concerns, and there was a hint of efficacy in the dose that we chose. The dose of 8 milligrams a day came from our experience with using this medicine in inflammatory bowel disease. We took the same dose to graft-versus-host disease. It appeared effective, and we carried this dose forward through the two randomized trials.

Study 815 was completed with help from the FDA's Orphan Drug Products Division. The inclusion criteria in this protocol included allogeneic transplant, signs and symptoms of GVH, that is: anorexia, nausea, vomiting, or diarrhea. All patients had to have biopsy-proven GVH of the mucosa obtained at endoscopy.

They also had to have absence of infection at baseline, that is, stool cultures and endoscopic biopsy specimens had to be negative for an infectious process.

We excluded patients with severe skin or liver GVH or patients with high-volume diarrhea. The normal diarrheal volume in Western countries is about 200 milliliters a day. One liter is a lot.

We excluded patients because these are indications of much more severe graft-versus-host

disease for which a strategy for minimizing prednisone seemed inappropriate. We also excluded people who had received steroids within 30 days.

Here is the schema that we followed. It is very similar in the two trials. There was a screening period, that is: endoscopy, symptom assessment, the histology report had to be back, and the 24-hour shell-vial report for CMV had to come back negative.

Patients were then randomized one to one to either an induction course of prednisone plus BDP or an induction course of prednisone plus placebo for 10 days.

Now, this strategy of an induction course of prednisone was stolen, if you will, from pulmonology. When you have an acute inflammatory asthma attack, you often take prednisone to gain control of the disease and then maintenance with a beclomathasone inhaler, the same process for gut GVH.

In patients who are doing well at 10 days, prednisone was very rapidly tapered in both groups, and so for an additional 20 days BDP or placebo was given, with a 10-day follow-on period to assess durability of response. All during this time, however, the GVH

 

prophylaxis that had been begun after transplant was continued.

Just to compare, these are the standard dosing schedules of prednisone used in the standard of care. This is the dosing exposure of prednisone in this protocol. In patients who responded to this and whose GVH was controlled by BDP, we are avoiding a very large dose of prednisone exposure.

The primary endpoint of this study was GVH treatment failure through study day 30. We had a hard endpoint in this study. We had research nutritionist working seven days a week who could calculate eating as a percentage of caloric needs.

We defined success and we defined failure as eating less than 70 percent of one's caloric needs, or if the attending physician thought that the patient required additional immunosuppressive drugs.

The secondary endpoint was GVHD treatment failure through study day 40. We recorded adverse events related to the study drug, and we were particularly interested in infectious complications.

One of our concerns was this is such a highly

potent topical steroid we would see more infections rather than less, and thus this was an important safety endpoint.

These are the results of the primary analysis: placebo arm, 59 percent failures; BDP arm, 29 percent failures.

We have recently done a time-to-event analysis as that was the specified analysis for the pivotal trial, and this is the result of that analysis with a P value of .03.

Note that in the briefing document there is an erroneous time-to-event analysis. These are the original data prepared by Dr. Ted Gooley who was the original statistician for Protocol 875.

Here is the secondary efficacy endpoint, the durability of treatment by study day 40, 10 days after discontinuation of study drug, 83 percent in placebo had failed compared to 48 percent in BDP arm. Here are the safety outcomes related to infection, roughly balanced between the two groups.

We concluded that oral BDP significantly lowered treatment failure rates at the end of the 30-

day treatment and 10-day followup. There was a greater proportion of patients able to eat 70 percent of their caloric requirements.

Now, this is clinically meaningful. This means that patients can get out of the hospital, can get off TPN, can go home and they can eat and maintain nutrition and can maintain oral intake and hydration.

There were no significant safety issues, that is, specifically no difference in the frequency of infection, and this provided I think a good platform from which to design the pivotal trial.

The pivotal trial had similar inclusion and exclusion criteria with regard to graft-versus-host disease. We wanted to capture the exact same kind of GVH that we had captured in the Phase II trial.

We discovered, however, that caloric intake was not a feasible endpoint in a multicenter trial. Many centers did not have research nutritionists who could calculate caloric needs.

The advantage of a very hard endpoint, we had to abandon, but I think we had a very good endpoint in that relied on very experienced transplant oncologists

to make a clinical decision as to whether their patients needed additional immunosuppressive therapy. GVHD treatment failure was the need for more therapy for graft-versus-host disease.

We thought that a longer treatment period might improve the efficacy, and we arbitrarily chose a 50-day treatment period. Practical considerations ruled here.

GVH diagnosis was somewhere around day 30. If we added 50 days to that, we would get to transplant day 80, and that's the usual landmark by which patients return home. We didn't want to delay patients in each of the centers for longer than necessary, and that's why day 50 was chosen.

In meetings with the FDA's Division of Gastrointestinal and Coagulation Drug Products, it was pointed out to us that we needed a hard, durable endpoint, that is, we were told that if the patient started vomiting and had diarrhea within days of stopping medicine, they didn't think that would be an approvable drug.

They wanted a robust, durable endpoint

demonstrating that the treatment effect could be maintained, and so we put into the study a 30-day durability endpoint, 30 days off of study drug. This protocol was reviewed with the FDA.

You have seen this schema. This is the same scheme as for 875 with two exceptions, screening period, randomization, prednisone induction, followed by a taper in patients who are doing well.

The treatment period after the prednisone taper started was 40 days for a total of 50 days treatment period. Again, the 30-day followup period off of study medicine, again, the GVH prophylaxis continued from before to through the transplant.

The primary endpoint was a timed GVH treatment failure through study day 50, that is, unresponsive or recurrent GVH requiring additional immunosuppressive drugs.

The immunosuppressive drugs chosen were almost always prednisone. This varied slightly from center to center. Each transplant oncologist in each center has their own favorite recipes, but predominantly and almost universally prednisone.

Secondary endpoints included GVHD treatment failure rates at the following days Karnofsky performance score, exposure to systemic corticosteroids.

The safety endpoints included survival at 200 days post-transplant, again, reflecting our concern that the treatment may lead to more infections and a worse outcome, and so this was a safety endpoint as originally designed. We looked at treatment-emergent adverse events and all laboratory values during treatment. In the original design, the planned sample size was 130 patients. Forty-nine GVH treatment failures were required to have an 80 percent power to detect a 55 percent reduction in the risk of GVHD treatment failure.

The randomization was stratified by study center, donor type, that is, HLA-matched sibling donors versus all others. Most of the all others were HLA-matched unrelated donors. In the use of topical corticosteroids, that is, skin creams containing corticosteroids at baseline, yes/no.

The statistical analysis plan was amended

prior to the database lock. The primary analysis would be stratified by donor type only. There were so few patients who were receiving topical corticosteroids, that this was not included.

The primary analysis for time-to-event endpoints was using the Kaplan-Meier method and a stratified log-rank test at the 5 percent significance level.

There are, as you well recognize from reading the briefing document, statistical issues with this trial. The overall false-positive error rate was spent on the primary endpoint whose P value was .118.

There was no adjustment to the significance levels. Retrospective adjustment of significant levels for an analysis of secondary endpoints is considered not meaningful once the results are known.

Given the clinical importance of the secondary endpoints in this study and the post-hoc survival analyses, we are reporting these results to aid your review of the data. These inferential results have not been adjusted for multiplicity.

Here are the patient characteristics of the

 

pivotal trial. Sixty-seven patients were randomized to placebo versus 62 to BDP. These are mainly young adults. There were some children in this trial as in the previous trial.

The diagnoses were fairly evenly matched. There were two imbalances between the two groups. Patients with hematologic malignancy who were at higher risk of relapse post-transplant comprised 65 percent of patients in the BDP versus 43 percent of patients in placebo.

Also non-myeloablative conditioning was given to 42 percent in BDP versus 22 percent in placebo. I should point out that non-myeloablative conditioning was at the time of these studies and even currently reserved for patients who were not eligible for myeloablative therapy by virtue of advanced age and comorbidities. In other words, these patients were sicker in general and older than our myeloablative patients.

Sixty-four and sixty-three percent were matched sibs. Bone marrow was the source of hematopoietic progenitor cells in a minority of patients. Peripheral blood stem cells had marched to

 

the fore by the time this study was done. Most patients were randomized from day 30 to 40.

My transplant oncology colleagues at the Hutchinson Center assigned on the basis of the literature the higher-risk versus the lower-risk underlying diseases by disease stage at the time of transplant.

The primary efficacy endpoint, the time to GVHD treatment failure through study day 50 is given here. There were 30 failures in the placebo arm versus 18 failures in the BDP arm.

The Kaplan-Meier estimates of study day 50 were 48 percent failures versus 31 percent failures. Giving a hazard ratio of 0.63, that is a 37 percent reduction in the risk of GVHD treatment failure. The stratified log-rank test was .118 and there was no interaction with the primary stratification variable, that is, the donor source.

This is the Kaplan-Meier plot of that exact same data. Placebo given here, BDP here. I'm going to come back to this because I want you to note that the P value and the hazard ratio is largely driven by early

 

treatment failures, that is, there were more treatment failures in the BDP arm while on prednisone-induction therapy than in the placebo arm. I will return to this issue because it is what drives the P value.

The secondary efficacy endpoint, this is the one that the FDA requested as being the durability of treatment effect. That is study day 80: 39 failures in placebo, 22 failures in BDP.

The Kaplan-Meier estimate, 65 percent failure rate for placebo; a 39 percent failure rate for BDP; hazard ratio, .54; 46 percent reduction in the hazard of treatment failure; significant at the .02 level. Also, an interaction test with the strata of donor source was not significant.

This is the Kaplan-Meier plot of the day 80 time-to-treatment failure endpoint. I include the value for the day 50 endpoint to emphasize that these things are obviously linked. These are not independent variables. Again, this was the treatment period, this was the 30-day followup period.

We looked at cumulative corticosteroid doses in this graphic. On the vertical axis is the median

prednisone dose in milligram per kilogram by study day 50, placebo versus BDP. This is not statistically significant.

Included in these data are the treatment failures and the treatment successes. Similarly, at study day 80 placebo versus BDP, this lumps success and failure.

The systemic corticosteroid dose by day 50 outcomes, looking at cumulative dose here by treatment failure, this I think documents the obvious. People who were treatment failures have much more steroid exposures than people who were treatment successes. The average daily dose much higher in the failures than in the successes.

Coming back to the original expectations, I think we have demonstrated the BDP maintains GVHD in remission. That robust day 80 endpoint to me is very compelling evidence that we have done this.

In patients who are treatment successes, we clearly reduced prednisone exposure. The next question is, have we achieved any of the expected downstream effects of avoiding prednisone?

 

This is survival at transplant day 200. Seventy-six percent in the placebo arm, 92 percent in the BDP arm, significant at the .01 level. There was a significant interaction with the randomization strata of matched sibling versus others.

The causes of death: there were 16 deaths in the placebo arm, 5 deaths in the BDP arm. The proximate causes of death was relapse of the underlying malignancy, infection, and some patients with graft-versus-host disease.

Now, there is a problem here with the day 200 endpoint. Some of the patients were randomized, and I'll show you this data, relatively close to the day 200 time period, which is the hallmark for transplant morbidity related to the early events of transplant. That data is shown here.

This is the percentage of patients and the time from transplant to the day of randomization. I showed you earlier the median is day 35 to day 37, but a small number of patients have GVH that appeared later and were randomized later, close to the day 200.

In discussion with the Agency, we were asked

to provide a time from randomization analysis, and I will show you that next. Here is survival one year post-randomization, not post-transplant but post-randomization.

The BDP arm here, the placebo arm here, a 46 percent reduction in the risk of mortality one year following randomization, significant, and a suggestive interaction with the strata.

Twenty-eight patients died in the placebo arm, 18 died in the BDP arm. Just as at day 200, relapse and infection were the dominant causes of death.

This is overall survival to the current, recent time. Notice that we have very good survival data out to, roughly, 18 months and there are a lot of sensored observations.

This plot was requested by the Agency, and therefore it is not event-driven; it is request-driven, if you will. There are relatively few events. We viewed this as a premature long-term survival analysis.

The causes of death: 32 died in the placebo arm, 27 in the BDP arm, relapse and infection the dominant causes of death. I would point out that these

late deaths, beyond one year following transplant, are largely unrelated to the problem of acute graft-versus-host disease.

Acute graft-versus-host disease, our desire was to keep more people alive one year after transplant. We achieved that. These late effects reflect the biology of the underlying disease and they reflect chronic graft-versus-host disease and its immunosuppression.

Now, we have done additional supplemental analyses driven by the data and the interaction signals that we got from the analysis. We wanted to assess these early treatment failures, which profoundly affect the primary endpoint.

We wanted to look at the impact of baseline factors on the BDP effect, that is, survival at one year. We were pleasantly surprised to see these survival data. This was expected.

We thought that we would achieve better outcomes, but we wanted to be sure that confounding variables, that is, the other things that might have contributed to mortality weren't responsible for this

survival effect.

We did subgroup analyses looking at conditioning regimen and donor type driven by the signs of interaction of the BDP effect to conditioning and donor type.

I want to display to you the BDP effect on survival from the earlier randomized trial versus the pivotal trial as a qualitative comparison between the two. This is not a meta-analysis, this is showing consistency of survival effect.

First, the treatment failure. Here is the reason for treatment failure in the first 10 days in placebo versus BDP, 8 patients BDP, 4 patients placebo, most of them for either persistent or recurrent or worse GI symptoms. In the judgment of the transplant-attending physician at each of the sites, this judgment was made that additional prednisone was needed.

Here is an analysis of the impact of baseline factors on BDP on mortality at one year post-randomization. These are data that I have shown you previously, the effect of BDP on mortality with a hazard ratio of .54.

 

One by one we added covariates into the model to get these sorts of data. Here is BDP with a covariate higher risk of relapse, essentially not increasing and not affecting the hazard ratio.

Here is BDP with the covariate non-myeloablative conditioning therapy -- not affecting the hazard ratio, not increasing the hazard ratio, that is, the BDP effect was still apparent.

Age; gender; bone marrow as a cell source as opposed to peripheral blood stem cells; the center, many of the patients, 40-some, 46 percent were done at the Hutchinson Center and multiple other centers contributed the rest; and the Karnofsky score.

Now, there was a significant interaction with the treatment assignment for non-myeloablative conditioning therapy, so we drilled down into this to see what that data looked like.

This is an analysis of the interaction between treatment of conditioning regimen, conditioning regimen's here, non-myeloablative versus myeloablative; proportion alive, 73 percent survival in the BDP group; 20 percent survival in the placebo group. I interpret

this as suggesting that in the placebo arm this sicker group of patients were profoundly affected by higher prednisone exposure.

In the myeloablative in terms of the survival endpoint, there was no difference overall stratified by conditioning regimen, 71 versus 58 percent.

This is the second interaction between donor type and treatment effect. You recall that the day 200 analysis of survival showed a significant interaction, and this was close enough to warrant this deeper analysis.

Donor type: unrelated and HLA mismatched here, matched siblings here. Sixty-five percent survival in BDP, 38 percent survival. In the placebo, there was an effect in matched siblings, but it was smaller. The overall, 71 versus 58 stratified by donor type.

Here is the slide demonstrating the consistency between the two randomized trials. This is not a pooled analysis. Mortality at transplant day 200, the odds ratio in favor of BDP in the pivotal trial, .29; in the previous randomized trial, .34.

By one year post-randomization, .54; a .55

hazard ratio. That is, a 46 and 45 percent reduction in the risk of mortality one year after randomization; overall, .71 and .47. I call to your attention these long-term survivals. There is no power to detect a significant difference.

I am now going to turn to the Safety Database for the pivotal trial. The number of patients evaluable from a safety perspective is listed here. Here are the trials in patients with GVHD. Here are normal volunteers, 177 patients total.

The adverse events in the pivotal trial are listed here. I guess the take-home message is there is not much difference between BDP and placebo for treatment-related AEs, SAEs, treatment-related SAEs, discontinuation of study drug, or those who died on treatment or within 30 days of the last dose.

These are adverse events occurring in greater than 50 percent of patients in the BDP group with a frequency that was numerically higher than in the placebo group.

For evaluation of safety, 66 patients on placebo, 61 in BDP. One patient in each group never

 

received study drug, but they are included in the survival analysis on an intent-to-treat basis.

Of some note, fatigue, hypocalcemia, hypophosphatemia, and muscle cramps were marginally were common in the BDP group. But when we looked carefully at all of the laboratory abnormalities related to calcium phosphate and the electrolytes that could lead to muscle cramps, there was no difference between the two groups.

The serious adverse events reported at greater than 5 percent frequency in either group: there were 44 of such in the placebo; 40 in the BDP. The most common were: underlying disease; fever; bacteremia; hypoxia, six in the placebo arm, none in the BDP arm; and nausea.

Adverse events possibly related to corticosteroid exposure or adrenal insufficiency, 66 versus 61: fatigue, hypertension, muscle cramps, cushingoid habitus, peripheral edema were marginally more common in the BDP arm. Note that cushingoid habitus was a relatively rare finding in either arm. We did HPA axis elevation. One safety concern about this drug, because it is an incomplete

 

glucocorticoid, it may suppress the adrenal axis. This is the biochemical evidence that indeed this topical steroid does have some adrenal axis suppression. A fairly large number of people had abnormal adrenal axis tests at baseline. At study day 50, 58 percent of people on placebo and 86 percent on BDP had abnormal tests.

Using a more modern, up-to-date version of what constitutes adrenal hyporesponsiveness, those data are 57 and 77 percent. I point out that 23 percent of the treatment successes in the BDP arm had normal adrenal responsiveness to ACTH .

We may wish to go into this, but I think the point is the amount of systemic metabolite of BDP does have some effect on the adrenal axis, but there is really no clinical consequences that we were able to see from this biochemical suppression.

Here are the infections by treatment arm. Number of patients with infectious AEs, 40 in the placebo, 31 in the BDP group. Fungal infections were notably more common in the placebo arm including 4 patients with deep fungal infections and none in the BDP

arm.

Viral infections, particularly cytomegalovirus and cytomegalovirus antigenemia were more common in the placebo arm, consistent with that slide that I showed you earlier about T-cell immune responses to antigens in people on prednisone.

Bacterial infections were, roughly, equal between the two groups. There was one case of nocardia in the placebo group and one case of MAI in the BDP group. We have also pulled out of the AE reporting what I call infection syndromes without specific organisms.

Respiratory infections were more common. Lung infiltrates presumably reflecting either bronchiolitis obliterans or an infectious pneumonia that occurred in seven patients on placebo and none in BDP.

Laboratory analysis revealed no meaningful differences in laboratory values between the treatment groups and no differences between groups in laboratory values associated with corticosteroid excess or deficiency, that is, electrolytes and glucose. The analyses showed virtually identical values between the two groups.

The summary of clinical trial results I will give you. In patients with GI graft-versus-host disease an induction course of prednisone plus oral BDP resulted in durable, clinically meaningful reductions in GVHD treatment failure.

In Study ENT 00-02, this was a 37 percent reduction in the risk treatment failure by study day 50 and a 46 percent reduction by study day 80. The previous randomized, placebo-controlled trial, 71 percent reduction in the risk of treatment failure by the end of the treatment period, 80 percent reduction by the end of the followup period.

The survival data shows that patients with GI GVHD randomized to BDP had meaningful reductions in mortality. In the pivotal trial, a 46 percent reduction in mortality by one year post-transplant.

This is the landmark for the end of the immunologic hostilities and all of the immunosuppression associated with GVHD. We consider this a highly relevant, clinically meaningful endpoint to the treatment of acute graft-versus-host disease.

Importantly, the BDP effect was not diminished

by any of the covariates. None of the competing causes of mortality affected the BDP impact on mortality at one year post-randomization.

Study 875 had a 45 percent reduction in mortality by one year post-transplant, with complete followup. These are remarkably similar to one another, and I think demonstrate the original hypothesis that lower exposure to prednisone would improve outcomes.

Safety in patients with GI GVHD randomized to BDP, the frequency adverse events was not notably different between placebo and BDP. There was biochemical but not clinical evidence of HPA axis suppression.

Finally, an analysis of the benefit/risk ratio, this was my original premise 16 years ago. I propose to you that I think it's come true. I think our data supports that BDP maintains GVHD in remission. There is clearly decreased prednisone exposure in patients who were not treatment failures. There were decreased prednisone adverse effects.

We did not specifically look at immune function, but the outcome data I think strongly suggests

 

that we have avoided much of the prednisone adverse event exposure. I think we have demonstrated better outcomes in terms of survival at one year post-randomization.

Oral BDP addresses an unmet medical need. The control of GVHD without protracted exposure to high-dose prednisone. The clinical benefit from control of GVHD, avoidance of prednisone exposure and improved survival were not accompanied by meaningful safety concerns.

I want to come back to avoidance of prednisone exposure. You know, it's not just the survival endpoint, what patients remember most about prednisone is how awful they feel on prednisone.

If one can avoid that, I view that as a substantial patient benefit. I think thus the risk-to-benefit ratio is strongly in favor of benefit to this very ill population of patients.

To reiterate the proposed indication, OrBec is indicated for the treatment of graft-versus-host disease involving the gastrointestinal tract in conjunction with an induction course of high-dose prednisone or

 

prednisolone.

I want to conclude maybe with a little bit of experiential disclosure here. I've been taking care of transplant patients for 30 years. The real tragedy is when someone develops this sort of graft-versus-host disease after a potentially curative procedure with underlying hematologic malignancy, and then dies not of the graft-versus-host disease but dies of the therapy. That is an absolute tragedy.

I propose to you that oral BDP really addresses this issue head on. We get better results in the treatment of this kind of graft-versus-host disease than with placebo.

Thank you.

CHAIRPERSON HUSSAIN: Thank you, Dr. McDonald.

Dr. Scher will start the FDA discussion.

FDA PRESENTATION

CLINICAL REVIEW (PowerPoint presentation is in progress.)

DR. SCHER: Good afternoon. I'm Dr. Nancy Scher. I shall present the FDA clinical review. I will discuss the two randomized trials, Study ENT 00-

 

02, which I will refer to as "02" and Study 875.

I shall mention the post-hoc efficacy endpoints and discuss clinical concerns about pooling efficacy data from the two trials. The FDA Statistical Reviewer, Dr. Sun-Mitchell, will then discuss the efficacy results and the statistical analysis. I shall return briefly to discuss the safety issue and summarize.

As you have heard OrBec is an oral corticosteroid, and we have heard the proposed indication. Study 02 was a multicenter, randomized, double-blind, placebo-controlled trial conducted from 2001 to 2005.

The primary efficacy endpoint was time-to-treatment failure through day 50. Secondary endpoints include the cumulative proportion of treatment failures by certain study dates. Safety endpoints included adverse events, mortality at day 200 post-transplant and hypothalamic-pituitary-adrenal," or HPA," axis function.

For Study 02 the populations were generally balanced for baseline demographics. The entry criteria were defined so that the study population

would be similar in manifestations of GI GVHD, but there was no attempt to limit or stratify prospectively for underlying hematologic diagnosis for relapse risk. From this point of view, the population was heterogeneous. Nearly half of the patients were from a single center. There was an imbalance for conditioning regimen between the two study arms. As you have heard, 42 percent of BDP patients received a non-myeloablative regimen compared with 22 percent of placebo patients. Clinical Trial 875 was a single-site, randomized, double-blind, placebo-controlled trial with an oral caloric primary endpoint. It was completed in 1996. Again, the population was heterogenous as far as underlying hematologic diagnoses. Demographics were fairly well-balanced. The next series of slides shows similarities and differences of design in patient populations for Trial 02 and 875. Study 02 required that patients have Grade II GI GVHD. The classification based on papers published in the literature in 1995 and 1998. Involvement of skin or liver could not be greater than

Grade II.

For Study 875, GI eligibility were similar, but the differences were that patients could have no liver GVHD and no skin GVHD greater than 50 percent involvement.

The allograft source varied in the two trials. Peripheral blood stem cells was the source in 90 percent of patients in 02, but only 20 percent of the patients in Study 875, reflecting changes in practice over nearly a decade separating the trials.

Similarly, there were differences in the percent of patients with non-myeloablative conditioning regimens as you have heard. Study 02 randomization was stratified as to center, allograft source, and topical steroids or not; 875 was stratified by baseline oral caloric intake.

Study drug daily dosing regimens were similar; however, the duration of study drug therapy was 50 days for 02 and 30 days for 875. There were different formulations used in the studies, tablets in 02 and capsules in 875. The Applicant has not provided data regarding bioequivalence of these preparations.

On the slide, "IR" stands for "immediate release" and "EC" stands for "enteric-coated." In 875, the "C" following these designations stands for "capsule."

As you have heard, patients were started on high-dose prednisone, and if GVHD were controlled, rapid taper was started after 10 days to different maintenance doses in the two trials.

It should be noted that the first 16 patients in Study 02 were treated with prednisone, 2 milligram per kilogram and tapered to 0.125. This was changed by amendment of the study due to the high incidence of HPA-axis inhibition associated with the regimen.

For 02, since the primary endpoint was time-to-treatment failure by day 50, the plan duration of followup was 80 days, 30 days after completion of study therapy. For this trial, data for survival and cause of death were to be obtained by telephone contact day 200 post-transplant as a safety endpoint.

For 875, since the primary endpoint was oral caloric intake by day 30, followup was specified through day 40.

For both trials important data were obtained retrospectively after the trials were completed. For both trials post-hoc analyses were done of survival one year post-randomization and overall survival post-randomization.

We have heard the presentation today as less pooling and more as comparison, but I will mention some of the issues with pooling efficacy data in this context.

There are some clinical difficulties with this approach. Dr. Sun-Mitchell will have more to say in her presentation. In general, there are differences between the two trials in design, therapy regimen and enrolled populations.

Among these are differences in treatment duration and prespecified followup. Significant advances in transplant procedures and supportive care during nearly a decade separating the trial, among other things this has resulted in differences in the proportion of patients receiving non-myeloablative conditioning regimens, none of course in the earlier trial, and also a greater proportion of patients

receiving peripheral blood stem cells as allagraft source versus bone marrow in the later versus the earlier trial.

At this time, Dr. Shan Sun-Mitchell will present the efficacy results and statistical analysis for FDA.

STATISTICAL CONSIDERATIONS

(PowerPoint presentation is in progress.)

DR. SUN-MITCHELL: Thank you. Dr. Scher presented the clinical review and some of our concerns regarding the implications. I'm here to address some of the statistical issues.

As Dr. Scher has already mentioned earlier, the primary endpoint for Study ENT 00-02 was treatment failure through day 50. This table shows the Sponsor's analysis report of the primary endpoint. FDA agrees with Sponsor's result.

The primary treatment comparison for the primary endpoint was not statistically significant with P value of .118 by stratified log-rank test, that is BDP that was not statistically significant, better than placebo.

As presented by Dr. Scher, after failing the primary endpoint the Sponsor considered multiple prespecified and nonspecified endpoints and conducted multiple analysis for Study ENT 02, Study 875, as well as for both studies combined.

These multiple endpoint analyses are considered only as exploratory, since the study failed the primary endpoint, and, hence, any further analyses will only increase a false-positive error rate.

This slide shows three post-hoc endpoints presented by the Sponsor as described by Dr. Scher in her presentation. Survival at day 200 post-transplant as an endpoint which was collected as a safety endpoint is based on the timing of the transplant not on date of randomization or study drug administration.

The time of onset of GVHD may be influenced by the conditioning regimen and there is an imbalance between the treatment arms with more patients in the BDP receiving non-myeoablative conditioning; hence, this is not a valid endpoint for the purpose of treatment comparison.

The two other survival endpoints, that is,

survival at one year post-randomization and overall survival post-randomization were not prespecified for either trial.

The followup of all patients for survival was not planned uniformly. Any subsequent therapy or other conditions that may inference survival were not augmented.

Using survival at one year post-randomization as one of the survival endpoints, the Sponsor conducted a post-hoc exploratory analysis for Study ENT-002. Sponsor's P value cannot be compared with .05, since the study failed on primary endpoint. All the allocated Type 1 error rate has been completely spent.

After failing the primary endpoint, the Sponsor performed many post-hoc analyses. Some of the problems with post-hoc analyses are outlined here. Study ENT 02 failed to demonstrate efficacy of the BDP treatment based on the primary endpoint.

Survival at one year is an arbitrary cutoff endpoint. There was no uniform followup for patients post-study treatment. Any post-treatments or other conditions may influence survival were not captured.

 

Hence, there exists a potential for bias in the subsequent analysis based on one-year survival and overall survival post-randomization endpoints.

All post-hoc analyses are considered exploratory since there is no time for an error left for further testing, and any subsequent analysis can only inflate the Type I error rate.

The Sponsor also performed post-hoc analysis by combining the two dataset from Study ENT 00-02 and 875 and submitted for review for a claim of efficacy. The Agency disagrees with the method of pooling two datasets, the reasons are as follows:

First, the two trials are not concurrent. As Dr. Scher pointed out in her presentation, the Study 875 was completed almost 10 years before the completion of the study ENT 02. Supportive care has changed during the decade between the two trials.

Secondly, the study designs for the two trials were different. Study ENT 02 was a multicenter study while Study 875 was a single-center study.

Next, primary objectives and study endpoints were different in the two trials as discussed by Dr.

 

Scher.

Next, the stratification factors for two trials were different. The stratification factors for Study ENT 02 were: (a) study center; (b) donor type; and (c) topical corticosteroid use. The only stratification factor for Study 875 was degree of anorexia, caloric intake.

Next, the original treatment time for patients was different between the two trials. The treatment here for ENT 02 was 50 days while treatment period for Study 875 was 30 days. In addition, duration of followup was different in the two studies.

Next, the enrolled populations for the two trials were different. As Dr. Scher pointed out in her presentation, some of the major differences in population are sources of transplant, conditioning regimens, and dosing schedules.

Finally, the followup on all patients for the retrospectively collected survival endpoint were not planned. Any subsequent therapy or other conditions were not documented.

Here are the guidelines regarding pooling data

 

and meta-analysis. ICH E9 states that when used for the purpose of claiming efficacy the meta-analysis should have its own prospectively written protocol.

The EMEA points to consider also states that "Prerequisites for a retrospective meta-analysis to provide sufficient evidence for a claim include -- some studies clearly positive--."

"A retrospective meta-analysis of only two studies originally intended to stand on their own is not expected to add any useful information."

The Sponsor also performed post-hoc exploratory analyses for the overall survival post-randomization as one of the endpoints in Study ENT 02 and Study 875. The results for both trials are listed in the table.

As we have discussed before, Study ENT 02 failed on the primary endpoint. Here the post-hoc exploratory analysis on survival endpoint for both trials also failed to show the statistical significance of the BDP treatment arm over the placebo arm.

Therefore, the methods of pooling data from two failed studies are not acceptable as recommended in

the guidelines ICH E9 and EMEA 2001 regarding pooling, meta-analysis presented earlier.

I will now summarize my presentation. The Registration Study ENT 02 did not show a statistically significant difference between BDP and placebo with respect to the primary endpoint of this study.

Because the study failed on primary endpoint, the Type I error rate that is allocated for the study was completely spent. Any subsequent analysis of prespecified and non-prespecified endpoints can only increase the false-positive error rate.

The Sponsor had conducted multiple analysis of several endpoints without adjustment of Type I error rate. One of the survival endpoints, that is, survival at day 200 post-transplant, is not a valid endpoint for the purpose of efficacy comparison between the BDP that arm and placebo arm.

The time of the onset of GVHD may be influenced by the conditioning regimen, and there is an imbalance between the treatment arms with more patients in BDP arm receiving non-myeloablative conditioning regimen.

Pooling/meta-analyses of combining the datasets into two studies are not acceptable due to major differences between the two studies.

Thank you for your attention. Dr. Scher will now continue and conclude the FDA's presentation.

SAFETY ISSUES AND SUMMARY

DR. SCHER: Thank you. The Applicant states that OrBec is a topical corticosteroid and its use has the potential to decrease patient exposure to systemic corticosteroids.

As stated, high-dose systemic corticosteroids increase the hazard of infection and may interfere with the beneficial graft-versus-leukemia or graft-versus-disease effect.

An important safety endpoint for Study 02 was comparison of hypothalamic-pituitary-adrenal suppression or HPA-axis suppression in the treatment arms.

An ACTH-stimulation test was administered at baseline and at day 51 to patients with normal baseline and no treatment failure by day 50.

Two different analyses were done. Each showed a significant increase in the proportion of the valuable

patients with HPA-axis suppression in the BDP arm compared with control. You see the numbers up there.

One comment, depending upon which analysis you did, the number of baseline patients who had abnormal function was either 20 to 25 percent, as Dr. McDonald mentioned, or closer to 5 percent, either way there were a number of patients that were not evaluable.

It was stated that the data were incomplete since treatment failures did not have day 51 testing, and this is true, but in view of the known greater exposure to high-dose systemic steroids in a control group, there would still be a significant difference in the arms.

The registration study failed the primary efficacy endpoint. Abnormal HPA-axis function was identified as a clinically significant safety issue. Finally, we believe that additional studies are necessary to demonstrate efficacy and safety.

Thank you for your attention.

CHAIRPERSON HUSSAIN: Thank you, Dr. Scher.

I'm going to suggest that we deviate slightly from the agenda, and while the presentations are fresh

in our minds, to maybe to go to questions to the Sponsor or to the FDA for clarifications.

I would ask that those of you interested in asking questions catch either my eye or Joanna's eye, and then we will call on you. Identify yourself before you speak. For the responders, please make it brief and to the point, so we can accommodate as many questions as possible.

QUESTIONS FROM THE COMMITTEE

CHAIRPERSON HUSSAIN: May I begin perhaps with a question to Dr. McDonald. Dr. McDonald, did you or did you not -- or your study meet its primary endpoint?

DR. RODELL: May I just introduce myself. My name is Tim Rodell, and I was the medical monitor on the pivotal trial and I'm going to be sort of moderating the Q-and-A session.

(Facility sound difficulties.)

CHAIRPERSON HUSSAIN: Thank you, Dr. Rodell.

DR. McDONALD: My presentation validated the FDA's presentation. We did not meet the primary endpoint. We did, however, meet what I consider a clinically meaningful, quite robust endpoint of the day

80 endpoint for the GVHD treatment efficacy. It means that many patients in the BDP arm were spared large doses of prednisone compared to placebo.

CHAIRPERSON HUSSAIN: Thank you.

Dr. Mortimer.

(Facility sound difficulties.)

DR. MORTIMER: [In progress.] I think there is a compelling argument that there is a difference between those two arms. I'm just curious about the comparison between the BDP arm compared between the placebo.

You made a comment about corticosteroids were systemically uncomfortable, and yet the incidence of fatigue seemed to be higher in the BDP arm. I just wondered how fatigue was actually measured. Was there an objective way of quantitating that?

DR. RODELL: Can I take that question?

(No verbal response.)

DR. RODELL: Fatigue was not objective measured or followed prospectively. It was simply reported as an adverse event more frequently in the patients on BDP.

 

CHAIRPERSON HUSSAIN: Dr. Harrington.

DR. HARRINGTON: Thank you, Dr. Hussain.

First, I would like to just get us away a little bit from the jargon of spending the alpha function here, and that will help maybe put my question into context.

Either the protection of the .05 level for a global test is to prevent people from not finding an outcome that supports, say, concluding that a treatment works at a primary endpoint and then going on a hunt throughout the data for something that might yield something that looks positive.

It's rare I think in these instances, and it's not the case here, that we see the evidence of a sort capricious hunt for supporting data. I think your other analyses are the natural ones that one would look at.

For me I think what is important is that when one moves away from the primary endpoint to other supporting endpoints, the story has to be really consistent and very robust.

I think the thing that is most intriguing me is this interaction that you've noticed, especially in

 

the survival with respect to the treatment and the myeloablative and non-myeloablative regimens.

You have really a very, very striking slide, say, number 61 in your slides which show very, very different outcomes here in the post-one-year randomization survival, depending on whether or not someone got a non-myeloablative conditioning regimen or not.

I would like you to sort of walk me through that and tell me what you think is going on there and whether in fact for people who got myeloablative regimens, they either weren't being spared the corticosteroids, survival was essentially the same there, the post-randomization; or, the corticosteroids weren't having the bad effect that you told us about before.

DR. RODELL: Let me ask Dr. McDonald to answer initially, and then I would like to ask Mr. Cruickshank, the statistician to comment on that, please.

DR. McDONALD: I think you are entirely correct. I mean, the data is displayed as you see it here. What's driving the improvement in survival is

 

part of this subgroup, but the non-myeloablative patients are the sickest patients here. I think they have the greatest thing to benefit from a protection from steroids.

I would like to ask the study statistician, Mr. Scott Cruickshank, to kind of discuss subgroup analysis here because it is driven by the interaction term as you noted.

(PowerPoint presentation is in progress.)

MR. CRUICKSHANK: Scott Cruickshank, statistician with Dor Bio Pharma. Thank you, Dr. Harrington for the question.

In light of this result here, we did examine the effects of BDP treatment with the patients that received myeloablative conditioning versus non-myeloablative. What you see here is an examination of your baseline characteristics: age, risk of relapse, source of donor cells, matching status, and time for randomization as well as baseline performance status.

You can see here that in general the non-myeloablatives generally were older, had more frequent higher risk of relapse. We see comparable numbers of

 

bone marrow and HLA-matched status was similar. The time for randomization to transplant generally differed by about a week.

DR. HARRINGTON: Let me ask a followup question, then, and pose it a bit differently. Once one abandons the primary endpoint, although I agree that your day 80 data is compelling but moves to an endpoint by one year post-randomization survival or a two-year post-randomization survival as strong evidence for the agent, then it becomes important to understand exactly how that recommendation would be written.

In this instance, I agree that the people in the non-myeloablative group seem to be helped quite a lot, if we believe the data, the data looked compelling, but the corresponding story is that the people in the myeloablative side weren't helped at all, at least in terms of their post-one-year survival.

How would you recommend use of the regimen given that at decision to treat the status of the conditioning regimen would be known?

DR. RODELL: I would like to comment on that, which I think is important to point out, and that is

 

that the differences that we are seeing with respect to effects were in the mortality data, but in fact were not seen in the time-to-treatment failure data.

DR. HARRINGTON: I agree.

DR. RODELL: There at least is an argument that some of the other potential benefits of this are not restricted to the non-myeloablative group. I think it is also important to point out that this is a small dataset.

The non-myeloablatives started being enrolled later on. I think we probably shouldn't over interpret the degree of difference that was seen between the two groups.

DR. HARRINGTON: All right.

DR. RODELL: Mr. Cruickshank, do you want to add anything to that?

DR. HARRINGTON: I do have a question pending for Dr. McDonald.

DR. McDONALD: Well, to reiterate Dr. Rodell's point, I think it's good to survive to one year, but it is not the only benefit from avoiding high-dose prednisone.

As I say, what patients remember the most about hematopoietic cell transplant is there mucositis and their prednisone exposure. Many patients who have come to transplant already knowing about prednisone, they dread going on prednisone because it makes them feel awful.

I don't want to denigrate the avoidance of prednisone as a good thing. I think the survival benefit, to me I do it as a proof of principle that avoiding prednisone could have good things happen downstream. I think that's all that we're claiming here.

CHAIRPERSON HUSSAIN: Dr. Richardson.

DR. RICHARDSON: I have several questions and then a comment and then I guess another question after that. I guess it should be directed to Dr. McDonald as he raised this particular point, which I didn't see in the material that we were presented earlier.

This is regarding Study 875. You mentioned that some patients were no TPN, which is obviously a major risk factor for infections in this group of folks also.

I guess I'm curious whether there were criteria for starting these patients on TPN? Specifically, if the patient, for example, was anorectic on day 10, I assume he received TPN at that point, or did he tough it out for the next 21 days?

How many patients were on TPN and was that a stratification factor? I assume these folks were excluded, if they were already on this prior to randomization. If a person was on BDP and required TPN, was he considered a treatment failure?

DR. RODELL: Dr. McDonald.

DR. McDONALD: At our center, and this was a single-center study, everybody whose caloric intake drops below 30 percent of caloric requirements is put on TPN. On average, this happens around day -2 before the marrow infusion.

That practice is based on previous studies showing that everyone is in massive negative-nitrogen balance and so, to maintain the nitrogen-balance issue, literally every one of our patients after high-dose myeloablative therapy is on TPN. That TPN continues until patients demonstrate their ability to eat better.

 

Now, when patients then develop graft-versus-host disease, let's say, for example, the TPN was stopped at day 15 and the patients were discharged to the outpatient category and then at day 30 developed acute graft-versus-host disease, they wouldn't necessarily go back on TPN if they were struggling with enough caloric intake.

They would get hydration through their Hickman lines, because people who are anorectic and nauseated and vomiting can't maintain hydration. They may not have gotten TPN.

The criteria for TPN literally happened long before graft-versus-host disease started. TPN was not a stratification factor. If people were on TPN while on BDP, that was not a treatment failure.

We analyzed treatment failures at specific time points -- at day 10, day 20, day 30 -- in this 30-day study. Our nutritionist tracked nutritional intake compared to caloric requirements. This was a very hard endpoint at those three time periods.

The other cause for failure was the attending physician saying, "This patient is doing awful. I'm

 

going to bail out of the study and start them on steroids." Those are the two endpoints.

DR. RICHARDSON: You mentioned that there was decreased prednisone exposure in people who were not treatment failures, and yet this reminds me of something that we are always confronted with in medical oncology, and that is, the argument that responders do better than nonresponders. I mean, we've been toughing that one out for decades.

Yet, if you look at the total amount of steroids in both arms, it appears to be same. If you look at the signs attributable to steroid excess, there were more signs in the BDP arm.

There were more abnormalities in the response testing for adrenal function in the BDP arm, so it seems to me that we get back to this responders/nonresponders argument. How do you counter that?

(PowerPoint presentation is in progress.)

DR. RODELL: This slide shows the actual cumulative corticosteroid exposure between the treatment arms at study day 50 and study day 80, so the milligrams-per-kilogram cumulative dose median was 19.4

in the placebo arm at day 50 and 15 in the treated arm.

These are not statistically different, but the difference is, as you pointed out, in the patients who were treatment failures, more different. I agree that there is a risk of circularity in that type of analysis.

But I think that if you look at actually the quantities of steroids that those patients received, some of them were receiving somewhere in the neighborhood of 40 to 50 milligrams per kilogram over the course of this. The criterion for treatment failure was simply any increase in corticosteroid dose, and that was continued for an extended period of time, in some cases beyond study day 80; so, we don't actually know how much the total dose was in some of those cases. With respect to the manifestations of corticosteroid exposure, I think the primary ones that we would focus on are infectious complications. Again, the numbers are small, but they certainly favor the treated group of patients and, ultimately, mortality.

DR. RICHARDSON: One final question, and I

 

think this is something that a lot of us probably wondered about as we were reading this also, and that is, that beclomathasone in corn oil is currently being used in a lot of centers including, as I understand it, Seattle. I guess the question in my mind is, what is the advantage of this compound over the compounded product?

DR. RODELL: Can I ask Dr. Hockenbery from the Fred Hutchinson to address that?

DR. HOCKENBERY: David Hockenbery from Fred Hutchinson Cancer Research Center. That's quite true, a number of patients at our center I just finished attending on the wards that had a diagnosis of graft-versus-host disease are receiving compounded beclomethasone through the pharmacy. That is not driven by our recommendations. That is driven by the transplant oncologists who have looked at our data and find them compelling and also by the patients who have learned of this data. We have no direct way of comparing the efficacy of that formulation versus our formulation, but I can tell you that the patients don't like to

 

swallow the corn oil. It's not something that they think is a very palatable form of administering this drug. We are asked quite frequently is there anything else that we be available. We don't have a way of compounding the extended-release formulation of beclomethasone, and so what clinicians have done at our center is use budesonide, which is another topical steroid that has been approved for inflammatory bowel disease, for example.

CHAIRPERSON HUSSAIN: Dr. Link.

DR. LINK: I would just like to get back to the question I think Dr. Harrington was asking, and that is that it looks like basically all of the benefit in terms of the one-year survival is in the non-myeloablative group. It's not exactly intuitive. I know they are sicker when they are going in, and that's why you do a non-myeloablative transplant, but they don't get as sick. That's the whole point.

I would have intuited actually the people who are going to get the sickest are those who have had the most intensive preparative regimen. They are

 

more likely to get bad graft-versus-host disease, and they would be the most likely to benefit. This is the opposite result. I guess what I really want to know, so take me through your rationale as to why this should be true. Why should it work for non-myeloablative or why should it improve the survival of non-myeloablative but not really have any benefit in terms of survival for the myeloablative group?

DR. RODELL: Can I ask Dr. Keith Sullivan from Duke who is here to address that question?

DR. SULLIVAN: Hi. I'm Keith Sullivan from Duke University, and I am a medical oncologist as well as a transplanter for the last 35 years. I think this is a really important discussion because we are seeing the field of transplantation move into the older individuals so that we can go ahead and capture patients who have refractory lymphomas or MDS or other diseases that occur in the older individual.

When I started transplant 35 years ago, our obligate age cutoff for an allograft was 50. Some have

 

said as the faculty age, the age for eligibility increases for our patients.

(General laughter.)

DR. SULLIVAN: Now we are considering transplant for individuals who are 60, 65, and 70 years of age for allografts.

Now, what Dr. Link has said and Dr. Harrington has reverberated also is extremely important. Because if anything, the deck was stacked against the active drug regimen. Because there were twice as many patients transplanted in relapse, and there is a substantial increase in patients who have transplanted with non-myeloablative regimens.

When non-myeloablative regimens or reduced-intensity regimens were rolled out about seven years ago, the great hope of this was that it would allow patients who had more organ dysfunction who couldn't qualify for a standard allograft or over older age, and so that's what has been concentrated in this group of individuals.

What we haven't seen, although we can do transplants, is a benefit as much as we had hoped for

 

because there has been a countervening (sic) issue of graft-versus-host disease, which is more frequent in older individuals. We have one benefit from the preparative conditioning regimen and another for graft-versus-host disease. That's why this is such an important discussion.

I think Dr. Link's discussion or Dr. Harrington's discussion of why is this working? Well, unfortunately, there wasn't a large dataset here of immune function, be do know that there is thymic activity even up to age 50 years of age.

We can see thymolpoiesis after transplant in individuals who are in their thirties and forties. If you start transplanting individuals who are in their fifties, sixties, and seventies, that's a more fragile group of patients. That's why they get more graft-versus-host disease.

They don't have thymic tutelage to allow tolerance. I think what you're seeing is a benefit specifically and, importantly, in individuals who otherwise would be succumbing from their GVHD.

CHAIRPERSON HUSSAIN: Yes, Dr. Scher?

DR. SCHER: Just a point of information. Dr. McDonald has alluded to it. In the subset of patients in Study 02 who received the non-myeloablative regimen, there were only 15 patients in the placebo arm, so we really can't make far-reaching conclusions, I think.

I just wanted to give you the numbers, since it was said the dataset was small. There were 15 in the placebo and 26 in the BDP at one year consideration when the analysis was done.

CHAIRPERSON HUSSAIN: Any other final comments? Questions?

Yes?

DR. SPORTES: Yes. I would like to ask our statistician colleagues to comment more on the early failures in the first 10 days which really don't make much sense clinically in the fact that both groups were supposed to probably reap the same benefit.

From what we see from toxicity later on, it doesn't seem like the OrBec had any significant increasing toxicity, therefore, that could account for this difference. What kind of impact do those, I think, four or five early failures increase on the OrBec side

have?

(PowerPoint presentation is in progress.)

DR. RODELL: Can I have Slide 569, while I'm starting to address that.

(Staff complies.)

DR. RODELL: Thank you. The "Baseline Characteristics of the Early Treatment Failures."

(Staff complies.)

DR. RODELL: We were also curious about this and spent a fair amount of time trying to figure out whether there was any sort of pathophysiologic rationale for why OrBec could have had an adverse effect on early treatment failures. Frankly, we were not particularly successful at doing that.

I think one of the things that puzzled us was that if you postulated that there was some adverse effect of OrBec in the first 10 days, it was hard to then understand how that effect would reverse in the following 40 days.

In addition, I think it is important to point out that in Study 875 that was not seen. In fact, in Study 875, the difference was in the other direction, so

 

there were more treatment failures in the placebo group in the first 10 days in 875.

This is simply a slide showing the characteristics of the patients with early treatment failures. As you can see, there really is not any particularly meaningful difference between groups in terms of preexisting characteristics.

The only difference that we have highlighted here is a difference of 3 patients out of 12 or 25 percent bone marrow source of donor cells versus 6 percent out of 36 in the other subjects -- I'm sorry, and this is in all other treatment failures up to I believe study day 50.

I think the short answer is we can't see a good physiologic reason for it. We can't see any things in terms of imbalances and preexisting conditions that could explain it. I think what we are sort of left with is statistical noise and random chance, but obviously that's a diagnosis of exclusion.

Let me ask Mr. Cruickshank to comment on that, if he would.

(PowerPoint presentation is in progress.)

 

MR. CRUICKSHANK: Thank you, Dr. Rodell.

Whenever the notion of "statistical noise" comes up, they always seem to point to me.

(General laughter.)

MR. CRUICKSHANK: I don't want to get too technical here, but I think there is an important point to be made to follow up to your point, and that is, when we express the hazard ratio or something along those lines over time, we can see that when the line is above zero represents when placebo is doing more favorably relative to BDP.

Values below zero represent when BDP is doing better than placebo, a very simplistic representation. You can see here that in the first 10 days is primarily when we are losing the effect, but over the remaining 70 days you can see that it is a fairly stable effect.

This phenomenon in here is really something to consider when one is looking at power. It says what is happening is we are getting some loss of power. This effect here is canceling out or negating to some extent the effect up there.

CHAIRPERSON HUSSAIN: If there are no other

questions, then I'm going to ask that we adjourn now and come back in about 15 minutes or so, so 3:05, and we will start with the public hearing.

Thank you.

MS. CLIFFORD: A quick announcement. If you have not registered or if you have not checked in for the open public hearing session, and you do intend to speak, please touch base with me as soon as you can.

Thanks.

(Recess.)

CHAIRPERSON HUSSAIN: Do we have everyone from the Sponsor back here? We have some questions that we have, and we're going to pose them to you before the public hearing.

Dr. Link.

DR. LINK: At the risk of being sort of a dog with a bone, I'm still trying to figure out the fact that it seems like all of the benefit in terms of survival came from patients who had non-myeloablative transplants. I like things to make sense in terms of why it worked.

Looking at Slide Number 50, where you show

extended followup like in the Kaplan-Meier analysis that there was a reduced need for steroids or fewer treatment failures in the BDP group from the point of view of GVH, who are those patients that benefitted? Now, you must have drilled down to see. Were they only non-myeloablative patients that benefitted?

What I would like you to do is try to make the case that it worked because we had reduced incidence of GVH in the non-myeloablative patients uniquely, therefore we gave them less steroids, and therefore, they survived at one year.

That would be nice. It would make sense to me. It would have some impact in terms of what group benefitted from BDP specifically. Did you look at that?

DR. RODELL: Let me ask Mr. Cruickshank to answer that.

(PowerPoint presentation is in progress.)

MR. CRUICKSHANK: The slide before you shows the subgroup analysis of time-to-treatment failure through study day 80 for the group of patients that received myeloablative conditioning and the group that received non-myeloablative conditioning. You can see

here that the treatment failure rates at day 80 were, roughly, comparable between the two subgroups.

The effect of treatment, a .5 hazard ratio for the myeloablative and .71 for the non-myeloablative suggests that the treatment effect of BDP for those two subgroups is generally consistent with the overall ITT.

Going back to your point about differential effects within the two subgroups for time-to-treatment failure, it doesn't suggest here that this effect is necessarily driving the one-year survival for the non-myeloablative subgroup.

DR. LINK: Well, aux contraire, so I would ask you why do you think that the myeloablative group didn't have a benefit in terms of one-year survival when they had just as much benefit in terms of reduction of GVH and steroid exposure?

MR. CRUICKSHANK: Tim, do you want to take that, please?

(PowerPoint presentation is in progress.)

DR. RODELL: I think, well, I'm starting to get a little speculative here, but I think we ought to show, Scott, the relative effect in patients who were

non-matched donor.

I think it may speak to the issue, that is, that when you look at the effects in patients who had less good matches, that is, patients who were not HLA-identical sibling donor sources.

You see a similar effect, that is, that it is stronger in the group that arguably is likely to have worse graft-versus-host disease and essentially be sicker. I think it's something that is seen essentially that it appears at least to have some relationship with what the risk is of the patients involved.

CHAIRPERSON HUSSAIN: Does that answer your question, Dr. Harrington, also?

DR. HARRINGTON: It does answer my question about the possible interaction. I'm not sure I heard an answer to Michael's last question, though, and maybe that is speculate, about why the benefit in terms of graft-versus-host failure did not translate into a benefit in survival in the myeloablative group?

DR. McDONALD: I can speculate. I think it may well be related to the underlying disease characteristics. The primary proximate cause of death

 

at the one-year endpoint was relapse of leukemia.

The study was not stratified for relapse risk. We did analyze it in retrospect, but that's a variable that we couldn't control, the biologic behavior of the underlying malignancy. That is one potential explanation.

CHAIRPERSON HUSSAIN: I have a question to the FDA. Either of the presenters could take it. Understanding that the day 80 time-to-failure or number of failures was a secondary endpoint, but in reality it is just an extension of time, so why is it not good enough?

DR. SCHER: I guess the answer is statistical.

CHAIRPERSON HUSSAIN: I guess I understand it's statistical. I understand that party line of failing primary endpoint, therefore everything is exploratory otherwise. But in this case, this is not a different endpoint. It is really just a matter of extending from day 50 to day 80.

DR. SCHER: Well, the Sponsor has said that they failed the day 50 endpoint because they had bad

 

luck. You know, the patients in the BDP arm just happened to fail during the time they were on prednisone.

What is statistics but a consideration of odds in some sense also. Clinically, the day 80 is okay. I think you have to look at the totality of the package, and that's just one point.

CHAIRPERSON HUSSAIN: Dr. Farrell.

DR. FARRELL: I think one of the things that has bothered us is the BDP is given for a maximum of 50 days, and you would expect the maximum effect of the treatment to be during that 50 days.

Why do you have one result at day 50 and one result at day 80? It's a little surprising to us, and we are not able to explain it. Because, you know, with most drug trials you're really getting the benefit with the treatment.

CHAIRPERSON HUSSAIN: I guess what I was trying to understand is it that if you were to design a study like this and you would have said, "I'm going to look at day 80 as opposed to day 50, would you have used a different sample size?

DR. SCHER: If I had designed a study like this, I think the focus of the focus of the study, the primary endpoint was appropriate to what they were initially looking at.

They were looking at Stage II, GI graft-versus-host disease and looking at the impact of the therapy at a defined time not very far after the therapy.

Now, if we are looking at a trial with a survival endpoint -- well, really this is one of our questions to the Committee, but it seems to me that you would also focus on the baseline hematologic disorder.

In fact, not only was there no attempt to balance or stratify by the baseline hematologic disorder, but the state for acute leukemia, whether patients were transplanted and relapse or remission, first relapse, second remission; whether they were in chronic phase of CML or an accelerated phase of CML, that very critical data was not collected until the trial was over.

This was part of the important clinical data that was collected post hoc, and the balance was what it

was. But it seems to me that one might want to prospectively define "relapse risk," if one were devising a survival trial rather than collecting the very important disease-specific data post hoc and then aligning, trying to look at where the risk fell. To me that is a greater concern.

CHAIRPERSON HUSSAIN: Dr. Sun-Mitchell.

DR. SUN-MITCHELL: I think the answer to your question, 80 days was one of the secondary endpoints. In other words, there were a lot of multiple analysis. The point is, why 80 days? Why not 40 days? Why not 70 days, et cetera?

The question comes, yes, this was prespecified as one of them, but you did see that they were also looking at other time endpoints also. When you are looking at so many multiple endpoints, it becomes difficult for us then to say, "Okay, 80 days is acceptable even though they failed on 50," that's number one.

Then, as you saw now with the analysis that was shown, even with the 80 days what we look for is consistency within the trial itself. In the

myeloablative group, if you think that there is some difference in the 80 days, why is it not showing up in the one-year survival and it's just going the opposite for the other group?

Also, the one-year survival seems to be totally driven by this very small subgroup. We have the internal consistency question, as well as our concern, as well as that multiple endpoints were tested. In that whole process, how do we look at just this one endpoint which seems reasonable?

CHAIRPERSON HUSSAIN: Thank you. We will start --

(Simultaneous discussion.)

CHAIRPERSON HUSSAIN: I'm sorry.

DR. SPORTES: Could I?

CHAIRPERSON HUSSAIN: Yes. Oh, sorry.

DR. SPORTES: Just a couple of comments.

CHAIRPERSON HUSSAIN: Yes, Dr. Sportes.

DR. SPORTES: As a transplanter, I really like to see a plateau as you see in Slide 50. I think it is in response to why would we expect to see a longer effect than the actual duration of treatment?

I think this is kind of the hallmark in bone marrow transplants. Why would we not see a difference at one year versus 200 days?

This is also, unfortunately, a hallmark of transplant. There is so much interaction with disease and the disease refractoriness that it is really hard to isolate the initial intervention to see the end result at a year.

Going back to this Slide 50, I think to me there is a lot of tantalizing hope in there, and seeing that there is a plateau with a BDP which physiologically and pathophysiologically to me makes a lot of sense in terms of transplant. That was one comment.

I want to, if I can switch gear a little bit, one thing that we haven't talk about is the possibility, although we've talked about it through the HPA inhibition, of drug absorption.

Budesonide was brought up, and there have been some fairly recent studies with new ancillary treatments that showed that there was a dramatic difference in systemic absorption of budesonide.

I haven't heard much at all about where that

would stand in OrBec, looking at some package inserts. Some allege that there are C3a/metabolism, some not. I think that is quite important in knowing whether or not we are truly dealing with a topical treatment, or will be dealing with that in two years.

MR. RODELL: Well, let me make one comment, and then ask Dr. McDonald to comment on the systemic absorption issue, and that has to do with the HPA axis data.

I think that we absolutely believe that there are small quantities of the active metabolite being absorbed, and it's certainly sufficient to have some effect on HPA axis, responsiveness in some patients.

In fact, it is interesting that a number of patients, about a quarter of the patients in the 02 Study actually did have normal HPA axis function at the end of 50 days.

We do think that there is real absorption, but the levels that are being absorbed based on both the side-effect profile as well as what Dr. McDonald will talk about we think are probably more significant than the local topical effect.

George.

(PowerPoint presentation is in progress.)

DR. McDONALD: Here we have marshaled the primary evidence I think that this is indeed a topical therapy. The first is well known to gastroenterologists.

When we have patients with ulcerative colitis, for example, when we give BDP in an enema form and then put a colonoscope in after a couple of weeks, the place where the enema fluid has touched the mucosa is clearly better, but above where the enema fluid never reached looks just as bad as ever.

I know with certainty, because I've done this for a lot of years, that BDP applied to inflamed mucosa makes it better. There is not much of a systemic effect where it didn't touch.

Now, we know that BDP is metabolized in the gut lumen. Studies were done by my colleague, Doug Levine, 20 some years ago where he fed oral BDP to patients with stable ileostomies, a wonderful way of assessing how much active drug would reach the distal gut.

 

Esterases in luminal fluid and in the mucosa, not P450 but nonspecific esterases, cleave one propionic acid group off of the BDP. BDP never gets into the circulation, but 17-BMP does, and it's potent.

Here is the metabolism. Here is BDP here. Here is 17-BMP. Notice that the receptor-binding affinity of BDP is, roughly, what prednisone is, but the metabolite has an enormous binding affinity and very potent topical corticosteroid because of this binding affinity.

Now, here is a comparison of the prednisone equivalence of 17-BMP that get into the bloodstream. These are data from a 2-milligram dose of OrBec in comparison to a prednisone dose.

Notice that the AUC, that is, the systemic exposure of OrBec, is 400 times or a 100 times less than 2.5 milligrams of prednisone. In other words, all the prednisone gets into the bloodstream systemically, a hundred percent of it.

Relatively little of 17-BMP gets into the bloodstream, but this is the key figure. This is a prednisone equivalent, but it's equivalent to the effect

of 2.5 milligrams of prednisone.

Yes, some active metabolite gets in, but a protein-binding difference, affinity with a receptor differs, and this is not a very potent systemic effect.

Of the other critical picture, this is Daly, Yates, et al., in "The British Journal of Pharmacology," this is human volunteers getting 4 milligrams of oral BDP in one dose.

This is a charcoal absorption line. Ignore that. This is 17-BMP. What is particularly notable about this is look how long one dose lasts at very low levels in the bloodstream. The same group gave intravenous BDP, and it was rapidly cleared.

The only way to interpret this data, this is the gut, the gut mucosa, holding on to 17-BMP and feeding it slowly into the systemic circulation where it's cleared. This is the strongest evidence I know of a prolonged residency time of this topical therapy in the gut where we want it to be active.

CHAIRPERSON HUSSAIN: Okay. Thank you.

We are going to begin with the public hearing. I would like to read a statement before the public

presenters, that "Both the FDA and the Drug Administration and the public believe in a transparent process for information-gathering and decision-making to ensure such transparency.

"At the open public hearing session of the Advisory Committee Meeting, the FDA believes that it is important to understand the context of an individual's presentation.

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Likewise, the FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relations. If you choose not to address this issue of financial

relationships at the beginning of your statement, it will not preclude you from speaking."

Thank you.

OPENING PUBLIC HEARING

MS. CLIFFORD: Our first speaker this afternoon is Sue Stewart. She is with the Blood and Marrow Transplant Information Network.

MS. STEWART: Thank you for the opportunity to address you today. I am Susan Stewart. I'm the executive director of a patient-driven organization called Blood and Marrow Transplant Information Network, or "BMT InfoNet."

This is one of the largest groups that provides information that provides information and support services to people primarily in the United States but throughout the world who are facing going through and living with the sequellae of a bone marrow, stem cell, or cord blood transplant.

As the executive director, I have had the privilege of talking to thousand of patients who have been through transplant, all too many of whom have lived with the horror or GI GVHD.

I think today we will have two speakers, one an adult survivor and one the mother of a child survivor, who have experienced GI GVHD, to give you just a taste of what it is like for a patient and a family to go through this experience.

But if I can leave with you three things, one is this is a horrific experience. When we talk about nausea and vomiting, it is far beyond anything you could imagine with your experience with nausea and vomiting. It is truly a horror.

When you talk about the effects of prednisone on patients who are taking high-dose steroids, it is not a minimal dose of steroids. It is a very high dosage of steroids which leaves people in a very diminished capacity in many cases for years on.

Had we had the time, Chris Mullen would have come from Dorchester, Massachusetts, 30 years old to tell you about the two hip replacements and ankle replacement that he has had as a result of prolonged exposure to high-dose steroids. There are many more like him.

It is a life-threatening illness. If we had

 

the opportunity, Bob, who doesn't want his last name mentioned, would have come with me from Chicago today but can't because he is on his bedside fighting for his life.

I just want to stress the importance of this to patients. Any tool that you can put in the arsenal of the physicians who are treating this awful disease would be very, very welcome.

I will say as a point of disclosure we have received a grant that has covered our travel here to the hearing from Dor Bio Pharma, but they have not in any way had input into or seen previously the presentations that we are about to give.

Thank you.

MR. DUGAN: Thank you, Susan. My wife would argue whether or not I'm an adult.

(General laughter.)

MR. DUGAN: I've been diagnosed four different times with malignancies, beginning at the age of 23. The last in the spring of 2003 with non-Hodgkin's lymphoma. It was then I was told that a bone marrow transplant was my only option.

 

During the intake process at the bone marrow unit, I was told of serious complications that could result from graft-versus-host disease. However, in my circumstances, I don't think I really paid too much attention. My head was spinning from so much troubling news that I really don't think it registered with me.

On August 1, 2003, I had an allogeneic transplant from a matched donor at the Fox Chase-Temple BMT Clinic in Philadelphia. The donor was my brother Jerry.

I remained there for 19 days. Then, on October 3 of that year, I was readmitted to the hospital due to complications stemming from GVHD, the disease that attacked my gastrointestinal system with ferocity, ravaging both my stomach and my bowels.

I was relegated to a diet of ice chips and intravenous feeding, TPN, for nearly three weeks during which time my weight dropped from 154 to 127 pounds. During that time I lost not only my weight but my fighting spirit, my self-worth, and nearly my faith.

The doctor's tried everything in their power to stem the tide, including a significant increase in my

dosage of steroids in the form of prednisone, the highest dosage reaching 100 milligrams a day.

It did nothing to relieve the diarrhea or to stop my continual weight loss. However, it was anything but a benign medication. The baggage that comes with prednisone, that I think Dr. McDonald alluded to earlier, hit me very hard.

The drug made me edgy, moody, something of a monster really. My hands trembled to the point where I couldn't write, and I struggled to get pills into my mouth. I was angry and flip with the nurses, my wife, and almost anyone else who came in contact with me.

The fact that the prednisone kept me from sleeping compounded the problem. My only relief from the nightmare that I was living at the time had been the escape that sleep brought me. When I was robbed of any prolonged rest, my edginess and surliness became elevated.

Recalling Jack Nicholson's dark, manic character in the movie "The Shining," just substitute the famous line "Here's Johnny" with "Here's Stevie" to get an idea of what I was like.

 

Through all of this is seemed the doctors were grasping at straws. The diarrhea, the weight loss, the sleeplessness, they could stop none of it. As one of them put it to me, "Dealing with GVHD is more art than science."

I was finally released from the hospital on November 5, 2003, after 33 days. Thirty-three days may not seem like a long time, but it was a lifetime to me.

During those 33 days, I did not see my two young daughters, who were 9 and 6 at the time, a very significant period in their lives as they changed and grew almost daily during that period. My wife and I made a conscious decision not to have them come see their skeletal-looking father, afraid that they would be traumatized.

Just as important, I missed the passing of my oldest brother Jay who died at age 57. I never got to say goodbye nor attend his funeral.

My release from the hospital was just the beginning. I remained basically bedridden for the next six months. My body lacked magnesium, and since I couldn't tolerate the pills. I was forced to have the

 

drug administered intravenously twice daily for two hours at a time. I lacked real appetite, and I had to basically force feed myself carbohydrates to try and regain some strength.

My children tried to comfort me and encourage me. But, frankly, I think they were scared of me and the way I looked. I missed Father's Day at their school and a First Communion for my youngest daughter. As you know, there are no reruns in life.

All of these problems and what I can only call "crimes" can be laid at the doorstep of GVHD and the havoc that it wreaked no my life and my GI system.

It was February 2005 before I was able to return to work on a part-time basis. I'm still hampered by the effects of GVHD and the steroids meant to control it. I'm constantly fatigued and prone to infections which linger for months. I'm 53 but I certainly feel like I know what it must be to be 73.

The high and prolonged dose of steroids has eaten away at my joints and my bones. Climbing stairs, getting in and out of cars, bending down, a whole host of everyday activities have been affected.

 

Being active athletically with my children is something they no longer expect of me. The most painful physical effect, though, is my inability to run even one lap of a track. Five months before my transplant, I ran the Philadelphia Marathon. The benefits and true joys of being a life-long runner are gone forever.

To me the transplant was something of a Faustian bargain. Yes, my life was prolonged, and that's surely a precious gift. However, GVHD has robbed me of much that I will never regain.

I will always have the memories of the friends, fellow warriors really, that I have made while I was in the hospital fighting GVHD, but the memories that are most striking are those who succumbed to GVHD while I was there.

Their passing is I'm sure now represented in databases that record such things, so the only reason some people might be aware of their having been alive is the fact that they are now dead. Their struggle is not noted and their spirit not represented.

Something should be done and quickly. No opportunity should be ignored. Were your child, parent,

 

or sibling a victim of severe GVHD of the stomach and gut, you would surely want to be able to offer more than prayers to help them.

Steroids are apparently a hit-or-miss solution, and that's not good enough. Is OrBec the answer? I don't know, but I think it's certainly worth finding out.

Thank you.

MS. PEARLMAN: I think I feel nausea and everything else up here right now. I think I know what that's like. Meet Matthew. This is my son (showing photograph).

That was last summer, pretransplant. It was taken at a going away party where at nine years old, blonde and beautiful he hugged friends and family bravely goodbye as he left for Minnesota Fairview Medical Center to receive a 5/6 unrelated matched transplant.

Now imagine the same innocent child just weeks later. He is so, so sick. He is unable to eat or drink due to GI GVHD and all the drugs thrown at the wall to fight it.

 

His only nutrition is TPN fed intravenously 24 hours a day, and even that made him puke uncontrollably and projectile. He has severe diarrhea, and I mean severe. It's so bad his pull-up in his bed I changed between 40 and 50 times a day. He would just say, "Mommy, I can't help it."

His face and body are now distorted. His hair on his head is gone. He has an unwanted mustache, sideburns, and back hair -- again, due to the drugs he is taking to control GVHD. He did think the mustache was kind of cool, though.

Seriously, this is Matt (showing photograph) probably at his sickest. He is bedridden, mouth sores so badly he can't even talk. I'm sorry (crying). The cyclosporin he is taking to suppress his immune system and control the GI GVHD has caused severe toxicity and seizures that put him in ICU.

I watched them put the ventilator and the tube down his throat to breathe. This not only happened once, this happened twice.

He has dangerously high-blood pressure now from all the GVHD medications, so he is given more

 

medicine to control the side-effects.

He is nine years old. He went in weighing 54 pounds. At this point he is about 42. He has all muscle loss, no muscle mass left. He did this for 180 days straight in a hospital bed unable to move.

This is a 10-by-10 room, the picture I paint for you, with limited visitors and he is completely miserable saying "Mommy, I just want to die. Get me out of here."

Kids he has met, they have died and he tells me he is scared. He knows this is a place he may never walk back out of. Yet, as a parent, you have to push them through the door. You have to shove the meds down their throat more than one time a day because you have no choice.

The prednisone he took to control the GVHD caused angry rages to be nice. He would grab my face and pull it till I had marks, screaming, "Get me out of here." As I mother, I just wanted to die.

The mood swings were stressful, to say the least. It makes PMS look like nothing or menopause, which I'm getting lucky to go into now.

 

We finally armed Matt with Nerf machine gun and we let him shoot at the nurses and the doctors. We gave him a 60-cc syringe of ice water, just to get a little smile and relief.

This is a hard picture to look at (showing photograph). You've heard it explained as mucosis (sic). Let me tell you the story. One day I walked into the hospital room at 6:00 a.m. My husband Mark said, "Diane, go to the bathroom, look in Matt's pull-up, but don't say a word."

I walked in, I opened this mess, and I screamed at the top of my lungs, "What now?" Directly due to Level II GVHD of the gut, Matt had slopped a 39-inch piece of skin-like tubing.

The docs explained, "While this is a large piece, it's common for tissue to come out of the GI tract."

Can you even imagine healing from the inside out from that? This by far was one of the worst days of my life.

Not only have I been through this gut-wrenching, pardon the pun, experience once with Matt, my

 

daughter also had a bone marrow transplant six years ago.

They both have Fanconi anemia, a devastating, possibly fatal blood disorder with an average age of only 22 even post-transplant. We lost her five different times. She still has horrible nightmares and residual effects, from her transplant, six years later.

By the grace of God, they are both with me. All I want on Sunday, on Mother's Day, is a hug. I absolutely ache inside for those mothers who have to visit a graveside instead just because a better drug or a better protocol was not available to them.

Now, this was Matthew in January (showing photograph). As you can clearly see, he looks nothing like that blonde and beautiful boy celebrating his departure to Minnesota.

Every day is a gift, so we didn't care what he looked like. But let me tell you, he did. His cousins didn't recognize him and ran from the room. It broke his heart.

The drugs changed him drastically from the inside out, and he absolutely hates it. He looks in the

 

mirror and says, "Where did I go?"

He is just now, 10 months later, off TPN and starting to eat, barely able to process real food. He weighs about 46 pounds. He is still experiencing uncontrollable and embarrassing bowel issues, still wearing a pull-up today. Today is his 300-day, post-transplant milestone, 300 days of this.

This is Matt and his baseball team (showing photograph). He didn't hit a home run. All he did is he is loved by his team and they are thrilled that he is with them.

They all shaved their heads to be like him while all the while he is desperately fighting to be like them. He just wants to be an average 10-year-old. He can hardly run the bases now. He only has 50 percent lung capacity, and we're waiting for test results of GVHD of the lungs.

It's hard for him to have the physical strength to even swing a bat. He is constantly reminded when he strikes out that he will never be like himself or his teammates again. He hasn't had a hit this year. It breaks my heart.

 

He had to run out of right field the other night during the game. I looked for the ball and he just kept running and I saw no ball and he had to go to the bathroom because the diarrhea was going down his leg.

Everyone understands. Again, as a mother as a parent, I ache for him. He is fighting for his life. He is fighting to be normal and he is begging still this day not to be held hostage by GVHD.

We have no idea what other long-term physical or mental effects he will endure from all the chemo, radiation drugs, and chronic GVHD.

These brave children have no choice but to trust us adults with their lives. It is imperative and our duty to uncover better treatments, do relentless research, discover successful drugs, and alleviate any possible pain for the future.

I ask you to please think of this decision if it was one you were facing for you or your children. Together we must fight half as hard as the kids are in those hospitals all over the world to save lives. We must protect all from the ravages of GVHD.

I thank you for your time.

MS. CLIFFORD: Thank you very much.

Our next speaker is Anna Kyrou.

MS. PKHRIKIAN-KYROU: Hello, everybody. It's a little bit hard. I would say my story is a little bit better because I had an option of getting beclomethasone back nine years ago. I had ALL pB cell. I had a transplant in 1997. Actually, it will be 10 years this month since my transplant.

Within about a month and a half after a transplant, things were going pretty well, but then the graft-versus-host started of the gut, and then it was followed by hospitalization after hospitalization, with months and months in the hospital.

I guess, if I estimate within that year, I probably spent out of 12 months, 9 in the hospital. I don't know. That's an estimate. The first admission for graft-versus-host was about three months. We tried everything. I've been on high-dose steroids, and I guess the side-effects you've heard a lot here from prednisone.

From some of them I'm still dealing with. I

 

have osteopenia. I've had some fractures in my spine. It's just something I always have to be -- as a 32-year-old woman, I always have to be aware about my bones and how fragile they may be.

While going through the treatment for graft-versus-host, I've also have been on various other drugs besides prednisone. I've tried ATG horse serum. We've tried -- I don't even remember what we tried. But there were many, many drugs that were tried. Well, not many, just a few I guess that were available.

Of course, the immunosuppression, I was on FK-506. Thank God I wasn't on cyclosporin for too long. As a result of the treatment, the graft-versus-host disease and the severe diarrhea and vomiting -- vomiting that goes on sometimes for hours and you pretty much throw up every two minutes, it's not pleasant -- anyways, after that I lost a lot of weight.

I was down from about 55 kilograms to 36. I was put on TPN. As a result of being on TPN and lipids, I've developed acute pancreatitis, which I have many attacks.

Basically, I'm telling all this story because

 

by the time I was put on beclomethasone, somebody asked a question about corn oil versus pills, so I started on corn oil, and because of the intolerance, I've developed intolerance to lipids at the moment, so I started on corn oil. As a result, I developed another acute pancreatitis, which is quite painful.

Basically, then we switched on to the capsules. I think that the beclomethasone was a turning point for the treatment of graft-versus-host for me. Because following the course of the treatment on beclomethasone, I finally was able to eat more on my own. I had significantly reduced diarrhea. I had reduced nausea.

When I went on beclomethasone it was probably like the early summer of '98, sometime in June. By August or September of '98, I was able to eat sort of decent food besides crackers and oatmeal that usually would take me three hours to consume.

By October of '98, after a year and a half of spending at Roswell Park Cancer Center, where I had my bone marrow transplant, I was finally able to return to Syracuse and attend graduate school, which was on hold

 

for the time being.

Anyways, I just want to thank you for developing the drug and thank you for an opportunity to be on it. I hope that all these statistical issues that have been mentioned here are not going to be in the way of approving it. I urge you to approve it.

Thank you. Bye-bye.

MS. CLIFFORD: Thank you.

Our next speaker is Philip McCarthy.

(PowerPoint presentation is in progress.)

MR. McCARTHY: Thank you. I have five slides.

(Pause.)

DR. McCARTHY: I'm Philip McCarthy from the transplant program at Roswell Park. I participated in the DOR acute graft-versus-host disease study examining BDP with steroids versus placebo and steroids. I've been involved in the design of potentially a future, large chronic GVHD study. I was asked by BMC Communications if I would speak about the RPCI experience with BDP. I paid for my travel here from Buffalo.

We actually published on this. This is

 

Iyer, et al., a long-term use of oral beclomethasone dipropionate for treatment of GI GVHD, which was in the biology of blood and marrow transplantation in 2005. The FDA got to know us very well because we would get a new IND every time we put a patient on study. In fact, we used to get a new IND every time we put a patient on another cycle, and each cycle is 28 days. They got tired of us. They actually made a deal with us that we could do it for each patient. We were cross-referenced with the original Enteron IND, and we had a particular interest in chronic, long-term use of this drug because of patients such as Anna where one cycle would be reasonable, but we were very interested in trying to use this long-term as a steroid-sparing drug, which I talk about at the very bottom there. We initially used it in capsule form. It actually is compounded in corn oil, which isn't very well tolerated. You can't tell them to put it on salad, because they are not supposed to eat salad. Then, later on, we compound it ourselves in capsules with the powder, which is not the greatest

 

because of the fact that it is being compounded by different pharmacies. We used it for the treatment of acute and chronic GVHD. There was actually a refractory to front-line immunosuppression. These are patients who are usually on a calcineurin inhibitor and methylprednisolone or an equivalent for 1 to 2 milligrams per kilo per day and were unable to wean or tolerate steroids without a GI flare. Again, as I mentioned, it's kind of paradoxic to say a steroid is a steroid-sparing agent, but that's how we used it. This is again data from the paper. It's all in the handouts which I left. We had nine responders, six nonresponders. We were focusing primarily on chronic, but at the time we had two patients with acute GVHD. As you can see, the BDP start time was 431 days post-transplant; in the responders, 113; and in the nonresponders, the nearest range. The median steroid dose was 19 milligrams of methylpred or equivalent with a range of 88. It was higher in the nonresponders. We had patients who were in a median

number of cycles of 28 days, 3 in the responders and 2 in the nonresponders. You can see there is one patient who received 20, 28-day cycles. This slide is essentially meant to show, and I don't have a pointer, that patients in the first three who are CRs, that means "complete response," they were able to completely wean off steroids. Then, in the PRs, which are the next six, you can see that two patients were able to have marked reductions in their steroid dosing. Some were already on very low doses and were maintained. Then, you could see at the bottom in the non-responders there were some we just had to go way up on their steroid dosing. This doesn't work for all patients, but in the ones who do respond we were able to use this to taper systemic steroids. Last slide, right now we are using this as a pharmacy-compounded agent. It does have variability. We prefer a standardized formulation for both upper- and lower-tract exposure. We have used this now in over 30 GI GVHD

 