U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	021324/0045
Drug Name:	ENTOCORT EC (budesonide) Capsules
Indication:	Treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon and the maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or the ascending colon for up to 3 months.
Applicant:	AstraZeneca Pharmaceuticals LP
Dates:	Received: June 30, 2015; PDUFA: April 30, 2016
Review Priority:	Standard
Biometrics Division:	DBIII
Statistical Reviewer:	Wen-Jen Chen, Ph.D.
Concurring Reviewers:	Yeh-Fong Chen, Ph.D. (Team Lead)
Medical Division:	Division of Gastroenterology and Inborn Errors Products
Clinical Team:	Anil Rajpal MD. (Team Lead)
Project Manager:	Lawrence Allan

Keywords: NDA review, clinical studies.

Table of Contents

1. EXECUTIVE SUMMARY

In accordance with the Pediatric Research Equity Act (PREA) 21 CFR 314.55, AstraZeneca Pharmaceuticals LP (AstraZeneca) submitted a supplemental New Drug Application (sNDA) for ENTOCORT EC (budesonide) Capsules to fulfil the two outstanding PREA commitments:

- CMT ID 261254 - Deferred pediatric study under PREA for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon in pediatric patients ages 5 to 17 years.
- CMT ID 261253 - Deferred pediatric study under PREA for the maintenance of remission in Crohn's disease in pediatric patients ages zero to 17 years of age.

AstraZeneca conducted two multi-center and open label studies to evaluate the safety of Entocort EC for the treatment (Study D9422C00001) and maintenance of remission (Study D9422C00002) in pediatric subjects with Crohn's Disease.

Besides Studies D9422C00001 and D9422C00002, the applicant submitted another safety and efficacy study (i.e., Study SD-008-3037) on October 7, 2002. The primary efficacy endpoint was remission rate, defined as CDAI equal or lower than 150. Study SD-008-3037 was originally planned to enroll 120 patients. However, due to poor enrolment, it was terminated when only 48 subjects were randomized.

As noted, Studies D9422C00001 and D9422C00002 were both open labeled and had single arm with the safety assessment as the primary objective and the efficacy assessment as the secondary objective. Due to the fact of being open label studies, the efficacy findings could be biased in favor of Entocort. As a result, the descriptive analysis results cannot be used to provide sound statistical conclusions. (b) (4)

Regarding Study 37 (SD-008-3037), which used an active control, had been terminated early, when only 40% of the planned subjects were randomized, (b) (4)

In addition, the applicant did not plan a non-inferiority analysis with a margin pre-specified. Please refer to ICH E10 for the prerequisite of the non-inferiority margin. (b) (4) the confidence intervals for each treatment's observed response can be included in the label.

2. INTRODUCTION

2.1 OVERVIEW

In the cover letter, the applicant indicated that in accordance with the Pediatric Research Equity Act (PREA) 21 CFR 314.55 AstraZeneca Pharmaceuticals LP (AstraZeneca) is

submitting a supplemental New Drug Application (sNDA) for NDA 21-345 ENTOCORT EC (budesonide) Capsules to fulfil the two outstanding PREA commitments:

- CMT ID 261254 - Deferred pediatric study under PREA for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon in pediatric patients ages 5 to 17 years.
- CMT ID 261253 - Deferred pediatric study under PREA for the maintenance of remission in Crohn's disease in pediatric patients ages zero to 17 years of age.

For CMT ID 261254, AstraZeneca conducted a multi-center and open label Study D9422C00001 (Study 1) to evaluate the safety of Entocort EC for the treatment of Crohn's Disease in pediatric subjects aged 5 to 17 years. For or CMT ID 261253, AstraZeneca also conducted a multi-center and open label Study D9422C00002 (Study 2) to evaluate the safety of Entocort EC as a maintenance treatment for Crohn's Disease in pediatric subjects aged 5 to 17 years.

The applicant indicated that the primary objective of both Study 1 and Study 2 was to investigate the safety of ENTOCORT EC in a pediatric population treated for mild to moderate Crohn's disease. The observed safety profile of ENTOCORT EC in pediatric patients is consistent with its known safety profile and no new safety concerns were raised.

Efficacy in Study 1 and Study 2 were evaluated by the Pediatric Crohn's Disease Activity Index (PCDAI) and Quality of Life (QOL) with Entocort EC treatment based on a subject questionnaire (IMPACT 3).

Finally, another Study 37 (SD-008-3037) (b) (4) was submitted on October 7, 2002. The primary variable was remission rate defined as a CDAI of 150 or lower. Study 37 compared the efficacy and safety of Entocort EC with prednisolone in the treatment of 48 pediatric subjects with active Crohn's disease. Of note, this study was terminated early due to poor enrolment.

2.2 DATA SOURCE

To assess the clinical efficacy of budesonide (b) (4) used in support of the proposed indication, this reviewer reviewed the original electronic NDA submission, dated 30 June 2015, located at \\CDSESUB1\evsprod\NDA021324\021324.enx

3. STATISTICAL EVALUATION

3.1 DATA AND ANALYSIS QUALITY

Since Study 37 was terminated early and the other two studies (Studies 1 and 2) were open label and one arm studies, (b) (4) Accordingly, this reviewer does not request the applicant to submit efficacy datasets for the three studies (for detail comments, refer to Section 3.2.5 "Statistical Reviewer's Findings and Comments").

3.2 EVALUATION OF EFFICACY

3.2.1 Description of Studies SD-008-3037, D9422C0001, and D9422C00002

The applicant submitted three phase 3 studies to support budesonide (b) (4) in the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon and the maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or the ascending colon for up to 3 months. All three studies were conducted in multi-centers, randomized and parallel-group designed. Only Study SD-008-3037 was a double blinded trial while the other two studies (D9422C0001, and D9422C00002) were open label studies.

3.2.1.1 Study Design and Objectives

(Directly extracted from the Sponsor's Clinical Study Report)

i) Study SD-008-3037

The primary objective of the study was to evaluate the efficacy of budesonide (b) (4) compared with prednisolone in children with active Crohn's Disease (CD) with respect to remission after 8 weeks' treatment.

The study was a randomized, double-blind, double-dummy, active-controlled multi-centre trial, using a parallel group design, stratified for pubertal development. The duration of treatment was 12 weeks and the study period was from April 24, 1998 to December 22, 2000.

The diagnosis was active Crohn's disease, defined by a Crohn's Disease Activity Index (CDAI) ≥ 200 units, limited to the ileum, ileo-caecal region and/or ascending colon apart from scattered apthous ulcers elsewhere.

A total of 120 children (60 Budesonide and 60 Prednisolone) between 6-16 years, male and female with active CD (CDAI ≥ 200) affecting the ileum and/or ascending colon were planned to be randomized to receive either budesonide (b) (4) 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) in the study. However, due to the decision to terminate the study prematurely only 48 children (22 Budesonid and 26 Prednisolone) were randomized.

The randomization was stratified in this particular study to ensure that 50% of the patients included were prepubertal as defined by Tanner stage ≤ II. Budesonide (b) (4) capsules are approved in many countries for the induction as well as the prolongation of remission of CD limited to the ileum and/or ascending colon in adults. This study was designed to confirm whether treatment with budesonide (b) (4) capsules are also efficacious and safe in children with active CD limited to the ileum and/or ascending colon. Prednisolone, a commonly used glucocorticosteroid for the treatment of CD, was used as reference therapy.

ii) Study D9422C00001

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

The secondary objectives were to

1) Characterize the disease activity in the trial population before and after treatment through the Pediatric Crohn's Disease Activity Index (PCDAI);
2) Assess quality of life (QOL) with Entocort EC treatment based on patients reported outcomes for questionnaires (IMPACT 3).

This was a multicenter, open-label, non-comparative study to evaluate the safety of Entocort EC for the treatment of mild-to-moderate Crohn's disease in pediatric subjects aged 5 years to 17 years, inclusive. This study planned to enroll approximately 110 subjects at study centers in the US and at multiple centers throughout Europe, and Canada. The study consisted of a screening and enrollment visit (Visit 1), an 8-week treatment phase (Visit 1 to Visit 4), followed by a 2-week taper phase, and a 2-week follow-up phase (Visit 5).

The subjects, who were considered in remission at the end of the 8-week treatment phase (Visit 4) as per their PCDAI score, were considered for immediate enrollment into an open-label, non-comparative Entocort EC maintenance study (Study code D9422C00002).

Eligibility for study enrollment was assessed at the screening and enrollment visit (Visit 1). Subjects were enrolled into the study after documenting that all the eligibility requirements were met and began to receive the investigational product (IP) at this visit. Day 1 started the first day of taking the IP.

The treatment phase of the study included 2 telephone visits/contacts during Visits 2 and 3 (Weeks 2 and 4, respectively, following first dose of the IP), and an office visit at Visit 4 (Week 8 following first dose of the IP). If during the telephone calls at Visits 2 and 3, the subject and/or the principal investigator (PI) felt that it was necessary for the subject to visit the office, an optional office visit could have been scheduled. If a subject was discontinued from the study at either Visit 2 or Visit 3, procedures for Visit 4/discontinuation were required to be completed at the time of discontinuation.

Subjects were maintained on their original dose of Entocort EC until Visit 4 (Week 8 following first dose of the IP) of the study. At Visit 4 (Week 8), subjects initially receiving the 9 mg (3x3 mg capsules) dose had their dose tapered to 6 mg (2x3 mg capsules) and subjects who initially received the 6 mg (2x3 mg capsules) dose had their dose tapered to 3 mg (1x3 mg capsule) for 2 more weeks of therapy.

Visit 5 (Week 12) was an office visit, unless the subject had previously discontinued or entered the maintenance study.

If a subject was eligible for the open-label maintenance study and consented to participate in this additional study at Visit 4, the subject was not required to undergo the full tapering regimen in this induction study beyond 6 mg, and Visit 4 of this study coincided with Visit 1 of the maintenance study.
Subjects could discontinue the IP and assessments at any time at the discretion of the investigator. Subjects were also free to withdraw from the study at any time, without prejudice to further treatment. For subjects who were discontinued, the subjects' and parents/guardians

of the subject were asked about the reasons for their discontinuation and about the presence of any AEs. If possible, they were seen and underwent final assessment by the investigator. AEs were followed and any IPs and study materials were returned by the subject/parents/guardians.

iii) Study D9422C00002

The primary objective of this study was to investigate the safety of Entocort EC in a pediatric mild-to-moderate Crohn's disease population for the maintenance of clinical remission.

The secondary objectives were to

1) Characterize the disease activity in the trial population before and after treatment through the Pediatric Crohn's Disease Activity Index (PCDAI);
2) Assess quality of life (QOL) with Entocort EC treatment based on patients reported outcomes for questionnaires (IMPACT 3).

This clinical study was a multi-center, open-label, non-comparative study to evaluate the safety of Entocort™ EC when used as a maintenance treatment for Crohn's disease in pediatric subjects aged 5 to 17 years, inclusive. In this study, approximately 50 subjects were planned to be enrolled from 15 study centers in the US and at multiple centers throughout Europe and Canada.

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

Eligibility for enrolment into the study was assessed at the screening and enrolment visit (Visit 1). Subjects were enrolled into the study after documenting that all eligibility requirements were met and then the subjects started receiving the investigational product (IP) at this visit. Subjects were dosed with Entocort™ EC 6 mg (2 x 3 mg capsules) qd for 12 weeks (Visit 4). Subjects could enter this study from the pediatric Entocort induction protocol (D9442C00001) but this was not mandatory. If subjects fulfilled the eligibility criteria as stated and were in Crohn's disease clinical remission, they could enter this study.

The maintenance treatment phase of the study included telephone visits at Visit 2 (Week 4, following first dose of the IP) and Visit 3 (Week 8, following first dose of the IP), and an office visit at Visit 4 (Week 12 following first dose of IP). If during the telephone calls at Visit 2 and Visit 3, the subject and/or the principal investigator (PI) felt that it was necessary for the subject to visit the office, an optional clinic visit could be scheduled. If the subject was discontinued at either Visit 2 or Visit 3, procedures for Visit 4/discontinuation had to be completed. Visit 4/discontinuation (Week 12, following first dose of the study drug) was an office visit at which time the subject's current dose of IP was tapered.

During the taper and follow-up phase from Week 12 to Week 16 (Visit 4 to Visit 5), the subject's dose was tapered to 3 mg (1 x 3 mg capsule) qd for 2 weeks (until Week 14). After 2-weeks at the tapered dose, Entocort™ EC was stopped. The subject was followed for a 2-

week period ending at Visit 5 (Week 16). Visit 5 was an office visit, unless the subject had previously discontinued.

Subjects could discontinue IP and assessments at any time at the discretion of the investigator. Subjects were also free to withdraw from the study at any time, without prejudice to further treatment. For subjects who were discontinued, the subjects and parents/guardians of the subject were asked about the reasons for their discontinuation and about the presence of any adverse events (AEs). If possible, they were seen and underwent final assessment by the investigator. Adverse events were followed, and any IPs and study materials were returned by the subject/parents/guardians.

3.2.1.2 Efficacy Endpoints and Analyses

i) Study SD-008-3037

Primary endpoint
The primary efficacy variable was remission where remission is defined as a CDAI ≤ 150 units.

Secondary endpoints
- Percentage improved, where improvement is defined as CDAI ≤ 150 units or a decrease in CDAI of ≥ 70 units from the baseline;
- Frequency of possible glucocorticosteroid side-effects;
- Frequency of patients having at least one treatment emergent possible glucocorticosteroid side-effect;
- Impact on adrenal function;
- Morning P-cortisol values;
- Time to remission;
- Quantitative changes in CDAI;
- Quantitative changes in PCDAI

Analysis Populations

The primary analysis was based on the intention to treat population defined as all randomized patients who received at least one dose of study drug. The primary evaluation was made after 8 weeks' treatment.

Primary and Secondary Efficacy Analyses

Chi-square tests were used to compare proportions. Quantitative variables were analyzed by analysis of variance, t-tests and Wilcoxon-tests. All tests were two-sided. P-values not exceeding 5% are considered significant. The outcome after 2, 4, 8 and 12 weeks were evaluated, but 8 weeks was considered the primary time-point.

Multiplicity adjustment
The applicant indicated that primarily P-values were used for evaluating pre-specified hypotheses with adjustment for multiplicity as appropriate. In the statistical evaluation of clinical trials, it has become common to use P-values as a "flagging" device applied to a large

number of variables in order to highlight differences worth further attention. Accordingly, for this trial, no multiplicity adjustment procedure was pre-specified to control study-wise error rate at two-sided significance level of 0.05 for the primary and secondary endpoint analyses.

Sample size

For sample size determination, the applicant indicated that with 50 patients per treatment group, the detectable difference in remissions would have been about 30% (significance level 5%, power 80%).

Missing Data

The primary analysis was used the last value extended principle from Visit 3 onwards, whenever data was missing.

ii) Study D9422C00001

Primary variables - Safety

The applicant indicated that the primary objective of the study was safety of Entocort EC in a pediatric mild-to-moderate Crohn's disease population for the maintenance of clinical remission. Thus, the safety measures including AEs, GCS possibly-related side effects, HPA-axis measurement (morning serum cortisol and DHEAS levels), laboratory test results, and physical examination and vital signs were assessed using safety analyses set.

Secondary variables - Efficacy

The applicant indicated that the Pediatric Crohn's Disease Activity Index (PCDAI) is a validated instrument used to assess disease activity in pediatric subjects. The following parameters were calculated on the basis of disease history, laboratory values, and physical examination.

- Assessment of disease history included: Abdominal pain and stool pattern, as well as a general well-being rating;
- Laboratory values included: Hematocrit, erythrocyte sedimentation rate, and albumin levels;
- Assessment of physical examination included: Height and weight, abdominal mass, presence of perirectal disease, and extra-intestinal manifestations.

The PCDAI was administered to the subject by the investigator at Visit 1 and Visit 4, and was part of the eCRF data.

Each item in the PCDAI is numerically weighted. Possible scores for these items are 0, 2.5, 5, and 10, depending on the item. When the index was completed, the scores on all of the items were summed to produce a composite PCDAI score. The PCDAI has a scoring range of approximately 0 to 100. A score of ≤ 10 is generally considered to represent inactive disease.

IMPACT 3 questionnaire is a validated instrument used to asses Quality of Life (QOL) for subjects with inflammatory bowel disease aged 9 years to17 years. The IMPACT 3 questionnaire was administered at Visit 1 and Visit 4, and was part of the eCRF data. It consists of 35 items categorized into the following 6 domains:

- Bowel symptoms;
- Systemic symptoms;
- Emotional functioning;
- Social functioning;
- Body image, and
- Treatment/interventions.

The response options for these 35 items were on a 5-point Likert scale. To obtain a total score for IMPACT 3, the scores for all 35 questions were summed. Therefore, possible scores ranged from 35 (the worst score) to 175 (indicating the best possible score with respect to QOL).

For subjects aged 9 years to 17 years, the questionnaire was self-administered. Subjects aged 8 years could complete this questionnaire with the help of a parent/guardian. Subjects aged 5 years to 7 years were not required to complete this questionnaire, as this tool has not been validated for that age group.

Analysis Populations

The safety analysis set consisted of all subjects who took at least 1 dose of Entocort EC.

The full analysis set (FAS) included all subjects included in the safety analysis set who had a complete post-baseline data for PCDAI assessment.

Analysis Methods

A comprehensive statistical agreement was prepared before the data base lock. All calculations were performed under the direction of Biostatistics group, AstraZeneca using statistical analysis system (SAS®) software version 9.1.3 or later.

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

Descriptive statistics is used to summarize the composite PCDAI scores and the IMPACT 3 variable score at baseline and after 8 weeks of therapy (Visit 1 and Visit 4), as well as the change in the scores from baseline. For the PCDAI data, additional descriptions include the proportion of subjects with scores ≤ 30, ≤ 20, and ≤ 10 at these time points and those subjects with a decrease of >12.5 points.

Sample size

The applicant indicated that no formal statistical analysis or hypothesis testing was planned, and as such, no formal sample size calculation was carried out. The planned number of 110 subjects in the study was expected to provide adequate safety and tolerability data to address the primary objective.

Missing Data

No missing data imputation was proposed.

iii) Study D9422C00002

Primary variables - Safety

The applicant indicated that the primary objective of the study was safety of Entocort EC in a pediatric mild-to-moderate Crohn's disease population for the maintenance of clinical remission. Thus, the safety measures including AEs, GCS possibly-related side effects, HPA-axis measurement (morning serum cortisol and DHEAS levels), laboratory test results, and physical examination and vital signs were assessed using safety analyses set.

Secondary variables - Efficacy

The applicant indicated the Pediatric Crohn's Disease Activity Index (PCDAI) is a validated instrument used to assess disease activity in pediatric subjects. The following parameters were calculated on the basis of disease history, laboratory values, and physical examination.

- Assessment of disease history included: Abdominal pain and stool pattern, as well as a general well-being rating;
- Laboratory values included: Hematocrit, erythrocyte sedimentation rate, and albumin levels;
- Assessment of physical examination included: Height and weight, abdominal mass, presence of perirectal disease, and extra-intestinal manifestations.

The PCDAI was administered to the subject by the investigator at Visit 1 and Visit 4, and was part of the eCRF data.

Each item in the PCDAI is numerically weighted. Possible scores for these items are 0, 2.5, 5, and 10, depending on the item. When the index was completed, the scores on all of the items were summed to produce a composite PCDAI score. The PCDAI has a scoring range of approximately 0 to 100. A score of ≤ 10 is generally considered to represent inactive disease.

IMPACT 3 questionnaire is a validated instrument used to asses Quality of Life (QOL) for subjects with inflammatory bowel disease aged 9 years to17 years. The IMPACT 3 questionnaire was administered at Visit 1 and Visit 4, and was part of the eCRF data. It consists of 35 items categorized into the following 6 domains:

- Bowel symptoms;
- Systemic symptoms;

- Emotional functioning;
- Social functioning;
- Body image, and
- Treatment/interventions.

The response options for these 35 items were on a 5-point Likert scale. To obtain a total score for IMPACT 3, the scores for all 35 questions were summed. Therefore, possible scores ranged from 35 (the worst score) to 175 (indicating the best possible score with respect to QOL).

For subjects aged 9 years to 17 years, the questionnaire was self-administered. Subjects aged 8 years could complete this questionnaire with the help of a parent/guardian. Subjects aged 5 years to 7 years were not required to complete this questionnaire, as this tool has not been validated for that age group.

Analysis Populations

The safety analysis set consisted of all subjects who took at least one dose of Entocort EC.

The full analysis set (FAS) included all subjects included in the safety analysis set who had a complete post-baseline data (Visit 4) for PCDAI assessment.

Analysis Methods

A comprehensive statistical agreement was prepared before the data base lock. All calculations were performed under the direction of Biostatistics group, AstraZeneca using statistical analysis system (SAS®) software version 9.1.3 or later.

No formal statistical analyses or hypothesis tests was performed on any of the data from this study. Descriptive summaries are produced based on type of variable. The continuous variable is summarized in terms of mean, standard deviation, median, minimum, and maximum. Discrete variable is summarized in terms of frequency and percentage. All variables were measured at the end of the 12-week treatment phase.

Accordingly, descriptive statistics is used to summarize the composite PCDAI scores and the IMPACT 3 variable score at baseline and after 12 weeks of therapy, as well as the change in the scores from baseline.

Summary statistics of individual components of the PCDAI and IMPACT 3 questionnaires are also produced. It is noted that only subjects aged 9 years to17 years were required to complete IMPACT 3 questionnaire. Subjects aged 8 years could complete the questionnaire with the help of their parent/guardian. The IMPACT 3 questionnaire was not administered to subjects aged 5 years to 7 years.

Sample size

The applicant emphasized that the primary objective of this study was to investigate the safety of Entocort™ EC (budesonide) in a pediatric Crohn's disease population for maintenance of

clinical remission. No formal statistical analysis or hypothesis testing was planned, and as such, no formal sample size calculation was performed. The planned number of 50 subjects in the study was expected to provide adequate safety and tolerability data to address the primary objective.

Missing Data

No missing data imputation was proposed.

3.2.2 Patient Disposition and Demographic and Baseline Characteristics

3.2.2.1 Study SD-008-3037

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.

Table 3.2.2.1.1 (Applicant's) Patients enrolled through the study.

	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

Of the 48 patients randomized, 33 (69%) were males and 15 (31%) were females. Their average age was 12.8 (range 8-16) years. All but 4 were Caucasians. The patients had had their disease under study diagnosed for a median time of 0 (range 0-6) years.

3.2.2.2 Study D9422C00001

A total of 123 subjects were enrolled at 25 centers across the US (47 [38.2%] subjects), Poland (40 [32.5%] subjects), Canada (19 [15.4%] subjects), Italy (15 [12.2%] subjects), and Germany (2 [1.6%] subjects). The first subject entered the study on 3 November 2011 and the last subject completed the study on 10 September 2014. The number of subjects, who were enrolled into the study, is provided in Table 3.2.2.2.1.

Table 3.2.2.2.1 (Applicant's) Subject disposition (All subjects)

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

a Informed consent received.
b Subjects who completed follow-up visit or Visit 4 (Week 8) if opted for maintenance phase study.
N Number of subjects in treatment group.
Source: Table 8 in the report of Study D9422C00001

The demographics characteristics of the subjects were consistent with the study eligibility criteria. The mean age of subjects was 13.7 years (range 6 years to 17 years). The majority of subjects (103 [95.4%] subjects) were of age >8 years. There was similar number of male (57 [52.8%]) and female (51 [47.2%]) subjects. The majority of the subjects were White (100 [92.6%] subjects).

The analysis sets and the number of subjects in each analysis set are summarized in Table 3.2.2.2.2.

Table 3.2.2.2.2 (Applicant's) Demographic characteristics (Safety analysis set)

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

Max Maximum; Min Minimum; n Number of Subjects in analysis. N Number of Subjects in treatment group. SD Standard deviation.
Source Table 11 in the report of Study D9422C00001

The baseline characteristics of the subjects were consistent with the study eligibility criteria. The mean height of subjects was 157.72 cm and the mean body weight was 48.09 kg (range 18.8 kg to 96.5 kg). The mean BMI of the subjects was 19.02 kg/m2. There were 28/43 male subjects and 36/49 female subjects who had Tanner Stage ≥ 3. Maturity level of the female subjects was same as the male subjects; the median Tanner stage was Stage 4. The mean PCDAI score was 19.1, indicating mild Crohn's disease at the study entry.

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

The baseline characteristics are presented in Table 3.2.2.2.3.

Table 3.2.2.2.3 (Applicant's) Subject baseline characteristics (Safety analysis set)

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

Baseline Visit 1 (Day 1).
Max Maximum; Min Minimum; n Number of subjects in analysis; N Number of subjects in treatment group; SD Standard deviation.
Source: Table 12 in the report of Study D9422C00001

3.2.2.3 Study D9422C00002

A total of 55 subjects were enrolled at 19 centers across the US (19 [34.5%]) subjects), Europe (27 [49.1%] subjects), and Canada (9 [16.4%] subjects). The first subject entered the study on 28 December 2011 and the last subject completed the study on 13 February 2014.

The majority of the subjects (43 subjects) enrolled in this study had entered after completion of Study 1; this was in accordance with the Clinical Study protocol (CSP) plan. Of the 55

enrolled subjects, 50 (90.9%) subjects received and 5 (9.1%) subjects did not receive treatment with Entocort EC. The reason for not receiving Entocort EC was eligibility criteria not fulfilled (5 [9.1%] subjects).

A total of 9 (16.4%) subjects discontinued the study. The most common reasons for discontinuation of study were AEs (3 [5.5%] subjects) and lack of efficacy (3 [5.5%] subjects). The majority (41 [74.5%]) of subjects completed the study.

The number of subjects who were enrolled into the study is provided in Table 3.2.2.3.1.

Table 3.2.2.3.1 (Applicant's) Subject disposition (All subjects)

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

a Informed consent received.
b Includes subjects who completed treatment phase and follow-up phase.
Source: Table 8 in the report of Study D9422C00002

Based upon Table 3.2.2.3.1, the applicant indicated that the demographic characteristics of the subjects were consistent with the study eligibility criteria. The mean age of subjects was 13.8 years (range 8 years to 17 years). The majority of subjects (48 [96%] subjects) were of age >8 years. There was slightly higher number of males (30 [60%] subjects) than females (20 [40%] subjects). The majority of the subjects were white (45 [90%] subjects).

The safety analysis sets and the number of subjects in each analysis set are summarized in Table 3.2.2.3.2.

Table 3.2.2.3.2 (Applicant's) Demographic characteristics (Safety analysis set)

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

n Number of subjects in analysis; N Number of subjects in treatment group.
SD Standard deviation.
Source Table 11 in the report of Study D9422C00002

The applicant indicated that the baseline characteristics of the subjects were consistent with the study eligibility criteria. The mean height of subjects was 160.79 cm and the mean body weight was 49.64 kg (range: 23.5 kg to 84.5 kg). The mean BMI of the subjects was 18.77 kg/m2. There were 9/15 male subjects and 14/19 female subjects who had Tanner Stage ≥3. Female subjects were slightly more mature than male subjects; the median Tanner stage was Stage 4 for female subjects and Stage 3 for male subjects. The mean PCDAI score was 5.1, indicating that Crohn's disease was in the clinical remission stage at the study entry.

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

The baseline characteristics are presented in Table 3.2.2.3.3.

Table 3.2.2.3.3 (Applicant's) Subject baseline characteristics (Safety analysis set)

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

n Number of subjects in analysis; N Number of subjects in treatment group;
SD Standard deviation;
Baseline Visit 1 (Day 1);
Source: Table 12 in the report of Study D9422C00002.

3.2.3 Sponsor's Efficacy Results and Conclusions

3.2.3.1 Study SD-008-3037

The primary efficacy variable was remission where remission is 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). Analyses of the quantitative CDAI were secondary.

After 8 weeks, (b) (4) % of the patients in the prednisolone group were in remission and 55% in the budesonide group. The difference is not statistically significant (P (b) (4); chi-square test).

The percentage of patients in remission is shown in Table 3.2.3.1.1.

(b) (4)

(b) (4)

3.2.3.2 Study D9422C00001

Pediatric Crohn's disease activity index

In section 7.1 "Efficacy results", the applicant emphasized that there were no primary efficacy variables in this study. Efficacy was a secondary objective. The primary objective of this study was safety.

(b) (4)

2 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

3.2.4 Sponsor's Conclusion

For Study SD-008-3037, the applicant indicated that the difference in percentage of patients in remission assessed by CDIA after 8 weeks, 55% for budesonide versus (b) (4)% for prednisolone, is not statistically significant. (b) (4)

For Study D9422C00001, the applicant concluded that

- (b) (4)
-

For Study D9422C00002, the applicant concluded that

- (b) (4)
-

3.2.5 Statistical Reviewer's Findings and Comments

3.2.5.1 Study SD-008-3037

For the assessments of the efficacy on the study drug budesonide (b) (4) this reviewer first makes comments on early termination. In addition, since budesonide (b) (4) was compared with prednisolone which was a commonly used glucocorticosteroid for the treatment of CD, this study was an active-controlled trial. However instead of conducting active controlled trial, the

applicant conducted a superiority trial. This reviewer then, gives comments on the issue of not using active-controlled trail.

Comments on early termination

- As noted by this reviewer, this study planned to randomize 120 children (60 Budesonide and 60 Prednisolone) between 6-16 years, male and female with active CD (CDAI $\geq$ 200). However, due to the decision to terminate the study prematurely only 48 children (22 Budesonid and 26 Prednisolone) were randomized. Since this study was terminated earlier, much smaller number of patients than that originally planned was randomized (only 40% subjects randomized). The efficacy analysis results for the primary and secondary endpoints may not be reliable.

Comments on active-controlled trial

- For an active-controlled trial, the applicant should have planned the non-inferiority analysis with a pre-specified margin to assess the efficacy of Budesonide. Please refer to ICH E10 for the prerequisite of the non-inferiority margin. The non-significant results reported in the NDA submission only indicated the failure to reject the null hypothesis of no effect differences between budesonide and budesonide; it does not imply that effects between budesonide and budesonide are equal or similar.

  ICH E10 emphasized that the margin chosen for a non-inferiority trial cannot be greater than the smallest effect size that the active drug would be reliably expected to have as compared with placebo in the setting of the planned trial. Identification of the smallest effect size that the active drug would be reliably expected to have is only possible when there is historical evidence of sensitivity to drug effects and, indeed, identification of the margin is based upon that evidence. In addition, the margin should also be identified based on past experience in placebo-controlled trials with adequate design under conditions similar to those planned for the new trial.

(b) (4)

to include the confidence intervals for each treatment's observed response in the label.

3.2.5.2 Study D9422C00001

(b) (4)

(b) (4)

3.2.5.3 Study D9422C00002

3.3 EVALUATION OF SAFETY

The evaluation of safety of rolapitant is not performed in this statistical review. Please refer to the medical review for this evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE AND AGE

Since each of the three studies did not provide significant evidence to support the proposed indication, no subgroup analysis is necessary to further assess whether the effect of study drug budesonide is consistent across subgroups (Gender, Race, and Age).

4.2 Other Special/Subgroup Populations – Not applicable.

5. SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

5.1.1 Study SD-008-3037

For the assessments of the efficacy on the study drug budesonide (b) (4) this reviewer has the following comments.

- As previously noted, the applicant originally planned to randomize 120 children (60 Budesonide and 60 Prednisolone) between 6-16 years, male and female with active CD (CDAI $\geq$ 200). Due to the decision of terminating the study prematurely, only 48 children (22 Budesonid and 26 Prednisolone) were randomized. As a result, much smaller number of patients than that originally planned was randomized (only 40% subjects randomized). The efficacy analysis results for the primary and secondary endpoints may not be reliable.

- For the active-controlled trial, the applicant should have planned the non-inferiority analysis with a pre-specified margin to assess the efficacy of Budesonide. Please refer to ICH E10 for the prerequisite of the non-inferiority margin. The non-significant results reported in the NDA submission only indicated the failure of rejecting no effect differences between budesonide and prednisolone; it does not imply that effects between budesonide and prednisolone are equal or similar.

  ICH E10 emphasized that the margin chosen for a non-inferiority trial cannot be greater than the smallest effect size that the active drug would be reliably expected to have as compared with placebo in the setting of the planned trial. Identification of the smallest effect size that the active drug would be reliably expected to have is only possible when there is historical evidence of sensitivity to drug effects and, indeed, identification of the margin is based upon that evidence. In addition, the margin should also be identified based on past experience in placebo-controlled trials with adequate design under conditions similar to those planned for the new trial.

5.1.2 Studies D9422C00001 and D9422C00002

(b) (4)

5.2 Conclusions and Recommendations

For the only efficacy Study SD-008-3037, based upon the comments made on the early termination and issue of active controlled trial, (b) (4) we have included the confidence intervals for each treatment's observed response in the label.

For Studies D9422C00001 and D9422C00002, as they are open label and one arm safety studies, (b) (4)

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

/s/

WEN JEN CHEN
04/04/2016

YEH FONG CHEN
04/04/2016