several-fold increases in AUC of budesonide. Grapefruit juice intake may increase systemic availability of budesonide, probably by inhibition of intestinal CYP3A4 activity. Therefore, if treatment with ENTOCORT together with any potent CYP3A4 is indicated, reduction of the ENTOCORT dose should be considered if side effects typical of systemic glucocorticosteroids occur. Oral contraceptives do not alter the plasma levels of budesonide. An increased pH obtained by gastric acid inhibitory drugs, such as omeprazole, will not have an impact on the pharmacokinetics of budesonide.

IV. DESCRIPTION OF CLINICAL DATA AND SOURCES

A. Overall Data

The sources of the data used in the review are from the clinical trials for ENTOCORT capsules in the treatment of mild to moderate active CD involving the ileum and/or ascending colon. A total of five completed, controlled, phase IIB/III efficacy and safety trials (Studies 08-3001, 08-3027, 08-3025, 08-3002, 08-3013) in patients with active CD were included in this NDA application and were reviewed. These 5 clinical studies provide the major data for the efficacy and safety review. The additional completed and ongoing studies in patients with CD provide additional data for the safety of ENTOCORT in the target population.

As of 1 June 2000, Entocort capsules have been approved for marketing in 42 countries. The number of units of ENTOCORT that have been sold through 30 June, 2000 corresponds to [redacted]. The indication of maintenance of remission has been approved in 24 countries, but this indication was rejected [redacted]

As of 01 June 2000, 182 adverse event reports, comprised of 383 symptoms from the marketed use of ENTOCORT have been reported to the sponsor which included 23 serious adverse events (SAE) and one death. Safety information from the postmarking spontaneously reports is included in the safety review.

B. Tables Listing the Clinical Trials

Table 1 summarizes information of the 5 completed randomized controlled efficacy and safety trials in patients with active Crohn's disease.

Table 1: Summary of Completed Controlled Efficacy and Safety Trials in Active Crohn's Disease

Study No. (Report No.) [Ref] Location No. Site(s)	Study Title/ Design	Treatment / Dose /Regimen	Duration of Treatment: Administration Schedule	Total Enrolled (Safety) No. Males / Females	Age Range (in years)
08-3001 (08-CR-3001) [Ref(s). 32] Canada 32 sites	Oral budesonide in Crohn's Disease. A dose finding placebo controlled study. / Randomized, double-blind, placebo-controlled with four parallel groups	Budesonide CIR capsules: 3 mg/day 9 mg/day 15 mg/day Placebo All treatments administered by twice daily dosing	Up to 12 weeks, after 8 weeks treatment followed a tapering period of 2-4 weeks.	258 (258) 67 (20M/47F) 61 (23M/38F) 64 (29M/35F) 66 (25M/41F)	 17-63 18-65 18-66 19-62
08-3002 (08-CR-3002) [Ref(s). 33] Sweden, Denmark, Germany, UK, Belgium, Netherlands 11 sites	Comparative study: Entocort® once daily versus prednisolone. / Randomized, double-blind with two parallel groups.	Budesonide CIR capsules: 9 mg/day Prednisolone: 40 mg/day tapered to 5 mg/day. All treatments were administered once daily.	10 weeks. After 8 weeks the budesonide treatment were tapered to 6 mg/day for the last two weeks	176 (175) 88 (30M/58F) 87 (37M/50F)	 18-67 18-85
08-3013 (08-CR-3013) [Ref(s). 34] Sweden, Germany, UK, Belgium, Italy, Netherlands, Ireland, Australia, New Zealand 34 sites	Oral budesonide once and twice daily versus oral prednisolone once daily in active Crohn's Disease. / Randomized, double-blind with three parallel groups.	Budesonide CIR capsules: 9 mg/day (once daily) 4.5 mg (twice daily). Prednisolone: 40 mg/day tapered to 30 mg/day, then to 5 mg/day.	12 weeks. After 8 weeks the budesonide treatment were tapered to 6 mg/day for two weeks and thereafter to 3 mg/day for the last two weeks	178 (177) 58 (21M/37F) 61 (28M/33F) 58 (23M/35F)	 17-71 20-71 19-70

Table 1 (Cont.): Summary of Completed Controlled Efficacy and Safety Trials in Active Crohn's Disease

Study No. (Report No.) [Ref] - Location No. Site(s)	Study Title/ Design	Treatment / Dose /Regimen	Duration of Treatment: Administration Schedule	Total Enrolled (Safety) No. Males / Females	Age Range (in years)
08-3025 (08-CR-3025) [Ref(s). 35] USA 24 sites	Budesonide controlled ileal release capsules once or twice daily in active Crohn's Disease. A placebo-controlled study. / Randomized, double-blind, placebo-controlled with three parallel groups.	Budesonide CIR capsules: 9 mg/day (once daily) 4.5 mg (twice daily). Placebo	10 weeks. After 8 weeks the budesonide treatment were tapered to 6 mg/day for the last two weeks	200 (200) 80 (19M/61F) 79 (35M/44F) 41 (18M/23F)	 18-73 18-71 18-63
08-3027 (08-CR-3027) [Ref(s). 36] Australia, Austria, Denmark, France, Greece, Ireland, Italy, Norway, Portugal, South Africa, Spain, UK 25 sites	Budesonide CIR capsules versus mesalazine, a controlled trial in patients with active ileocaecal Crohn's Disease. / Randomized, double-blind with two parallel groups.	Budesonide CIR capsules: 9 mg/day (once daily) Mesalazine (Mesalamine®): 2 g (twice daily).	16 weeks	182 (181) 93 (30M/63F) 88 (28M/60F)	 19-74 18-67

Results of these 5 clinical studies will be presented and discussed in detail in the following sections of this review.

Table 2 summarizes information of 6 completed controlled long-term trials in Crohn's disease. The sponsor doses not claim the indication of prolongation of remission in the present application. The data are used for safety evaluation mainly.

Table 2: Summary of 6 Completed Controlled Long-Term Trials in Crohn's disease

Study No. (Report No.) [Ref] Location No. Site(s)	Study Title/ Design	Treatment / Dose /Regimen	Duration of Treatment: Administration Schedule	Total Enrolled (Safety) No. Males / Females	Age Range (in years)
08-3003 (08-CR-3003) [Ref(s). 37] Canada 23 sites	Oral budesonide as maintenance treatment in Crohn's Disease. A placebo-controlled dose finding study. /Randomized, placebo-controlled, double-blind with three parallel groups.	Budesonide CIR capsules: 6 mg/day 3 mg/day Placebo All treatments were administered once daily.	12 months	105 (104) 36 (18M/18F) 33 (10M/23F) 35 (13M/22F)	 19-63 22-62 19-60
08-3004 (08-CR-3004) [Ref(s). 38] Belgium, Sweden, Denmark, Germany, Netherlands, UK 11 sites	Oral budesonide as maintenance treatment in Crohn's Disease. A placebo-controlled dose-finding study. / Randomized, placebo-controlled, double-blind with three parallel groups.	Budesonide CIR capsules: 6 mg/day 3 mg/day Placebo All treatments were administered once daily.	12 months	90 (88) 32 (15M/17F) 30 (10M 20F) 26 (11M/15F)	 21-71 18-69 22-52
08-3014 (08-CR-3014) [Ref(s). 39] Australia, Belgium, Germany, Ireland, Italy, Netherlands, Sweden, UK 20 sites	Oral budesonide as maintenance treatment in Crohn's Disease. A placebo-controlled study. / Randomized placebo-controlled, double-blind with three parallel groups.	Budesonide CIR capsules: 6 mg/day 3 mg/day Placebo All treatments were administered once daily.	12 months	75 (74) 22 (9M/13F) 25 (13M/12F) 27 (11M/16F)	 20-63 20-71 19-61
08-3046 (08-CR-3046) [Ref(s). 40] USA 22 sites	Budesonide controlled ileal release capsules as maintenance treatment in Crohn's Disease. A placebo-controlled study. / Randomized, double-blind and placebo-controlled with two parallel groups.	Budesonide CIR capsules: 6 mg/day Placebo All treatments were administered once daily.	12 months	110 (110) 55 (17M/38F) 55 (24M/31F)	 18-73 18-72

TABLE 2 (Cont.)
Summary of Completed Controlled Long-Term Trials in Crohn's Disease

Study No. (Report No.) [Ref] Location No. Site(s)	Study Title/ Design	Treatment / Dose /Regimen	Duration of Treatment: Administration Schedule	Total Enrolled (Safety) No. Males / Females	Age Range (in years)
08-3038 (08-CR-3038) [Ref(s). 41] France, Belgium, Denmark, Germany, South Africa, Israel 24 sites	Use of budesonide CIR-capsules in prednisolone-dependent patients with Crohn's Disease. / Randomized, double-blind and placebo-controlled with two parallel groups	Budesonide CIR capsules: 6 mg/day Placebo Tapering of prednisolone started concomitantly with first intake of budesonide or placebo. All treatments were administered once daily.	16-22 weeks, depending on prednisolone dose at entry.	117 (118) 59 (28M/31F) 59 (20M/39F)	 19-71 18-66
08-3008 (08-CR-3008) [Ref(s). 42] Sweden, Germany, Denmark, Belgium, France, UK, Italy, Netherlands 13 sites	Oral budesonide in postsurgical recurrence prevention of Crohn's Disease. A placebo-controlled multicenter study. / Randomized, double-blind, placebo controlled with two parallel groups.	Budesonide CIR capsules: 6 mg/day Placebo All treatments were administered once daily.	12 months	130 (129) 63 (35M/28F) 66 (27M/39F)	 20-76 17-81

Sponsor's table, copied from Vol. 35, paged 85-86.

There were additional 7 completed uncontrolled studies in patients with CD. All of these 7 studies were done in Europe or Canada and a total of 215 patients were involved for the treatment period between10 and 24 weeks. The safety data from these studies were included in the safety review.

A total of 20 phase I-IIA clinical Pharmacology studies were completed with total 230 subjects involved. These studies will be presented and discussed in detail in FDA Biopharmaceutics Review.

There are 7 ongoing studies that include 2 clinical pharmacology studies, 2 short-term controlled clinical studies, 2 controlled long-term clinical studies and one uncontrolled study. The one uncontrolled study is conducted in the U.S. and all of other 6 ongoing studies are conducted in either Europe or Canada.

Entocort was also tested for other indications which included one open study in 11 patients with chronic active HBs Ag-negative hepatitis, one study in active rheumatoid arthritis (total 143 patients enrolled), and 2 ongoing studies in collagenous colitis.

C. Postmarketing Experience

As of 1 June 2000, ENTOCORT capsules have been approved for marketing in 42 countries. The number of units of Entocort sold from its first introduction in 1995 through 30 June, 2000 corresponds [redacted]

A total of 182 reports, comprised of 383 symptoms from the marketed use of Entocort have been received by the sponsor. There were 23 SAE and one death that will be discussed in the section of safety review. The overall frequency of spontaneous reports of AEs associated with postmarketing use of Entocort capsules is low.

D. Literature Review

The sponsor submitted 53 published literatures related to Entocort. The reviewer has also searched the literatures related to Entocort up to the date and incorporated them into the review.

V. CLINICAL REVIEW METHODS

A. How the Review Was Conducted

A total of five randomized, double blind and controlled trials were submitted in this application which are key in support of this New Drug Application for ENTOCORT capsules in the treatment of mild to moderate active CD involving the ileum and/or ascending colon (Table 1). Studies 08-3001 and 08-3025 were conducted with placebo control. In Study 08-3027 the comparator was mesalamine, which is considered experimental because mesalamine has not been approved by FDA for the treatment of CD. The other two Studies 08-3002 and 08-3013 were comparisons to prednisolone which is the current standard of care for the treatment of active Crohn's disease. The sponsor selected Studies 08-3001 and 08-3027 as primary support for the efficacy of ENTOCORT; the three other studies are considered supportive.

Studies 08-3001 and 08-3027 were conducted under similar protocols. Study 08-3001 was a blinded comparison using placebo, while Study 08-3027 was a blinded comparison using Pentasa, a slow release formulation of mesalamine that is approved for Crohn's Disease in several countries around the world. Although not approved for this indication in the United States, it is used in this country to treat active Crohn's Disease in clinical practice. However, from the regulatory respect, mesalamine is considered experimental. Some clinical studies have shown that the response rate (the induction of remission) with mesalamine in active CD is approximately 45% compared with 19% with placebo (Singleton JW, et. Gastroenterology 104:1293-1301, 1993). Based on this experience, it is reasonable to assume that mesalamine would perform no worse than placebo in treating

CD, and therefore mesalamine is a valid control (placebo-like). ENTOCORT, from regulatory view point, needs to be shown statistically better than mesalamine in order to prove the efficacy effects in active CD. Therefore, the reviewer agrees with the sponsor for selecting Studies 08-3001 and 08-3027 as primary studies and will review these two trials as pivotal.

Study 08-3025 used placebo as a reference treatment and the response rate to ENTOCORT was comparable to those seen with the 9 mg/day dose in earlier trials (Study 08-3001 and 08-3027). Because the differences between the Entocort and placebo groups did not reach statistical significance for the primary efficacy endpoint, the sponsor considered this study as a secondary support study for efficacy. However, this study was a placebo-control study and conducted in the U.S., the reviewer will review this study intensively as a pivotal study.

In the other two Studies 08-3002 and 08-3013, the effects of ENTOCORT were compared with prednisolone. Prednisolone syrup has been approved in the U.S. for the indication of tiding the patient over a critical period of the disease in CD. Because glucocorticosteroids have been the most effective drugs in actively suppressing inflammation and inducing clinical remission in patients with Crohn's disease, the reviewer considers that these two studies are also key supporting trials for both efficacy and safety evaluation and the reviewer will review these two studies as pivotal studies.

In conclusion, the reviewer will review all five clinical studies in active CD as primary studies with equal intensity. All of studies submitted in the application will be considered in the safety evaluation. The contribution of each study to either safety or efficacy assessment, or both will be highlighted throughout this review.

B. Overview of Materials Consulted in Review

This submission consists of 207 volumes. Contents of these volumes are as follows:
Volume 1.1 – Index; Labeling;
Volume 1.2 - Summary;
Volume 1.3 through 1.6 - Chemistry, manufacturing and controls
Volume 1.7 through 1.25 – Nonclinical pharmacology and toxicology
Volume 1.26 through 1.34 – Human pharmacokinetics and bioavailability
Volume 1.35 through 1.120 – Clinical data sections
Volume 1.121 through 1.206 – Statistical data sections
Volume 1.207 – Electronic submission including Case Report Tabulations and Forms (deaths and adverse events discontinuations)

In this review I have examined material as follows:
Volume 1.1 – Index; Labeling;
Volume 1.2 - Summary;
Volume 1.35 through 1.120 – Clinical data sections
Volume 1.207 – Electronic submission including Case Report Tabulations and Forms (deaths and adverse events discontinuations)

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The Division of Scientific Investigations has been consulted for investigating 3 international sites, based of some inconsistent results between US and non-US trials.

D. Ethical Standard

The sponsor has submitted informed consent with each clinical trial protocol. To date glucocorticosteroids have been the most effective drugs in actively suppressing inflammation and inducing clinical remission in patients with Crohn's disease. The benefits of these drugs in CD, however, are offset by safety concerns associated with their use. Few placebo-controlled and dose finding studies exist with these drugs. Thus, dose recommendations are often vague and based on therapeutic traditions. Therefore, clinical trials for budesonide with placebo control were considered ethical and necessary for dosing defining, efficacy and safety evaluations.

Infliximab, a chimeric monoclonal antibody against tumor necrosis factor, is the only non-glucocorticosteroid therapy approved in the United States for the treatment of CD; and is indicated for use in patients with moderate to severe CD who have had an inadequate response to conventional therapy. Infliximab must be administered intravenously, and safety in active CD has not been established for more than one administration. Other drugs used to treat active CD, but not approved for this indication in the United States, include broad-spectrum antibiotics, immunosuppressives, such as azathioprine and 6-mercaptopurine and 5-aminosalicylic acid.

E. Evaluation of Financial Disclosure

The applicant submitted a FDA Form 3454 certifying that no investigator of any of the covered clinical studies had any financial interests to disclose.

VI. INTEGRATED REVIEW OF EFFICACY

A. Brief Statement of Conclusion

The clinical program with ENTOCORT demonstrated that administration of ENTOCORT at a dose of 9 mg once daily is effective in treating mild to moderate Crohn's Disease involving the ileum and/or ascending colon.

Study 08-3027 demonstrated that Entocort 9mg once daily in the morning was significantly better in inducing remission of CD than mesalamine (69% vs. 45%, p=0.001) with 24% therapeutic gain. Mesalamine is considered as active comparator because although this drug not approved for the treatment of CD in the US, it is widely used in this country to treat active CD in clinical practice.

One of the 2 placebo-control studies (08-3001), showed that Entocort 4.5 mg bid was

statistically significantly better in inducing remission of active CD (p=0.0004) with 31% therapeutic gain. Although the Entocort 4.5 mg bid regimen is different from 9 mg qd, from a clinical perspective there is no apparent difference in the efficacy, pharmacodynamics or safety of ENTOCORT 9 mg/day when given as a once-a-day or two divided dosing regimen. Therefore, study 08-3001 is considered supportive. The other placebo-control study (08-3025) showed that Entocort 9 mg once daily in the morning was numerically better in inducing remission of CD with 15% therapeutic gain. The lack of statistically significant difference in this study might be the consequence of less patients enrolled in the placebo group (2:1 enrollment, n=41) and more patients with mild disease (CDAI < 300) enrolled (71%) comparison with the first placebo study (08-3001, 62%). These imbalances might have resulted in a higher placebo response rate (33% in Study 08-3025; 20% in Study 08-3001).

In comparison with prednisolone, equal remission rates (60%) were found in the Entocort 9 mg once daily group and the prednisolone group in Study 08-3013, whereas there was a 13% less remission rate (52%) in the Entocort than in the prednisolone group (65%) in Study 08-3002. In the latter study, however, the difference between the two arms was not statistically significant with p=0.12. Owing to inconsistent results, no firm conclusion can be drawn, although Entocort might be less effective than prednisolone. To date glucocorticosteroids have been the most effective drugs in actively suppressing inflammation and inducing clinical remission in patients with CD.

B. General Approach to Review of the Efficacy of the Drug

Across 5 controlled trials in active CD, a total of 993 patients were treated. Table 3 summaries the efficacy results, percentage of remission rates (CDAI $\leq$ 150) and therapeutic gain after 8 weeks treatment in each trial.

Table 3: Percentage of Remission Rates (CDAI$\leq$150) and Therapeutic Gain* After 8 weeks Treatment by Clinical Studies

Study #	Entocort		Placebo	Prednisolone	Mesalamine	p-value
	9mg QD	4.5mg BID				
08-3027	69% (25%)*				45%	0.001
08-3001		51% (31%)	20%			0.0004
08-3025	48% (15%)	53% (20%)	33%			0.14
08-3002	52% (-13%)			65%		0.12
08-3013	60% (0)	42% (-18%)		60%		0.062

* The number in () is therapeutic gain.
Therapeutic gain (%) = remission rate in the Entocort group – remission rate in the control group
Reviewer's summary table.

All of 5 clinical studies were reviewed in detail. Studies 08-3027 (vs. mesalamine) and 08-3001 (vs. placebo) were the key primary studies to show the efficacy of Entocort in the treatment of active CD. Studies 08-3013 and 08-3002 (both vs. prednisolone) were

main supporting studies for the efficacy of Entocort in the treatment of active CD. Although Study 08-3001 used a different regimen (4.5 mg of Entocort twice daily instead of 9 mg once daily) and Study 3025 did not yield statistically significant difference, both studies are important and their results are part of the overall assessment of efficacy.

C. Detail Review of Trials

Across the 5 controlled trials in active Crohn's Disease, a total of 993 patients were treated that included 651, 107, 146 and 89 patients in the Entocort, placebo, prednisolone and mesalamine group respectively. Table 4 summarizes the number of patients with Entocort and comparative agents in controlled trials in active CD.

Table 4: Number of Patients Treated with Entocort and Comparative Agents in Controlled Trials in Active Crohn's Disease

Trial	Entocort	Placebo	Prednisolone	Mesalamine
08-3027	93			89
08-3001	192	66		
08-3025	159	41		
08-3002	88		88	
08-3013	119		58	
Total patients	651	107	146	89

Reviewer's table, modified from Vol. 35, page 253

1. Study Population

1.1 Inclusion Criteria

In the five double-blind trials, the major inclusion criteria were adults providing informed consent, active Crohn's Disease shown by a CDAI score between 200 and 450 inclusive and disease limited to the ileum, cecum and/or ascending colon as determined by X-ray, endoscopy or histology.

Salient specific patient inclusion criteria are listed for each of the five trials in Table 5.

Table 5: Specific Patient Inclusion Criteria

Trial	Age range	Qualifying CDAI score	Suitable diagnostic techniques for active disease	Other criteria
08-3001 [Ref(s). 32]	≥18 years	≥ 200	Small bowel barium x-ray Colonoscopy Verified within 24 months of study	None
08-3027 [Ref(s). 36]	≥18 years	≥ 200 but ≤ 400	Small bowel barium x-ray, endoscopy, histology, scintigraphy Verified within 24 months of study	Suitable for treatment with oral corticosteroids or mesalamine as sole therapy
08-3025 [Ref(s). 35]	≥18 years	≥ 200 but ≤ 450	Small bowel barium x-ray, colonoscopy Verified within 6 months of study	Suitable for treatment with oral corticosteroids as sole therapy
08-3002 [Ref(s). 33]	≥18 years	≥ 200	Small bowel barium x-ray, endoscopy, histology, scintigraphy Verified within 6 months of study	Suitable for treatment with oral corticosteroids as sole therapy
08-3013 [Ref(s). 34]	≥18 to ≤ 65 years	≥ 200	Small bowel barium x-ray, endoscopy, histology Verified within 24 months of study	None

Sponsor's table from Vol. 35, page 261

1.2 Exclusion Criteria

The exclusion criteria were adequate for this type of study. The main exclusion criteria in the five double-blind active CD trials were a confirmed history of rectal disease; ileostomy or prior extensive resection; active systemic infection; septic complication, abscess, perforation or active fistula requiring treatment; treatment with glucocorticosteroids within 14 days prior to Visit 1; treatment with immunosuppressive agents within 3 months of Visit 1; and treatment with 5-ASA agents or antibiotics within one day of Visit 1. Specific patient exclusion criteria for each trial are listed in Table 6.

Table 6: Specific Patient Exclusion Criteria

Exclusion Criteria	08-3001 [Ref(s). 32]	08-3027 [Ref(s). 36]	08-3025 [Ref(s). 35]	08-3002 [Ref(s). 33]	08-3013 [Ref(s). 34]
RELATED TO MEDICAL OR PHYSICAL CONDITIONS					
Females who were breast feeding, pregnant or likely to become pregnant during study	X	X	X	X	X
Required other drugs for treatment of Crohn's Disease	X	X	X	X	
≥ 100 cm of ileum resected	X	X	X	X	X
Ileostomy, pouch or colostomy	X	X	X	X	X
Confirmed active Crohn's Disease of rectum confirmed by rigid or flexible sigmoidoscopy within 2-4 weeks of Visit 1 or colonoscopy within 24 months of Visit 1 (6 months of Visit 1 for 08-3002 and 08-3025)	X	X	X	X	X
Active systemic infection	X	X	X	X	X
Septic complication, abscess, perforation or active fistula requiring treatment	X	X	X	X	X
Stool culture positive for enteric pathogen, *Clostridium difficile* or within ova and/or parasites	X		X		
Candidates for immediate surgery (or previous gastric surgery)	X	X	X	X	X
Diabetes mellitus	X	X	X	X	X
Clinically relevant asthma		X	X		
Peptic disease	X	X	X	X	X
Clinically significant hepatic, renal, cardiovascular or psychiatric abnormality	X	X	X	X	X
Active alcohol or drug abuse	X	X	X	X	X
Allergy to glucocorticosteroids	X	X	X	X	X
Allergy to mesalazine or other salicylates		X			
History of cancer	X		X		X
RELATED TO DRUG THERAPY					
Immunosuppressive agent within 3 months of Visit 1	X	X	X		X
Glucocorticosteroids within 1-2 weeks of Visit 1	X	X	X	X	X
Ketoconazole within 2 weeks of Visit 1		X	X		
Treatment with total parenteral nutrition or chemically-defined, nutritionally-complete amino acid-based, polymeric based or modular diets	X	X		X	X
Cholestyramine treatment or dose adjustment within 2 weeks of Visit 1		X		X	X

Table 6 (Cont.) Specific Patient Exclusion Criteria

Exclusion Criteria	08-3001 [Ref(s). 32]	08-3027 [Ref(s). 36]	08-3025 [Ref(s). 35]	08-3002 [Ref(s). 33]	08-3013 [Ref(s). 34]
H_2 receptor antagonists or proton pump inhibitors	X	X		X	X
Sulfasalazine, 5-ASA or 5-ASA derivative within 1 day of Visit 1	X		X	X	X
Metronidazole or any other antibiotic within 1 day of Visit 1	X		X	X	X
Immunization with live virus or bacteria within 3 months of Visit 1		X	X		X

Sponsor's table from Vol. 35, page 263

2 Efficacy Endpoints

The Crohn's Disease Activity Index (CDAI) was the main clinical assessment used for determining drug efficacy in the five controlled trials in active CD. The CDAI is a validated, weighted index for measuring disease activity based on signs and symptoms of CD, physical examination and hematocrit measurement. It provides a standardized index for measuring disease activity and is an accepted standard for use in clinical trials of CD. In each trial, calculation of the CDAI was done at the randomization visit and at each subsequent follow-up visit. Certain components of the CDAI are derived from a daily patient diary and reflected activity over the previous 7-day period. The following variables are considered in calculating the CDAI:

- Number of liquid or very soft stools per day (derived from patient diary)
- Abdominal pain rating (none, mild, moderate, severe) (derived from patient diary)
- General well-being rating (generally well, slightly under par, poor, very poor, terrible) (derived from patient diary)
- Existence of complications, including arthritis or arthralgia; iritis or uveitis; erythema nodosum, pyoderma gangrenosum or aphthous stomatitis; anal fissure, fistula or abscess; other fistula; fever over 37.8^0C (100^0F) during past week (derived from clinical examination)
- Use of diphenoxylate, loperamide or other opioids for diarrhea (derived from patient diary and elicited during clinical examination)
- Presence of abdominal mass (absent, questionable, definite) (derived from clinical examination)
- Body weight (derived from clinical examination)
- Hematocrit value (derived from blood sample)

2.1 Primary endpoint

In each trial, the main efficacy end point was the proportion of patients in each treatment group demonstrating clinical improvement defined as a CDAI score of $\leq$ 150. In the study protocols and reports, a CDAI score of $\leq$ 150 was defined as disease remission; however, this clinical endpoint is better defined as indicative of clinical improvement. For two of the five trials (Studies 08-3001 and 08-3025), it was specified that the proportion of patients with clinical improvement at Week 8 was the primary endpoint of interest. Although a primary time point was not specified for other three studies (08-3002, 08-3013 and 08-3027), they did include an 8-week evaluation.

2.2 Secondary efficacy endpoints

Secondary efficacy endpoints were variable from trial to trial and will be discussed in the individual trial presentation. The overall summary of secondary efficacy endpoints included:

1. Time to response (defined as the first follow-up visit where a CDAI score of $\leq$ 150 was recorded).

2. Mean value and mean change from baseline in total CDAI score at each post-randomization visit.

3. Quantitative change in each component of the CDAI score at each post-randomization visit.

4. Proportion of patients demonstrating a therapeutic benefit, defined as a CDAI score of $\leq$ 150 or a decrease from baseline in CDAI of $\geq$100, at each follow-up visit.

5. Physician's global evaluation.

6. Quality of life assessment.

3. Statistical Methods

Efficacy analyses in all trials were based on a modified intent-to-treat population, defined as all patients who received at least one dose of study drug and had data from at least one post-baseline visit. In the event of missing data, the last post-baseline value was carried forward.

The specific statistical methods used to analyze efficacy variables in each trial are summarized in Table 7. All statistical tests were two-sided with an alpha equal to 0.05.

Summary of Statistical Analyses of Efficacy

Efficacy Variable	Statistical Test Applied in Each Controlled Trial				
	08-3001 [Ref(s). 32]	08-3027 [Ref(s). 36]	08-3025 [Ref(s). 35]	08-3002 [Ref(s). 33]	08-3013 [Ref(s). 34]
Treatment Groups: ENTOCORT capsules Comparator	1.5, 4.5, 7.5 mg bid Placebo	9 mg qd Mesalamine	9 mg qd, 4.5 mg bid Placebo	9 mg qd Prednisolone	9 mg qd, 4.5 mg bid Prednisolone
Proportion of patients showing clinical improvement[a]	One-way analysis of variance followed by pair wise comparisons if overall treatment effect was significant	Chi-square	Chi-square tests involving 1) all three treatment groups and 2) combined ENTOCORT™ CIR groups with placebo	Chi-square	Chi-square
Proportion of patients showing therapeutic benefit[b]	Not analyzed	Chi-square	Chi-square tests involving 1) all three treatment groups and 2) combined ENTOCORT™ CIR groups with placebo	Chi-square	Not analyzed
Time to therapeutic response	Life-table analysis of percentage of responders at each visit; chi-square test of cumulative percentage of responders at each visit	Generalized Wilcoxon test	Generalized Wilcoxon tests involving 1) all three treatment groups and 2) combined ENTOCORT™ CIR groups with placebo	Generalized Wilcoxon test	Generalized Wilcoxon test
Change from baseline in CDAI scores (total and component scores)	One-way analysis of variance followed by pair wise comparisons if overall treatment effect was significant	Student t-test	One-way analysis of variance	Student t-test	One-way analysis of variance
Global evaluation	Variable not determined	Student t-test	Variable not determined	Student t-test	Variable not determined
Quality of life	One-way analysis of variance followed by pair wise comparisons if overall treatment effect was significant	Student t-test	One-way analysis of variance	Variable not determined	Variable not determined

[a] Clinical improvement defined as CDAI score of ≤ 150.
[b] Therapeutic benefit defined as CDAI score of ≤ 150 or a decrease of ≥ 100 from baseline in CDAI score.

The efficacy results from these five clinical trials will be presented in the following section.

4. COMPARISON WITH MESALAMINE - STUDY 08-3027

Title: Entocort capsules (budesonide CIR) versus oral SR Pentasa (mesalamine), a Controlled Multicentre trial in patients with Active Crohn's Disease

4.1 Objectives

The primary objective was to compare the efficacy of budesonide CIR capsules (Entocort CIR) with mesalamine controlled release tablets (SR Pentasa) in patients with active CD affecting the ileum and/or the ascending colon, using CDAI as the main efficacy variable.

A secondary objective is to compare the safety of budesonide CIR capsules with that of mesalamine slow release tablets.

4.2 Study Design

The trial was randomized, double-blind with parallel groups. Twenty centers in Australia, Austria, Denmark, France, Greece, Italy, Norway, Portugal, South Africa, Spain and the United Kingdom have participated in this multi-center trial between November 1994 and August 1996.

Patients with active CD affecting the ileum and/or the ascending colon, in this context defined as having a CDAI of 200 - 400, were randomly assigned to either budesonide CIR 9 mg once daily in the morning, or mesalamine 2g bid for sixteen weeks.

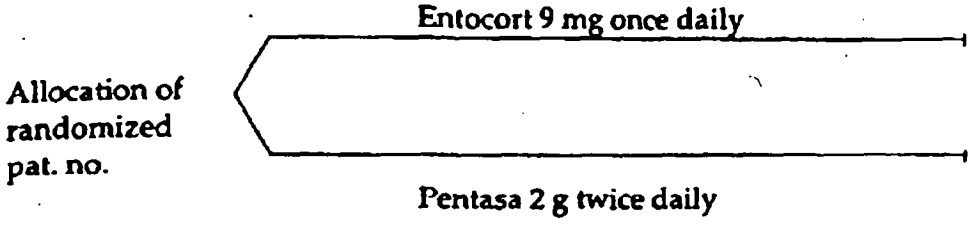
The total treatment period was 16 weeks (112 ± 4 days) and patients visited the clinic at:

Visit 1: entry visit
Visit 2: after 14 (± 2) days,
Visit 3: after 28 (± 2) days,
Visit 4: after 56 (± 3) days,
Visit 5: after 84 (± 3) days,
Visit 6: after 112 (± 3) days of treatment.

During the week before each visit (except visit 1), the patients would use diary cards for registration of signs and symptoms related to their disease. The data obtained from these diary cards, the hematocrit value and the results of the examinations at the clinic visits, were used for calculation of the CDAI. The sponsor did not specifically define primary endpoint at 8 weeks after treatment.

The figure below shows overall study design and investigational assessments.

Figure 1: Study Design and All Investigational evaluations in Study 08-3027



Visit No.	1	2	3	4	5	6
Week No.	0	2	4	8	12	16
Informed consent	x[a]					
Medical history	x					
Sigmoidoscopy	x					
Physical examination	x	x	x	x	x	x
Calculation of CDAI	x	x	x	x	x	x
Quality of life assessments (PGWB)	x	x	x	x	x	x
Lab. assessments	x	x	x	x	x	x
Synacthen test						x
Physician's global evaluation	x	x	x	x	x	x
Adverse events check	x	x	x	x	x	x
Diary cards*: dispense/check	x	x	x	x	x	x
Dispense study drug	x	x	x	x	x	
Drug counting and compliance check		x	x	x	x	x

* Diary cards:
daily recordings: - intake of study drug, number of bowel movements, abdominal pain rating and general well-being

a) patients receiving drugs for treatment of Crohn's disease before study start gave informed consent before dose changes to meet exclusion critiera (see 4.2) were made, i.e. prior to visit 1.

4.3 Demography and Disease History

A total of 182 patients were randomized and treated. Baseline patient characteristics (all patients treated) are summarized in Table 8.

Table 8: Summary of Baseline Patient Characteristics (all patients treated)

	Entocort 9 mg QD, n = 93 Median	Range	Pentasa 2 g BID, n = 89 Median	Range
Sex ratio (M/F)	30/63		28/61	
Age (years)	34	19 -74	31	18 - 67
Height (cm)	164	150 – 190	167	148 - 194
Weight (kg)	60	37 – 114	60	39 - 96
CDAI	266		278	
Disease duration (years)	0 - 34		4.6	
Current exacerbation (months)	1.8		2.0	
Disease location (ileal/coloric/both)	56/1/36		50/4/35	
Previous resection (Y/N)	35/58		37/52	
Time since resection (years)	3.7		4.5	
Total resected length (cm)	30		35	
Previously on 5-aminosalicylates (Y/N)	27/66		31/58	

Sponsor's table modified from Vol. 102, page 48

There was no significant difference between the treatment groups in patients baseline characteristics. However, significant more female patients than male patients (more than 2:1) were enrolled in the study and the sponsor did not provide any explanation for this imbalance. Most studies, regardless of geographic location, show relatively equal incidence of CD in both sexes (Sleisenger & Fordtran's, Gastrointestinal and Liver Disease, 6th Edition, page 1710). Although more female patients were randomized into the trial, similar sex ratio of patients in the both study groups were enrolled and this imbalance may not have any impact on final results.

4.4 Withdrawals, Compliance, and Protocol Violations

Withdrawals

Out of the 182 patients randomized and treated, 55 discontinued the study. In the Entocort group 16 of 93 (17%) were withdrawn and in the Pentasa group 39 of 89 (44%). The difference was highly significant (P <0.0001). Table 9 summarizes the treatment discontinuations during the study.

Table 9: Treatment Discontinuations

	Entocort	Pentasa
Randomized and treated	93	89
Withdrawn, SAE	3	5
Withdrawn, AE	0	3
Withdrawn, treatment failure	10	27
Withdrawn, other reason	3	4
Completed study	77 (83%)	50 (56%)

AE = adverse event; SAE = serious adverse event
Reviewer's table modified from Vol. 102, page 50

The major reason for withdrawal was treatment failure (10 patients in Entocort group and 27 in Pentasa group). Eight patients were withdrawn due to SAEs, 3 in the Entocort group and 5 in the Pentasa group. In the Pentasa group, additional 3 patients were withdrawn due to non-serious adverse events: one unintended pregnancy, one paraesthesia and one headache and dizziness. Withdrawals due to other reason were as follows: Entocort group - one patient refused to continue, one patient improved but did not wish to continue and one withdrew for social reasons; Pentasa group - two patients were wrongly included, one was lost to follow-up and one was non-compliant.

Compliance

The mean time in the study was 80 days for patients treated with Pentasa and 104 days for patients treated with Entocort.

Seven patients (one in the Entocort group and six in the Pentasa group) were defined as non-compliant, as less than 85% of the medication during the entire study period was consumed. In addition, two visits for two patients treated with Entocort were excluded from the per protocol analysis due to non-compliance.

Twenty-seven patients in the Entocort group and 31 in the Pentasa group had been previously treated with 5-aminosalicylates.

Two patients (1719 and 1301) in the Entocort group was excluded from the per protocol analysis due to intake of nasal steroids and Tarivid respectively. In addition, a total of 11 visits for 5 patients in the Pentasa group were considered not evaluable due to intake of non-allowed medication.

Protocol Violations

The primary analysis is based on all 182 patients treated. Twenty patients (14 in the

pentasa group and 6 in the Entocort group) were excluded from per protocol analysis. Violation of exclusion criteria was a most common reason in the Entocort group (3 cases), followed by CDAI < 200 (1 case), non-compliance (1 case) and lost to follow-up (1 case). Non-compliance (6 cases) was a most common reason in the pentasa group, followed by violation of exclusion criteria (3 cases), lost to follow-up (3 cases) and CDAI < 200 (2 cases).

4.5 Efficacy Results

4.5.1 Primary efficacy endpoint

The primary variable is the CDAI remission rate (where remission is defined as CDAI ≤ 150). Evaluations were made after 2, 4, 8, 12 and 16 weeks. The primary analysis was based on all patients treated and used the last value extended principle from visit 2 onwards, whenever data were missing regardless of the reason.

The CDAI remission rate was significantly higher in the Entocort group than in the Pentasa group after 8, 12 and 16 weeks. Table 10 summarizes the CDAI remission rate and therapeutic gain during treatment for all patients treated.

Table 10: Summary of the CDAI Remission Rate during Treatment for All Patients Treated.

	Entocort n = 91 * Remission	(%)	Pentasa n = 83 Remission	(%)	p-value (remission rate)
2 weeks	39	44	30	37	N.S.
Therapeutic gain (%)	7%				
4 weeks	43	48	32	39	N.S.
Therapeutic gain (%)	9%				
8 weeks	62	69	37	45	0.001
Therapeutic gain (%)	24%				
12 weeks	58	64	34	42	0.0044
Therapeutic gain (%)	22%				
16 weeks	56	62	29	36	0.0008
Therapeutic gain (%)	26%				

* n=89 at 2 weeks.
N.S.= no statistically significant difference.
Therapeutic gain (%) = remission rate in the Entocort group – remission rate in the control group
Reviewer's table, summarized from Vol. 102, page 74 and item 11

After 8 weeks, the remission rate was 69% in the Entocort group, compared to 45% in the Pentasa group (p=0.001). After 12 and 16 weeks, the remission rates were 64 and 62% in the Entocort group, and 42 and 36% in the Pentasa group (P=0.004 and 0.0008

respectively). Therapeutic gain was 9% after 4 weeks of treatment and increased to 24% after 8 weeks of treatment. Therapeutic gain maintained in the range of 22% to 26% between 8 weeks and 16 weeks of treatment.

4.5.2 Secondary efficacy endpoint

- **Therapeutic benefit rates**

Therapeutic benefit is defined as a decrease in the CDAI of at least 100 units and/or a CDAI of 150 or below.

The therapeutic benefit rates were also significantly higher for patients treated with Entocort than for patients receiving Pentasa after 8, 12 and 16 weeks. The percentage of therapeutic gain was similar with the therapeutic gain in remission rate (Table 11). The table below summarizes therapeutic benefit during treatment for all patients treated.

Table 11: Summary of Therapeutic Benefit Rate during Treatment for All Patients Treated

	Entocort, n = 91 *		Pentasa, n = 83		Therapeutic gain (%)	p-value
	Benefit	(%)	Benefit	(%)		
2 weeks	50	57	44	53	4%	N.S.
4 weeks	58	64	44	53	11%	N.S.
8 weeks	70	77	46	55	22%	0.0027
12 weeks	68	75	45	54	21%	0.0046
16 weeks	64	71	42	51	20%	0.0048

* n=89 at 2 weeks.
N.S.= no statistically significant difference.
Therapeutic gain (%) = benefit rate in the Entocort group –benefit rate in the control group
Reviewer's table, summarized from Vol. 102, page 74 and item 11

- **Time to Remission**

Median time to remission was 28 days for the Entocort group and 58 days for the Pentasa group (p = 0.12).

- **Quantitative changes in CDAI**

Table 12 summarizes changes in CDAI scores during treatment.

Table 12: Summary of Changes in CDAI Scores during Treatment

	Entocort, Mean	n = 91 * SD	Pentasa, Mean	n = 83** SD	Therapeutic gain (Mean)	p-value
Baseline	274	49	284	57		
2 weeks	164	80	203	113	-39	0.017
4 weeks	156	80	197	116	-41	0.017
8 weeks	141	87	192	131	-51	0.007
12 weeks	139	92	198	132	-59	0.0015
16 weeks	138	106	204	133	-66	0.0005

* n=93 at baseline and 89 at 2 weeks; **n=89 at baseline
Therapeutic gain (mean) = CDAI score (mean) in the Entocort group – CDAI score (mean) in the control group.
Reviewer's table, summarized from Vol. 102, page 74 and item 11

The decrease in mean CDAI score was significantly larger for patients receiving Entocort at all visits than the decrease of CDAI score in the control group. The therapeutic gain (mean of CDAI score) consisted of a decreased 51 CDAI score after 8 weeks of the treatment of Entocort.

- **Quantitative changes in the Quality of Life Index**

Although there was a significantly larger increase in the total Psychological General Well-Being (PGWB) score in the Entocort group than in the Pentasa group after 8 weeks treatment (p=0.048), PGWB subscales were no significantly increases which included anxiety range, depressed mood range, positive well-being range, self-control range and general health range.

4.6 Reviewer's Summary and Comments on Study 08-3027

A total of 182 patients were enrolled in the study. Significant more female patients than male patients (124/58) participated in this study, a ratio that is different from most studies which show, regardless of geographic location, relatively equal incidence of Crohn's disease in both sexes.

Although Pentasa is not approved for CD in the United States and is therefore considered experimental, it is widely used in this country to treat active CD in clinical practice.

ENTOCORT capsules were more effective than Pentasa slow release tablets in inducing remission in patients with mild to moderate active CD affecting the ileum and/or the ascending colon. The results for the primary variable (remission rate) as well as the secondary variables (therapeutic benefit rate and quantitative changes in CDAI) were in favor of ENTOCORT capsules compared to Pentasa. However, time to remission and

Psychological General Well-Being (PGWB) subscales were no significantly increases in the ENTOCORT group which included anxiety range, depressed mood range, positive well-being range, self-control range and general health range after 8 weeks.

Remission rate was statistically significant higher in the ENTOCORT group than in the Pentasa group after 8 weeks of treatment (69% vs. 45%, p=0.001). Therapeutic gain for the remission rate was 9% after 4 weeks of treatment and increased to 24% after 8 weeks of treatment. Therapeutic gain maintained in the range of 22% to 26% between 8 weeks and 16 weeks of treatment.

The treatment time in this study, 16 weeks, was longer than in previous acute studies with ENTOCORT. Treatment with ENTOCORT for an additional eight weeks did not result in a further decrease in CDAI. The difference between ENTOCORT and Pentasa did not diminish with time, suggesting that a longer treatment time with Pentasa would not have led to a greater improvement.

5. COMPARISON WITH PLACEBO - STUDIES 08-3001 AND 08-3025

Both Studies 08-3001 and 08-3025 used placebo as a comparator.

5.1 Study 3001

Title: Oral budesonide in Crohn's disease. A dose-finding placebo-controlled study.

5.1.1 Objectives

The primary objective of the study was to compare the efficacy, in term of the influence on CDAI, and safety of budesonide CIR capsules, with placebo treatment in patients with CD. A secondary objective was to find the optimal dose, in terms of efficacy and safety, among three different dose levels of budesonide.

5.1.2 Study Design

The study was randomized, double-blind and placebo-controlled, using a parallel group design. Thirty-two investigational centers in Canada participated in the study. The study was conducted between October 1991 to December 1992. A one-week run-in period was used to get a baseline CDAI. The patients were thereafter randomly allocated to treatment with either budesonide CIR 3, 9, or 15 mg daily, or placebo for 8 weeks, followed by a tapering period of two to four weeks. The study drugs were to be taken as a divided dose, twice daily. Follow-up visits were planned to be carried out after 2, 4, 8, 10, and 12 weeks of treatment. The daily doses of budesonide in the treatment groups are shown in the schedule below.

Weeks 0_____8_____10_____12

7.5 mg BID (15mg)----------→ 3 mg, BID→ 1.5 mg BID→

4.5 mg BID (9 mg)----------→ 3 mg, BID→ 1.5 mg BID →

1.5 mg BID (3 mg)----------→ 0 mg (placebo) ----------→

Placebo ----------→

The investigational evaluation/assessments at each clinic visit are shown in the flow chart below.

Table 13: Flow Chart of Investigational Evaluation/Assessments for Study 08-3001

Visit No.:	1	2	3	4	5	6	6.1[3]
Treatment week:	run-in	0	2	4	8	10	12
Medical history	X						
Physical examination	X	X	X	X	X	X	X
Informed consent	X						
Blood sampling for lab. assessments	X		X	X	X	X	X
Short ACTH test	X				X[1]	X	X
Stool culture	X						
Stool examination	X						
C. difficile toxin test	X						
Pregnancy test	X					X	X
Proctosigmoidoscopy	X						
Colonoscopy or barium x-ray	X						
CDAI calculation		X	X	X	X	X	X
Quality of Life assessments		X	X	X	X	X	X
Adverse events registration		X[2]	X	X	X	X	X
Dispense diary card	X	X	X	X	X	X	
Dispense drug		X	X	X	X	X	
Drug accountability and compliance			X	X	X	X	X

1 = selected centers only

2 = baseline

3 = visit 6.1 only for patients with a prolonged tapering period

5.1.3 Demography and Disease History

A total of 258 patients were randomized into one of the four arms of the study. The baseline characteristics of this patient population did not show considerable differences among the four treatment groups. However, more female than male patients were enrolled in the study across the 4 different treatment groups. Table 14 summarizes demography at baseline and disease history.

Table 14: Demography and Disease History of Study 08-3001

	ENTOCORT 15 mg (n = 64)		ENTOCORT 9 mg (n = 61)		ENTOCORT 3 mg (n = 67)		Placebo (n = 66)	
Parameter	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Sex Ratio (M/F)	29/35		23/38		20/47		25/41	
Age (years)	33	18-66	37	18-65	33	17-63	34	19-62
Weight (kg)	67	42-102	64	42-102	66	36-103	66	40-137
CDAI Score	285		297		293		287	
Disease Duration (years)	6.7		9.6		7.1		8.0	
Current Exacerbation (months)	5.0		3.9		3.5		4.3	
Previous Resection (Y/N)	30/34		29/32		25/42		34/32	
Disease Location								
Ileum	56		51		54		56	
Ileum and Colon	8		10		13		10	

Sponsor's table from Vol. 35, page 271

5.1.4 Withdrawals, Compliance, and Protocol Violations

Withdrawals

Out of the 258 patients treated in the study, 119 (46%) prematurely discontinued study treatment. The majority (81%) of these patients were withdrawn due to disease deterioration or no improvement (treatment failure). Table 15 summarizes premature discontinuation by treatment group for Study 08-3001.

Table 15: Premature Discontinuations by Treatment Group in Study 08-3001

Discontinued: N (%)	Bud 15mg 64 (100)	Bud 9mg 61 (100)	Bud 3mg 67 (100)	Placebo 66 (100)
AE	3 (4.7)	0	2 (3.0)	2 (3.0)
SAE	2 (3.1)	3 (4.9)	0	1 (1.5)
Disease deterioration	18 (28)	16 (26.2)	30 (44.8)	32 (48.5)
Lack of compliance	3 (4.7)	0	4 (6.0)	3 (4.5)
Total discontinued	26 (40)	19 (31)	36 (53.7)	38 (57.6)
Completed Study	38 (60)	42 (69)	31 (46.3)	28 (42.4)

AE = adverse event; SAE = serious adverse event
Reviewer's table, summarized from Vol. 42, page 82

The lowest frequencies of treatment failures were observed in the budesonide 15 mg group (28%) and the 9 mg group (26%), whereas the frequencies in the budesonide 3 mg and placebo group were higher (45 and 48% respectively). A Chi-square test showed a significant difference between the treatment groups (P = 0.014). Differences between the treatment groups with regard to treatment failure are also reflected by the time the patients stayed in the study. The mean time in the study was 55 days for the 15 mg group and 61 days for the 9 mg group compared to 50 and 47 for the 3 mg and placebo group, respectively. The differences between the budesonide 9 mg group and the two latter groups were statistically significant (P = 0.003).

Compliance

Compliance with the study regimen, checked by counting of returned capsules and checking the patients' diaries, was similar in all treatment groups. Violations of compliance were registered for 31 patients (48%) in the budesonide 15 mg group, 33 (54%) in the 9 mg group, 33 (49%) in the 3 mg group and 37 (56%) in the placebo group. Three patients in the budesonide 15 mg and placebo groups respectively were withdrawn from the study as a result of noncompliance compared to four in the 3 mg group and none in the 9 mg group (Table 10).

Protocol Violations

A total of 34 cases were classified as major protocol violators and excluded from the per protocol analyses. These included 10 patients in 9 mg group and 11 patients in placebo group. Using non-allowed medication was the most common reason (4 cases) in 9 mg group followed by using dietary supplement (2 cases), previous resection too extensive (1 case), shigelloides in stools at inclusion (1 case), stool culture missing (1 case), and CDAI below 200 at inclusion (1 case). Missing stool culture was the most common reason (3 cases) in placebo group followed by using non-allowed medication (2 cases) and CDAI below 200 at inclusion. Nineteen other cases were considered to represent minor protocol violations and were included in the per protocol analysis.

5.1.5 Efficacy Results

Primary Efficacy Endpoint

The efficacy analyses were based on all patients treated N = 258. The clinical improvement response rate, defined as a CDAI score of ≤ 150, after 8 weeks of treatment was significantly higher with Entocort 9 mg/day than with placebo (p = 0.0004) as shown in Table 16. The therapeutic gain by the treatment of Entocort was 31%.

Table 16: Clinical Improvement Response Rate at Week 8 (Study 08-3001)

Treatment group	No. patients Treated CDAI ≥ 200	No. (%) Patient with CDAI ≤ 150 at Week 8	Therapeutic gain (%) and p-value
Entocort 9 mg/day	61	31 (51%)	31%, p=0.0004
Placebo	64	13 (20%)	

Therapeutic gain (%) = remission rate in the Entocort group – remission rate in the control group
Reviewer's table summarized from Vol. 35, page 276

After 8 weeks of treatment, the highest remission rate of 51%, was observed in the budesonide 9 mg group, compared with 41% in the 15 mg group and 31% and 20% in the 3 mg and placebo groups, respectively. At this point the differences in remission rates between the placebo group and both the 9 and the 15 mg group were statistically significant (P= 0.0004 and 0.0087 respectively). Table 17 summarizes remission rate by treatment group during treatment.

Table 17: Remission Rate by Treatment Group during Treatment (Study 08-3001)

Remission n (%)	Bud 15 mg n = 64	Bud 9 mg n = 61	Bud 3 mg n = 67	Placebo n = 64*
2 weeks	17 (27)	20 (33)	6 (9)	7 (11)
therapeutic gain	16%	22%	None	
4 weeks	25 (40)	22 (36)	16 (24)	11 (17)
therapeutic gain	23%	19%	7%	
8 weeks	26 (41)	31 (51)	21 (31)	13 (20)
therapeutic gain	21%	31%	11%	
10 weeks	26 (41)	28 (46)	19 (28)	10 (16)
therapeutic gain	25%	30%	12%	
p-value at 8 weeks for remission rate	15 mg – placebo 0.0087 9 mg – placebo 0.0004 3 mg – placebo N.S. 15 mg – 9 mg N.S.			

*Two patients were lost to follow-up prior to providing any post baseline results.
Therapeutic gain (%) = remission rate in the Entocort group – remission rate in the control group
N.S. = No statistically significant difference.
Reviewer's table summarizes from Vol. 42, page 122

There was no statistically significant difference between the budesonide 3 mg group and the placebo group (p = 0.13) or the budesonide 9 and 15 mg groups (p = 0.34). Statistically significant differences between the placebo group and the budesonide 9 and 15 mg groups were observed at all visits during treatment. The highest therapeutic gain of 31% was observed in the budesonide 9 mg group after 8 weeks of treatment.

In the per protocol analysis, both budesonide 9 mg and 15 mg were significantly better (p= 0.0015 and 0.0056 respectively) than placebo in term of remission rates when the last visit extended principle was applied. However, reflecting high incidence of withdrawals due to treatment failure in the 3 mg group and the placebo group, no significant differences were observed when this principle was not applied.

Secondary Efficacy Endpoints

- **Change from baseline in the total CDAI score**

Table 18 summarizes the CDAI changes as compared to baseline during treatment by treatment groups.

Table 18: Summary of CDAI Reduction during Treatment for Study 08-3001

	Bud 15 mg, N=64 Mean (S.D.)	Bud 9 mg, N=61 Mean (S.D.)	Bud 3 mg, N=67 Mean (S.D.)	Placebo, N=66 Mean (S.D.)
At baseline	285 (56)	297 (63)	293 (69)	287 (74)
Decreases:				
2 weeks	80 (72)	95 (83)	53 (70)	26 (83)
therapeutic gain	54	69	27	
4 weeks	88 (81)	102 (94)	60 (95)	29 (98)
therapeutic gain	59	73	31	
8 weeks	88 (98)	121 (113)	63 (106)	21 (103)
therapeutic gain	67	100	42	
10 weeks	74 (100)	104 (107)	49 (108)	13 (103)
therapeutic gain	61	91	36	
P-value	15 mg – Placebo	0.0004		
At 8 weeks	9 mg – Placebo	< 0.0001		
	3 mg – Placebo	0.022		
	9 mg – 3 mg	0.0023		

Therapeutic gain = mean CDAI decrease in the Entocort group – mean CDAI decrease in the placebo group
Reviewer's table summarizes from Vol. 42, page 122

As reflected by the remission rates, the mean CDAI scores decreased more in the budesonide 9 and 15 mg groups than in the placebo group. The differences were statistically significant at all follow-up visits. The largest decrease was observed in the

budesonide 9 mg group (Table 18). The mean CDAI decreased 121 points in this group after 8 weeks (therapeutic gain of decreasing 100 CDAI score), compared with baseline, whereas the decrease in the 15 mg group was 88 points and in the budesonide 3 mg and placebo groups, 63 and 21 points, respectively. At that time, there was also a statistically significant difference between the budesonide 9 mg and 3 mg groups (P = 0.0023). In the per protocol analysis, the differences between the placebo group and the budesonide 9 mg and 15 mg groups remained statistically significant, irrespective of whether the last value extended principle was applied or not.

- **Change from baseline in Quality of Life Index Score**

The disease-specific quality of life was measured using the Inflammatory Bowel Disease Questionnaire (IBDQ). IBDQ consists of 32 questions relating to the patient's bowel symptoms, systemic symptoms and emotional and social function. Each question is scored on a scale of 1 (worst) to 7 (best), giving a score range of 32 to 224.

The largest increase in the total score was observed in the budesonide 9 mg group. After 8 weeks of treatment this difference was statistically significant in comparison placebo groups (40.1 vs. 11.7, p = < 0.0001). A significant difference in favor of budesonide 9 mg was also found when scores relating to bowel symptoms, systemic symptoms, social functions and emotional functions were grouped and analyzed separately. Table 19 summarizes the change from baseline in quality of life index score during treatment by treatment groups. No further benefit was observed from administration of budesonide at single daily dose of 15 compared to 9 mg.

Table 19: Summary of the Change from Baseline in Quality of Life Index Score (Total Scores, 32-224) during Treatment by Treatment Groups

	Bud 15 mg Mean (n)	Bud 9 mg Mean (n)	Bud 3 mg Mean (n)	Placebo Mean (n)
At Baseline	130.3 (64)	125.7 (57)	131.3 (65)	130.6 (65)
Increases:				
2 weeks	23.5 (57)	31 (56)	13.1 (62)	10.2 (62)
4 weeks	24.4 (59)	34.6 (57)	13.7 (62)	11.1 (62)
8 weeks	27 (60)	40.1 (57)	10 (62)	11.7 (62)
10 weeks	19.4 (60)	37.2 (57)	7.1 (62)	9.7 (62)
P-value	15 mg – Placebo	0.012		
At 8 weeks	9 mg – Placebo	< 0.0001		
	3 mg – Placebo	N.S.		
	15 mg – 9 mg	0.034		

Reviewer's table summarizes from Vol. 42, page 134

5.1.6 Reviewer's Summary of efficacy Results and Comments for Study 08-3001

A total of 258 patients were randomized in the study included 61 patients in the 9 mg group and 64 in the placebo group. More female than male patients (161/97) were

enrolled in the study across 4 different treatment groups.

This study showed that budesonide CIR at 9 mg or 15 mg/day doses was more efficacious than placebo in treatment of mild and moderate active CD for 8 weeks. There was no statistically significant difference between the budesonide 3 mg group and the placebo group ($p = 0.13$) or the budesonide 9 and 15 mg groups ($p = 0.34$). Therefore, 9 mg/day of budesonide would be a reasonable choice for further investigation of efficacy and safety in treatment of CD.

The treatment regimen in this clinical trial was 4.5 mg of budesonide twice daily and it is different from the sponsor's claim in the labeling - 9 mg once daily. However, from a clinical perspective there is no apparent difference in the efficacy, pharmacodynamics or safety of ENTOCORT 9 mg/day when given as a once-a-day or two divided dosing regimen (see section VIII for detail). Studies 08-3013 and 08-3025 were designed to compare these two regimens and will be discussed in the section below.

5.2 STUDY 08-3025

Title: Budesonide controlled ileal release capsules once or twice daily in active Crohn's disease. A placebo-controlled study.

5.2.1 Objectives

The objectives of this study were to assess the efficacy and safety of budesonide CIR 4.5 mg twice daily or 9 mg once daily compared to placebo, in patients with active CD affecting the ileum and/or the ascending colon. The primary efficacy variable was clinical improvement, defined as a decrease in CDAI to a score ≤ 150 after 8 weeks of treatment.

5.2.2 Study Design

This was a double-blind, placebo-controlled, randomized study with three parallel groups, in patients with active CD. This study involved 307 patients throughout 27 centers in the USA between September 1995 and August 1997. Patients were evaluated during a one- to two-week baseline period after which the eligible patients (200) were randomized to one of the following blinded treatments:

1. budesonide CIR 9 mg administered once daily in the morning for eight weeks, after which the dose was tapered to 6 mg for two weeks or

2. budesonide CIR 4.5 mg administered twice daily (once in the morning and once in the evening) for eight weeks, after which the dose was tapered to 3 mg twice daily for two weeks or

3. placebo administered twice daily for 10 weeks

The total treatment period was 10 weeks following a baseline period of 1-2 weeks. The detailed schedule of study procedures is presented in Table 20.

Table 20: Schedule of Study Procedures

Visit number	1	2[a]	3	4	5	6
Week	-1-2	0	2	4	8	10
Assessments:						
Informed consent	x					
Inclusion/Exclusion criteria	x	x				
Patient demographics	x					
Medical history	x					
Comprehensive examination with vital signs	x					x
Brief physical examination with vital signs		x	x	x	x	
Colonoscopy[b]	x					
Small bowel barium follow-through[b]	x					
CDAI		x[d]	x	x	x	x
Hematology, blood chemistry	x[c]			x		x
Urinalysis	x[c]			x		x
Stool	x[c]					
Hematocrit	x[c]	x	x	x	x	x
Sedimentation rate[e]	x			x		x
Serum pregnancy test	x[c]					x
Basal plasma cortisol		x			x	x
Cortrosyn® test		x			x	
IBDQ Quality of Life Questionnaire	x	x	x	x	x	x
SF-36 Quality of Life Questionnaire		x			x	x
Review adverse events		x	x	x	x	x
Possible glucocorticosteroid side effects assessment		x	x	x	x	x
Dispense new diaries	x	x	x	x	x	
Review daily diaries		x	x	x	x	x
Dispense study drug		x	x	x	x	
Return study drug/assess compliance			x	x	x	x

a) Allocation of patient number
b) If not done within 180 days of Visit 1
c) Repeat if a clinically relevant value is found before visit 2
d) The baseline phase should be extended up to a maximum of seven days if the baseline CDAI cannot be accurately determined due to possible interference from the baseline diagnostic procedures (i.e. colonoscopy, small bowel follow-through examination). This was added in Protocol Amendment 1.
e) Sedimentation rate was added in Protocol Amendment 1

During the baseline period, the disease activity was measured using the CDAI. During the treatment period, the patients attended the clinic five times (Visits 2-6) for efficacy and safety evaluations. Procedures to be performed during the clinic visits included physical examinations, CDAI assessments, completion of quality of life questionnaires and clinical laboratory assessments. In addition, basal and post-ACTH stimulated plasma cortisol levels were assessed.

5.2.3 Demography and Disease History

A total of 307 patients were considered for enrollment, of which 200 were randomized in 24 centers in the U.S.A. during September 1995 to August 1997. The major reason why patients considered for enrollment were not randomized was a CDAI score out of range (200-450). The demography and disease histories at baseline are summarized in Table 21.

Table 21: Summary of Baseline Patient Characteristics (all patients treated)

	Bud 9mg QD n= 80		Bud 4.5mg BID n= 79		Placebo n= 41	
	Median	Range	Median	Range	Median	Range
Sex ratio (M/F)	19/61		35/44		18/23	
Age (years)	36	18-73	38	18-71	36	18-63
Height (cm)	166	147-203	170	147-193	173	155-188
Weight (kg)	66	45-135	68	45-117	71	44-107
Race (C/B/O)	78/2/0		77/1/1		40/1/0	
CDAI	268		270		253	
Disease duration (years)	9.2		7.1		8.2	
Current exacerbation (months)	1.7		1.8		2.5	
Previous resection (Y/N)	41/39		41/38		22/19	
Time since resection (years)	6.9		3.2		2.9	

C=Caucasian; B=Black; O=Oriental
Reviewer's table modified from Vol. 82, page 66

Most of the baseline characteristics of this patient population were well balanced among the three treatment groups. However, significant less proportion of male patients were randomized in the 9 mg once daily group (23%, 19/61) than in other two groups (44% and 44%), although all in all less male patients were randomized in the study than female patients across the groups. Time since intestine resection in the 9 mg once daily group

(6.9 years) was significantly longer than other two groups (3.2 and 2.9 years). This more chronic disease may be an unfavorable factor for the 9 mg once daily group. It is not known if this imbalance may have an unfavorable impact on the efficacy results with the 9 mg budesonide once-a-day.

5.2.4 Withdrawals, Compliance, and Protocol Violations

Withdrawals

A total of 39 patients discontinued the study and two most common reasons were secondary to adverse events (17 cases) and disease deterioration (15 cases). Table 22 summarizes the reasons for discontinuation by treatment groups.

Table 22: Summary of the Reasons for Discontinuation by Treatment Groups

	Bud 9 mg QD n = 80	Bud 4.5 mg BID n = 79	Placebo n = 41
Adverse events	6	8	3
disease deterioration	5	2	8
lost to follow-up			1
non-compliance	1	1	1
pregnant	1		
not eligible	1	1	
Total	14	12	13

Reviewer's table summarized from Vol. 84, page 14 – 38

Compliance

Compliance was based on diary records of study drug intake. Of the 200 randomized patients, diary card data regarding drug intake were missing for five patients. Of the remaining 195 patients, 192 (96%) were compliant, i.e. they took at least 80% of scheduled doses of study medication during the time they were in the study. There was one patient in each treatment group as non-compliance (Table 22).

Protocol Violations

All patients who received at least one dose of the study drug and who had data from at least one follow-up visit have been included in the all-patients-treated analysis.

A total of 28 patients were considered not evaluable for the per protocol analysis: 24 patients violated the inclusion/exclusion criteria and 4 patients presented major protocol violations for other reasons (two were non-compliant with study medication and two were treated with non-allowed medication). Nine of the non-evaluable patients were in the budesonide once daily group, 14 in the budesonide twice daily group and 5 in the

placebo group. The difference between the groups is not statistically significant (p=0.79; Chi-square test). For the evaluable patients, some visits were considered not evaluable. Table 23 summarizes the reasons of protocol violations.

Table 23: Summary of the Reasons for protocol Violations by Treatment Groups

	Bud 9 mg QD n = 80	Bud 4.5 mg BID n = 79	Placebo n = 41
CDAI > 450	1		
CDAI < 200	2	3	1
Use of non-allowed medication	6	8	1
non-compliance		2	2
Positive compylobacter		1	
No recent colonscopy			1
Total	9	14	5

Reviewer's table summarized from Vol. 84, page 40 – 60

More patients in the budesonide-treated groups than placebo group were excluded for primary analysis. The most common reason for exclusion in both budesonide treated groups was use of non-allowed medication, while a common reason in the placebo group was non-compliance.

5.2.5 Efficacy Results

Primary efficacy endpoint

The primary efficacy variable was clinical improvement, defined as a decrease in CDAI to a score $\leq$ 150 after 8 weeks of treatment. The clinical improvement rate was numerically improved in both budesonide groups and in the placebo group. However, the differences (20% of therapeutic gain) between the budesonide treatment groups and placebo did not reach statistical significance. Table 24 summarizes the primary efficacy results (clinical improvement rate) after 8 weeks treatment.

Table 24: Summary of percentage of Clinical Improvement (CDAI $\leq$ 150) after 8 Weeks Treatment by treatment group.

Bud 9 mg QD N = 79	Bud 4.5 mg BID N = 78	Placebo N = 40	Therapeutic gain (%) and p-value
48%	53%	33%	15%; QD vs. placebo 20%; BID vs. placebo p=0.14

Reviewer's table summarized from Vol.82, page 67

The three treatment groups were also compared following two, four and ten weeks of treatment and the patients treated with 9 mg budesonide daily (pooled both budesonide groups into one group) were compared with placebo. Table 25 summarizes these results.

Table 25: Summary of Percentage of Clinical Improvement (CDAI ≤ 150) by Treatment Group.

	Bud 9 mg QD n = 79	Bud 4.5 mg BID n = 78	Placebo n = 40	p-value Bud QD, BID vs. placebo	p-value Pooled Bud vs. placebo
2 weeks	31%	40%	13%	0.012	0.0062
therapeutic gain	18%	27%			
4 weeks	43%	49%	33%	N.S.	N.S.
therapeutic gain	10%	16%			
8 weeks	48%	53%	33%	N.S.	N.S.
therapeutic gain	15%	20%			
10 weeks	60%	63%	49%	N.S.	N.S.
therapeutic gain	11%	14%			

Therapeutic gain (%) = remission rate in the Entocort group – remission rate in the placebo group.
N.S. = No statistically significant difference
Reviewer's table summarized from Vol.82, page 67

The clinical improvement rate was numerically higher in both budesonide groups and in the placebo group after 2, 4, 8, and 10 weeks treatment. However, the placebo rate is also increasing, from 13% at 2 weeks to 49% at 10 weeks. The differences between the experimental treatment groups and placebo did not reach statistical significance at 4, 8, and 10 weeks treatment.

Secondary efficacy endpoint

The differences between the active treatment groups and placebo did not reach statistical significance after 8 weeks treatment for all secondary efficacy endpoints analysis. These analyses included quantitative changes in CDAI (p=0.051), clinical improvement rate with per protocol analysis (p=0.31), treatment benefit rate (p=0.067), quality of life questionnaires- both total IBDQ score and subscores (total IBDQ score p=0.62).

5.2.6 Reviewer's efficacy Summary and Comments on Study 08-3025

A total of 200 patients were randomized in 24 centers in the U.S.A. for this placebo-control study. There were 2 budesonide treatment groups for a total of 159 patients and placebo group for 41 patients. The number of patients randomized in placebo group (n=41) was significant less than the patients in other groups in two previous studies (average 64/group in study 08-3001 and 91/group in study 08-3027) and this study.

A significant less proportion of male patients in the 9 mg once daily group (23%, 19/61) than in other two groups (44% and 44%) was enrolled, although less male patients were enrolled in the study than female patients across the groups. Time since resection in the 9

mg once daily group (6.9 years) was significantly longer than other two groups (3.2 and 2.9 years). However, it is unlikely that those balances might have influenced the trial results.

The study demonstrated that the remission rates after 8 weeks of treatment were in favor of ENTOCORT groups in comparison with placebo (48% and 53% vs. 33%) with a 15% and 20% of therapeutic gain, although there was no statistically significant difference between the Entocort groups and placebo group. The lack of statistically significant difference might be due to less patients randomized in the placebo group (2:1 enrollment, n=41) and more patients with mild disease enrolled (median CDAI=253, 71% < 300) in comparison with in the first placebo study (median CDAI=287, 62% < 300). These imbalances might explain the higher placebo response rate (33% vs. 20%) and lower dropout rate. See also section IX/D/3 Subgroup analysis for detail.

This study showed no significant difference between 4.5 mg bid and 9 mg qd dosing of budesonide.

6. COMPARISON WITH PREDNISOLONE - STUDIES 08-3002 AND 3013

Both Studies 08-3002 and 08-3013 used prednisolone as comparator. To date glucocorticosteroids have been the most effective drugs in actively suppressing inflammation and inducing clinical remission in patients with CD.

6.1 Study 08-3002

Title: A controlled trial of oral budesonide and prednisolone in active ileocecal CD.

6.1.1 Objectives

The primary objective was to compare the efficacy and safety of Entocort with prednisolone tablets measured as the effect on the CDAI in patients with active ileal or ileocecal CD. A secondary objective was to study the effect of the two treatment regimens on the Harvey-Bradshaw index. The Harvey-Bradshaw index includes the same variables as the CDAI but is less complicated since it does not involve the use of a diary. The variables are assessed at the day of the visit by the doctor and cover only one day.

6.1.2 Study Design

The study was randomized and double-blind with parallel groups. Eleven centers in Sweden, Denmark, Belgium, Germany, the Netherlands and the United Kingdom participated between February 1991 and September 1992. The patients were treated with either 9 mg budesonide CIR for eight weeks and 6 mg for further two weeks, or prednisolone. The prednisolone dose was 40 mg the first two weeks and was tapered successively down to 5 mg the last week. Both drugs were given once daily in the morning and no run-in period was used. Investigational assessments are summarized in Table 26.

Table 26: Investigational Events for Study 08-3002

Week Clinic visit No	0 1	2 2	4 3	8 4	10 5
Medical history	X				
Physical examination	X	X	X	X	X
Lab. assessment	X	X	X	X	X
Proctosigmoidoscopy	X				
Informed consent	X				
CDAI calculation	X	X	X	X	X
Harvey-Bradshaw calc.	X	X	X	X	X
Adverse event check	X	X	X	X	X
Drug counting		X	X	X	X
Diary cards check		X	X	X	X

The daily dosage of the trial drugs are as shown below. The medications were taken in the morning with breakfast.

Week	1	2	3	4	5	6	7	8	9	10
Budesonide	9	9	9	9	9	9	9	9	6	6 mg
Prednisolone	40	40	30	30	25	25	20	15	10	5 mg
No of capsules	3	3	3	3	3	3	3	3	2	2
No of tablets	4	4	3	3	3	3	2	2	1	1

6.1.3 Demography and Disease History

A total of 176 patients were randomized and treated with either budesonide CIR or prednisolone. The demography and disease history are presented in Table 27.

Table 27: Summary of Baseline Patient Characteristics (all patients treated)

	Budesonide n = 88		Prednisolone n = 88		Both groups n = 176	
	Median	Range	Median	Range	Median	Range
Sex ratio (M/F)	30/58		37/51		67/109	
Age (years)	35	18-67	36	18-85	36	18-85
Height (cm)	170	153-193	170	152-193	170	153-193
Weight (kg)	63	44-133	64	38-113	64	38-113
CDAI	275		279		277	
Harvey-Bradshaw index	9.3		9.3		9.3	
Disease duration (years)	7.1		7.3		7.2	
Current exacerbation (months)	11		8.2		9.6	
Previous resection (Y/N)	43/45		32/56		75/101	
Time since resection (years)	4.7		5.8		5.2	
Resection length (cm)	49		52		50	

Reviewer's table modified from Vol. 33, page 206

The groups were well matched for baseline characteristics.

6.1.4 Withdrawals, Compliance, and protocol Violations

Withdrawals

Out of the 176 patients, 31 (17.6%) discontinued treatment study. The most common reason for discontinuation in both groups was therapeutic failure (Table 28).

Table 28: Reasons for Discontinuation in Study 08-3002

	Budesonide N=88	Prednisolone N=88	Total N=176
AE	1	1	2
Serious AE	0	2	2
Therapeutic failure	14	9	23
Non-compliance	1	1	2
Erroneous inclusion	0	2	2
Completed study	72	73	145

More patients discontinued the study secondary to therapeutic failure in the budesonide group than in the prednisolone group.

Compliance

Two patients discontinued the treatment due to lack of compliance. Patient No.143 (budesonide) decided to stop her medication after visit 4. Patient No. 303 (prednisolone) stopped the treatment after visit 1 due to a misunderstanding.

No other patients were assessed as being non-compliant, defined here as a compliance less than 75%.

Protocol Violations

The primary analysis was based on all 176 patients treated, whereas 18 were excluded in the per protocol analysis. Table 29 summarizes the reasons for patients to be excluded in the per protocol analyses.

Table 29: Summary of the Reasons for Patients Excluded in the Per Protocol Analyses.

Number	Treatment	Reason
108	Prednisolone	Diagnosis never verified
114	Budesonide	H_2-blocker from study start
119	Prednisolone	CDAI < 200 at study start
135	Budesonide	Drugs for CD used (Flagyl)
205	Budesonide	Bowel resection > 100 cm
405	Prednisolone	Not allowed medication (steroids)
414	Budesonide	Lost to follow up after visit 1
705	Prednisolone	Pancolitis
813	Budesonide	Abscess
1001	Budesonide	Lost to follow up after visit 1
1003	Budesonide	Proctosigmoidoscopy not performed
1004	Prednisolone	Lost to follow up after visit 1
1105	Prednisolone	Proctosigmoidoscopy not performed
1108	Budesonide	Proctosigmoidoscopy not performed
1110	Budesonide	Proctosigmoidoscopy not performed
1111	Budesonide	Proctosigmoidoscopy not performed
1112	Prednisolone	Proctosigmoidoscopy not performed
1114	Budesonide	Proctosigmoidoscopy not performed and entry CDAI < 200

All these deviations were classified as major. Patients No. 306 (discontinued after visit 4 due to pregnancy) and No. 409 (B-glucose 12.4 mmol/L at entry) were considered to have minor deviations from protocol and were, therefore, included in the per protocol analysis.

6.1.5 Efficacy Results

Primary efficacy endpoint

Primary end-point was defined as a decrease in CDAI to 150 or below (clinical remission) or a decrease by 100 units (treatment success or benefit) after 4, 8 and 10 weeks. Table 30 summarizes the remission rates during the treatment period by study group.

Table 30: Summary of Remission (CDAI ≤ 150) Rates during the Treatment Period by Study Groups.

	Budesonide N=86		Prednisolone N=85		therapeutic	P Value
	Remission	%	Remission	%	gain (%)	
2 weeks	39	45%	48	56%	None	N.S.
4 weeks	34	40%	58	67%	None	0.0004*
8 weeks	45	52%	56	65%	None	N.S.
10 weeks	46	53%	57	66%	None	N.S.

Therapeutic gain (%) = remission rate in the Entocort group – remission rate in the control group
*Prednisolone statistically significantly different from budesonide.
N.S. = No statistically significant difference
Reviewer's table summarized from Vol. 59, page 233

After 8 weeks treatment 52% of the patients in the budesonide group and 65% in the prednisolone group were in clinical remission (CDAI ≤150). There were 13% of more patients in remission in the prednisolone group than in the Entocort group after 8 weeks of treatment. The differences in remission rates were not statistically significant after 2, 8 or 10 weeks treatment; however, it was statistically significant after 4 weeks treatment with 27% more patients in remission in the prednisolone group (p=0.0004). At week 4 the effectiveness of budesonide was lowest (40%) and that with prednisolone was the highest (67%). Although spurious, these results suggest that budesonide may be less effective than prednisolone. Confirmation of this inferiority in efficacy is needed.

A similar result was obtained measuring success rates (CDAI decrease > 100). Table 31 summarizes success rates during the treatment period by study group.

Table 31: Summary of Success (CDAI decrease > 100) Rates during the Treatment Period by Study Groups.

	Budesonide n=86 Success	%	Prednisolone n=85 Success	%	therapeutic gain (%)	P Value
2 weeks	52	60%	64	75%	None	N.S.
4 weeks	43	50%	71	84%	None	<0.0001*
8 weeks	54	63%	62	73%	None	N.S.
10 weeks	52	60%	64	75%	None	N.S.

Therapeutic gain (%) = success rate in the Entocort group – success rate in the control group
*Prednisolone statistically significantly different from budesonide.
N.S. = No statistically significant difference
Reviewer's table summarized from Vol.59, page 233

After 8 weeks treatment 63% of the patients in the budesonide group and 73% in the prednisolone group were in clinical success (CDAI decrease more than 100 from baseline). The differences in success rates were not statistically significant after 2, 8 or 10 weeks treatment, however, it was statistically significant after 4 weeks treatment ($p<0.0001$). About 10-34% more patients in the prednisolone group than in the Entocort group have CDAI score decrease more than 100 from baseline during the study.

Secondary efficacy endpoint

The Harvey-Bradshaw index was calculated as a secondary efficacy endpoint. The following five variables were measured:

1. General well-being the previous day
   (generally well, slightly below par, poor, very poor, terrible)
2. Abdominal pain the previous day (none, mild, moderate and severe)
3. Number of liquid or very soft stools the previous day
4. Abdominal mass
   (none, questionable, definite, definite and tender)
5. Complications
   (arthralgia, uveitis, erythema nodosum, aphthous ulcers, pyoderma gangrenosum, anal fissure, new fistula, abscess)

The Harvey-Bradshaw index includes the same variables as the CDAI (see section VI /C /2 Efficacy endpoints for detail) but is less complicated since it does not involve the use of a diary. The variables are assessed at the day of the visit by the doctor and cover only one day. The relative variation in the Harvey-Bradshaw index is, however, larger than

that of the CDAI, hence the Harvey-Bradshaw index seems to give a somewhat cruder comparison. Table 32 summarizes the decrease of the Harvey-Bradshaw index during the treatment period by study group. At all time points of evaluation, the therapeutic gain (budesonide better than prednisolone) was NONE.

Table 32: Summary of Decrease in The Harvey-Bradshaw Index during the Treatment Period by Study Groups.

	Budesonide n=86*		Prednisolone n=86*		p-value
Entry Mean ± SD	9.3	3.6	9.3	3.5	
	Decrease	SD	Decrease	SD	
2 weeks	3.7	3.6	4.9	3.5	0.031
4 weeks	3.7	3.0	5.5	3.3	0.0004
8 weeks	3.8	3.3	5.4	4.1	0.004
10 weeks	3.7	3.4	5.2	3.7	0.006

Reviewer's table summarized from Vol.59, page 233
* N=88 at entry

According to the results depicted in Table 32, the Harvey-Bradshaw index was decreased more in the prednisolone group than in the budesonide group and the differences in decrease of the Harvey-Bradshaw index were statistically significant for all of assessments (2, 4, 8 and 10 weeks visits). These results suggest that prednisolone might be more effective than budesonide in the treatment of active CD. This difference based on the Harvey-Bradshaw index assessment, needs to be confirmed.

6.1.6 Reviewer's Summary and Comments

A total of 176 patients were randomized and treated in this double-blind with active control study. The patients were treated with either 9 mg budesonide or prednisolone in 11 centers in Europe for 10 weeks. Both drugs were given once daily in the morning.

Prednisolone and prednisone have the same relative anti-inflammatory potency and relative mineralocorticoid potency. Prednisone 40 mg is widely used as a starting dose for treatment of active Crohn's disease.

After 8 weeks treatment 52% of the patients in the budesonide group and 65% in the prednisolone group were in clinical remission. The differences in remission rates were not statistically significant after 2, 8 and 10 weeks treatment, however, it was statistically significant after 4 weeks treatment (p=0.0004). A similar result was obtained measuring success rates. Although these were not statistically significant difference after 8 weeks treatment, the additional 13% of the patients reaching remission in the prednisolone group have to be considered and weighted against the safety profile of these drugs. According to FDA statistician's analysis, at the worst case, Entocort might be as high as

27% less effective than prednisolone in inducing remission of active CD.

Moreover, the Harvey-Bradshaw index was decreased more in the prednisolone group than in the budesonide group and the differences in decrease of the Harvey-Bradshaw index were statistically significant for all of assessments (2, 4, 8 and 10 weeks visits). These results suggest that prednisolone might be more effective than budesonide in the treatment of active CD based on the Harvey-Bradshaw index assessment and it needs to be confirmed. The Harvey-Bradshaw index includes the same variables as the CDAI but is less complicated since it does not involve the use of a diary. The variables are assessed at the day of the visit by the doctor and cover only one day. In the study, both indices were used and the results were analogous. The relative variation in the Harvey-Bradshaw index is, however, larger than that of the CDAI, hence the Harvey-Bradshaw index seems to give a somewhat cruder comparison.

6.2 STUDY 3013

Title: oral budesonide once and twice daily versus oral prednisolone once daily in active CD.

6.2.1 Objectives

The primary objective was to compare the efficacy and safety of budesonide CIR capsules dosed once daily in the morning or twice daily with prednisolone tablets in patients with active ileal or ileo-caecal CD.

Study Design

The study was randomized and double-blind with 3 parallel groups. Thirty-four investigational centers in the UK, Ireland, Italy, Australia, Germany, Sweden, Belgium and the Netherlands participated in the study between March 1992 and February 1994. A baseline CDAI was obtained during a run-in period of 3 to 7 days. The patients were subsequently randomized to either treatment with budesonide CIR capsules 9 mg once daily or 4.5 mg twice daily or prednisolone 40 mg once daily. Budesonide CIR was tapered to 6 mg after 8 weeks and to 3 mg after 10 weeks. Prednisolone was tapered to 30 mg after 2 weeks and then continuously throughout the study, reaching 5 mg after 9 weeks. The total treatment period was 12 weeks. Follow-up visits were carried out after 2, 4, 8 and 12 weeks of treatment. Dosage regimens are shown in Figure 2.

Figure 2: Dosage Regimens in Study 3013

Treatment week:	1	3	5	7	8	9	10	11	12
Budesonide QD (mg)	9	----------→				6	6	3	3
Budesonide BID (mg)	4.5	----------→				3	3	1.5	1.5
Prednisolone QD (mg)	40	30	25	20	15	10	5	--------→	

The investigational assessments at each clinic visit are shown in Table 33.

Table 33
Schedule of assessments - at the clinic

Visit	1	2	3	4	5	6
No of weeks on study drug therapy	Run in	0	2	4	8	12
Informed consent	x					
Demographics	x					
Medical history	x					
Medication log	x	x	x	x	x	x
Randomization		x				
CDAI calculation		x	x	x	x	x
Haematocrit	x		x	x	x	x
Vital signs	x				x	x
Clinical Chemistry and Haematology	x			x		x
B–glucose	x			x		x
P–cortisol		x	x		x	
Inflammatory indicators	x[3]	x	x	x	x	x
ACTH test		x			x	x[2]
Sigmoidoscopy	x					
Endoscopy[1] or radiology[1]	x					
Adverse Events		x	x	x	x	x
Dispense diary card	x	x	x	x	x	
Check diary card		x	x	x	x	x
Dispense study drug		x	x	x	x	
Drug accountability		x	x	x	x	x
Drug compliance			x	x	x	x

[1] = to be performed if the localisation of the disease had not been verified within the past 24 months
[2] = optional
[3] = sampling for analysis of S–Orosomucoid and S–CRP started at visit 2

6.2.3 Demography and Disease History

A total of 178 patients were randomized and 177 were treated. Patient 209 in the prednisolone group never took any study drug. The demography and disease history for all patients treated are presented in Table 34. The groups were well matched, although duration of current exacerbation was slightly longer in the budesonide b.i.d. group. Less male patients were enrolled in the study across the treatment groups. These imbalances should not have much impact on remission rate.

Table 34: Demography and disease history (all patients treated)

	Budesonide once daily (n=58)		Budesonide twice daily (n=61)		Prednisolone once daily (n=58)	
	Mean	Range	Mean	Range	Mean	Range
Sex ratio (M/F)	21/37		28/33		23/35	
Age (years)	36	17-71	38	20-71	36	19-70
Weight (kg)	63	41-118	63	35-94	61	39-93
CDAI	277		274		279	
Disease duration (years)	8.3		7.9		6.7	
Current exacerb. (months)	4.0		7.6		5.5	
Previous resection (Y/N)	28/30		27/34		34/24	
Time since resection (years)	5.8		5.3		4.6	0

6.2.4 Withdrawals, Compliance, and Protocol Violations

Withdrawals

Out of 177 patients treated in the study, 37 prematurely discontinued their treatment. The most common reason for discontinued their treatment was therapeutic failure in all 3 treatment groups. The frequencies of therapeutic failure observed were comparable between the three groups (16% in the budesonide groups and 12% in the prednisolone group). A Chi-square test showed no significant difference between the treatment groups (p=0.78). Table 35 summarizes the number of patients withdrawn and the reasons for