7.1.4 Summary and Conclusion – Autologous Transplantation in AML.

A definitive role for autologous transplantation has not yet been defined in the setting of AML. Clift reported that in Seattle they had observed a 70% relapse rate with autologous transplantation of AML in first CR.[18] An analysis of 671 AML patients transplanted in first CR by the European Cooperation Group for Bone Marrow Transplantation revealed a 46% probability of event free survival with a median follow-up of 30 months.[11]

There were four randomized, controlled trials presented in this review that clearly employed high dose busulfan in this setting. The randomization in these studies was between post-remission chemotherapy and autologous transplantation. The preparative regimen for autotransplantation was busulfan-based. All studies limited participation to AML in first CR at the time of randomization. Three included an adult population, and one was pediatric. Three used BU/CY combinations and one BU/Melphalan. All suggested no significant difference between post-remission chemotherapy compared to autologous transplantation in estimated overall survival or disease free survival, except for the intergroup trial reported by Cassileth, which found that HDAC was favored in comparison to autologous transplantation in terms of estimated 4y overall survival, p=0.05. There was higher treatment mortality on the autologous transplantation arms than on the chemotherapy arms. This was found to be statistically significantly different, in favor of chemotherapy, in the pediatric study reported by Ravindranath. There was no level 1 evidence of superior efficacy for autologous transplantation (with busulfan preparative regimen) compared to post-remission chemotherapy, and some evidence that treatment related mortality was worse with this modality. Thus, a recommendation for the use of busulfan in autologous transplantation for AML would be difficult to support.

7.1.5 Final Reviewer Comments – AML

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 the setting of both auto- and allo-transplantation for AML. The reviewer finds fault with the methodology that the sponsor employed in their analysis of the dataset. Not only were phase 2 studies given equal weight to randomized, controlled studies, but applicable studies from the "overall dataset" that reported survival data were not included. Study reports pertinent to either autologous transplantation or allogeneic transplantation were considered as separate groups. The endpoints of overall survival, DFS, and relapse were analyzed by tallying the number of patients who met each endpoint for each study and dividing by the total number at risk from all the studies. *The fact that these endpoints were each described in reference to different time frames or with varying amounts of median follow-up among this heterogeneous group of studies, was acknowledged but discounted in this analysis methodology. These studies also differed not only in the preparative regimen used, but in the stage of disease eligible to participate, the GVH prophylaxis regimens employed, and the type of supportive care delivered. The overall crude percentages associated with a busulfan preparative regimen were then presented in a summary for each of autologous and allogeneic transplantation. The time reference for Kaplan-Meier estimates of efficacy from the studies were combined to create a time range, and associated then with a combined range of estimated probabilities for these endpoints. This range was compared to "reference" ranges derived from the literature to derive a final summary conclusion of comparative efficacy for busulfan. This methodology of establishing*

efficacy is flawed for all the reasons discussed earlier and for all the reasons that a randomized, controlled prospective trial provides the highest level of evidence of efficacy.

The clinical role for bone marrow transplantation in AML is best defined in allogeneic transplantation. The review of the level 1 evidence for efficacy associated with a busulfan-based preparative regimen has been discussed in detail above, and the reviewer has concluded after review of the level I evidence of efficacy that BU/CY is an inferior conditioning regimen when compared to TBI-based therapy in this setting.

7.2 Chronic Myelogenous Leukemia

The reviewer took a similar literature based approach to evaluating the use of high dose busulfan as a component of conditioning for transplantation in CML. The following table summarizes the level of evidence provided in the articles in the sponsor's "core dataset" that pertain to CML.

Table 23 Summary List of Sponsor's Core Dataset Articles Pertaining to CML

CML- only patient population				
Study	**Level of Evidence**	**No. of Pt's**	**Study Design**	
Clift	I	142 (73/69)*	Randomized Controlled Open Label	
Biggs	III	115	Case series	
Galimberti	III	34	Uncontrolled, Prospective	
CML represented in a mixed disease study population				
Study	**Level of Evidence**	**No. of Pt's**	**Study Design**	**Diseases**
Ringden	I	57(30/27)** (167)	Randomized, Controlled, Open Label	AML, ALL, CML, "Lymphoma"
Angelucci	III	14 (30)	Retrospective, uncontrolled	ALL, ANLL, CML, MM, MDS
Ballester	III	4 (51)	Uncontrolled, Phase 1-2	NHL, MM, AML, CML, ALL
Chiang	III	11 (23)	Uncontrolled, Prospective	CML, ALL, AML, NHL, HD, MDS
Kapoor	III	43 (127)	Uncontrolled, Prospective	CML, AML, ALL, MDS, Lymphoma
Przepiorka	III	12 (30)	Prospective, Phase 1-2	AML, ALL, CML, MDS, Lymphoma

Przepiorka, 1996	III	**22** (85)	Uncontrolled, Prospective	AML, ALL, CML, MDS
Sahebi	III	**38** (65)	Retrospective?	AML, ALL, CML, MDS
Spitzer	III	**6** (33)	Retrospective	AML, ALL, CML, MDS, NHL, HD, CLL, PLL
Topolsky	III	**19** (25)	Retrospective?	AML, CML, ALL, MDS, MM
Tutschka	III	**21** (50)	Uncontrolled, Prospective	AML, CML, ALL
Vaughn	III	**1** (24)	Historic Control	AML, ALL, CML, HD, NHL
Vey	III	**9** (25)	Uncontrolled, Prospective	AML, ALL, CML, Lymphoma
von Bueltzingsloewen	III	**38** (101)	Retrospective	AML, ALL, CML, MDS

* Bold number represents the number of participants randomized to the busulfan arm
** Bold numbers in the mixed disease study population table represent the number of participants with CML in the study population

There are only two level one studies provided by the sponsor, and the remaining 15 studies provide only level III evidence. Only one of the level I studies is restricted to patients with CML, and that study also limited participation to patients in chronic phase. The level I study that enrolled multiple types of hematological malignancies allowed participation of both patients in first chronic phase and beyond first chronic phase, including blast crisis.

The following table summarizes the additional pertinent studies in the literature identified by the reviewer and not included in the sponsor's 43 article "core dataset".

Table 24 Summary List of Additional Pertinent CML Studies Identified by Reviewer

CML-only Patient Population				
Study	**Level of Evidence**	**No. of Pt's**	**Study Design**	
Devergie 4/95	**I**	120 (65/55)*	**Prospective, Randomized Controlled**	
Bonini	III	26	Retrospective, Uncontrolled	
Slattery	III	45	Retrospective	
CML represented in a mixed disease study population				
Study	**Level of Evidence**	**No. of Pt's**	**Study Design**	**Diseases**

Blume 4/93	I	**20**/14**CML (122)	**Randomized, Controlled, Prospective**	AML, CML, ALL
Bertz 6/97	III	16 (36)	Uncontrolled, Retrospective	AML, CML, ALL, MDS
Ljungman 12/97	III	44 (172)	Uncontrolled, Prospective	AML, CML, ALL, MDS
Kalaycioglu 1/95	III	99 (199)	Retrospective, Uncontrolled	AML, CML, MDS

* The bold number represents the number of participants randomized to a busulfan arm
** The bold number represents the number of participants with CML randomized to a busulfan arm.

There were two level I studies identified by the reviewer, and they are similar in structure to the level I studies submitted by the sponsor in its "core dataset." The study limited to CML patients only, also limits participation to patients in first chronic phase. The study that enrolled multiple hematological malignancies reported by Blume, however, did not allow early stage disease to participate, so that the patients with CML on this study had to have disease beyond first chronic phsase. All of the level I studies cited by the sponsor and reviewer employed allogeneic transplantation and randomized between a BU/CY regimen and a TBI-based regimen. All TBI regimens were combinations with cyclophosphamide, except for the SWOG study reported by Blume, which employed a TBI/VP-16 treatment arm. *All four find no statistically significant difference in Kaplan-Meier probabilities of DFS or OS between these treatment modalities at varying time points.*

The following table summarizes the findings in all four of the level I studies.

Table 25 Summary of Level I Studies Pertaining to CML

Citation	Design and Dose	Disease	BMT Type	% Engrafted Median Days	%Relapse	%Survival Median Survival	Adverse Events
Clift, RA. Blood. 1994 September; 84(6): 2036-2043. Marrow Transplantation for CML: A Randomized Study Comparing Cyclophosphamide and TBI with Busulfan and Cyclophosphamide 1988 –1992 accrual	Prospective, Randomized BU/CY= BU 4 mg/kg x 4d + CY 60 mg/kg x 2d VS. CY/TBI= CY 60 mg/kg TBI =6 fx's, Shielding not mentioned	CML, chronic phase <1y dx: BU/CY=50 CY/TBI=51 Age=6-55	Allogeneic Sibling donor BU/CY=73 CY/TBI=69 GvH prophylaxis: Cyclosporine + Methotrexate	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)	3y K-M persistent cytogenetic relapse: BU/CY = 13% CY/TBI = 13% Pt's treated with IFN at cytogenetic persistent relapse	3y K-M EFS: BU/CY = 71% CY/TBI = 68% P=0.43 3y K-M OS: BU/CY = 80% CY/TBI = 80%	VOD not reported Subset analysis of patients <1 year from diagnosis: 4y K-M estimated OS: BU/CY and CY/TBI = 86%
Blume, K. Blood. 1993 April; 81(8): 2187. A Prospective Randomized Comparison of Total Body Irradiation-Etoposide VS. Busulfan-Cyclophosphamide as Preparatory Regimens for Bone Marrow Transplantation in Patients With Leukemia Who Were No in First Remission: A SWOG Study 1987-1991 accrual	Prospective, Randomized. BU/CY= BU 4 mg/.kg x 4d + CY 60 mg/kg x 2d VS. TBI/VP-16 (60 mg/kg x 1) TBI in 11 fx's, shielding not mentioned Stratified for Good Risk=CR2 or Accelerated CML Poor Risk=CR3, Induction failure, In Relapse, Blast phase CML	Leukemia failing prior therapy at least once AML=40 BU/CY=18 TBI=22 ALL=48 BU/CY=23 TBI=25 CML=34 BU/CY=20 TBI=14 Age stratification for: 0-20yo 21-50yo	Allogeneic Sibling donor BU/CY=61 TBI/VP-16=61 GvH prophylaxis: Cyclosporine + prednisone	No Mention	RR of Relapse expressed as BU/CY:TBI/VP-16 RR=1.02 95% CI=0.56-1.86	Med. F/U= 30 mo RR of Mortality expressed as BU/CY:TBI/VP-16 Mortality RR = 0.97 95%CI=0.64-1.48) OS and DFS were subset analyzed by good risk and poor risk – 3y K-M estimated Study had 89% power to detect RR 2.3	BU/CY = 3/61 VOD TBI/VP-16 = 0/61 VOD

Citation	Design and Dose	Disease	BMT Type	% Engrafted Median Days	%Relapse	%Survival Median Survival	Adverse Events
Devergie, A. Blood. 1995 April; 85(8): 2263-2268. Allogeneic BMT for CML in First Chronic Phase: A Randomized Trial of Busulfan-Cytoxan Versus Cytoxan-TBI as Preparative Regimen: A Report from the French Society of Bone Marrow Graft (SFGM). (1988-1991 accrual)	Prospective, Randomized BU/CY= BU 4 mg/kg x 4d + CY 60 mg/kg x 2d VS. CY/TBI = CY 60 mg/kg x 2d 12 patients single dose TBI, remainder varying fx's + lung shielding	CML, first chronic phase Age = 1-54 yo Med. Age=36 yo	Allogeneic, HLA identical sibling BU/CY = 65 CY/TBI = 55 GvH prophylaxis = cyclosporine + methotrexate 31 treated with anti-p55 MoAB (8/8)	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)	Median f/u 42 months Relapse defined as persistent cytogenetic relapse. On multivariate analysis treatment with CY/TBI was correlated with increased risk of relapse: RR=4.10 P=0.04	5y K-M OS: BU/CY =60.6%± 11.7% CY/TBI=65.8%± 12.5% P=0.5 5y K-M DFS: BU/CY = 59.1% ± 11.8% CY/TBI=51% ± 14% P=0.75	TRM: BU/CY = 38% CY/TBI = 29% P=0.44 VOD: BU/CY = 5 3/5 result in death CY/TBI = 4 1/4 result in death
Ringden, O. Blood. 1994 May; 83(9):2723. Randomized Trial Comparing Busulfan with TBI as Conditioning in Allogeneic Marrow Transplant Recipients with Leukemia: A Report from the Nordic BMT Group. (1988-1992 accrual)	Prospective, Randomized BU/CY= BU 4mg/kg x 4d + CY 60 mg/kg x 2d VS. CY/TBI (60 mg/kg x 2d) One center didn't fx TBI; other gave 3-7 fx's; +lung shielding Early dz=CML in CP, Lymphoma and Acute leukemia in firs remission Advanced dz= Beyond first CP.	Hematologic malignancy AML N=69 BU/CY=37 TBI=32 ALL N=38 BU/CY=18 TBI=20 CML N=57 BU/CY=30 TBI=27 Lymphoma N=4 BU/CY=3 TBI=1	Allogeneic HLA Identical BU/CY = 88 CY/TBI = 79 CML first CP: BU/CY = 22 CY/TBI = 24 CML Second, AP: BU/CY = 7 CY/TBI = 2 CML Blast Crisis: BU/CY = 1 CY/TBI = 1	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	3y K-M estimated relapse: BU/CY= 22% CY/TBI = 26% P=0.9	3y K-M estimated OS: BU/CY=62% CY/TBI=76% P<0.03 3y K-M estimated DFS: BU/CY = 56% CY/TBI= 67% P=0.065 DFS in Subset Analysis = Adults >17 yo (p<0.02) and Advanced disease had lower DFS on BU/CY (p=0.005) Subset analysis of the CML patients found no significant difference in 3y DFS, p=0.25. (BU/CY=67% TBI=83%)	TRM = 28% BU/CY 9% TBI/CY p=0.006 VOD : BU/CY=12% TBI/CY=1% (p=0.009) H. Cystitis: BU/CY= 24% TBI/CU=8% (p=0.003)

Citation	Design and Dose	Disease	BMT Type	% Engrafted Median Days	%Relapse	%Survival Median Survival	Adverse Events
		Age = 1-55 Med. Age 34 yo					

7.2.1 Overview of Level I Evidence in CML

The two studies in the summary table that had patient populations limited to CML (Clift and Devergie) both also limited participation to patients with CML in first chronic phase, employed HLA-matched sibling donor allotransplants, employed similar GvH prophylaxis, and used similar BU/CY doses. The median time to transplantation from diagnosis in both studies was under one year. Radiation methods used in the TBI arm varied between the studies, as TBI was individualized by center in the SFGM trial reported by Devergie. In addition, approximately 25% of participants on the SFGM trial were randomized to receive anti-p55 MoAb (distributed evenly between treatment arms) concurrent with methotrexate and cyclosporine for GvH prophylaxis. There were more graft failures reported in this study, and these occurred more commonly on the BU/CY arm, but neither of these studies, with eligibility limited to CML in chronic phase, found statistically significant differences between preparative regimens in terms of Kaplan-Meier probability of overall survival or disease free survival.

The studies differed in their findings regarding relapse. The estimated probability of relapse was comparable between arms in the study reported by Clift, but the multivariate analysis reported by Devergie in the SFGM study revealed the risk of relapse in the SFGM study was higher on the CY/TBI arm. The relative risk of relapse with CY/TBI in the SFGM study was 4.10; p=0.04 (95% CI=1.00-20.28). Nine of the 11 relapses observed at a median follow-up of 42 months occurred on the CY/TBI arm, and 8/9 of those relapses occurred in patients whose TBI was fractionated. Use of MoAB for GvH prophylaxis was also found to be associated with increased relative risk of relapse on multivariate analysis (RR = 4.69; p=0.006). Despite the suggestion of statistically higher relative risk of relapse on the CY/TBI arm of the SFGM study and the statistically non-significant higher transplant related mortality on the same arm, there was no significant difference between the arms in the Kaplan-Meier probability of overall survival and disease free survival at 5 years.

The Seattle study (Clift) did find that more patients on the CY/TBI arm (45) required more than one hospitalization in the first 100 days than on the BU/CY arm (24), p=0.0002, Fishers exact. The most common reasons for readmission were fever and GVHD of the gut. The mean total number of inpatient hospitalization days was longer on the CY/TBI arm – 49.99 (range 27-91±15.08) vs. 43.55 (range 26-127±14.51), p=0.015, Wilcoxon. The Kaplan-Meier incidence of ≥ grade 2 acute GVHD was higher on the CY/TBI – 0.48 v. 0.35, p=0/049. In the SFGM study the absolute incidence of ≥ grade 2 acute GVHD was 43% on CY/TBI (23/53) and 41% on BU/CY (24/59). The latter was not an intent to treat analysis. If the denominator was changed to reflect the total number of patients in each arm, the percentages change to 41.8% on the CY/TBI arm and 36.9% on the BU/CY arm. GVHD prophylaxis in both studies employed methotrexate and cyclosporine, although the SFGM study did have a subset of patients who received anti-P55 MoAb in addition. There were 3 graft rejections on the BU/CY arm in the SFGM study and none on the CY/TBI arm.

The remaining two level I studies included multiple different types of hematological malignancies and were discussed earlier in the AML analysis - the SWOG study reported by Blume and the Nordic BMT Group study reported by Ringden. Both examined BU/CY in the setting of HLA-identical allo-transplantation, and both used the same busulfan and cyclophosphamide doses reported in the Clift and Devergie studies, but in the Blume study TBI was combined with etoposide. Fractionated TBI predominated in both studies, but varied by center in the Nordic BMT Group study, which did include one center that used single dose TBI. Both of these studies

included participants with CML beyond first chronic phase, and the SWOG study eligibility criteria actually required that all participants with CML have disease beyond first chronic phase. The Nordic BMT Group study stratified CML into patients in first chronic phase and those beyond first chronic phase – 46/57 CML patients had disease in first chronic phase. All four of the level I studies in CML included both pediatric and adult patients.

The SWOG study yielded results similar to the studies whose participants had CML in first chronic phase, in that no statistically significant difference in relative risk of mortality was noted between the treatment arms. The relative risk of relapse was similar between arms in this study as well. The Nordic BMT Group study, however, did find a statistically significant higher Kaplan-Meier estimated 3 year overall survival on the CY/TBI arm (76% vs. 62% on the BU/CY arm, $p<0.03$). Three year probabilities of relapse free survival and relapse were not significantly different between groups, but treatment related mortality was significantly higher on the BU/CY arm. A subset analysis of the CML population on this study (57/167 total participants) found no difference in the estimated 3 year disease free survival between arms (CY/TBI=83% vs. BU/CY=67%; $p=0.25$).

7.2.2 Summary and Conclusion – CML

All but one of the four level I studies found no superiority in their comparison of BU/CY and TBI-based preparative regimens in allo-transplantation of CML. These studies lacked power to detect significant differences between the arms. The one exception, the Nordic BMT Group study, demonstrated superior probability of 3 year overall survival and treatment related mortality associated with a CY/TBI preparative regimen for the study's entire population of mixed hematological malignancies. Subset analysis of the CML population in this study found no significant difference in DFS between arms. Based on the data provided from these four level I studies, it cannot be concluded that BU/CY is superior to a TBI preparative regimen, but can one conclude from the level I evidence presented in this review that BU/CY is equivalent to CY/TBI? The International Bone Marrow Transplant Registry data for CML as reported by Copelan[17] also demonstrated similarities between the regimens - BU/CY was associated with a 2 year leukemia-free survival of 52% ± 11%, compared to 59% ± 6% for CY/TBI. If one could conclude that the two regimens are equivalent, has CY/TBI been established as effective conditioning therapy for BMT in CML?

The biostatistical review team attempted to answer the question of equivalence by examining the data published in the two level 1 studies that limited participation to CML – the reports by Devergie and Clift. Unfortunately, the fact that the Kaplan-Meier probabilities in these two studies were reported in different time frames (3 years vs. 5 years) precluded combining the patient populations from the two studies in an effort to increase the power to establish equivalence between the studies. The biostatistical reviewer approached the equivalence issue within each individual study by calculating a confidence interval for the observed differences in the probabilities of survival associated with each treatment arm, and used the width of the resulting confidence interval to evaluate the validity of any claim of equivalence between the two arms. In the Clift article the confidence intervals for the 3 year Kaplan-Meier product limit estimates for survival were not provided. The biostatistical reviewer treated the estimates as proportions and, using binomial distribution, found the 95% confidence intervals for the difference of EFS between treatments arms (BU/CY minus CY/TBI) to be (-12%, 18%), while the 95% confidence interval for the difference in 3 year overall survival rates between the two arms was (-13% and 13%). In the Devergie article, when the Kaplan-Meier product limit

estimates were treated as proportions, the 95% confidence interval for the difference in DFS at 5 years between the treatment arms (BU/CY minus CY/TBI) was (-23%, 12%), and for the difference in overall survival rates at 5 years was (-10%, 25%). (This paper reported the Kaplan-Meier estimates with "± limits" that were not clearly specified to be standard errors or confidence intervals, but the biostatistical reviewer believed that they represented 95% confidence intervals) The biostatistical reviewer's derived confidence intervals for each of these two level 1 studies that limited participation to CML are not "tight", but in terms of overall survival the greatest derived inferiority with regard to BU/CY was 13%, which might be viewed as reasonable grounds for considering these two preparative regimens similar, based on these two level I studies.

Is CY/TBI an effective conditioning regimen for BMT in CML? The most commonly reported preparative regimen in the literature evaluating the efficacy of BMT in CML has been CY/TBI. This reflects in a large part this regimen's historical position in the development of transplantation as a clinical tool.[19] Allogeneic bone marrow transplantation has a definitive role in the treatment of chronic myelogenous leukemia. It is the only known curative therapy available for this disease. [20] Five year leukemia free survival (LFS) after HLA-identical sibling bone marrow transplantation for CML in chronic phase has been reported to range 50-60%,[21] while treatment with hydroxyurea is not associated with LFS. Clift has reported in 1993 that in Seattle's experience with 189 adults in chronic phase CML allotransplanted < 1 year from diagnosis, there was a 90% probability of 1 year survival and a 5 year probability of survival of 81%. The preparative regimens used were either CY/TBI or BU/CY.[22] Applebaum reported in 1995 that in 400 patients transplanted in Seattle for CML with matched sibling donor marrow (and conditioning with either CY/TBI or BU/CY) there was a 5 year probability of survival of 75% in those transplanted in chronic phase, 50% for transplants in acute phase, and 10% for those performed in bast crisis.[23] How does this compare to more conservative therapy?

In an effort to assess the relative efficacy of transplantation compared to outcomes that could be expected with less aggressive therapy, Gale, et al, published a retrospective, historical control study comparing the survival in this disease of 548 HLA-identical sibling transplant recipients reported to the International Bone Marrow Transplant Registry to the survival of 196 patients treated with either hydroxyurea or interferon in a randomized trial conducted by the German CML Study Group. The transplantation patients were diagnosed between 1983 and 1991 and had had a median follow-up of 4.3 years. The German CML Study Group patients were diagnosed between 1983 and 1990, and had a median follow-up of 6.5 years. Bias introduced by differences in time to treatment and baseline patient characteristics between the groups was recognized and an effort was made to compensate for these through the use of proportional hazards regression with fixed and time-dependent variables. Variables including age and Sokal score (a scoring system used to derive a hazard ratio for mortality based on spleen size, platelet count, percentage of peripheral blasts, and either age or sex plus hematocrit) were considered in the analysis. The median age was 35 yo on the transplant arm (15-54) and 41 yo on the hydroxyurea/interferon arm (15-55). Unfortunately, the preparative regimens used for transplantation were not specified in this publication.

When the transplant recipients who had sufficient data to assign Sokal scores (211/548) were evaluated for survival differences based on Sokal scores, no impact was detected. Because of this, Sokal scores on the transplantation arm were not factored into further comparative analyses between arms. The 7 year probability of survival was 58% (52-64%) for transplanted patients vs. 49% (34-63%) in the Sokal low risk patients treated on the interferon/hydroxyurea arm. A statistically significant advantage for transplant was not seen in this analysis until 7.8 years after diagnosis – after the survival curves had crossed. When the subset of patients transplanted within 1 year of diagnosis was compared to low-risk (Sokal) patients treated with

hydroxyurea/interferon, the 7 year probability of survival was 67% (60-73%) compared to 49% (34-63%), respectively. A statistically significant advantage was not seen until 6.5 years – again after the curves had crossed. The comparison of Sokal intermediate/high risk patients treated on the German study to transplanted patients demonstrated a 7 year probability of survival of 58% (52-64%) with transplantation and 21% (12-31%) on the hydroxyurea/interferon comparator arm. A statistically significant advantage was seen with transplantation at 4.7 years. The subset of transplanted patients who were treated within one year of diagnosis again demonstrated a superior 7 year probability of survival of 67% (63-73%) compared to 21% (12-31%) in the high risk hydroxyurea/interferon comparator. These curves crossed as well. The statistically significant survival advantage for transplantation was not seen until after 4 years. The curves in all these comparisons crossed - the early probability of survival was higher on the interferon/hydroxyurea. The comparative analysis of the transplanted vs. non-transplanted groups as a whole demonstrated an early statistically significant survival disadvantage in the first 1.8 years for patients transplanted with CML, but a delayed statistically significant advantage with the same treatment at 4.8 years. The median survival of the interferon treated patients in the German CML Study Group trial was 5.5 years.[24] The median survival of those treated with hydroxyurea was 4.7 years, and an additional cohort on that study treated with busulfan had a median survival of 3.8 years.

In a recent article by Lee,[20] et al, it has been recommended that patients <40 yo undergo allogeneic transplantation within a year of diagnosis because there have been data that suggest there is a survival advantage for transplantation in CML when it is performed within a year of diagnosis of chronic phase disease.[21] Patients who are aged 40-50 yo, desire curative therapy, and have related donors are also recommended to undergo allo-transplant within the first year for optimal life expectancy. Patients without a related donor in this age range who have a high Sokal score are considered a group that will benefit by going directly to allotransplantation as well.

Reviewer Comment on Sponsor's Literature Review Analysis: The sponsor has concluded from their analysis of the data derived from their 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 CML who underwent allogeneic transplantation." Because of the paucity of data regarding autologous transplantation in this disease, the sponsor has only included allogeneic transplantation in their conclusions for efficacy drawn from the literature analysis. The reviewer again finds fault with the methodology the sponsor employed for their analysis of this dataset. Not only were phase 2 studies given equal weight to randomized, controlled studies, but pertinent studies from the "overall dataset" that reported survival data were not included. The studies evaluated by the sponsor differed from each other in a number of ways, including the preparative regimens used and eligibility criteria by disease stage. The endpoints of overall survival, DFS, and relapse were analyzed by tallying the number of patients who met each endpoint for each study and dividing by the total number at risk from all those studies. The overall crude percentage associated with a busulfan preparative regimen was then presented in a summary table. The fact that these endpoints were each described in reference to different time frames or with varying amounts of median follow-up among this heterogeneous group of studies, was acknowledged but discounted in this analysis methodology. The time reference for Kaplan-Meier estimates of efficacy from the studies were combined to create a time range, and associated then with a combined range of estimated probabilities for these endpoints. This range was compared to "reference" ranges derived from the literature to derive a final summary conclusion regarding the comparative efficacy of busulfan.

Despite the reviewer's reservations regarding the sponsor's methodology for summarizing and analyzing the efficacy data from the literature, the reviewer concurs that the preponderance of

data does not indicate that a BU/CY preparative regimen is an inferior conditioning therapy in CML, and is, in fact, a commonly used regimen for allogeneic transplantation in this disease. However, as discussed above, these studies were not powered to detect significant differences between these treatment regimens, or equivalence. The confidence intervals derived by the biostatistical review team do not definitively demonstrate that BU/CY is equivalent to CY/TBI, but in terms of overall survival the maximum inferiority that could be anticipated associated with BU/CY, is relatively small – 13% - which may be a basis to conclude that the regimens are similar in efficacy. CY/TBI is a commonly used preparative regimen in this disease, but its efficacy is inferred from historical comparisons. BU/CY was used as preparative therapy in uncontrolled series that are found in the literature used to support the role of transplantation in CML.[23] Busulfan is the conditioning therapy for two phase 3 trials currently underway in Europe – "Phase 3 randomization Study of Consolidation/Maintenance Therapy for CML Using HU/IFN-A, Allo-BMT or Ara-C/IDA followed by IFN-A" sponsored by the German CML Group, and "Phase 3 Randomization Study of Interferon Alfa Alone vs. Before and After Idarubicin/Cytarabine and Autologous Stem Cell Transplantation vs. Allogeneic BMT for Newly Diagnosed CML in Chronic Phase CML" sponsored by the MRC. The conditioning regimen in the latter protocol uses busulfan and/or TBI. A search of the NCI PDQ data based of U.S. cooperative group trials did not reveal ongoing BMT studies in CML, although the ECOG activated a study in 1997 that it is conducting with the MRC, "Phase 3 Prospective Randomized Study Comparing Interferon vs. Autologous Peripheral Blood Stem Cell Transplantation vs. Allogeneic Bone Marrow Transplantation in Newly Diagnosed Chronic Phase CML," which appears to be the same study mentioned above in the European trials.

7.3 *Acute Lymphoblastic Leukemia*

The following table summarizes the level of evidence provided in the articles in the sponsor's "core dataset" that pertain to ALL.

Table 26 Summary List of Sponsor's Core Database Articles Pertaining to ALL

ALL – only patient population				
Study	**Level of Evidence**	**No. of Pt's**	**Study Design**	
Von Bueltzingsloewen	III	40	Uncontrolled, Retrospective	
ALL represented in a mixed disease study population				
Study	**Level of Evidence**	**No. of Pt's**	**Study Design**	**Diseases**
Ringden	I	38*(18/20) (167)	Randomized, Controlled, Open Label	AML, ALL, CML, "Lymphoma"
Angelucci	III	12 (30)	Retrospective, uncontrolled	ALL, ANLL, CML, MM, MDS
Ballester	III	2 (51)	Uncontrolled, Phase 1-2	NHL, MM, AML, CML, ALL

Chiang	III	**5** (23)	Uncontrolled, Prospective	CML, ALL, AML, NHL, HD, MDS
Kapoor	III	**19** (127)	Uncontrolled, Prospective	CML, AML, ALL, MDS, Lymphoma
Przepiorka	III	**2** (30)	Prospective, Phase 1-2	AML, ALL, CML, MDS, Lymphoma
Przepiorka	III	**19** (85)	Uncontrolled, Prospective	AML, ALL, CML, MDS
Sahebi	III	**7** (65)	Retrospective	AML, ALL, CML, MDS
Spitzer	III	**30** (77)	Retrospective	AML, ALL, CML, MDS, NHL, HD, CLL, PLL
Srivastava	III	**1** (24)	Uncontrolled, Retrospective?	ALL, NHL, HD, MM, solid tumors
Topolsky	III	**1** (25)	Retrospective?	AML, CML, ALL, MDS, MM
Tutschka	III	**6** (50)	Uncontrolled, Prospective	AML, CML, ALL
Vaughn	III	**3** (24)	Historic Control	AML, ALL, CML, HD, NHL
Vey	III	**2** (25)	Uncontrolled, Prospective	AML, ALL, CML, Lymphoma
von Bueltzingsloewen	III	**22** (101)	Retrospective	AML, ALL, CML, MDS

* The bold number represents the number of participants in the study with a diagnosis of ALL.

In summary, there is one level I study included in the sponsor's "core dataset" that includes patients with ALL, and that study involves participants with multiple types of hematological malignancies. The remaining 15 studies offer only Level III evidence. The only study that limited eligibility to ALL is a Level III study.

The following table summarizes the additional pertinent studies in the literature identified by the reviewer and not included in the sponsor's 43 article "core dataset".

Table 27 Summary List of Additional Pertinent ALL Studies Identified by Reviewer

ALL*- only patient population				
Study	**Level of Evidence**	**No. of Pt's**	**Study Design**	
Carpenter	III	26	Hisorical Control	
Copelan	III	39	Uncontrolled, Prospective?	