > 25 kg: 9 mg for up to 8 weeks, followed by 6 mg for 2 weeks (b) (4) Once daily in the morning
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

Table of Contents

1 Executive Summary

ENTOCORT EC (budesonide) capsules were approved in 1997 for treatment of mild to moderate active Crohn's disease and maintenance of clinical remission of mild to moderate Crohn's disease in adults. The approved adult dosage regimens are 9 mg once daily in the morning for treatment of mild to moderate Crohn's disease and 6 mg once daily for up to 3 months for maintenance of remission.

In this application, the sponsor proposes the use of Entercort EC for treatment of Crohn's disease (CD) for pediatric patients aged (b) (4) years and older. The proposed pediatric dosage regimen is 9 mg once daily in patients whose body weight is > 25 kg (b) (4) .

In support of the proposed indication, four clinical trials in pediatric patients were conducted: a pharmacokinetic study, a randomized, controlled efficacy and safety trial for the treatment of CD, two open-label safety studies for 8 week treatment and 12 week treatment. The sponsor proposes to extrapolate the pediatric efficacy from the adult studies. The sponsor also proposes to fulfill the Pediatric Research Equity Act (PREA) Post-Marketing Requirements: 1) the treatment of mild to moderate active Crohn's disease (CD) involving the ileum and/or ascending colon in pediatric patients ages 5 to 17 years, and 2) the maintenance of remission in CD in pediatric patients ages birth to 17 years of age. While the sponsor proposes to fulfill the PREA PMR on the maintenance of remission, the sponsor does not seek an indication of maintenance of clinical remission in pediatric patients. This review is focused on the pharmacokinetics of budesonide and the pharmacodynamic effects of Entocort EC on the HPA axis in pediatric patients.

1.1 Recommendations

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.

Comment to the DGIEP

In both pediatric and adult patients, the systemic exposure to budesonide was positively correlated with suppression of endogenous cortisol. However, the exposure-response (efficacy) relationship has not been established in either adults or pediatric patients to support a full extrapolation for the efficacy. We recommend that the efficacy of the proposed dose in pediatric patients be supported by the evidence of effectiveness in this patient population.

1.2 Post-Marketing Study

A post-marketing study is under discussion.

1.3 Summary of Clinical Pharmacology Findings

Efficacy

The sponsor proposes a dosing by weight band in pediatric patients aged (b) (4) - 17 years old: 9 mg once daily for pediatric patients > 25 kg (b) (4) . The efficacy of Entocort EC for the treatment of mild-to-moderate Crohn's Disease was studied after treatment with 9 mg Entocort EC for 8 weeks followed by treatment with 6 mg for 4 weeks in comparison to that after

treatment with prednisolone in a randomized, controlled trial (Study 3037). In Study 3037, the proportion of patients who achieved clinical remission (Crohn's Disease Activity Index < 150) at week 8 was 54.5% and lower than that after treatment with 9 mg Entocort EC for 8 weeks than after treatment with prednisolone i.e., (b) (4) %. The sponsor stated that Study 3037 was pre-maturely terminated due to a difficulty in enrollment and underpowered to draw a reliable conclusion. The efficacy was studied only at one dose level and the PK blood samples were not collected. As such the exposure-response relationship for efficacy was not studied in pediatric patients. For more detailed review of efficacy, please see the clinical review.

Hypothalamus-Pituitary-Adrenal (HPA) Axis Suppression

Suppression of endogenous cortisol concentrations and an impairment of the HPA axis function are often associated with glucocorticosterioids. The HPA axis suppression potential by Entocort EC was studied in pediatric patients ≥ 8 years old by administering adrenocorticotropin (ACTH) stimulation test before and after 8 week treatment (Study 3037). At baseline before treatment with Entocort EC, 91% (20/22) patients had a peak cortisol concentration > 18 µg/dL after ACTH stimulation and 73% (16/22) had a normal response to ACTH stimulation. On the other hand, after treatment with 9 mg Entocort EC, the proportion of patients with peak cortisol concentration > 18 µg/dL at 30 min after ACTH stimulation was 25% (4/16) and 6% (1/16) had a normal response[1] to ACTH stimulation. In the same study, among patients who were treated with prednisolone[2], no patient had a peak cortisol concentration > 18 µg/dL at 30 min after ACTH stimulation or had a normal response to ACTH stimulation. The observed abnormal response to the ACTH stimulation is consistent with the known HPA axis suppression potential by exogenous corticosteroids. The approved labeling for Entocort EC already has a warning about hypercorticism and adrenal suppression and the language about the HPA axis suppression potential should be extended to pediatric patients.

In another study (Study 3044), the correlation between the systemic exposure to budesonide and the suppression of endogenous cortisol was studied in pediatric patients (mean age: 12; 9-14 years old) with Crohns' Disease as well as in adult patients. After treatment with 9 mg Entocort EC for 7 days, the mean AUC_{0-24} for cortisol was decreased from baseline in both pediatric and adult patients. The mean decrease in cortisol AUC_{0-24} from baseline was higher in pediatric patients ≥ 9 years old than in adult patients (64%±18% versus 50% ±27%). In a cross-study comparison, the mean decrease in cortisol AUC in adult patients was similar to that in healthy subjects, 45% (Entocort EC Package Insert). In patients the degree of suppression was largely overlapped between age groups with a high inter-subjects variability (Figure 2A). The decrease in cortisol AUC_{0-24} from baseline was highly correlated (correlation coefficient: 0.6-0.7) with budesonide systemic exposure (AUC_{0-24}) in both pediatric patients and in adult patients (Figure 2B). The budesonide exposure-dependent decrease in endogenous cortisol measured was also observed by urinary cortisol excretion in adult patients[3]. On the other hand, the effect of age or body-weight on the % decrease in cortisol AUC_{0-24} from baseline was not apparent.

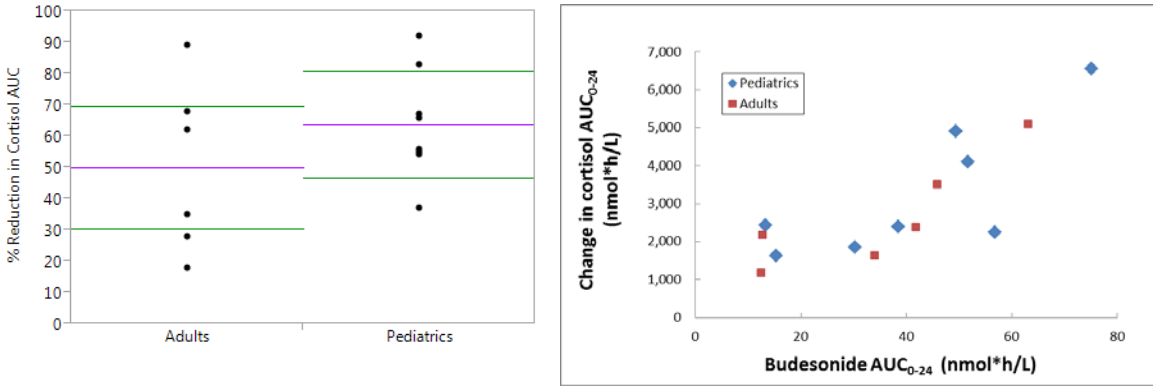
[1] As defined in the cosyntropin labeling, the normal response to the ACTH stimulation is defined by 1) morning cortisol level > 5 µg/dL; and 2) increase in cortisol level by ≥ 7 µg/dL above the morning (pre-challenge) level at 30 min following ACTH challenge; and cortisol level of > 18 µg/dL at 30 min following ACTH challenge

[2] 1 mg/kg daily for 4 weeks followed by weekly dose reduction over 8 weeks; at week 8, the dose was reduced to 50% of the initial dose

[3] Page 14 in the Biopharmaceutics Review of original NDA 21-324 by Dr. Sandip Roy.

Figure 1 Reduction of Cortisol AUC_{0-24} following Treatment with Entocort EC in Pediatric Patients and in Adult Patients[1]

(A) Percent change in cortisol AUC_{0-24} by age group **(B)** Absolute Change in Cortisol AUC_{0-24} versus budesonide AUC_{0-24}



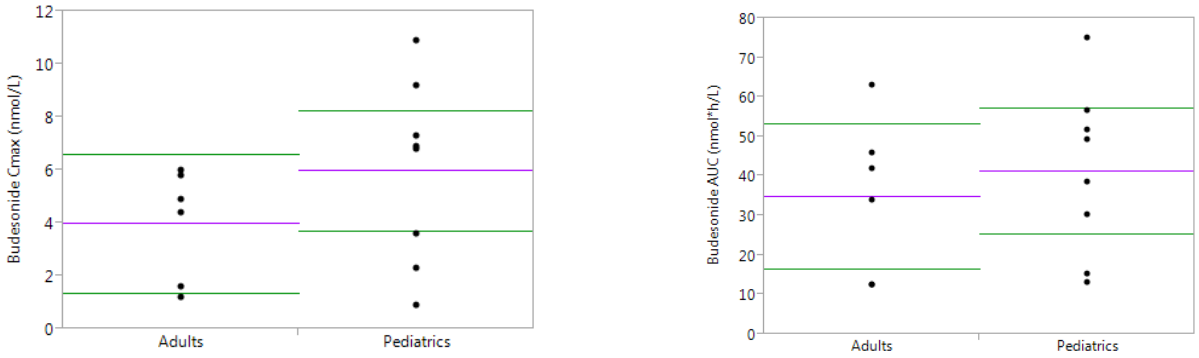
[1] 9 mg once a day for 7 Days

Pharmacokinetics of budesonide in pediatric patients with Crohn's Disease

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 Entocort EC 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 AUC_{0-24} for budesonide were higher in pediatric patients by 41% and 21%, respectively compared to those in adult patients (Figure 1). The distribution of AUC_{0-24} 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)

Figure 2 Individual Cmax (A) and AUC (B) values following 9 mg Entocort EC Once a Day for 7 Days in Pediatric Patients and in Adult Patients[1]

(A) Distribution of Individual C_{max} values **(B)** Distribution of Individual AUC_{0-24} values



[1] Mean in purple; 95% Confidence Interval for mean in green; n= 6 for adults and n=8 for pediatric patients

2 Question-Based Review

2.1 General Attributes of the drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?

ENTOCORT EC capsules were approved for treatment of mild to moderate active Crohn's disease and maintenance of clinical remission of mild to moderate Crohn's disease in adults in 1997. The approved adult dose is 9 mg once daily in the morning for treatment of mild to moderate Crohn's disease and 6 mg once daily for up to 3 months for maintenance of remission.

In this efficacy supplement, the sponsor proposes to fulfill two PREA Post-Marketing Requirements as below:

- PMR 1027-1: 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: the maintenance of remission in Crohn's disease in pediatric patients ages birth to 17 years of age

The initial submission on June 30, 2015 contained two separate claims, so it was divided into two efficacy supplements:

- S-012: For the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon in pediatric patients aged (b) (4) o 17 years of age
- S-013: For the maintenance of remission in Crohn's disease in pediatric patients ages birth to 17 years of age.

2.1.2 What is the formulation of the drug product used in pediatric studies?

The approved ENTOCORT EC capsules for adult patients are gelatin capsules containing enteric-coated granules. The available dosage strength is 3 mg budesonide. To improve the solubility, budesonide is micronized. The same formulation was used in pediatric studies.

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Budesonide is a corticosteroid. Corticosteroids have anti-inflammatory effects.
The proposed pediatric indication is the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon. The sponsor is not seeking an indication for maintenance of clinical remission in pediatric patients.

2.1.4 What are the proposed dosage(s) and route(s) of administration?

The proposed dosage is 9 mg once daily in the morning for up to 8 weeks, followed by 6 mg taken once daily in the morning for 2 weeks for patients aged (b) (4) to 17 years old.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

For the design features of the clinical trials, please see Table 1.

Table 2 Overview of Clinical Trials for ENTOCORT EC in Pediatric Patients

Study number Status Report location	Phase Study design	Number and location of study centers	Primary objective	Subject population Mean age (range)	Dose (oral capsules)
Pharmacodynamic/pharmacokinetic bridging study (completed in 2001)					
SD-008-3044 Completed NDA 21-324, 2 August, 2001 Module 5.3.3.2	Phase 1 MC., OL	6 centers in Canada and Sweden	To evaluate the rate and extent of systemic availability of budesonide in children with Crohn's disease and compare the results with those in adults with Crohn's disease after administration of Entocort EC	8 pediatric subjects with active Crohn's disease (5 M/3 F) 12.4 (9-14) yrs 6 adult subjects with active Crohn's disease (5 M/1 F) 33.2 (21-52) yrs	Entocort EC 9 mg daily for 7 days
Primary efficacy study in pediatric subjects (completed in 2000)					
SD-008-3037 Completed NDA 21-324, 2 August 2001 Module 5.3.5.2	Phase 3 MC, RD, DB, PG treatment groups stratified for pubertal development	22 centers in Belgium, Germany, France, the Netherlands, Spain, Sweden, Switzerland, and the UK	To investigate the efficacy of Entocort EC compared with prednisolone in pediatric subjects with active Crohn's disease	Entocort EC: 22 subjects (15 M/7 F) 13 (8-16) yrs Prednisolone: 26 subjects (18 M/8 F) 13 (8-16) yrs	Entocort EC: 9 mg once daily for 8 wks followed by 6 mg once daily for 4 wks. Prednisolone: 1 mg/kg daily for 4 wks followed by 8 wks of dose tapering
Primary safety studies in pediatric subjects (completed in 2014)					
D9422C00001 Completed Module 5.3.5.2	Phase 3 MC, OL	25 centers in Canada, Germany, Italy, Poland, and the US	To investigate the safety of Entocort EC in a pediatric population treated for mild-to-moderate Crohn's disease	108 subjects with active Crohn's disease (57 M/51 F) 13.7 (6-17) yrs	Entocort EC 6 mg (BW ≤25 kg) or 9 mg (BW >25 kg) once daily for 8 wks followed by 3 mg or 6 mg once daily, respectively, for 2 wks
D9422C00002 Completed Module 5.3.5.2	Phase 3 MC, OL	19 centers in Canada, Germany, Italy, Poland, and the US	To investigate the safety of Entocort EC in a pediatric mild-to-moderate Crohn's disease population for the maintenance of clinical remission	50 subjects with Crohn's disease in clinical remission (30 M/20 F) 13.8 (8-17) yrs	Entocort EC 6 mg once daily for 12 wks followed by 3 mg once daily for 2 wks

BW Body weight; DB Double-blind; F Females; M Males; MC Multicenter; OL Open label; PG Parallel groups; RD Randomized; UK United Kingdom; US United States; wks Weeks; yrs Years.

2.2.2 What is the clinical endpoint for efficacy?

In the controlled trial (Study 3037), the efficacy was evaluated based on the proportion of patients who achieved clinical remission defined as Crohn's Disease Activity Index (CDAI) score < 150. The CDAI is a composite scoring system and consisted of 8 subcomponents (Table 2)

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In addition, pediatric specific disease activity scoring system (PCDAI) was also explored. The PCDAI is calculated on the basis of disease history, laboratory values and physical examination. The disease history included abdominal pain rating, stool pattern, and general well-being. Laboratory values

included hematocrit, erythrocyte sedimentation rate, and albumin levels. The physical examination included measurements for weight and height velocity, abdominal mass, perirectal disease, and presence of extra-intestinal manifestations. The patients who achieve PCDAI score <30 are considered in remission.

Reviewer's comments: *The CDAI has been used as an efficacy endpoint for clinical trials in adult patients with Crohn's disease. Recently the limitations of CDAI such as an inter-correlation between subcomponents and the vagueness of the questionnaire for general well-being scoring have been re-visited. The review of acceptability of CDAI as the efficacy endpoint for this submission is deferred to the clinical reviewers.*

Table 3 Crohn's Disease Activity Index

	Clinical or laboratory variable	Subscore	Weighting factor
1	Daily number of liquid or soft stool for seven days	Sum of 7 days	x 2
2	Daily abdominal pain score for seven days	Sum of 7 days	x 5
3	Daily general well-being score for seven days	Sum of 7 days	x 7
4	Presence of complications	Sum of category	x 20
5	Taking Lomotil or opiates for diarrhea	0 or 1	x 30
6	Presence of an abdominal mass (0= none, 2 = questionable, 5 = definite)	0 or 2 or 5	x 10
7	Hematocrit of <0.47 in men and <0.42 in women (% -47, %-42)	Male: (47-x) Female: (42-x)	x 6
8	Percentage deviation from standard body weight	+/- std %	x 1

2.2.3 How the HPA axis suppression potential was assessed?

Exogenous corticosteroids including budesonide have a potential to suppress Hypothalamus-Pituitary Adrenal (HPA) axis that may lead to an adrenal insufficiency. Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted (Cortifoam® Product Insert).

During the development program, the potential HPA axis suppression following the treatment with budesonide was assessed by plasma cortisol concentrations over 24 hours in Study 3044 and the adrenocorticotropin (ACTH) stimulation test in Study 3037.

In Study 3044, plasma cortisol concentrations were measured over 24 hours at baseline before and after 7-day treatment with 9 mg Entocort EC.

In Study 3037, the ACTH stimulation test was done by administering 0.25 mg cosyntropin (Synthecan^{TM}) via either intravenous or intramuscular injection. Plasma cortisol concentrations were

measured before the cosyntropin injection and at 30 min and 60 min after cosyntropin injection. The ACTH stimulation test was performed at baseline prior to budesonide treatment and at week 8.

2.2.4 Is budesonide in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

Yes. Please see Section 2.6 for more details.

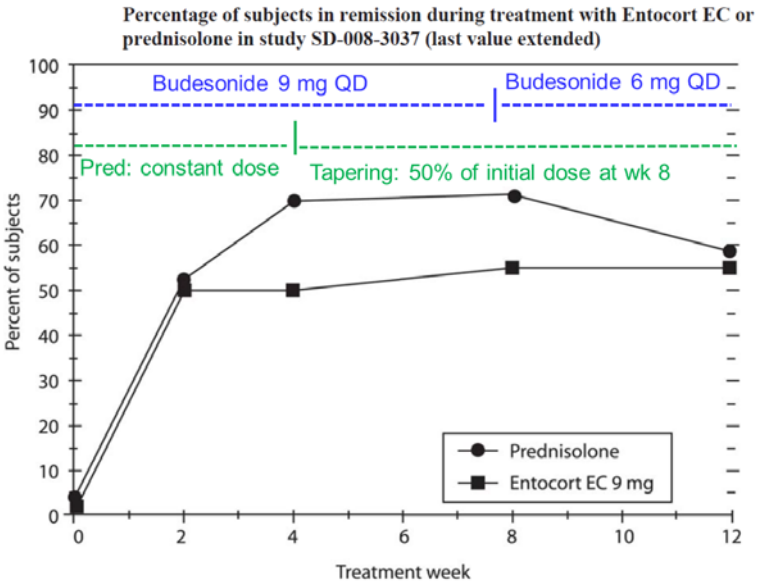
2.2.4 Exposure-Response Evaluation

2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy?

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.

In Study 3037, after 8 weeks of treatment with 9 mg at which point the efficacy was assessed, the dose was tapered to 6 mg over 4 weeks. The proportion of patients who achieved clinical remission by CDAI (< 150) appears constant after the dose reduction to 6 mg. The proportion of patients in remission (last value extended) was numerically lower after Entocort EC treatment than after prednisolone treatment (54.5% vs. (b) (4) %). Of note, Study 3037 was pre-maturely terminated due to a difficulty in enrollment and was claimed to be underpowered for meaningful statistical analysis. The detailed review of the efficacy by CDAI is deferred to the clinical reviewers and biostatics reviewers.

Figure 3 Proportion of Patients in Remission (CDAI < 150)



2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

The effect of budesonide on endogenous cortisol concentrations was compared between pediatric patients (n=8; aged 9 to 14 years) and adult patients (n=6) with active Crohn's disease following administration of ENTOCORT EC 9 mg once daily for 7 days. Compared to baseline values before treatment, the mean decrease in the AUC_{0-24} of cortisol was 64% (±18%) in pediatrics and 50% (±27%) in adults after ENTOCORT EC treatment.

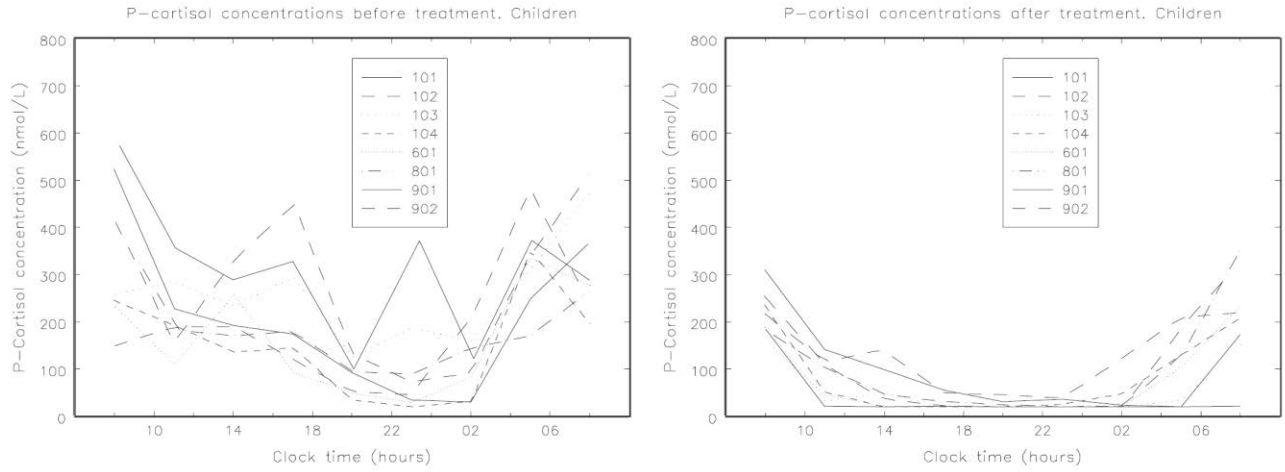
Table 4 Mean (SD) plasma cortisol concentrations and after 7 day treatment with Entocort EC 9 mg in Patients with active Crohn's Disease

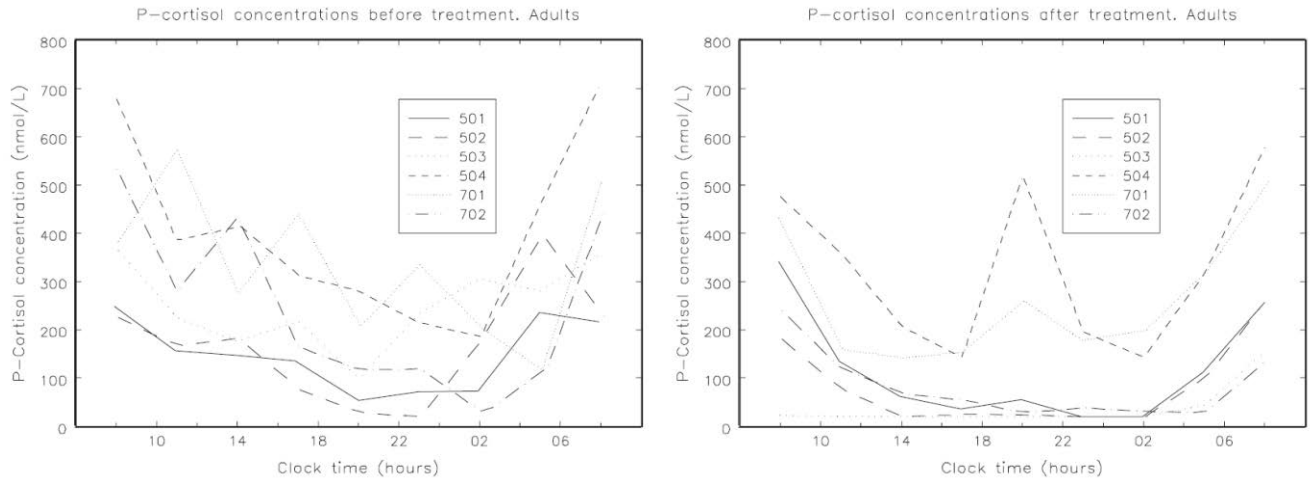
Cortisol AUC over 24 h	**Pediatrics (n=8)**	**Adults (n=6)**	**Adults (n=5)[1]**
Baseline	4881 (1339)	5776 (2181)	5160 (1760)
After 7 day treatment	1618 (697)	3121 (2660)	2298 (1939)
% Reduction	64 (17) (range: 37-92)	50 (27) (range: 18-89)	56 (25) (range: 28-89)

[1]Except patient 504 who had an unusual mid-night cortisol spike after treatment resulting in the lowest % reduction in cortisol AUC

Reviewer's comments: *There was a large intersubject variability in pediatric patients as well as in adult patients. Although the mean extent of decrease was greater in pediatric patients, the distribution of the % reduction was largely overlapped between pediatric patients and adult patients after 7 days of treatment. The plasma cortisol AUC_{0-24} at baseline and the % reduction of cortisol AUC from baseline after 7-day treatment with 9 mg Entocort EC was similar in pediatric patients (mean age 12) and young adults aged < 30 years old. Two adult patients over 45 years old had higher baseline cortisol AUC and a smaller % reduction of cortisol AUC from baseline. The sample size was limited in both age groups to draw a definitive conclusion.*

Figure 4 Individual Plasma Concentrations of Cortisol in Pediatric and Adult Patients

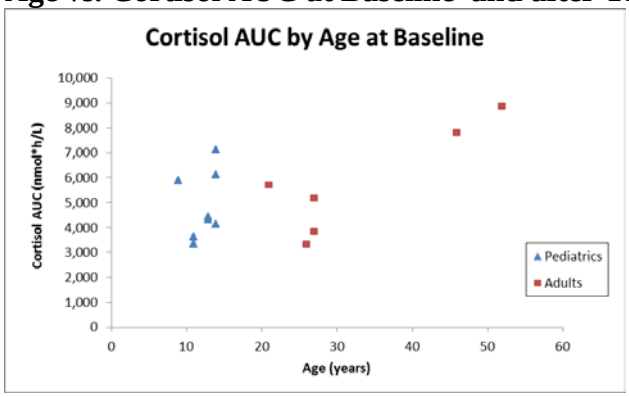


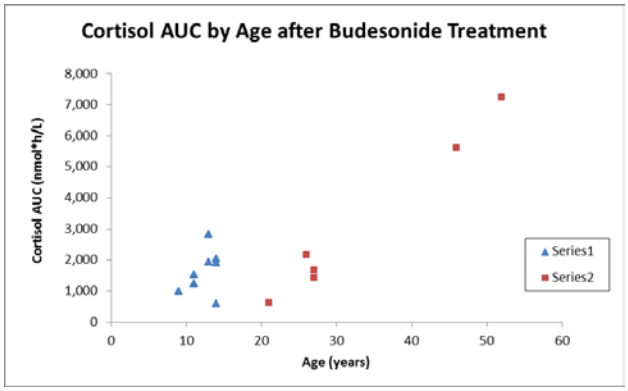


* Adult patient 504 had unusually high mid-night cortisol peak

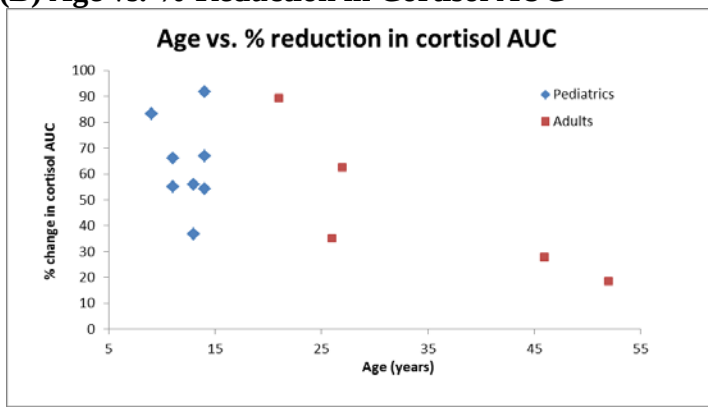
Figure 5 Correlation between Age and Endogenous Cortisol Concentrations (A) and the % change in Cortisol $AUC_{0\text{-}24}$ after Treatment with Entocort (B)

(A) Age vs. Cortisol AUC at Baseline and after Treatment





(B) Age vs. % Reduction in Cortisol AUC

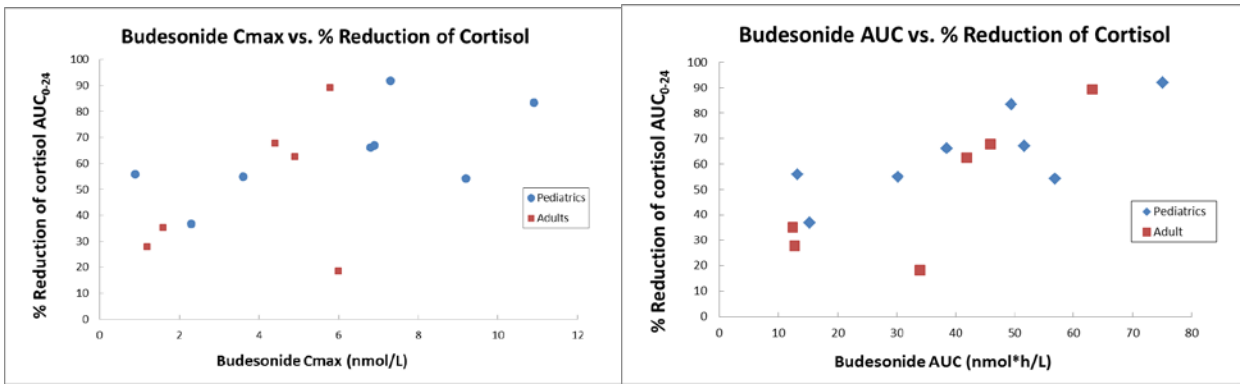


Reviewer's plots (Study 08-CR-3044)

Budesonide concentration and cortisol concentration

There was a positive correlation between the systemic exposure to budesonide and the endogenous cortisol concentrations when assessed by the cortisol concentration over 24 hours (AUC of plasma cortisol concentrations-time curve).

Figure 6 Correlation between Systemic Exposure to Budesonide and Percent Reduction of Cortisol Concentrations in Pediatric Patients and Adult Patients



Reviewer's analyses

In a controlled study, glucocorticosteroid related side effects were reported as expected in both prednisolone and budesonide treatment group.

Reviewer's comment: *While the sample size is limited in both treatment groups, the incident for overall glucocorticosteroid related adverse events was numerically lower with budesonide treatment than with prednisolone treatment. However, it does not obviate the necessity of proper precaution for potential HPA axis suppression when budesonide is used in pediatric patients with CD. The review of safety profile is deferred to clinical reviewers.*

Table 5 Percentage (%) of Patients with Symptoms/signs related to Glucocorticosteroid

	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

Source: Table 29 of CSR3037

2.2.4.3 Are there any unresolved dosing or administration issues?

(b) (4)

The sponsor proposes a body-weight band based dosing in pediatric patients aged (b) (4) years and older: 9 mg once daily dosing for pediatric patients ≥ 25 kg (b) (4)

The proposed dose of 9 mg, which is the same as the approved dose for adult patients resulted in similar systemic exposure to budesonide in pediatric patients aged ≥ 9 years old and weighed greater than 30 kg. In the controlled efficacy and safety study (Study 37), the lowest age and the body weight of the enrolled patients was 8 years and 26 kg, respectively. No pharmacokinetic data available for patients younger than 9 years old or patients weigh less than 30 kg.

(b) (4)

The proposed formulation is a gelatin capsule containing enteric-coated granules and was taken as whole capsules in the pediatric clinical trials. The review of FAERS by the DMEPA reviewer identified two cases in which capsules were opened before administration. In one case a pediatric patient who could not swallow capsules was instructed by her physician to place the contents of the Entocort EC capsules in applesauce and administer[4]. Dosing instruction of sprinkling granules on soft food was not studied during the development program. Therefore the DMEPA reviewer recommends the further clarification in the labeling for the dosing instruction to swallow whole capsule. If the administration of sprinkled granules on soft foods could be supported, it should be beneficial for pediatric patients who cannot swallow whole capsules.

2.2.5 Pharmacokinetic Characteristics

2.2.5.1 What are the PK parameters in pediatric patients?

The pharmacokinetics of budesonide was investigated in pediatric patients aged 9 to 14 years (mean 12 years old) after oral administration of ENTOCORT EC and intravenous administration of budesonide in the same study. Following administration of 9 mg ENTOCORT EC for 7 days (n=8), median time to peak plasma concentration of budesonide was 5 hours and mean peak plasma concentration was 6.0 ± 3.5 nmol/L. Mean AUC_{0-24} was 41.3 ±12.2 nmol•h/L. Mean absolute oral availability was 9.2% (3-17%; n=4) in pediatric patients.

After single dose intravenous administration of 0.5 mg budesonide (n=4), mean volume of distribution (V_{ss}) was 2.2 ± 0.4 L/kg and mean clearance was 0.81 ± 0.2 L/min. Mean elimination half-life was 1.9 hours in pediatric patients. The body-weight normalized clearance in pediatric patients was 20.5

[4] Matthew Barlow, RN, Label and Labeling Review of NDA 21-324/s-012 & NDA 21-324/s-013 dated March 7,2016

mL/min/kg and tended to be higher compared to 15.9 mL/min/kg after intravenous administration in adult patients.

The geometric mean Cmax and AUC_{0-24} in pediatric patients was higher by 41% and 21%, respectively than those in adult patients in the same study. Based on a cross-study comparison, the PK of budesonide was similar between adult patients and healthy subjects except for the median Tmax which was about 2 hours delayed in patients compared to that in healthy subjects. The reason for apparent difference in Tmax between patients and healthy subjects is not clear.

Table 6 Mean PK Parameters after Oral Administration of Entocort EC 9 mg[1]

Mean (% CV)	**Pediatric patients[3] (n=8)**	**Adult patients[3] (n=6)**	**Healthy adults[2,3] (n=13)**
Cmax (nmol/L)	6 (58)	4 (50)	5.3 (34)
Tmax[1] (h)	4.9	5	2.7
AUC (nmol·h/L)	41 (51)	35 (57)	37 (39)

[1] Median
[2] Study 08-3019 in original NDA; cross-study comparison
[3] Patients and healthy subjects took Entocort EC immediately before a meal on the day of PK blood sampling.

Table 7 Mean PK Parameters after Intravenous Administration of 0.5 mg Budesonide[1]

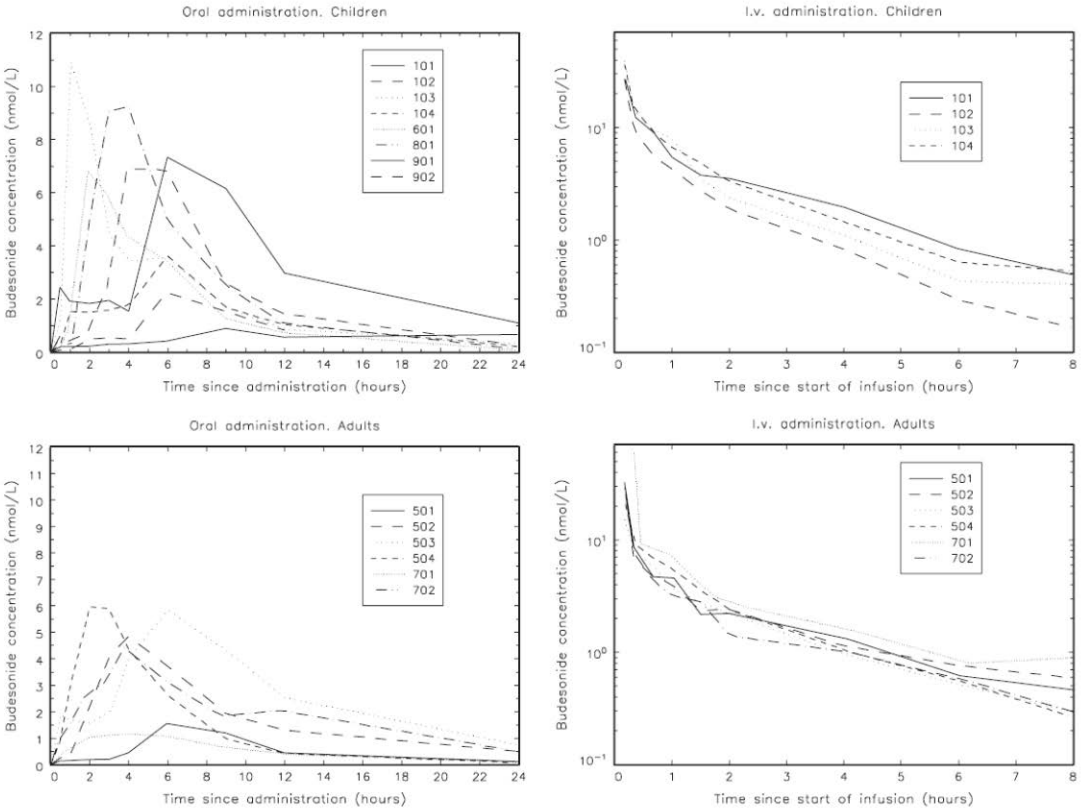
Mean(SD)	Children (n=4)	Adults (n=5)
AUC (nmol·h/L)	24.5 (5)	19.3 (2.5)
$T_{1/2}$ (h)[2]	1.9 (1.6-2)	2.3 (1.9-4.2)
CL (ml/min)	811 (211)	1019 (150)
CL (ml/min/kg)	20.5 (3.7)	16 (4.8)
Vss (L)	84.3 (13)	149 (29)
Vss (L/kg)	2.2 (0.4)	2.3 (0.5)

Source: Tables 5, 6 in CSR 08-CR-3044
[1]0.5 mg budesonide was infused over 10 minutes
[2]Median (min, max)

***Reviewer's comments**: This PK study was conducted at clinical centers outside the U.S. only. Per sponsor, the intravenous administration of budesonide to pediatric patients was not permitted in some countries. The*

APPEARS THIS WAY ON ORIGINAL

Figure 7 Individual Plasma Budesonide Concentrations in Pediatric Patients (upper row) and Adult Patients (lower row) after Oral Administration (right column) and Intravenous Administration (left column)

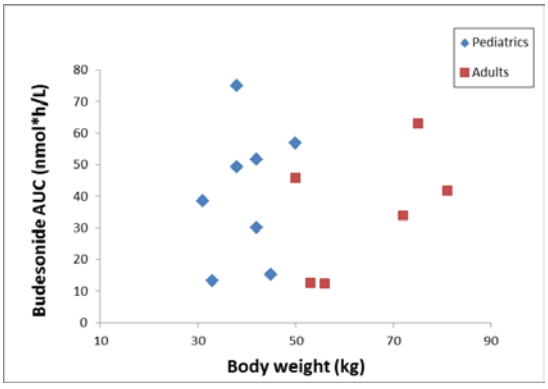


Effect of body weight on the systemic exposure

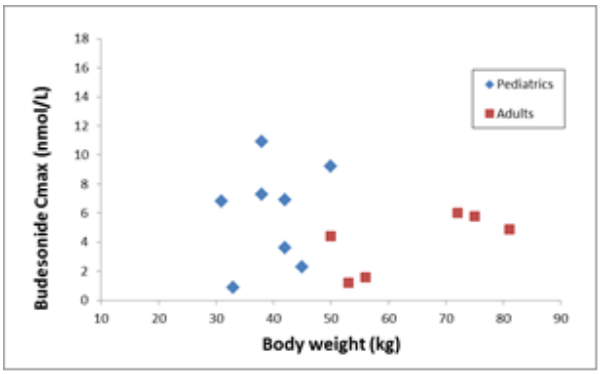
The effect of body weight on the systemic exposure to budesonide was not apparent in patients with weigh >30 kg.

Figure 8 Effect of Body Weight on the Systemic Exposure to Budesonide after Administration of 9 mg Entocort EC for 7 days

(A) Individual AUC values versus body weight



(B) Individual Cmax values versus body weight



Reviewer's plots

2.2.6 What is the potential of HPA axis suppression after treatment with Entocort EC?

The hypothalamus controls the secretion of ACTH from the anterior pituitary, which subsequently stimulates the secretion of cortisol by the adrenal cortex in humans. Exogenous corticosteroids including budesonide have a potential to suppress Hypothalamus-Pituitary Adrenal (HPA) axis that may lead to an adrenal insufficiency. The physiological response to an exogenous adrenocorticotrophic hormone (ACTH) challenge (ACTH stimulation test) was evaluated in patients who have received 9 mg Entocort EC (budesonide) once daily for 8 weeks.

ACTH stimulation test

The ACTH stimulation test was performed between 8 am and 10 am by administering 0.25 mg a synthetic analogue of ACTH (cosyntropin; Synacthen®) via either intravenously or intramuscularly. Blood samples were collected immediately before cosyntropin injection for basal level and at 30 minutes and 60 minutes after the injection. The normal response to the ACTH stimulation is defined by 1) morning cortisol level > 5 μg/dL; and 2) increase in cortisol level by ≥ 7 μg/dL above the morning (pre-challenge) level at 30 min following ACTH challenge; and cortisol level of > 18 μg/dL at 30 min following ACTH challenge[5]:

The response to ACTH challenge was compared before and after treatment with Entocort and that after treatment with prednisolone in pediatric patients aged 8 to 17 years with mild to moderate active Crohn's disease. Prednisolone was administered at approximately 1 mg/kg for 4 weeks and the dose was tapered over 4 weeks.

Reviewer's comments: *Corticosteroid including prednisolone has been used for Crohn's Disease since 1950's. Prednisolone was used as a control in this trial although it is not approved for Crohn's Disease.*

Basal plasma cortisol concentration

After 8 week treatment with Entocort EC, the mean basal plasma cortisol concentration in the morning was decreased to 4.9 μg/dL from 9.9 μg/dL at baseline. In the same study, the mean basal plasma cortisol concentration was 11.6 μg/dL at baseline and 2.1 μg/dL after 8 week treatment. The proportion of patients with morning plasma cortisol of >5 μg/dL (lower limit of normal range of cortisol) was decreased from 95% (21/22) to 50% (8/16) in the budesonide group and from 100% (23/23) to 22% (4/18) in the prednisolone group. Of note, normal morning cortisol level does not preclude a potential HPA axis suppression.

[5] Cosyntropin Package Insert: Plasma cortisol levels usually peak about 45 to 60 minutes after an injection of Cosyntropin and some prefer the 60 minute interval for testing for this reason. While it is true that the 60 minute values are usually higher than the 30 minute values, the difference may not be significant enough in most cases to outweigh the disadvantage of a longer testing period. If the 60 minute test period is used, the criterion for a normal response is an approximate doubling of the basal plasma cortisol value.

Table 8 Mean (SD) Concentration of Cortisol during the ACTH Stimulation Test

	Budesonide			Prednisolone		
µg/dL	basal	30 min	60 min	basal	30 min	60 min
At baseline	9.9 (3.6)	17.9 (3.2)	20.9 (3.6)	11.6 (4.3)	19.2 (4.2)	20.8 (5.6)
At week 8	4.9 (4.2)	8.3 (5.6)	9.3 (5.9)	2.1 (2.1)	5.4 (3.5)	6.6 (4.1)

Compared to the baseline, the proportion of patients who had peak plasma cortisol concentration greater than 18 µg/dL after ACTH challenge was significantly lower in both budesonide and prednisolone treatment groups (Table 8). After 8 week treatment, the proportion of patients with normal response to the ACTH challenge was decreased from 91% to 6% in the budesonide group and from 87% to 0% in the prednisolone group (Table 9).

Table 9 Percentage of Patients with Peak Plasma Cortisol > 18 µg/dL after ACTH stimulation

	Budesonide		Prednisolone	
µg/dL	30 min	60 min	30 min	60 min
At baseline	91% (20/22)	95% (21/22)	91% (21/23)	87% (20/23)
At week 8	25% (4/16)	31% (5/16)	0% (0/18)	6% (1/18)

Table 10 Percentage of Patients with Normal Response to the ACTH Stimulation Test

Treatment	Budesonide		Prednisolone	
Time after ACTH injection	30 min	60 min	30 min	60 min
Before treatment (n/N)	73% (16/22)	91% (20/22)	78% (18/23)	87% (20/23)
At week 8 (n/N)	6% (1/16)	13% (2/16)	0% (0/18)	6% (1/18)

Reviewer's comments:
After 8 week of treatment, the most patients had an abnormal response to the ACTH stimulation test. The ACTH stimulation test was not performed in other time points. The time to restore the normal response to ACTH stimulation after the completion of treatment was not evaluated. Of note the sponsor's original analyses were based on the normal function defined as basal cortisol concentration ≥150 nmol/L (5.4 µg/dL) and 2) either the peak cortisol concentration increase of ≥200 nmol/L (7.2 µg/dL) or concentration ≥400 nmol/L (14.5 µg/dL). The criterion for normal peak concentration defined in the cosyntropin labeling higher than the criterion used by the sponsor (18 µg/dL vs. 14.5 µg/dL= 400 nmol/L). In addition for the normal response to ACTH, both the increase of 7 mg/dL and the peak concentration of 14.5 mg/dL should be met based on the cosyntropin labeling whereas either the increase of ≥200 nmol/L (7.2 µg/dL) or concentration ≥400 nmol/L (14.5 µg/dL) can be met for the normal peak by the sponsor's original definition. Due to the stricter criteria based on the cosyntropin labeling, the proportion of patients with normal response to the ACTH stimulation is lower for both budesonide and prednisolone. The reanalysis does not change the overall conclusion of the HPA axis

suppression potential by oral budesonide and the necessity of precautionary labeling language for pediatric patients.

Dehydroepiandrosterone Sulfate (DHEA-S)

In open-label safety studies, D9422C00001 and study D9422C00002 DHEA-S levels were measured. After 8 week of treatment with Entocort EC, mean DHEAS and mean cortisol decreased (Table 10). The mean DHEAS decreased across all age groups (Table 11).

Reviewer's comments:

Similar to morning cortisol concentration, morning DHEA-S by itself has a limited diagnostic value. DHEA-S, which is synthesized by the adrenals, is a weak androgen, the most abundant C19 plasma steroid, and the major source of urinary 17-ketosteroids. It has been suggested that serum DHEA-S reflects adrenal androgen production and the measurement of serum concentrations may serve as an early indicator for the onset of adrenal suppression. However low DHEAS concentrations cannot differentiate between normal or adrenal insufficiency as DHEAS levels can be lowered by other factors (e.g., stress)[6]. While an adrenal insufficiency may not be confirmed without additional tests, the overall decrease in DHEA-S along with cortisol appears to be consistent with known effects of exogenous corticosteroid including budesonide. The labeling should include precautions about the potential HPA axis suppression in pediatric patients.

Table 11 Morning Cortisol and DHEAS Concentration at Baseline and after Entocort EC treatment[1]

Mean (SD) (range)	**Cortisol (n=103)**	**Dehydroepiandrosterone Sulfate (DHEAS) (n=99)**
Baseline (Day 1)	324 (160) (range: 61-933)	2.5(1.9)
Week 8	185 (170) (range:14-897)	1.4 (1.4)
Change from baseline	-140 (189) (range: -143, 485)	-1.1 (1.3) (range: -6.3, 2.9)
% Change from baseline	-32 (range: -100, 500)	-1.1 (range:-6.3, 2.9)

Source: *Tables 25 and 26 in CSR Study 0001*

1 9 mg once daily

[6] Gruvstad, E., et al., (2014) Comparison of methods for evaluation of the suppressive effects of prednisolone on the HPA axis and bone turnover: changes in s-DHEAS are as sensitive as the ACTH test, Int. J. Clin. Pharmacol. Therapeut, 52 (1): 15-26

Table 12 Mean (SD) DHEA-S concentration before and after 9 mg Entocort EC treatment for 8 week (*CSR 0001)*

Mean (SD) DHEAS (umol/L) by age group, sex and visit						
Age (years)	6	8-9	10-13	10-13	14-17	14-17
Sex	Girls	Both	Boys	Girls	Boys	Girls
n at baseline	1	7	16	15	36	29
Results at baseline	0.20	0.67 (0.60)	2.26 (1.43)	1.49 (0.98)	2.97 (2.12)	3.00 (1.88)
n at Week 8	1	6	12	15	36	29
Results at Week 8	0.20	0.32 (0.29)	0.77 (0.63)	0.60 (0.45)	1.61 (1.20)	2.07 (1.82)

2.3 Analytical Section

2.3.1 How is budesonide identified and measured in the plasma in the clinical pharmacology?

The method validation report titled "Validation of a method for the determination of 22RS budesonide in plasma by liquid chromatography atmospheric pressure chemical ionization tandem mass spectrometry (Report 580-RD-0388)" was submitted.

Briefly, budesonide was isolated from human plasma by solid phase extraction and analyzed by reversed phase liquid chromatography combined with negative ion atmospheric pressure chemical ionization and tandem mass spectrometry (HPLC-APCI-MS/MS). Standard samples prepared in human albumin solution were used for the calibration curve and ($^2H_8$) budesonide was used as internal standard.

2.3.2 How is cortisol measured in plasma?

Two methods were used for plasma cortisol throughout the development program. In early studies, i.e., SD-008-3037 and SD-008-3044, cortisol was measured using a capillary gas chromatography (GC) coupled with mass spectrometry. On the other hand for studies D9422C00001 and study D9422C00002, HPLC/MS/MS was used for plasma cortisol.

The bioanalytical method for cortisol used in study SD-008-3037 and study SD-08-3044 is described in 8094100005 Method Validation Report Cortisol BCO. Briefly, cortisol is extracted from the samples by a solid-phase extraction and derivatized with pentafluoropropionic anhydride (PFP). A capillary gas chromatography (GC) coupled with mass spectrometry was used with the internal standard D3-cortisol. Quantification is performed by monitoring the ion fragments at 782 M/z for cortisol and 785 M/z for the internal standard D3-cortisol.

The method validation for cortisol, used in study D9422C00001 and study D9422C00002 is described in the report titled "Validation of the HTLC/MS/MS for the quantitative measurement of serum and plasma cortisol". The analysis was done at a central laboratory, i.e. (b) (4). Briefly, cortisol in serum or plasma, together with an added internal standard of D2-cortisol, is diluted 2:5:5 with 0.1% ammonium acetate. High Throughput Liquid Chromatography (HTLC) coupled with tandem mass spectroscopy (MS/MS) was used to detect cortisol.

Dehydroepiandrosterone sulfate (DHEA-S)

DHEA-S was assayed using a commercially available assay kit, DPC IMMULITE 2000 DHEA-S assay which was a solid-phase, competitive chemiluminescent enzyme immunoassay at a central laboratory, i.e (b) (4)

2.3.3 What is the range of the standard curve? What are the lower and upper limits of quantification (LLOQ/ULOQ)? What are the accuracy, precision and selectivity at these limits?

Budesonide

The calibration curve was linear between 0.2 nmol/L and 6.4 nmol/L with an acceptable selectivity. The LLOQ was determined as 0.1 nmol/L. The % coefficient of variation was lower than 13.4% (accuracy) with the % deviation from the theoretical concentration was lower than 10% (precision). At the concentration of 6.4 nmol/L, the % C.V. was less than 3 % and the % deviation from the theoretical concentration was less 5%.

For Study 08-3044 the concentrations of quality controls were 0.025 nmol/L, 0.075nmol/L, and 4 nmol/L and the accuracy and the precision were within the acceptable limit.

Cortisol by GC/MS

The calibration curve was linear between 0 to 1000 nmol/L and the limit of quantification: 20 nmol/L. The limit of quantification was 20 nmol/L, and the coefficient of variation at 57, 721 and 1200 nmol/L were 5.4%, 7.1% and 5.9%, respectively. Within-run precision at 19 nmol/L was 9.3% and at 1081 nmol/L was 5.7%. The presence of budesonide or prednisolone did not interfere with cortisol detection.

The accuracy was assessed by the recovery of total cortisol after spiking of known amount of exogenous cortisol into a sample with endogenous cortisol. After measuring the endogenous cortisol concentration, the contribution of the spike to the final concentration of spiked sample was compared to the theoretical contribution of the spike to the final concentration of spiked sample.

Reviewer's comments: *The assessment of accuracy was apparently done in consideration of basal cortisol concentration. It could have been done using pooled plasma samples with and without baseline correction. The validation report includes a cross-comparison of assay done by HPLC coupled with UV spectrometry performed in other laboratory. There was a good correlation between GC-MS and HPLC-UV but not with HTLC/MS/MS. HPLC-UV was not used for pediatric trials.*

Cortisol by HTLC/MS/MS

The quality control was done at three concentrations of 15 ng/ml, 100 ng/ml, and 200 ng/ml. The lower limit of quantitation was 1 ng/ml and % CV at 1 ng/ml (LLOQ) was 19.8%.

For bioanalytical method validation, stripped serum (Biocell^{TM}) was used as matrix for quantification. The correlation coefficient between cortisol concentrations measured in serum and plasma was 1 (R^2=0.96).

Table 13 Intra assay Precision and Accuracy at three QC concentrations

Concentration	15 ng/ml (n=11)	100 ng/ml (n=11)	200 ng/ml (n=8)
Mean	15.9	102.2	202.7
%CV	3.5	3	4.6
% Accuracy	106	102.2	101.4

Table 14 Inter assay Precision and Accuracy at three QC concentrations

Concentration	15 ng/ml (n=25)	100 ng/ml (n=25)	200 ng/ml (n=25)
Mean	15.2	99.8	189.9
%CV	7.9	4.8	6.6
% Accuracy	101	99.8	95

3. Labeling Recommendation

- We recommend that the [redacted] removed from the labeling [redacted]

- Section 8.6. Hepatic insufficiency
  Reviewer's comments:
  The current labeling recommend considering dose reduction in patients with moderate to severe liver disease. For further clarification, we recommend a dose reduction to 3 mg for patients with moderate HI based on the 3.5-fold higher systemic exposure to budesonide in patients with moderate HI based on the study description in Section 12.3.
  On the other hand for patients with severe HI, we recommend "avoid use in patients with severe HI". It is because the effect of severe HI on the systemic exposure to budesonide or safety of budesonide in patients with severe HI was not studied while it is likely that the increase in systemic exposure would be greater than that in patients with moderate HI.

  Of note, the dose reduction from 9 mg to 3 mg in patients with moderate HI would reduce the local concentration of budesonide in the intestinal tract which may result in sub-optimal efficacy. The dose-response relationship was not studied under once daily dosing regimen in adults. In phase 2 trial in which a dose-response relationship was studied under twice daily dosing regimen, 1.5 mg twice daily dosing showed a numerically higher but not statically significant remission rate than that by placebo treatment while 4.5 mg twice daily dosing showed a statistically significant improvement in the remission rate compared to the placebo.

- Detailed edits for clinical pharmacology related information were conveyed to the sponsor and under negotiation as of this writing.

4 Appendices

4.1 OCP Filing Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	**NDA 21-324 S-012 NDA 21-324 S-013**	**Brand Name**	**Entocort EC Capsule**
OCP Division (I, II, III, IV, V)	**3**	**Generic Name**	**Budesonide**
Medical Division	**DGIEP**	**Drug Class**	**Corticosteroid**
OCP Reviewer	**Insook Kim, Ph.D.**	**Indication(s)**	**Treatment of mild to moderate active Crohn's disease involving the ileum and/or ascending colon in pediatric patients ages (b) (4) to 17 years**
OCP Team Leader	**Sue-Chih Lee, Ph.D.**	**Dosage Form**	**Capsule**
Pharmacometrics Reviewer	**Nitin Mehrotra, Ph.D.**	**Dosing Regimen**	• **Patients > 25 kg:** **9 mg once daily in the morning for 6 weeks followed 6 mg once daily in the morning for 2 weeks** (b) (4)
Date of Submission	**June 30, 2015**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**2/28/2016**	**Sponsor**	**AstraZeneca LP**
Medical Division Due Date	**2/28/2016**	**Priority Classification**	**Standard**
PDUFA Due Date	**4/30/2016**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**3**	**3**	
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				

Patients-				
single dose:				
multiple dose:	**X**	**1**	**1**	**PK is pediatric patients**
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	**X**			
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:	**x**	**3**	**3**	**HPA-axis suppression**
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**4**		

On **initial** review of the NDA/BLA application for filing:

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	**Content Parameter**	**Yes**	**No**	**N/A**	**Comment**
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)			X	

3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?			X	
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			X	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	X			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	X			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	X			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	X			
	Complete Application				
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?			x	

	Content Parameter	**Yes**	**No**	**N/A**	**Comment**
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
3	Is the appropriate pharmacokinetic information submitted?	X			
4	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
6	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	

7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	See comments
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
__Fileable_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Insook Kim, Ph.D.	8/28/15
Reviewing Clinical Pharmacologist	Date
Sue-Chih Lee, Ph.D.	8/28/15
Team Leader	Date

4.2 Individual Study Synopsis

Study 08-3044
Pharmacokinetics of budesonide controlled ileal release capsules in children and adults with Crohn's disease

Study period: April 24, 1998 - December 22, 2000
PK sample analysis: February 16, 2000 – June 12, 2001
This study was conducted at 4 centers in Sweden and at one center in Canada.

Objective

- To evaluate the bioavailability of budesonide in children with Crohn's disease and compare the results with those in adults with CD after administration of budesonide controlled Ileal Release (CIR) capsules.
- To study the systemic effects, measured as plasma cortisol levels and compare the results from the children with those from the adults

Reviewer's comments: *Budesonide CIR capsules used in this study were the same formulation as the approved Entocort EC.*

Number of Patients
Eight children (mean age 12 years) and six adults (mean age 33 years)

Diagnosis and Main Criteria for Inclusion
A diagnosis of Crohn's disease should be confirmed at least in the ileum and/or ascending colon verified by X-ray, colonoscopy and/or histology. Active Crohn's disease is defined as PCDAI ≥ 25 *or* CDAI ≥ 150 (children 6-14 years) and CDAI ≥ 200 (adults 18-70 years).

Treatment
All patients were treated with 9 mg (3 x 3 mg) budesonide CIR capsules in the morning for seven days and on the last day plasma concentrations of budesonide were measured. A diurnal plasma cortisol curve was measured before and during the last day of treatment with budesonide (day 7 of the oral treatment). The patients had to fast for at least 10 hours (neither food nor beverage) before they arrived at the clinic in the morning at Visits 2-4.

At Visit 3, an intravenous infusion of 0.5 mg budesonide was given at about 8 a.m. The dose was infused over 10 minutes (2 mL/min) into an arm vein via an indwelling catheter. After the infusion, the catheter was rinsed with 5 mL saline. The patients were instructed to drink 200 mL water and eat a standardized breakfast.

During six days before Visit 4, the patients were treated with budesonide CIR capsules 3 x 3 mg in the morning (at 8 a.m.) immediately before breakfast together with 200 mL water. The capsules had to be swallowed whole. The seventh dose was given at 8 a.m. at the clinic (Visit 4) together with 200 mL water. A standardized breakfast was served immediately after dose intake.

Standardized breakfast: Two slices of white bread with cheese and 300 mL coffee, tea, juice or water.

The patients were not allowed to drink grapefruit juice during six hours after dose intake at Visits 2-4.

Pharmacokinetic evaluation

PK Sampling Procedures

For intravenous infusion, PK blood samples were collected at pre-dose and at 10 min (end of infusion), 20 min, 40 min, and at 1 h, 1.5 h, 2 h, 4 h, 6 h, and 8 h after start of infusion.

For oral administration, PK blood samples were collected at pre-dose and at 0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 9 h, 12 h, and 24 hours after dose intake.

Pharmacodynamic evaluation

Systemic effects of budesonide measured as plasma cortisol suppression. The cortisol levels (AUC_{0-24h}) were compared between the baseline day (no treatment) and the last treatment day.

Sampling Procedures

Blood samples for plasma cortisol were taken at baseline (Visit 2) and on Day 7 (Visit 4) at 8 a.m., 11 a.m., 2 p.m., 5 p.m., 8 p.m., 11 p.m., 2 a.m., 5 a.m., and 8 a.m.

Patients

Table 15 Demographic data, year of diagnosis of CD and localization of CD

Patient No.	Sex	Age (year)	Weight (kg)	Height (cm)	Year of diagnosis	Localization of CD
101	F	13	33	147	1994	Ileum
102	M	13	45	164	1996	Proximal small intestine, rectum
103	M	9	38	146	1990	Ileum
104	F	11	42	151	1997	Ileum
601	M	11	31	142	1996	Ileum
801	M	14	50	174	1998	Ileum
901	F	14	38	146	1998	Ileum + colon
902	M	14	42	157	2000	Ileum + colon
Mean	-	**12.4**	**39.9**	**153.4**	-	-
501	F	26	56	161	1997	Ileum
502	M	27	81	177	1997	Ileum
503	M	21	75	188	1996	Ileum
504	M	52	72	167	1996	Ileum
701	M	46	53	165	1997	Ileum
702	M	27	50	165	1998	Colon ascendens
Mean	-	**33.2**	**64.3**	**170.5**	-	-

Table 2 from CSR 08-44

Reviewer's comment*: The age range of enrolled pediatric patients is rather narrow to include pediatric patients aged 9 to 14 years. Similarly 4 out of 6 adult patients were in their 20's.*

Pharmacokinetic results

The systemic exposure of budesonide after oral administration of 9 mg once daily for seven days were on average 41 nmol/L x h (range 13-75 nmol/L x h) in children and 35 nmol/L x h (range 12-63 nmol/L x h) in adults (AUC_{0-24h}). The estimated bioavailability in children was 9% (range 3-17%), and in adults 11% (range 3-21%).

Pharmacodynamic results

The mean plasma cortisol (AUC_{0-24h}) decreased from baseline to end of seven days of treatment by 64% (range 37-92%) in children and by 50% (range 18-89%) in adults.

Patient 601 was treated with Fluticasone (125 µg twice daily) up to the day before visit 2. Study drug treatment started the day after visit 2. Baseline plasma cortisol (AUC_{0-24h}) for patient No. 601 did not deviate from the other patients' values and the data was eventually included in the analysis.

Pharmacodynamics
During the 24 hours following the 7th oral dose of budesonide, the average AUC for plasma cortisol was decreased by 64% (range 37-92%) for the children and by 50% (range 18-89%) for the adults from baseline. The maximum plasma cortisol concentration was generally observed between 2 a.m. and 8 a.m. Before the treatment only two samples were below the limit of quantification. After the treatment with budesonide CIR 31 out of 126 samples were not measurable (21 samples in the children group and 10 samples in the adult group). The morning, 8 a.m., values of the plasma cortisol suppression were on average 27% and 25% in children and adults, respectively.

Reviewer's comments: *For the study results, please see the Question-Based Review.*

Study 3037 Efficacy and Safety of Budesonide CIR versus Prednisolone in Children with Active Crohn's Disease.

The study was a randomized, double-blind, double-dummy, active-controlled multi-center trial, using a parallel-group design, stratified for pubertal development. A total of 56 patients were enrolled at 22 centers in 8 countries. Of these, 48 were randomized at Visit 2.

Reviewer's comment: For the review of safety and efficacy, see clinical review and biostatics review. This review is focused on the ACTH stimulation test.

Diagnosis: Active Crohn's disease limited to the ileum, ileo-ceacal region and/or ascending colon apart from scattered apthous ulcers.

Test drug: Budesonide CIR capsules 9 mg once daily for 8 weeks followed by budesonide CIR capsules 6 mg once daily for 4 weeks.
Comparator: Prednisolone at a constant dose, determined by the patient's body weight, for 4 weeks followed by 8 weeks with tapering doses of the drug.
Duration of treatment: 12 weeks

Table 16 Prednisolone Dosing Table

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

ACTH stimulation test

In this study, ACTH stimulation test was performed at baseline before treatment and week 8.
The ACTH stimulation test was performed between 8 am and 10 am by administering 0.25 mg cosyntropin (Synacthen®) via either intravenously or intramuscularly. Blood samples were collected immediately before cosyntropin injection and at 30 minutes and 60 minutes after injection.

The peak and basal plasma cortisol concentrations after the ACTH test were defined normal if the following criteria were fulfilled:

1. Basal cortisol ≥150 nmol/L
2. Either peak cortisol ≥ 400 nmol/L or increase ≥200 nmol/L

The normal response to the ACTH test was defined if both criteria were met.

Table 17 The proportion of patients who had normal plasma cortisol level and normal response to ACTH stimulation test[1]

	Baseline (week 0)		**Week 8**	
% patients	PRED (n=26)	BUDE (n=22)	PRED (n=26)	BUDE (n=22)
Normal basal P-cortisol ≥ 150 nmol/L	100	95.5	22.2	**50**
Normal peak P-cortisol increase ≥ 200 nmol/L or peak ≥ 400 nmol/L	100	100	39	**44**
Normal function Normal basal and normal peak	100	95.5	11	**38**

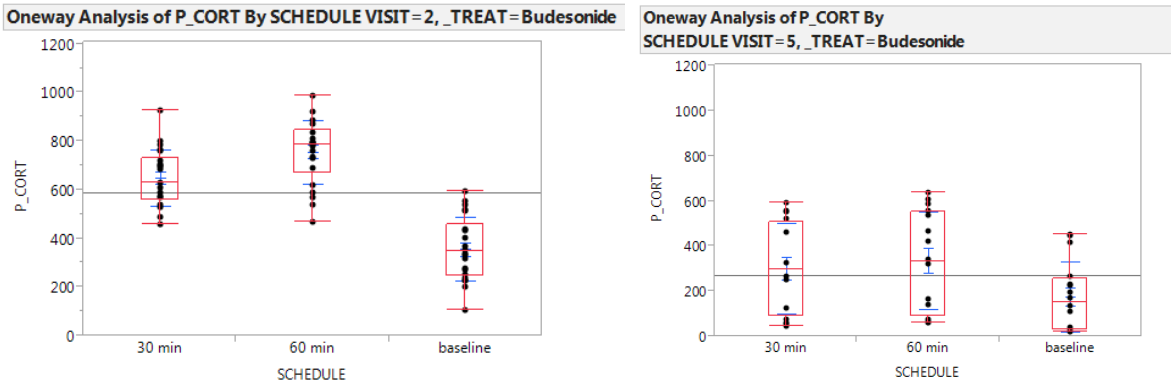
The data was re-analyzed based on the criteria as defined in the cosyntropin labeling. The normal response to the ACTH stimulation is defined by 1) morning cortisol level > 5 μg/dL; and 2) increase in cortisol level by ≥ 7 μg/dL above the morning (pre-challenge) level following ACTH challenge; and cortisol level of > 18 μg/dL following ACTH challenge:
After 8 week treatment, the proportion of patients with normal response to the ACTH challenge was decreased from 91% to 13% in the budesonide group and from 87% to 6% in the prednisolone group..

Reviewer's comments: *After 8 week of treatment, the most of patients had an abnormal response to the ACTH stimulation test. The ACTH stimulation test was not performed in other time points.*
The criterion for normal peak concentration defined in the cosyntropin labeling higher than the criterion used by the sponsor (18 μg/dL vs. 14.5 μg/dL= 400 nmol/L). In addition for the normal response to ACTH, both the increase of 7 mg/dL and the peak concentration of 14.5 mg/dL should be met based on the cosyntropin labeling whereas either the increase of ≥200 nmol/L (7.2 μg/dL) or concentration ≥400 nmol/L (14.5 μg/dL) can be met for the normal peak by the sponsor's original definition.

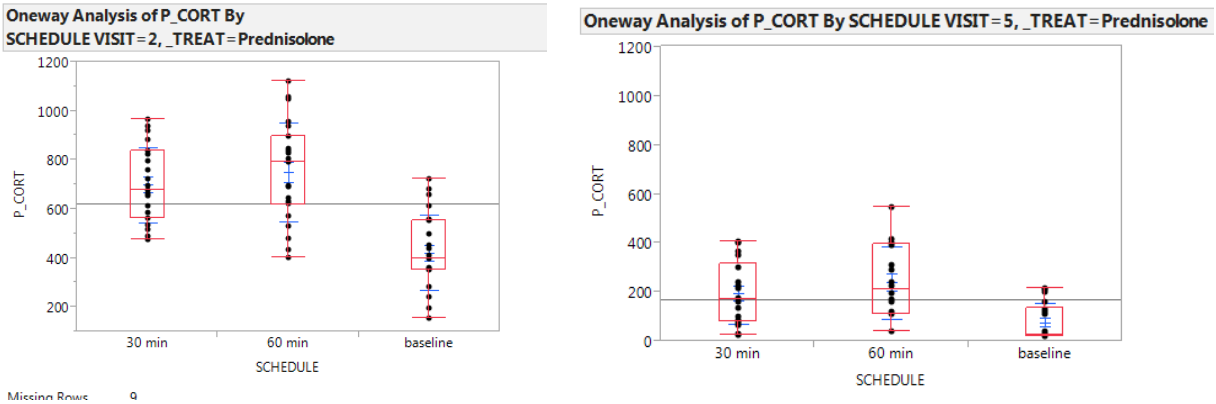
Due to the stricter criteria based on the cosyntropin labeling, the proportion of patients with normal response to the ACTH stimulation is lower for both budesonide and prednisolone. The reanalysis does not change the overall conclusion of the HPA axis suppression potential by oral budesonide.

Figure 9 Plasma cortisol concentrations during the ACTH stimulation test at baseline (visit 2) and at week 8 (visit 5)

(A) Budesonide



(B) Prednisolone



Reviewer's plots

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

INSOOK KIM
03/24/2016

SUE CHIH H LEE
03/25/2016