

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-324

STATISTICAL REVIEW(S)

MEMORANDUM

 DEPARTMENT OF HEALTH AND HUMAN SERVICES
 PUBLIC HEALTH SERVICE
 FOOD AND DRUG ADMINISTRATION
 CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 20, 2001

FROM: Director, Division of Biometrics II (HFD-715)

SUBJECT: Comments on NDA 21-324

TO: File (NDA 21-324, Entocort - budesonide modified release - capsules)

Both the primary statistical reviewer (Dr. Wang) and the secondary reviewer (Dr. Permutt) have made cogent arguments for somewhat different interpretations of the results of the trials submitted to this NDA (see their reviews dated 7/18/01). The results for the primary efficacy outcome from the submitted studies are contained in the following table copied from a similar table in Dr. Wang's review:

Primary efficacy outcome: remission rate at 8 weeks (% of patients who had CDAI* \leq 150)

Study (ITT)§	Sample size estimation	Placebo	(3mg) 1.5mg bid Entocort	(9mg) 4.5mg bid Entocort	9mg qd Entocort	(15mg) 7.5mg bid Entocort	2g bid mesalamine	40mg qd prednisolone
08-3001 (sig)*	P=.4 T15mg=.7 Ni=60	20% (13/66)	31% (21/67) p=0.12	51% (31/61) p<0.0001	NA	41% (26/64) p=0.0077	NA	NA
08-3027	P<.28 T=.5 Ni=85	NA	NA	NA	68% (63/93) p=0.0002	NA	42% (37/89)	NA
08-3025 (n.s.)*	P=.2, T=.5 Ni=80 Np=40	32% (13/41)	NA	52% (41/79)	48% (38/80)	NA	NA	NA
08-3002	C=.7, T=.5 Ni=75	NA	NA	NA	51% (45/88) p=0.091	NA	NA	64% (56/88)
08-3013 (n.s.)*	C=.7, T=.4 Ni=50	NA	NA	41% (25/61)	60% (35/58)	NA	NA	60% (35/58)

NA: Not Applicable

C: active control remission rate, prednisolone or mesalamine

T: treatment (budesonide) remission rate, P: placebo remission rate

§ Reviewer's evaluation (based on all randomized patients)

*: overall χ^2 test; (sig): statistical significance at 0.05 level; (n.s.): non-significance

The bottom two studies (08-3002 and 08-3013) are both prednisolone-controlled studies which failed to show a difference between Entocort and the control. Dr. Wang has argued that the lack of a pre-determined choice of non-inferiority margin makes a valid interpretation of these studies difficult. In addition, there are no within-study comparisons of prednisolone versus placebo presented in the submission that might have been helpful in evaluating the comparison between Entocort and prednisolone in these studies. Since there are three studies available that either

show a difference between Entocort and placebo or attempt to, I believe that the primary evidence should rest with these studies, with the acknowledgement that the two prednisolone-controlled studies do not necessarily detract from any evidence of efficacy shown in these three studies.

Studies 08-3001 and 08-3027 both, taken at face value, show statistical evidence of efficacy of Entocort. Study 08-3025 is not a positive study by the pre-determined analysis plan, but could be considered supportive if agreement were reached on the sufficiency of the evidence shown in the first two studies. I agree with Dr. Permutt's assessment that treating dropouts due to lack of efficacy as treatment failures represents a reasonable final determination of the results for these patients, with two caveats. First, the clinicians must agree that one would not reasonably expect such patients to actually end up as treatment successes had they continued in the trial, and, second, the clinicians are not concerned with the preponderance of treatment failures in mild as opposed to more severe placebo patients. Therefore, I would conclude that sufficient statistical evidence of efficacy in regard to the primary efficacy variable has been shown from studies 08-3001 and 08-3027, subject to the two caveats expressed above.

S. Edward Nevius, Ph.D.

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/s/

S. Edward Nevius

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BIOMETRICS

Comments on 7/18/01 statistical review by Sue-Jane Wang and 7/18/01 se
condary review by Thomas Permutt.

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Statistical Review and Evaluation

CLINICAL STUDIES

(SECONDARY REVIEW)

NDA 21-324

Name of drug: Entocort (budesonide modified-release) capsules

Applicant: Astra Zeneca

Indication: Crohn's disease

Project manager: Melodi McNeil

Medical officer: Ruyi He, M.D.

Classification: 3P

Dates: received 24 January 2001; user fee goal (6 months) 24 July 2001

Primary statistical reviewer: Sue-Jane Wang, Ph.D.

Secondary statistical reviewer: Thomas Permutt

INTRODUCTION

Crohn's disease is an inflammation of the gut, especially the ileum and colon. Budesonide is a glucocorticosteroid used as an anti-inflammatory drug in various conditions by various routes of administration. Entocort is an encapsulated oral dosage form meant to pass without release through the stomach and to be released in the intestines, with local activity there and relatively poor systemic absorption. It is therefore hoped that an anti-inflammatory effect may be seen in the intestines with less of the general toxicity of corticosteroids.

Sue-Jane Wang, Ph.D. has written a primary statistical review of this application. The primary review raises valid concerns related to the interpretation of the results of the clinical studies. Dr. Wang and I, however, evaluate the evidence of efficacy differently in view of those concerns.

Evidence regarding efficacy comes from five trials, summarized in the table below (Wang, p. 29). Dr. Wang distinguishes two of them (3001 and 3027) as statistically significant, but raises questions about the reliability of these results because of a substantial number of dropouts, unequally distributed between treatment groups. While the problem of dropouts is an important one in general, I do not think it should strongly affect the conclusions to be drawn from these two trials. In addition, I think two of the other three studies (3002 and 3013) may be seen, depending on medical judgment, as providing considerable additional evidence of efficacy, and the fifth study (3025) takes nothing away. Taking the five studies together, I think there is substantial evidence that Entocort was effective in treating Crohn's disease, but it may well have been less effective than prednisolone.

Primary efficacy outcome: remission rate at 8-weeks (% of patients who had CDAI* ≤ 150)

Study (ITT)§	Sample size estimation	Placebo	(3mg) 1.5mg bid Entocort	(9mg) 4.5mg bid Entocort	9mg qd Entocort	(15mg) 7.5mg bid Entocort	2g bid mesalamine	40mg qd prednisolone
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08-3027	P<.28 T=.5 Ni=85	NA	NA	NA	68% (63/93) p=0.0002	NA	42% (37/89)	NA
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C: active control remission rate, prednisolone or mesalamine

T: treatment (budesonide) remission rate, p: placebo remission rate

§ Reviewer's evaluation (based on all randomized patients)

*: overall χ^2 test, (sig): indicated a statistical significance at 0.05 level (n.s.): indicated a non-significance

In this secondary review, I discuss two areas where my perspective appears to differ somewhat from Dr. Wang's: first, the interpretation of data from studies with many dropouts; and second, the interpretation of the comparative studies to prednisolone. I then briefly comment on each of the five studies in the light of these differences and summarize the conclusions that I draw from them.

DROPOUTS

Many patients failed to complete the course of treatment in study 3001, in which there was a statistically significant difference between Entocort 4.5 mg b.i.d. and placebo. There were more dropouts from the placebo group than from the Entocort group. In study 3025, in which there were fewer dropouts, the differences among the three treatments (placebo, Entocort 4.5 mg b.i.d, and Entocort 9 mg q.d.) were not statistically significant. The primary statistical review also raises the problem of dropouts in connection with study 3027, in which Entocort 9 mg q.d. was statistically significantly better than mesalamine 2 g b.i.d.

In general, the problem of dropouts from randomized trials is a serious one. It is not just that the numbers of observations are reduced. Rather, it is that patients who drop out from the placebo arm may be systematically different from those who drop out from an active arm. Thus, comparisons between arms based on the patients who remain are not comparisons of groups balanced by randomization, but comparisons of groups partly selected during treatment, in a way that may be affected differently by the different treatments.

Nonetheless, I do not believe that this problem should much affect the interpretation of the results of the trials in this application. The reason is that a large majority of the dropouts

were for lack of efficacy, and that patients who dropped out were included in the analysis in an appropriately conservative way.

In study 3001, for example, according to Dr. He's review, 38 patients out of 66 in the placebo group dropped out, and 32 of them were for "disease deterioration." In the budesonide 9 mg group, 19 of 61 patients dropped out, and 16 were for "disease deterioration." As the primary efficacy outcome was binary—success or failure of treatment at 8 weeks—these patients were in a sense not lost to follow-up at all. Rather, they were followed to an outcome, namely a deterioration in their condition severe enough to warrant discontinuation of therapy. The most appropriate way to analyze such cases would be simply to count them as failures. The binary endpoint would then be a kind of composite one: patients would be successes if they remained on treatment for 8 weeks, and were in remission at that time; they would be failures if they were not in remission at 8 weeks, or dropped out before then.

Unfortunately, the primary analysis was slightly more complicated than that, being based on "last observation carried forward." That is, patients had a score of success or failure ascribed to them at the last visit before discontinuation, and this score was carried forward to the primary endpoint of 8 weeks. It may be theoretically possible that a patient could be called a success at the last visit even though he or she dropped out because of failure of therapy, but I do not think this could have happened in many cases, if any. The primary analysis thus amounts approximately to the simple, binary analysis of the composite endpoint of remaining on treatment with success at 8 weeks. The difference in the proportion of successes between treatments, therefore, can confidently be attributed to the effect of the active drug, and not to the kind of bias discussed above.

It is true that we do not know what would have happened to patients who dropped out, if they had remained on treatment for 8 weeks. Some patients who dropped out and so were considered failures might have been in remission at eight weeks. I do not think it is essential to know this, however, to interpret the trial as having had a positive result. The endpoint, strictly speaking, was not remission at 8 weeks. Rather, it was the composite of remaining in treatment 8 weeks, with remission. There was, however, a statistically significant difference between treatments on this endpoint, which appears to have been ascertained without any substantial bias and which seems to me to be meaningful.

COMPARISON TO PREDNISOLONE

Entocort 9 mg q.d. was compared in two trials to prednisolone, a standard treatment for Crohn's disease. Remission rates at 8 weeks were 51 percent for Entocort and 64 percent for prednisolone in study 3002, and 60 percent for both treatments in study 3013. The primary statistical review gives 97.5% upper confidence bounds for the inferiority (if any) of Entocort to prednisolone as 27 percent for study 3001 and 18 percent for study 3013.

The question of what inference can be drawn from these studies is not entirely a statistical one, and the primary statistical review therefore declines to answer it. It depends on what is known about the natural history of Crohn's disease and its treatment with

prednisolone, as well as on how confidently that knowledge can be applied to the populations of patients in these trials.

What a statistician can confidently state is this: Entocort, if it was inferior to prednisolone in these populations, was inferior by no more than 27 percent, or 18 percent for study 3013 alone. If the spontaneous remission rates at 8 weeks without treatment might reasonably be expected to come within 27 percent of the remission rate with prednisolone, then study 3001 offers no substantial evidence that Entocort was better than nothing, and similarly for study 3013. If this possibility can reasonably be excluded, then these studies do offer evidence of the efficacy of Entocort. The critical judgment to be made here is a medical one.

As is suggested in the primary statistical review, it might have been advantageous for such a judgment to be made prospectively, at the time the protocol was written and reviewed. Possibly sponsors and reviewers could have reached agreement at that time on an acceptable margin of inferiority. The fact of not having done so may make the question more difficult to answer objectively at this stage. Nevertheless, the question remains the same, and there is no less information available to answer it now than there was then: Can an outcome as close to that with prednisolone as 27 percent (or 18 percent) confidently be ascribed to an effective agent, or is it at all likely that a result as favorable as this would have been seen with no treatment? Like Dr. Wang, I must decline to answer this question because it is a medical one. I hope, however, that I have helped to clarify what part of the question remains unanswered, and what part is clear from a statistical standpoint.

THE FIVE TRIALS

In study 3027, Entocort 9 mg q.d. was statistically significantly better than mesalamine, with 68 percent remission at 8 weeks compared to 42 percent. Mesalamine is not an approved drug for Crohn's disease, and there may be some doubt as to its effectiveness. Unless mesalamine is worse than nothing, however, a drug that is better than mesalamine must be effective. I believe the results of this trial can be taken at face value notwithstanding the issue of dropouts.

In study 3001, Entocort 4.5 mg b.i.d. was statistically significantly better than placebo, with 51 percent remission at 8 weeks compared to 20 percent. It would naturally have been preferable to have tested the regimen that it is proposed to recommend (9 mg q.d.). However, in the two studies in which the two 9 mg/d regimens were compared (3013 and 3025), the single and divided doses were not much different in 3025 and the single dose was better in 3013. Efficacy of the divided doses in study 3001, therefore, strongly suggests that 9 mg q.d. would also have been effective. Here again, I believe the results can be taken at face value notwithstanding the issue of dropouts.

Study 3025 failed to show a statistically significant effect by the primary analysis. This analysis was an inappropriately insensitive omnibus test for any differences among Entocort 9 mg q.d., Entocort 4.5 mg b.i.d., and placebo, whereas clearly the important contrast is between placebo on the one hand and the two Entocort regimes on the other. In fact, both

these regimens were substantially better than placebo numerically, and not much different from each other: 52 percent remission at 8 weeks for Entocort 4.5 mg b.i.d., 48 percent for Entocort 9 mg q.d., and 32 percent for placebo.

Although the primary analysis was not ideal, it would have been acceptable if it had succeeded. So, to prefer another analysis after the fact would raise questions of multiplicity. Study 3025 cannot therefore be said to add significantly to the findings of other studies. It is substantially consistent with them, however, and so does not take anything away, either.

Studies 3002 and 3013 compared Entocort to prednisolone. The remission rates in study 3002 at 8 weeks were 51 percent for Entocort 9 mg q.d. and 64 percent for prednisolone. In study 3013 they were 60 percent for Entocort 9 mg q.d., 41 percent for Entocort 4.5 mg b.i.d., and 60 percent for prednisolone. Upper confidence bounds for the inferiority (if any) of Entocort 9 mg q.d. to prednisolone were 27 percent for study 3002 and 18 percent for study 3013. Whether these two trials can be considered to provide evidence of efficacy depends on a medical judgment about the likely outcome with no treatment as compared to the observed outcome with prednisolone. If it could have been within 27 percent or 18 percent, then these trials do not show that Entocort was effective. If it could not, then they do.

Depending on the answer to this question, there are from two to four trials showing Entocort to be effective in procuring remission of Crohn's disease. It may have been less effective than prednisolone, but it also appears to have been somewhat less toxic.

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Thomas Permutt
7/3/01 03:56:07 PM
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S. Edward Nevius
7/18/01 02:36:27 PM
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See primary statistical review by Sue-Jane Wang issued 7/18/01 and my
additional comments to follow.

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**STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES**

NDA # 21-324
Drug Name: Entocort (budesonide modified-release) Capsules
Sponsor: AstraZeneca
Indication: Mild to moderate Crohn's disease affecting the ileum and/or the ascending colon
Review Documents: SAS data sets, its related submissions dated 03/01/01 and 04/06/01
Medical Team: Ruyi He, M.D. and Hugo Gallo-Torres M.D. (HFD180)

HIGHLIGHTS OF EFFICACY AND SAFETY EVALUATION

- A significantly higher percentage of responders (patients having a CDAI score ≤ 150 at 8 weeks) was observed in those patients treated with budesonide in trials with moderate (budesonide) to high (placebo or mesalamine) dropout rates (Study 08-3001 & Study 08-3027). Such a statistically significant effect for budesonide was not concluded in trials with low (budesonide) to moderate (placebo) dropout rates (Study 08-3025). It is not clear whether the differences in dropout rate contribute to the significant treatment difference in favor of budesonide in trials with moderate to high differential dropout rates, given that differential dropouts were more profound in those patients whose baseline CDAI score < 300 (milder) but less so in those with ≥ 300 (moderate) in Study #08-3027 and differential dropouts were mostly observed in female patients in Study #08-3001, but, low to moderate differential dropouts were consistent between the milder and the moderate subgroups in Study #08-3025.
- Two active controlled studies (08-3002 and 08-3013) were inadequately designed to show the new treatment (budesonide) is non-inferior to the active control (prednisolone) at 8 weeks of treatment. The observed 95% CI worst limit of (bud - pred) was -27% in Study 08-3002 and -18% in Study 08-3013. There was no pre-specified non-inferiority margin. It is difficult to post-hoc conclude objectively that budesonide is non-inferior to prednisolone by 8 weeks of treatment.
- A significantly superior safety performance for budesonide compared to prednisolone in terms of higher proportion of patients with normal p-cortisol and a similar or lower incidence of patients with GCS related side effect was observed in the two active controlled studies.
- Among the 7 "more common" adverse events that are GCS related, "moon face" is a more serious event. From these clinical trial experiences of 8 weeks treatment, incidence of "moon face" appeared to be smaller with budesonide 9mg (11%) than with prednisolone (37%); the difference -26% (95% CI: -34%, -17%). Such incidence appeared to be worse than that of placebo (4%); the difference 7% (95% CI: 2%, 12%), based on the data pooled from studies 3002, 3001, 3013 and 3025. "Acne" appeared to occur more often with prednisolone (23%) than with budesonide 9mg (15%); the difference 8% (95% CI: 0.4%, 16%). The latter was similar to placebo (13%); the difference 2% (95% CI: -6%, 9%). The incidences of other GCS related adverse events, "bruise easily", "swollen ankles", "skin striae", "hirsutism" and "buffalo hump" were similar among budesonide 9mg, prednisolone and placebo. Budesonide appeared to be less toxic than Prednisolone.

BACKGROUND

Crohn's disease is a chronic inflammatory bowel disorder of unknown etiology. Although any portion of the digestive tract from mouth to anus may be involved, the most commonly affected parts are the distal ileum and the colon (Inflammatory Bowel Disease by Podolsky DK in New England Journal Medicine, 1991; 325:928-937). AstraZeneca (the sponsor) has submitted a comprehensive clinical development program (including a total of five major completed phase IIB/III efficacy and safety trials in patients with active Crohn's disease; six completed, placebo-controlled, phase III efficacy and safety trials for long-term treatment of Crohn's disease; two completed, phase II and five completed, phase III uncontrolled studies in Crohn's disease; and 21 completed, phase I-IIA, clinical pharmacology studies) in support of Entocort (budesonide) controlled ileal release (CIR) capsules for treatment of mild to moderate Crohn's disease affecting the ileum and/or the ascending colon. This review pertains to the five major clinical studies.

There were two active controlled agents used in three well-controlled studies. According to the medical review team, mesalamine (Pentasa) was approved to treat ulcerative colitis but not Crohn's disease in Europe and was not approved to treat Crohn's disease in US. In contrast, prednisolone is a standard treatment for Crohn's disease. In US, prednisolone was approved for Crohn's disease in solution form but not in tablet form used in these active controlled trials.

In the NDA submission, the sponsor pointed out that Pentasa® (mesalamine) has shown that the response rate is at least numerically superior to placebo and was agreed upon between the FDA and the sponsor (5/25/2000 pre-NDA meeting) as a valid control for comparison. According to the sponsor report, "slow release formulations of mesalamine are often used as first-line treatment in mild to moderate active Crohn's disease, although results in controlled studies are contradictory. Study 08-3027 was the first study to compare oral formulations of budesonide and mesalamine in patients with Crohn's disease".

TRIAL SYNOPSIS WITH REVIEWER'S COMMENTS

#08-3002 "A controlled trial of oral budesonide and prednisolone in active ileocecal Crohn's disease"

STUDY

This was a multi-center (6 countries, 11 sites), randomized, double-blind, active controlled European study. Eligible patients (n=176) with baseline Crohn's Disease Activity Index (CDAI, see Appendix A) greater than or equal to 200 were randomized to receive budesonide CIR 9mg qd (n=88) or prednisolone (n=88) for a total of 10 weeks. In this study, the design excluded the run-in period. Patients treated with prednisolone started at 40mg qd in the 1st two weeks and were then gradually tapered to 5mg in the last week.

The baseline characteristics between the two treatment groups can be found in Appendix 1. In general, demographics were similar, mean age was 36 years (range: 18-85 years). Male:female ratio was about 4:6. The percent of patients with previous resection at baseline was slightly higher with budesonide (49%) than with prednisolone (36%).

The primary objective of the trial was to compare the efficacy defined by CDAI and the safety of budesonide CIR capsules with prednisolone in those patients with active Crohn's disease by 8 weeks of treatment. The protocol specified primary variable was rate of CDAI success, defined as a final CDAI-score of ≤ 150 (remission). Treatment benefit, defined as a decrease in CDAI of 100 units at the end of the study period, was also a clinical endpoint of interest in addition to its quantitative CDAI score change. A secondary objective was to study the effect of the two treatment regimens on the Harvey-Bradshaw index (see Appendix B).

Primary efficacy outcome: remission rate

The efficacy outcome evaluated by remission rate was summarized in the Table below. The primary comparison is the "at 8 weeks" time point.

The remission rates by time points, APT LVE analysis - Study 08-3002

Remission rates [†]	At 2-wk	At 4-wk	At 8-wk	At 10-wk
Prednisolone 40mg qd tapering to 5mg at wk-10	56% (48/86)	67% (58/86)	65% (56/86)	66% (57/86)
Budesonide 9mg qd (n=88)	45% (39/86)	40% (34/86)	52% (45/86)	53% (46/86)
Nominal p-value (χ^2 -test)	0.22	0.0004	0.12	0.12

[†] Extracted from the sponsor Table 14 of 008-025-233

Other important efficacy: Treatment benefit and Harvey-Bradshaw index

Results of Efficacy outcomes evaluated at 8 weeks and 10 week - Study 08-3002

Study 08-3002 [†]	Success rate [‡]		Harvey-Bradshaw Index decreases from baseline mean(sd)	
	8 weeks	10 weeks	8 weeks	10 weeks
Prednisolone 40mg qd tapering to 5mg at wk-10 (n=85)	73%	75%	5.4 (4.1)	5.2 (3.7)
Budesonide 9mg qd (n=86)	63%	60%	3.8 (3.3)	3.7 (3.4)
Nominal p-value (χ^2 -test)	0.21	0.056	0.004	0.006

[†] Extracted from the sponsor Table 14 of reports 008-025-233

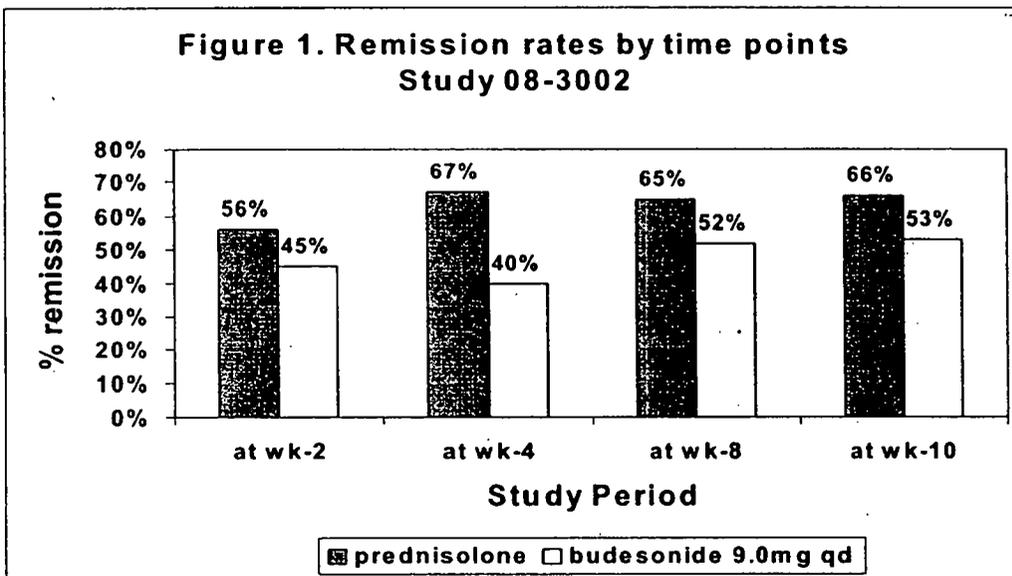
[‡] defined by treatment benefit

According to the protocol, success rate defined by treatment benefit was a pre-specified important clinical endpoint under the primary objective and Harvey-Bradshaw index (the larger the decrease from baseline indicates patients' better well-being) was the secondary

objective. When success was defined by treatment benefit, a numerically worse success rate was seen in the budesonide treated patients compared to prednisolone treated patients at 8 weeks and 10 weeks. For the secondary objective, a nominally significantly worse Harvey-Bradshaw index was observed with budesonide 9mg qd compared to prednisolone.

- Reviewer’s Evaluation and Comments

My analysis confirmed the above results. It appeared that the remission rate of prednisolone, the active controlled treatment, was peaked at 2 weeks of 67% and stable during the trial period of up to 10 weeks. In contrast, budesonide CIR 9mg qd was peaked at 8 weeks of 52% with similar rate of 53% by 10 weeks. A nominally significant more favorable effect with prednisolone was seen at wk-4. Numerically, budesonide 9mg qd was shown not superior to prednisolone by 8 weeks and 10 weeks. Numerically better remission rates were observed with prednisolone at all follow-up visits of 11% higher at 2 weeks, 27% higher at 4 weeks, 13% higher at 8 weeks, and 10 weeks, respectively. Graphical presentation of these remission rates by time points can be found in Figure 1.



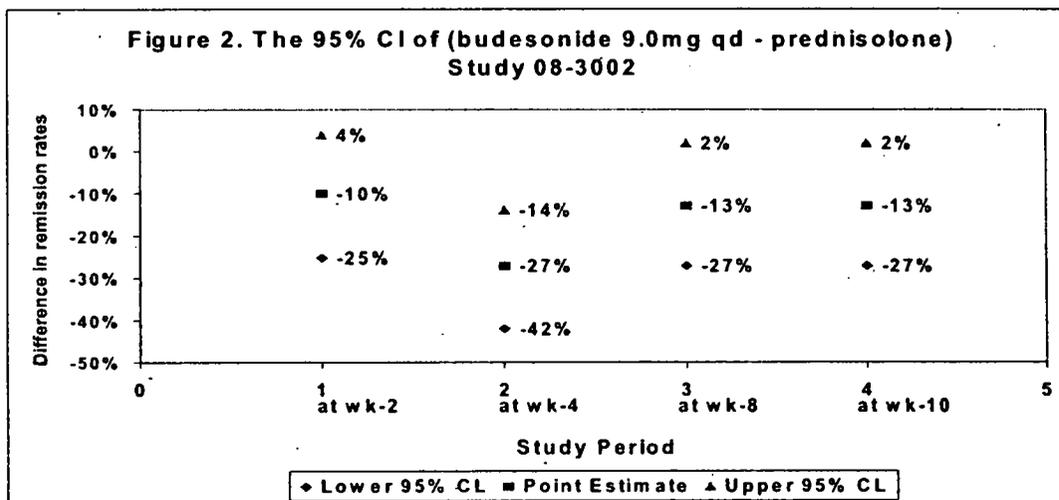
The sponsor’s assertion of equivalence or similarity because of not rejecting the null hypothesis of no treatment difference cannot be concluded from the data. The study was powered to show if budesonide would be inferior to prednisolone (at the design stage, remission rate was assumed 70% with prednisolone and 50% with budesonide). It needs to be emphasized that failing to reject the null hypothesis of “no treatment difference” can not in any way conclude that budesonide is similar or equivalent to prednisolone.

It seems reasonable to assume that prednisolone has a beneficial effect relative to placebo, although no such studies were provided. This assumption is based on the comparison of remission rates at 8 weeks of 65% with prednisolone versus those seen in the placebo controlled studies of 20% in Study 08-3001 (a Canadian placebo controlled

trial) and of 33% in Study 08-3025 (an US placebo controlled trial). Other than the different regions (US, Canada, Europe, South Africa, etc.) where these trials were conducted, all five well-controlled studies targeted similar patient populations (adult patients with active Crohn's disease defined by baseline CDAI score of at least 200). Some studies set the upper bound of CDAI to be 400 or 450.

Assuming that the effect of prednisolone relative to placebo is established, without a pre-specified non-inferiority margin, it is very difficult to evaluate objectively whether budesonide 9.0mg qd would not be much less effective than prednisolone. Such concerns were also brought up in the Points to Consider Document of Committee for Proprietary Medicinal Products (CPMP), the European Agency for the Evaluation of Medicinal Products Evaluation of Medicines for Human Use, 2000.

I calculated a conventional worst limit of the 2-sided 95% CI of budesonide effect relative to prednisolone (the active control treatment). The 95% interval estimates are provided in Figure 2. The results revealed that budesonide 9mg qd could be 27% less effective than prednisolone at 8 weeks and 10 weeks. The sponsor's assertion that "budesonide was at worst 13% less effective than prednisolone" is inappropriate since 13% was the point estimate which did not take into account the variability in the estimation. Had there been a prespecified non-inferiority margin, the worst estimate of 27% less effectiveness with budesonide relative to prednisolone would have been compared against the margin to assess non-inferiority. Nonetheless, the 27% difference is much larger than the often seen margins of 5% to 20%. Hence the study results can not lead one to assert that budesonide is non-inferior to prednisolone.



Comparable dropout rates

Eighty-two percent (72/88) of budesonide treated patients and 83% (73/88) of prednisolone treated patients completed the 10-week study. The percent of early discontinuation was similar, however, numerically more budesonide treated patients

(16%=14/86) withdrew from the study early due to therapeutic failure than prednisolone patients (10%=9/86).

Secondary efficacy outcomes

Time to remission: The sponsor's showed that budesonide treated patients had a significantly longer median time to remission (3.8 weeks) than that of prednisolone (3.3 weeks), $p=0.040$, suggesting a worse budesonide effect.

CDAI changes: The mean decrease in CDAI score was significantly larger in patients receiving prednisolone by 2 weeks, 8 weeks, 10 weeks ($p<0.008$) than that of budesonide, indicating a worse budesonide effect.

Subgroup analysis

The sponsor performed a few subgroup analyses. Across the gender subgroups, no apparent differences in the drug response were found. For patients' with ileal disease only versus both ileal and colonic involvement, prednisolone effect in terms of percent remission seemed to be driven by the subgroup of ileal disease only. Prednisolone effect seemed to be consistent across strata of baseline CDAI <300 vs. ≥ 300 and with respect to patients' previous resection status.

SAFETY: serious adverse events (SAE)

There was no pre-specified safety parameter. Using the safety outcome "p-cortisol (morning plasma cortisol concentration)", which was the pre-specified safety endpoint in the other active controlled study (Study 08-3013), the proportion of patients with values below the lower p-cortisol normal reference limit, i.e., 150 nmol/L, was significantly higher in the prednisolone group (76%=64/84) compared with that in the budesonide group (34%=28/83). The difference between the groups by eight weeks of treatment appeared to be highly significant (nominal $p<0.0001$), see the sponsor Table 21 of reports 008-025-240.

For the GCS associated side-effects, the sponsor reported that the proportions of patients with GCS-related side effects were nominally significantly less with budesonide qd (27%=24/88) than with prednisolone (49%=43/88), nominal p -value = 0.0043 (see the sponsor reports 008-025-218).

According to the sponsor, the adverse event profile did not differ to a great extent between the two groups. Most of the adverse events reported may be due to the underlying inflammatory disease, which is true also for the serious adverse events reported. Two discontinuations due to serious adverse events occurred in the prednisolone group (one bowel perforation and one enterocutaneous fistula) and none in the budesonide group.

SUMMARY OF REVIEWER'S EVALUATION AND COMMENTS

In this active controlled study, baseline characteristics between the budesonide 9mg qd and prednisolone seemed comparable. Early discontinuation rate also seemed comparable. However, numerically more budesonide patients withdrew early from the trial due to therapeutic failure (16% in budesonide and 10% in prednisolone). Budesonide 9mg qd was at least numerically inferior to prednisolone 40mg qd with respect to the remission rate at all visit weeks. At 8 weeks (primary efficacy endpoint), the point estimate of budesonide effect was 13% worse with the 95% confidence limit of 27% worse, as shown in Figure 5. Nominally, budesonide appeared to have a worse effect (nominal p-value < 0.05) in the secondary efficacy outcomes of longer time to remission, smaller CDAI change from baseline and worse Harvey Bradshaw index of QOL at wk-8.

The sponsor's assertion of equivalence or similarity because of not rejecting the null hypothesis of no treatment difference cannot be concluded. The study was powered to show if budesonide would be inferior to prednisolone (at the design stage, remission rate was assumed 70% with prednisolone and 50% with budesonide). It needs to be emphasized that failing to reject the null hypothesis of "no treatment difference" can not in any way conclude that budesonide is similar or equivalent to prednisolone.

For the efficacy evaluation, given that there was no pre-specified non-inferiority margin, a conventional worst limit of the 2-sided 95% CI of budesonide effect relative to prednisolone (the active control treatment) revealed that budesonide 9mg qd could be 27% less effective than prednisolone at 8 weeks and 10 weeks. The sponsor's assertion that "budesonide was at worst 13% less effective than prednisolone" is inappropriate. Had there been a prespecified non-inferiority margin, the worst estimate of 27% less effectiveness with budesonide relative to prednisolone would have been compared against the margin to assess non-inferiority. Nonetheless, the 27% difference is much larger than the often seen margins of 5% to 20%. Hence the study results cannot lead one to assert that budesonide is non-inferior to prednisolone.

For safety evaluation, the sponsor did not pre-specify the primary safety outcome. This reviewer used the safety endpoint "p-cortisol (morning plasma cortisol concentration)", pre-specified for Study 08-3013 (same active controlled design) for evaluation. The proportion of patients with normal p-cortisol by 8 weeks of treatment was higher for budesonide (66%) than that for prednisolone (24%). In addition, the incidence of GCS associated side-effects seemed to be smaller for budesonide qd (27%) than prednisolone (49%).

In summary, by 8 weeks of treatments, this study seemed to suggest an inferior efficacy for budesonide 9mg qd relative to prednisolone. In contrast, the safety in terms of proportion of patients with normal p-cortisol and incidence of patients with GCS related side effect seemed to be better for budesonide 9mg qd than prednisolone.

#08-3001 “Oral budesonide in Crohn’s disease: a dose-finding placebo-controlled study”

This was a multi-center (27 centers), randomized, double-blind, placebo-controlled, dose-ranging **Canadian** study. After 1-week run-in period of baseline CDAI (see Appendix A) establishment, eligible patients having a baseline CDAI score of ≥ 200 (n = 258) were randomized and stratified by previous use of gluco-corticosteroids (GCS) to receive placebo (n= 66), budesonide CIR 3mg (1.5mg bid) (n=67), 9mg (4.5mg bid) (n=61), or 15mg (7.5mg bid) (n=64) for 8 weeks followed by a tapering period of 2-4 weeks. **There was no once daily regimen.**

The baseline characteristics did not show considerable differences among the four treatment groups (Appendix 1). The mean age of Canadian patients at baseline was 34 years (ranges 17-66 years). Male: Female ratio was about 4:6. Baseline mean CDAI was 291 (ranges: 119-518), mean disease duration was 7.8 years (ranges: 0-40 years), mean current exacerbation was 4.2 months (ranges: 0-38 months), 46% of patients had previous resection, 43% had GCS taken previously, 84% had ileal only disease, and 50% were current smokers.

In this study, the percents of patients who discontinued from the study were 58% in placebo, 54% in 3mg budesonide, 31% in 9mg budesonide, and 41% in 15mg budesonide, respectively. It appeared that the primary reason of treatment discontinuation was disease deterioration or no improvement, i.e., treatment failure (see Appendix C for definition). Such failure rates were 48% in placebo, 45% in 3mg budesonide, 26% in 9mg budesonide, and 28% in 15mg budesonide. In general, 3mg budesonide seemed similar to that of placebo and 9mg budesonide similar to that of 15mg budesonide in terms of discontinuation rate and treatment failure rate.

Study 08-3001 [†]	PBO	3mg (1.5mg bid) budesonide	9mg (4.5mg bid) budesonide	15mg (7.5mg bid) budesonide
Sample size	66	67	61	64
% Dropout	58%	54%	31%	41%
% Dropout and had disease deterioration	48%	45%	26%	28%

[†] Extracted from Table 3 of sponsor 008-008-082

The primary objective of the trial was to compare the efficacy defined by CDAI and the safety of budesonide CIR capsules with placebo in those patients with active Crohn’s disease (baseline CDAI ≥ 200). Finding the optimal dose among the three different dose levels of budesonide was the secondary objective. The remission rate, the primary efficacy variable, was defined as percent of patients having a CDAI value of 150 or below. The CDAI is based on signs and symptoms recorded by the patient on a daily basis in the patient diary card, clinical examination and the patient’s hematocrit values recorded by the examiner, see Appendix A.

Primary efficacy outcome: remission rate

Remission rates across the 4 groups by time points, APT LVE Analysis, Study 08-3001[†]

Remission rates [‡]	At 2-week	At 4-week	At 8-week	At 10-week
Placebo (n=64)	11%	17%	20%	16%
3mg (1.5mg bid) (n=64)	10%	25%	33%	27%
9mg (4.5mg bid) (n=61)	33%	36%	51%	46%
15mg (7.5mg bid) (n=61)	28%	41%	43%	43%
Overall χ^2 -test			p=0.0026	

[†] Extracted from the sponsor's reports 008-008-0122

[‡] Excluded patients without baseline CDAI measurement

- Reviewer's Evaluation and Comments

My analysis confirmed the results of the primary efficacy analysis. The remission rates in 9mg and 15mg budesonide groups were larger than that of placebo at all visits (about 2 to 3 times higher remission rates), as shown in the above table. The sponsor stated that the comparison of all patients treated with last value extended (APT, LVE) differed from the per-protocol comparison when the last visit extended principle was not applied. It is noted that APT excluded patients without post baseline measurements.

I performed several sensitivity analyses to explore whether the significant finding on the remission rates still held after taking into account different dropout rates between the placebo/low dose and the moderate/high dose groups. It appeared that the remission was primarily observed in those patients who completed the study. Using the sponsor data set submitted on 04/06/01, there were 0 patient (0%) in placebo, 2 patients (6%) in 3mg group, 2 patients (11%) in 9mg group, and 2 patients (9%) in the 15mg group, who withdrew early from the study and had a remission response.

If the dropout cohort was used, the analysis showed that no responder was found among those who only stayed in the study for 2 weeks. Responders were generally those who completed the study. Had the dropout differential not contributed to the treatment difference (i.e., non-informative dropouts, namely, not affecting the response), the sensitivity analysis stratifying by patient's completion status would have demonstrated the results consistent with the results of the primary analysis. By such stratification, the statistical significance p=0.0026 for the primary efficacy endpoint changed to a p= 0.098. This is quite a change, at least suggesting that the results of the primary analysis do not seem robust. The dropouts are influential to statistical significance. Differential dropout was primarily observed in female patients. Given substantially higher dropout rates observed in the placebo/low dose groups and much lower dropout rates in the median/high dose groups, it raised an important question. Would the budesonide effect have been concluded had the dropout rates been benign or much lower in the treatment groups? That is, would there be a bias in favor of budesonide due to differential

dropouts? That is, more placebo patients who dropped out early would not be evaluated at 8 weeks for being a responder or not, especially, CDAI score for patients with Crohn's disease fluctuates over the treatment period, per discussion with Dr. He. A probable alternative interpretation is that the effect of budesonide caused the differential dropouts, which made those in whom the treatment is effective not withdraw from the study early. However, if statistical significance does not remain under differential and substantial dropout, interpretation about the efficacy of budesonide 9mg qd, in my view, needs to be cautious.

Secondary efficacy outcomes

Time to remission: The sponsor's time to remission analysis showed that remission was achieved by 60%, 67%, and 45% of the patients in the budesonide 15mg, 9mg, and 3mg groups, respectively, compared to 38% in the placebo group, with an overall $p=0.021$, Chi-square test.

CDAI changes: The mean CDAI scores decreased more in the budesonide 9mg and 15mg groups than in the placebo. The differences were statistically significant at all follow-up visits in the APT or the per-protocol analyses with and without using the LVE principle.

In addition, the sponsor analysis of the change in each of the eight CDAI variables suggested that the components showed either a budesonide effect (# of liquid or very soft stools and general well-being, abdominal pain, weight loss) or no significant difference (# of extra-intestinal complication, intake of anti-diarrhoeals, presence of abdominal mass or hematocrit) when compared to placebo.

QOL: the sponsor reported that the largest increase in the total score was observed in the budesonide 9mg group and that this difference by 8 weeks of treatment was statistically significant in comparison with all the other treatment groups (nominal $p < 0.0001$, overall χ^2 test).

Subgroup analysis

The sponsor performed a number of subgroup analyses on remission rate, viz., by previous use of GCS, by gender, location of ileal only vs. colonic involvement, by previous bowel resection (Yes/No), and by smoking status. The sponsor stated that these analyses failed to reveal any baseline characteristic that influenced the response to treatment. I summarized the results by gender in the Table below, a required subgroup analysis.

Reviewer Comments: It seems that the remission rate was similar among the three dosage budesonide groups in male patients, but the effect of budesonide appeared to be most profound numerically with 9mg budesonide in female patients. It turned out a higher percent of female placebo patients were dropped out compared to those female patients treated with budesonide.

The CDAI remission rates by 8 weeks by sex – Study 08-3001[†]

CDAI remission rates by 8 weeks	Placebo	Bud 3mg	Bud 9mg	Bud 15mg
Male	33% (8/24)	47%(9/19)	43%(10/23)	52% (14/27)
Female	13% (5/40)	27% (12/45)	55% (21/38)	35% (12/34)
Overall	20% (13/64)	33% (21/64)	51% (31/61)	43% (26/61)

[†] Extracted from the sponsor Table 19 of 008-008-126

SAFETY: Gluco-corticosteroid (GCS) related side-effects

Study 08-3001 [†]	Placebo	Bud 3mg	Bud 9mg	Bud 15mg
Side effects relating to use of GCS	26%	15%	26%	38%

[†] Extracted from 008-008-095

The sponsor reported that the proportions of patients with side-effects, defined by the investigator as related to use of GCS, were not significantly different in the budesonide 3mg (15%) and 9mg (26%) groups in comparison to placebo (26%). However, a higher frequency (38%) was observed in the budesonide 15mg group.

SUMMARY OF REVIEWER'S EVALUATION AND COMMENTS

The baseline characteristics among the four treatment groups did not show considerable differences in this Canadian placebo controlled trial. Budesonide CIR 9mg (p=0.0004) and 15mg (p=0.0087) were shown to be superior to placebo on the remission rate by 8 weeks of treatment, the primary efficacy outcome. The effect appeared to be more profound in female patients for the 9mg (4.5mg bid) budesonide. Secondary efficacy outcomes of time to remission, CDAI change from baseline, QOL all provided supportive findings.

Patients who achieved remission at 8 weeks were primarily the completers. Hence, the significant budesonide effect on remission rate could be attributed to a smaller remission rate potentially underestimated by the APT LVE analysis in the placebo group due to a high dropout rate. There was another placebo-controlled study for budesonide 4.5mg bid and 9.0mg qd conducted in the US that can be used for reference. The US trial had dropout rates only half that of this study and the rates were differential between the placebo and the budesonide groups. The apparent finding of a significant effect with budesonide 4.5mg bid and 7.5mg bid in the Canada study was not replicated in the US study. The remission rate of the placebo group was 11% (2 weeks) to 20% (8 weeks) in the Canadian trial with moderate to high dropouts, and 13% (2 weeks) to 46% (10 weeks) in the US trial with much lower dropouts. A question is in order. Would a significant budesonide effect still have been shown had this Canada study had a better follow-up with a comparable dropout rate as that of the US trial?

#08-3013 "Oral budesonide once and twice daily versus oral prednisolone once daily in active Crohn's disease"

BACKGROUND

In this trial, prednisolone is the active control comparator. According to the medical review team, prednisolone is a standard treatment for Crohn's disease. In US, prednisolone was approved for Crohn's disease in solution form but not in tablet form used in this trial.

STUDY

This was a multi-center (9 countries, 24 sites), randomized, double-blind, active controlled European study. After 3-7 days of run-in period, eligible patients (n=178) having a baseline CDAI \geq 200 were randomized to receive prednisolone 40mg (n=59 including one patient never treated), budesonide CIR 4.5mg bid (n=61) or budesonide CIR 9mg once daily (om) (n=58) for a total of 12 weeks, including a 4-week tapering period. Patients treated with Prednisolone started at 40mg and tapered to 30mg after two weeks and then gradually tapered to 5mg after 9-weeks. Budesonide CIR was tapered to 6mg after 8 weeks and to 3mg after 10 weeks. The follow-up visits were after 2, 4, 8, and 12 weeks of treatment.

The baseline characteristics among the three treatment groups can be found in Appendix 3. In general, demographics were similar, mean age was 37 years (range: 17-71 years). M:F ratio was about 4:6. Duration of current exacerbation was slightly longer in the budesonide bid group (7.6 months) compared to om group (4.0 months) and prednisolone group (5.5 months). Disease duration was slightly shorter in the prednisolone group.

The primary objective of the trial was to compare the efficacy defined by CDAI and the safety defined by p-cortisol (morning plasma cortisol concentration) of budesonide CIR capsules either om or bid with prednisolone in patients with active Crohn's disease (defined as baseline CDAI \geq 200). The protocol specified primary variable was CDAI, defined as a final CDAI-score of \leq 150 (remission).

Primary efficacy outcome: remission rate

Remission rates across the 3 groups by time points, APT LVE analysis - Study 08-3013

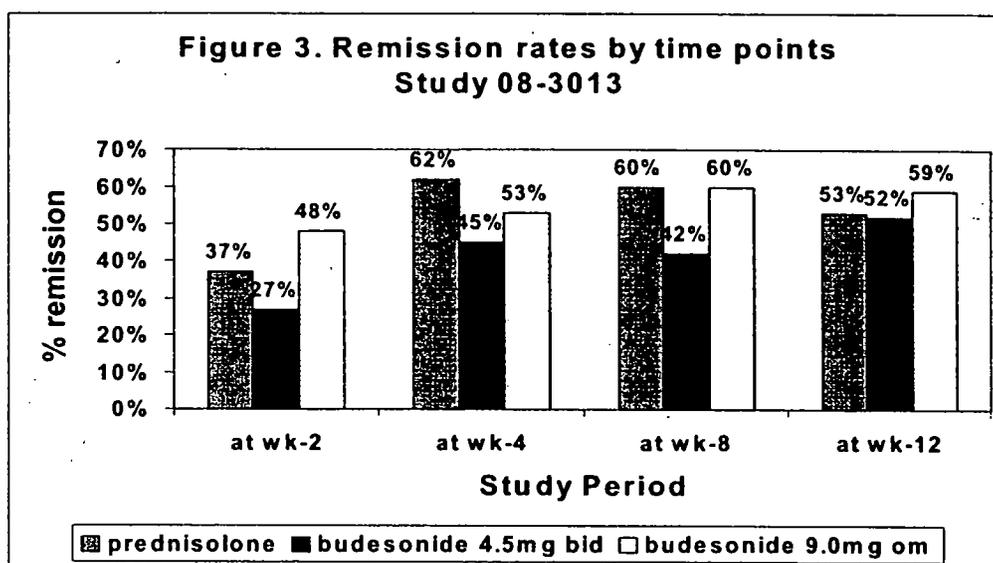
Remission rates [†]	At 2-wk	At 4-wk	At 8-wk	At 12-wk
Prednisolone 40mg qd tapering to 5mg at wk-10 (n=58)	37% (21/58)	62% (36/58)	60% (35/58)	53% (31/58)
Budesonide 4.5mg bid (n=61)	27% (16/60)	45% (27/60)	42% (25/60)	52% (31/60)
Budesonide 9mg qd (n=58)	48% (28/58)	53% (31/58)	60% (35/58)	59% (34/58)
Overall χ^2 -test	0.052	0.18	0.062	0.73

[†] Extracted from the sponsor Table 11a of 008-036-185

An overall test of any treatment differences among the three treated groups in terms of remission rate at 8 weeks, the primary efficacy outcome, did not conclude a significant difference ($p=0.062$ based in overall χ^2 -test).

- Reviewer's Evaluation and Comments

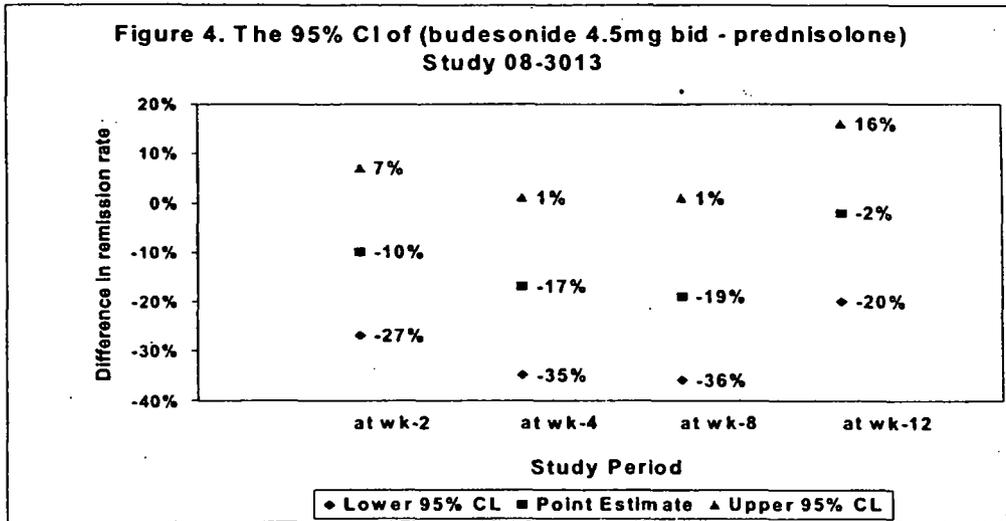
My analysis confirmed the results of the APT analysis. According to the sponsor, the per-protocol analysis showed statistical significance (overall test, $p=0.020$), suggesting a worse budesonide 4.5mg bid effect when compared to the control agent prednisolone, which was not quite supported by the APT analysis (overall test, $p=0.062$). Graphical presentation of the remission rates comparison is depicted in Figure 3.



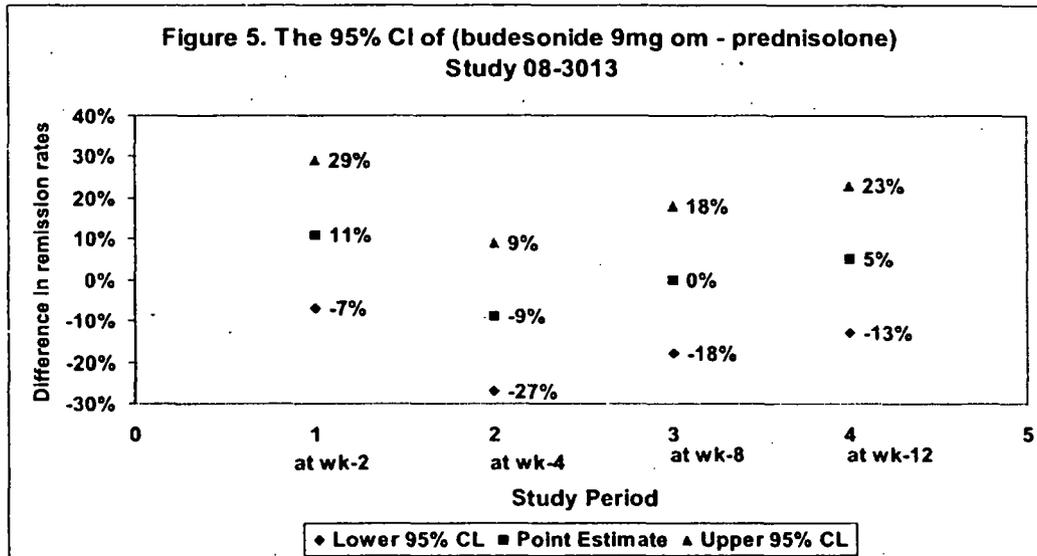
Based on the protocol, efficacy would be evaluated based on 3-groups comparison and safety would be based on 2-treatments (budesonide vs. prednisolone) comparison. The study was powered to show if budesonide would be inferior to prednisolone (at the design stage, remission rate was assumed 70% with prednisolone and 40% with budesonide). It needs to be emphasized that failing to reject the null hypothesis of no treatment difference does not in any way conclude that budesonide is similar or equivalent to prednisolone. I provided a 95% CI for the pairwise comparison of budesonide 4.5mg bid vs. prednisolone (shown in Figure 2) and of budesonide 9.0mg om vs. prednisolone (shown in Figure 3). The pre-specified time point for primary efficacy comparison is at 8 weeks.

For the comparison between budesonide 4.5mg bid and prednisolone (see Figure 4), the point estimates of the difference in remission rate were all negative suggesting a worse remission rate in budesonide 4.5mg bid treated patients. The corresponding worst 95% confidence limits were -27% at 2 weeks, -35% at 4 week, -36% at 8 weeks and -20% at

12 weeks. Note that the primary efficacy evaluation is the comparison at 8 weeks of the trial period. Between 8 weeks and 12 weeks is the tapering period of the treatments.



For the comparison between budesonide 9.0mg om and prednisolone (see Figure 5), except at 2 weeks, the point estimates of the difference in remission rate were either negative or close to 0%. The corresponding worst 95% confidence limits were -27% at 4 weeks, -18% at 8 weeks and -13% at 12 weeks, respectively.



Without a pre-specified non-inferiority margin, it is very difficult to objectively evaluate that budesonide is not inferior to prednisolone. In fact, the data suggested, though not

quite statistically significantly, that budesonide 4.5 mg bid was less effective than prednisolone.

Comparable dropout rates

84% (49/58) of the budesonide CIR 9mg om treated patient, 75% (46/61) of the 4.5mg bid treated patients and 78% (46/59) of the prednisolone treated patients completed the 12-week study. Note that one patient in the prednisolone arm was never treated. The percentages of early discontinuation were similar. Sixteen percent of budesonide treated patients (6/58 and 10/61) and 12% of prednisolone treated patients (7/58) withdrew early due to therapeutic failure defined as disease deterioration or no improvement.

Secondary efficacy outcomes

Time to remission: The sponsor's time to remission analysis failed to show a difference among the three arms. The median time to remission was 17 days for the budesonide om, 28 days for the prednisolone group, and 55 days for the budesonide bid, $p=0.15$, log-rank test and $p=0.1068$ with Generalized Wilcoxon test.

CDAI changes: The decrease in mean CDAI score was more in the budesonide om and prednisolone group than that in the budesonide bid group. The sponsor reported that the difference in reduction in CDAI score was not statistically significant by eight weeks ($p=0.093$), although the difference at 2 weeks was borderline significant, $p=0.050$.

Subgroup analysis

The sponsor performed a few subgroup analyses. Remission rates did not differ significantly between the male and female patients. There appeared to be a statistically significant interaction between treatment and the presence/absence of previous resection ($p=0.030$). The remission rate appeared to be more than twofold higher in not resected patients.

Reviewer's Comments:

The CDAI remission rates by 8 weeks by sex, APT LVE – Study 08-3013

CDAI remission rates by 8 weeks [†]	prednisolone (n=58)	4.5mg bid budesonide (n=60)	9.0mg om budesonide (n=58)
Male	61% (14/23)	48% (13/27)	48% (10/21)
Female	60% (21/35)	36% (12/33)	68% (25/37)
Overall	60% (35/58)	42% (25/60)	60% (35/58)

[†] Extracted from the sponsor Table 15c of 008-036-192

I summarized the required subgroup analysis results by gender. Both male and female prednisolone treated patients had an average remission rate of about 60%. In contrast, the remission rate was about twice in the om budesonide group (68%) compared to the bid budesonide group (36%) in female patients, and similar in male patients (48% each).

SAFETY

The primary safety outcome was p-cortisol (morning plasma cortisol concentration). According to the sponsor, the proportion of patients with p-cortisol values below the lower normal reference limit, i.e., 150 nmol/L, was significantly higher in the prednisolone group compared to both budesonide groups. The difference between the groups by eight weeks was highly significant ($p < 0.0001$). The results showed that by eight weeks 76% of the prednisolone treated patients had p-cortisol values below 150 nmol/L, compared with 41% in the budesonide om group ($p = 0.0004$) and with 36% in the budesonide bid group ($p < 0.0001$). The sponsor stated that there was no significant difference between the two budesonide groups, see the sponsor Table 14b of reports 008-036-189. When the 4.5mg bid and 9.0mg om budesonide groups were combined, the proportion of patients with p-cortisol values below the lower normal reference limits was 39% ($=42/109$). The significantly higher proportion with prednisolone ($76\% = 41/54$) than with budesonide (39%) was still observed, nominal p-value < 0.0001 .

The sponsor reported that the proportions of patients with GCS-related side effects were not significantly different between the three groups: 50% in the budesonide om group, 44% in the budesonide bid group, and 59% in the prednisolone group.

SUMMARY OF REVIEWER'S EVALUATION AND COMMENTS

In this study, demographics among the three groups were similar. Small to moderate early discontinuation rates of 16% to 25% were reported in the three treatment groups.

Although the sponsor's overall χ^2 test on the primary efficacy outcome of remission rate at 8 weeks failed to conclude a difference among the prednisolone, 4.5mg bid budesonide, and 9.0mg om budesonide, this does not in any way conclude that budesonide is similar to or equivalent to prednisolone (the study powered to show an inferior budesonide effect but no non-inferiority margin pre-specified).

It is difficult to maintain objectivity and do a post-hoc assessment of whether the budesonide 9.0mg once daily effect is not much less than the prednisolone effect because the prednisolone effect could not be properly estimated from these active controlled trials without a concurrent placebo and non-inferiority margin was not pre-specified. Assume that prednisolone effect exists (this seems reasonable because prednisolone treated patients showed a remission rate of 62% at 4 weeks, 60% at 8 weeks, which is nominally significantly higher than 20% of placebo in Study 08-3001 and 33% of placebo in Study 08-3025). From my evaluation by the 95% confidence interval in Figure 2 and Figure 3, it appeared that the estimated 4.5mg bid budesonide remission rate at 8 weeks could be less than that of prednisolone by 36%. The estimated 9.0mg om budesonide remission rate at 8 weeks can be less than that of prednisolone by 18%. Without a pre-specified non-inferiority margin, it is very difficult to assert that the effect of budesonide 9.0mg once daily is not much less than that of prednisolone objectively.

From the safety perspective, the primary safety parameter of p-cortisol measured by continuous scale ($p=0.0035$, primarily in the comparison of budesonide bid with prednisolone) or by percent of patients having a value below the lower normal reference limit ($p<0.0001$), appeared to show a significant difference in favor of budesonide compared to prednisolone. These results can be found in the sponsor Table 14b of 008-036-189. In addition, the percent of patients with GCS related side effects was similar among the budesonide 4.5mg bid (44%), budesonide 9.0mg om (50%), and prednisolone (59%) groups.

In summary, Study 08-3013 presented a case in which the efficacy of budesonide 9.0mg once daily relative to the active control comparator of prednisolone cannot be clearly shown. However, for safety measured by a pre-defined outcome of morning plasma cortisol concentration, budesonide 9.0mg once daily gave a statistically significantly higher proportion of patients with normal plasma corticoid levels (≥ 150 nmol/L) by 8 weeks than prednisolone and had comparable GCS related side effects. These proportions are 64% in 4.5mg bid group, 59% in 9.0 om group, and 34% in prednisolone group, respectively.

#08-3027 "Entocort capsules (budesonide CIR) versus oral SR Pentasa (mesalamine), a controlled multicentre trial in patients with active Crohn's disease"

BACKGROUND

Mesalamine (Pentasa), not placebo, is the active control arm for this study. According to the medical review team, mesalamine was approved to treat ulcerative colitis but not Crohn's disease in Europe. Mesalamine was not approved to treat Crohn's disease in US.

Reviewer's Comments: In other words, although mesalamine is the control comparator in this study, it is not indicated for the intended patient population in US or in Europe.

STUDY

This was a multi-center (12 countries: Australia, Austria, Denmark, France, Greece, Ireland, Italy, Norway, Portugal, South Africa, Spain, UK with 25 sites), randomized, double-blind; active controlled study. Eligible patients having a baseline $200 \leq \text{CDAI} \leq 400$ ($n=182$) were randomized to receive budesonide CIR 9mg qd ($n=93$) or oral slow release mesalamine 2g bid ($n=89$) for 16 weeks. In this study, the design excluded the run-in period and the tapering period.

The baseline characteristics did not show considerable differences between the two treatment groups (Appendix 4). Budesonide treated patients were slightly older (median age of 34 years versus 31 years with mesalamine), slightly lower baseline median CDAI (266 versus 278 with mesalamine), slightly longer median disease duration (6.1 years vs. 4.6 years with mesalamine). The median current exacerbation was 1.9 months (ranges: 0-

53 months) and percent of patients with previous resection was 40%. Male: Female ratio was about 3:7. Disease location was primarily in ilea.

The primary objective of the trial was to compare the efficacy defined by CDAI and the safety of budesonide CIR capsules with Pentasa (mesalamine) slow release tablets in those patients with active Crohn's disease with baseline CDAI score between 200 and 400. A secondary objective was to compare the safety by measuring quantitative changes in the adverse event profile.

Primary efficacy outcome: remission rate

Remission rates between budesonide and mesalamine APT LVE analysis- Study 08-3027[†]

Remission rates [‡]	At 2-wk	At 4-wk	At 8-wk	At 12-wk	At 16-wk
Mesalamine 2g bid (n=89)	37% (31/83)	39% (32/83)	45% (37/83)	42% (35/83)	36% (30/83)
Budesonide 9mg qd (n=93)	44% (39/89)	48% (44/91)	69% (63/91)	64% (58/91)	62% (56/91)
Nominal p-value (χ^2 -test)	0.39	0.19	0.001	0.0044	0.0008

[†] extracted from the sponsor's reports 008-068-074

[‡] Excluded patients without baseline CDAI measurement

- Reviewer's Evaluation and Comments

It appeared that effect of mesalamine 2g SR, the controlled treatment, was peaked at 8 weeks of 45% remission rate and was decreased to 36% at 16 weeks. In contrast, effect of budesonide CIR 9mg qd was peaked at 8 weeks of 69% and was only slightly decreased to 62% at 16 weeks. Significant budesonide effect was seen at wk-8, wk-12, and wk-16. I have verified the above results.

Sensitivity analysis due to differential dropout rates

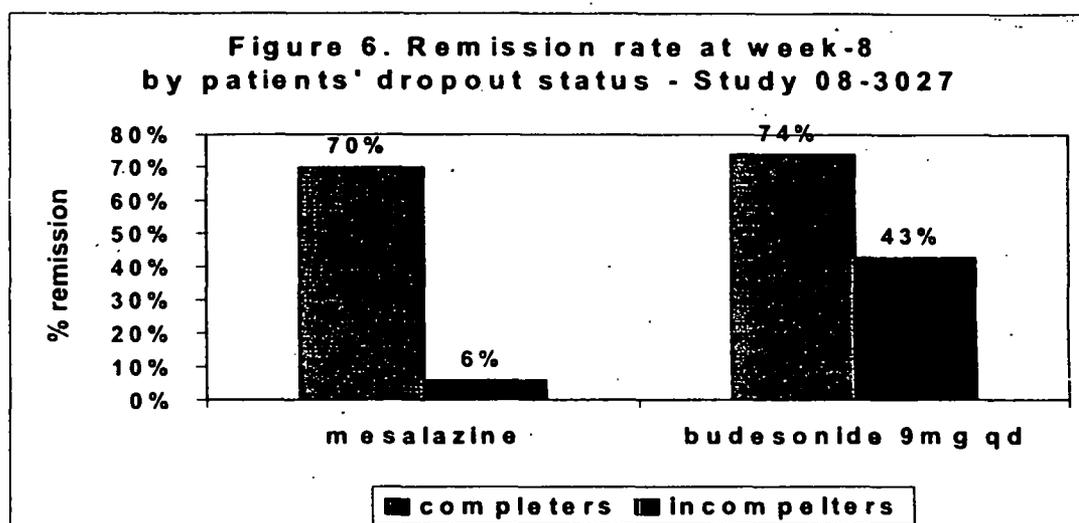
The last known CDAI value for patient #2302 was 163 at visit 3. This patient did not meet the criterion of achieving the remission. When this patient was classified as a failure, statistical significance still maintained. I have performed the intent-to-treat analysis including those patients without post baseline measurements and counted them as failures. Significantly higher remission rate in budesonide treated patients than those of mesalamine treated patients was consistent with the APT analysis. According to the sponsor, the per-protocol analysis showed similar results to those of the all patients treated analysis.

In this study, 83% (77/93) of budesonide treated patients completed the 16-week study and only 56% (50/89) with mesalamine treated patients. The percent of patients early discontinued the study with mesalamine (44%) was 2.6 times of that with budesonide (17%). Majority of the reasons were serious adverse event (SAE, 9% vs. 3%) and treatment failure (30% vs. 11%).

Study 08-3027 [†]	# patients	Completion(%)	Dropout(%)	SAE	Treatment failure(%)
Mesalamine 2g bid	89	56%	44%	9%	30%
Budesonide 9mg qd	93	83%	17%	3%	11%

[†] Extracted from Table 3 of sponsor 008-068-050

If dropouts are noninformative (i.e., not affecting the response), then the sensitivity analysis stratifying on patient's completion status might help understand the pattern of the remission rates between the completers (those who completed the study) and incompleters (those who discontinued the study earlier than the planned trial duration). It turned out that among those patients who completed the study, the remission rates were very similar between mesalamine treated and budesonide 9mg qd treated patients. The observed treatment difference in terms of remission rate at 8 weeks was primarily attributed to patients who discontinued the study early. The result is shown in the Figure 6 below. It is noted that differential dropout was more profound in patients whose baseline CDAI score was less than 300 (milder disease status) but less so in those with baseline CDAI greater than or equal to 300 (more moderate disease status).



Secondary efficacy outcomes

Therapeutic benefit rate: The sponsor presented the therapeutic benefit rates, defined as experiencing therapeutic benefit, and showed that budesonide treated patients (77%, 75%, 71%) had significantly higher rates when compared with the mesalamine group (55%, 54%, 50%) at 8 weeks, 12 weeks, and 16 weeks, respectively.

Time to remission: The sponsor also performed time to remission analysis and showed that budesonide treated patients had significantly shorter median time to remission (28 days) than that of mesalamine (84 days), $p=0.039$. However, the sponsor revised this analysis result by performing a worst case analysis, which yielded a median time to remission of 28 days for budesonide 9mg qd and 58 days for mesalamine, $p=0.12$.

According to the sponsor, “an error was made in the original analysis, in which the worst-case value was applied also to 7 patients who had been in remission before they were withdrawn due to disease deterioration (3 patients in the Entocort group and 4 patients in the Pentasa group).”

Reviewer’s Comments: It is interesting to note that during the trial periods, patients could withdraw from the study due to disease deterioration after remission had occurred.

CDAI changes: The decrease in mean CDAI score was significantly larger for patients receiving Budesonide by 2 weeks, 8 weeks, 12 weeks, and 16 weeks (p<0.05 at 2 weeks, 8 weeks and 12 weeks, p<0.01 at 16 weeks).

QOL: the sponsor reported that the larger increase in the total Psychological General Well-Being (PGWB) score was observed in the budesonide 9mg qd group and that this difference by 2, 8, 12, 16 weeks of treatment was statistically significant in comparison with mesalamine group. In addition, the physician’s global evaluation score improved in both treatment groups, particularly during the first two weeks. The change was significant in favor of budesonide at all follow-up visits.

Subgroup analysis

The CDAI remission rates by 8 weeks by sex – Study 08-3027

CDAI remission rates by 8 weeks [†]	Mesalamine 2g bid (n=89)	Budesonide 9mg qd (n=93)
Male	44% (12/28)	61% (18/30)
Female	45% (27/61)	73% (46/63)
Overall	44% (39/89)	69% (64/93)

[†] Extracted from the sponsor Table 17a of 008-068-076

It seems that the remission rates were similar between male and female in the mesalamine group. The effect of 9mg budesonide appeared to be numerically more profound within female treated patients.

SAFETY: nonfatal serious adverse event (SAE)

The percentage of patients with SAE – Study 08-3027

	Mesalamine 2g bid	Budesonide 9mg qd
SAE [†]	19% (17/89)	12% (11/93)

[†] Extracted from the sponsor Table 6 of 008-068-062

The sponsor reported that 19 SAE were observed in 17 patients treated with Mesalamine and 12 SAE were observed in 11 patients treated with budesonide. This resulted in lower SAE rate with budesonide (12%) than with mesalamine (19%).

SUMMARY OF REVIEWER'S EVALUATION AND COMMENTS

The baseline characteristics between the two treatment groups did not show considerable differences in this multinational controlled trial. Budesonide CIR 9mg was shown to be superior to mesalamine on the remission rate by 8 weeks of treatment ($p=0.001$), the primary efficacy outcome. The effect was numerically more profound in female patients. Forty-four percent of mesalamine treated patients discontinued the study early in contrasts to 17% of budesonide treated patients. Based on my analysis, the two treatment groups had essentially the same remission rates in the completers (see Figure 6). The highly statistical significance was mainly attributed to patients who withdrew from the study early.

A possible interpretation is that the effect of budesonide caused the differential dropouts, which made those in whom the treatment is effective not withdrawn from the study early. However, under differential and high dropout rates, interpretation of a superior efficacy for budesonide 9mg qd needs to be cautious.

#08-3025 "Budesonide controlled ileal release capsules once or twice daily in active Crohn's disease. A placebo-controlled study"

This was a randomized, multi-center (24 sites), double-blind, placebo-controlled US trial. After 1-2 weeks of baseline phase to establishing baseline CDAI, eligible patients having a baseline $200 \leq \text{CDAI} \leq 450$ ($n=200$) were randomized to receive budesonide CIR 9mg once daily ($n=80$), 4.5mg twice daily ($n=79$), or placebo ($n=41$) for 8 weeks followed by a tapering period of 2 weeks (6mg with 9mg qd, 3mg with 4.5mg bid, and 0mg with placebo).

The baseline characteristics among the three treatment groups can be found in Appendix 5. Median age of US patients at baseline was 37 years (ranges 18-73 years). Baseline median CDAI was 267 (ranges: 166-484), median disease duration was 8.2 years (ranges: 0-39 years). Median current exacerbation was 1.8 months (ranges: 0-104 months). Half of the patients had previous resection and 98% of patients were Caucasian.

Reviewer's comments: It is noted that the distribution of gender within each treatment group was somewhat unbalanced. The percents of male patients were 44% in placebo and 4.5mg bid budesonide groups, but 24% in 9.0mg qd budesonide group, nominal p -value=0.013, indicating a nominally significant gender distributional differences which was not seen in the other four well-controlled trials.

The primary objective of the study was to assess the efficacy and safety of budesonide CIR 4.5mg bid and 9.0mg qd, compared to placebo in those patients with active Crohn's disease affecting the ileum and/or the ascending colon. Active Crohn's disease was defined as baseline CDAI score being in the range of 200 to 450. The primary efficacy variable was clinical improvement, defined as a decrease in CDAI to a value of 150 or less at 8 weeks.

Primary efficacy outcome: remission rate

An overall test of no treatment differences among the three treatment groups in terms of remission rate at 8 weeks, the primary efficacy outcome, did not show a superior budesonide effect, p=0.14, overall χ^2 -test.

The remission rates across 3 groups by time points, APT LVE analysis - Study 08-3025

Remission rates [†]	At 2-week	At 4-week	At 8-week	At 10-week
Placebo (n=40)	13%	33%	33%	49%
Bud. 4.5mg bid (n=78)	40%	49%	53%	63%
Bud. 9mg qd (n=79)	31%	43%	48%	60%
Overall χ^2 -test	p=0.012	P=0.28	p=0.14	p=0.34

[†] Extracted from Table 10 of 008-048-067

- Reviewer's Evaluation and Comments

Although the protocol only stated that the remission is defined as a CDAI value of 150 or below at 8 weeks, remission rates in 9mg qd and 4.5mg bid budesonide groups were shown superior to placebo only at 2 weeks. There were observed numerical improvement at all other visits (4-weeks, 8 weeks, and 10 weeks). I have verified the above results.

Sensitivity analysis due to mild to moderate dropout rates:

The sponsor coded a placebo treated patient (#318) as remission at 8 weeks. This patient's last available CDAI score was 307 at visit 4 and should be coded as a non-remission patient using the last value extended rule. I performed the ITT analysis with and without changing the remission status of patient #318, the result in terms of statistical significance in testing if there is at least one treatment group differed from the others on the remission rate at 8 weeks was consistent.

Study 08-3025 [†]	Placebo	4.5mg bid budesonide	9.0mg qd budesonide
Sample size	41	79	80
Completion %	68%	85%	83%
Dropout rate %	32%	15%	17%
Dropout w/ disease Deterioration %	20%	3%	6%

[†] Extracted from Table 5 of sponsor 008-048-062

In this study, placebo had the lowest completion rate (68%), followed by 4.5mg bid budesonide (85%), and 9mg qd budesonide (83%), respectively. The dropout rate was about twice increase with placebo (32%) than with budesonide (16%). It appeared that the primary reasons of treatment discontinuation were disease deterioration and adverse event. Adverse events were similar among the three treatment groups (7% in placebo, 10% in 4.5mg bid group, and 8% in 9.0mg qd group). Disease deterioration rate was highest in placebo (20%) followed by 9mg qd budesonide (6%) and 4.5mg bid budesonide (3%). The low (placebo) to moderate (budesonide) differential dropouts were consistent between the milder and the moderate disease severity subgroups.

By stratifying patient's completion status, the analysis gave the results consistent with the overall comparison in terms of statistical significance. It is interesting to note that in this study, there is a nominal evidence of differential gender-distribution in that smaller percent of patients treated with 9mg qd budesonide (24%) than with placebo (44%) were males and yet, statistical significance was not observed given low to moderate dropouts. In contrast, statistical significance was observed in Study #08-3001 with moderate to high dropouts and the differential was primarily observed in the female subgroup.

The primary objective of the study was to assess the efficacy and safety of budesonide CIR 4.5mg bid and 9.0mg qd, compared to placebo in those patients with active Crohn's disease affecting the ileum and/or the ascending colon. Active Crohn's disease was defined as having a baseline CDAI score between 200 and 450. When each budesonide group was compared with placebo instead of testing whether remission rates differed among the three groups, a borderline significance was observed of 4.5mg bid budesonide vs. placebo, but not the 9.0mg qd budesonide vs. placebo. It is noted that 9.0mg qd budesonide is the sponsor's intended dosage form for marketing, which did not demonstrate a significantly higher remission rate compared to placebo based on either an overall 3-arm comparison or a post-hoc pairwise test of 9mg qd vs. placebo.

In contrast to the Canadian placebo controlled study in which dropout rate was 58% in placebo, this US placebo controlled study had a placebo dropout rate of 32%. In addition, dropout rates were 31% in Canadian trial and 16% in US trial in those patients treated with 9mg budesonide (4.5mg bid in Canadian trial, whereas 4.5mg bid and 9mg qd in US trial). Given half the dropout rates proportionally within each study group, a statistically significant treatment effect was observed in the high dropout Canadian trial but not observed in the moderate dropout US trial. This is of concern. One possible explanation may be the differences in treatment administration between the two countries.

Secondary efficacy outcomes

Time to remission: The sponsor also performed time to clinical improvement analysis and showed that time to clinical improvement differed among the three groups with median time to clinical improvement of 22 days in the budesonide twice daily group, and 35 days in budesonide once daily group, respectively, compared to 66 days in the placebo group, with an overall $p=0.0079$, generalized Wilcoxon test.

CDAI changes: the mean CDAI scores decreased more in the budesonide 9mg qd and 4.5mg mg bid groups than in the placebo. The differences were statistically significant at 2 weeks and 4 weeks following treatments, but **not at later visits of 8 weeks and 10 weeks.**

QOL: the sponsor reported that numerical improvement in total quality of life questionnaires evaluated using IBDQ (inflammatory bowel disease questionnaires) was greater in the active treatment groups than in the placebo group, but a comparison between the three groups showed **no significant differences by 8 weeks of treatment.**

Subgroup analysis

The sponsor performed a number of subgroup analyses on clinical improvement rate, e.g., by age (less than 30 years vs. at least 30years), by gender, by location of disease, by previous use of steroids, etc. The sponsor stated that “the clinical improvement rates were lower for patients with more severe disease at entry, for young patients, for those who had been treated with immuno-suppressants or antibiotics, for those without a high body mass index, and for those with a long current episode. None of the other factors had a significant influence on the remission rate, nor did any of the factors interact with treatment.”

Reviewer’s Evaluation and Comments

The sponsor did not provide the analysis results by gender. I summarized the remission rates by gender shown in the Table below. It is noted that the overall test did not show a significant budesonide effect, nonetheless, numerical higher remission rates were observed in the twice daily and once daily groups.

In this study, the 9mg qd group only had 24% male patients, remission rates were numerically higher in male treated patients (56%) than in female treated patients (46%). As for the placebo group, 44% of them were males. The remission rate was numerically higher in male treated patients (39%) than in female treated patients (26%).

The CDAI remission rates by 8 weeks by gender, APT LVE – Study 08-3025

CDAI remission rates by 8 weeks [†]	Placebo (n=41)	4.5mg bid budesonide (n=79)	9.0mg qd budesonide (n=80)
Male	39% (7/18)	51% (18/35)	56% (10/18)
Female	26% (6/23)	52% (23/44)	46% (28/61)
Overall	32% (13/41)	52% (41/79)	48% (38/79)

[†] Performed by this reviewer

SAFETY: possible gluco-corticosteroid (GCS) associated side-effects

Study 08-3025 [†]	Placebo (n=41)	Bud 4.5mg bid (n=79)	Bud 9.0mg qd (n=80)
Run-in period	46%	33%	39%
During treatment	59%	65%	63%

[†] Extracted from the sponsor Table 69 of 008-048-123

For safety, the sponsor reported 11 different signs and symptoms, possibly associated with GCS treatment. The percents of patients with at least one of these symptoms during the run-in period and the treatment period were summarized in the above table. It appeared that the incidence of GCS associated side effects in budesonide treated patients was similar to that of placebo treated patients.

The sponsor reported that there were no deaths during the study in any of the treatment groups, however, one patient in the budesonide 9mg once daily group (patient #288) was hospitalized 4.5 months after study completion due to worsening of Crohn's disease with subsequent death. The investigator did not consider the event related to the investigational product.

SUMMARY OF REVIEWER'S EVALUATION AND COMMENTS

The primary objective of the study was to assess the efficacy and safety of budesonide CIR 4.5mg bid and 9.0mg qd, compared to placebo in those patients with active Crohn's disease affecting the ileum and/or the ascending colon. The baseline characteristics were similar except the distribution of male and female patients, 44% in the placebo and 4.5mg bid budesonide groups, but only 24% in the 9.0mg qd budesonide group. When each budesonide group was compared with placebo instead of testing whether remission rates differed among the three groups, a borderline significance was observed of 4.5mg bid budesonide vs. placebo, but not the 9.0mg qd budesonide vs. placebo where 9.0mg qd is the sponsor's intended dosage for marketing. In addition, I performed a sensitivity analysis on the remission rate stratifying on sex. It appeared that a significant budesonide effect was not shown in the stratified analysis or within each sex subgroup.

The result that there was no significant difference among the placebo, 4.5mg bid, and 9.0mg qd groups seemed to be partially due to the apparent placebo effect (2.5-folds increase in remission rate). On the other hand, a lack of difference between budesonide and placebo might be indicative of small or little effect with budesonide if placebo response is known to exist. It is noted that twice placebo treated patients (32%) discontinued the trial early than those of budesonide treated patients (17% in 4.5mg bid group and 15% in 9.0mg qd group). However, assuming that the dropouts are not informative (i.e., not affecting the response), the analysis stratifying by patient's completion status still failed to show a significant budesonide effect from a comparison of the three treatment groups.

Overall Safety

This section is in response to Dr. Ruyi He's request for the safety evaluation. Of those sponsor Tables Dr. Ruyi He, the medical reviewer, has summarized, I have provided the 95% confidence intervals for key safety parameters, such as, the primary safety outcome and the GCS related adverse events, etc. They are summarized below.

The percent patients having nonfatal serious adverse events (SAE) in Budesonide 9mg/day (including both 4.5mg bid and 9.0mg qd) treated patients (10%=51/520) was similar to that of prednisolone (13%=19/145). Incidence in budesonide 9.0mg/day group was shown to be less than that in mesalamine (19%=17/88), 95% CI of the difference: 9% (1%, 18%).

Table 46: Summary of nonfatal SAEs in controlled studies in active Crohn's disease

	Budesonide 9 mg/d n=520	Placebo n=107	Prednisolone n=145	Mesalamine n=88
Total	55 SAEs in 51 patients (10%)	6 SAEs in 6 patients (6%)	22 SAEs in 19 patients (13%)	19 SAEs in 17 patients (19%)

Table 49: Number and Proportion (%) of Patients with Normal Plasma Cortisol Levels (>150 nmol/L) by 8 weeks[†]

Study	Entocort 9mg/day	Prednisolone	Safety Gain %*	Nominal p-value
08-3001	33/61 (54%)			
08-3002	48/73 (66%)	20/71 (28%)	38%	<0.0001
08-3013	65/109 (60%)	14/54 (26%)	34%	0.0001
08-3025	84/132 (64%)			
08-3027	51/76 (67%)			

[†] Dr. He summarized from Vol. 36, page 236

*safety gain % = (% of patients with normal cortisol levels in the Entocort group) - (% of patients with normal cortisol levels in the prednisolone group)

I checked the sponsor reports of 008-025-240 in Study 08-3002; proportions of patients with normal plasma cortisol level were 66%(=55/83) with budesonide 9mg/day and 24% (=20/84) with prednisolone, not those shown in the Table above in the row labeled 08-3002. For the Study 08-3013, I checked the sponsor reports of 008-036-189, the proportions were 61% (=67/109) with budesonide 9mg/day and 24% (=13/54) with prednisolone, not those shown in the Table above in the row labeled 08-3013. The nominal p-values using either those shown in the Table above or those reported by the sponsor were consistent. The 95% CI of the difference between budesonide 9mg/day and prednisolone were 38% (22%, 53%) in Study 08-3002 and 34% (19%, 49%) in Study 08-3013 using the per-protocol counts Dr. Ruyi He extracted from Vol. 36, page 236. Similar confidence intervals were observed using the all patients treated as summarized by me.

	Budesonide 6 mg/day n=208	Placebo n=209
Cushing syndrome	80 (38%)	51 (24%)

Dr. Ruyi He requested a comparison between budesonide 6mg/day and placebo on Cushing syndrome. I have calculated the 95% CI. The differences in Cushing syndrome rate were 14% (95% CI: 5%, 23%), indicating that the incidence differences in Cushing syndrome budesonide could be as high as 23%.

Comparison among budesonide 9mg, prednisolone and placebo in Table 50 for short-term (8 weeks) treatments

Table 50: Summary of Glucocorticosteroid (GCS) Adverse Events

	Short-term treatment (8 weeks)			Nominal p-value (overall χ^2 -test)
	Budesonide 9mg, n=427 ^A	Prednisolone N=145	Placebo N=107	
GCS AEs	145 (34%)	69 (48%)	29 (27%)	0.002
Acne	63 (15%)	33 (23%)	14 (13%)	0.0494
Moon face	46 (11%)	53 (37%)	4 (4%)	< 0.0001
Bruise easily	63 (15%)	13 (9%)	12 (11%)	0.169
Swollen ankles	32 (7%)	13 (9%)	6 (6%)	0.607
Hirsutism	22 (5%)	5 (3%)	2 (2%)	0.278
Skin striae	4 (1%)	0 (0%)	2 (2%)	0.288
Buffalo hump	6 (1%)	5 (3%)	2 (2%)	0.300

^A = Pooled from studies 08-3001, 08-3002, 08-3013 and 08-3025. Specific GCS evaluation was not done for Study 3027.

It is noted that the nominal p-values were provided for reference only as these were exploratory analyses. It indicated possible differences in incidence among the three treatment groups. The sponsor presented the GCS related adverse events by pooling across the studies, as shown in the Sponsor Table 50 summarized above. The sponsor pooled the data from Studies 08-3001, 08-3002, 08-3013, and 08-3025, but not 08-3027 because specific GCS evaluation was not done. According to the sponsor, the short-term treatment included safety evaluation of 8 weeks treatments.

Among the 7 “more common” adverse events that are GCS related, the medical review team considers “moon face” to be one of the more serious events. From these clinical trials’ 8 weeks experience, incidences of “bruise easily”, “swollen ankles”, “hirsutism”, “skin striae”, and “buffalo hump” were similar among budesonide 9mg (including 4.5mg bid and 9mg qd), prednisolone and placebo compared. “Acne” appeared to occur more often with prednisolone (23%=33/145) than with budesonide 9mg (15%=63/427), 95% CI of the difference: 8% (0.4%, 16%), the latter was similar to placebo (13%=14/107),

95% CI of the difference: 2% (-6%, 9%). Incidences of moon face, however, appeared to be smaller with budesonide 9mg (11%=46/427) than with prednisolone (37%=53/145), 95%CI of the difference: -26%(-34%, -17%). Such incidence appeared to be worse than placebo (4%=4/107), 95%CI of the difference: 7% (2%, 12%).

For long-term treatment, define as less than or equal to one year of treatment, budesonide 3mg-6mg treated patients yielded a nominally higher incidence of GCS related AEs (30%) than placebo treated patients (20%), 95% CI of the difference were 10% (3%, 18%). It appeared that the individual component incidences of the GCS related adverse events were shown not too different between budesonide 3-6mg and placebo.

Comparison between budesonide 3-6mg and placebo in Table 50 for long-term (less than or equal to 1 year) treatments

	Long-term treatment ≤1 year		
	Budesonide 3-6mg ^B , n=296	Placebo N=209	95% CI of (budesonide - placebo)
GCS AEs	90 (30%)	42 (20%)	10% (3%, 18%)
Acne	39 (13%)	19 (9%)	4% (-1%, 10%)
Moon face	28 (9%)	12 (6%)	3% (-1%, 8%)
Bruise easily	32 (11%)	15 (7%)	4% (-1%, 9%)
Swollen ankles	11 (4%)	7 (3%)	1% (-3%, 4%)
Hirsutism	16 (5%)	5 (2%)	3% (-0.3%, 6%)
Skin striae	3 (1%)	2 (1%)	0% (-2%, 2%)
Buffalo hump	5 (2%)	4 (2%)	0% (-3%, 2%)

^B = 3mg and 6mg in studies 08-3003,08-3004 and 08-3014; 6 mg in studies 08-3008 and 08-3046 sponsor's table, modified from Vol.36, page 225

REVIEWERS' OVERALL EVALUATION AND COMMENTS

I give a brief description of the trial designs of the five major studies according to the chronological order in the Table below. The active (prednisolone) controlled study (Study 08-3002, study period: Feb. 1991 to Sept. 1992) and the Canadian placebo controlled study (Study 08-3001, study period: Oct. 1991 to Dec. 1992) were conducted about the same time. Another active (prednisolone) controlled study (Study 08-3013, trial period: Mar. 1992 to Feb. 1994) started approximately in the middle of the two previous trials. After these three studies were completed, the active (mesalamine) controlled study (Study 08-3027, trial period: Nov. 1994 to Aug. 1996) was launched. In about half way of this study, the US placebo controlled study (Study 08-3025, trial period: Sept. 1995 to Aug. 1997) was launched.

CLINICAL STUDIES –chronological order

	08-3002**	08-3001*	08-3013**	08-3027*	08-3025
Trial design	-9mg qd† Ent -40mg/day qd Prednisolone!	-Placebo - 3mg bid† Ent - 9mg bid Ent -15mg bid Ent	-9.0mg om† Ent -4.5mg bid Ent -40mg/day Prednisolone	-9mg qd Ent. -2g bid Mesalamine!	-Placebo -4.5mg bid Ent -9.0mg qd Ent.
Stratification	n.a.	Previous GCS use		n.a.	n.a.
Primary	CDAI ≤ 150	CDAI† ≤ 150	CDAI ≤ 150	CDAI† ≤ 150	CDAI† ≤ 150
Run-in	n.a.	1-week	1-week	n.a.	1-2 weeks
Trial-period	8 weeks	8 weeks	8 weeks	16 weeks	8 weeks
Follow-ups	2,4,8,10wk	2,4,8,10,12wk	2,4,8,12wk	2,4,8,12,16wk	2,4,8,10wk
Tapering	2-weeks	2-4 weeks	4-weeks	n.a.	2-weeks
Duration	10 weeks	10-12 weeks	12 weeks	16 weeks	10 weeks
Study period	2/91-9/92	10/91-12/92	3/92-2/94	11/94-8/96	9/95-8/97
Regions	Europe	Canada	Multi-country	Multi-country	US
# of study sites.	11(6-country)	27	24 (9-countries)	25(12-countries)	24

† q.d. or o.m. once daily, b.i.d., twice daily,

† calculated at the randomization visit and all following visits.

! Pentasa® (Mesalamine)

* showed a statistical significance on the efficacy evaluation

** budesonide effect could not be clearly established to be not much less than prednisolone efficacy-wise, but showed a superior budesonide effect in terms of p-cortisol (morning plasma cortisol concentration) or gluco-corticosteroid related adverse events by 8 weeks of treatment

The primary efficacy outcome in all the five studies was percent of patients achieving a CDAI score ≤ 150 by 8 weeks of treatment irrespective of a run-in period. I inquired about “what is the clinical rationale of the primary efficacy evaluation being defined as remission (CDAI score ≤ 150) at 8 weeks and not at earlier weeks?” Per communication with Dr. Ruyi He, he explained that stable remission of a patient generally occurs by 8 weeks of treatment rather than before 8 weeks.

Results of all five studies at all the time points during the trial period, i.e., at 2 weeks, 4 weeks, 8 weeks, and 10 weeks or 12 weeks or 16 weeks are summarized in page 37 of this review. For the 8 weeks evaluation, I also performed intent-to-treat analyses, including all patients randomized. The results are given in the Table below.

Primary efficacy outcome: remission rate at 8 weeks (% of patients who had CDAI* ≤ 150)

Study (ITT)§	Sample size estimation	Placebo	(3mg) 1.5mg bid Entocort	(9mg) 4.5mg bid Entocort	9mg qd Entocort	(15mg) 7.5mg bid Entocort	2g bid mesalamine	40mg qd prednisolone
08-3002	C=,7,T=,5 Ni=75	NA	NA	NA	51% (45/88) p=0.091	NA	NA	64% (56/88)
08-3001 (sig)*	P=.4 T15mg=.7 Ni=60	20% (13/66)	31% (21/67) p=0.12	51% (31/61) p<0.0001	NA	41% (26/64) p=0.0077	NA	NA
08-3013 (n.s.)*	C=,7,T=.4 Ni=50	NA	NA	41% (25/61)	60% (35/58)	NA	NA	60% (35/58)
08-3027	P<.28 T=.5 Ni=85	NA	NA	NA	68% (63/93) p=0.0002	NA	42% (37/89)	NA
08-3025 (n.s.)*	P=.2, T=.5 Ni=80 Np=40	32% (13/41)	NA	52% (41/79)	48% (38/80)	NA	NA	NA

NA: Not Applicable

C: active control remission rate, prednisolone or mesalamine

T: treatment (budesonide) remission rate, P: placebo remission rate

§ Reviewer's evaluation (based on all randomized patients)

*: overall χ^2 test, (sig): indicated a statistical significance at 0.05 level (n.s.): indicated a non-significance

A statistically significant effect for budesonide 4.5mg bid was shown in the Canadian placebo controlled trial (Study 08-3001). A statistically significant effect for budesonide 9.0mg qd was shown in the active (mesalamine) controlled trial (Study 08-3027). The efficacy of budesonide 9mg qd was inconclusive in the US placebo controlled trial (Study 08-3025). From the two active (prednisolone) controlled trials (Study 08-3002 and Study 08-3013), it is unclear whether budesonide 9mg qd is not much less effective than prednisolone. Statistical significance was apparently shown in the trials with moderate to large and differential dropouts (Study 08-3001 and Study 08-3027), but not shown in the trials with low to moderate and differential dropouts (Study 08-3025) and not clear in low and comparable dropouts (Study 08-3002 and Study 08-3013); see the below table. **This is of concern.**

Dropout rates (% of patients early discontinued the treatment) across the studies

Study (ITT)§	Study region	Placebo	(3mg) 1.5mg bid budesoni.	(9mg) 4.5mg bid Budesoni.	9mg qd Budeson.	(15mg) 7.5mg bid budesoni.	2g bid Mesalamine	40mg qd Prednisolone
08-3002	6-country Europe	NA	NA	NA	18% (16/88)	NA	NA	17% (15/88)
08-3001	Canada	58% (38/66)	54% (36/67)	31% (19/61)	NA	41% (26/64)	NA	NA
08-3013	9-country	NA	NA	25% (15/61)	16% (9/58)	NA	NA	22% (13/58)
08-3027	12country	NA	NA	NA	17% (16/93)	NA	44% (39/89)	NA
08-3025	US	32% (13/41)	NA	15% (12/79)	17% (14/80)	NA	NA	NA

NA: Not Applicable

§ : based on all patients randomized, i.e., intent-to-treat patients

Trial	Trial 08-3001	Trial 08-3025
Population studied	Canada	US
Mean Age (median age)	34 years (19-62)	36 years (18-63)
Baseline mean CDAI	287 (119-479)	253 (197-425)
Sample size estimation	66	40 in placebo, 80 in budesonide
% male	38%	44%
Previous resection (%)	35%	54%
Disease duration (yrs)	8.0 (0-32)	8.2 (0-36)
Dropout rates*	58%(p), 43%(3mg), 31%(9mg), 41%(15mg)	32%(p), 15%(4.5mg bid), 17%(9mg qd)
Remission rates	20%(p), 31%(3mg), 51%(9mg), 41%(15mg)	30%(p), 52%(4.5mg bid), 48%(9mg qd)

Baseline characteristics in the placebo arms of the two placebo controlled studies were comparable except that a higher percent of patients with previous resection was seen in the US trial (54%) than in the Canadian trial (35%); see the table above.

Differential placebo remission rates by 8 weeks of treatment (the primary efficacy outcome) were observed. In the Canadian study, the remission rates were 11% at 2 weeks, 20% at 8 weeks and 16% at 10 weeks. However, the remission rates were 13% at 2 weeks, 33% at 8 weeks and 49% at 10 weeks in the US trial.

The Canadian trial had about twice the dropout rates as the US trial did. Such differences in dropout rates between the two countries might be due to differences in the treatment administration. The remission rates were similar for budesonide 9mg qd and 4.5mg bid, but placebo seemed to have a higher remission rate in US trial than in Canadian trial (33% vs. 20%) by 8 weeks of treatments and (49% vs. 16%) by 10 weeks of treatments.

The Canadian placebo controlled trial (Study 08-3001) showed a statistically significant budesonide effect. It seemed that the budesonide effect was numerically more profound in female patients. As in the Table below, the dropout rates in female patients were moderate (9mg and 15mg groups) to large (placebo and 3mg groups) and differential. These differences might explain the budesonide effect in female patients. There was no obvious differential dropout rate in the male patients.

The dropout rates by sex – Study 08-3001[†]

Dropout rates	Placebo	Bud 3mg	Bud 9mg	Bud 15mg
Male	48% (12/25)	40%(8/20)	39%(9/23)	48% (14/29)
Female	63% (26/41)	60% (28/47)	26% (10/38)	34% (12/35)
Overall	58% (38/66)	54% (36/67)	31% (19/61)	41% (26/64)

[†] Summarized by this reviewer

In contrast, the US study (Study 08-3025) did not conclude an effect for budesonide. As in the Table below, the differential dropout rates were low (bud.) to moderate (placebo) in both sexes in Study 08-3025.

The dropout rates by sex – Study 08-3025[†]

Dropout rates	Placebo	Bud 4.5mg bid	Bud 9mg qd
Male	28% (5/18)	14%(5/35)	11%(2/18)
Female	35% (8/23)	16% (7/44)	18% (11/61)
Overall	32% (13/41)	15% (12/79)	16% (13/79)

[†] Summarized by this reviewer

The apparent finding of a significant effect for budesonide 4.5mg bid and 7.5mg bid in the Canada study was not replicated in the US study. Had the dropout differential not contributed to the treatment difference (i.e., dropouts were non-informative), the analysis stratifying by patient's completion status would have demonstrated the results consistent with the results of the primary analysis. However, by such stratification, significant treatment difference ($p=0.0026$) on remission rate in Study 08-3001 became not statistically significant, $p=0.098$. This is quite a change and causes a concern. Given the differential dropout rates in these studies as described above, would a significant budesonide effect still have been shown had this Canada study had a better follow-up with a comparable dropout rate as that of the US trial? Could it be just the differences in

the treatment administration between the two countries? Similarly, in the Study 08-3027, the dropout rates were 44% with mesalamine and 17% with budesonide 9mg qd. Had the dropout rate in the mesalamine treated patients been much lower and possibly comparable to that of budesonide, say, 20% to 25%, would a significant budesonide effect relative to mesalamine still have been shown? In fact, the significant treatment effect in terms of remission rate at 8 weeks was mainly attributed to patients who did not complete the study. A closer look at the data suggested that on average the patients who completed the trial period had essentially the same remission rates between the two treatment groups (see Figure 6).

Although the primary reason of dropout was mainly disease deterioration, data seemed to suggest that the differential dropouts occurred more profound in those patients with milder baseline CDAI score in Study 08-3027 and more profound in female patients with Study 08-3001.

As noted, the primary efficacy outcome was percent of patients achieving a CDAI score ≤ 150 by 8 weeks of treatment irrespective of a run-in period. It might help the interpretation of a plausible treatment effect if responders showed a general trend of remission over the treatment weeks. As Dr. He pointed out, the clinical rationale of the primary efficacy was that stable remission of a patient generally occurs by 8 weeks of treatment rather than before 8 weeks with the caveat that evaluation of the CDAI included subjective elements answered by the patients themselves and some objective lab measurements. Given a high placebo remission rate in the US study (33% by 8 weeks and 49% by 10 weeks), the fluctuation of CDAI scores over the treatment weeks suggests that a patient might have been a responder if not dropping out of the study early. Consequently, a significant treatment effect seen in Study 08-3001 and Study 08-3027 might not seem evident as they have been complicated by many factors explained above.

The two active (prednisolone) controlled studies were inappropriately designed and powered to assess whether budesonide is not inferior to prednisolone. Both trials did not pre-specify the non-inferiority margin. Based on the conventional worst limit of the 2-sided 95% CI for the effect of budesonide relative to prednisolone, budesonide 9mg qd could be 27% less effective than prednisolone at 8 weeks in Study 08-3002 and 18% in Study 08-3013. Such a difference is larger than the often used margins of, say, 5% to 15%. Therefore, it is very difficult to conclude objectively that budesonide is non-inferior to prednisolone by 8 weeks of treatment.

The safety parameter was pre-specified in one active controlled study (Study 08-3013) but not in the other active controlled study (Study 08-3002). I used the safety endpoint "p-cortisol (morning plasma cortisol concentration)", pre-specified for Study 08-3013, for safety evaluation in both trials. A higher proportion of patients with normal p-cortisol by 8 weeks of treatment was observed with budesonide than prednisolone. A similar incidence in GCS related side effect was seen in Study 08-3013 and a smaller incidence of GCS associated side-effects was observed with budesonide qd than prednisolone in Study 08-3002.

The sponsor presented the GCS related adverse events by pooling across the studies, as shown in the Sponsor Table 50 summarized in the Overall Safety Section. Among the 7 “more common” adverse events that are GCS related, the medical division considers “moon face” to be one of the more serious events. From these clinical trials’ 8 weeks experience, incidences of “bruise easily”, “swollen ankles”, “hirsutism”, “skin striae”, and “buffalo hump” were similar among budesonide 9mg (including 4.5mg bid and 9mg qd), prednisolone and placebo compared. “Acne” appeared to occur more often with prednisolone (23%=33/145) than with budesonide 9mg (15%=63/427), 95%CI of the difference: 8% (0.4%, 16%), the latter was similar to placebo (13%=14/107), 95% CI of the difference: 2% (-6%, 9%). Incidences of moon face, however, appeared to be smaller with budesonide 9mg (11%=46/427) than with prednisolone (37%=53/145), 95%CI of the difference: -26%(-34%, -17%). Such incidence appeared to be worse than that of placebo (4%=4/107), 95%CI of the difference: 7% (2%, 12%).

CONCLUSION

A significantly higher percentage of responders (patients having a CDAI score ≤ 150) by 8 weeks of budesonide treatment was observed in trials with moderate dropout rate for budesonide to high dropout rate for placebo or mesalamine (Study 08-3001 and Study 08-3027). The differential dropout was more profound in those patients whose baseline CDAI score was less than 300 (milder), less so in those with baseline CDAI greater than or equal to 300 (more moderate) in Study 08-3027 and was more profound in female patients in Study 08-3001. The trial (Study 08-3025) with low dropout for budesonide to moderate dropout for placebo did not show a statistically significant effect for budesonide, its differential dropouts were consistent between milder and moderate disease severity subgroups. There appeared to be a problem with interpretation of the results. That is, the differential dropouts complicated the interpretation of the efficacy results seen in the Canada placebo-controlled trial (#08-3001, $p=0.003$), the US placebo-controlled trial (#08-3025, $p=0.14$) and the active-controlled trial (#08-3027, $p=0.001$). Since the reason of patients’ dropping out of the study seemed to be primarily lack of efficacy, a possible interpretation is that budesonide is so effective that more patients would complete the trial. However, if budesonide were so effective, then its effect would have been observed consistently in the completers and in the US trial with relatively low dropout rates. The fluctuation of CDAI scores over the treatment weeks might make a patient a responder, e.g., at any of the evaluation weeks, alternating weeks, or some weeks only, if he or she did not drop out of the study. In addition, statistical significance was quite different depending on the differential dropout rates and occurrence of remission could be variable over the treatment weeks. Because of all these uncertainties, it is very difficult to provide a consistent interpretation for the results of these studies.

The two active controlled studies (08-3013 and 08-3002) were inadequately designed and powered to investigate whether budesonide effect is not much less effective than prednisolone. It is difficult to post-hoc conclude objectively that budesonide is non-inferior to prednisolone by 8 weeks of treatment without a pre-specified noninferiority margin on remission effect, the primary efficacy outcome. Safety superiority for budesonide compared to prednisolone was observed in terms of proportion of patients

with normal p-cortisol by 8 weeks of treatment. In addition, a similar or smaller incidence in GCS related side effect was observed with budesonide 9mg qd than with prednisolone. From these clinical trial experiences of 8 weeks treatment, "moon face", one of the more serious GCS related adverse events, appeared to show a smaller incidence with budesonide 9mg (11%) than with prednisolone (37%). Such incidence appeared to be worse than that of placebo (4%). Entocort 9mg qd appeared to be less toxic than prednisolone.

**APPEARS THIS WAY
ON ORIGINAL**

Sue-Jane Wang, Ph.D.
Senior Mathematical Statistician

Thomas Permutt, Ph.D.
Concur: Mathematical Statistician (Team Leader)

Concur:

S. Edward Nevius, Ph.D.
Division Director, Division of Biometrics II

NDA# 21,324
HFD-180/He, Gallo-Torres, Talarico, McNeil
HFD-715/Wang, Permutt, Nevius
HFD-700/Anello

This review contains 40 pages, including several reviewer tables within each study and overall evaluation and 6 reviewer figures in addition to those tables extracted from the sponsor's NDA reports.

Appendix A: CDAI calculation (008-037-091), see pages 38-39 of this review.

Appendix B: Harvey-Bradshaw Index (the sponsor's report of 008-026-069), see page 40 of this review.

Appendix C: †Definition of Treatment Failures: if

- the patient's episode of Crohn's disease develops into a severe fulminant case requiring systemic steroid therapy, hospitalization or surgery
- the patient remains very ill after two weeks of treatment or thereafter defined as:
 - (1) CDAI score > 400 points
 - (2) Increase in the CDAI score > 100 points over the baseline value
- the patients remains very ill after four weeks of treatment or thereafter define as:
 - (1) CDAI score > 300 points and the patient has not benefited from the therapy, i.e., the CDAI score is not 100 points lower than the baseline value
 - (2) Increase in the CDAI score > 100 points over the baseline value

† from the sponsor's report on page 008-009-049

Appendix 1: Baseline characteristics of Study 08-3002†

Baseline characteristics Study 08-3002	Prednisolone (n=88) mean (range)	Budesonide 9mg qd (n=88) Mean (range)
Male (%)	37 (42%)	30 (34%)
Age (years)	36 (18-85)	35 (18-67)
CDAI	279 ()	275 ()
Harvey-Bradshaw index	9.3 ()	9.3 ()
Disease duration (years)	7.3 ()	7.1 ()
Current exacerbation (months)	8.2 ()	11.0 ()
Previous resection (Y%)	32 (36%)	43 (49%)
Time since resection (years)	5.8 ()	4.7 ()
Total resected length (cm)	52 ()	49 ()

† Extracted from 008-025-206

Appendix 2: Demography and disease history of 08-3001†

Study 08-3001	Placebo (n=66)	1.5mg bid (3mg) (n=67)	4.5mg bid (9mg) (n=61)	7.5mg bid (15mg) (n=64)
Male (%)	25 (38%)	20 (30%)	23 (38%)	29 (45%)
Age (years)	34	33	37	33
Mean (range)	(19-62)	(17-63)	(18-65)	(18-66)
CDAI:	287	293	297	285
Mean (range)				
Disease duration (yrs)	8.0 ()	7.1 ()	9.6 ()	6.7 ()
Duration of episode (ms)	4.3 ()	3.5 ()	3.9 ()	5.0 ()
Previous resection (%)	52%	37%	48%	47%
location: ileum only (%)	85%	81%	84%	88%

† Extracted from 008-008-078

Appendix 3: Baseline characteristics of Study 08-3013†

Study 08-3013	Prednisolone qd (n=58)	4.5mg bid budesonide (n=61)	9mg qd budesonide (n=58)
Male (%)	23 (40%)	28 (46%)	21 (36%)
Age (years)	36 (19-70)	38 (20-71)	36 (17-71)
CDAI	279	274	277
Disease duration (years)	6.7	7.9	8.3
Current exacerbation (months)	5.5	7.6	4.9
Previous resection (%)	34 (59%)	27 (44%)	28 (48%)
Time since resection (years)	4.6	5.3	5.8

† Extracted from the sponsor Table 1 of 008-036-150

Appendix 4. Baseline characteristics of Study 08-3027†

Baseline characteristics Study 08-3027	Pentasa (n=89) (mesalamine) 2g bid	Entocort (n=93) (budesonide) 9mg qd
Male (%)	28 (31%)	30 (32%)
Age (years) [median (range)]	31 (18-67)	34 (19-74)
CDAI [median (range)]	278	266
Disease duration (years) [median (range)]	4.6	6.1
Current exacerbation (mons) [median (r)]	2.0	1.8
Disease location (ileal only) (%)	50 (56%)	56 (60%)
Previous resection (%)	37 (42%)	35 (38%)
Time since resection (years) [median (r)]	4.5	3.7
Total resected length (cm) [median (r)]	35	30
Previous on 5-aminosalicylates (%)	31 (35%)	27 (29%)

† Extracted from Table 1 of 008-068-048

Appendix 5: Baseline characteristics of Study 08-3025†

Study 08-3025	Placebo (n=41)	4.5mg bid budesonide (n=79)	9mg qd budesonide (n=80)
Male (%)	18 (44%)	35 (44%)	19 (24%)
Age (years)	36 (18-63)	38 (18-71)	36 (18-73)
CDAI	253	270	268
Disease duration (years)	8.2	7.1	9.2
Current exacerbation (months)	2.5	1.8	1.7
Previous resection (%)	22 (54%)	41 (52%)	41 (51%)
Time since resection (years)	2.9	3.2	6.9

† Extracted from Table 9 of 008-048-066

The sponsor's reports, APT LVE analysis - Study 08-3002 (6 countries)

Remission rates	At 2-wk	At 4-wk	At 8-wk	At 10-wk
Prednisolone 40mg qd tapering to 5mg at wk-10 (n=86)	56% (48/86)	67% (58/86)	65% (56/86)	66% (57/86)
Budesonide 9mg qd (n=86)	45% (39/86)	40% (34/86)	52% (45/86)	53% (46/86)
Nominal p-value (χ^2 -test)	0.22	0.0004	0.12	0.12

The sponsor's reports, APT LVE analysis - Study 08-3001 (Canada)

Remission rates	At 2-wk	At 4-wk	At 8-wk	At 10-wk
Placebo (n=64)	11%	17%	20%	16%
3mg (1.5mg bid) (n=64)	10%	25%	33%	27%
9mg (4.5mg bid) (n=61)	33%	36%	51%	46%
15mg (7.5mg bid) (n=61)	28%	41%	43%	43%
Overall χ^2 test			p=0.0026	

The sponsor's reports, APT LVE analysis - Study 08-3013 (9 countries)

Remission rates	At 2-wk	At 4-wk	At 8-wk	At 12-wk
Prednisolone 40mg qd tapering to 5mg at wk-10 (n=58)	37% (21/58)	62% (36/58)	60% (35/58)	53% (31/58)
Budesonide 4.5mg bid (n=60)	27% (16/60)	45% (27/60)	42% (25/60)	52% (31/60)
Budesonide 9mg qd (n=58)	48% (28/58)	53% (31/58)	60% (35/58)	59% (34/58)
Overall χ^2 test	0.052	0.18	0.062	0.73

The sponsor's reports, APT LVE analysis - Study 08-3027 (12 countries)

Remission rates	At 2-wk	At 4-wk	At 8-wk	At 12-wk	At 16-wk
Mesalamine 2g bid (n=89)	37% (31/83)	39% (32/83)	45% (37/83)	42% (35/83)	36% (30/83)
Budesonide 9mg qd (n=93)	44% (39/89)	48% (44/91)	69% (63/91)	64% (58/91)	62% (56/91)
Nominal p-value (χ^2 -test)	0.39	0.19	0.001	0.0044	0.0008

The sponsor's reports 008-008-087; 008-008-122 (APT, LVE) Study 08-3025 (US)

Remission rates	At 2-week	At 4-week	At 8-week	At 10-week
Placebo (n=40)	13%	33%	33%	49%
4.5mg bid (n=78)	40%	49%	53%	63%
9mg qd (n=79)	31%	43%	48%	60%
Overall χ^2 test	p=0.012	p=0.28	p=0.14	p=0.34

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/s/

Sue Jane Wang
7/13/01 04:34:29 PM
BIOMETRICS

Thomas Permutt
7/13/01 04:39:40 PM
BIOMETRICS
See my secondary review.

S. Edward Nevius
7/18/01 02:29:52 PM
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See my additional comments to follow.

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