DOR BioPharma, Inc.

1101 Brickell Avenue • Suite 701-S • Miami, FL 33131
Tel: 786-425-3848 • Fax: 786-425-3853
www.dorbiopharma.com

orBec®

(oral beclomethasone dipropionate, BDP)

for Treatment of Graft-versus-Host Disease (GVHD) of the Gastrointestinal (GI) Tract

Briefing Document

Oncologic Drug Advisory Committee Meeting

May 9th, 2007

Afternoon Session

NDA #22-062

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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1. LIST OF ABBREVIATIONS

ACTH.....adrenocorticotropic hormone
AE .....adverse events
aGVHD .....acute graft-versus-host disease
aGVHDAI .....acute GVHD Activity Index
ATG .....anti-thymocyte globulin
AUC .....area under curve
BDP.....oral beclomethasone dipropionate, orBec®
BMP .....beclomethasone mono-propionate
BMT .....bone marrow transplantation
BOH .....beclomethasone
BOOP.....bronchiolitis obliterans organizing pneumonia
CHO .....chinese hamster ovary
CI.....confidence interval
CMH .....Cochran-Mantel-Haenszel
CMV .....cytomegalovirus
CTL .....cytotoxic lymphocyte
EC .....enteric coated
FDA.....Food and Drug Administration
FHCRC .....Fred Hutchinson Cancer Research Center
FR.....France
GI .....gastrointestinal
GI GVHD.....gastrointestinal graft-versus-host disease
GVHD .....graft-versus-host disease
GVL .....graft versus leukemia
HCT.....hematopoietic cell transplantation
HLA .....human leukocyte antigen
HPA.....hypothalamic-pituitary-adrenal
HR.....hazard ratio
IFN .....interferon
IL.....interleukin
IND .....investigational new drug
IR.....immediate release
ITT .....intent-to-treat
IV .....intravenous
IVIG .....intravenous immunoglobulin
LPS.....lipopolysaccharide
MHC .....major histocompatibility
MMF .....mycophenolate mofetil
NDA.....new drug application
NK.....natural killer
ODAC .....Oncologic Drug Advisory Committee

1. LIST OF ABBREVIATIONS (CONTINUED)

PK .....pharmacokinetics
QID .....four times a day
SAE.....serious adverse events
SC.....subcutaneous
SPA .....special protocol assessment
SD .....standard deviation
Th1 .....T helper type 1
TNF .....tumor necrosis factor
US .....United States

2. EXECUTIVE SUMMARY

2.1 Proposed Indication and Regulatory History

The oral beclomethasone dipropionate (BDP) indication requested in NDA 22-062 is for the treatment of graft-versus-host disease (GVHD) involving the gastrointestinal tract in conjunction with an induction course of high-dose prednisone or prednisolone. Data from seven clinical studies were included in the new drug application (NDA) submission to support this indication. This briefing document provides a summary of those data with particular attention to the pivotal phase 3 randomized, double-blind, placebo controlled study.

BDP has been studied under US investigational new drug (IND) application since 1991; initially this was an investigator initiated IND and sponsorship was transferred to Enteron Pharmaceuticals (a subsidiary of DOR BioPharma, Inc.) on March 23, 1999. FDA Office of Orphan Drug Products granted BDP Orphan Designation for oral administration in the treatment of intestinal GVHD on March 27, 1998 and awarded the sponsors two FDA grants in support of clinical research, the first in 1991 and the second in 2005. Fast Track designation was granted in October 25, 2000. The pivotal Phase 3 study was conducted under a Special Protocol Assessment (SPA) through the Division of Gastrointestinal and Coagulation Drug Products and the NDA (submitted September 21, 2006) has been reviewed in the Division of Drug Oncology Products in the Office of Oncology Drug Products.

2.2 Background

Allogeneic hematopoietic cell transplantation (HCT) is a procedure that increasingly is used for the treatment of hematologic malignancies, immunodeficiency disorders, and some inborn errors of metabolism, with approximately 12,000 procedures expected to be performed in the United States in 2007. Many patients treated with allogeneic HCT for hematologic malignancy achieve long-term remission of their underlying malignancy and in some cases may be considered cured. Following the initial conditioning regimen of chemotherapy and irradiation and infusion of allogeneic donor cells, the primary causes of morbidity and mortality is are regimen-related toxicity, graft failure, infection, acute

graft-versus-host disease (aGVHD) and the complications of its treatment and relapse of malignancy. Acute GVHD, which occurs in approximately 60% (7,000) of HCT recipients, results from the attack of donor T cells and generation of cytokines in recipient tissues and primarily targets the skin, liver and gastrointestinal (GI) tract. The extent and severity of GI GVHD is an important determinant of non relapse mortality which varies from 10 – 100% by transplant day 200, depending on grade of GVHD. The mortality rate among patients who develop grade II GVHD is 24% and 25% among patients with hematologic malignancy who received myeloablative conditioning regimens and HLA matched sibling or matched unrelated donor allografts, respectively. Most experts now believe that a parallel attack of donor T cells on host leukemia or lymphoma cells is also responsible for a lower rate of relapse of malignancy among patients who develop aGVHD, an effect termed the "graft versus leukemia" (GVL) effect.

The onset of aGVHD is usually 2-8 weeks after transplant but may be later depending on the conditioning regimen. The severity of aGVHD is graded from I through IV, based on the degree of abnormality in the affected organs. Symptoms of acute GI GVHD may include anorexia, nausea, vomiting, diarrhea, protein loss, abdominal pain, and bleeding. In its most severe form, GVHD leads to ulcerations in, and ultimately sloughing of, the mucosal lining of the GI tract. Treatment of GI GVHD is most commonly with prednisone or methyl prednisolone at doses of 1-2 mg/kg/day and frequently results in remission of GVHD; however, the toxicity of prolonged exposure to high dose corticosteroids frequently leads to patient debility and immune suppression. For the majority of patients with aGVHD, mortality is not due to uncontrolled GVHD, but to immunosuppression resulting in opportunistic infections. Relapse may also be related to suppression of the desired GVL effect due to the systemic immunosuppressive side effects of prolonged corticosteroid administration that is required to treat aGVHD. While high dose corticosteroids currently may be considered the standard of care in aGVHD, no drugs are currently approved by the FDA for its treatment.

Oral beclomethasone dipropionate (BDP) represents a first-in-class oral, locally acting therapy designed to treat both the upper and lower GI tract manifestations of GVHD. BDP is intended to reduce exposure to systemic immunosuppressive drugs to treat

GI GVHD and therefore reduce the frequency of opportunistic infections and suppression of the GVL effect. BDP is a highly potent corticosteroid that is not absorbed into systemic circulation, its primary metabolite, 17-BMP, does have systemic exposure, but appears to cause only limited systemic glucocorticoid effects. The primary effect of BDP on intestinal inflammatory disease is believed to result from its local effects within GI mucosa. Beclomethasone dipropionate has been marketed in the United States and worldwide since the early 1970's as the active pharmaceutical ingredient in a nasal spray and in a metered dose inhaler for the treatment of patients with allergic rhinitis and asthma, indications in which it has been shown to be active with minimal systemic side effects. For patients with GVHD involving the GI tract, BDP is formulated for oral administration as a single product consisting of two tablets (each tablet contains 1 mg BDP), one tablet is formulated to release BDP in the stomach and the other tablet is formulated to release BDP in the alkaline environment of the mid-small intestine. The recommended dose is 8 mg/day (the two tablets given 4 times a day [QID]) for 50 days.

2.3 Unmet Medical Need

Currently, no therapeutics have been approved by the FDA for use in the treatment of aGVHD or GI GVHD. Given the toxicity of the current therapies, an unmet medical need exists for safer, more-effective agents.

2.4 Basis for Licensure

In the pivotal phase 3 clinical trial, BDP demonstrated a strong trend toward an improvement in treatment failure rate at Day 50 post-randomization, the primary endpoint of the trial, with a nominally statistically significant improvement in treatment failure rates at Day 80, a prospectively defined secondary endpoint. These improvements were accompanied by a clinically meaningful improvement in survival at Day 200 post-transplant that persisted at 1 year post-randomization and persists as a trend in overall survival through to the time of the data cutoff (September 1, 2005). The predominant mortality benefit was seen in those patients with the worst predicted outcome, those whose donors were HLA-matched unrelated donors or family members other than HLA-match siblings; however, the benefit was seen in the overall intention-to-treat (ITT)

population. Other than degree of HLA match, no covariates were identified that contributed meaningfully to outcome.

The hypothesis that the impact of BDP on patient outcomes would be mediated by a reduction in exposure to systemic immunosuppression is supported by the finding that the predominant causes of increased mortality in patients randomized to placebo were infection and relapse of their underlying malignancy, both of which are associated with immunosuppression. While the safety analysis for the phase 3 study of BDP versus placebo indicates no significant differences between the 2 arms in terms of adverse event (AE) frequency, severity, and laboratory analysis, absolute numbers of events in the organ class "infection and infestations" was lower in the BDP arm (51% for BDP versus 61% for placebo). Hypothalamic pituitary adrenal (HPA) axis evaluation shows some suppression of the HPA axis with BDP and AE reporting includes reports of cushingoid features in 15% of BDP patients versus 9% of placebo patients both indicating some degree of systemic absorption and adrenal suppression by 17-BDP.

The improvement in mortality seen in the pivotal phase 3 trial is supported by a retrospective analysis of mortality in the placebo-controlled phase 2 study in an essentially identical patient population which, although not statistically significant, shows consistent survival outcomes. The results of selected survival outcomes from both studies are presented in Table 2-1. The results of the corresponding integrated analysis of the 2 studies are shown in Figure 2-1.

No drugs are currently licensed for the treatment of acute GI GVHD. Current standard of care in the disease is high dose corticosteroids, which carry significant toxicity. The mortality benefit in the BDP arms of these trials, combined with the favorable risk benefit ratio and the lack of alternative therapies make BDP a major advance in the therapy of grade II acute GI GVHD.

Table 2-1. Survival Data for Subjects Enrolled in Study ENT 00-02 and Study 875 At 200 Days After HCT and at 1 Year After Randomization to Study (ITT Analysis)

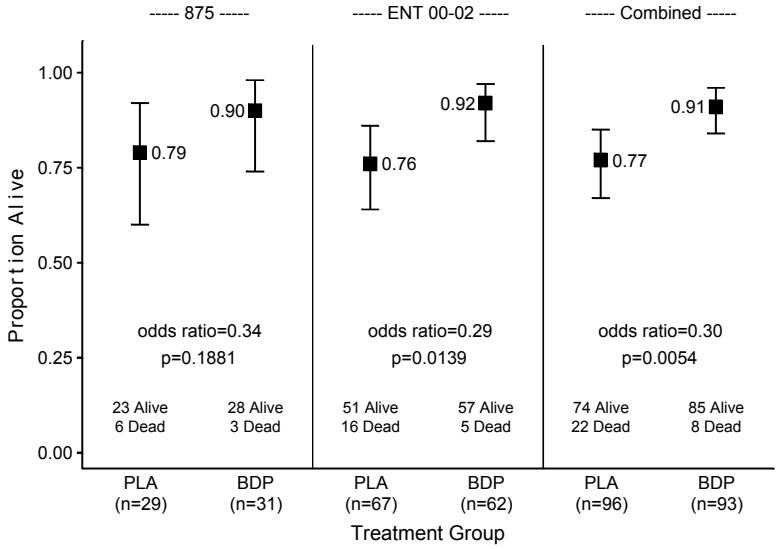
	Phase 3 Study ENT 00-02		Phase 2 Study 875	
	Placebo	BDP	Placebo	BDP
Number of subjects randomized	67	62	29	31
Number (%) died by transplant day 200	16 (24%)	5 (8%)	6 (21%)	3 (10%)
Odds ratio (95% CI)	0.29 (0.10, 0.82)		0.34 (0.07, 1.72)	
P-value	0.0139		0.1881	
Hazard ratio (95% CI)[a]	0.33 (0.12, 0.89)		0.44 (0.11, 1.75)	
P-value[a]	0.0294		0.2415	
Number (%) died by 1-year post-random	28 (42%)	18 (29%)	9 (31%)	6 (19%)
Hazard ratio (95% CI)	0.54 (0.30, 0.99)		0.55 (0.20, 1.56)	
P-value	0.0431		0.2556	

[a] Adjusted for the time between transplantation and randomization.

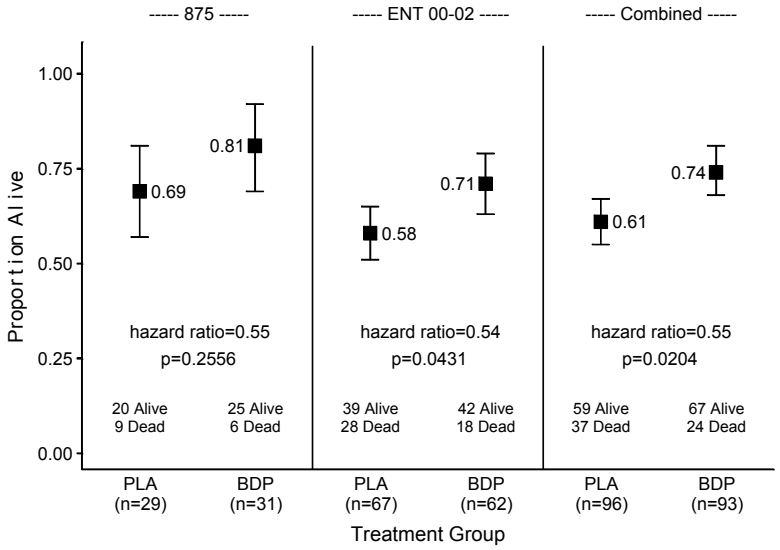
CI = confidence interval; HCT = hematopoietic cell transplantation

Figure 2-1. Survival Outcomes for Studies 875 and ENT 00-02, and Both Studies Combined (Integrated ITT Analysis Sets)

Survival at Day 200 Post-Transplantation:



Survival at One Year Post-Randomization:



2.5 Overview of the BDP Clinical Development Program

The clinical development program for BDP included 2 studies in healthy volunteers and 4 studies in subjects with established acute GI GVHD who previously underwent allogeneic HCT for a variety of hematologic disorders. The safety database also includes 1 study in subjects with Crohn's disease (n = 4); this study was terminated early due to lack of resources; there were no safety concerns in this study.

The healthy volunteer studies included 12 subjects who received a single 6-mg dose of BDP as one of 4 combinations of immediate- release (IR) and enteric coated (EC) tablets under fed or fasting conditions (Study ENT 00-01) and 12 subjects who received single doses of BDP administered orally as 1) 6 x 1 mg BDP IR tablets, 2) 6 x 1 mg BDP EC tablets, and 3) 6 mg BDP as a liquid suspension (Study ENT 05-BA).

The 4 studies in subjects with acute GI GVHD included an uncontrolled phase 1 study (Study 615), a compassionate-use study in subjects with contraindications to high-dose corticosteroid therapy (Study 1500), a phase 2, randomized, double-blind, placebo-controlled study (Study 875), and the pivotal study (Study ENT 00-02), a phase 3, randomized, double-blind, placebo-controlled study. The total number of subjects included in these 4 studies is summarized in Table 2-2.

Table 2-2. Study Designs: Studies of BDP in Subjects With GI GVHD

Study Number	Phase	Description	Sponsor	Number of Subjects Enrolled		
				BDP	Placebo	Total
615	1	Uncontrolled study	Investigator initiated[a]	42	0	42
1500	1	Uncontrolled study	Investigator initiated	16	0	16
875	2	Single center, randomized, placebo-controlled study	Investigator initiated[a]	31	29	60
ENT 00-02	3	Multicenter, randomized, placebo-controlled trial	Enteron Pharmaceuticals (subsidiary of DOR BioPharma, Inc.)	62	67	129
			Total	***151***	***96***	***247***

[a] Funded by an Orphan Products Development Grant from the US Food and Drug Administration.

2.6 Evidence of Clinical Efficacy

2.6.1 Pivotal Phase 3 Study ENT 00-02

Study ENT 00-02 ("A Phase III Randomized Placebo-Controlled, Multi-Center Study of the Safety, Efficacy, and Pharmacokinetics of Oral Beclomethasone 17, 21-Dipropionate in Conjunction with Ten Days of High Dose Prednisone Therapy in the Treatment of Subjects with Grade II Graft vs. Host Disease with Gastrointestinal Symptoms") enrolled 129 subjects with symptoms of acute GI GVHD whose endoscopy and mucosal biopsy specimens demonstrated findings consistent with GI GVHD, and whose stool and mucosal biopsy cultures were negative for pathogens. Subjects with GI GVHD who had limited skin and liver aGVHD were also eligible for the study.

Protocol treatment consisted of study drug (BDP 8 mg/day or placebo, both administered in a double-blind manner in 4 divided doses per day) plus a 10-day induction course of prednisone (1 mg/kg/day). A rapid prednisone taper over 7 days began on Study day 11 after which all subjects received physiologic replacement doses of prednisone (0.0625 mg/kg/day) through Study day 80. Administration of blinded study drug

continued unchanged from Study days 1-50 or until GVHD treatment failure or subject withdrawal. GVHD treatment failure was defined as the requirement for increased doses of immunosuppressive drugs beyond those specified in the protocol; subjects with uncontrolled signs or symptoms of GVHD who required higher doses of corticosteroids, use of additional steroids, or addition of additional immunosuppressive agent(s) were identified using best clinical judgment of the investigator at each study site.

The primary endpoint was the "time to GVHD treatment failure through study day 50" (i.e., the planned end of the 50-day protocol treatment period). Prospectively defined secondary endpoints included cumulative treatment failure rates by study days 10, 30, 50, 60, and 80, which in the final analysis were assessed as the time to treatment failure through study day 80 (i.e., the planned end of the 80-day study period). Other prospectively defined endpoints included functional performance status, and safety endpoints of survival through Day 200 post-transplant, systemic corticosteroid exposure over the 80-day study period, hypothalamic-pituitary-adrenal (HPA) axis function, GVHD assessments of GI, skin, and liver involvement at selected time points, and treatment emergent AEs (all AEs occurring after start of investigational drug). Survival at 1 year post-randomization and overall survival were evaluated, as FDA-requested these *post-hoc* analyses.

The randomization was stratified by study center, topical corticosteroid use at baseline (yes, no), and donor type (HLA matched sibling, all others). The statistical analysis plan specified the primary efficacy analysis to be stratified by donor type only. The primary efficacy analysis was based on the ITT principle and included all randomized subjects who were analyzed according to their randomized study drug assignment. Safety was assessed based on all subjects who received at least one dose of study drug. Hypothesis tests of the primary and secondary endpoints were performed using a 2-sided significance level of 0.05. The protocol and statistical analysis plan did not include specifications for adjusting the significance level to account for inflation of the overall type 1 error rate due to the testing of secondary endpoints and post-hoc analyses. As described below in Section 2.6.1.1, the primary analysis of the primary efficacy endpoint for this study failed to achieve the predefined level of statistical significance. In light of this result, analyses

were performed in an exploratory manner for the secondary endpoints defined for this study. The inferential results reported from these analyses may be viewed as descriptive measures since all of the type 1 error that was allocated for this study was spent on the aforementioned primary endpoint and retrospective adjustment of the significance level is considered not meaningful once the results are known. However, given the clinical importance of some of the secondary endpoints and post-hoc analyses (i.e., survival), inferential results unadjusted for multiplicity are reported to facilitate interpretation of the data from this study and to assist with the overall clinical evaluation of the benefits and risks of BDP treatment.

A total of 129 subjects were randomized between July 2001 and July 2004 at 14 centers in the United States and 2 centers in France. Approximately half (47%) of the overall study population was enrolled at the Fred Hutchinson Cancer Research Center in Seattle, WA. Sixty-two subjects (48%) were randomized to receive BDP treatment, and 67 subjects (52%) were randomized to receive placebo. With the exception of 2 subjects (1 subject in each treatment group), all subjects received at least 1 dose of study drug following randomization. The treatment groups were well balanced with respect to race, gender, and age at randomization. Overall, the study population was predominately white (85%), male (60%), with median age of 47 years (range: 6 to 70). Three subjects younger than 18 years (ages 6, 13, and 17), and 7 subjects 65 years or older were enrolled.

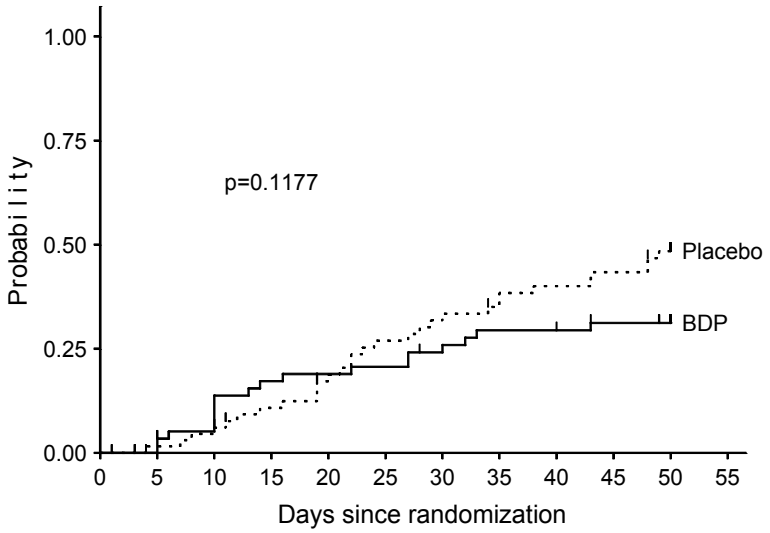
Although the study population consisted of a heterogeneous group of cancer diagnoses, the treatment groups were generally well balanced with respect to the primary diagnosis. The majority of subjects received their transplant for a primary diagnosis of leukemia, with acute myelogenous leukemia (32%), acute lymphocytic leukemia (12%), and chronic myelogenous leukemia (12%) the most prevalent. There were 2 variables for which the treatment arms were imbalanced: subjects whose primary diagnosis is associated with an increased risk of relapse after transplant (65% in BDP arm versus 43% in placebo arm) and type of conditioning regimen (myeloablative versus non-myeloablative) received (42% non-myeloablative in BDP arm versus 22% in placebo arm). The imbalances between treatment groups for these 2 factors were related because

a greater percentage of subjects in the study population with a poorer prognosis received a non-myeloablative conditioning regimen (66%) compared to recipients of myeloablative conditioning regimens (48%). Detailed demographic data are presented in Section 4.2).

2.6.1.1 Primary Efficacy Endpoint: Time to GVHD Treatment Failure by Study Day 50 (Study ENT 00-02)

The ITT analysis of the primary endpoint using standard time-to-event methodology indicated that BDP was associated with a 37% lower risk of GVHD treatment failure during the 50-day protocol treatment period (hazard ratio = 0.63; 95% CI: 0.35, 1.13), although this result failed to achieve statistical significance (p = 0.1177 by the stratified log-rank test) (Figure 2-2.). It should be noted that a larger proportion of subjects in the BDP group (8 subjects, 13%) met the criteria for GVHD treatment failure during the 10-day prednisone induction period compared to placebo (4 subjects, 6%). The reason for the greater number of early treatment failures in the BDP group has not been determined, but this outcome resulted in crossing Kaplan-Meier curves for this endpoint (see Figure 2-2.), thus making the assumption of proportional hazards questionable and interpretation of the aforementioned hazard ratio problematic.

Figure 2-2. Primary Efficacy Endpoint: Time to GVHD Treatment Failure through Study Day 50 (Study ENT 00-02: ITT Analysis Set)



	1-10	11-20	21-30	31-40	41-50
BDP	8/62	3/50	4/47	2/42	1/39
Placebo	4/67	8/61	9/50	4/41	5/36

(#events/#at risk)

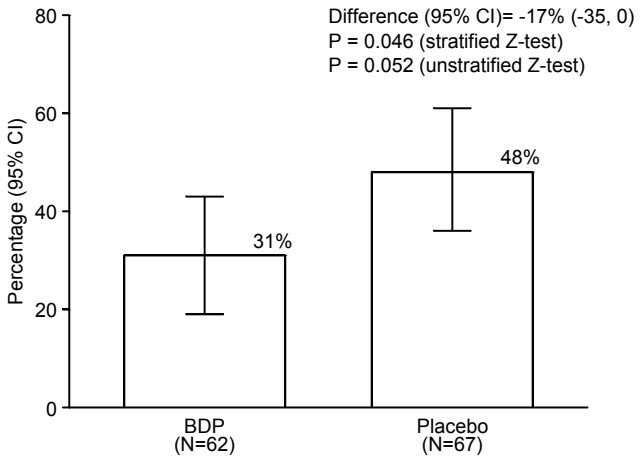
P-value is based on the stratified log-rank test. The stratified version of this test was pre-specified as the primary analysis method and is based on the 2-level randomization stratification factor for donor type (HLA-matched sibling, unrelated or HLA-mismatched donor). Study day 50 represents the planned end of the 50-day protocol treatment period. Nominal significance level of 0.05 (2-sided). No adjustment for multiple testing.

2.6.1.2 Secondary Efficacy Endpoint: Proportion of Subjects With GVHD Treatment Failure by Study Day 50 (Study ENT 00-02)

A supplemental categorical analysis was performed to compare the proportion of subjects in each treatment group who met the criteria for GVHD treatment failure on or before study day 50. (The categorical analysis at study day 50 was pre-specified in the study protocol and statistical analysis plan as a secondary efficacy analysis.)

The Kaplan-Meier estimate of the proportion of subjects with GVHD treatment failure by study day 50 was 31% in the BDP group and 48% in the placebo group (p=0.05 by the stratified Z-test) (Figure 2-3.).

Figure 2-3. Secondary Efficacy Endpoint: Proportion of Subjects with GVHD Treatment Failure by Study Day 50 (Study ENT 00-02: ITT Analysis Set)



Proportions are estimated from the Kaplan-Meier point estimates at study day 50. P-value is based on the Z-test test. Nominal significance level of 0.05 (2-sided). No adjustment for multiple testing.

Corticosteroid Use

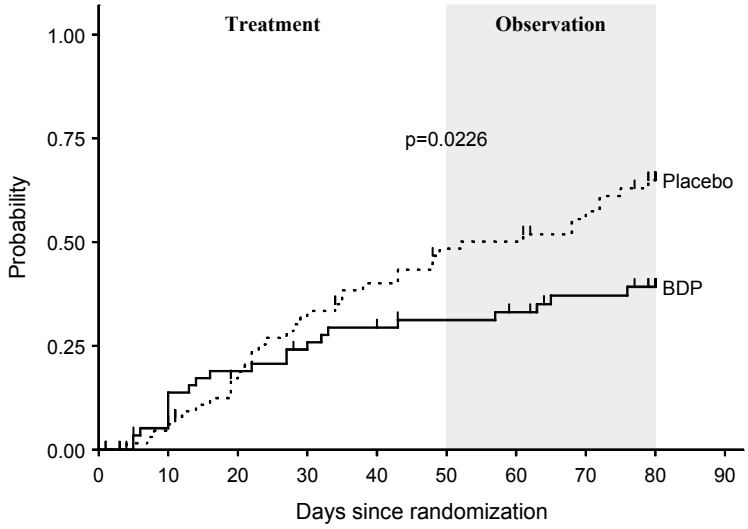
Comparisons between treatment groups at the end of the planned 50-day protocol treatment period (study day 50) indicated the median cumulative dose of systemic corticosteroids received by subjects in the BDP group was 15.3 mg/kg (range: 3.0 to 84.1) and 19.4 mg/kg (range: 4.0 to 93.5) for the placebo group.

2.6.1.3 Secondary Efficacy Endpoint: Time to GVHD Treatment Failure by Study Day 80 (Study ENT 00-02)

A secondary analysis was performed to assess the effect of BDP treatment on time to GVHD treatment failure during the entire 80-day study period, which consisted of the planned 50-day protocol treatment period (primary endpoint) plus the planned 30-day post-treatment observation period. This endpoint was included in the study design to provide an assessment of the durability of the effect on treatment failure seen at Day 50. For this analysis, the risk of treatment failure was 46% lower for subjects randomized to

BDP relative to placebo (hazard ratio = 0.54; 95% CI: 0.32, 0.93; p = 0.0226 by the stratified log-rank test) (Figure 2-4) indicating a sustained and clinically significant effect.

Figure 2-4. Secondary Efficacy Endpoint: Time to GVHD Treatment Failure Through Study Day 80 (Study ENT 00-02: ITT Analysis Set)



	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80
BDP	8/62	3/50	4/47	2/42	1/39	1/37	2/35	1/30
Placebo	4/67	8/61	9/50	4/41	5/36	1/30	4/29	4/23

(#events/#at risk)

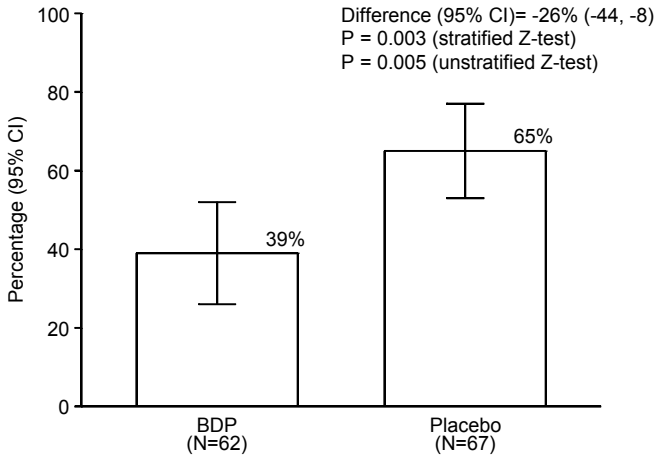
P-value is based on the stratified log-rank test. The stratified version of this test was pre-specified as the primary analysis method and is based on the 2-level randomization stratification factor for donor type (HLA-matched sibling, unrelated or HLA-mismatched donor). Study Day 80 represents the planned end of the 80-day study period. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

2.6.1.4 Secondary Efficacy Endpoint: Proportion of Subjects With GVHD Treatment Failure by Study Day 80 (Study ENT 00-02)

A supplemental categorical analysis was performed to compare the proportion of subjects in each treatment group who met the criteria for GVHD treatment failure on or before study day 80. (The categorical analysis at study day 80 was pre-specified in the study protocol and statistical analysis plan as a secondary efficacy analysis.) The Kaplan-

Meier estimate of the proportion of subjects with GVHD treatment failure by study day 80 was 39% for the BDP group compared with 65% for placebo (p = 0.003 by the stratified Z-test) (Figure 2-5).

Figure 2-5. Secondary Efficacy Endpoint: Proportion of Subjects with GVHD Treatment Failure by Study Day 80 (Study ENT 00-02: ITT Analysis Set)



Proportions are estimated from the Kaplan-Meier point estimates at study day 80. P-value is based on the Z-test test. Nominal significance level of 0.05 (2-sided). No adjustment for multiple testing.

Corticosteroid Use

Comparisons between treatment groups at the end of the 30-day post-treatment observation period (study day 80) indicated the median cumulative dose received by subjects was 19.0 mg/kg (range: 3.0 to 125.0) in the BDP group and 29.4 mg/kg (range: 4.0 to 135.1) in the placebo group. This represents a reduction of 35% in the median cumulative corticosteroid requirement for subjects treated with BDP compared to placebo.

2.6.1.5 Safety Endpoint: Survival at 200 Days Post-transplantation (Study ENT 00 02)

This endpoint was prospectively defined in the protocol and statistical analysis plan as a safety endpoint that required all subjects to be followed for survival in a blinded manner for 200 days post-transplant. Survival assessment at Day 200 post transplant is an established endpoint in the transplant setting and is predictive of longer term survival. An ITT analysis of this endpoint showed that the BDP group had a higher survival rate (92%) at day 200 post-transplant compared to the placebo group (76%) (odds ratio = 0.29; 95% CI: 0.1-0.82; p = 0.0139 by the Cochran-Mantel-Haenszel [CMH] test). The mortality difference between the BDP and placebo groups was primarily observed in the subgroup of subjects whose donor was unrelated or a family member other than an HLA-matched sibling (p=0.0476 by the Breslow-Day test of homogeneity of the odds ratios across randomization strata). Overall, relapse of the underlying malignancy (5% in the BDP group and 10% in the placebo group), infection (2% in the BDP group and 9% in the placebo group), and GVHD (2% in the BDP group and 5% in the placebo group) were reported as the proximate causes of death during this period.

These results demonstrate a decreased risk of early mortality for subjects treated with BDP; however, the evaluation of BDP treatment effects on early mortality measured relative to the date of transplant could be confounded by the varying time period among subjects for the number of days between their transplant procedure and randomization in the study (overall median of 36 days, range 18 to 190). Although the BDP and placebo groups were well matched with respect to the number and range of days between transplantation and randomization (BDP: median = 37 days, range: 18 to 190; placebo: median = 35 days, range: 18 to 171), a supplemental analysis was performed to incorporate the number of days between transplantation and randomization for each individual patient. (Further details of this analysis are described in Section 4.2.6.) When survival at 200 days post-transplantation was analyzed accounting for the variable time period between transplant and randomization, subjects in the BDP group had a 67% reduction in the risk of mortality by transplant day 200 relative to placebo (hazard ratio = 0.33; 95% CI: 0.12-0.89; p = 0.0294 by Wald chi-square test).

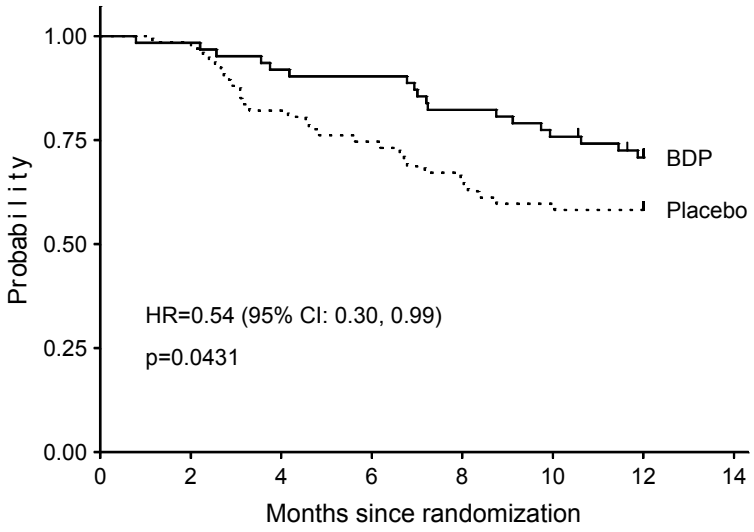
2.6.1.6 FDA-required Post-hoc Analysis: Overall Survival Post-transplantation (Study ENT 00-02)

Although not prospectively defined in the protocol or statistical analysis plan, longer term survival data measured relative to the date of randomization were collected in a retrospective manner based on requests by FDA representatives during the pre-NDA meeting with the study sponsor on November 1, 2005. To comply with this request, the survival status as of September 1, 2005 (data cutoff date) was sought from study sites for all randomized subjects, along with the date of death and proximate and contributory causes of death. As of the data cutoff date, 70 of the 129 subjects who were randomized in this study were alive or lost to follow-up.

The analysis of the post-randomization survival data was based primarily on the follow-up information measured up to 1 year post-randomization, and was supplemented by an analysis based on all available follow-up data (i.e., overall survival). Both of these analyses were based on all randomized subjects (ITT principle), and include the 2 subjects who did not receive any study drug (1 subject in each treatment group). With the exception of 2 subjects who were classified as lost to follow-up during the first year after randomization, all surviving subjects were followed for at least 1 year from their date of randomization into the study.

Within 1 year of randomization, 18 subjects (29%) died in the BDP group died and 28 subjects (42%) died in the placebo group. The estimated survival rates 1 year after randomization were 71% for the BDP group and 58% for the placebo group. During this 1-year period, the overall risk of mortality was 46% lower for subjects randomized to BDP compared with subjects in the placebo group (hazard ratio = 0.54; p = 0.0431 by the stratified log-rank test) (Figure 2-6). Overall, relapse of the underlying malignancy (13% in the BDP group and 19% in the placebo group) and infection (5% in the BDP group and 13% in the placebo group) were the most frequently reported proximate causes of death during this period.

Figure 2-6. FDA-requested Post-hoc Analysis: Survival 1 Year Post-Randomization (Study ENT 00-02: ITT Analysis Set)



	0-2	3-4	5-6	7-8	9-10	11-12
BDP	1/62	4/61	1/57	5/56	4/51	3/47
Placebo	1/67	11/66	5/55	6/50	4/44	1/40

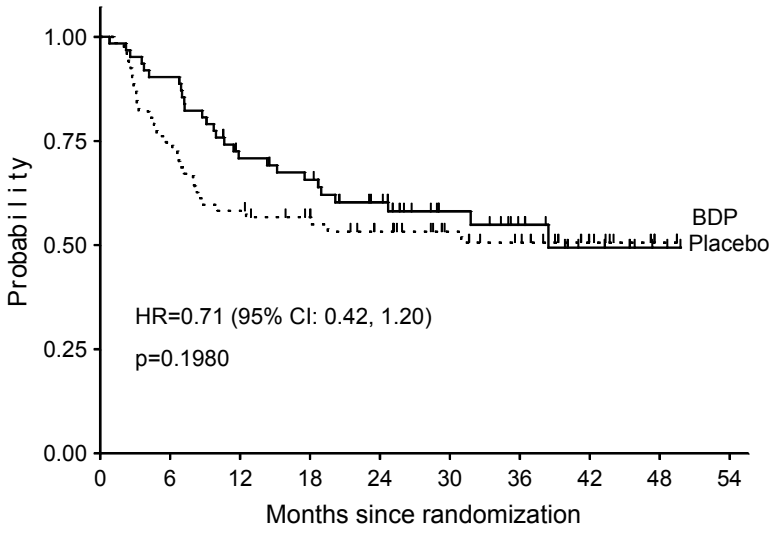
(#events/#at risk)

For purposes of this analysis, all subjects surviving more than one year (365 days) post-randomization were right-censored as of the one year time point. Hazard ratio estimated from a univariate Cox proportional hazards model stratified by the two-level randomization stratification factor for donor type (HLA-matched sibling, unrelated or HLA-mismatched donor). P-value calculated from the stratified log-rank test. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

As of the data cutoff date (September 1, 2005), median follow-up was 35.6 months for subjects in the placebo group (25-75th percentiles: 25.2 to 42.3 months) and 29 months for the BDP group (25-75th percentiles: 24.7 to 40.1 months). Three subjects whose date of last contact was before January 1, 2005 were classified as lost to follow-up as of the data cutoff date. Overall, 27 subjects (44%) died in the BDP group, and 32 subjects (48%) died in the placebo group (hazard ratio = 0.71; p = 0.1980 by the stratified log-rank test) (Figure 2-7). As of the September 1, 2005 data cutoff date, median survival was 38.5 months for the BDP group and not yet reached for the placebo group. Overall, relapse of the underlying malignancy (23% in the BDP group and 22% in the placebo

group) and infection (8% in the BDP group and 13% in the placebo group) were the most frequently reported proximate causes of death.

Figure 2-7. FDA-requested Post-hoc Analysis: Overall Survival Post-Randomization (Study ENT 00-02: ITT Analysis Set)



	0-6	7-12	13-18	19-24	25-30	31-36	37-42	43-48	49-54
BDP	6/62	12/56	3/42	3/38	1/30	1/18	1/12	0/6	0/2
Placebo	17/67	11/50	1/39	2/34	0/28	1/20	0/16	0/9	0/2

(#events/#at risk)

Hazard ratio estimated from a univariate Cox proportional hazards model stratified by the 2-level randomization stratification factor for donor type (HLA-matched sibling, unrelated or HLA-mismatched donor). P-value calculated from the stratified log-rank test. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

Data from ENT 00-02 demonstrate the following clinically meaningful outcomes with BDP treatment:

- reduction in the frequency of GVHD treatment failure following a rapid tapering of prednisone dosage;
- reduction in exposure to high-dose corticosteroids; and
- survival advantage may be due to lower rates of mortality from opportunistic infections and relapse, both of which are associated with high dose corticosteroid administration.

A manuscript describing Study ENT 00-02 (Hockenbery et al, 2007) is provided in Section 9 (Attachment 1).

2.6.2 Supportive Evidence of Clinical Efficacy: Study 875

2.6.2.1 Phase 2 Study 875

Study 875 ("Controlled Study of Prednisone With or Without Oral Beclomethasone Dipropionate for the Initial Treatment of Patients with Intestinal Graft-versus-Host Disease") enrolled 60 subjects with anorexia and poor oral intake due to GI GVHD using identical subjects selection criteria as Study ENT 00-02. Protocol treatment consisted of BDP (8 mg/day) or placebo plus a 10-day induction course of prednisone. Study drug (BDP or placebo) was administered in a double-blind manner. Response was defined as the ability to eat ≥ 70% of a subject's estimated caloric requirement. Subjects who were responding after 10 days of treatment with prednisone and study drug continued to take blinded study drug for an additional 20 days while prednisone was rapidly tapered.

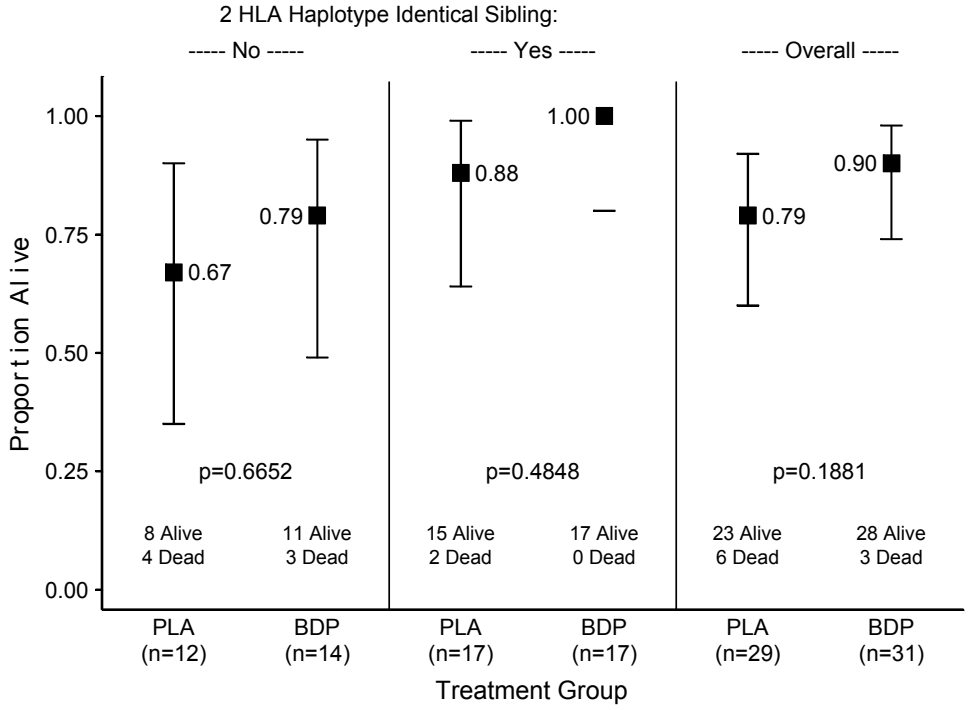
The primary efficacy endpoint for this study was the proportion of subjects who successfully maintained their oral caloric intake to ≥ 70% of their estimated caloric requirements without recurrent symptoms of aGVHD to study day 30. Oral caloric intake was assessed by the nutritionist for hospitalized subjects and on the basis of food diaries for outpatients. Secondary efficacy endpoints included the evaluation of GI signs and symptoms, functional performance status, and the number of infectious complications.

After the initial 10 days of protocol-treatment, the proportion of subjects with caloric intake ≥ 70% was 22 of 31 (71%) for subjects in the BDP group and 16 of 29 (55%) for subjects in the placebo group; these subjects continued to take study drug while the prednisone dose was rapidly tapered. At study day 30 (the primary endpoint evaluation), significantly more subjects in the BDP group than in the placebo group succeeded in achieving ≥ 70% of their estimated daily caloric requirements without flares of aGVHD (71% [22/31] in the BDP group versus 41% [13/31] in the placebo group; p = 0.02 by the chi-square test). The 22 subjects in the BDP group who had responded to short duration treatment with prednisone by study day 10 were still responding at study day 30, suggesting that once a subject responds to short duration treatment with prednisone,

aGVHD could be maintained in remission by daily dosing with BDP. This beneficial effect of BDP was noted to be durable after completion of treatment. Specifically, at the final study evaluation on study day 40 (i.e., 10 days after the planned discontinuation of BDP or placebo) 52% (16/31) of the subjects in the BDP group were still responding compared to 17% (5/29) in the placebo group ($p = 0.005$ by chi-square test). A manuscript describing Study 875 (McDonald et al, 1998) is provided in Section 9 (Attachment 2).

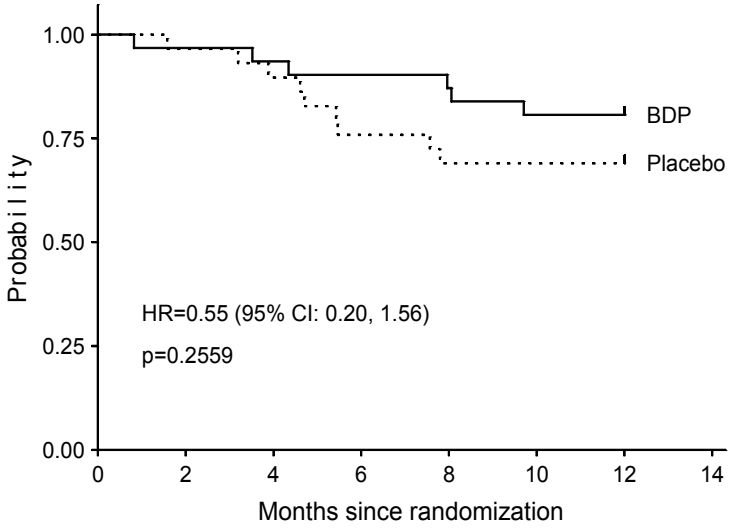
As for Study ENT 00-02, the FDA requested a retrospective analysis of survival data from Study 875. Similar to the survival outcomes observed for Study ENT 00-02, an analysis of survival at Day 200 post-transplantation in Study 875 showed that the BDP group had a higher survival rate (90%) compared with the placebo group (79%) (odds ratio = 0.34; 95% CI: 0.07-1.72; $p = 0.1881$ by the Cochran-Mantel-Haenszel test). Similarly, the risk of mortality by 200 days post-transplantation 56% lower for the BDP group compared with the placebo group (hazard ratio = 0.44; $p = 0.2415$ by Wald chi-square test). After 1 year from the date of randomization in Study 875, 6 of the 31 subjects (19%) who were randomized to receive BDP had died versus 9 of the 29 (31%) subjects who were randomized to receive placebo. The risk of mortality during this 1-year period was 45% lower for subjects in the BDP group compared with the placebo group (hazard ratio = 0.55; 95% CI: 0.20-1.56; $p = 0.2556$ by the stratified log-rank test) (Figure 2-10).

Figure 2-8. FDA-requested Post-hoc Analysis: Survival at Day 200 Post-Transplantation (Study 875: ITT Analysis Set)



P-value is based on Fisher's exact test for treatment comparisons within strata and Cochran-Mantel-Haenszel test for treatment comparison across strata. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

Figure 2-9. FDA-requested Post-hoc Analysis: Survival 1 Year Post-Randomization (Study 875: ITT Analysis Set)



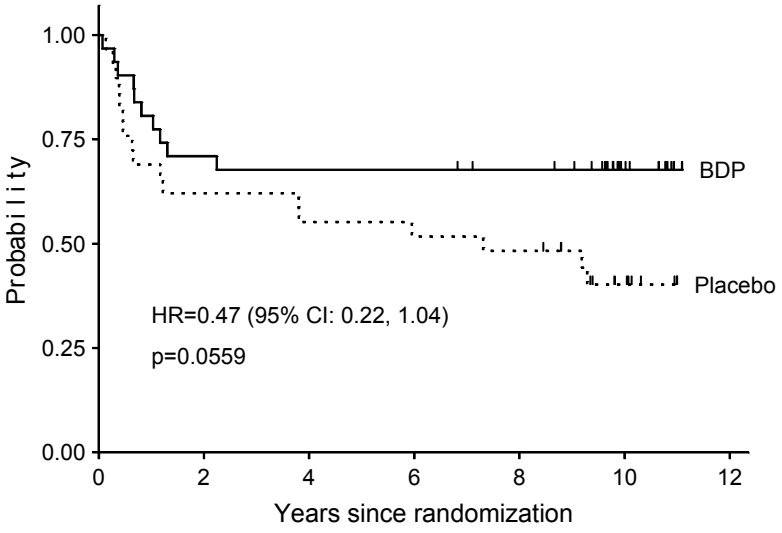
	0-2	3-4	5-6	7-8	9-10	11-12
BDP	1/31	1/30	1/29	1/28	2/27	0/25
Placebo	1/29	2/28	4/26	2/22	0/20	0/20

(#events/#at risk)

For purposes of this analysis, all subjects surviving more than 1 year (365 days) post-randomization were right-censored as of the 1-year time point. Hazard ratio estimated from a univariate Cox proportional hazards model stratified by the2-level factor for donor type (HLA-matched sibling, unrelated or HLA-mismatched donor). P-value calculated from the stratified log-rank test. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

Although the survival difference 1 year after randomization was not statistically significant for Study 875, this phase 2 study was not adequately powered to detect such differences. However, of interest is the apparent consistency of effect of BDP treatment (as measured by the hazard ratios) between Studies 875 and ENT 00-02 for both the Day 200 post-transplant and 1-year post-randomization survival endpoints. After approximately 10 years of continued follow-up, the apparent early beneficial survival effects appear to be maintained: The overall risk of mortality was 53% lower for subjects originally treated with BDP compared versus placebo (hazard ratio = 0.47; 95% CI: 0.22-1.04; p = 0.0559 by the stratified log-rank test) (Figure 2-10).

Figure 2-10. FDA-requested Post-hoc Analysis: Overall Survival Post-Randomization (Study 875: ITT Analysis Set)



	0-2	3-4	5-6	7-8	9-10	11-12
BDP	9/31	1/22	0/21	0/21	0/0	0/8
Placebo	11/29	2/18	1/16	3/15	0/0	0/7

(#events/#at risk)

Hazard ratio estimated from a univariate Cox proportional hazards model stratified by the two-level factor for donor type (HLA-matched sibling, unrelated or HLA-mismatched donor). P-value calculated from the stratified log-rank test. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

2.7 Clinical Safety

2.7.1 Introduction

BDP shares glucocorticoid and mineralocorticoid cellular effects with other corticosteroids but its pharmacology is differentiated by its limited systemic absorption. Corticosteroids are potent anti-inflammatory agents that have multiple potential adverse effects including immunosuppression and susceptibility to infections, glucose intolerance, hypertension, salt and water retention, electrolyte abnormalities, weight gain, muscle weakness and loss of muscle mass, osteoporosis, skin abnormalities, cataracts, glaucoma, growth abnormalities in children, neuropsychiatric derangements and multiple other abnormalities.

Beclomethasone dipropionate has been in use for many years by topical routes other than oral and has a well established safety profile. While the effect of BDP is predominately believed to be local, its primary metabolite, 17-BMP, may be systemically absorbed and result in systemic side effects. The mucosal effects of BDP and 17-BMP may result in mucosal infections which may become systemic in otherwise immunosuppressed patients. Therefore, safety assessment of subjects enrolled on BDP studies examines not only collected AEs but also includes in some studies specialized assessment for adrenal suppression that might be caused by any systemic exposure to BDP or 17-BMP.

The safety data are presented in this document with a detailed focus on data from the pivotal phase 3 study, ENT 00-02, supported by summary information from all other studies. It is important to note that the development program for this product was assessed as a therapy for a GI illness (and was originally reviewed in FDA's Division of Gastrointestinal and Coagulation Drugs). As is typical in many GI studies the severity of AEs was graded and recorded as mild, moderate or severe based on the following definitions and investigator judgment:

- MILD No limitations of usual activities.
- MODERATE Some limitation of usual activities.
- SEVERE Inability to carry out usual activities.

Each clinical study in this report is presented individually in Section 5 (Clinical Safety) of this document. An integrated safety analysis was problematic from an analytic standpoint due to the different methods of safety reporting in each study. Based on this information, it was determined that the most comprehensive data are in Study ENT 00-02 which will be the focus of this Executive Summary section.

2.7.2 Summary of Safety in Study ENT 00-02

Study ENT 00-02 ("A Phase III Randomized Placebo-Controlled, Multi-Center Study of the Safety, Efficacy, and Pharmacokinetics of Oral Beclomethasone 17, 21-Dipropionate in Conjunction with Ten Days of High Dose Prednisone Therapy in the Treatment of Patients with Grade II Graft vs. Host Disease with Gastrointestinal Symptoms") enrolled

subjects with histologically-confirmed Grade II GVHD with GI symptoms who could swallow the study tablets without difficulty.

Safety was evaluated based on the following assessments:

- Treatment-emergent AEs. Verbatim AEs were assigned a preferred term and system organ class according to MedDRA (version 7.0);
- Systemic corticosteroid exposure based on the cumulative prednisone, or equivalent, dose in mg/kg over the course of the 80-day study period;
- GVHD assessments of diarrhea (GI), rash (skin), and total serum bilirubin (liver) at selected time points;
- HPA axis function as measured by plasma concentrations of adrenocorticotrophic hormone (ACTH), resting morning cortisol, and change in plasma cortisol concentration following a standard test dose of intravenous cosyntropin;
- Survival through Day 200 post-transplant (presented with the efficacy data).

2.7.3 Adverse Events

In this highly complex and seriously ill patient population, AEs were reported for almost all subjects in both BDP and placebo groups (Table 5-8). Those AEs occurring more commonly in the BDP group are listed in Table 2-3. Overall, the incidence of treatment-emergent AEs were comparable between BDP and placebo groups (Table 5-10). Interestingly, across a broad spectrum of AEs, the incidence of AEs was generally more frequent for subjects in the placebo group compared with the BDP group. The most frequently reported AEs by preferred term were (BDP, placebo): GVHD (43%, 41%), blood magnesium decreased (39%, 42%), fatigue (46%, 35%), hypertension (39%, 35%), and peripheral edema (31%, 38%).

Treatment Related Adverse Events

The incidence of treatment-related AEs was higher in the placebo group (44%) than in the BDP group (34%) (Table 5-8). The most frequently reported treatment-related AEs by preferred term were (BDP, placebo): adrenal insufficiency (8%, 5%), fatigue (8%, 3%), hyperglycemia (7%, 2%) (Table 5-11).

Hypothalamic-Pituitary Axis (HPA) Evaluation

The majority of subjects had normal HPA axis function as measured by cosyntropin stimulation test at baseline (80% for placebo versus 75% for BDP). At study day 51, there was a statistically significant difference in the proportion of evaluable subjects with abnormal HPA axis function (58% for placebo versus 86% for BDP, p = 0.0007). The overall significance of these data is unclear however, because HPA axis evaluation was not performed in treatment failures, which were more frequent in the placebo group, and resulted in higher doses of systemic corticosteroids which would result in greater HPA axis suppression.

Serious Adverse Events

SAEs were reported in approximately 40% of subjects in both groups (Table 5-8). The most common serious AEs were (BDP, placebo): GVHD (7%, 6%), pyrexia (3%, 8%), bacteremia (5%, 3%), and hypoxia (0%, 6%) (Table 5-12).

Deaths on Study

A total of 12 deaths occurred during the approximate 80-day study period (3 of the 12 twelve deaths occurred days 83, 87, and 94). Of these 12 deaths, 3 occurred in the BDP arm and 9 in the placebo arm. Subjects may have had multiple medical diagnoses at the time of death and given the complexity and severity of the illness in this subject population this is an expected finding. Consequently some subjects may have died primarily due to infection, primarily due to relapse of their malignancy, and primarily due to both relapse and infection.

The findings associated with death in the 3 BDP subjects were as follows: viral infection (BK virus); relapse and cellulitis/bacteremia (*Pseudomonas* and *Staphyloccocus*); progressive GVHD leading to bowel perforation. The findings associated with death in the 9 placebo subjects were as follows: relapse; relapse and cellulitis; bacterial sepsis (*S. aureus*); sepsis (*P. aeruginosa*); relapse and presumed fungal infection (pulmonary nodules that resolved with antifungal treatment); bronchiolitis obliterans organizing pneumonia (BOOP); sepsis; relapse; fungal infection (pulmonary aspergillosis).

Table 2-3. Study ENT 00-02: Treatment-emergent Adverse Events Occurring in ≥ 10% of Subjects in the BDP Group With Higher Frequency Than in the Placebo Group

Preferred term MedDRA (version 7)	Placebo N=66	BDP N=61
GVHD	27 (40.9%)	26 (42.6%)
fatigue	23 (34.8%)	28 (45.9%)
hypertension	23 (34.8%)	24 (39.3%)
bacteremia	13 (19.7%)	14 (23.0%)
hypokalaemia	14 (21.2%)	13 (21.3%)
hypocalcaemia	10 (15.2%)	12 (19.7%)
dizziness	10 (15.2%)	11 (18.0%)
erythema	8 (12.1%)	13 (21.3%)
hypophosphatemia	9 (13.6%)	12 (19.7%)
skin hyperpigmentation	10 (15.2%)	10 (16.4%)
cough	9 (13.6%)	9 (14.8%)
muscle cramp	6 (9.1%)	11 (18.0%)
pain in extremity	8 (12.1%)	9 (14.8%)
weight decreased	7 (10.6%)	9 (14.8%)
cushingoid	6 (9.1%)	9 (14.8%)
arthralgia	6 (9.1%)	8 (13.1%)
hyponatremia	7 (10.6%)	7 (11.5%)
osteopenia	7 (10.6%)	7 (11.5%)
tongue coated	5 (7.6%)	7 (11.5%)
dehydration	2 (3.0%)	9 (14.8 %)
leukocytosis	4 (6.1%)	7 (11.5%)
hyperbilirubinemia	3 (4.5%)	7 (11.5%)
chest pain	1 (1.5%)	7 (11.5%)

Note: Subjects were counted only once for each preferred term; percentages are based on the number of subjects evaluable for safety in each treatment group.

2.8 Risk/Benefit Assessment

The proposed indication for BDP is for the treatment of GVHD involving the GI tract in conjunction with an induction course of high-dose prednisone or methyl prednisolone. In 4 studies in subjects with GI GVHD who previously underwent allogeneic HCT,

treatment with BDP demonstrated a consistent safety profile and (while not achieving statistical significance on the primary endpoint in the pivotal trial) demonstrated clinical efficacy based on the following observations:

1. A clinically meaningful reduction in the frequency of GVHD treatment failure was observed with BDP treatment following a rapid tapering of prednisone dosage in 2 randomized trials where treatment failure was based on clinically relevant measures of either immunosuppressive use or caloric intake.
    - Treatment failure was defined as the requirement for increased doses of immunosuppressive drugs beyond those specified in the protocol for Study ENT 00-02.
    - Treatment failure was defined as the inability to eat ≥ 70% of a subject's estimated caloric requirement in Study 875.
2. A reduction in exposure to high-dose corticosteroids was observed with BDP treatment.
3. A consistent survival advantage was observed with BDP treatment in the placebo-controlled studies ENT 00-02 and 875. This survival advantage may be due to lower rates of mortality from opportunistic infections and relapse, both of which are associated with high dose corticosteroid administration.

The survival advantage described above was not accompanied by any safety findings that would either limit the use of the investigational product in the intended population or worsen quality of life in patients to whom it was administered. Although prior to this development program, high-dose corticosteroids were considered the standard of care, the data summarized above demonstrate that BDP in combination with a short induction course of corticosteroids addresses an unmet medical need by reducing the morbidity and mortality associated with existing standard of care treatment for Grade II acute GI GVHD while preserving anti-GVHD efficacy (i.e., GVL effect).

Given the limited number of centers in the United States performing allogeneic HCT, the publication of the results of the pivotal BDP trial in the medical journal *Blood* (Hockenbery et al, 2007), and the survival advantage observed, it is likely that

institutional review boards at appropriate centers would not approve another placebo-controlled trial in this indication. It should also be noted that while BDP is not yet available commercially, there is a practice in some centers performing allogeneic HCT to treat patients with GI GVHD using unregulated beclomethasone dipropionate compounded in corn oil for the treatment of GI GVHD. The combination of these events is expected to lead to an increase in unregulated compounding and off-label use of beclomethasone dipropionate. The results of the pivotal, phase 3 study (Study ENT 00-02) are summarized in Table 2-4.

Table 2-4. Summary of Endpoints Relating to Efficacy and Survival in Subjects Randomized to BDP Versus Placebo in the Phase 3 Pivotal Trial ENT 00-02

Efficacy Endpoints	Survival Endpoints
GVHD-treatment failure by Study Day 50: ▪ Time to event analysis (primary endpoint): HR 0.63; p = 0.1177 ▪ Comparison of proportions: 31% BDP versus 48% placebo; p = 0.05	Mortality at transplant day 200: ▪ HR 0.33; p = 0.0294
GVHD-treatment failure by Study Day 80: ▪ Time to event analysis: HR 0.54; p = 0.0226 ▪ Comparison of proportions: 39% BDP versus 65% placebo; p = 0.003	Mortality 1 year after randomization: ▪ HR 0.54; p = 0.0431

BDP = oral beclomethasone dipropionate; GVHD = graft-versus-host disease; HR = hazard ratio

In summary, no investigational products are currently approved by the FDA for the treatment of established GI GVHD in recipients of allogeneic HCTs. Given this lack of comparators and the favorable benefit-to-risk profile of BDP compared with that of the current standard of care, BDP represents a clinically meaningful advance in the treatment of GI GVHD.

Taken together, the data provided and the clinical scenario described above support the approval of BDP in the treatment of GI GVHD in conjunction with an induction course of high-dose corticosteroids.

3. INTRODUCTION

3.1 Background

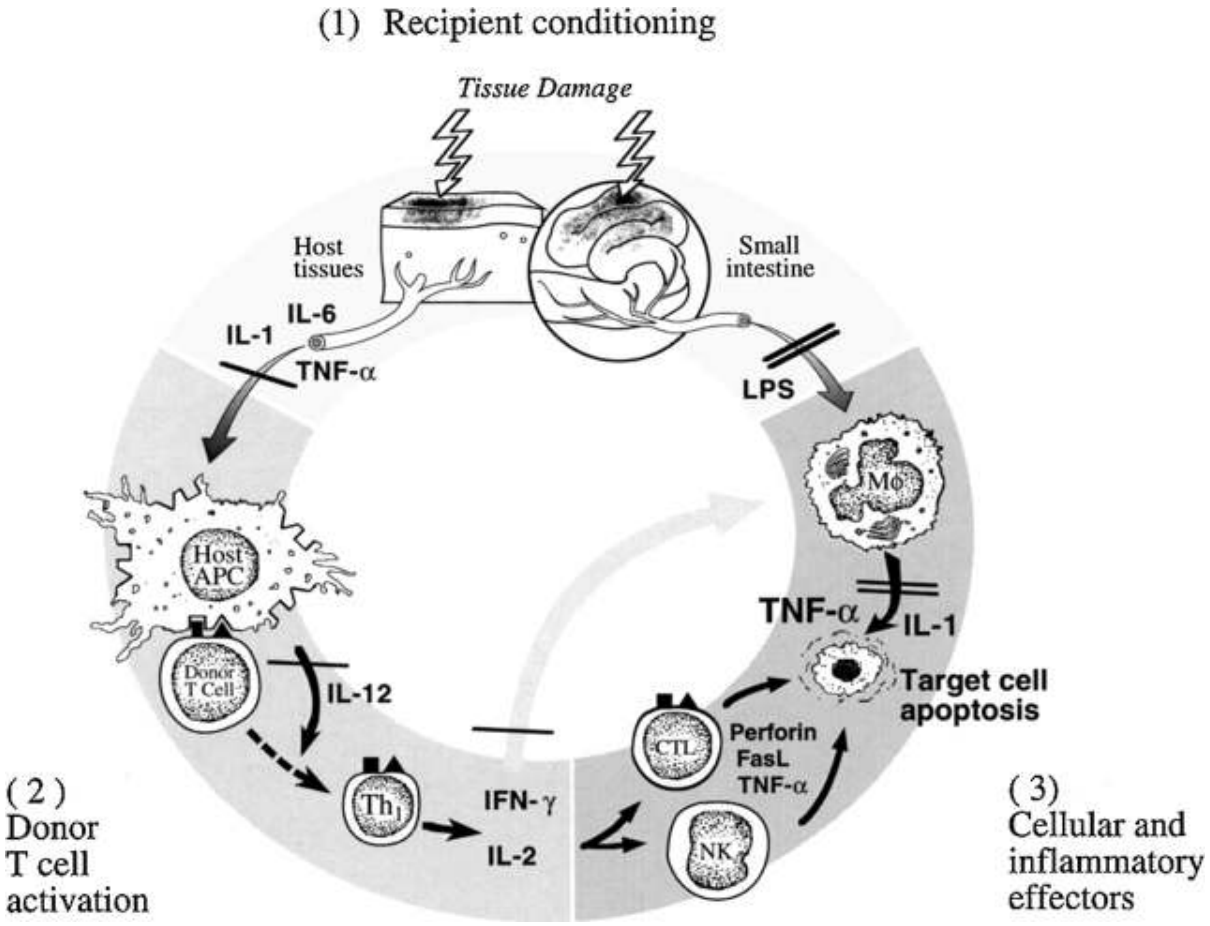
Allogeneic HCT is being used with increasing frequency in patients with malignant diseases, immunodeficiency disorders, and some inborn errors of metabolism (Thomas 2004). Allogeneic transplants are commonly used to treat hematologic malignancies because autologous transplants may be ineffective and because of the increasing recognition that aGVHD following allogeneic transplantation may increase the efficacy of the transplantation against the underlying malignancy through a GVL effect (Baron et al, 2005).

During the process of allogeneic HCT, a syndrome characterized by damage to intestinal mucosa, small bile ducts in the liver, and skin may occur (Sullivan 2004). This syndrome, which has been termed aGVHD, is caused by donor lymphocytes attacking host cells and by release of cytokines and chemokines in affected tissues. Acute GVHD is defined as an inflammatory disease that occurs after allogeneic HCT, affecting multiple organs, most commonly the GI tract, skin, and liver. The onset of aGVHD is usually 2-8 weeks after transplant. The severity of aGVHD is graded from I through IV, based on the degree of abnormality in the affected organs. GVHD in the intestinal tract may involve the esophagus, stomach, small intestine, and colon. Severity of GI GVHD ranges from a clinically mild disease to fatal exfoliation of intestinal mucosa. GI involvement represents a prominent feature of aGVHD (McDonald and Sale 1984; Spencer et al, 1986a; Spencer et al, 1986b; Weisdorf et al, 1990; Snover 1990). Other causes of GI problems after transplantation include the GI toxicity of myeloablative therapy used to prepare patients for transplantation (i.e., conditioning therapy); infections with viruses, bacteria, and fungi; and side effects of medications (Strasser and McDonald 2004). In the last decade, there has been substantial progress in eliminating GI infections as a cause of symptoms after transplant, largely due to prophylactic use of antifungal and antiviral drugs (Schwartz et al, 2001; Strasser and McDonald, 2004), such that aGVHD is the most common cause of GI disease after day 20 post transplant, when intestinal mucosa has regenerated from toxic damage (Epstein et al, 1980; Cox et al, 1994; Wu et al, 1998; Schwartz et al, 2001).

3.2 The Pathophysiology of Acute Graft Versus-host Disease

The pathophysiology of aGVHD can be viewed as a 3-step process and is absolutely dependent on the presence and function of donor T cells in the donor inoculum (Figure 3-1). In step 1, the conditioning regimen (irradiation and/or chemotherapy) leads to the damage and activation of host tissue by the release of the inflammatory cytokines tumor necrosis factor- alpha (TNF-α) and interleukin-1 (IL-1). These cytokines can increase the expression of major histocompatibility (MHC) antigens and adhesion molecules on host antigen presenting cells (dendritic cells), enhancing the recognition of host MHC and/or minor histocompatibility antigens by mature donor T cells. Donor T-cell activation in step 2 is characterized by proliferation of T-helper type 1(Th1) T cells and secretion of interleukin-2 (IL-2) and interferon- gamma (IFN-γ), thus promoting T cell expansion and cytotoxic lymphocyte (CTL) and natural killer (NK) cell responses. The effectors of tissue damage in step 3 include the products of mononuclear phagocytes (IL-1 and TNF-α), which are triggered via signals provided by lipopolysaccharides (LPS). Damage to the intestinal mucosa in step 1 and damage by cytolytic effectors activated in step 2 allows translocation of LPS from the intestinal lumen into the circulation. This mechanism may amplify local tissue injury and further promote an inflammatory response, which, together with the CTL and NK component, leads to target tissue destruction in the HCT host. The importance of T cells for GVHD and GVL effects is demonstrated by depletion of T cells from the donor graft. This prevents GVHD, but is also associated with increased rates of relapse and infective complications, which negate any beneficial effect. However, if inflammatory cytokine dysregulation during GVHD is prevented, while maintaining donor T cell cytotoxicity to host and hematopoietic antigens, leukemia eradication after BMT can be demonstrated in the absence of GVHD. The "Holy Grail" of HCT remains complete separation of GVHD and GVL while preserving cognate T cell responses to non-host (e.g., infectious) antigens. The key to this achievement lies in administration of antigen-specific immunotherapy (Ferrara and Antin; 2004).

Figure 3-1. GVHD Pathophysiology



Recipients of allogeneic hematopoietic cells generally receive therapy to prevent aGVHD, usually with cyclosporine or tacrolimus plus methotrexate; newer prophylactic regimens may also include mycophenolate mofetil (MMF) or sirolimus (rapamycin). When GVHD develops, treatment consists of immunosuppressive drugs, usually prednisone or methyl prednisolone at a dose of 1-2 mg/kg/day or more. The initial response rate to immunosuppressive therapy is 50 to 90%, depending on disease severity (Martin et al, 1990; McDonald et al, 1998) and the clinical presentation (Van Lint et al, 2006).

Patients with severe GVHD who respond poorly or not at all receive extended courses of high-dose prednisone plus another immunosuppressive drug. Typically, in steroid

refractory GVHD administration of agents such as antithymocyte globulin, MMF, rapamycin, monoclonal antibodies directed against T-cell antigens, and anti-cytokine biologics are added to the immunosuppressive regimen initially prescribed to treat aGVHD (Martin et al, 1990; Sullivan 2004). In some centers methyl prednisolone at doses of 4 to 10 mg/kg/day are used to treat refractory GVHD. Systemic administration of glucocorticoids at high doses for prolonged periods of time often causes fluid and electrolyte disturbances, muscle weakness, osteopenia, and severe immunosuppression, leading to an increased risk of fatal infection.

Grading of GVHD serves a variety of purposes, including retrospective assessment of peak severity, real-time assessment of severity at pre-specified time points, determination of the need for treatment, assessment of treatment response, prognostication for survival, and evaluation of new methods to prevent GVHD in prospective studies. The most widely used grading systems for grading aGVHD represent variations of criteria originally proposed by Glucksberg et al in 1974 on the basis of clinical intuition (Glucksberg et, 1974). Variations of the Glucksberg system (where aGVHD is graded I to IV) have been published to improve its utility for specific purposes. Although these grading systems have descriptive validity and a general relationship to outcome, several problems hamper the application of current grading systems for the purpose of predicting mortality among patients with aGVHD:

- Relation of disease severity in skin, gut, and liver to outcome was never evidence-based, but instead reflected the judgment of experienced clinicians.
- Assignment of a peak GVHD score is done in retrospect; clinicians cannot use the current grading system for peak score in real-time.
- The systems do not account for the time to response after treatment. Thus, patients whose symptoms resolve completely after a short course of immunosuppressive therapy may be scored identically to patients who require months of high-dose immunosuppressive drug therapy to control symptoms.
- Significant inter-observer errors exist in the current grading systems, largely because of subjective biases.

- Assignment of grade IV GVHD is often used descriptively to indicate that GVHD caused a patient's death, irrespective of the severity of symptoms. In this situation, the grading reflects the outcome and cannot be used to predict the outcome. Indeed, neither the Glucksberg nor the International Bone Marrow Transplant Registry (IBMTR) system performs well as a prognostic tool, as neither explains much of the variation in either early or late survival.

An evidence-based system for predicting the prognosis in patients who have developed aGVHD was published recently (Leisenring 2006). An aGVHD Activity Index (aGVHDAI) is scaled from 0 to 100, with higher numbers correlating well with non-relapse mortality at transplant day-200 (the day of hematopoietic cell infusion is day zero). Four components that comprise the aGVHDAI are collected at 10-day intervals from the onset of aGVHD to transplant day-100: inability to eat adequate calories, need for ongoing prednisone therapy to control symptoms, total serum bilirubin, and patient performance score. This index measures the burden of aGVHD across time with day-200 mortality as the endpoint. Thus, prognosis in patients with aGVHD is optimally measured not by peak severity, but by assessing the persistence across time of severe anorexia and inability to eat, need for immunosuppressive drugs (especially prednisone) to control symptoms of GVHD, the degree of jaundice, and how debilitated the patient has become.

An empiric system for assessing prognosis was also published recently, using the clinical response to initial therapy with glucocorticoid medication to determine prognosis. In this research, a 5-day course of prednisolone at 2 mg/kg/day was prescribed for all patients presenting with aGVHD; the response after 5 days was prognosis-determining: those whose symptoms responded after 5 days of therapy had their prednisolone doses tapered to 1 mg/kg/day, with transplant-related mortality of 27%, compared to 49% in non-responders (Van Lint et al, 2006). In this study, both responders and non-responders to 5 days of therapy had prolonged exposure to glucocorticoid medications.

Among patients with aGVHD there is a wide range of total exposure to systemic corticosteroids. For patients who present with either a mild skin rash or nausea, vomiting

or anorexia, symptoms often respond to a 2 to 4 week course of prednisone at 1-2 mg/kg/day, after which the dose is slowly tapered to avoid corticosteroid side effects (Sullivan 2004; Van Lint et al, 2006). Patients who present with more severe symptoms (extensive skin involvement, high-volume secretory diarrhea, abdominal pain, jaundice, intestinal bleeding) are treated initially with methylprednisolone at 2 mg/kg/day for 4 weeks, followed by a slow taper over 4 to 6 weeks if there has been a response. During and after tapering doses of prednisone, recurrence of GI symptoms is frequent but not easy to predict in individual patients. Patients who experience a worsening of symptoms during or following the prednisone taper are retreated with higher doses of prednisone at 1 - 2 mg/kg/day, and these patients generally respond. The frequency of response of GI symptoms after second and third courses of corticosteroids is 80 to 90%, but each course of treatment is for a minimum of 1 to 3 weeks, followed again by tapering of the prednisone to allow recovery of the HPA axis and to avoid a flare of GVHD that would result from abrupt decreases in prednisone doses. The side effects of prolonged high-dose corticosteroid treatment are well known, and include susceptibility to infections (bacteremia, fungemia, mold infections, herpesviruses, adenovirus, JC/BK virus, and Epstein-Barr virus), hyperglycemia, hypertension, neuropsychiatric symptoms, muscle weakness, infections, bone demineralization, and body habitus changes (cushingoid features, including moon facies, buffalo hump, and thinning and striae of the skin).

All of the above factors make a priority the identification and development of therapeutics for GI GVHD that spare patients prolonged exposure to systemic immunosuppressive therapy, particularly prednisone, while effectively controlling GI symptoms, with low toxicity. When continued high-level systemic immunosuppressive therapy is needed to control the signs and symptoms of GVHD, the risk of fatal infections is substantially increased (Nichols et al, 2001; Marr et al, 2002; Hakki et al, 2003; Fukuda et al, 2003).

Recently, two developments in hematopoietic transplantation have occurred that increase the importance of adequate treatments for GVHD. The first is the increasingly frequent recognition of intestinal GVHD in these patients, particularly GVHD involving the upper GI tract, such that in some centers the frequency of the diagnosis has increased from

40-50% to over 70% (Martin et al, 2004). This finding is rendered more significant by the recognition that outcome from GVHD may be predominantly driven by the intestinal component (Hill and Ferrara, 2000). The second recent development is the advent of the use of non-myeloablative allogeneic transplants in which the recipient immune system is suppressed but not ablated completely.

3.3 Product Rationale

BDP is a synthetic diester of beclomethasone, a corticosteroid analog that has appeal in the treatment of GI GVHD by virtue of its ability to direct therapy to inflamed GI mucosa. Because corticosteroids are highly effective agents against both primary and recurrent GVHD (Martin et al, 1990; Martin et al, 1991) and because oral topically-active corticosteroids may allow reductions in prednisone exposure, thereby reducing the risk from prolonged systemic corticosteroids, BDP is an attractive therapy in the treatment of GI GVHD. Topically-active corticosteroids have been used effectively for over 25 years for inflammatory diseases of the GI tract (ulcerative colitis, Crohn's disease, lymphocytic gastroenteritis, and eosinophilic gastroenteritis) as both oral and enema formulations, with minimal complications (Rutgeerts et al, 1994; Levine 1994; Lofberg et al, 1994).

Because of its long use in humans by other routes, the safety of topically-active BDP has been characterized extensively in the literature. It shares class effects with other corticosteroids that may be limited by incomplete systemic absorption and has other local toxicities related to its topical activity, primarily infections. To summarize these studies from the literature, BDP has a very favorable safety profile, particularly in comparison to the systemic corticosteroids for which it is substituted.

3.4 Indication Sought

Treatment of acute GVHD involving the GI tract in conjunction with an induction course of high-dose prednisone or methyl prednisolone.

3.5 Treatment Regimen

BDP is dosed as one immediate-release (IR) tablet plus one enteric-coated (EC) tablet, taken 4 times daily for 50 days, with each tablet containing 1 mg of BDP (i.e., 2 tablets

taken 4 times daily, for a total of 8 mg BDP daily). BDP therapy should be started simultaneously with an induction course of prednisone therapy at a dose of 1 mg/kilogram of body weight/day, for 10 days. If the patient's symptoms of GVHD have responded after 10 days of treatment, prednisone doses can be rapidly tapered over 1 week to physiologic replacement doses.

3.6 Unmet Medical Need

With the single exception of intravenous immunoglobulin, which is seldom used in clinical practice to treat GVHD, there are no FDA-approved drugs for prevention or treatment of GVHD.

BDP for the treatment of GVHD was granted Orphan Designation and Fast Track Status by the FDA on March 27, 1998 and October 25, 2000, respectively.

3.7 Clinical Background

In 1991, investigators at the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle, WA hypothesized that use of BDP, an oral corticosteroid with limited systemic bioavailability, in patients with GI GVHD would reduce the need for systemic corticosteroids and other immunosuppressives, reduce resultant infectious and other complications of immunosuppression, and improve clinically important outcomes. Four (4) clinical trials were conducted in patients with established acute GI GVHD who previously underwent allogeneic HCT for a variety of hematologic disorders. These studies included an uncontrolled phase 1 study (Study 615), a compassionate use study in patients with contraindications to high-dose corticosteroid therapy (Study 1500), a phase 2 randomized, double-blind, placebo-controlled study (Study 875), and the pivotal study (Study ENT 00-02). The last 2 studies (Study 875 and ENT 00-02) are the only randomized controlled studies of oral BDP conducted and serve as the data source for the efficacy analyses presented in this briefing document. The total number of subjects included in the above studies is summarized in Table 3-1.

Table 3-1. Enrollment Summary Among BDP Studies in Subjects with GVHD

	Placebo (N)	BDP (N)	Total (N)
Uncontrolled studies			
Protocol 615	0	42	42
Protocol 1500	0	16	16
Total – uncontrolled studies	*0*	*58*	*58*
Controlled studies			
Protocol 875 (Phase 2 supportive)	29	31	60
Protocol ENT 00-02 (Phase 3	67	62	129
Total – controlled studies	*96*	*93*	*189*
Total – controlled and uncontrolled	*96*	*151*	*247*

N = number of subjects enrolled (in uncontrolled studies) and randomized (in controlled studies).

Three additional studies were conducted (2 studies in healthy volunteers and 1 study in patients with Crohn's disease) for a total of 7 clinical trials evaluating administration of oral BPD:

- a phase 1 study in healthy volunteers (ENT 00-01) - 12 patients entered, 10 completed
- a bioavailability study in healthy volunteers (ENT 05-BA) – 12 patients entered, 11 completed
- a study in patients with Crohn's disease (ENT 01-04) – 4 patients entered.

The phase 1 study in healthy volunteers evaluated the systemic pharmacokinetics of both the immediate-release and enteric-coated BDP dosage forms. The second study in healthy volunteers compared the systemic bioavailability of the immediate-release and enteric-coated BDP dosage forms to an oral liquid suspension. The 1 study in patients with Crohn's disease (Study ENT 01-04) was initiated but then stopped early for business reasons. A summary of all clinical trials with BDP is provided in Table 3-2; more detailed information is provided in Section 9 (Attachment 3).

Table 3-2. Summary of Clinical Studies Evaluating oral BPD

Study Category	Study No.	Location	Study Characteristics	Doses of BDP IR/EC	Duration of Treatment	Number Enrolled
Clinical pharmacology studies in healthy volunteers	ENT 00-01	US	Open-label, randomized, four-treatment, four-period, pharmacokinetic crossover study in healthy volunteers	6 mg (six 1 mg IR tablets fasted, six 1 mg EC tablets fasted, three 1 mg IR tablets + three 1 mg EC tablets fasted, and three 1 mg IR tablets + three 1 mg EC tablets fed), oral	Single doses	12
	ENT 05-BA	US	Open-label, randomized, three-treatment, three-period pharmacokinetic crossover study in healthy volunteers	6 mg (six 1 mg IR tablets, six 1 mg EC tablets, and liquid suspension), oral	Single doses	12
Blinded, controlled studies	875	US	Single-center, placebo-controlled, parallel groups, in subjects with GI GVHD	8 mg daily (one 1 mg IR capsule and one 1mg EC capsule 4 times daily), oral	30 days	60
	ENT 00-02	US, FR	Multi-center, placebo-controlled, parallel groups, in subjects with GI GVHD	8 mg daily (one 1 mg IR tablet and one 1mg EC tablet 4 times daily), oral	50 days	129

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EC = enteric coated; FR = France; GVHD = graft-versus-host disease; IR = immediate release; PK = pharmacokinetics; US = United States

Table 3-2. Summary of Clinical Studies Evaluating oral BPD

Study Category	Study No.	Location	Study Characteristics	Doses of BDP IR/EC	Duration of Treatment	Number Enrolled
Open-label, uncontrolled studies	615	US	Single-center, single-arm, uncontrolled, in subjects with GI GVHD	8 mg daily (one 1 mg IR capsule and one 1mg EC capsule 4 times daily), oral	28 days	42
	1500	US	Single-center, single-arm, uncontrolled, in subjects with GI GVHD with contraindications to high-dose immunosuppressive therapy	8 mg daily (two 1 mg IR capsules 4 times daily), oral	28 days	16
Study in Crohn's Disease	ENT 01-04	US	Randomized, placebo-controlled, safety, efficacy, dose response, PK of BDP IR/EC in subjects with Crohn's disease		8 weeks	4

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EC = enteric coated; FR = France; GVHD = graft-versus-host disease; IR = immediate release; PK = pharmacokinetics; US = United States

The pre-pivotal clinical trials were all conducted at a single center; the Fred Hutchinson Cancer Research Center (FHCRC, Seattle, WA). Two of the 3 studies (Studies 615 and 875) were conducted prior to Enteron Pharmaceuticals (a wholly-owned subsidiary of DOR BioPharma, Inc.) assuming responsibility for the IND for oral BDP March 23, 1999 and were funded in part from grants provided by the Orphan Products Division of the FDA. The third study (Study 1500) was conducted on a compassionate-use basis while the pivotal study was being planned.

The results from these pre-pivotal studies provided a strong clinical rationale for the use of BDP for the treatment of GVHD and thus for proceeding with a phase 3 study. Based on the results of the previous trials, a single pivotal phase 3 study (ENT 00-02) was designed and conducted following an End-of-Phase 2 meeting with the FDA (September 8, 2000) and a written agreement on the clinical trial design through a special protocol assessment (SPA) (December 28, 2000, Serial No. 0019 and the FDA's response dated March 23, 2001)

Enrollment in the pivotal study (ENT 00-02) was completed in July 2004, and the last patient reached study day 80 on September 17, 2004. The study design was similar to that of Study 875: a 10-day induction course of prednisone was given to gain rapid control of the signs and symptoms of GVHD, followed by a rapid tapering of prednisone dose while oral BDP was continued for a total of 50 days (30 days in Study 875). Following the prednisone taper, subjects randomized to oral BDP had significantly fewer GVHD-treatment failures by study day 50 than subjects receiving placebo, and this effect was durable during 30 days of follow-up. Survival at transplant day 200 and at 1 year post-randomization was significantly better in the BDP group, largely because of fewer fatal infections and relapses of malignancy. Because of this survival advantage in the BDP group, the cohort of patients from Study 875 was re-examined for survival; the reductions in mortality at transplant day-200 and at 1 year post-randomization in this protocol were similar in magnitude to those seen in the pivotal trial. There were no material adverse safety findings associated with BDP treatment. SAEs, AEs resulting in study drug discontinuation and AEs associated with study drug were more frequent, although not statistically significantly so, in the placebo group. No significant

differences in laboratory values were seen between groups. Suppression of the HPA axis was seen in BDP treated subjects but this was not associated with either hypo- or hyperadrenocortisolism.

We conclude that the original hypothesis, formulated in 1991, has been proven. Oral BDP, given as a combined formulation of gastric release and mid-gut release, allows prednisone to be rapidly tapered after an induction course, with fewer flares of GVHD activity, compared to placebo. The proposed advantages of this approach, that is, fewer prednisone side-effects, particularly fatal infections, were apparent by transplant day 200, as well as a statistically meaning survival advantage that was sustained out to 1 year post-randomization. Few clinically significant AEs were related to oral BDP, and thus, the benefit to risk of this therapy for GI GVHD is strongly favorable.

3.8 Basis for Licensure

In the pivotal phase 3 clinical trial, BDP demonstrated a trend toward an improvement in the time to treatment failure by Study Day 50 post-randomization, the primary endpoint of the trial, with a nominally statistically significant improvement in treatment failure rates by Study Day 80, a prospectively defined secondary endpoint. These improvements were accompanied by a clinically meaningful improvement in survival at Day 200 post-transplant which persisted at 1 year post-randomization and persists as a trend in overall survival through to the time of the data cutoff (September 1, 2005). The predominant mortality benefit was seen in those patients with the worst predicted outcome, those with non-sibling or human-leukocyte-antigen (HLA) mismatched donors; however, the benefit was seen in the overall ITT population. Other than degree of HLA match, no covariates were identified that contributed meaningfully to outcome.

The hypothesis that the impact of BDP on patient outcomes would be mediated by a reduction in exposure to systemic immunosuppression is supported by the finding that the predominant causes of increased mortality in patients randomized to placebo were infection and relapse of their underlying malignancy, both of which are associated with immunosuppression. While the safety analysis for the phase 3 study of BDP versus placebo indicates no significant differences between the 2 arms in terms of AE frequency,

severity, and laboratory analysis, absolute numbers of events in the organ class "infection and infestations" was lower in the BDP arm (51% for BDP versus 61% for placebo). Hypothalamic pituitary adrenal (HPA) axis evaluation shows some suppression of the HPA axis with BDP and AE reporting includes reports of cushingoid features in 15% of BDP patients versus 9% of placebo patients both indicating some degree of systemic absorption and adrenal suppression of BDP.

The improvement in mortality seen in the pivotal phase 3 trial is supported by a retrospective analysis of mortality in the placebo-controlled phase 2 study in an essentially identical patient population which, although not statistically significant, shows consistent survival outcomes. The results for selected survival outcomes from both studies are presented in Table 3-3. The results of the corresponding integrated analysis of the 2 studies are shown in Figure 3-2.

No drugs are currently licensed for the treatment of acute GI GVHD. Current standard of care in the disease is high dose corticosteroids, which carry significant toxicity. The mortality benefit in the BDP arms of these trials, combined with the favorable risk benefit ratio and the lack of alternative therapies make BDP a major advance in the therapy of acute GI GVHD.

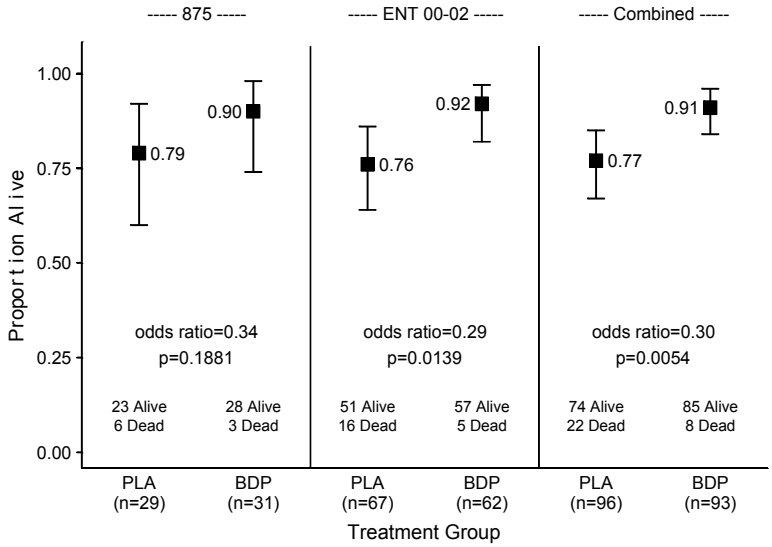
Table 3-3. Survival Data for Subjects Enrolled in Studies ENT 00-02 and 875 at 200 Days After HCT and at 1 Year After Randomization to Study (ITT Analysis)

	Phase 3 Study ENT 00-02		Phase 2 Study 875	
	Placebo	BDP	Placebo	BDP
Number of subjects randomized	67	62	29	31
Number (%) died by transplant day 200	16 (24%)	5 (8%)	6 (21%)	3 (10%)
Odds ratio (95% CI)	0.29 (0.10, 0.82)		0.34 (0.07, 1.72)	
P-value	0.0139		0.1881	
Hazard ratio (95% CI)[a]	0.33 (0.12, 0.89)		0.44 (0.11, 1.75)	
P-value[a]	0.0294		0.2415	
Number (%) died by 1-year post-random	28 (42%)	18 (29%)	9 (31%)	6 (19%)
Hazard ratio (95% CI)	0.54 (0.30, 0.99)		0.55 (0.20, 1.56)	
P-value	0.0431		0.2556	

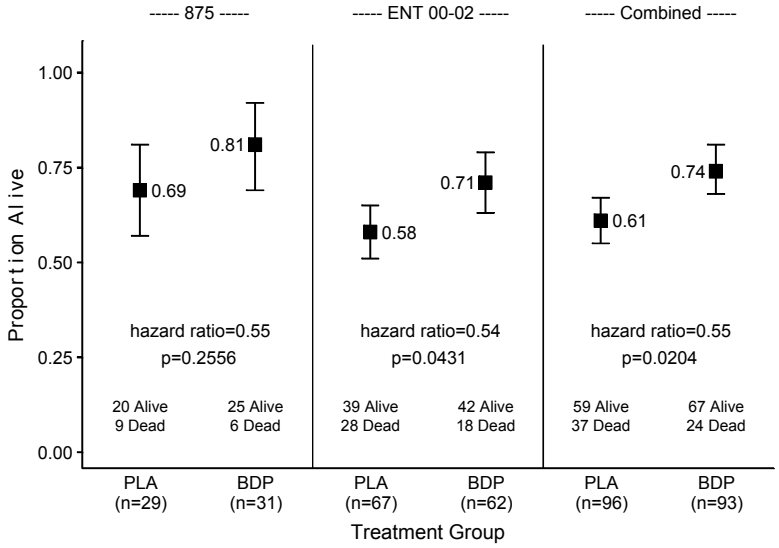
[a] Adjusted for the time between transplantation and randomization.

Figure 3-2. Survival Outcomes for Studies 875 and ENT-002, and Both Studies Combined (Integrated ITT Analysis Sets)

Survival at Day 200 Post-Transplantation:



Survival at One Year Post-Randomization:



4. CLINICAL EFFICACY

4.1 Introduction

Two randomized, double-blind, placebo-controlled trials were conducted to support the efficacy of BDP treatment in the proposed indication. One of the trials was a phase 2 study (Study 875) and the other the pivotal phase 3 study (Study ENT 00-02), which was initiated following an end of phase 2 meeting with the FDA on September 8, 2000 and written agreement on the trial design through Special Protocol Assessment.

4.2 Pivotal Phase 3 Study ENT 00-02

Study ENT 00-02 ("A Phase III Randomized Placebo-Controlled, Multi-Center Study of the Safety, Efficacy, and Pharmacokinetics of Oral Beclomethasone 17, 21-Dipropionate in Conjunction with Ten Days of High Dose Prednisone Therapy in the Treatment of Patients with Grade II Graft vs. Host Disease with Gastrointestinal Symptoms") enrolled 129 subjects with symptoms of acute GI GVHD whose endoscopy and mucosal biopsy specimens demonstrated findings consistent with GI GVHD, and whose stool and mucosal biopsy cultures were negative for pathogens. Subjects with GI GVHD who had limited skin and liver acute GVHD were also eligible for the study.

Protocol treatment consisted of study drug (BDP 8 mg/day or placebo, both administered in a double-blind manner in 4 divided doses per day) plus a 10-day induction course of prednisone (1 mg/kg/day). A rapid prednisone taper over 7 days began on study day 11 after which all patients received physiologic replacement doses of prednisone (0.0625 mg/kg/day) through study day 80. Administration of blinded study drug continued unchanged from study days 1-50 or until GVHD treatment failure or subject withdrawal. GVHD treatment failure was defined as the requirement for increased doses of immunosuppressive drugs beyond those specified in the protocol; subjects with uncontrolled signs or symptoms of GVHD who required higher doses of corticosteroids, use of additional steroids, or addition of additional immunosuppressive agent(s) were identified by the investigator using best clinical judgment of the investigator.

The primary endpoint was the "time to GVHD treatment failure through study day 50" (i.e., the planned end of the 50-day protocol treatment period). Prospectively defined secondary efficacy endpoints included functional performance status and cumulative treatment failure rates by study days 10, 30, 50, 60, and 80, which in the final analysis was assessed as the time to treatment failure through study day 80 (i.e., the planned end of the 80-day study period). Survival at one year post-randomization and overall survival were evaluated as FDA requested post-hoc analyses.

The randomization was stratified by study center, topical corticosteroid use at baseline (yes, no), and donor type (HLA-matched sibling vs. unrelated or HLA-mismatched). The statistical analysis plan specified the primary efficacy analysis to be stratified by donor type only. The primary efficacy analysis was based on the intention-to-treat principle and included all randomized subjects who were analyzed according to their randomized study drug assignment. Hypothesis tests of the primary and secondary efficacy endpoints were performed using a two-sided significance level of 0.05. The protocol and statistical analysis plan did not include specifications for adjusting the significance level to account for inflation of the overall type 1 error rate due to the testing of secondary endpoints and post-hoc analyses. As described previously and below in Section 4.2.1, the primary analysis of the primary efficacy endpoint for this study failed to achieve the predefined level of statistical significance. In light of this result, analyses were performed in an exploratory manner for the secondary endpoints defined for this study. The inferential results reported from these analyses may be viewed as descriptive measures since all of the type 1 error that was allocated for this study was spent on the aforementioned primary endpoint and retrospective adjustment of the significance level is considered not meaningful once the results are known. However, given the clinical importance of some of the secondary endpoints and post-hoc analyses (i.e., survival), inferential results unadjusted for multiplicity are reported to facilitate interpretation of the data from this study and to assist with the overall clinical evaluation of the benefits and risks of BDP treatment.

A total of 129 subjects were randomized between July 2001 and July 2004 at 14 centers in the United States and 2 in France (Table 4-1). Approximately half (47%) of the

overall study population was enrolled at the Fred Hutchinson Cancer Research Center in Seattle, WA. Sixty-two subjects (48%) were randomized to receive BDP treatment, and 67 subjects (52%) were randomized to receive placebo. Six subjects were randomized to receive BDP (n = 3) or placebo (n = 3) within a randomization strata for donor type that did not match the donor information reported from other data sources. The primary efficacy analysis was stratified by the donor type based on the assigned randomization strata. Sensitivity analyses were performed based on the donor type reported from other data sources.

The treatment groups were well balanced with respect to race, gender, and age at randomization (Table 4-2). Overall, the study population was predominately white (85%), male (60%), with median age of 47 years (range: 6 to 70). Three subjects younger than 18 years (ages 6, 13, and 17), and 7 subjects 65 years or older were enrolled.

Although the study population consisted of a heterogeneous group of diagnoses, the treatment groups were generally well balanced with respect to the primary cancer diagnosis (Table 4-3). The majority of subjects received their transplant for a primary diagnosis of leukemia, with acute myelogenous leukemia (32%), acute lymphocytic leukemia (12%), and chronic myelogenous leukemia (12%) being the most prevalent.

There were two baseline variables for which the treatment arms were imbalanced: subjects whose primary diagnosis is associated with a poor prognosis (65% in BDP arm vs. 43% in placebo arm) and type of conditioning regimen (myeloablative vs. non-myeloablative) received (42% non-myeloablative in BDP vs. 22% in placebo) (Table 4-4). The imbalances between treatment groups for these two factors were related because a greater percentage of subjects in the study population with a poorer prognosis received a non-myeloablative conditioning regimen (66%) compared to recipients of myeloablative conditioning regimens (48%).

Table 4-1. Randomization Summary (Study ENT 00-02: ITT Analysis Set)

	Placebo		BDP		Overall	
Subjects randomized	67		62		129	
Donor type (assigned randomization strata)[a]						
HLA-matched sibling donor	43	64%	39	63%	82	64%
Unrelated or HLA-mismatched donor	24	36%	23	37%	47	36%
Donor type (reported from other sources)						
HLA-matched sibling donor	40	60%	38	61%	78	60%
Unrelated or HLA-mismatched donor	27	40%	24	39%	51	40%
Study center						
Fred Hutchinson Cancer Research Cntr	31	46%	29	47%	60	47%
Vanderbilt University	7	10%	6	10%	13	10%
Hackensack University Medical Cntr	5	7%	7	11%	12	9%
City of Hope	4	6%	5	8%	9	7%
Presbyterian/St. Luke's Medical Cntr	4	6%	5	8%	9	7%
Baylor University	4	6%	3	5%	7	5%
Oncology & Hematology Assoc.	2	3%	3	5%	5	4%
Duke University Medical Cntr	2	3%	1	2%	3	2%
Roswell Park	3	4%	0	0%	3	2%
Wayne State University	1	1%	1	2%	2	2%
Children's Hospital of Denver	0	0%	1	2%	1	<1%
Groupe Hospitalier Pitie – Salpetriere	1	1%	0	0%	1	<1%
Hospital Necker – Enfants Malades	1	1%	0	0%	1	<1%
Memorial Sloan-Kettering	0	0%	1	2%	1	<1%
Oklahoma Oncology	1	1%	0	0%	1	<1%
Rush Presbyterian/St. Luke's Medical Cntr	1	1%	0	0%	1	<1%

[a] Six subjects were randomized to receive BDP (n=3) or placebo (n=3) within a randomization strata that did not match the donor information reported from other data sources. The primary efficacy analysis was stratified by donor type based on the assigned randomization strata. Sensitivity analyses were performed based on the donor type reported from other data sources.

HLA = human leukocyte antigen; ITT = intention-to-treat

Table 4-2. Demographics (Study ENT 00-02: ITT Analysis Set)

	Placebo		BDP		Overall	
Subjects randomized	67		62		129	
Sex						
Male	41	61%	36	58%	77	60%
Female	26	39%	26	42%	52	40%
Race						
White	56	84%	54	87%	110	85%
American Hispanic	7	10%	4	6%	11	9%
Asian	1	1%	3	5%	4	3%
Black	3	4%	1	2%	4	3%
Age group						
<10 years	0	0%	1	2%	1	<1%
10 to <14	0	0%	1	2%	1	<1%
14 to <18	1	1%	0	0%	1	<1%
18 to <25	6	9%	1	2%	7	5%
25 to <45	23	34%	22	35%	45	35%
45 to <65	35	52%	32	52%	67	52%
≥65	2	3%	5	8%	7	5%
Age (years)						
Mean (± SD)	44.5 (± 13.40)		45.9 (± 13.58)		45.2 (± 13.45)	
Median	47.0		47.0		47.0	
Range	17 to 66		6 to 70		6 to 70	

ITT = intention-to-treat; SD = standard deviation

Table 4-3. Primary Cancer Diagnosis (Study ENT 00-02: ITT Analysis Set)

	Placebo		BDP		Overall	
Subjects randomized	67		62		129	
Primary cancer diagnosis						
Acute myelogenous leukemia	22	33%	19	31%	41	32%
Acute lymphocytic leukemia	7	10%	9	14%	16	12%
Chronic myelogenous leukemia	8	12%	8	13%	16	12%
Non-Hodgkin's lymphoma	7	10%	6	10%	13	10%
Myelodysplastic syndrome	6	9%	2	3%	8	6%
Multiple myeloma	1	1%	6	10%	7	5%
Chronic lymphocytic leukemia	4	6%	2	3%	6	5%
Chronic myelomonocytic leukemia	3	5%	2	3%	5	4%
Aplastic anemia	2	3%	1	2%	3	2%
Hodgkin's disease	2	3%	1	2%	3	2%
Myelofibrosis	2	3%	1	2%	3	2%
Acute promyelocytic leukemia	0	0%	2	3%	2	2%
Other[a]	4	6%	4	6%	8	6%
Acute myelogenous leukemia	22	33%	19	31%	41	32%
In first remission	15	22%	9	15%	24	19%
In second or later remission	2	3%	5	8%	7	5%
Persistent or relapsed disease	5	7%	5	8%	10	8%
Chronic myelogenous leukemia	8	12%	8	13%	16	12%
In chronic phase	4	6%	5	8%	9	7%
In accelerated phase or blast crisis	3	5%	3	5%	6	5%
Not reported	1	1%	0	0%	1	<1%
Risk of relapse post-transplant[b]						
Higher risk	29	43%	40	65%	69	53%
Lower risk	22	63%	22	35%	60	47%

[a] Other primary diagnoses include (1 each): Biphenotypic acute leukemia, extramedullary leukemia tumor, renal cell carcinoma, myeloproliferative syndrome, plasmacytic leukemia, and polythyemia vera.

[b] Subjects were considered to have a lower risk of relapse post-transplantation if the indication for transplantation was one of the following diagnoses: aplastic anemia, chronic lymphocytic leukemia, chronic myelogenous leukemia in chronic phase, chronic myelomonocytic leukemia, acute myelogenous leukemia in first remission, myelodysplastic syndrome, myelofibrosis, myeloproliferative syndrome, and polycythemia vera. Subjects with other diagnoses were considered to have a higher risk of relapse post-transplant.

Table 4-4. Transplant History (Study ENT 00-02: ITT Analysis Set)

	Placebo		BDP		Overall	
Subjects randomized	67		62		129	
Source of transplant						
Peripheral blood stem cells	62	93%	54	87%	116	90%
Bone marrow	5	7%	8	13%	13	10%
Conditioning regimen						
Myeloablative	52	78%	36	58%	88	68%
Non-myeloablative	15	22%	26	42%	41	32%
Days between transplantation and randomization						
n	67		62		129	
Mean (± SD)	45.7 (± 31.80)		48.3 (± 32.56)		47.0 (± 32.07)	
Median	35.0		37.0		36.0	
Range	18 to 171		18 to 190		18 to 190	

4.2.1 Primary Endpoint: Time to GVHD Treatment Failure through Study Day 50 (Study ENT 00-02)

Forty-eight subjects were judged by the investigators to be GVHD treatment failures during the 50-day protocol treatment period (Table 4-5). Fourteen subjects discontinued study drug early during this period for reasons unrelated to GVHD treatment failure. The time to GVHD treatment failure was right-censored for these subjects based on the date of the subject's last dose of study drug.

The intention-to-treat (ITT) analysis of the primary endpoint based on a stratified Cox proportional hazards model indicated that BDP was associated with a 37% lower risk of GVHD treatment failure during the 50-day protocol treatment period (hazard ratio = 0.63; 95% CI: 0.35-1.13), although this result failed to achieve statistical significance ($p = 0.1177$ by the stratified log-rank test) (Table 4-6). It should be noted that a larger proportion of subjects in the BDP group (8 subjects, 13%) met the criteria for GVHD treatment failure during the 10-day prednisone induction period compared to placebo (4 subjects, 6%). The reason for the greater number of early treatment failures in the BDP group has not been determined, but this outcome resulted in crossing Kaplan-Meier curves for this endpoint, thus making the assumption of proportional hazards

questionable and interpretation of the aforementioned hazard ratio problematic (Figure 4-1).

Table 4-5. GVHD Treatment Failure Status through Study Day 50 (Study ENT 00-02: ITT Analysis Set)

	Placebo		BDP		Overall	
Subjects randomized	67		62		129	
Met criteria for GVHD treatment failure						
Yes	30	45%	18	29%	48	37%
No	37	55%	44	71%	81	63%
Completed 50-day treatment period[a]	30	45%	37	60%	67	52%
Withdrawn from study early	7	10%	7	11%	14	11%
Adverse event	3	4%	3	5%	6	5%
Protocol violation	1	1%	4	6%	5	4%
Non-compliance	3	4%	0	0%	3	2%
Action which resulted in GVHD treatment						
Increased dose of corticosteroids	28	42%	18	29%	46	36%
Changed immunosuppressant medications	1	1%	0	0%	1	<1%
Received open-label BDP	1	1%	0	0%	1	<1%
Sites of recurrent GVHD which resulted in treatment failure						
Gut	23	34%	15	24%	38	29%
Skin	4	6%	0	0%	4	3%
Gut & skin	0	0%	2	3%	2	2%
Liver	1	1%	1	2%	2	2%
Lung	1	1%	0	0%	1	<1%
Not reported	1	1%	0	0%	1	<1%

[a] Completed the 50-day protocol treatment period without meeting the criteria for GVHD treatment failure.

Table 4-6. Primary Endpoint: Time to GVHD Treatment Failure through Study Day 50 (Study ENT 00-02: ITT Analysis Set)

	Placebo	BDP
Subjects randomized	67	62
Number of GVHD treatment failures	30	18
Median days to treatment failure (95% CI)	Not reached	Not reached
Adjusted hazard ratio (95% CI)	0.63 (0.35, 1.13)	
Stratified log-rank test	$\chi^2 = 2.447$, 1 df, P = 0.1177	
Treatment by strata interaction	$\chi^2 = 0.014$, 1 df, P = 0.9072	

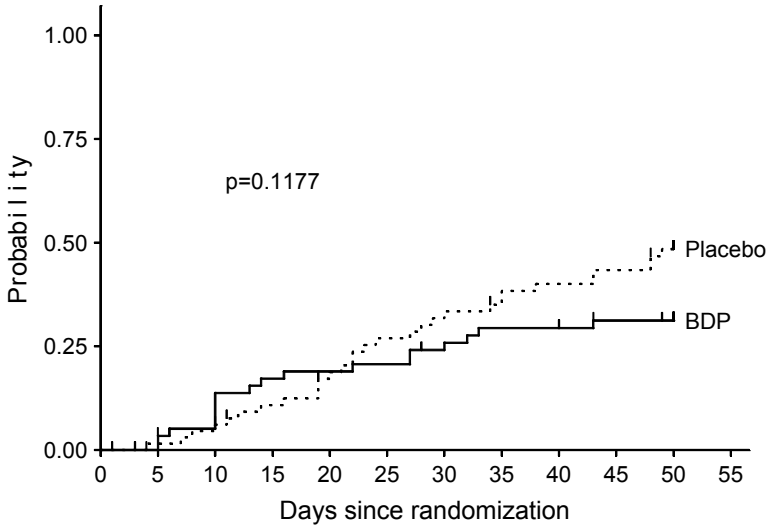
The time to GVHD treatment failure for subjects who withdrew from study early without treatment failure beforehand was right-censored on the day of their last dose of study drug.

Median days to treatment failure for each treatment group was estimated from the 50th percentile of the compliment of the Kaplan-Meier distribution.

The hazard ratio was estimated from a stratified Cox proportional hazards model based on the 2 level randomization stratification variable for donor type (HLA-matched sibling vs. unrelated or HLA-mismatched donor). Placebo serves as the reference treatment group for interpretation of the hazard ratio.

Stratified log-rank test was calculated based on the 2 level randomization stratification variable for donor type. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

Figure 4-1. Primary Endpoint: Time to GVHD Treatment Failure through Study Day 50 (Study ENT 00-02: ITT Analysis Set)



	1-10	11-20	21-30	31-40	41-50
BDP	8/62	3/50	4/47	2/42	1/39
Placebo	4/67	8/61	9/50	4/41	5/36

(#events/#at risk)

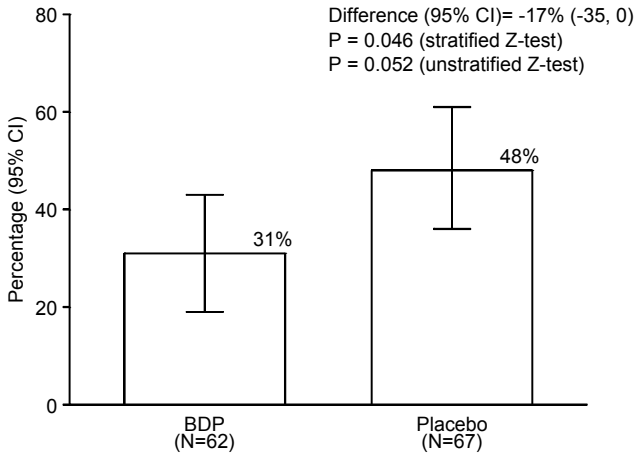
P-value is based on the stratified log-rank test. The stratified version of this test was prespecified as the primary analysis method and is based on the 2-level randomization stratification factor for donor type (HLA-matched sibling vs. unrelated or HLA-mismatched donor). Study Day 50 represents the planned end of the 50-day protocol treatment period. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

4.2.2 Secondary Endpoint: Proportion of Subjects with GVHD Treatment Failure by Study Day 50 (Study ENT 00-02)

A supplemental categorical analysis was performed to compare the proportion of subjects in each treatment group who met the criteria for GVHD treatment failure on or before study day 50. (The categorical analysis at study day 50 was specified in the study protocol and statistical analysis plan as a secondary efficacy endpoint.)

The Kaplan-Meier estimate of the proportion of subjects with GVHD treatment failure by study day 50 was 31% in the BDP group and 48% in the placebo group (p = 0.046 by the stratified Z-test) (Figure 4-2).

Figure 4-2. Secondary Endpoint: Proportion of Subjects with GVHD Treatment Failure by Study Day 50 (Study ENT 00-02: ITT Analysis Set)



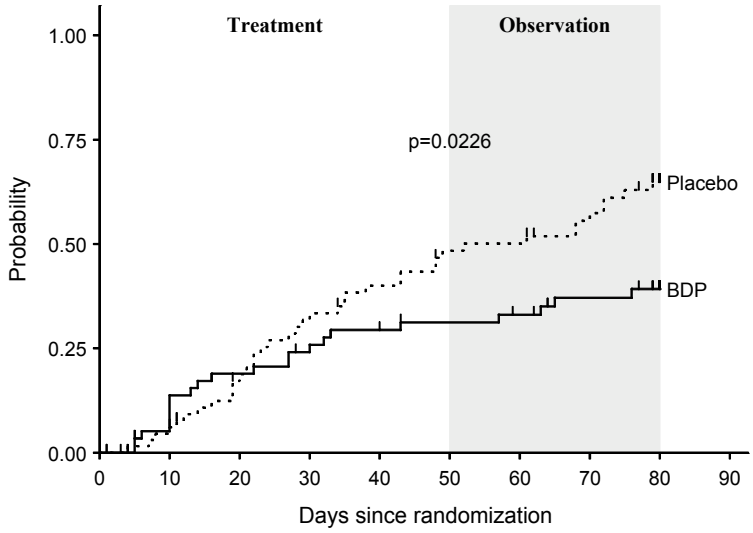
Proportions are based on the Kaplan-Meier point estimates at Study day 50. Study day 50 represents the planned end of the 50-day protocol treatment period. P-value is based on the Z-test test. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

4.2.3 Secondary Endpoint: Time to GVHD Treatment Failure through Study Day 80 (Study ENT 00-02)

A secondary analysis was performed to assess the effect of BDP treatment on time to GVHD treatment failure during the entire 80-day study period, which consisted of the planned 50-day protocol treatment period (primary endpoint) plus the planned 30-day post-treatment observation period. This endpoint was included in the study design to provide an assessment of the robustness of the effect on treatment failure seen at study day 50. For this analysis, the risk of treatment failure was 46% lower for subjects randomized to BDP relative to placebo (hazard ratio = 0.54; 95% CI: 0.32-0.93;

p = 0.0226 by the stratified log-rank test) (Figure 4-3 and Table 4-7) indicating a sustained and clinically significant effect.

Figure 4-3. Secondary Endpoint: Time to GVHD Treatment Failure through Study Day 80 (Study ENT 00-02: ITT Analysis Set)



	1-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80
BDP	8/62	3/50	4/47	2/42	1/39	1/37	2/35	1/30
Placebo	4/67	8/61	9/50	4/41	5/36	1/30	4/29	4/23

(#events/#at risk)

P-value is based on the stratified log-rank test. The stratified version of this test was prespecified as the primary analysis method and is based on the 2-level randomization stratification factor for donor type (HLA-matched sibling, unrelated or HLA-mismatched donor). Study Day 80 represents the planned end of the 80-day study period. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

Table 4-7. Time to GVHD Treatment Failure through Study Day 80 (Study ENT 00-02: ITT Analysis Set)

	Placebo	BDP
Subjects randomized	67	62
Number of GVHD treatment failures	39	22
Median days to treatment failure (95% CI)	52 (35, 75)	Not reached
Adjusted hazard ratio (95% CI)	0.54 (0.32, 0.93)	
Stratified log-rank test	$\chi^2 = 5.200$, 1 df, P = 0.0226	
Treatment by strata interaction	$\chi^2 = 0.136$, 1 df, P = 0.7127	

The GVHD time to treatment failure for subjects withdrawn early from study without treatment failure beforehand was right-censored on the day of their last dose of study drug, or last study visit, whichever occurred last.

Median days to treatment failure for each group were estimated from the 50th percentile of the compliment of the Kaplan-Meier distribution.

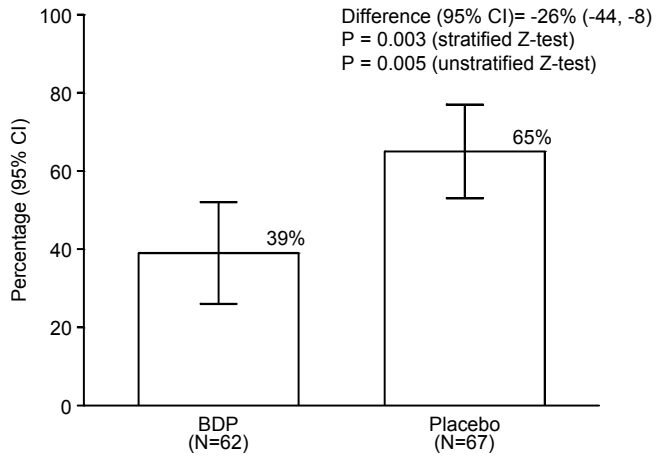
The hazard ratio was estimated from a stratified Cox proportional hazards model based on the 2 level randomization stratification variable for donor type (HLA-matched sibling vs. unrelated or HLA-mismatched donor). Placebo serves as the reference treatment group for interpretation of the hazard ratio.

Stratified log-rank test was calculated based on the 2 level randomization stratification variable for donor type. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

4.2.4 Secondary Endpoint: Proportion of Subjects with GVHD Treatment Failure by Study Day 80 (Study ENT 00-02)

A supplemental categorical analysis was performed to compare the proportion of subjects in each treatment group who met the criteria for GVHD treatment failure on or before study day 80. (The categorical analysis at study day 80 was specified in the study protocol and statistical analysis plan as a secondary efficacy analysis.) The Kaplan-Meier estimate of the proportion of subjects with GVHD treatment failure by study day 80 was 39% for the BDP group compared to 65% for placebo (p=0.003 by the stratified Z-test) (Figure 4-4).

Figure 4-4. Secondary Efficacy Endpoint: Proportion of Subjects with GVHD Treatment Failure by Study Day 80 (Study ENT 00-02: ITT Analysis Set)



Proportions are based on the Kaplan-Meier point estimates at Study day 80. Study day 80 represents the planned end of the 80-day study period. P-value is based on the Z-test test. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

4.2.5 Secondary Endpoint: Functional Performance Status Scores (Study ENT 00-02)

Karnofsky performance status (KPS) scores are summarized in Table 4-8 by treatment group and planned protocol assessment time points. This analysis excludes the two subjects in the BDP group who were younger than 16 years of age and whose functional performance assessment was evaluated using the Lansky Performance Scale.

The distribution of KPS scores at baseline were comparable between the BDP and placebo groups (median score of 70 for both groups). For the post-baseline functional performance assessments during the 50-day protocol treatment period, KPS scores tended to increase over time relative to baseline, but were similar between treatment groups at study day 50. During the 30-day post-treatment observation period, KPS scores tended to plateau in both groups and returned towards their respective baseline levels by study day 80.

The analysis of KPS scores was also performed using a repeated measures mixed effects model. The results based on this approach are consistent with those described above (data not shown).

Table 4-8. Secondary Endpoint: Karnofsky Performance Status Scores (Study ENT 00-02: ITT Analysis Set)

	Placebo	BDP
Subjects randomized	67	62
Subjects evaluable	67	60
Study day 0 (baseline)		
n	65	60
Mean (± SD)	65.8 (± 13.10)	67.8 (± 12.63)
Median	70.0	70.0
Range	30 to 90	40 to 100
Study day 50		
n	66	60
Mean (± SD)	76.2 (± 15.32)	77.0 (± 15.55)
Median	80.0	80.0
Range	20 to 100	0 to 100
Study day 80		
n	66	60
Mean (± SD)	72.9 (± 24.60)	74.8 (± 20.71)
Median	80.0	80.0
Range	0 to 100	0 to 100

Excludes 2 subjects who were younger than 16 years of age and whose functional performance status was assessed using the Lansky Performance Scale.

Missed assessments were imputed using last observation carried forward (LOCF) method.

4.2.6 Secondary Endpoint: Survival at 200 Days Post-Transplantation (Study ENT 00-02)

This endpoint was prospectively defined in the protocol and statistical analysis plan as a safety endpoint that required all subjects to be followed for survival in a blinded manner for 200 days post transplant. An ITT analysis of this endpoint showed that the BDP group had a higher survival rate (92%) at day 200 post-transplant compared to the

placebo group (76%) (odds ratio = 0.29; 95% CI: 0.1-0.82; p = 0.0139 by the Cochran-Mantel-Haenszel test) (Table 4-9). The mortality difference between the BDP and placebo groups was primarily observed in the subgroup of subjects whose donor was unrelated or HLA-mismatched (p = 0.0476 by the Breslow-Day test of homogeneity of the odds ratios across randomization strata) (Table 4-9, Figure 4-5). Overall, relapse of the underlying malignancy (5% in the BDP group and 10% in the placebo group), infection (2% in the BDP group and 9% in the placebo group), and GVHD (2% in the BDP group and 5% in the placebo group) were reported as the proximate causes of death during this period (Table 4-9).

These results indicated a decreased risk of early mortality for subjects treated with BDP; however, the evaluation of BDP treatment effects on early mortality measured relative to the date of transplant could be confounded by the varying time period among subjects for the number of days between their transplant procedure and randomization in the study (overall median of 36 days, range 18 to 190). Although the BDP and placebo groups were well matched with respect to the number and range of days between transplantation and randomization (BDP: median = 37 days, range: 18 to 190; placebo: median = 35 days, range: 18 to 171), a supplemental analysis was performed to incorporate the number of days between transplantation and randomization for each individual patient. When survival at 200 days post-transplant was analyzed accounting for the variable time period between transplantation and randomization, subjects in the BDP group had a 67% reduction in the risk of mortality by transplant day 200 relative to placebo (hazard ratio = 0.33; 95% CI: 0.12-0.89; p = 0.0294 by the Wald chi-square test) (Table 4-10).

Table 4-9. Secondary Endpoint: Survival at Day 200 Post-Transplantation (Study ENT 00-02: ITT Analysis Set)

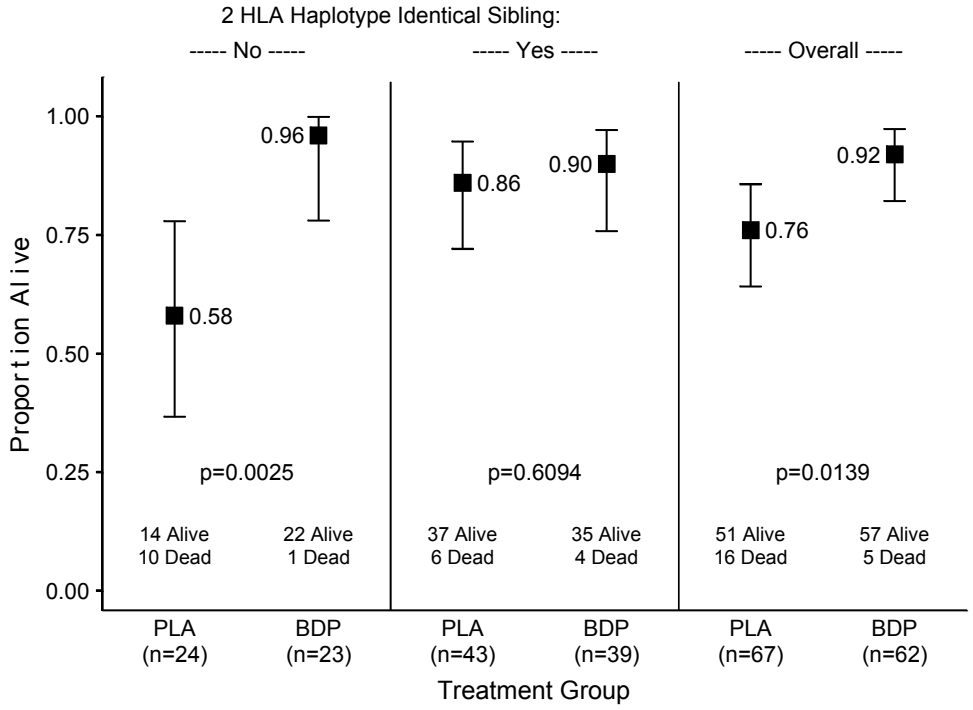
	Placebo		BDP	
Subjects randomized	67		62	
Survival status				
Alive	51	76%	57	92%
Dead	16	24%	5	8%
Proximate cause of death				
Relapse of underlying malignancy	7	10%	3	5%
Infection	6	9%	1	2%
GVHD	3	5%	1	2%
Contributing causes of death				
No	5	7%	3	5%
Yes	11	16%	2	3%
Relapse of underlying malignancy	2	3%	0	0%
Infection	3	5%	2	3%
GVHD	7	10%	0	0%
Other: Multi-organ failure	6	9%	0	0%
Other: Respiratory failure	1	1%	0	0%
Day 200 survival rate (95% CI)	0.76 (0.64, 0.86)		0.92 (0.82, 0.97)	
Stratified test of association between treatment and Day 200 survival status	CMH = 6.0461, 1 df, P = 0.0139			
Adjusted odds ratio (95% CI)	0.29 (0.10, 0.82)			
Test of homogeneity of the odds ratios	χ^2 = 3.9248, 1 df, P = 0.0476			

The ITT analysis set includes all randomized subjects, including the two subjects who withdrew from study prior to taking any study drug (Patient ID 002-13-304 randomized to receive placebo was reported to be alive on Day 200; Patient ID 002-04-304 randomized to receive BDP was reported to be alive on Day 200).

The upper and lower limits of the 95% confidence interval are calculated using the Clopper-Pearson method.

The test of association between treatment and survival status and estimation of the odds ratio are based on the Cochran-Mantel-Haenszel (CMH) procedure. The CMH test and odds ratio were calculated based on the 2 level randomization stratification factor for donor type (HLA-matched sibling vs. unrelated or HLA-mismatched donor). Placebo serves as the reference treatment group for interpretation of the odds ratio. The test of homogeneity of the odds ratios across stratum is based on the Breslow-Day test. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

Figure 4-5. Secondary Endpoint: Survival at Day 200 Post-Transplantation (Study ENT 00-02: ITT Analysis Set)



P-value is based on the chi-square test for treatment comparisons within strata and Cochran-Mantel-Haenszel test for treatment comparison across strata. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

Cox Regression Analysis of Day 200 Post-Transplantation Survival

The number of deaths (21) does not allow the inclusion into the Cox regression model of more than 1 or 2 variables in addition to the treatment group variable. The only factors that were largely imbalanced between the treatment groups was the planned intensity of the transplant conditioning regimen (myeloablative or non-myeloablative) and primary diagnosis (high relapse risk or low relapse risk). Adjustment for these factors did not, however, alter the estimated hazard ratio for mortality for BPD treatment vs. placebo (Table 4-10). Moreover, the estimated BDP treatment effect also remained generally unchanged after adjusting for various other factors, including study center, age and gender, baseline Karnofsky performance status, and transplant source (marrow,

peripheral blood stem cells). Similar results were also observed for other multivariate models evaluated (data not shown).

Table 4-10. BDP Treatment Effect on Survival 200 Days Post-Transplantation Using Covariate Adjusted Cox Models (Study ENT 00-02: ITT Analysis Set)

Model	Hazard Ratio	95% CI	P-value
BDP treatment effect without covariates	0.33	(0.12, 0.89)	0.0294
BDP treatment effect with covariate			
Non-myeloablative conditioning regimen	0.33	(0.12, 0.91)	0.0330
Higher risk of relapse post-transplantation	0.32	(0.11, 0.88)	0.0274
Fred Hutchinson Cancer Research Center	0.33	(0.12, 0.89)	0.0291
Male	0.33	(0.12, 0.89)	0.0291
Age on transplant date (per 1-yr increase)	0.33	(0.12, 0.91)	0.0312
Bone marrow as source of stem cells	0.35	(0.13, 0.96)	0.0404
Baseline Karnofsky performance status	0.35	(0.13, 0.96)	0.0420

The hazard ratio for each model was estimated from a counting process form of the Cox model stratified by the 2-level randomization factor for donor type (HLA-matched sibling vs. unrelated or HLA-mismatched donor). The variable for BDP treatment was defined in the model as a time-dependent covariate, taking on a value of 1 during the period between randomization to BDP and death (or last follow-up if alive). Otherwise, the value of the variable was zero.

The model for baseline Karnofsky performance status excludes 2 subjects less than 18 years of age whose baseline functional performance status was evaluated using the Lansky performance status scale.

4.2.7 FDA-requested Post-hoc Analysis: Survival Post-Randomization (Study ENT 00-02)

Although not prospectively defined in the protocol or statistical analysis plan, longer term survival data measured relative to the date of randomization were collected in a retrospective manner based on requests by FDA representatives during the pre-NDA meeting with the study sponsor on November 1, 2005. To comply with this request, the survival status as of September 1, 2005 (data cutoff date) was sought from study sites for all randomized subjects, along with the date of death and proximate and contributory causes of death. As of the data cutoff date, 70 of the 129 subjects who were randomized in this study were alive or lost to follow-up.

The analysis of the post-randomization survival data was based primarily on the follow-up information measured up to 1 year post-randomization, and was supplemented by an analysis based on all available follow-up data (i.e., overall survival). Both of these

analyses were based on all randomized subjects (intention-to-treat principle), and include the 2 subjects who did not receive any study drug (1 subject in each treatment group). With the exception of two subjects who were classified as lost to follow-up during the first year after randomization, all surviving subjects were followed for at least 1 year from their date of randomization into the study.

Survival One Year Post-Randomization

Within 1 year of randomization, 18 subjects (29%) died in the BDP group died and 28 subjects (42%) died in the placebo group. The estimated survival rates 1 year after randomization were 71% for the BDP group and 58% for the placebo group. During this 1-year period, the overall risk of mortality was 46% lower for subjects randomized to BDP compared with subjects in the placebo group (hazard ratio = 0.54; p = 0.0431 by the stratified log-rank test) (Table 4-11, Figure 4-6). The mortality difference between the BDP and placebo groups was primarily observed in the subgroup of subjects whose donor was unrelated or HLA-mismatched (Figure 4-7) and recipients of non-myeloablative conditioning regimens (Figure 4-8). Overall, relapse of the underlying malignancy (13% in the BDP group and 19% in the placebo group) and infection (5% in the BDP group and 13% in the placebo group) were the most frequently reported proximate causes of death during this period (Table 4-11).

Table 4-11. FDA Requested Post-Hoc Analysis: Survival One Year Post-Randomization (Study ENT 00-02: ITT Analysis Set)

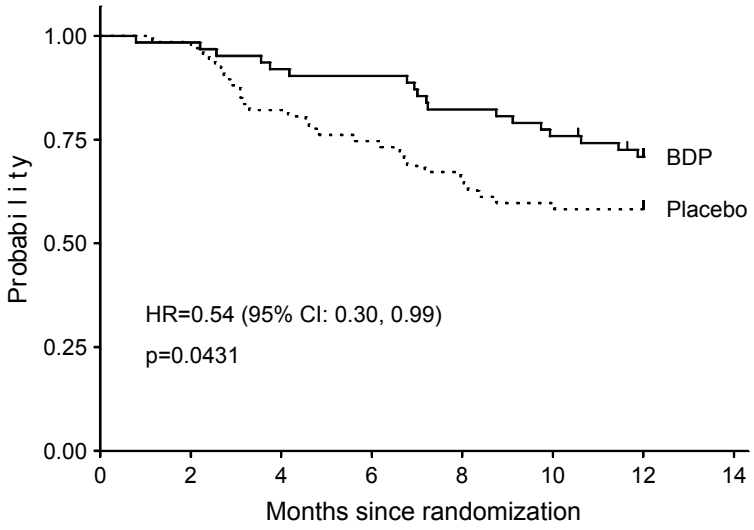
	Placebo		BDP	
Subjects randomized	67		62	
Survival status one-year post-randomization				
Alive	39	58%	42	68%
Dead	28	42%	18	29%
Lost to follow-up	0	0%	2	3%
Proximate cause of death				
Relapse of underlying malignancy	13	19%	8	13%
Infection	9	13%	3	5%
GVHD	3	4%	3	5%
Other	3	4%	3	5%
Unknown	0	0%	1	2%
One-year survival rate (95% CI)	0.58 (0.51, 0.65)		0.71 (0.63, 0.79)	
Duration of survival (months)				
Median (95% CI)	Not reached		Not reached	
Adjusted hazard ratio (95% CI)	0.54 (0.30, 0.99)			
Stratified log-rank test	$\chi^2 = 4.0909$, 1 df, P = 0.0431			
Test for treatment by strata interaction	$\chi^2 = 1.9581$, 1 df, P = 0.1617			

The analysis is based on the September 1, 2005 data cut-off date. For purposes of this analysis, all subjects surviving greater than one year (365 days) post-randomization were right-censored as of the one year time point.

The one-year survival rate was estimated using the Kaplan-Meier method. Greenwood's formula was used to calculate the standard errors of the Kaplan-Meier estimate and corresponding upper and lower limits of the 95% confidence interval.

Hazard ratio estimated from a stratified Cox proportional hazards model based on the two-level randomization stratification factor for donor type (HLA-matched sibling vs. unrelated or HLA-mismatched donor). Placebo serves as the reference treatment group for interpretation of the hazard ratio. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

Figure 4-6. FDA Requested Post-Hoc Analysis: Survival One Year Post-Randomization (Study ENT 00-02: ITT Analysis Set)

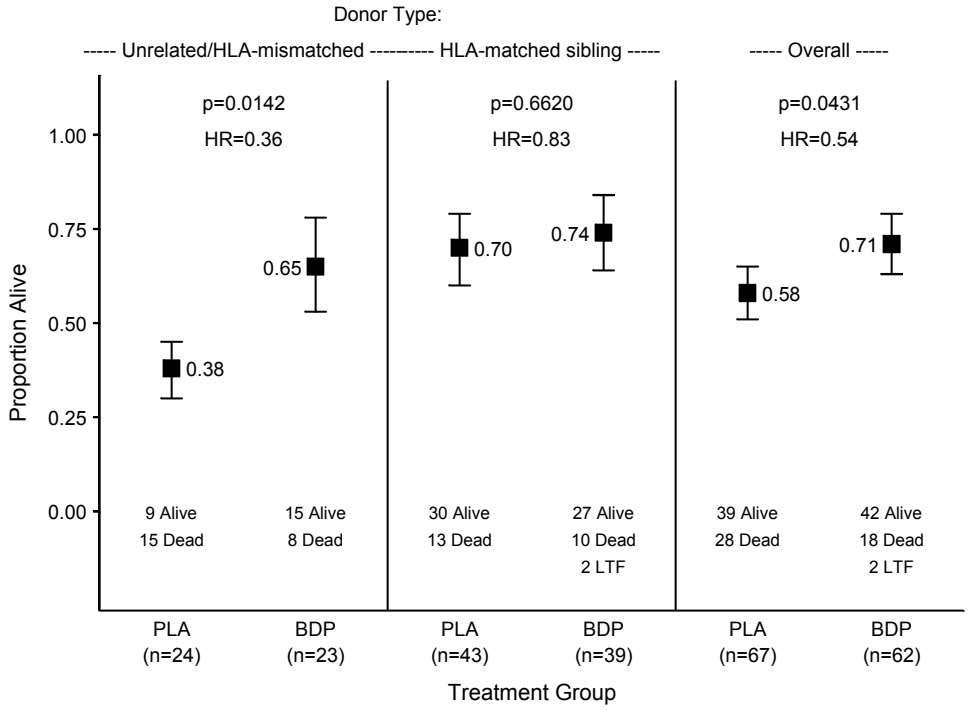


	0-2	3-4	5-6	7-8	9-10	11-12
BDP	1/62	4/61	1/57	5/56	4/51	3/47
Placebo	1/67	11/66	5/55	6/50	4/44	1/40

(#events/#at risk)

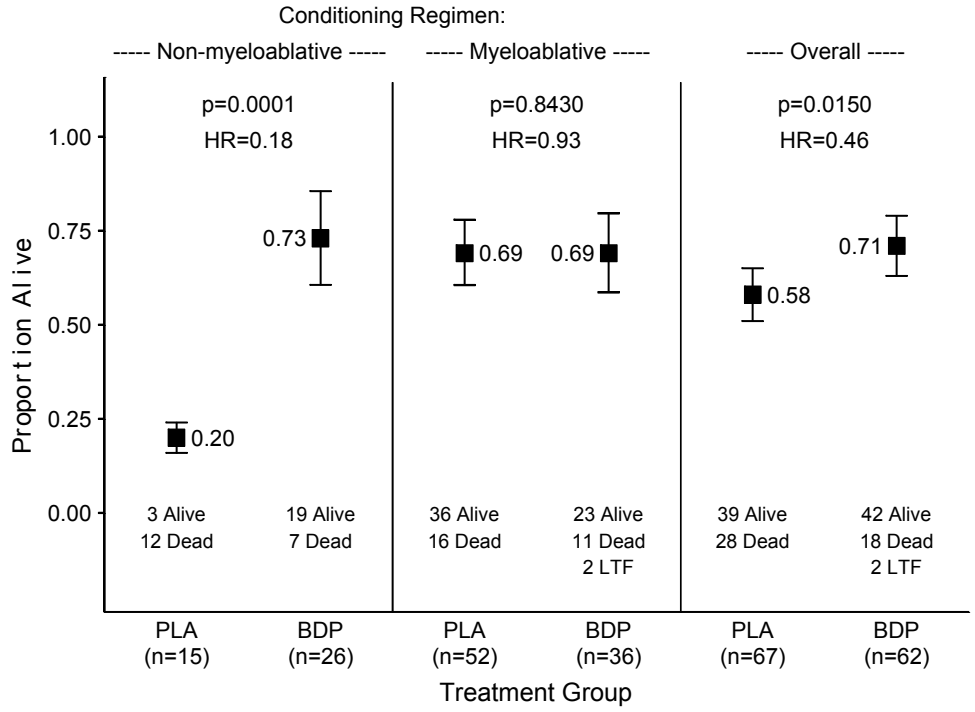
For purposes of this analysis, all subjects surviving more than one year (365 days) post-randomization were right-censored as of the one year time point. Hazard ratio estimated from a Cox proportional hazards model stratified by the two-level randomization stratification factor for donor type (HLA-matched sibling vs. unrelated or HLA-mismatched donor). P-value calculated from the stratified log-rank test. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

Figure 4-7. Subgroup Analysis of One Year Survival Post-Randomization by Donor Type (Study ENT 00-02: ITT Analysis Set)



For treatment comparisons within the above subgroups, the hazard ratio and p-value are based on a univariate Cox proportional hazards model and log-rank test, respectively. The overall analysis is based on a Cox model and log-rank test (both stratified by donor type). Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

Figure 4-8. Subgroup Analysis of One Year Survival Post-Randomization by Conditioning Regimen Type (Study ENT 00-02: ITT Analysis Set)



For treatment comparisons within the above subgroups, the hazard ratio and p-value are based on a univariate Cox proportional hazards model and log-rank test, respectively. The overall analysis is based on a Cox model and log-rank test (both stratified by myeloablative and non-myeloablative conditioning regimens). A statistically significant interaction term was detected in the overall stratified model between treatment and conditioning regimen (p=0.0093). For purposes of this analysis, the significant interaction term was not included in the model from which the above overall results are based. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

Cox Regression Analysis of Survival One Year Post-Randomization

The robustness of the estimated effect of BDP treatment on survival during 1 year post-randomization was evaluated using Cox regression models. The two factors that were largely imbalanced between the treatment groups at baseline was the planned intensity of the transplant conditioning regimen (myeloablative or non-myeloablative) and primary diagnosis (high relapse risk or low relapse risk). Adjustment for these factors did not, however, alter the estimated hazard ratio for mortality for BPD treatment vs. placebo

(Table 4-12). Moreover, the estimated BDP treatment effect also remained generally unchanged after adjusting for various other factors, including study center, age and gender, baseline Karnofsky performance status, and transplant source (marrow, peripheral blood stem cells). Similar results were also observed for other multivariate models evaluated (data not shown).

Table 4-12. BDP Treatment Effect on Survival One Year Post-Randomization Using Covariate Adjusted Cox Models (Study ENT 00-02: ITT Analysis Set)

Model	Hazard Ratio	95% CI	P-value
BDP treatment effect without covariates	0.54	(0.30, 0.99)	0.0462
BDP treatment effect with covariate			
Non-myeloablative conditioning regimen	0.44	(0.23, 0.83)	0.0116
Higher risk of relapse post-transplantation	0.50	(0.27, 0.92)	0.0263
Fred Hutchinson Cancer Research Center	0.53	(0.29, 0.97)	0.0395
Male	0.54	(0.30, 0.99)	0.0465
Age on transplant date (per 1-yr increase)	0.53	(0.29, 0.97)	0.0394
Bone marrow as source of stem cells	0.54	(0.29, 0.98)	0.0436
Baseline Karnofsky performance status	0.55	(0.30, 1.01)	0.0535

Hazard ratio estimated from a stratified Cox proportional hazards model based on the two-level randomization stratification factor for donor type (HLA-matched sibling vs. unrelated or HLA-mismatched donor). Placebo serves as the reference treatment group for interpretation of the hazard ratio. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

The model for baseline Karnofsky performance status excludes 2 subjects less than 18 years of age whose baseline functional performance status was evaluated using the Lansky performance status scale.

Overall Survival Post-Randomization

As of the data cutoff date (September 1, 2005), median follow-up was 35.6 months for subjects in the placebo group (25-75th percentiles: 25.2 to 42.3 months) and 29 months for the BDP group (25-75th percentiles: 24.7 to 40.1 months). Three subjects whose date of last contact was before January 1, 2005 were classified as lost to follow-up as of the data cutoff date. Overall, 27 subjects (44%) died in the BDP group, and 32 subjects (48%) died in the placebo group (hazard ratio=0.71; p=0.1980 by the stratified log-rank test)

(Table 4-13, Figure 4-9). As of the September 1, 2005 data cutoff date, median survival was 38.5 months for the BDP group and not yet reached for the placebo group. Overall, relapse of the underlying malignancy (23% in the BDP group and 22% in the placebo group) and infection (8% in the BDP group and 13% in the placebo group) were the most frequently reported proximate causes of death (Table 4-13).

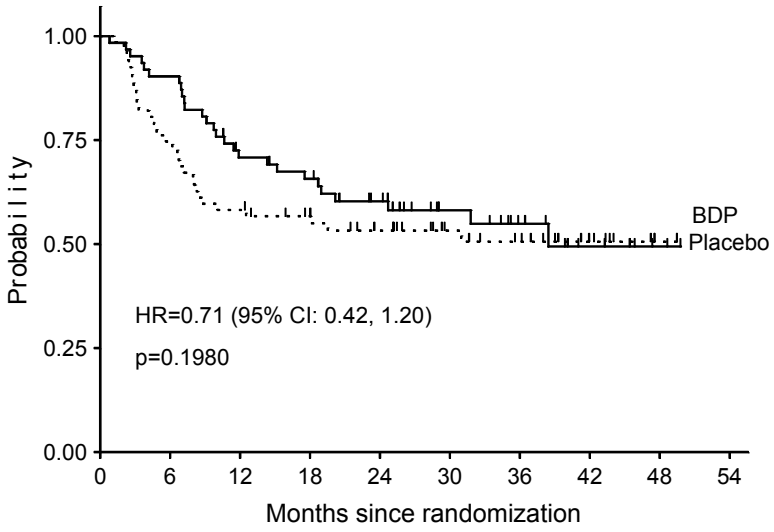
Table 4-13. FDA Requested Post-Hoc Analysis: Overall Survival Post-Randomization (Study ENT 00-02: ITT Analysis Set)

	Placebo		BDP	
Subjects randomized	67		62	
Overall survival status as of the last contact				
Alive	34	51%	33	53%
Dead	32	48%	27	44%
Lost to follow-up	1	2%	2	3%
Proximate cause of death				
Relapse of underlying malignancy	15	22%	14	23%
Infection	9	13%	5	8%
GVHD	3	5%	3	5%
Other	3	4%	4	6%
Unknown	2	3%	1	2%
Duration of follow-up (months)				
Median (25th-75th percentiles)	35.6 (25.2, 42.3)		29.0 (24.7, 40.1)	
Duration of overall survival (months)				
Median (95% CI)	Not reached yet		38.5 (18.9, not reached)	
Adjusted hazard ratio (95% CI)	0.71 (0.42, 1.20)			
Stratified log-rank test	$\chi^2 = 1.6573$, 1 df, P = 0.1980			
Test for treatment by strata interaction	$\chi^2 = 2.1799$, 1 df, P = 0.1398			

The analysis is based on the September 1, 2005 data cut-off date.

Hazard ratio estimated from a stratified Cox proportional hazards model based on the two-level randomization stratification factor for donor type (HLA-matched sibling vs. unrelated or HLA-mismatched donor). Placebo serves as the reference treatment group for interpretation of the hazard ratio. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

Figure 4-9. FDA Requested Post-Hoc Analysis: Overall Survival Post-Randomization (Study ENT 00-02: ITT Analysis Set)



	0-6	7-12	13-18	19-24	25-30	31-36	37-42	43-48	49-54
BDP	6/62	12/56	3/42	3/38	1/30	1/18	1/12	0/6	0/2
Placebo	17/67	11/50	1/39	2/34	0/28	1/20	0/16	0/9	0/2

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Hazard ratio estimated from a Cox proportional hazards model stratified by the two-level randomization stratification factor for donor type (HLA-matched sibling vs. unrelated or HLA-mismatched donor). P-value calculated from the stratified log-rank test. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

Cox Regression Analysis of Overall Survival Post-Randomization

The estimated effect of BDP treatment on overall survival post-randomization was evaluated using Cox regression models. The two factors that were largely imbalanced between the treatment groups at baseline was the planned intensity of the transplant conditioning regimen (myeloablative or non-myeloablative) and primary diagnosis (high relapse risk or low relapse risk). Adjustment for these factors did not, however, alter the estimated hazard ratio for mortality for BPD treatment vs. placebo (Table 4-14.). Moreover, the estimated BDP treatment effect also remained generally unchanged after adjusting for various other factors, including study center, age and gender, baseline

Karnofsky performance status, and transplant source (marrow, peripheral blood stem cells). Similar results were also observed for other multivariate models evaluated (data not shown).

Table 4-14. BDP Treatment Effect on Overall Survival Post-Randomization Using Covariate Adjusted Cox Models (Study ENT 00-02: ITT Analysis Set)

Model	Hazard Ratio	95% CI	P-value
BDP treatment effect without covariates	0.71	(0.42, 1.20)	0.1998
BDP treatment effect with covariate			
Non-myeloablative conditioning regimen	0.57	(0.33, 1.01)	0.0527
Higher risk of relapse post-transplantation	0.64	(0.37, 1.09)	0.1007
Fred Hutchinson Cancer Research Center	0.69	(0.41, 1.17)	0.1690
Male	0.71	(0.42, 1.19)	0.1952
Age on transplant date (per 1-yr increase)	0.69	(0.41, 1.16)	0.1639
Bone marrow as source of stem cells	0.71	(0.42, 1.20)	0.1965
Baseline Karnofsky performance status	0.72	(0.43, 1.21)	0.2171

Hazard ratio estimated from a stratified Cox proportional hazards model based on the two-level randomization stratification factor for donor type (HLA-matched sibling vs. unrelated or HLA-mismatched donor). Placebo serves as the reference treatment group for interpretation of the hazard ratio. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

The model for baseline Karnofsky performance status excludes 2 subjects less than 18 years of age whose baseline functional performance status was evaluated using the Lansky performance status scale.

4.3 Phase 2 Study 875

Study 875 ("Controlled Study of Prednisone With or Without Oral Beclomethasone Dipropionate for the Initial Treatment of Patients with Intestinal Graft-versus-Host Disease") enrolled subjects with anorexia and poor oral intake due to GI GVHD using identical subjects selection criteria as Study ENT 00-02. Protocol treatment consisted of BDP (8 mg/day) or placebo plus a 10-day induction course of prednisone. Study drug (BDP or placebo) was administered in a double-blind manner. Response was defined as the ability to eat ≥ 70% of a subject's estimated caloric requirement. Subjects who were responding after 10 days of treatment with prednisone and study drug continued to take blinded study drug for an additional 20 days while prednisone was rapidly tapered. The primary efficacy endpoint for this study was the proportion of subjects who successfully maintained their oral caloric intake to ≥ 70% of their estimated caloric

requirements without recurrent symptoms of aGVHD to study day 30. Oral caloric intake was assessed by the nutritionist for hospitalized subjects and on the basis of food diaries for outpatients.

A total of 60 subjects were randomized between August 1994 and January 1996 at the Fred Hutchinson Cancer Research Center in Seattle, WA. Thirty-one subjects (52%) were randomized to receive BDP treatment, and 29 subjects (48%) were randomized to receive placebo. The treatment groups were well balanced for gender, race, and age at randomization (Table 4-15). Overall, the majority of subjects were male (60%) and white (83%); median age was 36.5 years across both treatment groups (range: 6 to 66). The treatment groups were generally well balanced for the primary cancer diagnosis and disease status prior to allogeneic hematopoietic cell transplantation (Table 4-16). The majority of subjects underwent transplantation for a primary diagnosis of leukemia, with chronic myelogenous leukemia (35%), acute myelogenous leukemia (18%), acute lymphocytic leukemia (13%), and myelodysplastic syndrome (10%) the most prevalent. Additionally, all subjects received myeloablative conditioning regimens (Table 4-17).

Table 4-15. Demographics (Study 875: ITT Analysis Set)

	Placebo		BDP		Overall	
Subjects randomized	29		31		60	
Sex						
Male	16	55%	20	65%	36	60%
Female	13	45%	11	35%	24	40%
Race						
White	24	83%	23	74%	47	83%
American Hispanic	2	7%	2	6%	4	7%
Black	1	3%	3	10%	4	7%
Other	2	7%	1	3%	3	5%
Asian	0	0%	1	3%	1	2%
Unknown	0	0%	1	3%	1	2%
Age group						
<10 years	0	0%	1	3%	1	2%
10 to <14	2	7%	1	3%	3	5%
14 to <18	3	10%	1	3%	4	7%
18 to <25	3	10%	3	10%	6	10%
25 to <45	7	24%	20	65%	27	45%
45 to <65	13	45%	5	16%	18	30%
≥65	1	3%	0	0%	1	2%
Age (years)						
Mean (± SD)	38.8 (± 16.72)		33.5 (± 11.81)		36.1 (± 14.51)	
Median	39.0		35.0		36.5	
Range	11 to 66		6 to 57		6 to 66	

Table 4-16. Primary Cancer Diagnosis (Study 875: ITT Analysis Set)

	Placebo		BDP		Overall	
Subjects randomized	29		31		60	
Primary cancer diagnosis						
Chronic myelogenous leukemia	11	38%	10	32%	21	35%
Acute myelogenous leukemia	5	17%	6	19%	11	18%
Acute lymphocytic leukemia	4	14%	4	13%	8	13%
Myelodysplastic syndrome	4	14%	2	6%	6	10%
Non-Hodgkin's lymphoma	2	7%	3	10%	5	8%
Refractory anemia with excess blasts	3	10%	0	0%	3	5%
Aplastic anemia	0	0%	2	6%	2	3%
Acute promyelocytic leukemia	0	0%	2	6%	2	3%
Acute myelomonocytic leukemia	0	0%	1	3%	1	2%
Paroxysmal nocturnal hemoglobinuria	0	0%	1	3%	1	2%
Acute myelogeneous leukemia	5	17%	6	19%	11	18%
In first remission	3	10%	3	10%	6	10%
Persistent or relapsed disease	0	0%	3	10%	3	5%
Newly diagnosed	2	7%	0	0%	2	3%
Chronic myelogeneous leukemia	11	38%	11	38%	21	35%
In chronic phase	8	28%	8	28%	16	27%
In accelerated or blast crisis	2	7%	2	7%	4	7%
In remission	1	3%	1	3%	2	3%
Acute lymphocytic leukemia	4	14%	4	13%	8	13%
Relapsed	2	7%	2	6%	4	7%
In remission	2	7%	2	6%	4	7%
Non-Hodgkin's lymphoma	2	7%	3	10%	5	8%
Relapsed	2	7%	2	6%	4	7%
In remission	0	0%	1	3%	1	2%
Risk of disease relapse following transplant						
Lower risk	17	59%	14	45%	31	52%
Higher risk	12	41%	17	55%	29	48%

Table 4-17. Transplant History (Study 875: ITT Analysis Set)

	Placebo		BDP		Overall	
Subjects randomized	29		31		60	
Transplant source						
Bone marrow	25	86%	22	71%	47	78%
Peripheral blood	4	14%	8	26%	12	20%
Not reported	0	0%	1	3%	1	2%
Conditioning regimen						
Myeloablative	29	100%	31	100%	60	100%
Donor type						
HLA-matched sibling	17	59%	17	55%	34	57%
Unrelated or HLA-mismatched donor	12	41%	14	45%	26	43%
Days between transplantation and randomization						
n	29		31		60	
Mean (± SD)	46.2 (± 24.20)		44.4 (± 20.06)		45.3 (± 21.99)	
Median	33.0		37.0		34.5	
Range	20 to 106		22 to 100		20 to 106	

4.3.1 Primary and Secondary Endpoints: Proportion of Subjects with Caloric Intake ≥ 70% of Estimated Daily Requirements at Study Days 10, 30, and 40 (Study 875)

After the initial 10 days of protocol-treatment, the proportion of subjects with caloric intake ≥ 70% was 22 of 31 (71%) for subjects in the BDP group and 16 of 29 (55%) for subjects in the placebo group; these subjects continued to take study drug while the prednisone dose was rapidly tapered. At study day 30 (the primary endpoint evaluation), significantly more subjects in the BDP group than in the placebo group succeeded in achieving ≥ 70% of their estimated daily caloric requirements without flares of aGVHD (71% [22/31] in the BDP group versus 41% [13/31] in the placebo group; p=0.02 by the chi-square test). The 22 subjects in the BDP group who had responded to short duration treatment with prednisone by study day 10 were still responding at study day 30, suggesting that once a subject responds to short duration treatment with prednisone, aGVHD could be maintained in remission by daily dosing with BDP. This beneficial effect of BDP was noted to be durable after completion of treatment. Specifically, at the

final study evaluation on study day 40 (i.e., 10 days after the planned discontinuation of BDP or placebo) 52% (16/31) of the subjects in the BDP group were still responding compared to 17% (5/29) in the placebo group (p=0.005 by the chi-square test).

4.3.2 FDA Requested Post-Hoc Analysis: Survival at 200 Days Post-Transplantation (Study 875)

Although not prospectively defined in the protocol or statistical analysis plan, survival data were collected in a retrospective manner based on requests by FDA representatives during the pre-NDA meeting with the study sponsor on November 1, 2005. The survival data from this study are intended to support the review of the survival data from the phase 3 study ENT 00-02. To comply with this request, the survival status as of November 31, 2005 (data cutoff date) was sought from the study investigator at the Fred Hutchinson Cancer Research Center, along with the date of death and proximate and contributory causes of death. As of the data cutoff date, 33 of the 60 subjects who were originally randomized in this study were alive or lost to follow-up.

All surviving subjects were followed for survival through 200 days post-transplant. Three subjects (10%) in the BDP group and 6 subjects (21%) in the placebo group died within 200 days of the date of transplant (Table 4-18).

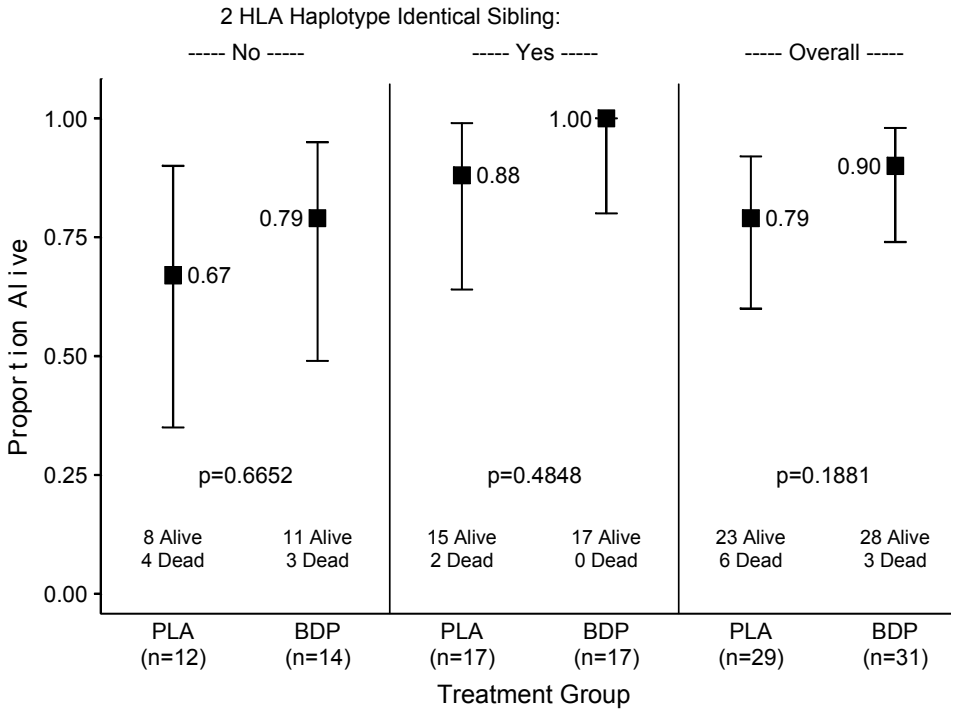
The estimated survival rates on day 200 post-transplant were 0.90 (95% CI: 0.74, 0.98) for the BDP group 0.79 (95% CI: 0.60, 0.92) for the placebo group. The odds of mortality were lower for subjects randomized to BDP compared to placebo (adjusted odds ratio 0.34, 95% CI: 0.07, 1.72, p=0.1881 by the CMH test stratified by donor type). Although the difference between the BDP and placebo groups was greater in the subgroup of subjects whose donor was unrelated or HLA-mismatched, the test for homogeneity of the odds ratios did not indicate any major differences in survival between treatment group and the subgroups formed by this stratification factor (p=0.3092 by the Breslow Day test) (Table 4-18 and Figure 4-10).

Table 4-18. FDA Requested Post-Hoc Analysis: Survival at 200 Days Post-Transplantation (Study 875: ITT Analysis Set)

	Placebo		BDP	
Subjects randomized	29		31	
Survival status				
Alive	23	79%	28	90%
Dead	6	21%	3	10%
Proximate cause of death				
Infection	5	17%	1	3%
Relapse of underlying malignancy	1	3%	0	0%
GVHD	0	0%	0	0%
Other	0	0%	1	3%
Unknown	0	0%	1	3%
Day 200 survival rate (95% CI)	0.79 (0.60, 0.92)		0.90 (0.74, 0.98)	
Stratified test of association between treatment and Day 200 survival status	CMH = 1.7323, 1 df, P = 0.1881			
Adjusted odds ratio (95% CI)	0.34 (0.07, 1.72)			
Test of homogeneity of the odds ratios	χ^2 = 1.0343, 1 df, P = 0.3092			

The upper and lower limits of the 95% confidence interval are calculated using the Clopper-Pearson method. The test of association between treatment and survival status and estimation of the odds ratio are based on the Cochran-Mantel-Haenszel (CMH) procedure. The CMH test and odds ratio were calculated based on the 2 level factor for donor type (HLA-matched sibling vs. unrelated or HLA-mismatched donor). Placebo serves as the reference treatment group for interpretation of the odds ratio. The test of homogeneity of the odds ratios across stratum is based on the Breslow-Day test. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

Figure 4-10. FDA Requested Post-Hoc Analysis: Survival at Day 200 Post-Transplantation (Study 875: ITT Analysis Set)



P-value is based on the chi-square test for treatment comparisons within strata and Cochran-Mantel-Haenszel test for treatment comparison across strata. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

4.3.3 FDA-requested Post-hoc Analysis: Survival Post-Randomization (Study 875)

The analysis of the post-randomization survival data was based primarily on the follow-up information measured up to 1 year post-randomization, and was supplemented by an analysis based on all available follow-up data (i.e., overall survival). Both of these analyses were based on all randomized subjects (intention-to-treat principle).

Survival One Year Post-Randomization

Survival during the first year after randomization in Study 875 is summarized by treatment group in Table 4-19 and Figure 4-11.

All surviving subjects were followed for survival through one year post-randomization. Overall, 6 subjects (19%) in the BDP group died within one year of randomization, and 9

subjects (31%) in the placebo group died during the same period (adjusted hazard ratio 0.55; 95% CI: 0.20, 1.56; p=0.2559 by the log-rank test stratified by donor type). The median survival time was not achieved for either treatment group by the end of the first year from randomization.

The estimated survival rate at one-year post-randomization was 0.81 (95% CI: 0.63, 0.93) for the BDP group and 0.69 (95% CI: 0.49, 0.85) for the placebo group. Infection and relapse of the underlying malignancy were the most common proximate causes of death (Table 4-19). The test of homogeneity of the hazard ratios did not suggest the presence of an interaction between treatment group and donor type (p=0.7147 by Wald chi-square test).

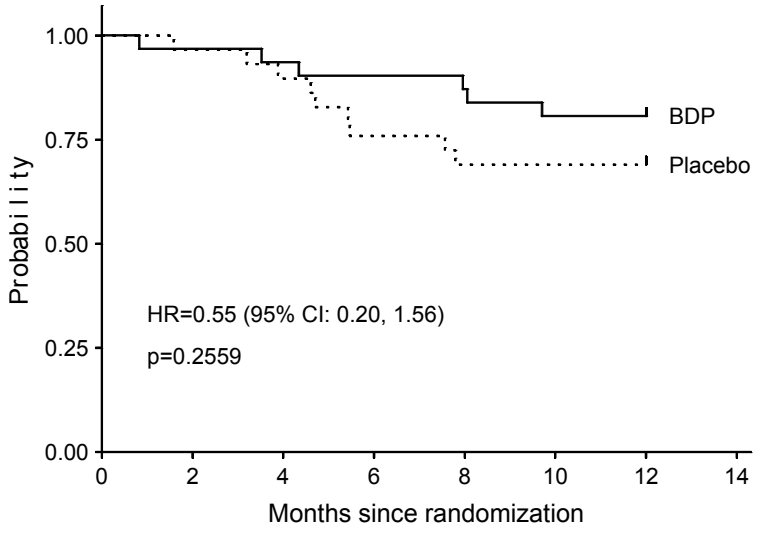
Table 4-19. FDA Requested Post-Hoc Analysis: Survival One Year Post-Randomization (Study 875: ITT Analysis Set)

	Placebo		BDP	
Subjects randomized	29		31	
Survival status one-year post-randomization				
Alive	20	69%	25	81%
Dead	9	31%	6	19%
Proximate cause of death				
Infection	6	21%	2	6%
Relapse of underlying malignancy	1	3%	1	3%
Other	2	7%	2	6%
Unknown	0	0%	1	3%
One-year survival rate (95% CI)	0.69 (0.49, 0.85)		0.81 (0.63, 0.93)	
Adjusted hazard ratio (95% CI)	0.55 (0.20, 1.56)			
Stratified log-rank test	$\chi^2 = 1.2910$, 1 df, P = 0.2559			
Test for treatment by strata interaction	$\chi^2 = 0.1336$, 1 df, P = 0.7147			

For purposes of this analysis, all subjects surviving greater than one year (365 days) after randomization were right-censored as of the one year time point.

The upper and lower limits of the 95% confidence interval are calculated using the Clopper-Pearson method. Hazard ratio estimated from a Cox proportional hazards model stratified by the two-level factor for donor type (HLA-matched sibling vs. unrelated or HLA-mismatched donor). Placebo serves as the reference treatment group for interpretation of the hazard ratio. Stratified log-rank test calculated based on the two-level factor for donor type. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

Figure 4-11. FDA Requested Post-Hoc Analysis: Survival One Year Post-Randomization (Study 875: ITT Analysis Set)



	0-2	3-4	5-6	7-8	9-10	11-12
BDP	1/31	1/30	1/29	1/28	2/27	0/25
Placebo	1/29	2/28	4/26	2/22	0/20	0/20

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For purposes of this analysis, all subjects surviving more than one year (365 days) post-randomization were right-censored as of the one year time point. Hazard ratio estimated from a Cox proportional hazards model stratified by the two-level factor for donor type (HLA-matched sibling vs. unrelated or HLA-mismatched donor). P-value calculated from the stratified log-rank test. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

Overall Survival Post-Randomization

Overall survival after randomization in Study 875 is summarized by treatment group in Table 4-20 and Figure 4-12.

As of November 31, 2005, the median length of follow-up was 10.1 years for the placebo group (25-75th percentiles: 9.4 to 11.0 years) and 9.9 years for the BDP group (25-75th percentiles: 9.6 to 10.6 years). As of the above data cutoff date, 33 of the 60 subjects who were randomized in this study were found to be alive or lost to follow-up.

Overall, 7 subjects were lost to follow-up as of the data cutoff date. Five of the 7 subjects were originally randomized to receive BDP treatment; all were right-censored on the date

of last contact which ranged from 6.8 to 9.6 years from randomization. The risk of mortality during the post-randomization follow-up period was 53% lower for subjects randomized to BDP compared to placebo (adjusted hazard ratio 0.47; 95% CI: 0.22, 1.04; p=0.0559 by the log-rank test stratified by donor type). Median survival following randomization was 7.3 years for placebo and was not yet reached for the BDP group. The test of homogeneity of the hazard ratios did not suggest the presence of an interaction effect between treatment group and donor type (p=0.6845 by the Wald chi-square test). However, within the subgroup whose donor was unrelated or HLA-mismatched, subjects randomized to BDP tended to have lower mortality relative to subjects randomized to placebo (hazard ratio 0.41; 95% CI: 0.14, 1.21; p=0.0954 by the log-rank test).

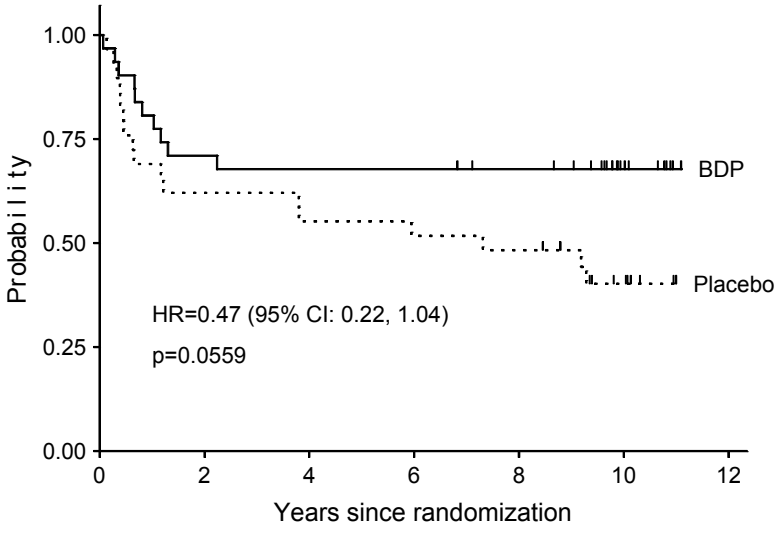
Table 4-20. FDA Requested Post-Hoc Analysis: Overall Survival Post-Randomization (Study 875: ITT Analysis Set)

	Placebo		BDP	
Subjects randomized	29		31	
Survival status as of the last contact				
Alive	10	35%	16	52%
Dead	17	59%	10	32%
Lost to follow-up	2	7%	5	16%
Duration of follow-up (years)				
Median	10.1		9.9	
25th-75th percentiles	9.4, 11.0		9.6, 10.6	
Duration of overall survival (years)				
Median (95% CI)	7.3 (1.2, not reached yet)		Not reached yet	
Adjusted hazard ratio (95% CI)	0.47 (0.22, 1.04)			
Stratified log-rank test	$\chi^2 = 3.6564$, 1 df, P = 0.0559			
Test for treatment by strata interaction	$\chi^2 = 0.1651$, 1 df, P = 0.6845			

The analysis is based on a data cutoff date of November 31, 2005. All deaths reported as of this date are included in the analysis.

Hazard ratio estimated from a Cox proportional hazards model stratified by the two-level factor for donor type (HLA-matched sibling vs. unrelated or HLA-mismatched donor). Placebo serves as the reference treatment group for interpretation of the hazard ratio. Stratified log-rank test calculated based on the two-level factor for donor type. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

Figure 4-12. FDA Requested Post-Hoc Analysis: Overall Survival Post-Randomization (Study 875: ITT Analysis Set)



	0-2	3-4	5-6	7-8	9-10	11-12
BDP	9/31	1/22	0/21	0/21	0/0	0/8
Placebo	11/29	2/18	1/16	3/15	0/0	0/7

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Hazard ratio estimated from a Cox proportional hazards model stratified by the two-level factor for donor type (HLA-matched sibling vs. unrelated or HLA-mismatched donor). P-value calculated from the stratified log-rank test. Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

4.4 Integrated Analysis of Studies 875 and ENT 00-02

The integrated analysis set consists of all subjects randomized in the phase 2 study 875 and pivotal study ENT 00-02. A total of 189 subjects were randomized in the two studies: 93 who received BDP and 96 who received placebo.

The following survival endpoints were analyzed for this integrated summary:

- Survival at 200 days after the date of transplantation
- Survival at one year from the date of randomization
- Overall survival measured from the date of randomization

The integrated analysis of survival was performed according to the intention-to-treat principle and includes all subjects randomized in studies 875 and ENT 00-02.

Hypothesis tests were performed at a nominal two-sided significance level of 0.05. No adjustment was made to the significance level for multiple testing. The integrated analysis was stratified by study (875, ENT 00-02) and donor type (HLA- matched sibling, unrelated or HLA-mismatched). The rationale for including donor type as a stratification factor is primarily due to the differences that were observed in study ENT 00-02 between treatment and survival for subjects whose donor was HLA-matched vs. unrelated or HLA-mismatched.

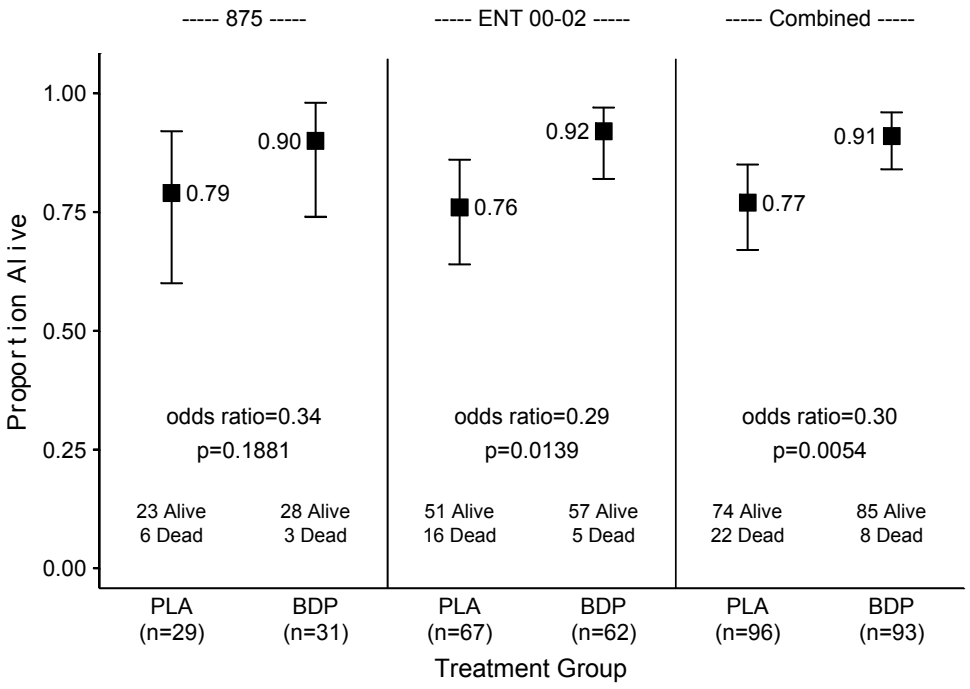
Survival at Day 200 Post-Transplantation

The survival status 200 days post-transplantation is summarized by treatment group in Figure 4-13 for protocols 875 and ENT 00-02, and for both studies combined.

Overall, eight subjects (9%) in the BDP group and 22 subjects (23%) in the placebo group died within 200 days of the date of transplantation. The estimated survival rates on Day 200 was 91% (95% CI: 84%, 96%) for the BDP group and 77% (95% CI: 67%, 85%) for the placebo group.

The odds of mortality were 70% lower for subjects randomized to BDP compared to placebo (odds ratio 0.30, p=0.0054 by the CMH test). The test for homogeneity of the odds ratios across studies and donor type did not indicate any major differences in survival between treatment and the subgroups formed by these stratification factors (p=0.1718 by the Breslow Day test).

Figure 4-13. Survival at Day 200 Post-Transplantation for Studies 875 and ENT 00-02, and Both Studies Combined (Integrated ITT Analysis Sets)



P-value is based on the Cochran-Mantel-Haenszel test (stratified by donor type for within study comparisons and donor type and study for the combined analysis). Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

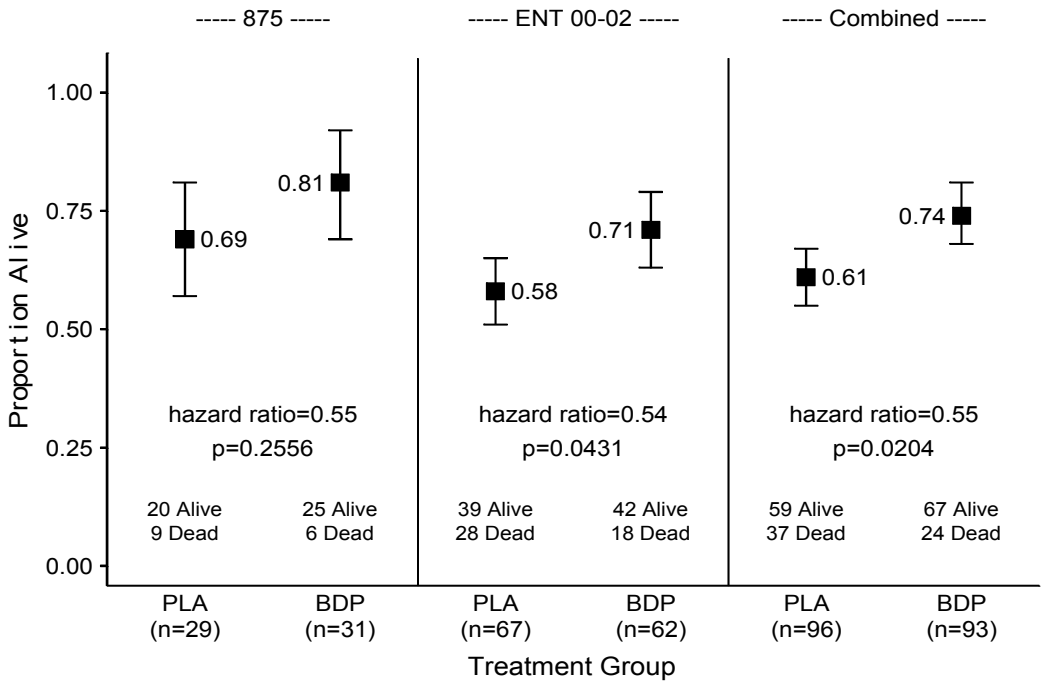
Survival One Year Post-randomization

Survival during the one-year period after randomization is summarized by treatment group in Figure 4-14 for protocols 875 and ENT 00-02, and for both studies combined.

A total of 24 subjects (26%) in the BDP group and 37 subjects (39%) in the placebo group died within one year of randomization in study 875 and ENT 00-02. Two subjects were lost to follow-up during this period and were last known to be alive 321 and 354 days after randomization. Both subjects were randomized to BDP, and both were right-censored as of their date of last contact. The estimated survival rates one-year after randomization was 74% (95% CI: 68%, 81%) for the BDP group and 61% (95% CI:

55%, 67%) for the placebo group. During this one-year period, the overall risk of mortality was 45% lower for subjects randomized to BDP compared to placebo (hazard ratio 0.55, p=0.0204 by the stratified log-rank test). The test for homogeneity of the hazard ratios across studies and donor type did not indicate any major differences in survival between treatment and the subgroups formed by these stratification factors (p=0.5536 by the Wald chi-square test).

Figure 4-14. Survival One Year Post-Randomization for Studies 875 and ENT 00-02, and Both Studies Combined (Integrated ITT Analysis Sets)



P-value is based on the log-rank test (stratified by donor type for within study comparisons and donor type and study for the combined analysis). Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

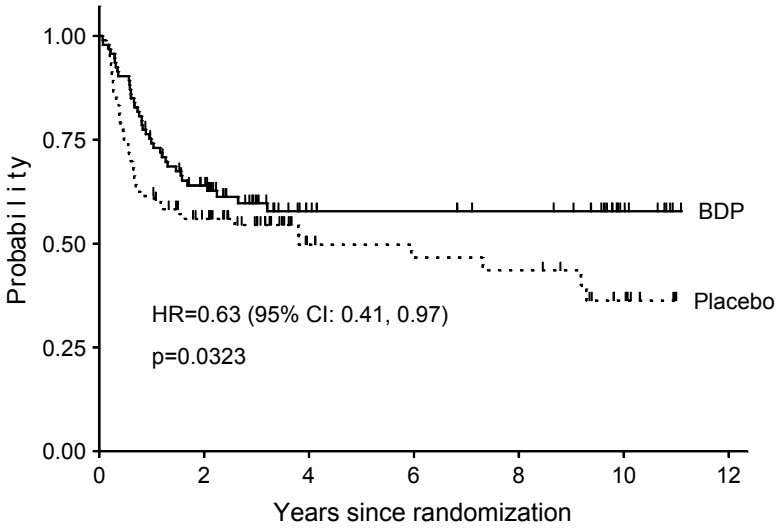
Overall Survival Post-randomization

Overall survival measured from the date of randomization in studies 875 and ENT 00-02 is summarized by treatment group in Figure 4-15 for both studies combined.

As of the respective data cutoff dates for each study, 37 subjects (40%) in the BDP group and 44 subjects in the placebo group were reported dead. A total of 10 subjects were lost to follow-up as of the data cutoff dates (3 subjects in the placebo group and 7 subjects in the BDP group). All of these subjects were right-censored based on their date of last contact. Median follow-up for both studies combined was 3.5 years for subjects in the placebo group (25-75th percentiles: 2.4 to 9.4 years) and 3.6 years for BDP (25-75th percentiles: 2.4 to 9.7 years).

The risk of mortality was 37% lower for subjects randomized to BDP compared to placebo (hazard ratio 0.63, p=0.0323 by the stratified log-rank test). The test for homogeneity of the hazard ratios across studies and donor type did not indicate any major differences in survival between treatment and the subgroups formed by these stratification factors (p=0.3789 by the Wald chi-square test).

Figure 4-15. Overall Survival for Studies 875 and ENT 00-02 Combined (Integrated ITT Analysis Sets)



	0-2	3-4	5-6	7-8	9-10	11-12
BDP	33/93	4/52	0/23	0/21	0/0	0/8
Placebo	42/96	3/46	1/18	3/15	0/0	0/7

(#events/#at risk)

P-value is based on the log-rank test (stratified by donor type and study). Nominal significance level of 0.05 (two-sided). No adjustment for multiple testing.

5. CLINICAL SAFETY

5.1 Introduction

BDP shares glucocorticoid and mineralocorticoid cellular effects with other corticosteroids but its pharmacology is differentiated by its limited systemic absorption of BDP itself and rapid clearance of its primary metabolite 17-BMP from the circulation. Corticosteroids are potent anti-inflammatory agents that have multiple potential adverse effects including immunosuppression and susceptibility to infections, glucose intolerance, hypertension, salt and water retention, electrolyte abnormalities, weight gain, muscle weakness and loss of muscle mass, osteoporosis, skin abnormalities, cataracts, glaucoma, growth abnormalities in children, neuropsychiatric derangements, adrenal gland suppression and multiple other abnormalities.

Beclomethasone dipropionate has been in use for many years by topical routes other than oral and has a well established safety profile. While the effect of BDP is believed to be predominately within the GI mucosa its primary metabolite, 17-BMP, may be systemically absorbed and result in systemic side effects and may result in mucosal infections which may become systemic in otherwise immunosuppressed patients. Therefore, safety assessment of subjects enrolled on BDP studies examines not only collected AEs but also includes in some studies specialized assessment for adrenal suppression that might be caused by any systemic exposure to BDP or BMP.

The safety database for BDP includes 269 subjects (174 BDP, 95 placebo) from 7 studies: 4 studies in subjects with GI GVHD (n= 245; two patients were randomized into study ENT 00-02 but did not received study treatment for a total of 247 subjects), 1 study in subjects with Crohn's disease (n = 4), and 2 clinical pharmacology studies in healthy volunteers (n = 24). The numbers of subjects enrolled in these 7 studies are summarized in Table 5-1.

Table 5-1. Total Number of Subjects in BDP Clinical Studies

Study Population and Study Number	BDP	Placebo
Clinical studies in GI GVHD	151	96
ENT 00-02	62[a]	67[a]
615	42	0
875	31	29
1500	16	0
Clinical study in Crohn's disease: ENT 01-04 [b]	3	1
Clinical pharmacology studies		
ENT 00-01	12	0
ENT 05-BA	12	0
Total	178 [a]	97 [a]

[a] One subject in this group was randomized but did not receive investigational product.
[b] Study ENT 01-04 was discontinued because of lack of resources.

The safety data are presented in this report with a detailed focus on data from the pivotal phase 3 study, ENT 00-02, supported by summary information form all other studies. It is important to note that the development program for this product was assessed as a therapy for a GI illness (and was originally reviewed in FDA's Division of Gastrointestinal and Coagulation Drugs Products). As is typical in many GI studies the severity of AEs was graded and recorded as mild, moderate or severe based on the following definitions and investigator judgment:

- MILD No limitations of usual activities.
- MODERATE Some limitation of usual activities.
- SEVERE Inability to carry out usual activities.

Each clinical study in this report is presented individually (the only exception being the analysis of special populations). An integrated safety analysis was problematic from an analytic standpoint due to the different methods of safety reporting in each study. The pivotal phase 3 study, ENT 00-02, as well as studies ENT 00-01, ENT 05-BA, and ENT 00-04 collected all AEs. However, safety reporting in Studies 615, 875, and 1500 was based on reporting of treatment related and unexpected AEs and laboratory

abnormalities only; in anticipation of the large number of expected background AEs common in hematopoietic cell transplant patients, these clinical trials did not collect AEs expected in the HCT population. HPA axis testing was included in studies ENT 00-02, ENT 00-04, and 615. Caloric intake was assessed in studies 615 and 875. A formal comparison of the incidence of infections between BDP and placebo groups was conducted in Study 875 (McDonald et. al, 1998). Based on this information, it was determined that the most comprehensive data are in Study ENT 00-02; therefore this report will focus primarily on those data.

5.2 Study ENT 00-02

5.2.1 Study Design (Study ENT 00-02)

Study ENT 00-02 ("A Phase III Randomized Placebo-Controlled, Multi-Center Study of the Safety, Efficacy, and Pharmacokinetics of Oral Beclomethasone 17, 21-Dipropionate in Conjunction with Ten Days of High Dose Prednisone Therapy in the Treatment of Patients with Grade II Graft vs. Host Disease with Gastrointestinal Symptoms") enrolled subjects with histologically-confirmed Grade II GVHD with GI symptoms who could swallow the study tablets without difficulty.

Safety was evaluated based on the following assessments:

- Treatment-emergent AEs. Verbatim AEs were assigned a preferred term and system organ class according to MedDRA (version 7.0);
- Systemic corticosteroid exposure based on the cumulative prednisone, or equivalent, dose in mg/kg over the course of the 80-day study period;
- GVHD assessments of diarrhea (GI), rash (skin), and total serum bilirubin (liver) at selected time points;
- HPA axis function as measured by plasma concentrations of ACTH, resting morning cortisol, and change in plasma cortisol concentration following a standard test dose of intravenous cosyntropin; and
- Survival through Day 200 post-transplant.

5.2.2 Subject Disposition (Study ENT 00-02)

Of the 129 subjects who were randomized, 127 subjects (61 in the BDP group and 66 in the placebo group) received investigational product and were included in the safety

analysis set. (Table 5-2). Two subjects (1 in each group) who were randomized never received investigational product.

Among the 61 subjects who received at least one dose of BDP, 37 (61%) subjects completed the 50-day dosing period compared with 30 (45%) subjects in the placebo group. The primary reasons for the premature discontinuation of study drug were (BDP, placebo) lack of efficacy/treatment failure (29%, 45%), AE (5%, 5%), protocol violation (6%, 1%), and non-compliance (0%, 5%). In general, the reasons for discontinuation of study drug were balanced between groups, except more subjects in the placebo group (30 [45%]) compared with the BDP group (18 [29%]) discontinued treatment because of lack of efficacy/treatment failure.

Similar number of subjects in each group completed the 80-day study period (51 [76%] subjects in the placebo group and 44 [71%] subjects in the BDP group). The primary reasons for premature withdrawal from study were (BDP, placebo) protocol violations (11%, 7%), AEs (3%, 6%), unlikely to survive/entered hospice care (5%, 4%), lost to follow-up (6%, 0%), consent withdrawn (2%, 3%), and non-compliance (2%, 3%).

Overall in the study, a higher proportion of subjects discontinued investigational product due to AEs in the placebo group (22 [33%]) compared with the BDP group (15 [25]%) (Table 5-3). The AEs that most frequently led to discontinuation of investigational product were (BDP, placebo): GVHD (10%, 20%), abdominal pain (5%, 3%), nausea (0%, 6%), and vomiting (0%, 6%) (Table 5-3).

Table 5-2. Subject Disposition (All Randomized Subjects)
(Study ENT 00-02)

	Placebo		BDP		Overall	
Subjects randomized	67		62		129	
Completed 50-day protocol treatment						
Yes	30	45%	37	60%	67	52%
No	37	55%	25	40%	62	48%
Reason study drug prematurely						
Lack of efficacy/ treatment failure	30	45%	18	29%	48	37%
Adverse Event	3	5%	3	5%	6	5%
Protocol violation	1	1%	4	6%	5	4%
Non-compliance	3	5%	0	0%	3	2%
Completed 80-day study period						
Yes	51	76%	44	71%	95	74%
No	16	24%	18	29%	34	26%
Reason prematurely withdrawn from study						
Protocol violation	5	7%	7	11%	12	9%
Adverse Event	4	6%	2	3%	6	5%
Unlikely to survive/entered hospice care	3	4%	3	5%	6	5%
Lost to follow-up	0	0%	4	6%	4	3%
Consent withdrawn	2	3%	1	2%	3	2%
Non-compliance	2	3%	1	2%	3	2%

Table 5-3. All Treatment Emergent Adverse Events Which Resulted in Permanent Discontinuation of Study Drug Summarized by MedDRA Preferred Term and Treatment Group (Safety Population)

Preferred Term	Placebo (N=66)	BDP (N=61)	Total (N=127)
TREATMENT EMERGENT ADVERSE EVENT REPORTED	22 (33.3%)	15 (24.6%)	37 (29.1%)
GRAFT-VERSUS-HOST DISEASE	13 (19.7%)	6 (9.8%)	19 (15.0%)
ABDOMINAL PAIN	2 (3.0%)	3 (4.9%)	5 (3.9%)
NAUSEA	4 (6.1%)	0 (0.0%)	4 (3.1%)
VOMITING	4 (6.1%)	0 (0.0%)	4 (3.1%)
DIARRHOEA	1 (1.5%)	2 (3.3%)	3 (2.4%)
ANOREXIA	2 (3.0%)	0 (0.0%)	2 (1.6%)
LEUKAEMIA RECURRENT	1 (1.5%)	1 (1.6%)	2 (1.6%)
LIVER FUNCTION TEST ABNORMAL	1 (1.5%)	1 (1.6%)	2 (1.6%)
WEIGHT DECREASED	1 (1.5%)	1 (1.6%)	2 (1.6%)
ACUTE LYMPHOCYTIC LEUKAEMIA	0 (0.0%)	1 (1.6%)	1 (0.8%)
ACUTE MYELOID LEUKAEMIA RECURRENT	0 (0.0%)	1 (1.6%)	1 (0.8%)
BRONCHOSPASM	0 (0.0%)	1 (1.6%)	1 (0.8%)
COUGH	1 (1.5%)	0 (0.0%)	1 (0.8%)
CRYPTOGENIC ORGANIZING PNEUMONIA	1 (1.5%)	0 (0.0%)	1 (0.8%)
DEHYDRATION	0 (0.0%)	1 (1.6%)	1 (0.8%)
ERUCTATION	0 (0.0%)	1 (1.6%)	1 (0.8%)
FATIGUE	1 (1.5%)	0 (0.0%)	1 (0.8%)
FLATULENCE	0 (0.0%)	1 (1.6%)	1 (0.8%)
GASTROINTESTINAL HAEMORRHAGE	1 (1.5%)	0 (0.0%)	1 (0.8%)
HYPOXIA	1 (1.5%)	0 (0.0%)	1 (0.8%)

Adverse events are coded using MedDRA (version 7).
Preferred terms are sorted by descending order of frequency in the total column.
Subjects were counted only once for each preferred term.
Percentages are based on the number of subjects evaluable for safety in each treatment group.

(Page 1 of 2)

Table 5-3. All Treatment Emergent Adverse Events Which Resulted in Permanent Discontinuation of Study Drug Summarized by MedDRA Preferred Term and Treatment Group (Safety Population)

Preferred Term	Placebo (N=66)	BDP (N=61)	Total (N=127)
PANCYTOPENIA	1 (1.5%)	0 (0.0%)	1 (0.8%)
PULMONARY MASS	1 (1.5%)	0 (0.0%)	1 (0.8%)
PYREXIA	1 (1.5%)	0 (0.0%)	1 (0.8%)
RASH	0 (0.0%)	1 (1.6%)	1 (0.8%)
RASH PRURITIC	0 (0.0%)	1 (1.6%)	1 (0.8%)
SEPSIS	1 (1.5%)	0 (0.0%)	1 (0.8%)
SKIN DESQUAMATION	0 (0.0%)	1 (1.6%)	1 (0.8%)

Adverse events are coded using MedDRA (version 7). (Page 2 of 2)
Preferred terms are sorted by descending order of frequency in the total column.
Subjects were counted only once for each preferred term.
Percentages are based on the number of subjects evaluable for safety in each treatment group.

5.2.3 Extent of Exposure (Study ENT 00-02)

The overall extent of exposure to study drug is summarized in Table 5-4 for the 127 subjects who received at least one dose of BDP or placebo. Duration of treatment was similar between groups.

Table 5-4. Exposure to Investigational Product (Study ENT 00-02: Safety Population)

	Placebo		BDP	
Subjects randomized	67		62	
Subjects administered ≥1 tablet of study drug	66		61	
Duration of treatment				
1 to 10 days	9	14%	11	18%
11 to 20 days	8	12%	3	5%
21 to 30 days	8	12%	6	10%
31 to 40 days	5	8%	2	3%
41 to 50 days	36	55%	39	64%
Duration of treatment (days)				
n	66		61	
Mean (± SD)	35.7 (± 16.30)		37.0 (± 17.94)	
Median	47.0		50.0	
Range	4 to 50		1 to 50	
Mean total daily dose (mg/day)				
n	NA		61	
Mean (± SD)	N/A		7.3 (± 1.04)	
Median	N/A		7.7	
Range	N/A		2.0 to 7.9	
Total cumulative dose (mg)				
n	NA		61	
Mean (± SD)	N/A		282.5 (± 140.98)	
Median	N/A		378.0	
Range	N/A		2 to 394	

N/A = not applicable.

5.2.4 Overall Corticosteroid Exposure (Study ENT 00-02)

The overall extent of systemic corticosteroid exposure during the 80-day study period is summarized in Table 5-5. By the end of both the 50-day protocol treatment period and the 30-day post-treatment observation period, subjects in the BDP group generally had lower systemic corticosteroids requirements compared to subjects in the placebo group, although the differences at these time point did not achieve statistical significance (p-value= 0.1163 and 0.2851, respectively).

It should be noted that for the first 16 subjects 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 subjects 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. Subjects who received the lowered starting dose of prednisone were maintained on a physiologic replacement dose of 0.0625 mg/kg/day. Sensitivity analyses were performed to assess the impact of the 16 subjects who received the higher starting dose of prednisone.

Table 5-5. Cumulative Systemic Corticosteroid Exposure (Study ENT 00-02: Safety Population)

	Placebo	BDP
Subjects randomized	67	62
Subjects administered ≥1 dose of corticosteroid	66	61
Cumulative dose through study day 10 (mg/kg)		
n	66	61
Mean (± SD)	11.4 (± 3.93)	10.8 (± 3.81)
Median	10.0	10.0
Range	3.0 to 20.2	3.0 to 20.1
Cumulative dose through study day 30 (mg/kg)		
n	66	61
Mean (± SD)	19.1 (± 11.28)	17.9 (± 10.32)
Median	14.3	13.2
Range	4.0 to 66.9	3.0 to 51.2
Cumulative dose through study day 50 (mg/kg)		
n	66	61
Mean (± SD)	27.8 (± 18.70)	23.4 (± 17.7)
Median	19.4	15.3
Range	4.0 to 93.5	3.0 to 84.1
Cumulative dose through study day 60 (mg/kg)		
n	66	61
Mean (± SD)	31.7 (± 22.70)	26.7 (± 21.12)
Median	24.9	16.7
Range	4.0 to 106.2	3.0 to 91.1
Cumulative dose through study day 80 (mg/kg)		
n	66	61
Mean (± SD)	38.4 (± 28.84)	31.5 (± 25.5)
Median	29.4	19.0
Range	4.0 to 135.1	3.0 to 125.0

Intravenous (IV) doses of methylprednisolone were standardized to a common oral prednisone equivalent based on the conversion factor: prednisone dose = 1.2 × methylprednisolone dose. Excludes doses of BDP administered as open-label treatment.

5.2.5 Concomitant Medications (Study ENT 00-02)

As expected for this population of HCT recipients, all subjects received multiple concomitant medications. This report focuses on the following categories of concomitant medications: corticosteroids, immunosuppressives (non-steroidal), and anti-infectives (grouped as antibacterials, anti-virals, and anti-fungals). These groupings are most relevant to the clinical relevant outcomes examined based on principles of immunosuppressive exposure and related morbidities.

5.2.5.1 Steroidal Medications

Steroid dose intensity was assessed using CRF diaries and was reported separately (Table 5-5). An assessment of the steroid usage recorded in the regular concomitant medication CRF was also conducted. Overall usage was similar between the two arms (BDP, placebo) (36%, 42%). The most commonly recorded medications were as follows: hydrocortisone (7%, 11%), clobetasol propionate (8%, 6%), triamcinolone (5%, 6%), beclomethasone dipropionate (compounded agent, not study medication) (3%, 6%). It is noteworthy that some patients were administered beclomethasone dipropionate in locally compounded formulations and that this rate was higher in the placebo arm.

5.2.5.2 Immunosuppressive Medications

All subjects enrolled were administered immunosuppressive medications as prophylaxis against GVHD, and as shown in (Table 5-6) virtually all subjects received one or more immunosuppressive medications. The only material imbalance in immunosuppressive medications administered was for mycophenolate mofetil (MMF), which was administered more frequently to subjects in the BDP group than in the placebo group (31.1% vs. 16.7% respectively); MMF is more commonly used in the non-myeloablative setting, therefore, this result is consistent with the baseline imbalance between the two groups for type of conditioning regimen (myeloablative versus non-myeloablative) such that more subjects in the BDP arm received non-myeloablative conditioning regimen (Table 4-4).

A summary of immunosuppressive regimens given prophylactically and during the study is provided in Table 5-7. The most common prophylaxis regimens were (BDP, placebo):

cyclosporin plus methotrexate (31%, 58%) and cyclosporin plus MMF (41%, 14%). The most common regimens given during the study were (BDP, placebo): cyclosporin (51%, 67%) and cyclosporin plus MMF (20%, 6%).

While there appeared to be an imbalance between the 2 study arms in the numbers of subjects receiving single agent immunosuppressive therapy during the period of study drug administration such that more subjects in the placebo arm were on single agents (83%) than in the BDP arm (69%), this was driven by the prophylaxis regimen at baseline, which in turn was driven by the type of conditioning regimen. Those subjects who received myeloablative conditioning regimen were most commonly given prophylaxis with cyclosporin plus methotrexate; the methotrexate dosing typically ends at transplant day 11; therefore, by the time these subjects would have been enrolled on study they would be on single agent cyclosporin as their ongoing prophylaxis treatment in many cases. Because there was an imbalance in the baseline variable of type of conditioning regimen such that more subjects receiving myeloablative regimens were enrolled onto the placebo arm, this is an expected finding. To further explore this issue, and assess what impact this may have had on the time-to-treatment failure by study day 80, a Cox a model with type of immunosuppressive regimen used during the study drug treatment period (single versus multiple) showed a continued benefit for BDP treatment, though of borderline significance ($p = 0.04$); the hazard ratios for the unadjusted versus adjusted model remained similar as well (0.54, 0.57 favoring BDP). Therefore, while the number of immunosuppressive agents during study drug treatment may be a confounding factor to some extent, the beneficial effect of BDP remains.

Table 5-6. Immunosuppressive Medications Summarized by WHO-DRL Medication Name and Treatment Group (Safety Population)

Medication Name	Placebo (N=66)	BDP (N=61)	Total (N=127)
RECEIVED IMMUNOSUPPRESSIVE MEDICATION	66 (100.0%)	59 (96.7%)	125 (98.4%)
CICLOSPORIN	52 (78.8%)	46 (75.4%)	98 (77.2%)
TACROLIMUS	16 (24.2%)	15 (24.6%)	31 (24.4%)
MYCOPHENOLATE MOFETIL	11 (16.7%)	19 (31.1%)	30 (23.6%)
METHOTREXATE	14 (21.2%)	10 (16.4%)	24 (18.9%)
HYDROCORTISONE	5 (7.6%)	7 (11.5%)	12 (9.4%)
METHYLPREDNISOLONE	5 (7.6%)	1 (1.6%)	6 (4.7%)
PREDNISONE	4 (6.1%)	0 (0.0%)	4 (3.1%)
DEXAMETHASONE	3 (4.5%)	0 (0.0%)	3 (2.4%)
METHYLPREDNISOLONE SODIUM SUCCINATE	2 (3.0%)	1 (1.6%)	3 (2.4%)
PSORALENS FOR TOPICAL USE	2 (3.0%)	0 (0.0%)	2 (1.6%)
SIROLIMUS	0 (0.0%)	2 (3.3%)	2 (1.6%)
DIPHENHYDRAMINE HYDROCHLORIDE	1 (1.5%)	0 (0.0%)	1 (0.8%)
MONOCLONAL ANTIBODIES	1 (1.5%)	0 (0.0%)	1 (0.8%)
TETRACOSACTIDE	1 (1.5%)	0 (0.0%)	1 (0.8%)
TRIAMCINOLONE	1 (1.5%)	0 (0.0%)	1 (0.8%)

Medications are coded using 2004 WHO-DRL Dictionary.
Medication names are sorted by descending order of frequency in the total column.
Subjects were counted only once for each medication.
Percentages are based on the number of subjects evaluable for safety in each treatment group.

(Page 1 of 1)

Table 5-7. Summary of GVHD Prophylaxis Regimen and Immunosuppressive Drugs Given Through Study Day 80 (Study ENT 00-02: Safety Population)

	Placebo		BDP		Overall	
Subjects administered ≥1 tablet of study drug	66		61		127	
GVHD prophylaxis regimen						
Cyclosporin, methotrexate	38	58%	19	31%	57	45%
Cyclosporin, MMF	9	14%	25	41%	34	27%
Cyclosporin alone	1	2%	1	2%	2	2%
Cyclosporin, methotrexate, MMF	1	2%	0	0%	1	<1%
Cyclosporin, methotrexate, corticosteroids	1	2%	0	0%	1	<1%
Cyclosporin, methotrexate, thymoglobulin	0	0%	1	2%	1	<1%
Cyclosporin, methotrexate, IVIG	1	2%	0	0%	1	<1%
Cyclosporin, methotrexate, other	1	2%	0	0%	1	<1%
Cyclosporin, MMF, ATG	0	0%	1	2%	1	<1%
Cyclosporin, rapamycin	0	0%	1	2%	1	<1%
Tacrolimus, methotrexate	8	12%	5	8%	13	10%
Tacrolimus, methotrexate, IVIG	2	3%	4	7%	6	5%
Tacrolimus, MMF	2	3%	3	5%	5	4%
Tacrolimus, methotrexate, ATG	1	2%	0	0%	1	<1%
Tacrolimus alone	0	0%	1	2%	1	<1%
Not reported	1	2%	0	0%	1	<1%
Immunosuppressive drugs given during treatment with study drug and protocol-specified prednisone dose						
Cyclosporin	44	67%	31	51%	75	59%
Cyclosporin, MMF	4	6%	12	20%	16	13%
Cyclosporin, tacrolimus	1	2%	1	2%	2	2%
Cyclosporin, tacrolimus, MMF	0	0%	2	3%	2	2%
Cyclosporin, MMF, other dermatological preparation	1	2%	0	0%	1	<1%
Cyclosporin, other dermatological preparation	1	2%	0	0%	1	<1%
Tacrolimus	10	15%	10	16%	20	16%
Tacrolimus, MMF	3	5%	2	3%	5	4%
Tacrolimus, hydrocortisone	1	2%	0	0%	1	<1%
MMF	1	2%	0	0%	1	<1%
Sirolimus	0	0%	1	2%	1	<1%
None reported	0	0%	2	3%	2	2%

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Abbreviations: ATG=antithymocyte globulin; IVIG=intravenous immunoglobulin; MMF=mycophenolate mofetil.

[a] Denominator for the calculation of percentages is based on the number of deaths in each group.

Source: ENT 00-02, Data source: immeds.sas7bdat, Program source: s_immeds.sas, Run date: 05MAR2007

Table 5-7. Summary of GVHD Prophylaxis Regimen and Immunosuppressive Drugs Given Through Study Day 80 (Study ENT 00-02: Safety Population)

	Placebo		BDP		Overall	
Subjects administered ≥1 tablet of study drug	66		61		127	
Immunosuppressive drugs given after last dose of study drug through study day 80						
Cyclosporin	43	65%	32	52%	75	59%
Cyclosporin, MMF	3	5%	10	16%	13	10%
Cyclosporin, prednisone	1	2%	0	0%	1	<1%
Cyclosporin, tacrolimus, MMF	1	2%	0	0%	1	<1%
Cyclosporin, tacrolimus	1	2%	0	0%	1	<1%
Cyclosporin, other dermatological preparation	1	2%	0	0%	1	<1%
Tacrolimus	11	17%	11	18%	22	17%
Tacrolimus, MMF	3	5%	1	2%	4	3%
Tacrolimus, MMF, sirolimus	0	0%	1	2%	1	<1%
MMF	1	2%	1	2%	2	2%
Beclomethasone dipropionate	0	0%	1	2%	1	<1%
Sirolimus	0	0%	1	2%	1	<1%
None reported	1	2%	3	5%	4	3%
Prednisone dosed in excess of protocol-specified doses following discontinuation of study drug						
Yes	42	64%	24	39%	66	52%
No	19	29%	31	51%	50	39%
Data not available	5	8%	6	10%	11	9%
Immunosuppressive drugs taken in proximity to death (N=46) within first year of study						
Yes[a]	13	46%	6	33%	19	41%
No	15	54%	12	67%	27	59%

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Abbreviations: ATG=antithymocyte globulin; IVIG=intravenous immunoglobulin; MMF=mycophenolate mofetil.

[a] Denominator for the calculation of percentages is based on the number of deaths in each group.

Source: ENT 00-02, Data source: immeds.sas7bdat, Program source: s_immeds.sas, Run date: 05MAR2007

5.2.5.3 Anti-infective Medications

An analysis of concomitant medications reported for all subjects demonstrates nearly identical rates of usage between the BDP and placebo (BDP, placebo) study arms for the three major classes of agents: anti-bacterials (98%, 99%), anti-virals (100%, 100%), and anti-fungals (100%, 100%). These rates are consistent with the expected usage in this

patient population. The most commonly administered agents in each class were as follows:

- Anti-bacterial: bactrim (75%, 80%), levofloxacin (30%, 42%), vancomycin (33%, 32%), penicillin (18%, 21%), metronidazole (16%, 21%)
- Anti-viral: acyclovir (84%, 77%), valaciclovir (46%, 42%), ganciclovir (34%, 39%), valganciclovir (12%, 18%)
- Anti-fungal: fluconazole (79%, 80%), nystatin (16%, 24%), metronidazole (16%, 21%)

5.2.6 Adverse Events (Study ENT 00-02)

5.2.6.1 All Adverse Events

In this highly complex and seriously ill patient population, AEs were reported for almost all subjects in both BDP and placebo groups (Table 5-8). Based on a summary by MedDRA system organ classes, AEs were reported more frequently, or at an indistinguishably different rate, in the placebo group compared with the BDP group, with the notable exception of endocrine disorders including the cushingoid diagnosis (Table 5-9; also see Section 5.2.6.4). Overall, the incidence of treatment-emergent AEs based on MedDRA preferred term classifications (version 7) were comparable between BDP and placebo groups (Table 5-10). Interestingly, across a broad spectrum of AEs, the incidence of AEs was generally more frequent for subjects in the placebo group compared with the BDP group. The most frequently reported AEs by preferred term were (BDP, placebo): GVHD (43%, 41%), blood magnesium decreased (39%, 42%), fatigue (46%, 35%), hypertension (39%, 35%), and peripheral edema (31%, 38%).

Adverse events occurring more than 1.5 times more frequently in the BDP than the placebo group are provided in Figure 5-1. Events occurring more frequently in the placebo group are displayed in Figure 5-2. Two diagnoses were reported to be statistically significant more frequently in the BDP group than in the placebo group. These were dehydration (14% versus 3%, n = 9 versus 2, respectively) and chest pain (11.5% versus 1.5%, n = 7 versus 1, respectively). However, the reporting differences for dehydration did not appear to represent an actual difference in hydration status between

groups because laboratory values reflective of hydration status (BUN and total CO_2) were not different between groups. A similar analysis could not be performed for chest pain, but the actual incidence numbers are small enough to be consistent with a chance occurrence, and no difference in cardiac events was seen between groups.

The incidence of treatment-related AEs was higher in the placebo group (44%) than in the BDP group (34%) (Table 5-8). The most frequently reported treatment-related AEs by preferred term were (BDP, placebo): adrenal insufficiency (8%, 5%), fatigue (8%, 3%), hyperglycemia (7%, 2%) (Table 5-11).

Table 5-8. Summary of Treatment Emergent Adverse Events (Study ENT 00-02: Safety Population)

	Placebo		BDP		Overall	
Subjects randomized	67		62		129	
Subjects evaluable for safety	66		61		127	
Subjects with at least one adverse event	66	100%	60	98%	126	99%
Subjects with at least one treatment-related adverse event	29	44%	21	34%	50	39%
Adverse events regardless of causality by worst severity						
Mild	0	0%	5	8%	5	4%
Moderate	35	53%	30	49%	65	51%
Severe	31	47%	25	41%	56	44%
Treatment-related adverse events by worst severity						
Mild	15	23%	11	18%	26	20%
Moderate	9	14%	6	10%	15	12%
Severe	5	8%	4	7%	9	7%
Subjects with at least one SAE	27	41%	23	38%	50	39%
Subjects with at least one treatment-related SAE	2	3%	2	3%	4	3%
Subjects who discontinued study drug due to adverse event	22	33%	15	25%	37	29%
Subjects who discontinued study drug due to SAE	9	14%	7	11%	16	13%
Subjects who discontinued study drug due to treatment-related adverse event	3	5%	3	5%	6	5%
Subjects who discontinued study drug due to treatment-related SAE	2	3%	1	2%	3	2%
Subjects who died on treatment or within 30 days of last dose of therapy	1	2%	2	3%	3	2%

Analysis includes all randomized subjects who received at least one dose of study drug. Two subjects withdrew from study prior to taking any study drug (ID 002-13-304 randomized to receive placebo and ID 002-04-304 randomized to receive BDP).
No AEs were reported for one subject (ID 002-13-303). This subject received one confirmed dose of study drug on study day 1 (2 mg BDP) and was subsequently found to be positive for *C. difficile* infection and withdrawn from study.
Treatment-related AEs includes adverse events judged by the investigator as possibly related, probably related, and related. The incidence of serious adverse event is based on the events recorded on the adverse event CRF.

Table 5-9. Treatment-emergent Adverse Events with System Organ Class Incidence of 5 Percent or More of Subjects (Safety Population) (Study ENT 00-02)

Total Preferred Term	Fold Increase BDP/PLA	Placebo (N=66)	BDP (N=61)	(N=127)
GASTROINTESTINAL DISORDERS	0.9	57 (86.4%)	46 (75.4%)	103 (81.1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1.1	50 (75.8%)	51 (83.6%)	101 (79.5%)
INVESTIGATIONS	1.0	51 (77.3%)	46 (75.4%)	97 (76.4%)
METABOLISM AND NUTRITION DISORDERS	1.0	49 (74.2%)	47 (77.0%)	96 (75.6%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0.9	45 (68.2%)	38 (62.3%)	83 (65.4%)
NERVOUS SYSTEM DISORDERS	0.9	43 (65.2%)	37 (60.7%)	80 (63.0%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1.0	41 (62.1%)	38 (62.3%)	79 (62.2%)
INFECTIONS AND INFESTATIONS	0.8	40 (60.6%)	31 (50.8%)	71 (55.9%)
PSYCHIATRIC DISORDERS	0.9	37 (56.1%)	31 (50.8%)	68 (53.5%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0.9	36 (54.5%)	29 (47.5%)	65 (51.2%)
VASCULAR DISORDERS	0.9	35 (53.0%)	28 (45.9%)	63 (49.6%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0.8	33 (50.0%)	24 (39.3%)	57 (44.9%)
IMMUNE SYSTEM DISORDERS	1.0	29 (43.9%)	27 (44.3%)	56 (44.1%)
RENAL AND URINARY DISORDERS	0.9	28 (42.4%)	24 (39.3%)	52 (40.9%)
EYE DISORDERS	0.8	19 (28.8%)	14 (23.0%)	33 (26.0%)
CARDIAC DISORDERS	0.7	16 (24.2%)	11 (18.0%)	27 (21.3%)
ENDOCRINE DISORDERS	1.2	13 (19.7%)	14 (23.0%)	27 (21.3%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0.7	14 (21.2%)	9 (14.8%)	23 (18.1%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED	1.4	8 (12.1%)	10 (16.4%)	18 (14.2%)
HEPATOBILIARY DISORDERS	1.6	6 (9.1%)	9 (14.8%)	15 (11.8%)
EAR AND LABYRINTH DISORDERS	1.3	4 (6.1%)	5 (8.2%)	9 (7.1%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1.3	4 (6.1%)	5 (8.2%)	9 (7.1%)

AEs are coded using MedDRA (version 7). * p<0.05 by two-sided, Fisher's exact test. (Page 1 of 1)
System organ classes are sorted by descending order of frequency in the total column.
Subjects were counted only once for each system organ class.
Percentages are based on the number of subjects evaluable for safety in each treatment group
Includes treatment emergent AEs occurring in 5% or more of total subjects or AEs with system organ class of 'Endocrine Disorders'.

Table 5-10. Treatment-emergent Adverse Events with Preferred Term Incidence of 5 Percent or More of Subjects (Safety Population) (Study ENT 00-02)

Preferred Term	Fold Increase BDP/PLA	Placebo (N=66)	BDP (N=61)	Total (N=127)
GRAFT-VERSUS-HOST DISEASE	1.0	27 (40.9%)	26 (42.6%)	53 (41.7%)
BLOOD MAGNESIUM DECREASED	0.9	28 (42.4%)	24 (39.3%)	52 (40.9%)
FATIGUE	1.3	23 (34.8%)	28 (45.9%)	51 (40.2%)
HYPERTENSION	1.1	23 (34.8%)	24 (39.3%)	47 (37.0%)
OEDEMA PERIPHERAL	0.8	25 (37.9%)	19 (31.1%)	44 (34.6%)
INSOMNIA	0.9	21 (31.8%)	18 (29.5%)	39 (30.7%)
TREMOR	0.9	20 (30.3%)	17 (27.9%)	37 (29.1%)
HEADACHE	0.9	20 (30.3%)	16 (26.2%)	36 (28.3%)
CYTOMEGALOVIRUS ANTIGEN	0.8	20 (30.3%)	14 (23.0%)	34 (26.8%)
HYPERGLYCAEMIA	1.0	17 (25.8%)	15 (24.6%)	32 (25.2%)
ANAEMIA	0.7	16 (24.2%)	11 (18.0%)	27 (21.3%)
BACTERAEMIA	1.2	13 (19.7%)	14 (23.0%)	27 (21.3%)
DRY SKIN	0.6	17 (25.8%)	10 (16.4%)	27 (21.3%)
HYPOKALAEMIA	1.0	14 (21.2%)	13 (21.3%)	27 (21.3%)
PYREXIA	0.5	17 (25.8%)	8 (13.1%)	25 (19.7%)
RENAL INSUFFICIENCY	0.7	15 (22.7%)	10 (16.4%)	25 (19.7%)
CONSTIPATION	0.7	14 (21.2%)	9 (14.8%)	23 (18.1%)
RASH	0.5	16 (24.2%)	7 (11.5%)	23 (18.1%)
ASTHENIA	0.8	13 (19.7%)	9 (14.8%)	22 (17.3%)
DRY MOUTH	0.8	13 (19.7%)	9 (14.8%)	22 (17.3%)
HYPOCALCAEMIA	1.3	10 (15.2%)	12 (19.7%)	22 (17.3%)
NAUSEA	0.9	12 (18.2%)	10 (16.4%)	22 (17.3%)
ABDOMINAL PAIN	0.8	12 (18.2%)	9 (14.8%)	21 (16.5%)

AEs are coded using MedDRA (version 7). * p<0.05 by two-sided, Fisher's exact test. (Page 1 of 4)
Preferred terms are sorted by descending order of frequency in the total column.
Subjects were counted only once for each preferred term.
Percentages are based on the number of subjects evaluable for safety in each treatment group.
Includes treatment emergent AEs occurring in 5% or more of total subjects or AEs with system organ class of 'Endocrine Disorders'.

Table 5-10. Treatment-emergent Adverse Events with Preferred Term Incidence of 5 Percent or More of Subjects (Safety Population) (Study ENT 00-02)

Preferred Term	Fold Increase BDP/PLA	Placebo (N=66)	BDP (N=61)	Total (N=127)
ANXIETY	0.8	12 (18.2%)	9 (14.8%)	21 (16.5%)
DIZZINESS	1.2	10 (15.2%)	11 (18.0%)	21 (16.5%)
ERYTHEMA	1.8	8 (12.1%)	13 (21.3%)	21 (16.5%)
HYPOPHOSPHATAEMIA	1.4	9 (13.6%)	12 (19.7%)	21 (16.5%)
SKIN HYPERPIGMENTATION	1.1	10 (15.2%)	10 (16.4%)	20 (15.7%)
COUGH	1.1	9 (13.6%)	9 (14.8%)	18 (14.2%)
DIARRHOEA	0.7	11 (16.7%)	7 (11.5%)	18 (14.2%)
HYPERKALAEMIA	0.7	11 (16.7%)	7 (11.5%)	18 (14.2%)
VOMITING	0.9	10 (15.2%)	8 (13.1%)	18 (14.2%)
BACK PAIN	0.6	11 (16.7%)	6 (9.8%)	17 (13.4%)
MUSCLE CRAMP	2.0	6 (9.1%)	11 (18.0%)	17 (13.4%)
PAIN IN EXTREMITY	1.2	8 (12.1%)	9 (14.8%)	17 (13.4%)
TACHYCARDIA	0.8	10 (15.2%)	7 (11.5%)	17 (13.4%)
UPPER RESPIRATORY TRACT INFECTION	0.6	11 (16.7%)	6 (9.8%)	17 (13.4%)
PRURITUS	0.6	10 (15.2%)	6 (9.8%)	16 (12.6%)
WEIGHT DECREASED	1.4	7 (10.6%)	9 (14.8%)	16 (12.6%)
CUSHINGOID	1.6	6 (9.1%)	9 (14.8%)	15 (11.8%)
ARTHRALGIA	1.4	6 (9.1%)	8 (13.1%)	14 (11.0%)
DYSPEPSIA	0.8	8 (12.1%)	6 (9.8%)	14 (11.0%)
HYPONATRAEMIA	1.1	7 (10.6%)	7 (11.5%)	14 (11.0%)
NEUTROPENIA	0.4	10 (15.2%)	4 (6.6%)	14 (11.0%)
ORTHOSTATIC HYPOTENSION	0.3*	11 (16.7%)	3 (4.9%)	14 (11.0%)
OSTEOPENIA	1.1	7 (10.6%)	7 (11.5%)	14 (11.0%)

AEs are coded using MedDRA (version 7). * p<0.05 by two-sided, Fisher's exact test. (Page 2 of 4)
Preferred terms are sorted by descending order of frequency in the total column.
Subjects were counted only once for each preferred term.
Percentages are based on the number of subjects evaluable for safety in each treatment group.
Includes treatment emergent AEs occurring in 5% or more of total subjects or AEs with system organ class of 'Endocrine Disorders'.

Table 5-10. Treatment-emergent Adverse Events with Preferred Term Incidence of 5 Percent or More of Subjects (Safety Population) (Study ENT 00-02)

Preferred Term	Fold Increase BDP/PLA	Placebo (N=66)	BDP (N=61)	Total (N=127)
PANCYTOPENIA	0.3*	11 (16.7%)	3 (4.9%)	14 (11.0%)
THROMBOCYTOPENIA	0.8	8 (12.1%)	6 (9.8%)	14 (11.0%)
DYSPNOEA	0.7	8 (12.1%)	5 (8.2%)	13 (10.2%)
HYPOMAGNESAEMIA	0.9	7 (10.6%)	6 (9.8%)	13 (10.2%)
GASTROOESOPHAGEAL REFLUX DISEASE	1.1	6 (9.1%)	6 (9.8%)	12 (9.4%)
TONGUE COATED	1.5	5 (7.6%)	7 (11.5%)	12 (9.4%)
ACQUIRED HYPOGAMMAGLOBULINAEMIA	0.9	6 (9.1%)	5 (8.2%)	11 (8.7%)
ADRENAL INSUFFICIENCY	1.3	5 (7.6%)	6 (9.8%)	11 (8.7%)
ANOREXIA	1.3	5 (7.6%)	6 (9.8%)	11 (8.7%)
DEHYDRATION	4.9*	2 (3.0%)	9 (14.8%)	11 (8.7%)
HYPERLIPIDAEMIA	1.3	5 (7.6%)	6 (9.8%)	11 (8.7%)
HYPOTENSION	0.1*	10 (15.2%)	1 (1.6%)	11 (8.7%)
LEUKOCYTOSIS	1.9	4 (6.1%)	7 (11.5%)	11 (8.7%)
LIVER FUNCTION TEST ABNORMAL	0.9	6 (9.1%)	5 (8.2%)	11 (8.7%)
RIGORS	0.9	6 (9.1%)	5 (8.2%)	11 (8.7%)
DYSGEUSIA	0.3	8 (12.1%)	2 (3.3%)	10 (7.9%)
HYPERBILIRUBINAEMIA	2.6	3 (4.5%)	7 (11.5%)	10 (7.9%)
KERATOCONJUNCTIVITIS SICCA	1.1	5 (7.6%)	5 (8.2%)	10 (7.9%)
CONTUSION	0.3	7 (10.6%)	2 (3.3%)	9 (7.1%)
CATHETER SITE ERYTHEMA	0.6	5 (7.6%)	3 (4.9%)	8 (6.3%)
CHEST PAIN	7.7*	1 (1.5%)	7 (11.5%)	8 (6.3%)
DEPRESSION	0.6	5 (7.6%)	3 (4.9%)	8 (6.3%)
DYSPNOEA EXERTIONAL	0.4	6 (9.1%)	2 (3.3%)	8 (6.3%)

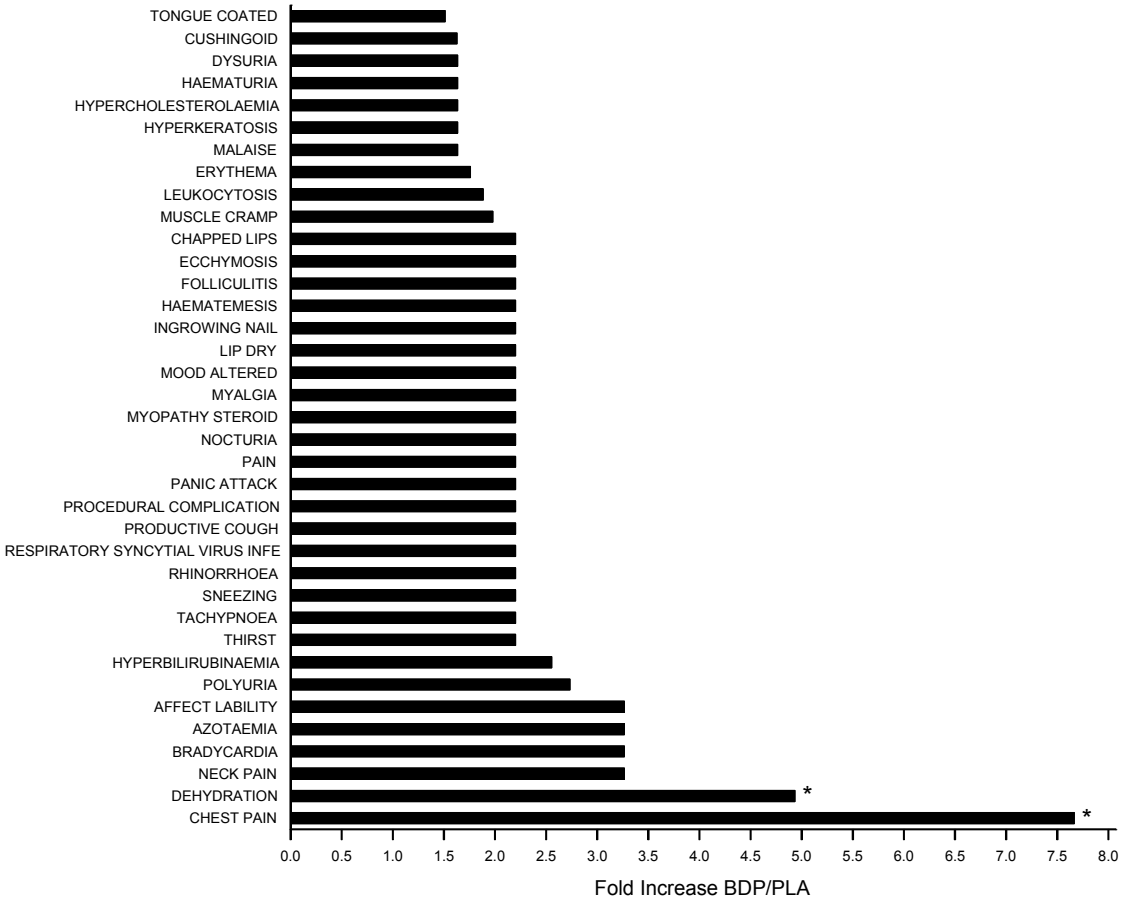
AEs are coded using MedDRA (version 7). * p<0.05 by two-sided, Fisher's exact test. (Page 3 of 4)
Preferred terms are sorted by descending order of frequency in the total column.
Subjects were counted only once for each preferred term.
Percentages are based on the number of subjects evaluable for safety in each treatment group.
Includes treatment emergent AEs occurring in 5% or more of total subjects or AEs with system organ class of 'Endocrine Disorders'.

Table 5-10. Treatment-emergent Adverse Events with Preferred Term Incidence of 5 Percent or More of Subjects (Safety Population) (Study ENT 00-02)

Preferred Term	Fold Increase BDP/PLA	Placebo (N=66)	BDP (N=61)	Total (N=127)
BLOOD CREATININE INCREASED	0.2	6 (9.1%)	1 (1.6%)	7 (5.5%)
FLATULENCE	1.5	3 (4.5%)	4 (6.6%)	7 (5.5%)
LUNG INFILTRATION	0.0*	7 (10.6%)	0 (0.0%)	7 (5.5%)
NASAL CONGESTION	0.4	5 (7.6%)	2 (3.3%)	7 (5.5%)
OEDEMA	0.4	5 (7.6%)	2 (3.3%)	7 (5.5%)
POLLAKIURIA	0.8	4 (6.1%)	3 (4.9%)	7 (5.5%)
POLYURIA	2.7	2 (3.0%)	5 (8.2%)	7 (5.5%)
VISION BLURRED	0.4	5 (7.6%)	2 (3.3%)	7 (5.5%)
ADRENAL SUPPRESSION	0.0	2 (3.0%)	0 (0.0%)	2 (1.6%)
ADRENAL CORTICAL INSUFFICIENCY	0.0	1 (1.5%)	0 (0.0%)	1 (0.8%)
HIRSUTISM	0.0	1 (1.5%)	0 (0.0%)	1 (0.8%)
HYPOGONADISM MALE	0.0	1 (1.5%)	0 (0.0%)	1 (0.8%)

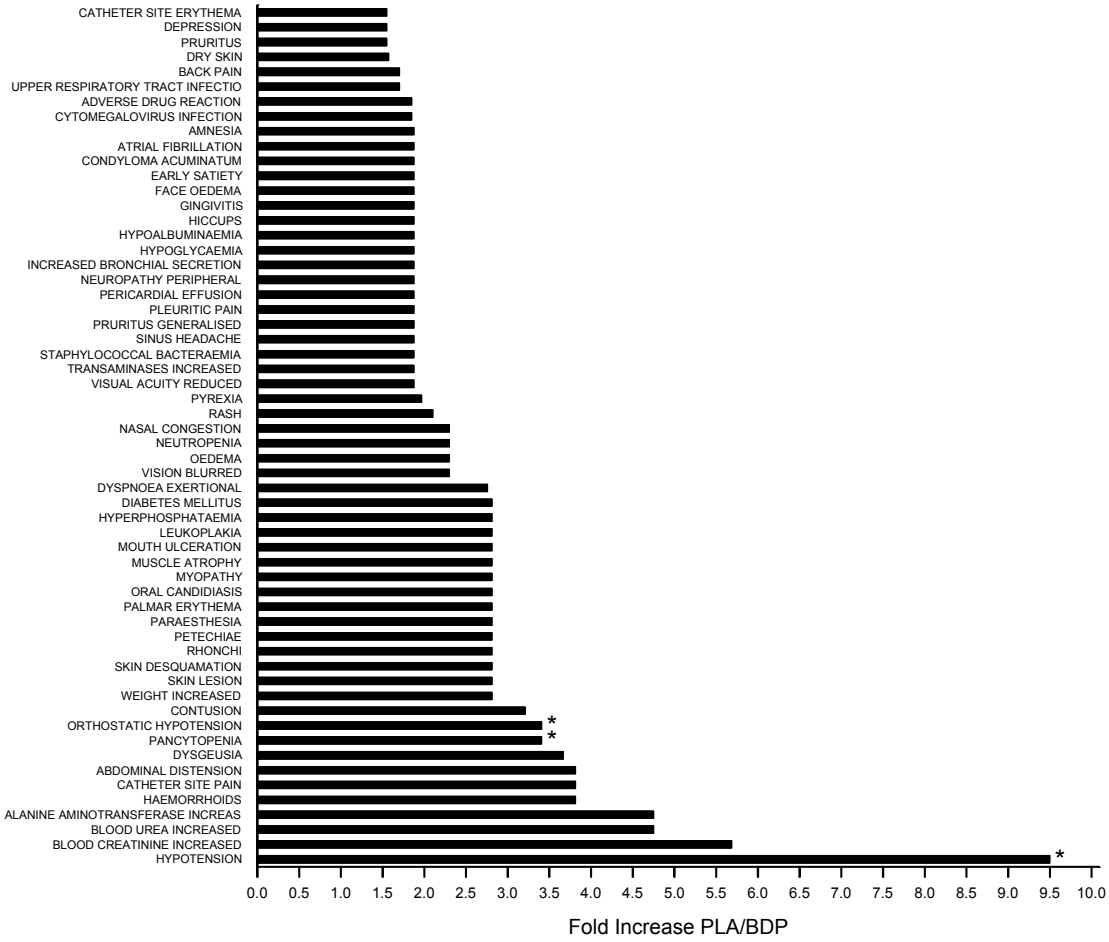
AEs are coded using MedDRA (version 7). * p<0.05 by two-sided, Fisher's exact test. (Page 4 of 4)
Preferred terms are sorted by descending order of frequency in the total column.
Subjects were counted only once for each preferred term.
Percentages are based on the number of subjects evaluable for safety in each treatment group.
Includes treatment emergent AEs occurring in 5% or more of total subjects or AEs with system organ class of 'Endocrine Disorders'.

Figure 5-1. Adverse Events for All Severity Grades Over-represented in the BDP Arm Versus Placebo Arm (Safety Population) (Study ENT 00-02)



Note: Only AEs ≥ 1.5 fold. * p <0.05 by two-sided, Fisher's exact test. For some groups, fold increase values is an underestimation as some groups did not have any event.

Figure 5-2. Adverse Events for All Severity Grades Overrepresented in the Placebo Arm vs. BDP Arm (Safety Population) (Study ENT 00-02)



Note: Only adverse events ≥ 1.5 fold. * p <0.05 by two-sided, Fisher's exact test. For some groups, fold increase values is an underestimation as some groups did not have any event.

Table 5-11. All Treatment Emergent Adverse Events Related to Study Drug Summarized by MedDRA Preferred Term and Treatment Group (Safety Population)

Preferred Term	Placebo (N=66)	BDP (N=61)	Total (N=127)
TREATMENT EMERGENT TREATMENT RELATED ADVERSE EVENT REPORTED	29 (43.9%)	21 (34.4%)	50 (39.4%)
ADRENAL INSUFFICIENCY	3 (4.5%)	5 (8.2%)	8 (6.3%)
FATIGUE	2 (3.0%)	5 (8.2%)	7 (5.5%)
HYPERGLYCAEMIA	1 (1.5%)	4 (6.6%)	5 (3.9%)
LIVER FUNCTION TEST ABNORMAL	3 (4.5%)	1 (1.6%)	4 (3.1%)
ANOREXIA	1 (1.5%)	2 (3.3%)	3 (2.4%)
ASTHENIA	1 (1.5%)	2 (3.3%)	3 (2.4%)
DYSGEUSIA	3 (4.5%)	0 (0.0%)	3 (2.4%)
HYPONATRAEMIA	3 (4.5%)	0 (0.0%)	3 (2.4%)
OEDEMA PERIPHERAL	1 (1.5%)	2 (3.3%)	3 (2.4%)
ORAL CANDIDIASIS	3 (4.5%)	0 (0.0%)	3 (2.4%)
VOMITING	2 (3.0%)	1 (1.6%)	3 (2.4%)
ABDOMINAL PAIN	1 (1.5%)	1 (1.6%)	2 (1.6%)
ADRENAL SUPPRESSION	2 (3.0%)	0 (0.0%)	2 (1.6%)
CUSHINGOID	0 (0.0%)	2 (3.3%)	2 (1.6%)
DIARRHOEA	1 (1.5%)	1 (1.6%)	2 (1.6%)
HYPERKALAEMIA	0 (0.0%)	2 (3.3%)	2 (1.6%)
INSOMNIA	1 (1.5%)	1 (1.6%)	2 (1.6%)
LEUKOCYTOSIS	1 (1.5%)	1 (1.6%)	2 (1.6%)
NAUSEA	1 (1.5%)	1 (1.6%)	2 (1.6%)
ABDOMINAL PAIN UPPER	0 (0.0%)	1 (1.6%)	1 (0.8%)
ACUTE MYELOID LEUKAEMIA RECURRENT	0 (0.0%)	1 (1.6%)	1 (0.8%)

Adverse events are coded using MedDRA (version 7). (Page 1 of 4)
Preferred terms are sorted by descending order of frequency in the total column.
Subjects were counted only once for each preferred term.
Percentages are based on the number of subjects evaluable for safety in each treatment group.
Table includes adverse events judged by the investigator as possibly, probably, and related to study drug.

Table 5-11. All Treatment Emergent Adverse Events Related to Study Drug Summarized by MedDRA Preferred Term and Treatment Group (Safety Population)

Preferred Term	Placebo (N=66)	BDP (N=61)	Total (N=127)
ADRENAL CORTICAL INSUFFICIENCY	1 (1.5%)	0 (0.0%)	1 (0.8%)
AMNESIA	0 (0.0%)	1 (1.6%)	1 (0.8%)
ANXIETY	0 (0.0%)	1 (1.6%)	1 (0.8%)
ASPERGILLOSIS ORAL	1 (1.5%)	0 (0.0%)	1 (0.8%)
BACTERAEMIA	0 (0.0%)	1 (1.6%)	1 (0.8%)
BLOOD CREATININE INCREASED	1 (1.5%)	0 (0.0%)	1 (0.8%)
BLOOD LACTATE DEHYDROGENASE INCREASED	1 (1.5%)	0 (0.0%)	1 (0.8%)
BLOOD UREA INCREASED	1 (1.5%)	0 (0.0%)	1 (0.8%)
COGNITIVE DISORDER	1 (1.5%)	0 (0.0%)	1 (0.8%)
CONFUSIONAL STATE	0 (0.0%)	1 (1.6%)	1 (0.8%)
CONSTIPATION	1 (1.5%)	0 (0.0%)	1 (0.8%)
DEHYDRATION	0 (0.0%)	1 (1.6%)	1 (0.8%)
DERMATITIS ACNEIFORM	0 (0.0%)	1 (1.6%)	1 (0.8%)
DIZZINESS	0 (0.0%)	1 (1.6%)	1 (0.8%)
DIZZINESS POSTURAL	1 (1.5%)	0 (0.0%)	1 (0.8%)
DRY SKIN	1 (1.5%)	0 (0.0%)	1 (0.8%)
ELECTROCARDIOGRAM ABNORMAL	0 (0.0%)	1 (1.6%)	1 (0.8%)
ERUCTATION	0 (0.0%)	1 (1.6%)	1 (0.8%)
ERYTHEMA	1 (1.5%)	0 (0.0%)	1 (0.8%)
FEELING HOT	1 (1.5%)	0 (0.0%)	1 (0.8%)
FLATULENCE	0 (0.0%)	1 (1.6%)	1 (0.8%)
GASTRITIS	1 (1.5%)	0 (0.0%)	1 (0.8%)
GASTROOESOPHAGEAL REFLUX DISEASE	1 (1.5%)	0 (0.0%)	1 (0.8%)

Adverse events are coded using MedDRA (version 7).
Preferred terms are sorted by descending order of frequency in the total column.
Subjects were counted only once for each preferred term.
Percentages are based on the number of subjects evaluable for safety in each treatment group.
Table includes adverse events judged by the investigator as possibly, probably, and related to study drug.

Table 5-11. All Treatment Emergent Adverse Events Related to Study Drug Summarized by MedDRA Preferred Term and Treatment Group (Safety Population)

Preferred Term	Placebo (N=66)	BDP (N=61)	Total (N=127)
GRAFT-VERSUS-HOST DISEASE	1 (1.5%)	0 (0.0%)	1 (0.8%)
HEADACHE	0 (0.0%)	1 (1.6%)	1 (0.8%)
HICCUPS	1 (1.5%)	0 (0.0%)	1 (0.8%)
HYPERBILIRUBINAEMIA	0 (0.0%)	1 (1.6%)	1 (0.8%)
HYPERTENSION	1 (1.5%)	0 (0.0%)	1 (0.8%)
HYPOKALAEMIA	0 (0.0%)	1 (1.6%)	1 (0.8%)
HYPOMAGNESAEMIA	1 (1.5%)	0 (0.0%)	1 (0.8%)
LEUKOPENIA	0 (0.0%)	1 (1.6%)	1 (0.8%)
MOOD SWINGS	0 (0.0%)	1 (1.6%)	1 (0.8%)
MUSCLE CRAMP	1 (1.5%)	0 (0.0%)	1 (0.8%)
MYALGIA	1 (1.5%)	0 (0.0%)	1 (0.8%)
NIGHT SWEATS	0 (0.0%)	1 (1.6%)	1 (0.8%)
ORAL FUNGAL INFECTION	0 (0.0%)	1 (1.6%)	1 (0.8%)
PAIN IN EXTREMITY	0 (0.0%)	1 (1.6%)	1 (0.8%)
PALATAL DISORDER	1 (1.5%)	0 (0.0%)	1 (0.8%)
PANCYTOPENIA	1 (1.5%)	0 (0.0%)	1 (0.8%)
PNEUMONIA	1 (1.5%)	0 (0.0%)	1 (0.8%)
PRURITUS	1 (1.5%)	0 (0.0%)	1 (0.8%)
PULMONARY MASS	1 (1.5%)	0 (0.0%)	1 (0.8%)
RASH MACULAR	1 (1.5%)	0 (0.0%)	1 (0.8%)
RASH PRURITIC	0 (0.0%)	1 (1.6%)	1 (0.8%)
RIGORS	0 (0.0%)	1 (1.6%)	1 (0.8%)
STAPHYLOCOCCAL BACTERAEMIA	1 (1.5%)	0 (0.0%)	1 (0.8%)

Adverse events are coded using MedDRA (version 7). (Page 3 of 4)
Preferred terms are sorted by descending order of frequency in the total column.
Subjects were counted only once for each preferred term.
Percentages are based on the number of subjects evaluable for safety in each treatment group.
Table includes adverse events judged by the investigator as possibly, probably, and related to study drug.

Table 5-11. All Treatment Emergent Adverse Events Related to Study Drug Summarized by MedDRA Preferred Term and Treatment Group (Safety Population)

All Treatment Emergent Adverse Events Related to Study Drug Summarized by MedDRA Preferred Term and Treatment Group
(Safety Population)

Preferred Term	Placebo (N=66)	BDP (N=61)	Total (N=127)
STOMACH DISCOMFORT	0 (0.0%)	1 (1.6%)	1 (0.8%)
SWELLING	1 (1.5%)	0 (0.0%)	1 (0.8%)
THROMBOCYTOPENIA	0 (0.0%)	1 (1.6%)	1 (0.8%)
TONGUE COATED	0 (0.0%)	1 (1.6%)	1 (0.8%)
TREMOR	0 (0.0%)	1 (1.6%)	1 (0.8%)
UPPER RESPIRATORY TRACT INFECTION	1 (1.5%)	0 (0.0%)	1 (0.8%)
VISION BLURRED	0 (0.0%)	1 (1.6%)	1 (0.8%)
VULVOVAGINAL DRYNESS	1 (1.5%)	0 (0.0%)	1 (0.8%)
WEIGHT DECREASED	1 (1.5%)	0 (0.0%)	1 (0.8%)

Adverse events are coded using MedDRA (version 7). (Page 4 of 4)
Preferred terms are sorted by descending order of frequency in the total column.
Subjects were counted only once for each preferred term.
Percentages are based on the number of subjects evaluable for safety in each treatment group.
Table includes adverse events judged by the investigator as possibly, probably, and related to study drug.

5.2.6.2 Serious and Severe Adverse Events

SAEs were reported in approximately 40% of subjects in both groups (Table 5-8). The most common SAEs were (BDP, placebo): GVHD (7%, 6%), pyrexia (3%, 8%), bacteremia (5%, 3%), and hypoxia (0%, 6%) (Table 5-12).

A total of 118 serious adverse events (SAEs) were reported, including treatment emergent SAEs, as well as SAEs that occurred greater than 30 days after the last dose of study drug administration. Forty-six of the SAEs occurred in the BDP group, and 72 in the placebo group. Following database lock and analysis of SAEs, one additional SAE was uncovered during a site audit that was not included in the current analyses. This event occurred in subject 07-304 (placebo group), was reported as sepsis and hypoxia, started on January 19, 2004, was resolved on February 2, 2004 and was judged by the investigator as unrelated to study drug.

Because multiple symptoms and signs characteristic of a single diagnosis were frequently reported separately, prior to unblinding, all SAEs were summarized by the Medical Monitor in a clinically relevant fashion for analysis. This summarization procedure resulted in fewer final SAE reports than the numbers noted above because of the combination of several signs and symptoms into one diagnosis and summary. An evaluation of the narrative summaries of SAEs assessed as non-fatal and not included in the deaths (described in Section 5.2.6.3) was conducted and included 20 subjects in the BDP group with 25 reports and 22 subjects in the placebo group with 31 reports. These were qualitative evaluations of the primary medical diagnosis for each event. Based on this assessment, there was no significant difference in the rates of the following events: GVHD (worsening/relapse), malignancy relapse, infection (e.g., sepsis and pneumonia), and steroid related AEs (e.g., hyperglycemia and steroid myopathy). Bacterial and viral organisms cultured from subjects with infections were not different between the 2 arms and were typical of those seen in the transplant population; they included *S. pneumoniae, Staphylococcus, P. aeruginosa, C. difficile, C. freundii, M. catarrhalis, Enterococcus, Diphtheroids, A. xylosoxidans, Torulopsis, adenovirus,* and *cytomegalovirus*. SAE reports of fungal infections (Norcardia, and Candida) were described in the placebo group only.

Assessment of events identified as "severe" by the investigators demonstrated that the incidence of severe AEs was similar in the two arms (BDP 41%, placebo 47%) (Table 5-8). The severe AEs that occurred with frequency greater than 5% in either group were (BDP, placebo): GVHD (5%, 8%), pyrexia (2%, 5%), hyperglycemia (5%, 0%), and pneumonia (0%, 5%) (Table 5-13).

Table 5-12. Serious Adverse Events of Greater Than 5% Frequency in Either Treatment Group, Summarized by MedDRA Preferred Term and Treatment Group; Data Source: Adverse Event CRF (Safety Population)

Preferred Term	Placebo (N=66)	BDP (N=61)	Total (N=127)
SERIOUS ADVERSE EVENT REPORTED	29 (43.9%)	24 (39.3%)	53 (41.7%)
GRAFT-VERSUS-HOST DISEASE	4 (6.1%)	4 (6.6%)	8 (6.3%)
PYREXIA	5 (7.6%)	2 (3.3%)	7 (5.5%)
BACTERAEMIA	2 (3.0%)	3 (4.9%)	5 (3.9%)
HYPOXIA	4 (6.1%)	0 (0.0%)	4 (3.1%)
NAUSEA	3 (4.5%)	1 (1.6%)	4 (3.1%)

Adverse events are coded using MedDRA (version 7). (Page 1 of 1)
The Adverse Event CRF is the data source for this table.
Preferred terms are sorted by descending order of frequency in the total column.
Subjects were counted only once for each preferred term.
Percentages are based on the number of subjects evaluable for safety in each treatment group.

Table 5-13. Severe Treatment Emergent Adverse Events of Frequency Greater Than 5% in Either Treatment Group, Summarized by MedDRA Preferred Term and Treatment Group (Safety Population)

Preferred Term	Placebo (N=66)	BDP (N=61)	Total (N=127)
SEVERE TREATMENT EMERGENT ADVERSE EVENT REPORTED	31 (47.0%)	25 (41.0%)	56 (44.1%)
GRAFT-VERSUS-HOST DISEASE	5 (7.6%)	3 (4.9%)	8 (6.3%)
HEADACHE	2 (3.0%)	2 (3.3%)	4 (3.1%)
LEUKAEMIA RECURRENT	2 (3.0%)	2 (3.3%)	4 (3.1%)
NAUSEA	2 (3.0%)	2 (3.3%)	4 (3.1%)
PYREXIA	3 (4.5%)	1 (1.6%)	4 (3.1%)
VOMITING	2 (3.0%)	2 (3.3%)	4 (3.1%)
BACTERAEMIA	2 (3.0%)	1 (1.6%)	3 (2.4%)
DIARRHOEA	2 (3.0%)	1 (1.6%)	3 (2.4%)
DYSPNOEA	2 (3.0%)	1 (1.6%)	3 (2.4%)
HYPERGLYCAEMIA	0 (0.0%)	3 (4.9%)	3 (2.4%)
PNEUMONIA	3 (4.5%)	0 (0.0%)	3 (2.4%)

Adverse events are coded using MedDRA (version 7). (Page 1 of 1)
Preferred terms are sorted by descending order of frequency in the total column.
Subjects were counted only once for each preferred term.
Percentages are based on the number of subjects evaluable for safety in each treatment group.

5.2.6.3 Deaths Within the Approximate 80 Day Study Period

A total of 12 deaths occurred during the approximate 80-day study period (3 of the 12 twelve deaths occurred days 83, 87, and 94). Of these 12 deaths, 3 occurred in the BDP arm and 9 in the placebo arm. Subjects may have had multiple medical diagnoses at the time of death and given the complexity and severity of the illness in this subject population this is an expected finding. Consequently some subjects may have died primarily due to infection, primarily due to relapse of their malignancy, and primarily due to both relapse and infection.

The findings associated with death in the 3 BDP subjects were as follows: viral infection (BK virus); relapse and cellulitis/bacteremia (*Pseudomonas* and *Staphyloccocus*); and progressive GVHD leading to bowel perforation. The subject with progressive GVHD was enrolled in violation of the protocol eligibility criteria because his clinical symptoms were more severe than permitted by the eligibility criteria (severe diarrhea and more extensive skin involvement). Two of the 3 subjects had treatment failure on or before day 10 (one was discontinued before day 50 due to an AE of relapsed disease).

The findings associated with death in the 9 placebo subjects were as follows: relapse; relapse and cellulitis; bacterial sepsis (*S. aureus*); sepsis (*P. aeruginosa*); relapse and presumed fungal infection (pulmonary nodules that resolved with antifungal treatment); bronchiolitis obliterans organizing pneumonia (BOOP); sepsis; relapse; and fungal infection (pulmonary aspergillosis). Four of the 9 subjects had treatment failure on or before day 50 (one at day 11).

Other time periods were also examined. Three subjects died within 30 days of last dose of investigational agent: 2 in the BDP arm and 1 in the placebo arm, and are all included in the above analysis. A total of 21 deaths occurred during the 200-day post-transplant period; 5 (8%) were in the BDP group, and 16 (24%) were in the placebo group (Section 4.2.6).

While the numbers of subjects are too small to reach statistical significance, there were a larger number of deaths in the placebo arm than in the BDP arm looking at both the approximate 80-day treatment period and 200 days post transplantation. Causes of death

were primarily due to infection and relapse with the rate of deaths due to infection being higher in the placebo arm.

5.2.6.4 Corticosteroid-related Adverse Events

Adverse events related to corticosteroid use

Adverse events in the MedDRA system organ class, endocrine disorders (including the cushingoid diagnosis), were reported more frequently in the BDP group than the placebo group (19.7% versus 23.0%, respectively for endocrine disorders as a whole (Table 5-9).

Assessment of specific AEs (BDP, placebo) by preferred term which might be related to side effects of steroid therapy demonstrated higher rates in the placebo arm for peripheral edema (31%, 38%), depression (5%, 8%), adrenocortical insufficiency (0%, 2%), and adrenal suppression (0%, 2%); higher rates in the BPD arm for fatigue (46%, 35%), cushingoid (15%, 9%), muscle cramps (18%, 9%); and similar rates between both arms for GVHD (43%, 41%), hypertension (39%, 35%), hyperglycemia (25%, 26%), hyokalemia (21%, 21%), and osteopenia (12%, 11%) (Table 5-10). Assessment of laboratory values for glucose and electrolytes demonstrated similar levels between the two arms as well (data in NDA submission). Overall there appeared to be systemic effects of corticosteroid absorption in both arms with possibly a trend toward more effects in the BDP arm for the symptomatic manifestations.

HPA Axis Function

The association between HPA axis function and study drug was assessed by measuring plasma concentrations of ACTH, resting morning cortisol, and change in plasma cortisol concentration after a standard test dose of intravenous (IV) cosyntropin both at baseline and study day 51. All subjects who had normal adrenal responsiveness at baseline and who reached study day 50 without treatment failure were eligible for evaluation on study day 51. A subject was considered to have evidence of abnormal HPA function if at least one of the results for the 3 tests was below the limit specified in Table 5-14. In retrospect, the clinical study design regarding HPA function assessment was flawed because HPA axis evaluation was not performed at study day 51 for treatment failures who, given the much larger exposure to systemic corticosteroids they received, would be

also expected to have abnormal HPA axis function; therefore, comparisons and conclusions regarding differences between the two study arms or between failures and non-failures cannot be made.

Table 5-14. Reference Limits for Normal HPA Axis Function

Test	Limit
Resting morning plasma cortisol concentration	≤5 µg/dL
Plasma cortisol concentration after cosyntropin stimulation	≤18 µg/dL
Increase in plasma cortisol after cosyntropin stimulation	≤7 µg/dL

The majority of subjects had normal HPA axis function as measured by cosyntropin stimulation test at baseline (80% for placebo versus 75% for BDP).

At study day 51, there was a statistically significant difference in the proportion of evaluable subjects with abnormal HPA axis function (58% for placebo versus 86% for BDP, p = 0.0007). The overall significance of these data is unclear due to the study design flaw described above.

It should also be noted that it was recognized that a single dose of exogenous corticosteroid could suppress morning plasma cortisol thereby confounding the results. An additional modified analysis was conducted to control for this affect. The result of this modified analysis compared to the pre-specified study analysis described above identified fewer subjects as abnormal at baseline but similar results for day 51. These data were included in the NDA submission.

5.2.6.5 Infectious Adverse Events

Infections (by system organ class grouping) were less commonly reported as AEs in the BDP group than in the placebo group than in the BDP group (50.8% versus 60.6%, respectively) (Table 5-9).

Assessment of AEs (BDP, placebo) by preferred term which might be infectious in etiology demonstrated higher occurrence rates in the placebo arm for cytomegalovirus

antigen positivity (23%, 30%), fever (13%, 26%), upper respiratory infection (10%, 17%), and lung infiltrates (0%, 11%); higher rates in the BDP arm for tongue coated (12%, 8%); and similar rates between the BDP and placebo arms for bacteremia (23%, 20%). Overall there appeared to be higher rates of infectious AEs in the placebo arm. The assessment of deaths also identified higher rates of infection being associated with death in those subjects on the placebo arm suggesting a consistent effect across safety parameters evaluated (Section 5.2.6.3).

5.2.7 Clinical Laboratory Evaluations (Study ENT 00-02)

In this complex and extremely sick patient population, each subject had multiple laboratory abnormalities, virtually all of which were almost certainly due to their underlying disease and/or were secondary to the transplant procedure (data submitted in NDA).

Overall, there were no clinically meaningful differences between treatment groups during the 50-day protocol treatment period and 30-day post-treatment follow-up period for any of the laboratory tests evaluated. This includes the laboratory measures that would be expected to be influenced by exogenous corticosteroid therapy such as potassium, bicarbonate, and glucose.

The only notable hematology parameter is the eosinophil count, which, as would be expected, declined in both treatment groups in a comparable manner during the 10-day induction period on high-dose prednisone. Following the initiation of the prednisone taper on study day 10, the eosinophil counts returned to the baseline levels in both groups in a similar manner.

5.3 Safety Data From Non-Pivotal Studies

The safety data from the other clinical studies in the BDP development program are provided in Sections 5.4 through 5.9. As discussed in Section 5.1, due to the design of these studies and the methodology for data collection, the data are not as comprehensive as for the pivotal phase 3 study ENT 00-02. Consequently, there will be summaries of data provided but no integrated analysis.

5.4 Study 875

5.4.1 Study Design (Study 875)

Study 875 ("Controlled Study of Prednisone With or Without Oral Beclomethasone Dipropionate for the Initial Treatment of Patients with Intestinal Graft-versus-Host Disease") enrolled subjects with Grade II GVHD with GI symptoms who could swallow the study capsules without difficulty.

The following safety assessments (evaluated at study days 10, 20, 30, and 40) were measured:

- nausea, appetite, and abdominal pain using 6-point severity scales
- vomiting using the Spencer Scale,
- diarrheal grade and volume and bowel movement frequency,
- GI bleeding, and
- Karnofsky Performance score

Nausea, appetite, vomiting, diarrheal grade and volume, daily stool frequency, abdominal pain, GI bleeding, and Karnofsky Performance were analyzed at Baseline and at study days 10, 20, 30, and 40; and comparisons in change from Baseline to each of these days were made using the Wilcoxon signed-rank test. Infection was analyzed using cumulative incidence curves.

5.4.2 Subject Disposition (Study 875)

Sixty subjects (31 in the BDP group and 29 in the placebo group) received investigational product and were included in the safety analysis set.

One subject in the BDP group (UPN 09033) was unable to swallow the capsules and was withdrawn from the study as a treatment failure on study day 8. This child was classified as a failure on study day 10; she has no data thereafter but is counted as a failure at study day 30.

In the BDP group, 9 of 31 subjects (29%) were considered treatment failures; all were removed from the study on or before study day 10 (Table 5-15). In the placebo group,

17 of 29 subjects (59%) were considered treatment failures, 13 of whom were removed from the study by study day 10 and 4 of whom were removed from the study between study days 11 and 30. Subjects who did not drop out were followed for at least 30 days.

Table 5-15. Summary of Subject Discontinuation by Treatment Group

	BDP + Prednisone	Placebo + Prednisone
No. Enrolled	31	29
Total No. Discontinued by Study Day 10	9 (29%)	13 (45%)
Total No. Discontinued by Study Day 30	9 (29%)	17 (59%)

5.4.3 Extent of Exposure (Study 875)

Subjects received study drug beginning on study day 1 until treatment failure (defined as oral intake <70% ECR at specified study visits or physician decision to increase prednisone dosing) at which time the subject was removed from study drug and from further study evaluations. No subject discontinued study drug due to intolerance or safety. One subject (UPN 09033) in the BDP group discontinued because of an inability to swallow the study capsules. All 31 subjects randomized to BDP took study drug for at least 10 days; the proportion of subjects remaining on BDP at 15 days was approximately 75%, which remained stable until the end of the study, after 30 days of treatment.

5.4.4 Adverse Events (Study 875)

5.4.4.1 All Adverse Events

Many AEs occurred each day in subjects with GI GVHD following allogeneic hematopoietic cell transplantation. Unless they were infectious in nature (colonization of the intestinal tract with pathogenic organisms or frank enteric or intestinal infection), AEs were not reported as such unless they were felt by the attending physician to be related (possibly or probably) to the study drug. Four such AEs were reported (Table 5-16).

Table 5-16. Listing of Treatment-related AEs by Subject (Study 875)

UPN	Study Drug	Adverse Events Related to Study Drug (not including infectious disease endpoints)
07072	BDP	None; developed ankle and knee pain during prednisone taper
08407	BDP	At study day 30 evaluation, complained of "gas-like" epigastric pain relieved by antacid; more intense heartburn after study drug discontinued
09033	BDP	Unable to swallow study capsules
08887	Placebo	At study day 10 evaluation, complained of nocturnal heartburn

5.4.4.2 Serious Adverse Events

No treatment related SAEs or other significant SAEs occurred during the 30-day study period or during 30 days post-treatment.

5.4.4.3 Deaths

No deaths occurred during the 30-day study period or during 30 days post-treatment.

5.4.4.4 Infectious Adverse Events

Safety-related events were classified into 5 groups: fever ≥ 38.5 °C, bacteremia or fungemia, cytomegalovirus (CMV) antigenemia, episodes of other specified infections, and any infection. Within these groups, data were collected on the number of subjects ever having the event, the number of subject-days of the event, and the number of episodes of the event (possibly recurring in the same subject).

Table 5-17 displays a summary of these outcomes and their comparisons between the BDP and placebo groups. Numbers of persons, numbers of days with infection, and numbers of episodes are very similar between the 2 treatment arms, and there are no significant differences in these safety-related outcomes.

Table 5-17. Signs of Infection in Subjects on Treatment (Study 875)

Infection	BDP (N=30)	Placebo (N=29)
Fever ≥ 38.5 °C		
No. of days with fever	0.3 ± 0.9	0.3 ± 1.0
No. of subjects with fever	4	4
Bacteremia or Fungemia		
No. of days with Bacteremia or Fungemia	0.3 ± 0.7	0.2 ± 0.8
No. of Bacteremia or Fungemia episodes	0.4 ± 1.2	0.3 ± 0.8
No. of subjects with Bacteremia or Fungemia	5	4
CMV Antigenemia		
No. of days with CMV Antigenemia	0.4 ± 1.2	0.3 ± 0.7
No. of CMV Antigenemia episodes	0.4 ± 1.2	0.3 ± 0.7
No. of subjects with CMV Antigenemia	7	5
Episodes of Other Infection		
No. of other episodes of infection	0.3 ± 0.6	0.4 ± 0.8
No. of subjects with episodes of infection	8	8
Any Infection		
No. of subjects with any infection	15	14

CMH = Cochran-Mantel-Haenszel; CMV = cytomegalovirus

5.4.5 Clinical Laboratory Evaluations (Study 875)

Because of the life-threatening nature of their illness, laboratory evaluations were performed frequently as part of their normal care and monitoring. Values were reviewed by the attending physician as they became available. Although laboratory abnormalities were frequent, they were reported as AEs only if they were believed by the investigator to be related to the study drug. Detailed analysis of these data was not performed.

5.5 Study 615

5.5.1 Study Design (Study 615)

Study 615 ("Oral Beclomethasone Dipropionate for the Treatment of Patients with Intestinal Graft-versus-Host Disease") was a phase 1/2 study designed primarily to assess tolerance and safety of BDP. Subjects enrolled on study were placed into one of three

categories based on the severity of their GVHD; the severity of the AEs experienced by subjects may differ by category, and it is important to note that they may not be able to be compared to subjects across the other BDP clinical studies:

Category 1. Subjects with mild GI GVHD (symptoms of nausea, vomiting, anorexia, or diarrhea) not being treated with prednisone (cyclosporine ± methotrexate only). These subjects received oral BDP alone as corticosteroid treatment in this study.

Category 2. Subjects with mild GI GVHD being treated with prednisone (0.25 to 2 mg/kg), but no anti-thymocyte globulin (ATG) or monoclonal anti T-cell antibody therapy, and with intestinal symptoms that failed to respond to prednisone or had recurred during prednisone taper. These subjects continued to receive prednisone at the dose that was being administered at the time GI GVHD was documented by intestinal biopsy, and oral BDP was added to the treatment regimen.

Category 3. Subjects with severe GI GVHD, typically with other manifestations of GVHD as well, who were being treated with prednisone (1 to 4 mg/kg/day) as well as other immunosuppressive therapy. These subjects continued to receive high dose corticosteroids, at the dose when GI GVHD was documented by intestinal biopsy, and oral BDP was added to the treatment regimen.

Subjects were evaluated at baseline and at study days 7, 14, 21, and 28 for changes in signs and symptoms of GI GVHD including anorexia, nausea, abdominal pain, vomiting, diarrhea, oral caloric intake, stool frequency, GI bleeding, and Karnofsky performance score. Subjects on BDP alone were evaluated for adrenal axis function at baseline and on study days 7, 14, and 28 by measurement of serum cortisol and ACTH concentrations and by the increment in serum cortisol following an IV dose of 0.25 mg cosyntropin.

On study days 7, 14, 21, and 28, AEs were evaluated as follows: All AEs either possibly or probably related to study drug, and any AE involving an infectious disease endpoint (bacteremia, septicemia, fungemia, cellulitis, pneumonia, other site-specific infections, and fever associated with one of the previous), were recorded. Adverse events common to all subjects undergoing hematopoietic cell transplantation, including alopecia, thrombocytopenia, leukopenia, and anemia, were recorded in subject medical records but were not identified as AEs for the purpose of this study.

All episodes of bacteremia, enteric infection, colonization of the oropharynx, or intestinal infection with Aspergillus species that occurred in subjects on oral BDP resulted in discontinuation of the subject from the study drug and the study protocol, whether or not there was any attribution of cause to BDP by the principal investigator. A manuscript describing Study 615 (Baehr et al, 1995) is provided in Section 9 (Attachment 4).

5.5.2 Subject Disposition (Study 615)

All 42 subjects who enrolled into the study received BDP and were included in the safety analysis set. Twenty-seven subjects received BDP alone as initial therapy (the BDP group), and 15 were receiving prednisone at the time of enrollment, which was continued concomitantly with BDP (the BDP plus predisone group).

Of the 27 subjects in the BDP group, 2 subjects moved to the BDP plus prednisone group when prednisone was prescribed for treatment of newly developed skin and liver GVHD shortly after starting oral BDP. Of the remaining 25 subjects in the BDP group, 16 completed the study as scheduled, and 9 withdrew from the study prematurely.

Of the 17 subjects in the BDP plus prednisone group (15 subjects plus the 2 subjects who moved from the BDP group), 11 completed the study as scheduled, and 6 withdrew from the study prematurely.

5.5.3 Extent of Exposure (Study 615)

Of the 42 subjects, 39 subjects (93%) received BDP for at least 7 days, 34 (81%) subjects received BDP for at least 14 days, 28 (67%) subjects received BDP for at least 21 days, and 27 subjects (64%) received BDP for the full 28-day period. Four of the 27 subjects who received BDP for 28 days were treated with BDP for longer than the 28-day treatment period following initial clinical improvement with a desire to avoid systemic immunosuppressive therapy.

5.5.4 Adverse Events (Study 615)

5.5.4.1 All Adverse Events

Adverse events were recorded on the research charts as such only if they were thought by the investigator to be likely related to the study drug. Adverse events that were common

manifestations or complications of the subject's underlying condition were not considered to be related to the study drug and were not recorded or reported as AEs. Adverse events are listed in Table 5-18.

Of the 5 AEs that were recorded, 3 were GI symptoms (nausea, crampy abdominal pain during first week relieved by food, and bloated feeling after bowel movements) and 2 were abnormal taste sensations. All but one (nausea), resolved without withdrawal of study drug. These 5 AEs that were judged likely related to study drug administration were all minor in nature and resolved within a few days with continued drug administration.

Table 5-18. Adverse Events Likely Related to BDP by Subject (Study 615)

UPN	Previous Prednisone Use	Study Day of Adverse Event	Description of Event
6747	No	Unknown	Nausea
6758	No	3	"Funny taste" after first two daily doses
6940	No	Week 1	Crampy abdominal pain after doses during the first week of treatment only, resolved after food intake
7340	No	Unknown	Feeling bloated after bowel motions
7109	Yes	Unknown	"Salty taste" after enteric coated BDP capsules

5.5.4.2 Serious Adverse Events

Only treatment related AEs were reported collected. No treatment related SAEs were reported. However, the majority, if not all the infections that occurred on study were either bacteremias or fungal infections and would therefore probably have met one of the regulatory criteria for a SAE.

5.5.4.3 Deaths

There were no deaths during study drug administration. However, 5 deaths occurred during the approximate 30-day period after study drug discontinuation, all in subjects receiving high dose prednisone in addition to BDP. Four of the deaths were due to

infections common in this population; none were attributed to study drug treatment. These deaths are listed in Table 5-19

Table 5-19. Deaths During or Within 30 Days of Completion or Discontinuation of BDP (Study 615)

UPN	Days on BDP	Study Day of Death	Cause(s) of Death
4344	14	18	pancreatitis, respiratory failure
6807	19	22	pulmonary aspergillosis
6824	12	13	CMV pneumonia, multi-organ failure
7136	27	39	uncal herniation, brain abscess
7191	13	20	pulmonary aspergillosis

UPN = unique patient number

5.5.4.4 Corticosteroid-related Adverse Events

HPA Axis Function

Of note, adrenal function testing of subjects who received BDP alone showed subclinical (i.e., by laboratory tests alone) evidence of adrenal suppression in approximately half of the subjects who completed to the end of the study. However, all subjects remained at least partially responsive to exogenous ACTH.

5.5.4.5 Infectious Adverse Events

In this study, infections were to be reported as AEs and result in the discontinuation of study drug. Infections were reported in nine subjects (4 in the BDP group and 5 in the BDP plus prednisone group): One subject developed C. difficile colitis after 6 days on BDP. There were 8 other subjects withdrawn from study because of infection, 3 with bacteremia, 3 with pneumonia, and 2 with oropharyngeal infection (Table 5-20). All infectious disease events resulting in early termination of study drug were unremarkable in the context of this highly immunosuppressed patient population, and none were judged to be related to study drug. Although these AEs were not classified as "serious" or "non-serious" at the time of reporting, the majority, if not all of the infections were either

bacteremias or fungal infections, and would therefore, probably have met one of the regulatory criteria for a SAE.

Screening oropharyngeal and stool cultures were done at baseline and through the study. Throat cultures were more frequently positive in subjects receiving prednisone and BDP in comparison to BDP alone but there were no clinically meaningful differences between these groups in the frequency of positive stool cultures across time.

Table 5-20. Infectious Disease Events by Subject (Study 615)

UPN	Previous Prednisone Use	Study Day of Adverse Event	Description of Event
6732	No	12	*K. pneumoniae/A. calcoaceticus* bacteremia
6814	No	21	*Corynebacterium* bacteremia
7185	No	16	*Rhizopus* sinusitis
7035	No	6	*Clostridium difficile* infection after 5 days of treatment
6643	Yes	7	Herpes simplex stomatitis
6824	Yes	12	CMV pneumonia
7590	Yes	14	*S. epidermidis* bacteremia
7191	Yes	14	Pulmonary aspergillosis
6807	Yes	19	Pulmonary aspergillosis

5.5.5 Clinical Laboratory Evaluations (Study 615)

Because of the life-threatening nature of their illness, laboratory evaluations were performed frequently in study participants as part of their normal care and monitoring. Values were reviewed by the attending physician as they became available. Although laboratory abnormalities were frequent, they were reported as AEs only if they were believed by the investigator to be related to the study drug. Detailed analysis of these data was not performed.

5.6 Study 1500

5.6.1 Study Design (Study 1500)

Study 1500 ("Oral Beclomethasone Dipropionate Capsules for Treatment of Patients with Intestinal Graft-versus-Host Disease: Compassionate Use in Patients with Contraindications to High-Dose Immunosuppressive Therapy") enrolled subjects for whom GVHD was a complication of hematopoietic cell transplantation that had been carried out for malignancy or a pre-malignant condition and for whom corticosteroid use was contraindicated. Reasons for contraindication may have included severe myopathy and weakness, vertebral compression fractures, serious fungal infections, cushingoid manifestations, hyperglycemia and psychosis.

Subjects received 8 mg/day of BDP in four divided doses for 28 days. A second 28-day cycle of BDP treatment was permitted.

5.6.2 Subject Disposition (Study 1500)

Sixteen subjects received investigational product and were included in the safety analysis set. Eight of these received a second 28-day cycle of BDP.

None of the reported AEs resulted in the early discontinuation of study drug or withdrawal from study.

5.6.3 Extent of Exposure (Study 1500)

Exposure is summarized in Table 5-21.

Table 5-21. Summary of Study Drug Administration in Study 1500 (Safety Population)

	Overall	
No. subjects enrolled[a]	16	
Status of initial 28-day dosing period		
Started initial dosing period	16	100%
Completed initial dosing period as planned	16	100%
Status of second 28-day dosing period		
Started extended dosing period	8	33%
Completed extended dosing period as planned	8	33%
Duration of treatment[b] (days)		
n	16	
Mean (± SD)	42.9 (± 14.40)	
Median	42.0	
Range	29 to 58	
Mean total daily dose[b] (mg/day)		
n	16	
Mean (± SD)	8.0 (± 0)	
Median	8.0	
Range	8.0 to 8.0	
Total cumulative dose[b] (mg)		
n	16	
Mean (± SD)	343.5 (± 115.21)	
Median	340.0	
Range	232.0 to 464.0	

[a] Sixteen subjects were enrolled on protocol 1500 at least once. One subject was enrolled on two separate occasions. For purposes of this analysis, the study drug administration data for the second enrollment period are excluded for this subject.

[b] Includes the initial and extended 28-day dosing periods.

5.6.4 Adverse Events (Study 1500)

5.6.4.1 All Adverse Events

All subjects enrolled reported at least one AE during the first or second or both 28-day BDP treatment periods. Ten of the 16 subjects (62.5%) experienced one or more AEs

classified under the system organ class "general disorders and administration site conditions." The other system organ classes with incidence of 5 or more subjects included "infections and infestations" (n = 6, 37.5%), "GI disorders" (n = 5, 31.3%), "musculoskeletal and connective tissue disorders" (n = 5, 31.3%), and "investigations" (n = 5, 31.3%).

The most frequently reported preferred term was pyrexia, which occurred in 4 of the 16 subjects (25.0%). All other preferred terms reported during this study had an incidence of 2 or fewer subjects.

The majority of the AEs reported were considered mild to moderate in severity. One female subject (ID 1500-01-17) of 52 years reported severe anxiety that started 13 days after the initiation of BDP treatment. The event persisted for 15 days until resolution of the event on study day 27.

5.6.4.2 Serious Adverse Events

One SAE was reported during the study: Subject ID 1500-01-07, male subject 13 years of age with chronic myelogenous leukemia in chronic phase, developed abdominal cramps, low grade temperature, and loose stools that resulted in hospital readmission for flare of GVHD.

5.6.4.3 Deaths

There were no deaths on study.

5.6.5 Clinical Laboratory Evaluations (Study 1500)

There were no laboratory tests required in the protocol. However, multiple laboratory tests that are part of post-transplant care were obtained for each subject.

5.7 Study ENT 00-01 (Clinical Pharmacology Study in Healthy Volunteers)

5.7.1 Study Design (Study ENT 00-01)

Study ENT 00-01 was entitled "Bioavailability of Beclomethasone Dipropionate from Immediate Release and Enteric Coated Tablets and the Effect of Food." All subjects enrolled were healthy volunteers who were assigned to one of the following groups:

- 6 x 1 mg BDP IR tablets administered under fasting conditions
- 6 x 1 mg BDP EC tablets administered under fasting conditions
- 3 x 1 mg BDP IR tablets and 3 x 1 mg BDP EC tablets administered under fasting conditions
- 3 x 1 mg BDP IR tablets and 3 x 1 mg BDP EC tablets administered after a high fat/high calorie meal.

5.7.2 Subject Disposition (Study ENT 00-01)

Ten of the 12 subjects completed dosing. Two subjects withdrew for personal reasons.

5.7.3 Concomitant Medications (Study ENT 00-01)

Only one subject (no. 6) received a concomitant medication: ibuprofen was administered for abdominal cramping secondary to dysmenorrhea.

5.7.4 Adverse Events (Study ENT 00-01)

5.7.4.1 All Adverse Events

Seven of the twelve patients that completed dosing experienced an AE for a total of fifteen AEs. The most prevalent AE was headache (5). Additional AEs included nausea (2), dry mouth (2), dry eyes (2), itchy eyes (1), dizziness (1), abdominal cramping (1) and watery eyes (1). All AEs were considered mild in severity and were of short duration.

5.7.4.2 Serious Adverse Events

No SAEs were reported.

5.7.4.3 Deaths

There were no deaths.

5.8 Study ENT 05-BA (Clinical Pharmacology Study in Healthy Volunteers)

5.8.1 Study Design (Study ENT 05-BA)

Study ENT 05-BA was entitled, "An Open-Label, Randomized, Crossover Bioavailability Study of Beclomethasone Dipropionate in Healthy Volunteers." All subjects enrolled were healthy volunteers who were assigned to one of the following three groups:

- Single dose of BDP administered as 6 x 1mg BDP IR tablets

- Single dose of BDP administered as 6 x 1mg BDP EC tablets
- Single dose of BDP (6 mg) administered orally as a liquid suspension

5.8.2 Subject Disposition (Study ENT 05-BA)

All 12 subjects completed all three dosing periods.

5.8.3 Concomitant Medications (Study ENT 05-BA)

A total of 13 concomitant medications were reported for this study, with one or more concomitant medications reported for 8 of the 12 subjects (67%). Tylenol was taken for headache relief in six subjects (F-2, F-3, F-4, F-6, M-4, and M-5). Subject F-3 also took Benadryl, Sudafed, and Tylenol Sinus for an upper respiratory infection and Zithromax for acute bronchitis. Subject F-5 took Tylenol for menstrual cramps. F-6 took Excedrin Migraine for a headache and M-1 took amoxicillin for nasal congestion.

5.8.4 Adverse Events (Study ENT 05-BA)

5.8.4.1 All Adverse Events

A total of 47 AEs were reported, with one or more AEs reported for 9 of the 12 subjects (75% of the study population). All AEs were mild or moderate in severity. There were no AEs classified as probably or definitely related to study treatment. Eleven AEs related (possibly) to study treatment were reported in 6 subjects. One subject, F-2, had two instances of possibly related headaches of mild (Grade 1) and moderate (Grade 2) severity commencing on the first day of immediate release and suspension treatment, respectively. Both events resolved after one day. Subject F-3 experienced a Grade 2 headache on the day suspension therapy was initiated, and it was resolved the next day. Subject F-4 reported a Grade 1 headache on the day of initiating suspension therapy. This event was later upgraded to a Grade 2 headache, and resolved the next day. Subject F-5 had two instances of loose stools, both Grade 1, shortly after initiating suspension and enteric-coating therapy, respectively, and both resolved the next day. Subject M-2 experienced Grade 2 insomnia on the day of IR therapy initiation, and it resolved 2 days later. Finally, subject M-4 experienced a Grade 1 headache on the day of initiating suspension therapy, which was upgraded to Grade 2 that same day and lasted for 2 days. Subject M-4 also experienced Grade 2 dyspepsia on the day of IR therapy initiation, which resolved later that same day.

5.8.4.2 Serious Adverse Events

No SAEs were reported.

5.8.4.3 Deaths

There were no deaths.

5.9 Study ENT 01-04 (Crohn's Disease)

5.9.1 Study Design (Study ENT 01-04)

Study ENT 01-04 was entitled, "Beclomethasone 17, 21-dipropionate (BDP) in Crohn's Disease Patients: A Randomized, Placebo-Controlled, Phase 2, Dose-Response Study." All subjects enrolled were Crohn's patients who were assigned to one of the following groups:

1. Low-dose group patients received one 1 mg BDP immediate release (IR) tablet and one 1 mg BDP enteric-coated (EC) tablet b.i.d. (twice-daily) (4 mg/day).
2. High-dose group patients received two 1 mg BDP IR tablets plus two 1 mg BDP EC tablets q.i.d. (four-times-daily) (16 mg/day).
3. Middle-dose group received one 1 mg BDP IR tablet and one 1 mg BDP EC tablet q.i.d. (8 mg/day).
4. Placebo-group patients received one placebo IR tablet q.i.d. and one placebo EC tablet q.i.d., matching the dosing regimen of the middle-dose group.

Patients in only the 8 mg/day (middle-dose) group were double-blinded. Those in the 4 mg/day (low-dose) and 16 mg/day (high-dose) groups were single-blinded. The study was conducted at three centers in the U.S. Forty-eight patients were planned to be enrolled per protocol. The sponsor halted the study because of slow enrollment and changed priorities. At the time of study cessation, four patients had been enrolled. Of the four patients who were actually enrolled, 1 patient received high dose BDP, 2 received low dose BDP, and 1 received placebo.

5.9.2 Subject Disposition (Study ENT 01-04)

In study ENT 01-04, safety data are available on the three subjects who completed the study: one who received BDP 16 mg/day, one who received BDP 4 mg/day, and one who

received placebo. One subject was randomized in error, discontinued on day 14 and did not return for follow up.

Only one AE was reported that was judged by the investigator as possibly related to study drug: thickening of the tongue (subject 001-01) who received BDP 16 mg/day.

No deaths or serious or significant AEs were reported.

This study was discontinued because of lack of resources.

5.10 Special Populations

5.10.1 Pediatric Experience

Only 16 subjects under the age of 18 received BDP, which is not a large enough sample to draw any meaningful conclusions about the pediatric age group. One 6-year-old child was unable to swallow the tablets sand could therefore not be treated.

5.10.2 Geriatric Experience

The experience in subjects over age 65 was also too small to draw meaningful conclusions; however, no differences were seen in this group as compared to the overall population. It is notable that for the majority of the development program, myeloablative transplants were the only transplant procedure being performed, a procedure rarely used in geriatric populations. With increasing use of non-myeloablative transplants, more patients in this age group are now being treated (reference personal communications, GB McDonald, Center for International Bone and Marrow Transplant Research website).

6. NONCLINICAL

6.1 Introduction

No new nonclinical pharmacology, pharmacokinetic, toxicology, or safety studies have been performed by DOR on BDP in support of its use in the treatment of acute GI GVHD. At both the end-of-phase 2 meeting on July 12, 2004 and the pre-IND (nonclinical) meeting on September 1, 1998, the Agency agreed that a comprehensive review of the literature would be acceptable for fulfilling the requirements of the nonclinical pharmacology and toxicology sections of the NDA. The safety profile of BDP is well-established due to its long history of clinical use, and there is significant pharmacology, pharmacokinetic, and safety information available in the published literature about BDP as well as glucocorticoids in general.

6.2 Pharmacology/Pharmacokinetic Overview

The anti-inflammatory and immunosuppressive effects of BDP and its metabolite, 17-beclomethasone mono-propionate (17-BMP), are considered to be its primary pharmacodynamic mode of action for the treatment of GI GVHD. It cannot be readily determined in man, which of the known mechanisms of action of glucocorticoids is operating when BDP is dosed orally, but the in vitro studies of Naumann et al indicate that 17-BMP is acting by both genomic and non-genomic mechanisms (Naumann et al, 2006).

The anti-inflammatory activity of BDP results from both its genomic effects (repression of transcription factors leading to reduced synthesis of pro-inflammatory cytokines, inhibition of expression of adhesion molecules, and apoptosis of T cells), as well as potent non-genomic effects (immune suppression, apoptosis of T cells).

BDP seems to be devoid of any non-corticosteroid activity. General pharmacology studies have shown that BDP has no anti-convulsive activity, analgesic activity, or renal and cardiovascular activity even at high doses (Ohguro et al, 1970).

The major degradation pathway of BDP in human plasma has been proposed to be from BDP to 17-BMP and 21-BMP (with interconversion between these 2 metabolites), and

then to beclomethasone (BOH) (Foe et al, 1998). The BDP metabolite 17-BMP is ~25 times more potent than BDP itself and has glucocorticoid receptor binding affinity 13 times that of dexamethasone (Wurthwein et al, 1992; Wurthwein and Rohdewald, 1990). BDP and BOH bind to the glucocorticoid receptor with approximately half and three-fourths, respectively, of the binding affinity of dexamethasone, and 21-BMP has no apparent affinity for the receptor. In addition to having greater binding affinity to glucocorticoid receptors, 17-BMP has higher apparent variability than the other metabolites.

Table 6-1. Relative Binding Affinities of Beclomethasone Compounds at Glucocorticoid Receptors from Human Lung Cytosol

Pure corticosteroid	Relative Binding Affinity at Glucocorticoid Receptors
Dexamethasone	100
BDP	43
17-BMP	1345
21-BMP	0.9
BOH	76

BDP = oral beclomethasone dipropionate; BMP = beclomethasone mono-propionate;
BOH = beclomethasone

Unchanged BDP was not detected in the plasma of rats following oral administration of ^{3}H-BDP (Chanoine et al, 1991). The primary metabolite (17-BMP) was found in the plasma of the rats, suggesting rapid transformation of parent to metabolite in gut, plasma, or both. Intravenous administration of ^{3}H -BDP resulted in the brief appearance of unchanged BDP with a half-life of 3-4 minutes, and the immediate appearance of high concentrations of 17-BMP suggesting rapid transformation of the parent to the metabolite within plasma. Hydrolysis of BDP to 17-BMP is also likely to occur rapidly in the intestines, with further hydrolysis from 17-BMP to BOH at a very slow rate. The half-lives of BDP and 17-BMP in simulated intestinal fluid were 2.1 minutes and 12 hours, respectively (Wurthwein and Rohdewald, 1990).

The oral bioavailability of BDP must be estimated based on either the area under the time-concentration curve for 17-BMP as the sum of measured BDP, 17-BMP and BOH

values. The total oral bioavailability of 17-BMP in 12 human subjects, estimated as the geometric mean ration for the dose normalized (AUC_{oral}/AUC_{iv}) 100 was 41% (90% confidence interval, 31-54%). Bioavailability of oral BDP was calculated to be 21% when the method of summing areas under time-concentration curves for BDP and its metabolites was used.

The predominant route of excretion of BDP radioactivity was in feces, regardless of the route of administration. The presence of radioactivity in the bile of rats indicates that BDP and/or its metabolites enter enterohepatic recirculation. The percentage of radioactivity excreted in urine was less than 17% in all studies, suggesting that the liver is the primary organ of clearance from plasma.

Hydrolysis of BDP to 17-BMP may occur in both intestinal fluid or in mucosal epithelial cells (Levine et al, 1987; Wurthwein, 1990). The BDP metabolite 17-BMP is ~25 times more potent than BDP itself and has glucocorticoid receptor binding affinity 13 times that of dexamethasone (Wurthwein et al, 1992; Wurthwein, 1990). Evidence for a prolonged residence time for orally delivered BDP and 17-BMP can be seen in the human volunteer studies of Levine et al and Daley-Yates et al, specifically persistence over 8 hours of BDP and 17-BMP in ileostomy effluent and a longer elimination half-life of 17-BMP after oral dosing, compared to intravenous dosing (Levine et al, 1987; Daley-Yates et al, 2001).

Administration of oral BDP to healthy volunteers in a gelatin capsule for delivery to the stomach resulted in only 13% of the administered dose being recovered in ileostomy effluent as BDP or 17-BMP. Formulating BDP in an enteric-coated capsule that dissolved at alkaline pH resulted in a higher recovery of 43% of the administered dose in ileostomy effluent (Levine et al, 1987).

In summary, the combination of avid glucocorticoid receptor binding affinity, high tissue concentration, prolonged residence time in the GI mucosa, and enterohepatic circulation of 17-BMP suggest that oral BDP provides for significant topical activity in the mucosa of the GI tract. In addition, a relatively low absolute oral bioavailability of 17-BMP after DBP administration, estimated at 21-41%, with high clearance, may limit systemic

corticosteroid activity (Daley-Yates et al, 2001). Finally, formulation of BDP in an enteric-coated capsule resulted in a higher rate of delivery to the small intestine and lower GI tract compared to an immediate release formulation.

6.3 Toxicology Overview

The published literature describes single- and repeated-dose toxicity studies of BDP in mice, rats, rabbits, and dogs; and reproductive toxicity studies of BDP in mice, rats, rabbits, and monkeys. The results of these studies indicate that the toxicity profile of BDP is defined by, and is thus a consequence of, the well-known pharmacology of corticosteroids. In addition to the published literature, additional information about the nonclinical safety profile of BDP is available from the product labeling of the marketed forms of BDP (e.g., Beconase AQ and QVAR). The toxicity of BDP, like most of the corticosteroids, is related to its metabolic and endocrine effects, as well as its anti-inflammatory and immunosuppressant actions.

Single-dose studies in mice, rats, rabbits, and dogs indicate low toxicity when BDP is administered orally, subcutaneously, intraperitoneally, and by inhalation. There were no mortalities in mice and rats with oral doses of 3000 and 3750 mg/kg, respectively.

In repeated-dose studies of oral, subcutaneous, topical, and inhaled BDP in rats, rabbits, and dogs of up to 1 year in length, toxicities included reduction in body weight gains, cushingoid syndrome in dogs, decreased lymphocytes, decreased weight and atrophy of the thymus, spleen, adrenals, low blood cortisol, and hepatic glycogen deposition and fatty liver changes.

The genotoxicity of BDP has been evaluated in *in vitro* studies in bacterial cells and mammalian Chinese Hamster ovary (CHO) cells and in the mouse micronucleus test in vivo. Genotoxicity studies were negative.

The carcinogenicity of BDP was assessed in rats exposed to BDP for 95 weeks: for 13 weeks by inhalation doses of up to 0.4 mg/kg; and for the remaining 82 weeks by combined oral and inhalation doses of up to 2.4 mg/kg. There was no evidence of

carcinogenicity in rats given inhaled BDP for 13 weeks followed by combined oral and inhaled doses of up to 2.4 mg/kg for a total of 82 weeks.

Reproductive toxicity studies were conducted in mice, rats, rabbits, dogs and monkeys with oral, subcutaneous, and inhaled BDP. Fetal mortality was increased, and fetal growth decreased. Cleft palate and delays in skeletal ossification were noted in newborns.

In rats, beclomethasone dipropionate caused decreased conception rates at an oral dose of 16 mg/kg/day. Impairment of fertility, as evidence by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route at a dose of 0.5 mg/kg/day. reproductive effects of BDP did not affect the second generation.

6.4 Conclusions

The pharmacology of BDP and corticosteroids in general is well understood, as is its toxicity profile from a large amount of animal and human data. The safety profile of BDP requires that its clinical use be guided by the risk/benefit assessment for the disease being treated. The non-clinical safety data for BDP does not conflict with the proposed clinical use of oral BDP for acute GI GVHD.

7. RISK/BENEFIT ASSESSMENT

The proposed indication for BDP is for the treatment of GVHD involving the GI tract in conjunction with an induction course of high-dose prednisone or prednisolone. In 4 studies in subjects with GI GVHD who previously underwent allogeneic HCT, treatment with BDP demonstrated a consistent safety profile and (while not achieving statistical significance on the primary endpoint in the pivotal trial) demonstrated clinical efficacy based on the following observations:

1. A clinically meaningful reduction in the frequency of GVHD treatment failure was observed with BDP treatment following a rapid tapering of prednisone dosage in 2 randomized trials where treatment failure was based on clinically relevant measures of either immunosuppressive use or caloric intake.
    - Treatment failure was defined as the requirement for increased doses of immunosuppressive drugs beyond those specified in the protocol for Study ENT 00-02.
    - Treatment failure was defined as the inability to eat ≥ 70% of a subject's estimated caloric requirement in Study 875.
2. A reduction in exposure to high-dose corticosteroids was observed with BDP treatment.
3. A consistent survival advantage was observed with BDP treatment in the placebo-controlled studies ENT 00-02 and 875. This survival advantage may be due to lower rates of mortality from opportunistic infections and relapse, both of which are associated with high dose corticosteroid administration.

The survival advantage described above was not accompanied by any safety findings that would either limit the use of the investigational product in the intended population or worsen quality of life in patients to whom it was administered. Although prior to this development program, high-dose corticosteroids were considered the standard of care, the data summarized above demonstrate that BDP in combination with a short induction course of corticosteroids addresses an unmet medical need by reducing the morbidity and mortality associated with existing standard of care treatment for acute GI GVHD while preserving anti-GVHD efficacy (i.e., GVL effect).

Given the limited number of centers in the United States performing allogeneic HCT, the publication of the results of the pivotal BDP trial in the medical journal *Blood* (Hockenbery et al, 2007), and the survival advantage observed, it is likely that institutional review boards at appropriate centers would not approve another placebo-controlled trial in this indication. It should also be noted that while BDP is not yet available commercially, there is a practice in some centers performing allogeneic HCT to treat patients with GI GVHD using unregulated beclomethasone dipropionate compounded in corn oil for the treatment of GI GVHD. The combination of these events is expected to lead to an increase in unregulated compounding and off-label use of beclomethasone dipropionate. The results of the pivotal, phase 3 study (Study ENT 00-02) are summarized in Table 7-1.

Table 7-1. Summary of Endpoints Relating to Efficacy and Survival in Subjects Randomized to BDP Versus Placebo in the Phase 3 Pivotal Trial ENT 00-02

Efficacy Endpoints	Survival Endpoints
GVHD-treatment failure by Study Day 50: ▪ Time to event analysis (primary endpoint): HR 0.63; p = 0.1177 ▪ Comparison of proportions: 31% BDP versus 48% placebo; p = 0.05	Mortality at transplant day 200: ▪ HR 0.33; p = 0.0294
GVHD-treatment failure by Study Day 80: ▪ Time to event analysis: HR 0.54; p = 0.0226 ▪ Comparison of proportions: 39% BDP versus 65% placebo; p = 0.003	Mortality 1 year after randomization: ▪ HR 0.54; p = 0.0431

BDP = oral beclomethasone dipropionate; GVHD = graft-versus-host disease; HR = hazard ratio

In summary, no investigational products are currently approved by the FDA for the treatment of established GI GVHD in recipients of allogeneic HCTs. Given this lack of comparators and the favorable benefit-to-risk profile of BDP compared with that of the current standard of care, BDP represents a clinically meaningful advance in the treatment of GI GVHD.

Taken together, the data provided and the clinical scenario described above support the approval of BDP in the treatment of GI GVHD in conjunction with an induction course of high-dose corticosteroids.

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9. ATTACHMENTS

Attachment 1 – Hockenbery DM, Cruickshank S, Rodell TC, et al. A randomized, placebo-controlled trial of oral beclomethasone dipropionate as a prednisone-sparing therapy for gastrointestinal graft-versus-host disease. *Blood*. In press. Prepublished online as a *Blood* First Edition Paper January 23, 2007.

Attachment 2 – McDonald GB, Bouvier M, Hockenbery DM, et al. Oral beclomethasone dipropionate for treatment of intestinal graft-versus-host disease: a randomized controlled trial. *Gastroenterology.* 1998;115:28-35.

Attachment 3 – Summary of Clinical Trials

Attachment 4 – Baehr P, Levine D, Bouvier M, Hockenbery D, et al. Oral beclomethasone dipropionate for treatment of human intestinal graft-versus-host disease. *Transplantation.* 1995;60:1231-1238.