1989 and 1995. One hundred day mortality dropped dramatically within that same timeframe – down from 22% to 5%. Data from the Autologous Blood and Marrow Transplant Registry, which generally contains data from uncontrolled trials, has reported a 3 year probability of progression free survival of 32% in patients with metastatic breast cancer achieving CR before high-dose therapy, 13% in those in PR at the time of high dose therapy, and only 7% for those who are non-responders to conventional therapy.[46] Randomized, controlled trials are ongoing. One such trial, published by Bezwoda[47] in 1995, found an advantage for high-dose therapy with stem cell support in 90 randomized patients with previously untreated metastatic breast cancer in terms of overall survival. Median survival was 45 weeks on conventional chemotherapy doses of CNV vs. 80 weeks on high dose CNV (cyclophosphamide + mitoxantrone + etoposide). On the high dose arm the overall response rate was 95%, and 51% achieved CR. Busulfan was not a part of the treatment plan in this trial.

An article by Fields, et al, describing the phase 1-2 experience in high dose therapy for breast cancer at the H. Lee Moffitt Cancer Center indicates that the BU/CY regimen (busulfan 4 mg/kg/d x 4 + cyclophosphamide 60 mg/kg/d x 2) is being evaluated in adjuvant treatment of Stage III breast cancer. Only fifteen patients were enrolled at the time of the report, and event free survival for ten patients was compared with that of 49 other patients on 3 other regimens evaluated for stage III breast cancer adjuvant therapy. No significant difference was noted among the regimens. In the analysis of the autotransplants reported to the Autologous Blood and Marrow Transplant Registry between January 1989 and June 1995 reported by Antman[46], the conditioning regimens for breast cancer were varied, but cyclophosphamide + thiotepa ± carboplatin was used in 43% of patients in 1989, increasing to 60% in 1994. Busulfan was not included in any of the other 5 regimens described in the report by Antman, but may have been present in the category "other" which accounted for 30% of conditioning regimens in 1989 and declined to 18% in 1994. In none of the ongoing randomized trials of autografts in stage II, III, or IV breast cancer tabulated in the report by Antman, is busulfan used in the high dose regimen prior to stem cell rescue.

7.8.2 Summary and Conclusion – Breast Carcinoma

In conclusion, there is no level I evidence to support the use of busulfan as a part of high-dose therapy prior to stem cell rescue in breast carcinoma. The role for transplantation in this disease is still being defined, and most investigations have been conducted with a high dose regimen that does not include busulfan.

Reviewer Comment on Sponsor's Literature Review Analysis: The sponsor has concluded from their analysis of the data derived from the 43 article "core dataset" that the "totality of these data provide evidence that high-dose oral busulfan-based preparative regimens are efficacious in patients with breast cancer who underwent autologous transplantation." The sponsor combined the data from 3 of the "core dataset" articles, and didn't include the article by Ghalie (the only study with a population limited to breast carcinoma) in the "core dataset" in their analysis. This article appears to have not been included in the analysis because it involved tandem autotransplantion. The first was performed after a Thiotepa/CY/Carboplatin regimen, and the second after a BU/Etoposide regimen. Thirty-two of the 44 patients that entered this study underwent the second transplant. VOD was reported in 39% of the patients who underwent second transplant and was fatal in 25% of those who developed it. The reviewer again finds fault with the methodology employed by the sponsor for their analysis. Not only were these not randomized, controlled trials, but the endpoints of overall survival, DFS, and relapse were

analyzed by tallying the numbers of patients who met each endpoint for each study and dividing by the total number at risk from all those studies combined. The resulting overall crude percentage associated with a busulfan preparative regimen was then reported. The fact that these endpoints were each described over different time frames or differing amounts of median follow-up among this heterogeneous group of studies, was acknowledged, but not factored into this analysis. Such a compilation of outcomes from multiple studies is relatively meaningless.

7.9 Other Solid Tumors

The following table summarizes the level of evidence provided in the articles in the sponsor's "core dataset" identified by the sponsor that pertain to solid tumors other than breast carcinoma.

Table 40 Summary List of Sponsor's Core Dataset Articles Pertaining to Solid Tumors

Solid Tumors represented in a mixed disease study population				
Study	**Level of Evidence**	**No. of Pt's**	**Study Design**	**Diseases**
Schiffman	III	Ovarian ca=13 Ewings Sarcoma=3 Primitive neuroectodermal tumor=2 Nasopharyngeal tumor=1 Rectal carcinoma=1 Small cell lung ca = 1 Liposarcoma = 1 Neuroendocrine tumor=1 (104)	Uncontrolled, Prospective, Phase 2	MM, Breast, Lymphoma, Ovarian, Sarcoma, others
Spitzer	III	Germ cell tumor of ovary = 1	Uncontrolled, Retrospective	AML, ALL, MDS, CML, NHL, HD, CLL, Prolymphocytic leukemia, germ cell tumor of ovary
Srivastava	III	Ewings sarcoma=2 Neuroepithelioma = 1 Rhabdomyosarcoma=1 Choriocarcinoma=1 (24)	Uncontrolled, Retrospective	MM, NHL, HD, ALL, Breast, Sarcoma, others

Weaver	III	Soft tissue sarcoma=3 Primitive neuroectodermal tumor=1 Seminoma=1 Yolk sac tumor=1 Anal carcinoma=1 Neuroblastoma=1 (28)	Uncontrolled, Prospective, Phase 1	Breast, HD, NHL, Sarcoma, others

The reviewer did not find additional relevant studies regarding the use of a busulfan based conditioning regimen for transplantation in other solid tumors, including ovarian carcinoma. There are no Level 1 studies for review in these various malignancies, and it is clear that the patient numbers in each subtype are quite low. There were 14 patients with an ovarian malignancy, and 1 of these patients had a germ cell tumor. There were 3 patients with primitive neuroectodermal tumors, and 7 with soft tissue sarcomas. These numbers are too few to support discussion of an indication for busulfan conditioning in each one of these diseases, even if one were willing to base such a discussion on level III evidence.

7.10 Genetic Diseases

The following table summarizes the articles submitted by the sponsor in the 43 article "core dataset" to support the efficacy of high dose busulfan as part of a preparative regimen for transplantation in genetic diseases.

Table 41 Summary List of Sponsor's Core Dataset Articles Pertaining to Genetic Diseases

Genetic Diseases				
Study	**Level of Evidence**	**No. of Pt's**	**Study Design**	**Diseases**
Jabado	III	44	Historical Control	Wiskott-Aldrich Syndrome = 9 T cell immunodeficiency = 7 Leukocyte adhesion deficiency = 2 HLA class II deficiency = 9 Osteopetrosis = 9 Chediak-Higashi Syndrome =1 Familial hemophagocytic lymphohistiocytosis = 7

No level I studies supporting the use of busulfan-based preparative therapy for transplantation in the setting of genetic disease were submitted by the sponsor. The small patient population representing each disease category in the only, non-randomized study submitted by the sponsor makes it impossible to assess high dose busulfan for an indication in each of the diseases in this general category. This study report focused on the relative efficacy of infusion of anti-adhesion antibody directed against CD 11a molecule, anti-LFA-1 alone (historical control) vs. anti-LFA + anti-CD2 for prevention of graft rejection. Patients received bone marrow from HLA-nonidentical related donors or HLA-identical unrelated donors. The preparative regimen was

buslfan 4 mg/kg/d x 4d (or 5 mg/kg/d x 4d if the patient was < 5yo) + cyclophosphamide 50 mg/kg/d x 2d. Etoposide 100 mg/m^2/d x 2d was added to the preparative regimen for patients with osteopetrosis, Chediak-Higashi syndrome, and familial hemophagocytic lymphohistiocytosis. Engraftment failed in 13 patients, and varied with the underlying disease. With a median follow-up of 39.3 months, 40.9% had sustained engraftment, with correction of the underlying disease. Nineteen patients (43.2%) developed fatal infections. Most infections occurred within 3 months of transplantation. VOD occurred in 3 patients and was fatal in one.

Because of the lack of randomized, controlled trials in this indication and the small number of patients with diverse diseases in the uncontrolled study that was submitted, there is no support for a labeled indication in these diseases.

7.11 Overall Summary of the Literature Review

Did the literature review identify adequate and well-controlled trials that demonstrated clear efficacy and safety data supporting the sponsor's proposed labeled indication that follows?

The foundation for the reviewer's efforts to answer the five review issues raised by this proposal and outlined in the introduction of this literature review section was this: the randomized, controlled trial design is the best provider of valid efficacy and safety data. The existence of data from such a trial design is especially critical from a regulatory standpoint when assessing efficacy proposals based on a "literature NDA", because the raw data is not available for review and the Agency is unable to audit the study conduct in the fashion that normally contributes to its assessment of the validity of the study's conclusions. The importance of the randomized design for assessment of safety is particularly evident in an area such as stem cell transplantation, where the complexities of the underlying disease, concurrent medications, application of varying definitions for toxicities like VOD, make it particularly difficult to ferret out whether adverse events are actually related to one particular agent. The potential for the introduction of bias into any efforts to compare the results of uncontrolled trials in this treatment modality is tremendous. It is readily apparent that attempts to make comparisons across studies are hampered by the heterogeneity of patient populations represented in the various uncontrolled trials available for review. Methods of efficacy analysis were also frequently not homogenous among studies.

By asking first if such level I evidence was provided in each proposed disease, answers to the secondary questions pertinent to appropriate labeling (including which types of stem cell transplantation and which specific combination regimens were indicated) became evident. The table that follows summarizes the conclusions the reviewer believes can be drawn from a disease-based examination of available level I evidence. If there were no randomized controlled trials available for review in a particular disease entity, the reviewer has concluded that there were not adequate data demonstrating busulfan's efficacy and safety as a preparative therapy for stem cell transplantation in that disease. If a randomized, controlled trial was available, the decision

regarding whether evidence supported busulfan's use in a conditioning regimen for transplantation was based on whether an adequate number of patients with that disease participated in the trial and whether the efficacy and safety outcomes in the trial supported such an indication. If more than one randomized, controlled study was available, the efficacy and safety results from each was considered and weighed against the others'.

Table 42 Summary of Level I Evidence by Disease

Disease	Number of Level I Studies	No. of Patients Treated with Busulfan in a Level I Study	Level I Data Supports Busulfan Preparative Regimen
AML Allogeneic	3	106/200 treated with busulfan had AML	No
AML Autologous	4	356/583 total on study were treated with busulfan for autotransplant	No
CML	4	188/287 treated with busulfan had CML	**Yes**
ALL	2	41/149 treated with busulfan had ALL	No
Non-Hodgkin's Lymphoma	1	3/88 treated with busulfan had "lymphoma"	No
Hodgkin's Disease	1	3/88 treated with busulfan had "lymphoma"	No
MDS	0	0	No
Multiple Myeloma	0	0	No
Breast carcinoma	0	0	No
Ovarian carcinoma	0	0	No
Genetic Disease	0	0	No

There were no level 1 studies for review in MDS, multiple myeloma, breast carcinoma, ovarian carcinoma, or genetic diseases and their inclusion in the labeled indication cannot be supported. The fact that the exact therapeutic role of bone marrow transplantation in some of these diseases has not been clearly defined to date has been discussed earlier. In non-Hodgkin's lymphoma and Hodgkin's disease there was only one level 1 study for review, and the number of participants in that study with "lymphoma" was miniscule. Thus, evidence does not support the inclusion of these diseases in the labeled indication as proposed by the sponsor. The role of transplantation (allogeneic and autotransplantation) in these diseases was discussed at length in this review in their pertinent sections.

CML was the disease entity with the greatest number of randomized, controlled trials available for review - all 4 in the setting of allogeneic transplantation. Two of the studies limited participation to CML in chronic phase and showed no significant difference in the efficacy endpoints of Kaplan-Meier probabilities of overall survival and disease free survival between the

BU/CY and TBI-based preparative regimens, while another study that enrolled a mixed group of hematological diseases showed no significant difference in relative risk of mortality. Treatment related mortality was compared in two of these studies and was not found to be statistically significantly different between arms in one (Clift; disease limited to CML), and statistically significantly higher with BU/CY in the other (Ringden; mixed hematological disease population). VOD occurred with greater frequency on the busulfan arm of these studies, but was not statistically analyzed, except in the Nordic BMT Group Study by Ringden (mixed hematological disease population) in which it occurred with statistically significantly greater frequency on the BU/CY arm. The one study of the four that demonstrated inferiority of the BU/CY conditioning regimen was the Nordic BMT Group study, which only demonstrated superior Kaplan-Meier estimated 3 year overall survival and treatment related mortality associated with a CY/TBI regimen when the entire population of mixed hematological malignancies was considered. The subset analysis of the CML patients treated in the Nordic BMT study found no significant difference between arms in DFS.

As discussed at length earlier in the CML section of this literature review, these level I studies not only do not provide a preponderance of evidence that busulfan-based conditioning for transplantation in CML is associated with superior efficacy and safety compared to CY/TBI, but they do not provide clear evidence of equivalence either. The confidence intervals derived by the biostatistical reviewer for the survival probabilities in the Clift and Devergie studies that limited participation to CML in chronic phase did not provide unequivocally, secure evidence of equivalence. However, the derived "worst case scenario" for BU/CY vs. CY/TBI in terms of overall survival was a difference of 13%. This may be viewed as evidence of similarity between the regimens. The use of CY/TBI as the standard for comparison was also examined in the same section. Its apparent position as the "standard" of comparison in these randomized trials is derived from this regimen's place in the historical development of transplantation. The efficacy attributed to transplantation in CML has been primarily derived from historical comparisons to other treatment modalities, and some of those comparisons were based on transplantation after conditioning with either BU/CY or CY/TBI. BU/CY, CY/TBI, and TBI/Etoposide are referred to in the literature as the most commonly used conditioning regimens in allogeneic transplantation for CML.[23] (Applebaum, et al) Busulfan is currently used for conditioning for transplantation in two European phase 3 studies in CML (under the auspices of the MRC and the German CML Study Group), although similar U.S. cooperative group studies in CML could not be identified by the reviewer – except for apparent participation in the MRC trial by ECOG. This regimen offers an advantage over CY/TBI in terms of its broader availability, as a radiation oncology unit is not required, and applicability to patients who are not candidates for radiation therapy.

There were seven randomized, controlled trials that utilized a busulfan preparative regimen for transplantation in AML. Four studies pertained to autologous transplantation and three to allogeneic transplantation. The reviewer concluded that the 4 studies in autologous transplantation did not support a labeled indication for busulfan's use in autologous transplantation for AML. Three of the four studies enrolled both adult and pediatric patients with AML in first CR. None showed superior efficacy in terms of probability of DFS or overall survival for autologous transplantation with busulfan conditioning compared to post-remission chemotherapy, however treatment related mortality and deaths from VOD were higher on the autologous arm (though this was not analyzed for statistical significance). The remaining autologous study reported by Ravindranath was limited to pediatric patients with AML in first CR and did show that treatment related mortality was significantly higher with autologous transplantation (with a busulfan conditioning regimen) than with intensive consolidation chemotherapy. The Kaplan-Meier estimated 3 year overall survival and EFS on the allogeneic arm was signficantly superior to that on the autologous arm ($p=0.01$ and $p=0.007$, respectively).

The Kaplan-Meier estimated 3 year OS and EFS was not found to be statistically significantly different when the autologous transplantation and ICC arms were compared.

The three randomized, controlled studies of busulfan conditioning in allogeneic transplantation for AML do not come to a unanimous efficacy conclusion. Two find that the Kaplan-Meier probability of survival is inferior with a BU/CY conditioning regimen compared to CY/TBI (2-year probability of survival in one and 3-year probability in the other). One limited participation to AML in first CR and the other involved participants with not only multiple hematological malignancies, but AML in CR1 and >CR1. In the latter study, treatment related mortality was significantly higher on the BU/CY arm. In the other, although treatment related mortality and VOD deaths were higher on the BU/CY arm, the differences were not found to be statistically significant ($p<0.06$). Probability of relapse and 2-year disease free survival was superior on the CY/TBI comparator arm in the study limited to AML in first CR. These studies, however, have been criticized in the literature for having what has been called an unusually low treatment related mortality on the TBI arm. The remaining (third) study found no statistically significant superiority for either conditioning arm in terms of relative risk of mortality in treating a mixture of hematological malignancies that were all in advanced stage. The 40/122 total participants on this study (SWOG) with AML had disease that was beyond first CR. The comparator arm in this study was not CY/TBI like the other two studies, but TBI/VP-16. There were more cases of VOD on the BU/CY arm, but this was not analyzed for statistical significance. Because two of the three randomized, controlled trials available demonstrate a statistically significant probability of inferior overall survival associated with a BU/CY conditioning regimen for allogeneic transplantation in AML, the reviewer has concluded that there is not level I data to support labeling in this indication.

Finally, the review of the two available randomized, controlled studies in ALL yielded no strong supportive information. Neither of these studies limited participation to patients with ALL. In one, nearly half of the patients with ALL had disease in first CR, and in the other participation was limited to patients with advanced stage hematological malignancies. Both utilized allogeneic transplantation and a BU/CY120 regimen. In the first study, the Kaplan-Meier probability of 3-year overall survival, as well as treatment related mortality, were statistically significantly inferior on the BU/CY arm (compared to CY/TBI). VOD was significantly more frequent on the BU/CY arm as well. The other study compared BU/CY to TBI/VP-16 and found no significant difference between arms in relative risk of mortality. There were more cases of VOD on the BU/CY arm, but this was not analyzed for significance. The reviewer does not believe that these data provide a preponderance of evidence supporting the proposed labeling for a busulfan-based conditioning regimen for allogeneic transplantation in ALL.

In summary, none of the literature presented for review by the sponsor, combined with additional articles identified by the medical reviewer, unequivocally supports an indication for busulfan's use in any of the indications proposed by the sponsor. CML was the disease with the most level I evidence examining the use of high dose busulfan in the allogeneic transplant setting, and the data did not demonstrate superiority to the comparator arm (CY/TBI), nor were the studies powered to permit a conclusion that BU/CY is equivalent to CY/TBI. This efficacy data was derived from a relatively small number of patients (n=188) treated in this context. However, the literature indicates that allo-BMT is accepted as a beneficial treatment modality in a subset of patients with CML, and BU/CY and CY/TBI are both cited as the most commonly used regimens in this setting. Supportive data from the IBMTR has been mentioned earlier in this discussion. The uncontrolled studies submitted provide safety data from a large number of patients, but interpretation of this data is hampered by the lack of a control arm in a complex treatment modality recognized to be associated with significant morbidity. It is regrettable that the large

number of patients that have undergone transplantation have not yielded the clear answers that are needed and are best derived from a randomized, controlled study design.

The reviewer began this literature review with five questions that arose from the sponsor's proposed labeling:

Those questions are repeated below with the answers the reviewer has derived from the literature review:

Are there sufficient data to support the use of high dose busulfan in combination with a variety of chemotherapeutic agents? Or, alternatively, which chemotherapeutic agent combinations that include high dose busulfan as a component have adequate data supporting their efficacy and safety?

The best level I evidence for the use of high dose busulfan as a conditioning regimen for transplantation is in allogeneic transplantation for CML. All four level 1 studies identified in that setting used BU/CY (BU/CY120, specifically). Therefore, level I evidence only supports busulfan's use in this specific chemotherapeutic combination regimen.

Are there sufficient data to support the use of high dose busulfan in combination with radiation therapy?

There were no level I studies supporting the safety and efficacy of high dose busulfan combined with radiation therapy conditioning regimens for bone marrow transplantation.

Since "hematopoietic progenitor cell transplantation" includes allogeneic bone marrow transplant, autologous bone marrow transplant, and peripheral blood stem cell transplantation (both autologous and allogeneic), are there data to support the use of high dose oral busulfan in each of these settings? Should demonstration of efficacy and safety in one, e.g. allogeneic bone marrow transplant, translate into efficacy and safety in each of the other modalities?

Level I evidence only supported the use of high dose oral busulfan in the setting of allogeneic transplantation with HLA-matched related donor marrow.

The last two questions will be combined: *Are there sufficient data to support efficacy and safety of high dose oral busulfan in bone marrow transplantation in each of the following diseases – AML, ALL, CML, MDS, non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, breast cancer, ovarian cancer, and genetic diseases? Is there evidence to support the efficacy of bone marrow transplantation in each of these diseases?*

These issues have been discussed at length above. The reviewer has concluded that the evidence is best in CML, but even there it is equivocal. The first sentence in the proposed label suggests that busulfan should be viewed in combination with other therapy as a mechanism to enable the performance of bone marrow transplantation. Conditioning regimens for transplantation have a 3-fold role in the process – ablating recipient marrow to enable donor marrow to engraft, suppressing recipient immunity to prevent graft rejection by the host, and treating residual disease present at the time of conditioning. The success of busulfan's role in treating residual disease can only be derived from the level I efficacy data, which suggests efficacy similar to CY/TBI in the setting of allogeneic transplantation for CML. Does conditioning with high dose busulfan permit engraftment? As the most persuasive level I studies were available in the setting of CML, the reviewer now qualifies this question to read – does conditioning with BU/CY120 permit engraftment in HLA-matched related donor allogeneic marrow transplantation for CML? The engraftment data provided in the four level I studies reviewed are summarized in the table below:

Table 43 Summary of Engraftment Data from the Randomized Studies in Allogeneic Transplantation for CML.

Study	Disease	Engraftment Data
Clift	CML, chronic phase	One patient on CY/TBI died before engraftment (on D18) ANC ≥ 500: BU/CY = 22.26 d (mean) CY/TBI = 22.55 d (mean) Platelets ≥ 20,000: BU/CY = 21.0 (mean) CY/TBI = 22.49 (mean)
Devergie (SFGM)	CML, chronic phase	4/65 BU/CY failed to engraft (1) or rejected graft (3) 0/55 CY/TBI failed to engraft p=0.18 (In addition 2 on each arm died before engraftment before day 35)

Study	Disease	Engraftment Data
Ringden (Nordic BMT Group)	CML, AML, ALL, NHL	86/88 BU/CY Engrafted 78/79 CY/TBI Engrafted ANC > 500 = 20d BU/CY (11-44) = 20d CY/TBI (12-39) Last Platelet Transfusion= Day 19 BU/CY Day 19 CY/TBI
Blume (SWOG)	CML, AML, ALL	None provided

These engraftment data also appear similar between the regimens.

Based on the literature-based answers to the questions raised by the proposed indication for intravenous busulfan, the reviewer believes that this indication must be significantly altered to limit intravenous busulfan's used to a combination regimen with cyclophosphamide in the setting of HLA-matched related donor allogeneic bone marrow transplantation. The only disease setting for which there is level I evidence that BU/CY has efficacy similar to that of CY/TBI is CML.

8 Overall Summary and Conclusions Regarding NDA #20,954

The major clinical issues in this application were summarized in Section 1.5 of this review, and were:

- The comparability of the intravenous formulation of busulfan and oral busulfan, in terms of efficacy (as measured by myeloablation and engraftment) and safety.
- The assessment of whether high dose (oral) busulfan-based conditioning regimens have been established as safe and efficacious, based on available evidence found in the literature.
- The comparability of the pharmacokinetic profiles of the intravenous and oral formulations of busulfan.

The pharmacokinetic profile comparison of the two formulations is addressed in depth in the Biopharmaceutics review, and the medical reviewer refers the reader to that review for a detailed discussion of this comparison. The intravenous formulation was found to have a similar, but not superior, pharmacokinetic profile when compared to oral busulfan.

The first two bullets were the primary focus of the medical review. The answer to the first issue came from the examination of the two phase 2 trials submitted in this application, and the comparison of their results to data found within the literature review. The reviewer believes that the myeloablation, engraftment, and safety data from OMC-BUS-3 and OMC-BUS-4 were comparable to that found in the literature.

The issues involved in drawing efficacy conclusions from the literature review regarding oral busulfan-based conditioning regimens for transplantation were complex, and have been discussed

at length in Section 6.0. The review team based any conclusion regarding efficacy of such a regimen in any disease on the availability of randomized, controlled trials. The reviewer has concluded that the strongest evidence of efficacy may be found in the setting of allogeneic transplantation for CML. The particular conditioning regimen with data to support its use in CML is BU/CY120, which is also the combination evaluated in this application's phase 2 studies of intravenous busulfan. Even in the case of CML, BU/CY has not been established as superior to CY/TBI. It has been associated with a higher incidence of VOD than CY/TBI, but offers advantages in its applicability to patients for whom radiation is either contra-indicated or unavailable.

BU/CY is clearly a commonly used conditioning regimen for hematopoietic stem cell transplantation in a number of settings, but randomized, controlled trials are limited in terms of their existence and scope, and have actually yielded conflicting results in some diseases. The sponsor has proposed that intravenous busulfan is indicated in a variety of conditioning regimens, for varying types of stem cell transplantation, and in a long list of diseases. The only setting in which Level I evidence was available and/or was not persuasively negative was allogeneic transplantation for CML with BU/CY120. The reviewer believes that labelling should reflect this.

9 ODAC Meeting Summary

The Oncology Drug Advisory Committee meeting was held January 13, 1999. The following questions were submitted to the committee for their vote. The results of the vote are included with each individual question.

This NDA has three principal components:

I. Two phase 2 clinical trials that assess myeloablation, engraftment and safety associated with a Busulfex™/cyclophosphamide conditioning regimen for stem cell transplantation - OMC-BUS-3 (autogolous-42 patients) and OMC-BUS-4 (allogenic-62 patients).

II. Clinical studies to assess the Busulfex Injection pharmacokinetic profile relative to oral busulfan.

III. Literature review to determine the diseases where there is substantial evidence of the safety and efficacy of stem cell transplantation using an oral busulfan containing chemotherapy regimen.

Table 1: Summary of Comparative Engraftment Efficacy – Intravenous Busulfex™ vs. Oral Busulfan (Autologous)

	Median Time to ANC >500	Graft Failure (%)
OMC-BUS-3 (autologous)	10.5 days	0%
Autologous Literature	25-32 days	1.6 – 1.7%

Table 2: Summary of Comparative Engraftment Efficacy – Intravenous Busulfex™ vs. Oral Busulfan (Allogeneic)

	Median Time to ANC >500	Graft Failure (%)
OMC-BUS-4 (allogeneic)	13 days	0%
Allogeneic Literature	19-20 days	2.3 – 6.1%

Table 3: Summary of Comparative Safety – OMC-BUS-3 (intravenous Busulfex™) vs. the Literature (oral busulfan)

	OMC-BUS-3	Literature
VOD	2% (n=1)	3.2% - 6.1%
Death ≤ Day +28 ≤ Day +100 > Day +100	 0 0 19% (n=8)	 – 6.5%-15% –
Pulmonary	2% (n=1)	–

Table 4: Summary of Comparative Safety – OMC-BUS-4 (intravenous Busulfex™) vs. the Literature (oral busulfan)

	OMC-BUS-4	Literature
VOD	8.2% (n=5)	5.9% - 12%
Pulmonary	8.2% (n=5)	3.9% - 16.9%
GVHD	18% (n=11)	≥ Grade 2 Acute GVHD=26-41% Chronic GVHD=45%
Death ≤ Day +28 ≤ Day +100 > Day +100	 3.3% (n=2) 13.1% (n=8) 16.4% (n=10)	 – 4.1% - 21% –
Non-Leukemia Related Mortality	18% (n=11)	28%; and K-M 2y est. 27%±7%

Table 7: Summary of Level I Evidence Provided in the Literature Review

Disease	Number of Level I Studies	No. of Patients Treated with Busulfan <u>in a Level I Study</u>	Level I Data Supports Busulfan Preparative Regimen
AML Allogeneic	3	**106/200 treated with busulfan had AML**	No
AML Autologous	4	**356/583 total randomized to autotransplant with busulfan conditioning**	No
CML (allo)	4	**188/287 treated with busulfan had CML**	**Yes**
ALL (allo)	2	**41/149 treated with busulfan had ALL**	No
NHL/Hodgkin's Disease (allo)	1	**3/88 treated with busulfan had "lymphoma"**	No
MDS	0	0	No

1. Do the phase 2 studies OMC-BUS-3 (autologous) and OMC-BUS-4 (allogeneic) demonstrate

   a. adequate evidence of myeloablation and engraftment?

   Yes – 15 **No - 0**

   b. adequate evidence of safety?

   Yes – 14 **No – 1**

2. Is the pharmacokinetic profile of Busulfex™ Injection

   a. Similar to oral busulfan?

   Yes – 15 **No – 0**

   b. Superior to oral busulfan?

   Yes – 0 **No - 15**

3. Does the literature review demonstrate substantial evidence of the safety

And efficacy of oral busulfan containing chemotherapy regimens in stem cell transplantation for the following

a. chronic myelogenous leukemia?

Yes – 15 **No – 0**

b. acute myelogenous leukemia? *This question was split by the committee into two separate votes on the different types of hematopoietic stem cell transplantation for which literature reports of randomized, controlled trials exist:*

Allogeneic Stem Cell Transplantation	**Yes – 5**	**No – 7**	**Abstain – 3**
Autologous Stem Cell Transplantation	**Yes – 1**	**No – 12**	**Abstain – 2**

c. acute lymphocytic leukemia?

Yes – 0 **No - 15**

d. myelodysplastic syndrome?

Yes – 4 **No – 7** **Abstain - 4**

e. malignant lymphomas? *This question was split by the committee into two separate votes on the different types of hematopoietic stem cell transplantation:*

Allogeneic Stem Cell Transplantation	**Yes – 3**	**No – 12**
Autologous Stem Cell Transplantation	**Yes – 3**	**No – 12**

4. Is this NDA for Busulfex™ Injection approvable?

Yes – 15 **No – 0**

10 Recommended Regulatory Action

Based on the data provided from the BUSULFEX™ phase 2 trials, the analysis of the literature review of the safety and efficacy of high-dose oral busulfan –containing conditioning therapy for hematopoietic stem cell transplantation, and with the recommendation of the Oncology Drug Advisory Committee, approval of BUSULFEX™ is recommended for use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia.

/S/ 1/26/99

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