U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 21602
Supplement #:	0042
Drug Name:	Velcade® (Bortezomib)
Indication(s):	No new indication was sought
Applicant:	Millennium Pharmaceutical Inc.
Date(s):	Submission Date: March 25, 2015
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Review Priority:	Priority
Biometrics Division:	V
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Keywords: Second complete remission, written request, pediatric exclusivity

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1 EXECUTIVE SUMMARY

Bortezomib (Velcade®) received marketing approvals for the treatment of patients with previously untreated and relapsed multiple myeloma (MM) and mantle cell lymphoma (MCL). This supplemental New Drug Application (sNDA) is submitted to fulfill a written request for pediatric exclusivity determination and to update labeling Section 8.4 on pediatric use of Velcade. Reference is made to pediatric written response amendment 2 dated November 13, 2012. The effectiveness of Velcade in pediatric patients has not been established. Therefore, no new indication is sought. Children's Oncology Group (COG) Study AALL07P1, a phase II pilot trial, was submitted to support the proposed revisions.

In Study AALL07P1, the primary efficacy endpoint was second complete remission (CR2) rate at the end of block 1 therapy for pediatric and young adult patients with relapsed acute lymphoblastic leukemia (ALL) treated with Velcade in combination with intensive re-induction chemotherapy. CR2 at the end of Block 1 therapy, which included 35 days of study treatment, was evaluated in the first 60 evaluable pre-B cell ALL patients to enroll in stratum 1 (patients who relapsed less than 18 months from diagnosis [n=27]) and stratum 2 (patients who relapsed 18-36 months from diagnosis [n=33]).

The CR2 rate at the end of Block 1 therapy was 68.3% (95% CI: [55.0%, 79.7%]) for first 60 evaluable pediatric and young adult patients (<= 21 years) with pre-B cell ALL relapsed within 36 months of diagnosis. The CR2 rate was 63.0% (95% CI: 42.4, 80.6) for patients relapsed within 18 months of diagnosis (stratum 1), and 72.7% (95% CI: 54.5, 86.7) for patients relapsed between 18 and 36 months of diagnosis (stratum 2).

No new safety concerns were observed when Velcade was added to the standard pediatric pre-B cell ALL chemotherapy backbone regimens as compared to reported safety results from a historical study in which the backbone regimen was given alone.

Because this study was a single arm trial, all statistical analyses are descriptive. The statistical reviewer considers study AALL07P1 results support the change of the labeling section 8.4 on pediatric use of Velcade and fulfill the requirement for a Phase II study in the written request. Pediatric exclusivity was granted for studies conducted with Velcade by the Pediatric Exclusivity Board effective August 14, 2015.

2 INTRODUCTION

2.1 Overview

The applicant submitted Study AALL07P1 to support the labeling changes on pediatric use of Velcade and to fulfill a written request for pediatric exclusivity determination. This study was an open-label phase 2 study to determine the feasibility and safety of adding Velcade to intensive induction chemotherapy for patients with relapsed B-cell precursor ALL, relapsed T-cell ALL, and relapsed T-cell lymphoblastic lymphoma (LL). The goal of this study aimed to improve outcomes in relapsed ALL by combining Velcade with the backbone chemotherapy regimen used for treatment of relapsed ALL in the previous COG study AALL01P2.

The primary objective of study AALL07P1 was to estimate the toxicity, second complete remission (CR2) rate at the end of Block 1 therapy, which included 35 days of study treatment, and 4-month event-free survival (EFS) for pediatric and young adult patients with relapsed ALL treated with Velcade in combination with intensive re-induction chemotherapy. The primary efficacy endpoint was second complete remission (CR2) rate at the end of block 1 therapy. CR2 is defined as re-induced complete remission in relapsed patients.

This study enrolled patients in 5 strata based on disease type, age, and time from initial diagnosis to relapse:

- Stratum 1: pre-B-cell ALL patients less than or equal to 21 years old with relapse less than 18 months from diagnosis (R<18 months)
- Stratum 2: pre-B-cell ALL patients less than or equal to 21 years old with relapse 18 to 36 months from diagnosis (R=18-36 months)
- Stratum 3: pre-B-cell ALL patients greater than 21 years old
- Stratum 4: T-cell ALL in first relapse
- Stratum 5: T-cell LL in first relapse

Study AALL07P1 enrolled 140 patients across 5 strata, among which 47 patients were in stratum 1 and 57 were in stratum 2. Only CR2 rate for first 60 evaluable patients in stratum 1 (27 patients) and stratum 2 (33 patients) were summarized to support the proposed revisions in this sNDA submission.

2.2 Data Sources

The application's data (including raw and analysis datasets) for this study located at the following link: (b) (4)

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant provided raw datasets, analysis data sets and the defined files for the variables in the submission. The reviewer was able to duplicate the analysis results based on the applicant's submitted datasets.

3.2 Patient Disposition, Demographic and Baseline Characteristics

Table 1 shows the summary of patients' disposition for first 60 eligible patients in strata 1 and 2. The majority of patients (37%, including 8 patients in Stratum 1 and 14 patients in Stratum 2) completed planned therapy. The most common primary reason for discontinuation of therapy was progressive disease, which occurred in 10 patients (17%), 22% in Stratum 1 and 12% in Stratum 2.

Table 1 Patient Disposition

	Stratum 1 Pre-B ALL Age <=21 Relapse < 18 mth from dx N=27 n (%)	Stratum 2 Pre-B ALL Age <=21 Relapse 18-36 mth from dx N=33 n (%)	Total Pre-B ALL Age <= 21 N=60 n (%)
Subjects off protocol therapy	27 (100)	33 (100)	60 (100)
Primary reason off protocol therapy			
Completion of planned therapy	8 (30)	14 (42)	22 (37)
Progressive disease	6 (22)	4 (12)	10 (17)
Physician determines it is in patient's best interest	3 (11)	6 (18)	9 (15)
Second relapse at any site	6 (22)	2 (6)	8 (13)
Death	2 (7)	3 (9)	5 (8)
Refusal of further protocol therapy by patient/parent/guardian	2 (7)	3 (9)	5 (8)
Adverse events/side effects/complications	0	1 (3)	1 (2)

[Source: Table 14.1.1.1A in Study AALL07P1 CSR Supplement submitted on June 10, 2015 Pages 2 and 3 and statistical reviewer's analysis]

Table 2 shows the summary of demographic characteristics for first 60 eligible patients in strata 1 and 2. For the first 60 evaluable patients in Strata 1 and 2, the distribution of gender was similar across the 2 strata with a total of 31 female patients (52%) overall. The majority of patients were white (41 patients, [68%]). The majority of the patients (58.3%) were between the ages of 2 and 11 years, inclusive, with a median age of 8.5 years at enrollment.

Table 2 Demographic characteristics

	Stratum 1 Pre-B ALL Age <=21 Relapse < 18 mth from dx N=27 n (%)	Stratum 2 Pre-B ALL Age <=21 Relapse 18-36 mth from dx N=33 n (%)	Total Pre-B ALL Age <= 21 N=60 n (%)
Sex, n (%)			
Male	14 (52)	15 (45)	29 (48)
Female	13 (48)	18 (55)	31 (52)
Race, n (%)			
White	17 (63)	24 (73)	41 (68)
Black or Africa American	5 (18)	6 (18)	11 (18)
Asian	1 (4)	2 (6)	3 (5)
Missing	4 (15)	1 (3)	5 (8)
Age (years)			
Mean (SD)	8.2 (6.3)	10.3 (5.9)	9.4 (6.1)
Median	8.0	9.0	8.5
Min, Max	1.0, 21.0	2.0, 21.0	1.0, 21.0
Category, n (%)			
< 2	4 (14.8)	0	4 (6.7)
2 – 11	15 (55.6)	20 (60.6)	35 (58.3)
12 – 16	4 (14.8)	6 (18.2)	10 (16.7)
>16	4 (14.8)	7 (21.2)	11 (18.3)
Baseline Height (cm)			
Mean (SD)	121.4 (37.5)	138.5 (27.7)	130.8 (33.3)
Median	125.4	138.9	134.5
Min, Max	29.5, 188.0	78.0, 189.0	29.5, 189.0
Baseline weight (kg)			
Mean (SD)	39.2 (32.0)	46.4 (26.6)	43.2 (29.1)
Median	29.1	39.7	37.3
Min, Max	7.5 126.4	10.8, 108.6	7.5, 126.4

[Source: Table 14.1.1.2A in Study AALL07P1 CSR Supplement submitted on June 10, 2015 Pages 4 and 5, and statistical reviewer's analysis]

Table 3 shows the baseline disease characteristics for first 60 evaluable patients in strata 1 and 2. The majority (52 patients, 86.7%) of the first 60 evaluable patients had a baseline ECOG performance score of 0. Only one patient from stratum 2 was refractory to at least one TKI. All first 60 evaluable patients had relapse in the bone marrow, 10 (16.7%) also had relapse in central nervous system (CNS), and one also had relapse in left kidney. Median percentage of ALL blasts in bone marrow at the time of relapse was 82.5%, and the median percentage of ALL blasts in the periphery was 15.0%. Median first peripheral WBC count at time of relapse was $5.3*10^3$/uL with a range of $0.3 *10^3$/uL to $2100*10^3$/uL.

Table 3 Patients' baseline disease characteristics

	Stratum 1 Pre-B ALL Age <=21 Relapse < 18 mth from dx N=27 n (%)	Stratum 2 Pre-B ALL Age <=21 Relapse 18-36 mth from dx N=33 n (%)	Total Pre-B ALL Age <= 21 N=60 n (%)
Baseline ECOG performance status, n (%)			
0	23 (85.2)	29 (87.9)	52 (86.7)
1	3 (11.1)	4 (12.1)	7 (11.7)
2	1 (3.7)	0	1 (1.7)
Ph+ ALL refractory to at least 1 TKI, n (%)			
Yes	0	1 (3.0)	1 (1.7)
No	0	0	0
Not Applicable	27 (100.0)	32(97.0)	59 (98.3)
Site of relapse (for all subjects), n (%)			
Bone marrow	25 (92.6)	24 (72.7)	49 (81.7)
Bone marrow, CNS	1 (3.7)	9 (27.3)	10 (16.7)
Bone marrow, left kidney	1 (3.7)	0	1 (1.7)
Marrow blasts			
Mean (SD)	73.7 (19.8)	78.4 (20.4)	76.3 (20.1)
Median	78.0	86.0	82.5
Min, Max	30.0, 98.0	5.0, 100.0	5.0, 100.0
First peripheral blasts			
Mean (SD)	24.0 (28.5)	23.7 (25.8)	23.8 (26.8)
Median	12.0	17.0	15.0
Min, Max	0, 84.0	0, 95.0	0, 95.0
First peripheral WBC count (10^3/uL) at time of relapse			
Mean (SD)	40.4 (134.7)	75.2 (363.8)	59.5 (283.0)
Median	4.7	5.4	5.3
Min, Max	0.3, 700.0	1.5, 2100.0	0.3, 2100.0

ECOG: Eastern Cooperative Oncology Group; ALL: Acute Lymphoblastic Leukemia; TKI: Tyrosine Kinase Inhibitor; CNS: central nervous system; SD: Standard deviation; WBC: White blood cell
[Source: Table 14.1.1.3A in Study AALL07P1 CSR Supplement submitted on June 10, 2015 Pages 6 and 7, and statistical reviewer's analysis]

3.3 Efficacy analysis results

Table 4 summarizes the efficacy results for fulfilling written request for pediatric exclusivity and supporting labeling change in section 8.4 of Pediatric use. The overall CR2 rate at the end of block 1 therapy for first 60 evaluable patients was 68.3%, with 95% CI (55.0%, 79.7%). Median EFS was 7.0 months with 95% CI (2.9, 10.3) months. The 4-month EFS rate was 55.0% with 95% CI (41.6%, 66.5%).

Table 4 Efficacy results for first 60 evaluable patients

	Stratum 1 Pre-B ALL Age <=21 Relapse < 18 mth from dx N=27 n (%)	Stratum 2 Pre-B ALL Age <=21 Relapse 18-36 mth from dx N=33 n (%)	Total Pre-B ALL Age <= 21 N=60 n (%)
CR2 rate at the end of Block 1 therapy, n (%) (95% CI)	17 (63.0) (42.4, 80.6)	24 (72.7) (54.5, 86.7)	41 (68.3) (55.0, 79.7)
Event-free survival (EFS)			
Number of Event, n (%)	22 (81.5)12/03	21 (63.6)	43 (71.7)
Median EFS (Months) (95% CI)	3.0 (2.2, 7.1)	8.6 (3.5, 17.4)	7.0 (2.9, 10.3)
4-month EFS rate (%) (95% CI)	40.7 (22.5, 58.2)	66.7 (47.9, 80.0)	55.0 (41.6, 66.5)

CR2: second complete remission; CI: confidence interval
[Source: Table 14.1.1.3A in Study AALL07P1 CSR Supplement submitted on June 10, 2015 Pages 8 and 10, and statistical reviewer's analysis]

Reviewer's note: The Study AALL07P1 was designed to test the null hypothesis that adding bortezomib to the standard backbone chemotherapy derived in Study AALL01P2 gives an overall (across strata) CR2 rate of 67%. The alternative hypothesis was that CR2 rate was 79%. In addition, CR2 rate at the end of Block 1 therapy was 72%, 4-month EFS rate was 65% from a historical study (Raetz et al.) for the similar target population. Therefore, the effectiveness of Velcade in pediatric patients was not established in Study AALL07P1.

Study AALL07P1 was submitted to fulfill the phase 2 study requirement in the written request for pediatric exclusivity. Please refer to the pediatric written request amendment 2 for NDA 21602 dated November 13, 2012 for further details. Table 5 summarizes the written request items and corresponding response submitted in this sNDA submission. From statistical point of view, Study AALL07P1 fulfills the written request for the type of study, indications to be studied, study objectives, age groups and total number of patients to be studied, minimum number of patients in certain age groups, study endpoints, the statistical design, and analysis methods.

Table 5 Pediatric Exclusivity Determination for Velcade®

Written Request Items	Information Submitted
Type of study: Non randomized study to evaluate activity, safety, and PK of bortezomib administered with multi-agent ALL re-induction therapy in patients with relapse within 18 months of diagnosis (stratum 1) or relapse 18-36 months from diagnosis (stratum 2). **Indications to be studied**: Pre-B-cell ALL in first relapse within 36 months of original diagnosis. **Objectives**: To estimate CR2 rate achieved at the end of Block 1 therapy, and the four month event-free survival; to evaluate the toxicity and pharmacokinetics of the regimen. **Age group in which the study will be performed**: Patients of age 1 to 21 years are eligible; however, a minimum of 5 patients in the 12-16 age group and 25 in the 2-11 age group will be enrolled. **Number of patients to be studied**: At least 30 patients are to be enrolled in Stage 1. If the number of patients with CR2 at the end of Stage 1 meets the pre-specified decision boundaries and the adverse event profile is favorable, 30 additional patients will be enrolled in Stage 2. **Study endpoints**: Toxicities of when administered with ALL multi-agent re-induction chemotherapy, CR2 rate after block 1 re-induction therapy; 4-month EFS **Statistical information**: The study will use a stratified two-stage phase II design to test the null hypothesis that adding bortezomib to the AALL01P2 backbone gives an overall (across strata) CR2 response rate of 67%. CR2 response will be assessed at the end of Stage 1 and, if necessary, again at Stage 2. The power of a global one-sample test against the alternative hypothesis that the CR2 response is 79% is at least 80% assuming a one-sided alpha of 10%. A total of 60 patients will be potentially enrolled. A total of 30 patients will be enrolled in Stage 1. Decision boundaries may be used to assess CR2 with respect to the null hypothesis at the end of Stage 1 and also to decide whether to enroll 30 additional patients in Stage 2. The overall CR2 rate must be estimated at the end of the study with an appropriate 2-sided 95% confidence interval. Descriptive statistics will be provided for CR2 responses by stratum.	Study AALL07P1 was a single-arm trial which enrolled 140 patients across 5 strata defined in section 2.1, among which 47 patients were in stratum 1 and 57 were in stratum 2. Analyses results from first 60 evaluable patients from strata 1 and 2 were submitted in this sNDA submission. All 60 patients had pre-B cell ALL in first relapse within 36 months of original diagnosis, and were ≤ 21 years old, with 35 patients in the 2-11 age group and 10 in the 12-16 age group. The overall CR2 rate was 68.3% (95% CI: [55.0%, 79.7%]). The CR2 rate was 63.0% (95% CI: 42.4, 80.6) for patients in stratum 1, and 72.7% (95% CI: 54.5, 86.7) for patients in stratum 2. Please refer to clinical and pharmacokinetic reviews respectively for this sNDA submission for toxicity and PK profiles of bortezomib administered with multi-agent ALL re-induction therapy in patients with relapse within 36 months of diagnosis.

4 SUMMARY AND CONCLUSIONS

4.1 Conclusions and recommendations

In summary, based on study AALL07P1, the results demonstrated a second complete remission rate at the end of Block 1 therapy of 68.3% (95% CI: [55.0%, 79.7%]), a median EFS of 7.0 months (95% CI: [2.9, 10.3], and 4-month EFS rate of 55.0% (95% CI: [41.6%, 66.5%]) for first 60 evaluable pediatric and young adult patients (<= 21 years) with pre-B cell ALL treated with Velcade in combination with intensive re-induction chemotherapy.

In conclusion, this statistical reviewer confirms the applicant's results submitted. The statistical reviewer considers study AALL07P1 results support the change of the labeling section 8.4 on pediatric use of Velcade and fulfill the requirement for a Phase II study in the written request. Pediatric exclusivity was granted for studies conducted with Velcade by the Pediatric Exclusivity Board effective August 14, 2015.

4.2 Labeling recommendations

The proposed addition of section 8.4 on pediatric use of Velcade in the product labeling is acceptable.

Reference

Raetz EA, Borowitz MJ, Devidas M, Linda SB, Hunger SP, Winick NJ, et al. Reinduction platform for children with first marrow relapse of acute lymphoblastic Leukemia: A Children's Oncology Group Study. J Clin Oncol 2008; 26(24):3971-3978.

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/s/

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