ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING

May 9, 2007

FDA BRIEFING DOCUMENT

orBec® (beclomethasone dipropionate tablets, BDP)

Proposed Indication: orBec® is an anti-inflammatory corticosteroid indicated for the treatment of graft versus host disease (GVHD) involving the gastrointestinal (GI) tract in conjunction with an induction course of high-dose prednisone or prednisolone

SUMMARY

The applicant has submitted a New Drug Application for orBec®. The proposed orBec® labeling states "Proposed Indication: orBec® is an anti-inflammatory corticosteroid indicated for the treatment of graft versus host disease (GVHD) involving the gastrointestinal (GI) tract in conjunction with an induction course of high-dose prednisone or prednisolone".

The NDA contains two randomized clinical trials (one major, ENT 00-02, and one supportive, 875) to demonstrate efficacy.

This ODAC briefing document provides a draft summary of the Agency's clinical and statistical reviews of the orBec application. The Agency's findings are:

1. The major trial designed to prove orBec's efficacy failed its primary endpoint.
2. Therefore any other analyses, whether pre-specified based on secondary endpoints or the result of retrospective data collection, are exploratory and hypothesis generating. This conclusion is based on the fact that additional analyses increase the probability of a false positive result.
3. The major trial designed to prove orBec's efficacy had at least one imbalance between treatment arms. The impact of this imbalance is unknown.
4. The applicant's post-hoc proposal to combine data from the major trial and the supportive trial to demonstrate efficacy based on post-hoc analysis and endpoints is problematic because of differences between the trials and patient populations. Some concerns include:
    a) Trials had different primary endpoints and objectives
    b) Trials had different designs
    c) Changes in transplant procedures occurred during the 10 years between the start of the supportive trial and the completion of the major trial
    d) Changes in supportive care occurred during the 10 years between the start of the supportive trial and the completion of the major trial
    e) Trials had different dosing regimens/schedules.

CLINICAL STUDIES

The Applicant submitted the results from two randomized clinical trials (one major, ENT 00-02, and one supportive, 875) to demonstrate efficacy. The major study, ENT 00-02, was a phase 3, multi-center, randomized, double-blind, placebo-controlled trial of BDP in conjunction with an induction course of high dose prednisone in 129 patients with grade 2 GI GVHD following allogeneic transplant performed for a variety of hematologic disorders. The primary objective of the major trial was to evaluate whether administration of BDP would decrease the time to treatment failure through Study Day 50. The supportive study, 875, was a single institution, randomized, double-blind, placebo-controlled, phase 2 trial conducted from 1994-1996 in 60 patients with GI GVHD post allogeneic transplant performed for a variety of hematologic disorders. The primary objective of the supportive study was to evaluate ability to increase oral caloric intake to 70% or more of the patient's estimated daily caloric requirements at day 30.

The following tables compare the major and supportive trials for this review. Differences between the two trials are highlighted in bold, including differences in trial design, eligibility, transplant related factors, dosing regimen, duration of study therapy, and study endpoints.

Table 1: Major and Supportive Trials for OrBec

Study #	**Description**	**Patient Population/ #**	**Dates**	**Allograft Source**	**Non-myelo-ablative Conditioning Regimen**
ENT 00-02	**Multi**-center, Phase 3 placebo-controlled, double blind, Safety, PK & Efficacy	Grade 2 GVHD with GI symptoms >=10 days post allogeneic transplant N=129	June 2001-July **2004**	Peripheral blood stem cells: **90%** 2 HLA matched sibling: 60%	Yes **32%**
875	**Single** center, Phase 2 Placebo-controlled, double blind, Safety & Efficacy	GVHD with GI symptoms post allogeneic transplant N=60	Aug. **1994-** Jan. 1996	Peripheral blood stem cells: **20%** 2 HLA matched sibling: 57%	No

Table 2: Major and Supportive Trials for OrBec (continued)

Study #	**Randomization Stratification Factors**	**Study Therapy**	**Therapy Duration**	**Primary Endpoint**
ENT 00-02	• **Center** • **Allograft source (2 HLA haplotype identical sibling or not)** • **Topical corticosteroid use or not**	BDP 1 mg ***IR*** + 1 mg ***EC*** QID or placebo, plus prednisone 1mg/kg/d x10 days, then taper to **0.0625 mg/kg/d** over 1 week	**50** days	**Time to Treatment Failure** by Study Day **50**
875	**Oral caloric intake:** • **< 40% of estimated caloric requirements (ECR) or** • **>=40% of ECR**	BDP 1 mg ***IRC***+ 1 mg ***ECC*** QID or placebo, plus prednisone 1 mg/kg/d x10 days, taper to **1.25 mg/kg/d** by d17	**<=30** days	Ability to take **>= 70% of caloric requirement orally by** Study Day **30**

IR = Immediate-release tablet *IRC = Immediate-release capsule*
EC = Enteric-coated tablet *ECC = Enteric-coated capsule*

Study ENT-002

The primary objective of this multi-center study was to compare the efficacy, defined as time to treatment failure at Day 50, of an oral BDP regimen (1 mg/kg/day prednisone for 10 days plus 2 mg oral BDP QID for 50 days) with the efficacy of standard of care (1 mg/kg/day of oral prednisone administered for 10 days plus matching placebo tablets for 50 days) in patients with Grade II GVHD with GI symptoms. Patients underwent stratified randomization to the treatment arms based on center, the source of the allograft (two HLA haplotype identical sibling versus all others), and topical corticosteroid use.

The secondary objectives of this study were as follows:

1. To compare the proportion of treatment failures in the two groups on Study Days 10, 30, 50, 60, and 80.
2. To compare the treatment groups with respect to cumulative corticosteroid exposure.
3. To compare the treatment groups with respect to the incidence and degree of HPA axis suppression in patients who have not experienced treatment failure by Study Day 50.

4. To evaluate the safety of BDP by comparing the treatment groups with respect to treatment-emergent adverse events.
5. To compare the groups with respect to GVHD progression determined through the assessment of diarrhea (GI), rash (skin), and bilirubin levels (liver).
6. To compare the treatment groups with respect to total deaths and cause of death through 200 days post-transplant.
7. To investigate the pharmacokinetic (PK) profile of single and multiple dose administration of 2 mg oral BDP four times daily (split evenly between the immediate release [IR] and the enteric coated [EC] tablets) for 50 days in patients with Grade II GVHD with GI symptoms.

A patient was judged a <u>treatment failure</u> if one of the following events occurred:

- Required use of prednisone or equivalent IV corticosteroids at doses higher than that specified in the protocol in response to uncontrolled signs or symptoms of GVHD; or
- Required use of any additional other steroid (including "open-label BDP") in response to uncontrolled signs or symptoms of GVHD; or
- Required the addition of immunosuppressant medications other than those permitted by the protocol (see below) in response to uncontrolled signs or symptoms of GVHD.

The protocol specified that patients were to be 10 or more days post allogeneic hematopoietic cell transplant with symptoms consistent with grade 2 GI GVHD and endoscopic evidence of GVHD. (Criteria for grading of acute GVHD were based on Przepiorka *et al* 1995 and Wu *et al* 1998.) The diagnosis of GVHD was to be confirmed by endoscopic biopsy *or skin biopsy.* Non GI-involvement could not be more severe than grade 2 in other sites. Absence of intestinal infection was to be confirmed. Ability to swallow study drug and absence of persistent vomiting were required. The following table, taken from the CSR shows the criteria employed for grading of GVHD.

Table 3: Functional Grading of Acute GVHD (from applicant Table 9.1)

Grade[a]	Extent of Organ Involvement		
	Skin	Liver	Gut
I	Rash on ≤50% of skin[b]	None	Adults: None Children: Diarrhea <5 mL/kg/day[d]
II	Rash on >50% of skin OR	Bilirubin 2-3 mg/dL OR	Adults: Diarrhea >500 mL/day, or persistent nausea, or clinically significant appetite loss[c] Children: Diarrhea 5 to 10 mL/kg/day, or persistent nausea, or clinically significant appetite loss[c]
III-IV	Generalized erythroderma with bullous formation OR	Bilirubin >3 mg/dL OR	Adults: Diarrhea >1000 mL/day[c] Children: Diarrhea >10 mL/kg/day[c]

[a] Criteria for grading given as degree of organ involvement due to GVHD required conferring that grade.
[b] Use "Rule of Nines" or burn chart to determine extent of rash.
[c] Gut symptoms must be accompanied by histological evidence of GVHD in the stomach or duodenum.
[d] Adults ≥16 years of age; children <16 years.

Patients continued baseline GVHD prophylaxis with immunosuppressive drugs, which could include cyclosporine, tacrolimus, sirolimus, methotrexate, and mycophenolate mofetil, but not non-study systemic corticosteroids. Actual doses and regimens of these drugs were not pre-specified, adding to baseline heterogeneity of the study population. A dose increment in baseline immunosuppressive drugs would not be considered "treatment failure" if the adjustment were made to maintain therapeutic serum or plasma drug levels. However, addition of *another immunosuppressive* was considered treatment failure, as was a change in the protocol-specified prednisone dosing.

An exception to this policy was the acceptance of increased doses of prednisone "prescribed for < 96 hours to cover the possibility of adrenal hyporesponsiveness during an anticipated period of medical stress." Although systemic corticosteroid use within 30 days prior to study entry was an exclusion criterion, exemptions were made for use of "corticosteroids such as Decadron as an anti-emetic during conditioning therapy, or use of single doses of corticosteroid in conjunction with infusion of blood products or medications."

If the investigators determined at day 10 that GVHD was adequately controlled, prednisone was to be tapered rapidly over 7 days to a replacement dose of 0.0625 mg/kg/day to be continued until day 80, the completion of the trial. Study assessments continued through day 80, including for patients who were felt to be treatment failures, although study drug was discontinued. A patient was deemed a treatment failure if GVHD signs and symptoms required the use of high dose non-study corticosteroids, or the addition of other immunosuppressive drugs. The only protocol-specified post-study follow up (after day 80) was contact to ascertain survival status on day 200 post-transplant, and date and cause of death if deceased.

Trial Results Study ENT 00-02

From July 2001 through July 2004, 129 patients were enrolled from 14 US centers and 2 centers in France. Sixty patients (47%) were enrolled from Fred Hutchinson Cancer Research Center. Randomization was stratified by study center, source of allograft (two HLA haplotype identical siblings versus all others) and use of topical steroids.

The treatment arms appeared balanced with respect to demographic factors. The majority of patients received their transplant for a primary diagnosis of leukemia, with acute myelogenous leukemia (32%), acute lymphocytic leukemia (12%), and chronic myelogenous leukemia (12%) the most prevalent. Although the study population consisted of a heterogeneous group of diagnoses, the treatment groups were generally well balanced with respect to the primary diagnosis, disease phase, and risk of relapse post-transplant. Nearly all patients (98%) had grade 2 GVHD of the intestine/gut at baseline.

An imbalance between treatment arms was observed based on the types of transplant. The percentage of patients who received a non-myeloablative conditioning regimen was approximately two-fold higher in the BDP group compared to placebo (n=26 [42%] versus n=15 [22%], respectively). The percentage of patients who had bone marrow as the source of their transplant, rather than peripheral stem cells, was higher in the BDP group compared to the placebo group (n=8 [13%] versus n=5 [7%], respectively).

For the first 16 patients entered, the starting dose of prednisone was 2 mg/kg/day (n=7 BDP, n=9 placebo). After 10 days of treatment at this initial dose level, the dose of prednisone was tapered over 7 days, after which patients received a maintenance physiologic replacement dose of 0.125 mg/kg/day. Due to evidence of suppressed HPA axis function at the end of the 50-day protocol treatment period, the protocol was amended to reduce the starting dose of prednisone from 2 mg/kg/day to 1 mg/kg/day. Patients who received the lowered starting dose of prednisone were maintained on a physiologic replacement dose of 0.0625 mg/kg/day.

Most patients received a calcineurin inhibitor plus either methotrexate or mycophenolate mofetil (MMF) for prophylaxis of GVHD at baseline. In view of the higher percent of patients with non-myeloablative vs. ablative transplants in the BDP compared with the placebo treatment group (42% vs. 22%), a greater percent of BDP (46%) than placebo patients (17%) was treated with the regimen including MMF. In a retrospective analysis requested by FDA, the applicant obtained information regarding post-baseline concomitant therapy with immunosuppressive drugs. During treatment with study drug and through day 80, 88% of placebo patients and 70% of BDP patients received a calcineurin inhibitor, whereas 13% of placebo patients and 22% of BDP patients received MMF. Prednisone was dosed in excess of protocol-specified doses following discontinuation of study drug through Study Day 80 in 64% of placebo patients

and 39% of BDP patients, for whom data were available (data unavailable for 8% and 10 % of placebo and BDP patients, respectively).

The intent-to-treat (ITT) analysis of the primary efficacy endpoint of time to treatment failure through Study Day 50 is summarized in the table below. The adjusted hazard ratio for patients in the BDP treatment group relative to the placebo group was 0.63 (95% confidence interval: 0.35, 1.13), and the primary comparison for this endpoint was not statistically significant (p=0.1177, stratified logrank test). The applicant's analysis of the primary endpoint failed to demonstrate an improvement in time-to-treatment failure through Study Day 50. The FDA agrees with the applicant's analysis.

Table 4: Time to Treatment Failure through Study Day 50 (Reviewer Table)

	Placebo	**BDP**
Patients Randomized	67	62
Number of Treatment Failures	30	18
Adjusted hazard ratio (95% CI)	0.63 (0.35, 1.13)	
Stratified logrank test	$\chi 2 = 2.447$, 1 df, P = 0.1177	

Reviewer comment: Even after failure of the primary endpoint, the applicant conducted multiple analyses on many pre-specified and non-pre-specified endpoints. These are considered as exploratory or hypothesis generating.

Study 875

Study #875 was a single center, randomized, double-blind, placebo-controlled, phase 2 trial conducted from 1994-1996 at FHCRC. Patients were randomized to BDP or placebo in conjunction with a trial of high dose prednisone for GI GVHD. Randomization to the treatment arms was stratified by degree of anorexia based on caloric intake (i.e., < 40% of estimated caloric requirements [ECR] versus ≥ 40% ECR). The primary endpoint was the number of patients who successfully increased their oral caloric intake to ≥ 70% of their estimated caloric requirements by Study Day 30 without need for additional prednisone or other immunosuppressive drugs to control signs and symptoms of GVHD. Patients who demonstrated a response (oral caloric intake increased to ≥ 70% ECR by Day 10) continued study therapy for an additional 20 days. Patients who did not meet the response definition by Study Day 10 were removed from the study.

As specified in the protocol, the objectives for this trial were:

1. To compare the frequency of initial clinical responses after 10 days of therapy with either prednisone 1 mg/kg plus oral BDP (8 mg) or prednisone 1 mg/kg plus placebo

capsules, with responses to be measured by oral caloric intake and symptom scores.
2. In patients with a satisfactory initial response after 10 days, to compare the frequency of durable responses during 20 additional days of treatment with either prednisone (rapidly tapered from 1 mg/kg to) plus oral BDP (8 mg) or prednisone plus placebo, responses to be measured by oral caloric intake and need for additional prednisone.

Secondary endpoints were to "assess frequency and severity of individual gastrointestinal symptoms after 10, 20, and 30 days on protocol."

For entry into the protocol, patients were required to be post allogeneic transplant with intestinal GVHD, but without infection. Patients required endoscopic or colonoscopic findings consistent with GVHD and biopsy evidence of intestinal GVHD. Patients were enrolled only if they were able to eat <70% of their estimated daily caloric requirements. Patients were excluded if they were already receiving prednisone or had moderate to severe GVHD defined as:

- Skin GVHD other than a slowly evolving rash involving < 50% of body surface
- Liver GVHD
- Enteric GVHD with diarrhea volume > 1000 ml.

(Note: These criteria, in contrast to ENT 00-02, exclude subjects with any concomitant liver GVHD or with grade 2 (present classification) skin GVHD, and do not specifically require diarrhea > 500 ml/day (but < 1000), per the current classification of grade 2 GVHD.)

Patients were permitted to continue concomitant immunosuppressive therapy with "cyclosporine, methotrexate, or FK-506 but not HAT (Human anti-TAC)."

Trial Results Study 875

The trial was conducted from August 1994 through January 1996 at FHCRC. Thirty-six males and 24 females were randomized, including 8 patients under age 18. Treatment arms appeared balanced for demographic factors except that information on race was not available. This was a heterogenous group of patients as far as primary hematologic diagnosis, with 35% of patients with chronic myelogenous leukemia (CML), 18% acute myelogenous leukemia (AML), 13% acute lymphocytic leukemia (ALL), 10% myelodysplastic syndrome (MDS), 8% non-Hodgkin's lymphoma (NHL). The allograft source was peripheral blood stem cells in approximately 20% of patients and bone marrow in approximately 80%, with 57% receiving stem cells from a 2 HLA matched sibling donor. Seventeen patients in each treatment arm received stem cells from HLA matched siblings.

Baseline immunosuppressive therapy was similar for both treatment groups. There were 22 /29 (76%) placebo patients and 20/31 (65%) BDP patients who received cyclosporine plus methotrexate for prophylaxis of GVHD. There were 5/29 (17%) and 3/31 (10%) in the placebo and BDP groups, respectively, receiving tacrolimus plus

methotrexate, the next most common prophylactic regimen. In a retrospective analysis requested by FDA, the applicant obtained information regarding post-baseline concomitant therapy with immunosuppressive drugs. During treatment with study drug and through day 40, 100% of placebo patients and 97% of BDP patients received a calcineurin inhibitor. Prednisone was dosed in excess of protocol-specified doses following discontinuation of study drug through day 40 in 72% of placebo patients and 39% of BDP patients.

There were noted to be 25/60 patients with protocol violations, 13 in the BDP group and 12 in the placebo group. Most deviations were felt to be minor (minor dosing errors/missed doses). One patient in each group was incorrectly classified as a treatment success on Study Day 10, but subsequently excluded when calorie counts showed the respective oral intakes to be < 70% ECR.

The pre-specified primary endpoint for this trial was the number of patients who successfully increased their oral caloric intake to ≥ 70% of estimated caloric requirement (ECR) by Study Day 30. Table 5 shows the incidence by study arm of patients who achieved daily oral caloric intake >= 70% of ECR at Study Day 30.

Table 5: Daily Oral Intake >= 70% ECR at Day 30 (Reviewer Table)

	Placebo	BDP
Patients randomized	29	31
Patients with oral intake ≥ 70% ECR (n, %)	12 (41%)	22 (71%)
95% CI	(0.24, 0.61)	(0.52, 0.86)
p-value Fisher's exact test	P= 0.036	

This analysis of the pre-specified primary endpoint for study 875 was verified by the FDA statistical reviewer.

In 2001, after completion of the study, the applicant further explored a new endpoint of time-to-treatment-failure at day 30, and did not find a difference between treatment arms., (The applicant defined failure as the requirement for additional prednisone to treat new or worse signs or symptoms of GI GVHD *or*, at day 10 or day 30 evaluation, daily oral intake of <70% ECR.)

POST-HOC ANALYSES

The applicant has added several post-hoc endpoints and analyses subsequent to the completion of study ENT 00-02. These analyses are provided by trial and by combining the results from both trials. These analyses were performed after retrospective data collection as both trials had been completed. In fact, trial 875 had completed almost 10

years previously. Data regarding survival and certain baseline disease characteristics were obtained retrospectively from records. The applicant has submitted post-hoc analyses of efficacy based on the following non-pre-specified endpoints:

- Survival at Day 200 Post-Transplant
- Survival at One Year Post-Transplant
- Overall survival Post-Randomization.

As discussed further below, the applicant has performed these analyses for each trial and pooled together available data for both trials.

According to the International Conference on Harmonization (ICH) Guidance E9: *"Under exceptional circumstances a meta analytic approach may also be the most appropriate way, or the only way, of providing sufficient overall evidence of efficacy via an overall hypothesis test.* ***When used for this purpose the meta-analysis should have its own prospectively written protocol****".*

According to EMEA 2001 "Points to consider on applications with 1. Meta-analyses; 2. One pivotal study, Section II.1.3 Regulatory prerequisites of retrospective meta-analysis: *"Prerequisites for a retrospective meta-analysis to provide sufficient evidence for a claim include: - Some studies clearly positive"…"A retrospective meta-analysis of only two studies originally intended to stand on their own is not expected to add any useful information."*

Pooling Considerations

Important differences between the 2 trials make the issue of pooling problematic. These include:

1) The two trials were not concurrent. Advances in transplant procedures (source of stem cells and conditioning regimens) and supportive care occurred during the decade separating the trials. During this time, peripheral blood stem cells became a primary source of stem cells in addition to bone marrow. Also the scientific field of transplantation advanced permitting non-myeloablative transplants.
2) The trials differed in terms of enrolled populations (source of transplant and myeloablative versus non-myeloablative as outlined in Table 1 above). Thirty-two per cent of patients in ENT 00-02 underwent non-myeloablative transplants, compared with all patients undergoing myeloablative transplants in study 875.
3) Study 875 was a single center study, whereas ENT 002 was a multi-center study.
4) The stratification factors were different between two studies.
5) Primary objectives and the endpoints are different in two studies.
6) Patients were treated for different duration of time in the two studies.
7) There were differences in conditioning regimens, dosing schedule, and

eligibility.

8) The follow-up on all patients for survival was not planned and any subsequent therapy or co-morbid conditions were not documented.
9) Durations of study follow-up were different for two studies.
10) Slightly different formulations were used for the 2 trials. The earlier trial used orBec capsules and the newer trial used orBec tablets, the to-be-marketed formulation.

Discussion of Survival Endpoints

Survival at Day 200

Survival at Day 200 from the time of transplant was a safety endpoint in the ENT 00-02 trial. This endpoint was not pre-specified for the 875 trial. Since the endpoint definition is based on the timing of the transplant and not on randomization date or study drug administration, these analyses are not useful to demonstrate the efficacy of orBec.

Survival at One Year Post Transplant

This endpoint was not a pre-specified endpoint for either trial. This endpoint was defined from date of randomization to one year post randomization. Since this endpoint is contained within the endpoint of overall survival, please see discussion regarding overall survival below.

Overall Survival

This endpoint was also not a prospectively defined endpoint for either trial. This endpoint was defined from date of randomization. Survival data was obtained retrospectively from FHCRC records, or by questionnaire to non-FHCRC investigators.

Results: Overall Survival Analysis

The results for each trial separately as well as for the combined analysis are shown in the table below. Neither Trial 875 nor ENT 00-02 demonstrated an improvement in overall survival. Only the pooled analysis suggests a survival difference may exist. However, the Agency disagrees with the pooling of the trial results and considers all of these analyses to be hypothesis generating for a future trial.

Table 6: Post-Hoc Overall Survival Analyses (Reviewer Table)

	875		ENT 00-02		Studies Combined	
	Placebo	BDP	Placebo	BDP	Placebo	BDP
Subjects Randomized	29	31	67	62	96	93
Subjects Dead	17 (59%)	10 (32%)	32 (48%)	27 (44%)	49 (51%)	37 (40%)
Hazard Ratio (95% CI)	0.47 (0.22, 1.04)		0.71 (0.42, 1.20)		0.63 (0.41, 0.97)	
Stratified Logrank Test*	p=0.0559		p=0.1980		p=0.0323	

* Due to the lack of a pre-specified plan, the significance of these p-values is unknown.

Previously during a meeting between FDA and the applicant, FDA suggested pooling the data in order to generate a possible hypothesis to be tested future studies.

Reviewer comments:

- *The design of trial ENT 00-02 seems appropriate to evaluate the effect of study drug on a short-term clinical outcome, such as the pre-specified primary endpoint, comparing treatment failure in the 2 study arms during the 50-day treatment period.*
- *The study was not designed to evaluate survival, with a short pre-specified follow-up.*
- *There was no attempt to stratify for, or even prospectively obtain baseline disease characteristics expected to have major impact on long-term survival, such as remission status for patients with acute leukemia, or phase of disease for patients with chronic myelogenous leukemia (CML).*
- *There was no attempt to enroll a uniform population of hematopoietic transplant patients with similar relapse and survival risk.*
- *There was an imbalance favoring the BDP arm in the proportion of patients who received non-myeloablative vs. ablative conditioning regimens, which may have influenced outcome.*
- *All patients were treated with a baseline GVHD prophylaxis regimen, but the actual regimen and dosages were not pre-specified, adding to baseline heterogeneity of the study population.*
- *The design of trial 875 also seems appropriate to evaluate the effect of the study drug on the short-term clinical outcome of caloric intake, but not appropriate to study a long term outcome for reasons similar to the reasons outlined for ENT 00-02.*
- *There was no uniform follow up of patients post study treatment and any post study treatment or co-morbid conditions that may influence survival were not captured.*

Exploratory Overall Survival Subset Analysis by Conditioning Regimen

A subset analysis of survival was conducted in view of the imbalance between BDP and placebo treatment arms for patients with myeloablative vs. non-myeloablative conditioning regimens. There were 42% of BDP patients and 22%

of placebo patients who received a non-myeloablative transplant. The next table shows the FDA statistical reviewer's analysis.

Table 7: ENT 00-02 Overall Survival Post-Randomization by Conditioning Regimen (Reviewer Table)

	Intent-to-Treat		Non-Myeloablative		Myeloablative	
	Placebo	BDP	Placebo	BDP	Placebo	BDP
Subject randomized	67	62	15	26	52	36
Survival Status						
Alive	34 (51%)	33 (53%)	3 (20%)	14 (54%)	31 (61%)	19 (56%)
Dead	32 (48%)	27 (44%)	12 (80%)	12 (46%)	20 (39%)	15 (44%)
Hazard ratio	0.71		0.23		0.96	
(95% CI)	(0.42, 1.20)		(0.09, 0.58)		(0.49, 1.88)	

Reviewer comment: It appears that the ITT results are driven by a very small number of patients in the non-myeloablative subset.

SAFETY CONSIDERATIONS

The major safety issue for this application is HPA suppression. The applicant hypothesized that the topical effects of oral BDP on the inflamed gastrointestinal mucosa would result in fewer treatment failures, and, therefore, a lesser requirement for systemic glucocorticoid therapy, i.e. prednisone. One potential benefit of a lesser requirement for systemic steroids would be a decrease in hypothalamic-pituitary-adrenal (HPA) axis suppression. However, when the applicant compared the results of ACTH stimulation tests conducted on Day 0 and Day 51 for patients enrolled in ENT-002., suppression of the hypothalamic-pituitary-adrenal (HPA) axis occurred more frequently in the oral BDP group compared to the placebo group. The applicant analyzed these results using 2 different methodologies to determine whether a patient had abnormal HPA axis suppression.

The applicant's results obtained by 2 different analyses were very similar, demonstrating that more patients treated with BDP manifested an abnormal ACTH stimulation test than patients treated with placebo. For the first analysis (evaluable patients = 52), 85.7% of BDP-treated patients manifested abnormal ACTH stimulation tests on Study Day 51 compared with 58.3% of placebo-treated patients. For the second analysis (evaluable patients = 63), 77.1% (27/35) of BDP-treated patients manifested abnormal ACTH stimulation tests on Study Day 51 compared with 57.1% (16/28) of placebo-treated patients.

The applicant states that 1) These analyses are technically incomplete since ACTH stimulation tests were not required Study Day 51 for patients previously designated to be treatment failures; and 2) Treatment failure resulted in greater exposure to systemic corticosteroids (median cumulative glucocorticoid exposure 36.1 mg/kg vs. 15.2 mg/kg in treatment failures vs. non-treatment failures, respectively, by Day 50); since more treatment failures occurred in the placebo group, more placebo patients would have manifested HPA axis suppression if all randomized/treated patients had been tested on Day 51. The review team does not dispute these statements. However, for patients without treatment failure, the 85.7% incidence of suppression of the HPA axis in BDP-treated patients seems to contradict the applicant's hypothesis that therapy with orBec spares patients from the systemic effects of absorbed corticosteroids.

IN SUMMARY

The pivotal study ENT 00-02 did not demonstrate efficacy based on the protocol specified primary analysis. Due to the differences in trial design, dosing regimens, methodology, the Agency cannot rely on the post-hoc pooled analyses to prove efficacy for orBec, and such analyses are considered to be exploratory/ hypothesis generating for future studies. The Agency recommends that the applicant demonstrate orBec's efficacy through the use of prospectively designed trial(s).