CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	21602 42
Priority or Standard	Priority
Submit Date(s)	3/25/15
Received Date(s)	3/25/15
PDUFA Goal Date	9/25/15
Exclusivity Determination	9/21/15
Division / Office	DHP/OHOP
Reviewer Name(s)	Patricia Dinndorf
Review Completion Date	8/14/15
Established Name	Bortezomib
Trade Name	Velcade
Therapeutic Class	Proteasome inhibitor
Applicant	Millennium Pharmaceuticals
Formulation(s)	Single-use vial 3.5 mg as a lyophilized powder
Dosing Regimen	Not applicable
Indication(s)	None
Intended Population(s)	None

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend that the Pediatric Exclusivity be granted for Velcade (bortezomib) and pediatric information be included in the Velcade labeling.

My recommendation is based on the review finding that the Applicant completely responded to all the elements in the Pediatric Written Request.

1.2 Risk Benefit Assessment

The risk profile of bortezomib in the pediatric population appears to be similar to that seen in the adult population. However, this submission provided no evidence of activity for botezomib in the pediatric population of patients with relapsed or refractory acute leukemia. Therefore, the risks associated with bortezomib use in the pediatric population are without benefit and such a use is not recommended.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable.

1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: Bortezomib
Proprietary Name: Velcade
Applicant: Millennium Pharmaceuticals, Inc.
Pharmacological Class: Proteasome inhibitor
Proposed Indication: There is no proposed pediatric indication.
Proposed Dosage and Administration: There is no proposed dose or route of administration in pediatric patients

2.2 Tables of Currently Available Treatments for Proposed Indications

There is no proposed indication in pediatric patients.

2.3 Availability of Proposed Active Ingredient in the United States

Bortezomib is available as a single-use vial 3.5 mg as a lyophilized powder.

2.4 Important Safety Issues With Consideration to Related Drugs

Not applicable.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Regulatory History	
July 1998	Original IND 56515 submitted
January 2001	ADVL0015 opens under CTEP IND 58443
January 2004	ADVL0317 opens under CTEP IND 58443
May 2003	Original NDA 21602 accelerated approval for treatment of multiple myeloma patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy
March 2005	Accelerated approval for treatment of multiple myeloma patients who have received as least one prior therapy
December 2006	Regular approval for patients with mantle cell lymphoma who have received as least one prior therapy
June 2008	Regular approval for treatment of patients with multiple myeloma
	Regular approval treatment of patients with mantle cell lymphoma.
March 2009	AALL07P1 opens under CTEP IND 58443
April 2010	Original Pediatric Written Request
January 2011	Amendment #1 Pediatric Written Request
June 2011	AAML1031 (Bortezomib and Sorafenib) under CTEP IND 114480
November 2012	Amendment #2 Pediatric Written Request
March 2015	sNDA 21602 42 submitted to fulfill Pediatric Written Request

2.6 Other Relevant Background Information

The applicant is not seeking approval of bortezomib for any pediatric indications.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contains the debarment certificate, sufficient datasets, and relevant CRFs. The overall quality and integrity of the submission is adequate.

3.2 Compliance with Good Clinical Practices

The study reports for ADVL0015, ADVL0317, AALL07P1, and AAML1031 include the following statement:

> This study was performed in accordance with Good Clinical Practice (GCP), according to the International Conference on Harmonisation (ICH) final guideline (01 May 1996) and including the archiving of essential documents.

3.3 Financial Disclosures

Form 3454 is attached and option 1 chosen:

> As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

There are 2 appendices.

- Appendix A: List of Investigators with no financial interest n=478
- Appendix B: List of investigators where the applicant was unable to obtain financial disclosure information. There were 53 investigators listed. The reason for inability to obtain forms included:
  - No longer at site n=42
  - Maternity Leave n=4
  - Retired n=4
  - Removed from the protocol n= 2
  - Leave of absence n= 2
  - Rarely on site n=1

REVEWER COMMENT:
The data from studies ADVL0015, ADVL0317, and AAML1031 was limited to PK and safety data. It is unlikely financial interest of the investigators with missing forms would have resulted in significant inaccuracies. There were 140 patients enrolled on AALL07P1 from 79 institutions (number of patients from individual institutions - median 1, mean 1.8, range 1 to 6). It is unlikely financial interest of the investigators with missing forms could have resulted in a significant change of the efficacy results, especially as the study failed to demonstrate efficacy.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Not applicable.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Not applicable.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

(copied from submission eCTD Efficacy Supplement submitted 3/25/15 Section 2.5 Clinical Overview page 7-8)

Bortezomib a dipeptidyl boronic acid, is a selective inhibitor of the 20S proteasome, and it has unique pro-apoptotic effects. Proteasome inhibition stabilizes many cell cycle regulatory proteins that are overexpressed in leukemia cells. Previous studies have shown that proteasome inhibition may sensitize malignant hematologic cells to apoptosis induced by both radiation and chemotherapy. Apoptosis following proteasome inhibition is seen in leukemia cell lines and in primary ALL lymphoblasts but not in normal hematopoietic progenitors. Important regulatory proteins affected by inhibition of the ubiquitin proteasome pathway system include nuclear factor-κB (NF-κB), p53, Bax, and other cell cycle regulatory proteins such as the cyclin-dependant kinase inhibitors p27 and p21. It is believed that proteasome inhibition alters the ratio of pro-apoptotic and antiapoptotic proteins within a cell, resulting in an increased sensitivity to apoptosis.

4.4.2 Pharmacodynamics

See clinical pharmacology review.

4.4.3 Pharmacokinetics

See clinical pharmacology review.

5 Sources of Clinical Data

Four trials were conducted in support of this application. In addition results of a trial of backbone chemotherapy in pediatric patients with first relapse of pre B-cell ALL were used as the historical control of the phase 2 ALL trial.

5.1 Tables of Studies/Clinical Trials

Trials Included in the Submission			
Protocol ID Section	**Report Type**	**Title**	**Comment**
ADVL0015 5.3.1	Clinical Study Report	A Phase I Study of PS-341 in Pediatric Patients with Refractory Solid Tumors	Phase 1 Solid Tumors Enrolled n=15 MTD 1.2 mg/m^2 BIW x 2 wks (Blaney 2004)
ADVL0317 5.3.2	Clinical Study Report	A Phase I Study of PS-341 in Pediatric Patients with Refractory /Recurrent Leukemias	Phase 1 Leukemia Enrolled n=12 MTD 1.3 mg/m^2 BIW x 2 wks (Horton 2007)
AALL07P1 5.3.3	Clinical Study Report	A Phase II Pilot Trial of Bortezomib in Combination with Intensive Re-Induction Therapy for Children with Relapsed Acute Lymphoblastic Leukemia (ALL) and Lymphoblastic Lymphoma (LL)"	Phase 2 Relapsed ALL Response evaluated in 1st 60 patient enrolled stratum 1 & 2 Relapse < 18 mos (st 1) n=27 Relapse 18-36 mos (st 2) n= 33 (Horton 2013, Horton 2014)
AAML1031 5.3.4	Abbreviated Clinical Study Report	A Phase III Randomized Trial for Patients with de novo AML using Bortezomib and Sorafenib for Patients with High Allelic Ratio FLT3/ITD	Phase 3 *De novo* AML PK Subset n=54
AALL01P2 5.3.5	Final Study COG Progress Report & Literature Report	Intensive Induction Therapy for Children with Acute Lymphoblastic Leukemia who Experience a Bone Marrow Relapse	Phase 2 Control AALL07P1 Relapse < 18 mos n=15 Relapse 18-36 mos n=41 (Raetz 2008)

5.2 Review Strategy

The main focus of this review is to evaluate whether the Millennium Pharmaceuticals has successfully fulfilled the requirement set forth in the issued pediatric written request for the eligibility determination on the pediatric exclusivity. To that end, the study reports for the 4 clinical studies submitted in this supplement were reviewed and summarized in section 5.3. The information submitted for AALL01P2, the control data for AALL07P1 was reviewed and summarized in section 5.3.5. The pediatric written request is included in the appendix 9.5 of this review. A point by point review of the requirements included in the written request and completeness of the submission to meet these requirements is presented in section 5.4.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 ADVL0015 Phase 1 Solid Tumors

Number/Clinical Trial Title: ADVL0015/ A Phase I Study of PS-341 in Pediatric Patients with Refractory Solid Tumors

Dose:
Level 1 - 1.2 mg/m^2/dose
Level 2 - 1.6 mg/m^2/dose

Route: IV bolus over 3 to 5 seconds

Schedule:
(copied from submission Section 5.3.3.2 ADVL0015 Study Report page 10 of 52)
Figure 1: ADVL0015 Administration Schedule

Week	1		2		3
Day	1	4	8	11	REST/
	↑	↑	↑	↑	EVAL

↑ = PS-341 administered intravenously

Population:
- Age < 22 years
- Solid Tumors not eligible for other therapy of higher priority

Enrollment:
Level 1 – n=9
Level 2 – n=6
DLT Evaluable Population – n=11
Safety Evaluable Population – n=15

Date of Study:
January 18, 2002 to February 17, 2003

Results:

Demographics

Table 1: ADVL0015 Demographics

Demographics			
	Level 1 N=9	**Level 2 N=6**	**Total N=15**
Gender			
Male	3	2	5
Female	6	4	10
Age in Years			
Mean	11	9	10
Median	13	6.5	10
Range	5 to 16	4 to 17	4 to 17
Race			
White	7	5	12
Black	1		1
Asian	1		1
Other		1	1
Body Surface Area			
Mean	1.2	1.0	1.1
Median	1.3	0.8	1.2
Range	0.7 to 1.75	0.7 to 1.72	0.7 to 1.75

Baseline Characteristics

Table 2: ADVL0015 Baseline Characteristics

Baseline Characteristics			
	Level 1 N=9	**Level 2 N=6**	**Total N=15**
Diagnosis			
Rhabdomyosarcoma	3		3
Ependymoma		1	1
Ewing's Sarcoma	1		1
Glioma	1		1
Hepatoblastoma	1		1
Wilm's Tumor	1	1	2
Osteosarcoma	2	1	3
Adenosarcoma		1	1
Neuroblastoma		2	2
Prior Therapy			
Chemotherapy	9	6	15
Surgery	8	6	14
Any Radiation Therapy	8	4	12
Radiation to > 20% BM	3	2	5
Stem Cell Transplant		2	2

Exposure:

Table 3: ADVL0015 Exposure to Bortezomib

Exposure			
Number of Cycles	**Level 1 N=9**	**Level 2 N=6**	**Total N=15**
1	8	5	13
2		1	1
6	1		1

There were 7 patients assigned to level 1 who received the 4 planned doses of the first cycle and 2 patients who received 3 of 4 planned doses. There were 4 patients assigned to level 2 who received the 4 planned doses of the first cycle and 2 patients who received 3 of 4 planned doses.

Disposition:
(copied from submission Section 5.3.3.2 ADVL0015 Study Report page 28 of 52)

Table 4: ADVL0015 Disposition

	VELCADE Dose (mg/m^2)		
Patient Disposition, n (%)	**1.2 n = 9**	**1.6 n = 6**	**Total N = 15**
Reason off protocol therapy	9 (100)	6 (100)	15 (100)
Relapse/progressive disease	6 (67)	5 (83)	11 (73)
Decision of the patient's family to withdraw the patient from the protocol therapy	2 (22)	1 (17)	3 (20)
Death	1 (11)	0	1 (7)

Efficacy:
There were no objective anti-tumor responses.

Safety:
Treatment Emergent Adverse Events (TEAE)
(copied from submission Section 5.3.3.2 ADVL0015 Study Report page 38 of 52)

Table 5: ADVL0015 Summary of Treatment Emergent Adverse Events

	VELCADE Dose (mg/m^2)		
Adverse Event Category, n (%)	**1.2 n = 9**	**1.6 n = 6**	**Total N = 15**
Any TEAE[a]	9 (100)	6 (100)	15 (100)
Grade 3 or higher AE[a]	7 (78)	6 (100)	13 (87)
Drug-related AE[b]	8 (89)	5 (83)	13 (87)
Drug-related Grade 3 or higher AE	4 (44)	4 (67)	8 (53)
On-study deaths[c]	1 (11)	1 (17)	2 (13)

DLT

Protocol definition of DLT:

Non-Hematologic Dose-Limiting Toxicity

Non-hematologic dose-limiting toxicity is defined as any Grade III or Grade IV nonhematologic toxicity attributable to the investigational drug with the specific exclusion of:

- Grade III nausea and vomiting
- Grade III transaminase (AST/ALT) elevation which returns to Grade I prior to the time for the next treatment course
- Grade III fever or infection

Hematologic dose limiting toxicity

For patients with solid tumors and adequate blood counts on study entry, DLT will be defined as Grade IV neutropenia or Grade IV thrombocytopenia of > 7 days duration, which requires transfusion therapy on greater than 2 occasions in 7 days, or which causes a delay of ≥ 14 days beyond the planned interval between treatment courses.

Other dose limiting toxicity

Any ≥ Grade II non-hematologic toxicity causing a ≥ 7-day interruption of therapy or dose reduction prior to week 3 will also be considered dose limiting.

The DLT-evaluable population included patients who experienced a DLT at any time during protocol therapy, or patients without a DLT who completed 1 full cycle of therapy per protocol guidelines and had twice-weekly CBCs. Of the 15 patients, 11 patients were evaluable for toxicity. Two patients were not fully assessable for toxicity because they did not complete the first cycle of therapy secondary to rapid disease progression; 2 additional patients were not fully assessable because twice-weekly CBCs were not obtained during Cycle 1.

There were 5 patients treated at level 1 and 6 patients treated at level 2 in the DLT-evaluable population.

There were 2 DLTs identified in 6 subjects treated at level 2, both grade 3 thrombocytopenia which resulted in the patients not receiving the full course of therapy. Therefore, level 1 - 1.2 mg/m^2/dose on days 1, 4, 8, and 11 of a 21 day cycle was determined to be the MTD in the pediatric solid tumor population. Of note, one of the 2 subjects with dose limiting thrombocytopenia had previously been treated with stem cell trans[plant and had been exposed to extensive (>20% BM) radiation.

Deaths

Two patients died while on study due to progressive disease. Ten additional patients died following the end of the study.

Adverse Events Leading to Discontinuation
None.

Conclusion:
(copied from submission Section 5.3.3.2 ADVL0015 Study Report page 50 of 52)

- No patients in this study demonstrated an objective antitumor response to bortuzumib.
- Overall, there were 2 DLTs (Grade 3 platelet count) reported at the 1.6-mg/m^2 dose level.
- Two patients (1 patient in each treatment group) died while on study due to disease progression.
- All patients in both treatment groups experienced at least 1 TEAE during the study. There were 13 patients (87%) who experienced treatment-related AEs (8 patients [89%] in the 1.2-mg/m2 treatment group and 5 patients [83%] in the 1.6-mg/m^2 treatment group). Of these, the most frequently reported treatment-related AEs included hemoglobin (9 patients [60%]), nausea (6 patients [40%]), platelet count (5 patients [33%]), and neutrophil count (4 patients [27%]).
- There were 3 patients reporting Grade 4 TEAEs overall. Grade 4 TEAEs included neutrophil count, hyperkalemia, and dyspnea, of which only the TEAE of neutrophil count (1 patient at the 1.2-mg/m^2 dose level) was considered by the investigator to be related to study drug.

5.3.2 ADVL0317 Phase 1 Hematologic Malignancies

Number/Clinical Trial Title: ADVL0317 / A Phase I Study of PS-341 in Pediatric Patients with Refractory /Recurrent Leukemias

Dose:
Level 1 - 1.3 mg/m^2/dose
Level 2 - 1.7 mg/m^2/dose

Route: IV bolus over 3 to 5 seconds

Schedule:
(copied from submission Section 5.3.3.2 ADVL0317 Study Report page 11 of 59)
Figure 2: ADVL0317 Administration Schedule

Cycle 1

Week	1		2		3		
Day	1 ↑ x PKs[a] PBMCs[d]	4 ↑ x PKs[a]	8 ↑ x BMA[b] PBMCs[d]	11 ↑ x PKs[a]	15 x	18 x BMA[c] PBMCs[d]	22[e] x

Population:
- Age > 12 months and ≤ 21 years
- Leukemia including acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), and chronic myelogenous leukemia (CML) in blast crisis
- No curative therapy or therapy known to prolong survival

Enrollment:
Enrolled n=12
Exposed to bortezomib n=11
Level 1 – n=5 (a subject with pneumonia assigned to this level was not treated)
Level 2 – n=6

Date of Study:
January 5, 2004 to December 29, 2005

Results:

Demographics

Table 6: ADVL0317 Demographics

Demographics			
	Level 1 N=5	**Level 2 N=6**	**Total N=11**
Gender			
Male	1	6	7
Female	4	0	4
Age in Years			
Mean	12	13.5	12.8
Median	13	12.5	13
Range	1 to 18	10 to 18	1 to 18
Race			
White	4	4	8
Black		2	2
Other	1		1
Body Surface Area			
Mean	1.4	1.4	1.4
Median	1.4	1.4	1.4
Range	0.4 to 2.1	1.0 to 2.1	0.4 to 2.1

Baseline Characteristics

Table 7: ADVL0317 Baseline Characteristics

Baseline Characteristics			
	Level 1 N=5	**Level 2 N=6**	**Total N=11**
Diagnosis			
ALL B-cell precursor	**5**	**3**	**8**
AML		**3**	**3**
Prior Therapy			
1 Regimen		**2**	**2**
2 Regimens	**3**		**3**
3 Regimens	**2**	**3**	**5**
6 Regimens		**1**	**1**
Radiation Therapy	**1**	**4**	**5**
Stem Cell Transplant	**1**	**3**	**4**

Exposure:

Table 8: ADVL0317 Exposure to Bortezomib

Exposure			
Number of Cycles	**Level 1 N=5**	**Level 2 N=6**	**Total N=11**
1	**3**	**6**	**9**
2	**2**		**2**

There were 4 patients at level 1 that received the 4 planned doses of the first cycle. No patients at level 2 received all 4 planned doses of the first cycle. There were 3 patients who received 3 of 4 planned doses; 1 patient who received 2 of 4 planned doses; 2 patients who received 1of 4 planned doses.

Disposition:
(copied from submission Section 5.3.3.2 ADVL0317 Study Report page 34 of 59)

Table 9: ADVL0317 Disposition

	VELCADE Dose (mg/m^2)		
Characteristic, n (%)	**1.3 n = 6**	**1.7 n = 6**	**Total N = 12**
Enrolled	6	6	12 (100)
Completed protocol therapy	0	0	0
Reason for off protocol therapy	6	6	12 (100)
Clinical (including physical examination) or laboratory evidence of progressive disease	4	4	8 (67)
Toxicity requiring removal from study	1	1	2 (17)
Physician determines it is not in the patient's best interest	1	0	1 (8)
Refusal of further protocol therapy by patient, parent, or guardian	0	1	1 (8)

One subject enrolled at level 1 (1.3 mg/m^2) did not receive bortezumib due to infection.

Efficacy:
There were no objective antitumor responses using bortezumib as a single agent.

Safety:

Treatment Emergent Adverse Events (TEAE)

Table 10: ADVL0317 Summary of Treatment Emergent Adverse Events

Treatment Emergent Adverse Events			
	Level 1 N=5	**Level 2 N=6**	**Total N=11**
Any adverse event	5	6	11
Grade 3 or higher adverse event	4	5	9
Drug-related adverse event	5	3	8
Drug-related grade 3 or higher adverse event	3	2	5
On-study deaths	1	3	4

DLT

Protocol definition of DLT:

DLT will be defined as any of the following events that are at least (possibly, probably or definitely) attributable to PS-341. In addition, any toxicity that results in a dose reduction or dose omission during the first cycle will be considered dose-limiting.

- Non-hematologic dose-limiting toxicity is defined as any grade 3 or grade 4 non- hematological toxicity attributable to the investigational drug with the specific exclusion of:
  - Grade 3 nausea and vomiting
  - Grade 3 transaminase (AST/ALT) elevation that returns to grade 1 or baseline prior to the time for the next treatment cycle
  - Grade 3 fever or infection
  - Alopecia
- Hematologic dose-limiting toxicity will be defined as bone marrow aplasia > 6 weeks duration from the first treatment day; specifically, failure to recover a peripheral ANC > 500/μL and platelets > 20,000/μL as documented by bone marrow aplasia, not malignant infiltration.

Two patients treated at level 2 experienced DLTs. Patient 709010 experienced febrile Neutropenia (CTCAE v3 grade 4), hypotension (CTCAE v3 grade 4), and increased creatinine (CTCAE v3 grade 3), and patient 733009 experienced confusion (CTCAE v3 grade 3).

Deaths

(copied from submission Section 5.3.3.2 ADVL0317 Study Report page 50 of 59)

Table 11: ADVL0317 Deaths

VELCADE Dose	Patient Identification	Cause of Death	Days From First/ Last Dose	On or Off Study[a]	Treatment Related
1.3 mg/m^2	600305	Aspergillus infection	90/59	Off	Not related
	706799	Progressive disease	419/387	Off	Not related
	710219	Progressive disease	20/10	On	Not related
	743696	Progressive disease	49/38	Off	Not related
1.7 mg/m^2	705830	Progressive disease	10/3	On	Not related
	709010	Hypoxia	9/2	On	Minor contribution[b]
	733009	Progressive disease	22/19	On	Not related
	735838	Progressive disease	97/90	Off	Not related
	738270	Progressive disease	116/116	Off	Not related

a On-study deaths were defined as deaths that occurred within 30 days of the last dose of bortezumib.

b As recorded on the case report form (CRF) to report deaths on or off study, the investigator assessed the side effects of protocol therapy to have had a minor contribution [relationship] to the patient's death

Conclusion:

- There were no objective antitumor responses using bortezumib as a single agent.
- Two patients treated at level 2 experienced DLTs. Patient 709010 experienced febrile Neutropenia (CTCAE v3 grade 4), hypotension (CTCAE v3 grade 4), and increased creatinine (CTCAE v3 grade 3), and patient 733009 experienced confusion (CTCAE v3 grade 3). Level 2 exceeded the MTD.
- There were 3 patients who received a full cycle of 4 doses evaluable for DLT in level 1. None experienced a DLT.
- Level 1, 1.3 mg/m^2 on day 1, 4, 8, and 11, was determined to be the MTD in pediatric patients with hematologic malignancies.

REVIEWER COMMENT
Generally the MTD is confirmed by expanding the cohort to 6 evaluable patients, to confirm the incidence of DLTs is < 30%. This was not done in this study.

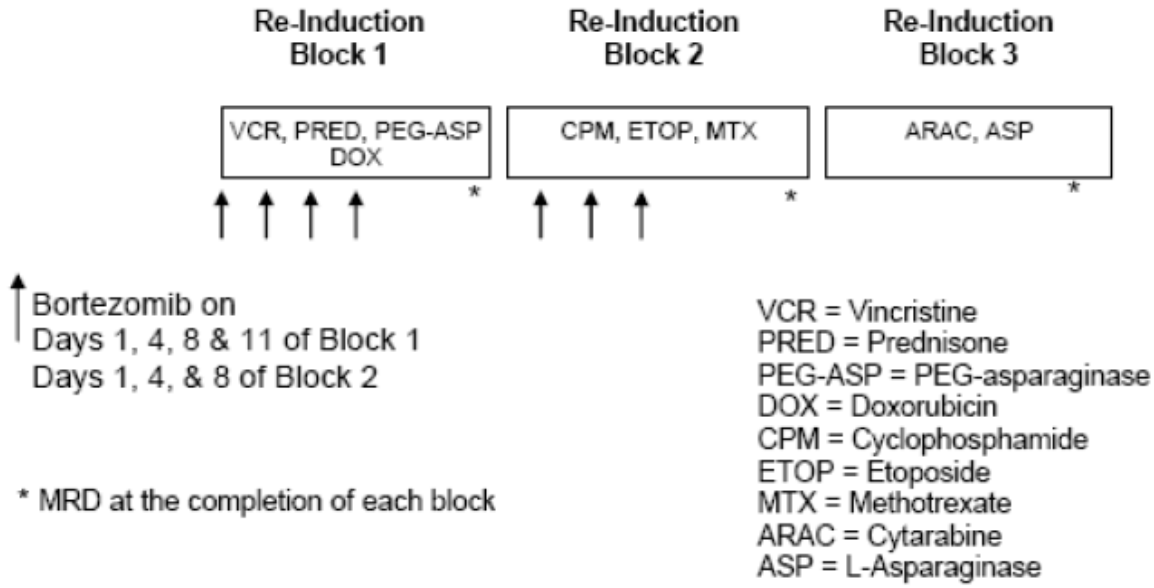
5.3.3 AALL07P1 Phase 2 Relapsed ALL

Number/Clinical Trial Title: AALL07P1 / "A Phase 2 Pilot Trial of Bortezomib in Combination with Intensive Re-induction Therapy for Children with Relapsed Acute Lymphoblastic Leukemia (ALL) and Lymphoblastic Lymphoma (LL)

Dose: 1.3 mg/m^2

Route: IV bolus over 3 to 5 seconds

Schedule:
(copied from submission Section 5.3.5.2 ALL07P1 Study Report page 14 of 136)
Figure 3: AALL07P1 Treatment Schedule



Details regarding the backbone chemotherapy schedule are presented in Appendix 9.3.

Population:

- Age ≥ 1 year of age and ≤ 31 years of age
- Lymphoblastic Malignancy
  - Pre-B ALL in first early (< 36 months from diagnosis) isolated bone marrow (BM) or combined BM/extramedullary relapse;
  - T-cell ALL in first isolated BM or combined relapse;
  - T-cell lymphoblastic lymphoma in first relapse.
- Patients with Philadelphia chromosome positive ALL not eligible unless refractory to at least one tyrosine kinase inhibitor (TKI) therapy. Patients that are unable to tolerate TKI therapy due to toxicity are eligible.

Strata:

- 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

Enrollment:

The study was designed to formally analyze response in the first 2 strata. The pre-specified number was 60 evaluable patients in strata 1&2. The protocol was amended to allow additional accrual. This was to ensure that an adequate number of patients be accrued to evaluate pharmacokinetics in relevant age groups. The investigators did not expect to be able to enroll adequate numbers of patients in strata 3-5 to ask a formal question, but planned to look at the results descriptively.

(copied from submission Section 5.3.5.2 ALL07P1 Study Report page 59 of 136)

Table 12: AALL07P1 Enrollment and Populations

	Stratum						
	1	2	1 + 2	3	4	5	
	Pre-B-cell ALL, Age ≤ 21 yrs			Pre-B-cell ALL	T-cell ALL		Overall
Populations, N	Relapse < 18 mos (N = 47)	Relapse 18-36 mos (N = 57)	(N = 104)	> 21 yrs (N = 4)	1st relapse (N = 22)	T-cell LL (N = 10)	Total (N = 140)
Safety Population[a]	47	57	104	4	22	10	140
All-Evaluable Population in Strata 1 and 2[b]	34	44	78	--	--	--	78
First 60 Evaluable Population in Strata 1 and 2[c]	27	33	60	--	--	--	60

a Safety population is defined as all patients who received at least 1 dose of VELCADE.
b The all-evaluable population in Strata 1 and 2 includes the patients considered as response-evaluable on the basis of study chair assessment (patients who received at least 1 dose of VELCADE and completed Block 1 of therapy or patients who experienced progressive disease or death).
c The first 60 evaluable population in Strata 1 and 2 includes the first 60 patients considered as response-evaluable on the basis of study chair assessment. This population was the minimum required population per the pediatric Written Request.

Date of Study:

July 10, 2009 to December 31, 2013

Results:

Demographics:

Demographics will be presented for the entire population in

This definition was not strictly adhered to as patients who had received bortezomib but died of toxic complications (day 8 – ID 807686; day 11 817967) or progressive disease (removed therapy for progressive disease day 23 - 795092). On 6/10/15 the applicant

submitted revised demographics, disposition and activity analysis including these 3 subjects in the First 60 Evaluable Population. This revised population is presented in the demographic and disposition in Table 14 and Table 17.

Table 13, that is the safety population and for the population used to evaluate the activity, the First 60 Evaluable Population in Table 14. As defined in the statistical analysis plan:

> Patients in strata 1 and 2 who receive at least 1 dose of bortezomib and complete Block 1 of therapy will be evaluable for response. Patients who fail (progressive disease, toxic death) will also be evaluable for response. The population will be based on the Study Chair Response Evaluation electronic case report form (eCRF) question: Is the patient evaluable for response assessment? (according to protocol criteria). The response-evaluable population will be used for the analysis of response at the end of Block 1.

This definition was not strictly adhered to as patients who had received bortezomib but died of toxic complications (day 8 – ID 807686; day 11 817967) or progressive disease (removed therapy for progressive disease day 23 - 795092). On 6/10/15 the applicant submitted revised demographics, disposition and activity analysis including these 3 subjects in the First 60 Evaluable Population. This revised population is presented in the demographic and disposition in Table 14 and Table 17.

Table 13: AALL07P1 Demographics Safety Population

Demographics Safety Population						
	Stratum 1 B ALL ≤ 21 yr <18 month	**Stratum 2 B ALL ≤ 21 yr 18-36 month**	**Stratum 3 B ALL > 21 yr**	**Stratum 4 T ALL**	**Stratum 5 T LL**	**Total**
	N=47	**N=57**	**N=4**	**N=22**	**N=10**	**N=140**
Gender						
Male	26	30	2	17	5	80 (57%)
Female	21	27	2	5	5	60 (43%)
Age in Years						
Mean	9.2	10.3	23.2	12.9	13.8	10.9
Median	8.7	9.3	23.3	13.5	14.8	10.1
Range	1.0 to 22.0	2.4 to 21.9	22.4 to 23.7	3.0 to 26.8	2.0 to 25.1	1.0 to 26.8
< 2	7	0				7 (5%)
2 to 11	25	36		9	3	73 (52%)
12 to 16	7	10		8	5	30 (21%)
>16	8	11	4	5	2	30 (21%)
Race						
White	32	40	2	16	8	98 (70%)
Black	8	8		3	1	20 (14%)
Asian	1	3		1		5 (4%)
American Indian Alaska Native	1	1		1		3 (2%)
Native Hawaiian			1		1	2 (1%)

Pacific Islander						
Missing	5	5	1	1		12 (8%)
Country						
United States	44	53	4	20	10	131 (94%)
Canada	2	4		1		7 (5%)
Puerto Rico	1					1
India				1		1

Table 14: AALL07P1 Demographics First 60 Evaluable Population

Demographics First 60 Evaluable Population			
	Stratum 1 B ALL ≤ 21 yr <18 month	**Stratum 2 B ALL ≤ 21 yr 18-36 month**	**Total**
	N=27	**N=33**	**N=60**
Gender			
Male	14	15	29 (48%)
Female	13	18	31 (52%)
Age in Years			
Mean	8.2	10.3	9.4
Median	8.0	9	8.5
Range	1.0 to 21	2 to 21	1.0 to 21
< 2	4		4 (7%)
2 to 11	15	20	35 (58%)
12 to 16	4	6	10 (17%)
>16	4	7	11 (18%)
Race			
White	17	24	41 (68%)
Black	5	6	11 (18%)
Missing or Other	5	3	8

Exposure:
(copied from submission Section 2.7.4 Summary of Safety page 31 of 79)

Table 15: AALL07P1 Exposure

	First 60 Evaluable Population			Safety Population			
	Stratum 1 R <18 mos	Stratum 2 R 18-36 mos	Strata 1+2	Stratum 1 R <18 mos	Stratum 2 R 18-36 mos	Strata 1+2	Overall Total
VELCADE Exposure, n (%)	(N=27)	(N=33)	(N=60)	(N=47)	(N=57)	(N=104)	(N=140)
Number of patients with at least 1 dose							
Block 1	27 (100)	33 (100)	60 (100)	47 (100)	57 (100)	104 (100)	140 (100)
Block 2	22 (81)	30 (91)	52 (87)	33 (70)	44 (77)	77 (74)	102 (73)
Maximum number of doses received							
Block 1 (4 doses)	26 (96)	31 (94)	57 (95)	44 (94)	53 (93)	97 (93)	131 (94)
Block 2 (3 doses)	21 (95)	30 (100)	51 (98)	32 (97)	44 (100)	76 (99)	99 (97)
Median duration of treatment (days)							
Overall[a]	85.0	84.0	84.5	67.0	74.5	72.0	73.0
In Block 1[b]	42.0	41.0	41.5	42.0	41.0	41.5	41.0
In Block 2[b]	35.5	40.0	38.5	36.0	40.0	39.0	39.0

(copied from submission Section 2.5 Clinical Overview page 19 of 47)
Among all pediatric patients, the median number of doses administered was 7, which was also the maximum number of doses. In the Overall Safety population (N=140), the median duration of treatment was 73 days (range 7-147). Among patients in Strata 1

and 2, the median duration of treatment was 84.5 days (range 22-147) in the First 60 Evaluable population compared with 72 days (range 7-147) for the 104 patients in Strata 1 and 2 of the Safety population.

REVIEWER COMMENT:
The data sets were inadequate to allow verification of exposure results presented in Table 15. The data sets did provide verification that all patients in the First 60 Evaluable Population did receive bortezomib in Block 1 of therapy and the majority 56 of 60 (93%) did receive the 4 protocol-specified doses. The data sets verified in Block 2 of therapy 52 patients received bortezomib, and 49 received the 3 protocol-specified doses.

Disposition:

Table 16: AALL07P1 Disposition - Safety Population

Disposition Safety Population						
	Stratum 1 B ALL ≤ 21 yr <18 month	**Stratum 2 B ALL ≤ 21 yr 18-36 month**	**Stratum 3 B ALL > 21 yr**	**Stratum 4 T ALL**	**Stratum 5 T LL**	**Total**
	N=47	**N=57**	**N=4**	**N=22**	**N=10**	**N=140**
Subjects off protocol therapy	45	56	4	21	9	135 (96%)
Subjects on protocol therapy	2	1	0	1	1	5 (4%)
Primary Reason Off Therapy						
Completed	10	22	2	9	3	46 (33%)
Progressive disease	9	7	0	2	4	22 (16%)
Relapse	10	4	1	1	1	17 (12%)
Physician decision	9	14	0	9	1	33 (25%)
Patient/family request	5	4	1	0	0	10 (7%)
Death	2	3	0	0	0	5 (4%)
Adverse Events	0	2	0	0	0	2 (1%)

Table 17: AALL07P1 Disposition – Analysis Population

Disposition First 60 Evaluable Population			
	Stratum 1 B ALL ≤ 21 yr <18 month	**Stratum 2 B ALL ≤ 21 yr 18-36 month**	**Total**
	N=27	**N=33**	**N=60**
Subjects Off protocol Therapy	27	33	60
Primary Reason Off Therapy			
Completed	8	14	22
Progressive disease	6	4	10
Relapse at any site	6	2	8
Physician decision	3	6	9
Patient/family request	2	3	5
Adverse Events	0	1	1

Clinical Review
Patricia Dinndorf
sNDA 21602 42 Exclusivity Determination
Velcade (bortezomib) for Injection
Efficacy:
Activity is being evaluated in patients in stratum 1 and stratum 2. These results are being compared to the activity results from a published trial using an identical backbone of chemotherapy without bortezomib, AALL01P2, see section 5.3.5.

The primary activity endpoint is the CR rate at the end of Block 1 of therapy (CR2). The secondary activity endpoint was an assessment of 4 month EFS.

The statistical analysis plan specifies the analysis population consists of the first 60 evaluable patients enrolled on stratum 1 and stratum 2. The EFS at 4 months was evaluated 9.5 months after the 60th evaluable patient on stratum 1 and stratum 2 was enrolled (cutoff date 12/31/13).

(copied from response to FDA request submitted 6/10/15 eCTD sequence 140 section 14 page 8/12)

Table 18: AALL07P1 Response End of Block 1 - Analysis Population

	Stratum 1 Pre-B ALL Age <= 21 Relapse <18 mth from dx N=27	Stratum 2 Pre-B ALL Age <= 21 Relapse 18-36 mth from dx N=33	Total Pre-B ALL Age <= 21 N=60
End of Block 1			
Number of Subjects with Complete Response (CR) n (%)	17 (63)	24 (73)	41 (68)
95% Exact Confidence Interval[a]	(42.4, 80.6)	(54.5, 86.7)	(55.0, 79.7)
Number of Subjects with Other Responses n (%)			
Partial Response (PR)	3 (11)	3 (9)	6 (10)
Stable Disease (SD)	2 (7)	3 (9)	5 (8)
Progressive Disease (PD)	3 (11)	1 (3)	4 (7)
Not Evaluated	0	1 (3)	1 (2)
Not Reported	2 (7)	1 (3)	3 (5)

(copied from submission Section 5.3.5.2 ALL07P1 Study Report page 74 of 136)

Table 19: AALL07P1 Response End of Block 1 - Safety Population

	Stratum					
	1	2	1 + 2	3	4	5
	Pre-B-cell ALL, Age ≤ 21 yrs					
Response	Relapse < 18 mos	Relapse 18-36 mos		Pre-B-cell ALL > 21 yrs	T-cell ALL 1st relapse	T-cell LL
Number of patients in each stratum, n	47	57	104	4	22	10
Number of patients with CR, n (%)	27 (57)	36 (63)	63 (61)	3 (75)	15 (68)	1 (10)
(95% CI)[a]	(42.2, 71.7)	(49.3, 75.6)	(50.5, 70.0)			
Number of patients with:						
CR unconfirmed (CRu)[b]	0	0	0	0	0	1 (10)
Partial response	5 (11)	7 (12)	12 (12)	0	1 (5)	4 (40)
Stable disease	7 (15)	9 (16)	16 (15)	1 (25)	3 (14)	0
Progressive disease	4 (9)	1 (2)	5 (5)	0	1 (5)	3 (30)
Not evaluated	1 (2)	2 (4)	3 (3)	0	2 (9)	0
Not reported	3 (6)	2 (4)	5 (5)	0	0	1 (10)

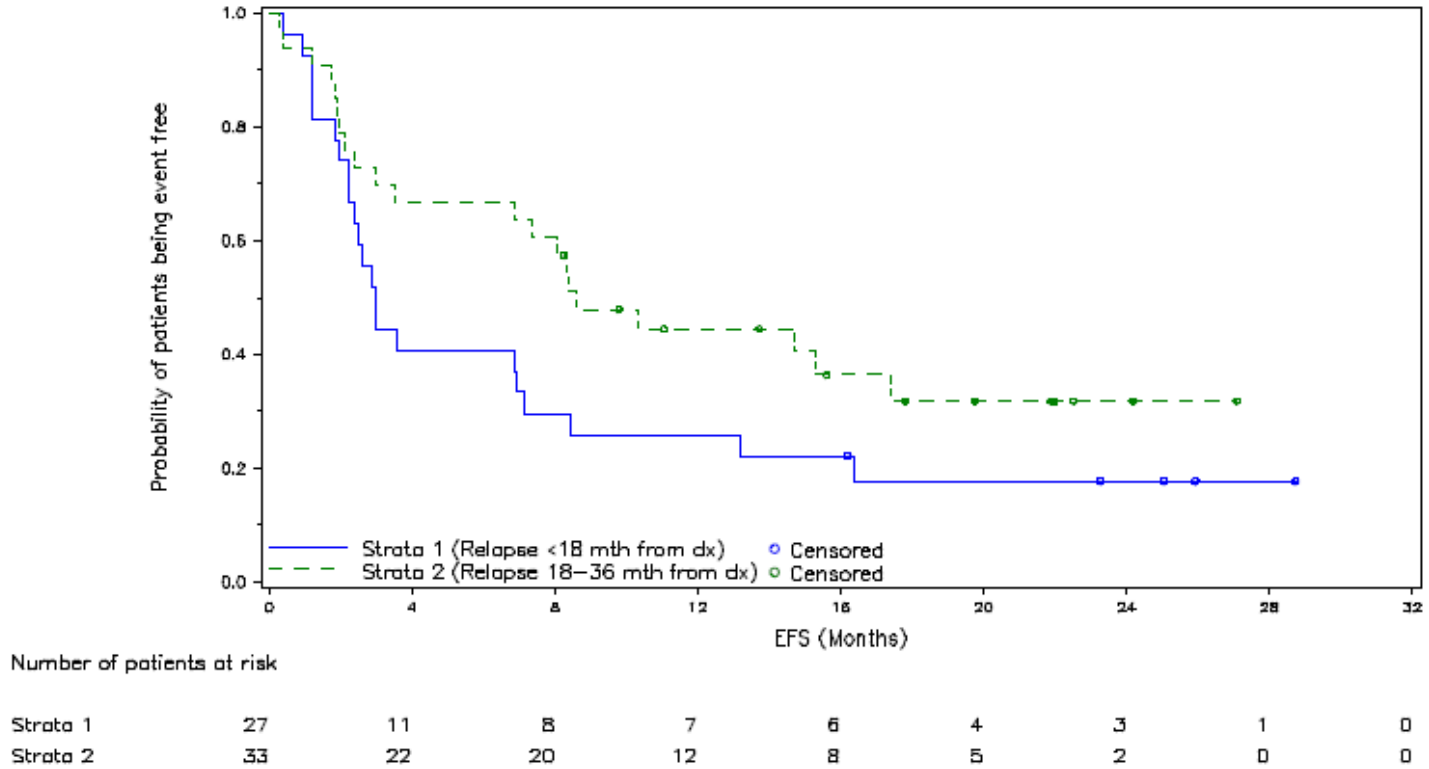
Clinical Review
Patricia Dinndorf
sNDA 21602 42 Exclusivity Determination
Velcade (bortezomib) for Injection
(copied from response to FDA request submitted 6/10/15 eCTD sequence 140 section 14 page 10/12)

Table 20: AALL07P1 EFS – Analysis Population

	Stratum 1 Pre-B ALL Age <= 21 Relapse <18 mth from dx N=27	Stratum 2 Pre-B ALL Age <= 21 Relapse 18-36 mth from dx N=33	Total Pre-B ALL Age <= 21 N=60
Event Free Survival (EFS) (days)[a]			
Number with Events (%)	22 (81)	21 (64)	43 (72)
Number Censored (%)	5 (19)	12 (36)	17 (28)
25th percentile (95% CI)	59 (28.0, 76.0)	73 (37.0, 224.0)	66 (53.0, 88.0)
Median (95% CI)	92 (67.0, 217.0)	262 (108.0, 531.0)	214 (88.0, 315.0)
75th percentile (95% CI)	402 (110.0, NE)	NE (448.0, NE)	NE (315.0, NE)
Min, Max	13, 876*	9, 826*	9, 876*
Kaplan Meier Estimate of EFS at 4 months[b]	41 [n=11]	67 [n=22]	55 [n=33]
95% CI	(22.5, 58.2)	(47.9, 80.0)	(41.6, 66.5)
Kaplan Meier Estimate of EFS at 12 months[b]	26 [n=7]	45 [n=12]	36 [n=19]
95% CI	(11.5, 43.1)	(27.1, 60.6)	(24.3, 48.3)

(copied from response to FDA request submitted 6/10/15 eCTD sequence 140 section 14 page 11/12)

Figure 4: AALL07P1 Kaplan Meier Plot of EFS - Analysis Population



(copied from submission Section 5.3.5.2 ALL07P1 Study Report page 78 of 136)

Table 21: AALL07P1 EFS - Safety Population Strata 1&2

	Pre-B-cell ALL (Age ≤ 21 years)		
Event-free Survival[a] (days)	Stratum 1 Relapse < 18 mos (N = 47)	Stratum 2 Relapse 18-36 mos (N = 57)	Strata 1 + 2 (N = 104)
Number of events, n (%)	34 (72)	33 (58)	67 (64)
Number censored, n (%)	13 (28)	24 (42)	37 (36)
25th percentile (95% CI)	67 (38.0, 88.0)	73 (56.0, 120.0)	67 (58.0, 89.0)
Median (95% CI)	100 (80.0, 188.0)	255 (120.0, 466.0)	175 (100.0, 246.0)
75th percentile (95% CI)	217 (113.0, NE)	NE (448.0, NE)	500 (262.0, NE)
Minimum, Maximum	13, 876[b]	9, 826[b]	9, 876[b]
Kaplan-Meier estimates:			
EFS at 4 months[c]	37 (n=14)	63 (n=31)	52 (n=45)
(95% CI)	(22.7, 52.1)	(49.0, 74.6)	(41.9, 61.9)
EFS at 12 months[c]	21 (n=7)	42 (n=14)	33 (n=21)
(95% CI)	(9.8, 35.1)	(28.2, 56.0)	(23.4, 43.3)

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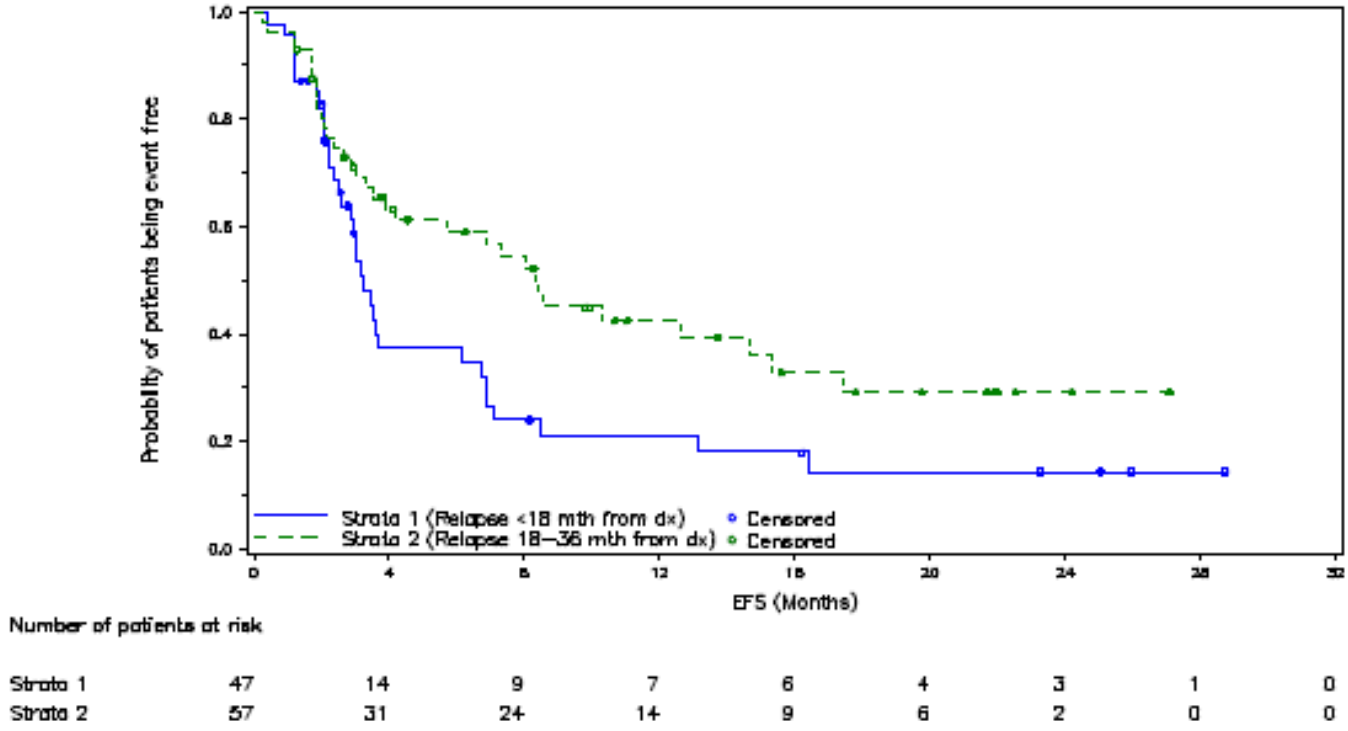
Figure 5: AALL07P1 Kaplan Meier Plot of EFS - Safety Population Strata 1&2



Treatment Emergent Adverse Events (TEAE)

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Table 22: AALL07P1 Summary of Treatment Emergent Adverse Events - Safety Population

	Stratum						
	1	2	1 + 2	3	4	5	
	Pre-B-cell ALL, Age ≤ 21 yrs						
Categories of TEAEs, n (%)	Relapse < 18 mos (N = 47)	Relapse 18-36 mos (N = 57)	(N = 104)	Pre-B-cell ALL > 21 yrs (N = 4)	T-cell ALL 1st relapse (N = 22)	T-cell LL (N = 10)	Overall Total (N = 140)
At least 1 TEAE	44 (94)	55 (96)	99 (95)	4 (100)	22 (100)	10 (100)	135 (96)
Grade ≥ 3 TEAE	43 (91)	55 (96)	98 (94)	4 (100)	22 (100)	10 (100)	134 (96)
VELCADE-related TEAE[a]	38 (81)	46 (81)	84 (81)	4 (100)	21 (95)	7 (70)	116 (83)
VELCADE-related Grade ≥ 3 TEAE	38 (81)	45 (79)	83 (80)	4 (100)	21 (95)	6 (60)	114 (81)
AdEERS-reported TEAE	21 (45)	31 (54)	52 (50)	1 (25)	13 (59)	5 (50)	71 (51)
VELCADE-related AdEERS	16 (34)	24 (42)	40 (38)	1 (25)	12 (55)	1 (10)	54 (39)
VELCADE-related severe toxicities[b]	14 (30)	17 (30)	31 (30)	1 (25)	14 (64)	4 (40)	50 (36)
AEs resulting in VELCADE discontinuation	1 (2)	3 (5)	4 (4)	0	1 (5)	0	5 (4)
AEs resulting in VELCADE dose modifications	6 (13)	11 (19)	17 (16)	1 (25)	5 (23)	2 (20)	25 (18)
On-study deaths[c]	16 (34)	16 (28)	32 (31)	1 (25)	6 (27)	2 (20)	41 (29)

Table 23: AALL07P1 Treatment Emergent ≥ Gr 3 Adverse Events ≥ 10% - Safety Population

	Stratum						
	1	2	1 + 2	3	4	5	
	Pre-B-cell ALL, Age ≤ 21 yrs						
MedDRA System Organ Class, n (%) Preferred Term, n (%)	Relapse < 18 mos (N = 47)	Relapse 18-36 mos (N = 57)	(N = 104)	Pre-B-cell ALL > 21 yrs (N = 4)	T-cell ALL 1st relapse (N = 22)	T-cell LL (N = 10)	Overall Total (N = 140)
Patients with at least 1 Grade ≥ 3 TEAE[a]	43 (91)	55 (96)	98 (94)	4 (100)	22 (100)	10 (100)	134 (96)
Investigations	**38 (81)**	**49 (86)**	**87 (84)**	**3 (75)**	**18 (82)**	**9 (90)**	**117 (84)**
Platelet count decreased	32 (68)	41 (72)	73 (70)	3 (75)	17 (77)	8 (80)	101 (72)
Neutrophil count decreased	29 (62)	38 (67)	67 (64)	3 (75)	17 (77)	8 (80)	95 (68)
White blood cell count decreased	29 (62)	36 (63)	65 (63)	3 (75)	11 (50)	5 (50)	84 (60)
Lymphocyte count decreased	15 (32)	16 (28)	31 (30)	2 (50)	5 (23)	1 (10)	39 (28)
Alanine aminotransferase increased	7 (15)	16 (28)	23 (22)	2 (50)	4 (18)	2 (20)	31 (22)
Aspartate aminotransferase increased	4 (9)	9 (16)	13 (13)	1 (25)	3 (14)	2 (20)	19 (14)
Lipase increased	3 (6)	8 (14)	11 (11)	0	4 (18)	1 (10)	16 (11)
Blood and lymphatic system disorders	**34 (72)**	**45 (79)**	**79 (76)**	**3 (75)**	**16 (73)**	**6 (60)**	**104 (74)**
Anaemia	26 (55)	38 (67)	64 (62)	3 (75)	16 (73)	6 (60)	89 (64)
Febrile neutropenia	24 (51)	23 (40)	47 (45)	0	11 (50)	2 (20)	60 (43)
Infections and infestations	**26 (55)**	**37 (65)**	**63 (61)**	**4 (100)**	**14 (64)**	**6 (60)**	**87 (62)**
Sepsis	4 (9)	6 (11)	10 (10)	0	0	1 (10)	11 (8)
Metabolism and nutrition disorders	**21 (45)**	**33 (58)**	**54 (52)**	**2 (50)**	**11 (50)**	**5 (50)**	**72 (51)**
Hypokalaemia	14 (30)	20 (35)	34 (33)	2 (50)	7 (32)	2 (20)	45 (32)
Hyperglycaemia	6 (13)	11 (19)	17 (16)	1 (25)	4 (18)	0	22 (16)
Hyponatraemia	8 (17)	9 (16)	17 (16)	0	1 (5)	1 (10)	19 (14)
Hypoalbuminaemia	7 (15)	3 (5)	10 (10)	1 (25)	3 (14)	2 (20)	16 (11)
Hypocalcaemia	5 (11)	8 (14)	13 (13)	1 (25)	0	0	14 (10)
Decreased appetite	3 (6)	9 (16)	12 (12)	0	1 (5)	1 (10)	14 (10)
Hypophosphataemia	5 (11)	6 (11)	11 (11)	0	0	2 (20)	13 (9)
General disorders & administration site conditions	**10 (21)**	**20 (35)**	**30 (29)**	**2 (50)**	**8 (36)**	**4 (40)**	**44 (31)**
Death	7 (15)	8 (14)	15 (14)	1 (25)	6 (27)	2 (20)	24 (17)
Pyrexia	4 (9)	8 (14)	12 (12)	0	1 (5)	1 (10)	14 (10)
Gastrointestinal disorders	**12 (26)**	**20 (35)**	**32 (31)**	**1 (25)**	**5 (23)**	**2 (20)**	**40 (29)**
Stomatitis	5 (11)	8 (14)	13 (13)	0	2 (9)	0	15 (11)
Respiratory, thoracic and mediastinal disorders	**11 (23)**	**15 (26)**	**26 (25)**	**1 (25)**	**2 (9)**	**1 (10)**	**30 (21)**
Hypoxia	4 (9)	8 (14)	12 (12)	0	1 (5)	1 (10)	14 (10)
Vascular disorders	**11 (23)**	**14 (25)**	**25 (24)**	**0**	**3 (14)**	**2 (20)**	**30 (21)**
Hypotension	10 (21)	11 (19)	21 (20)	0	3 (14)	1 (10)	25 (18)
Hypertension	2 (4)	7 (12)	9 (9)	0	0	1 (10)	10 (7)

Reviewer Comment
The ≥ grade 3 adverse events reported in ≥ 10% of patients are the expected toxicities seen in patients undergoing multi-agent chemotherapy reinduction.

Deaths

(copied from submission Section 5.3.5.2 ALL07P1 Study Report page 118 of 136)

Table 24: AALL07P1 Deaths – Safety Population

	Stratum						
	1	2	1 + 2	3	4	5	
	Pre-B-cell ALL, Age ≤ 21 yrs			Pre-B-cell ALL	T-cell ALL		Overall
Categories, n (%)	Relapse <18 mos (N = 47)	Relapse 18-36 mos (N = 57)	(N = 104)	> 21 yrs (N = 4)	1st relapse (N = 22)	T-cell LL (N = 10)	Total (N = 140)
All deaths	27 (57)	26 (46)	53 (51)	2 (50)	9 (41)	3 (30)	67 (48)
Related to study treatment	2 (4)	4 (7)	6 (6)	0	0	0	6 (4)
Primary cause of death							
Due to disease	17 (36)	19 (33)	36 (35)	1 (25)	8 (36)	3 (30)	48 (34)
Due to protocol treatment	1 (2)	0	1 (< 1)	0	0	0	1 (< 1)
Unknown	2 (4)	1 (2)	3 (3)	0	0	0	3 (2)
Due to other cause	7 (15)	6 (11)	13 (13)	1 (25)	1 (5)	0	15 (11)
Deaths within 30 days of last dose[a]	2 (4)	5 (9)	7 (7)	0	1 (5)	0	8 (6)
Related to study treatment	1 (2)	3 (5)	4 (4)	0	0	0	4 (3)
Primary cause of death							
Due to disease	1 (2)	3 (5)	4 (4)	0	1 (5)	0	5 (4)
Due to protocol treatment	1 (2)	0	1 (< 1)	0	0	0	1 (<1)
Unknown	0	0	0	0	0	0	0
Due to other cause	0	2 (4)	2 (2)	0	0	0	2 (1)
Deaths within 180 days of last dose[a]	16 (34)	16 (28)	32 (31)	1 (25)	6 (27)	2 (20)	41 (29)
Related to study treatment	2 (4)	4 (7)	6 (6)	0	0	0	6 (4)
Primary cause of death							
Due to disease	10 (21)	10 (18)	20 (19)	1 (25)	5 (23)	2 (20)	28 (20)
Due to protocol treatment	1 (2)	0	1 (< 1)	0	0	0	1 (< 1)
Unknown	1 (2)	1 (2)	2 (2)	0	0	0	2 (1)
Due to other cause	4 (9)	5 (9)	9 (9)	0	1 (5)	0	10 (7)

The case report of the patient with death categorized as due to protocol treatment (ID 807686) was reviewed. This patient received 3 doses of bortezomib; single doses of vincristine, doxorubicin, and pegaspargase; and 9 days of prednisone. On day 9 the patient developed gram positive sepsis, with capillary leak syndrome and multi-organ failure and died.

Reviewer Comment
Although bortezomib may have contributed to the sepsis, it is not clear it was the major factor given the patients underlying disease and the concomitant chemotherapy based on the case report.

The majority of deaths on this trial were related to underlying disease, and infections. Infections are associated with active leukemia and as a consequence of myelosuppressive chemotherapy. The incidence of fatal infections in this study does not appear to be excessive in this population.

Conclusion:

- There is no evidence that the addition of bortezomib improved the activity of the backbone multi-agent chemotherapy regimen.
- No safety signals were detected by the addition of bortezomib to backbone multi-agent chemotherapy regimen.

5.3.4 AAML1031 Phase 3 AML (PK data only)

Number/Clinical Trial Title: AAML1031 / "A Phase III Randomized Trial for Patients with de novo AML using Bortezomib and Sorafenib for Patients with High Allelic Ratio FLT3/ITD

Dose: 1.3 mg/m^2
Induction I - Day 1, 4, 8.
Induction II - Day 1, 4, 8
Intensification I - Day 1, 4, 8
Intensification II – Day 1, 4, 8
Route: IV bolus over 3 to 5 seconds

Schedule:

Figure 6: AAML1031 Study Schema

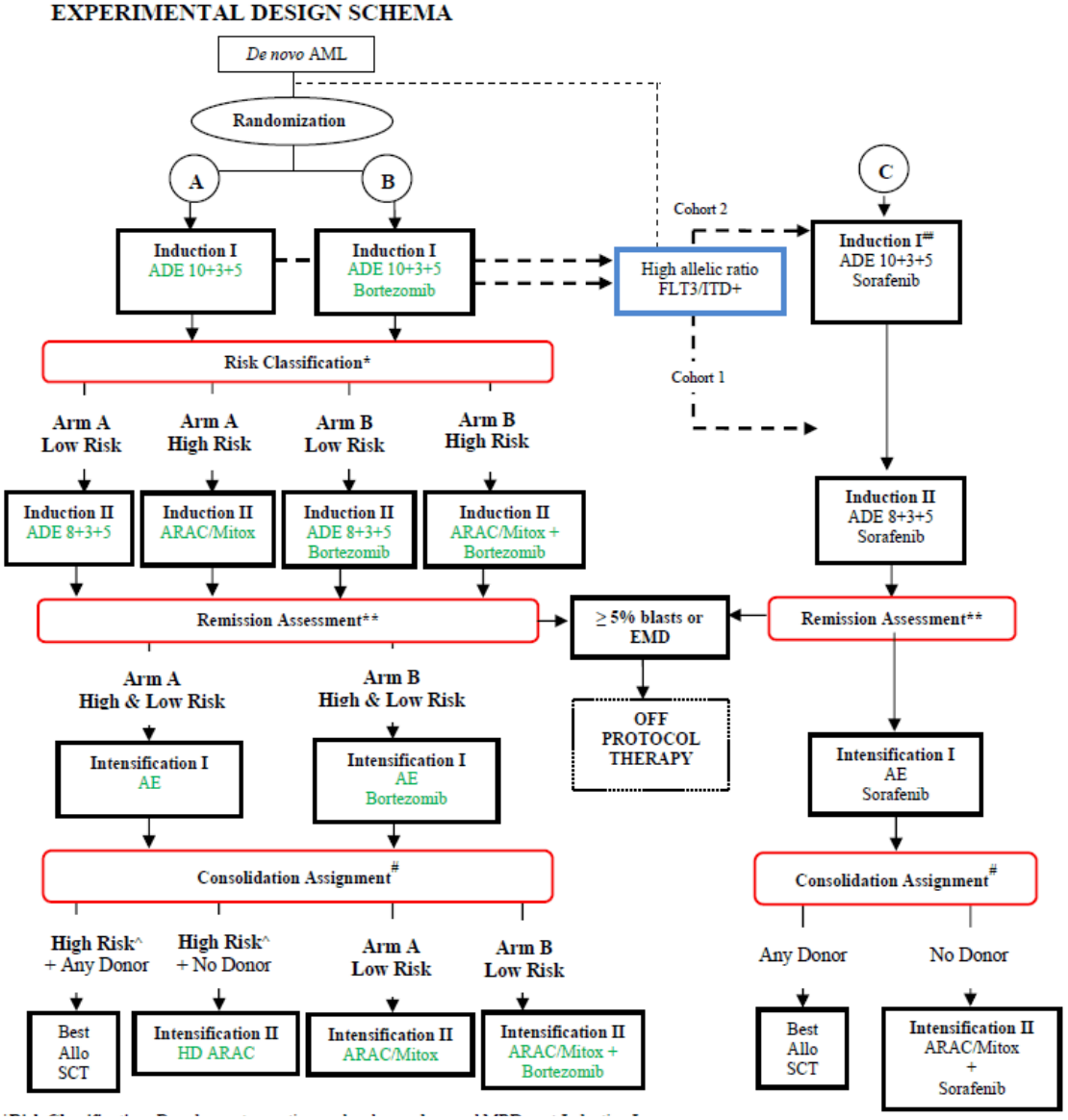
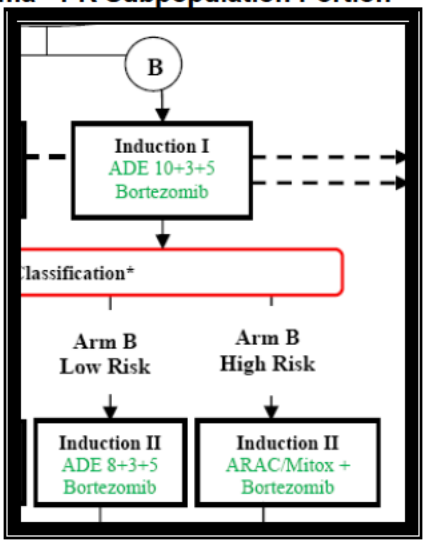


Figure 7: AAML1031 Study Schema - PK Subpopulation Portion



Population:

- Age < 30 years
- *De novo* AML, untreated (except hydroxyurea, ATRA, IT Ara-C)
- Low Risk (LR): Inv(16), t(8;21), nucleophosmin, CEBPα with any MRD status or standard risk cytogenetics with negative MRD at end of Induction I.
- High Risk (HR): Monosomy 7, del(5q) with any MRD status or standard risk cytogenetics with positive MRD at end of Induction I.

A subset of patients aged 2 to 16 years who agree to PK testing will be included in the population PK analysis. PK will be evaluated during the Induction II portion of the study.

Enrollment:
Planned : 1050 patients without high allelic ratio FLT3/ITD+; PK subset not to exceed 60 patients
Enrolled: PK subset 54 patients

Date of Study:
6/20/11 – Ongoing
PK subset PK collection: 4/20/12 to 8/6/13;
PK subset PK data collection: 12/31/13

Substantive Amendments:
12/20/11 - The addition of a bortezomib PK correlative study. This study was an extension of the bortezomib PK study incorporated into the protocol for Study AALL07P1. Additional patient data (ie, concomitant medications and specific AE reports) were collected from patients who consented to participate.

Results:

Demographics:

Table 25: AAML1031 Demographics - PK Subpopulation Portion

AAML1031 Demographics – PK Population	
	N=54
Gender	
Male	30
Female	24
Age in Years	
Mean	10.8
Median	11
Range	3 to 16
2 to 11	28
12 to 16	26
Race	
White	34
Black	10
Asian	3
American Indian Alaska Native	1
Missing or Other	6
Institutional Risk Group Classification	
Low Risk	40
High Risk	14

Exposure:
Drug exposure information was collected only during Induction II and all patients received the planned 3 doses of bortezomib in combination with standard chemotherapy. Most patients (46 patients [85%]) in the safety population did not have dose modifications to protocol treatment. Five patients (9%) had dose reductions of 1 or more components of treatment because of toxicity (2 patients in Induction I and 3 patients in Induction II).

Disposition:
No details provided. At time of data capture 49 patients remained on therapy and 5 were off protocol therapy.

Efficacy:
Not evaluable with available data.

Safety:
Treatment Emergent Adverse Events
(copied from submission Section 5.3.5.2 AAML1031 Study Report page 25 of 32)
Table 26: AAML1031 Treatment Emergent ≥ Gr 3 Adverse Events ≥ 10%

	Backbone + VELCADE N = 54		
Preferred Term	**Any AE n (%)**	**Grade ≥ 3 n (%)**	**AdEERS Reported[a] n (%)**
Patients with at least 1 TEAE	49 (91)	49 (91)	16 (30)
Hypokalaemia	19 (35)	19 (35)	0
Febrile neutropenia	17 (31)	17 (31)	3 (6)
Decreased appetite	13 (24)	13 (24)	0
Neutrophil count decreased	13 (24)	13 (24)	1 (2)
Stomatitis	10 (19)	10 (19)	0
Hypotension	10 (19)	9 (17)	6 (11)
Rash maculo-papular	9 (17)	9 (17)	0
Electrocardiogram QT prolonged	9 (17)	0	0
Streptococcus test positive	8 (15)	8 (15)	0
Pyrexia	7 (13)	7 (13)	2 (4)
Hyponatraemia	6 (11)	5 (9)	1 (2)
Lung infection	6 (11)	6 (11)	1 (2)
Staphylococcus test positive	6 (11)	6 (11)	0

Deaths
(copied from submission Section 5.3.5.2 AAML1031 Study Report page 26 of 32)
Among the 54 patients, no deaths were reported from the first dose of bortezomib in Induction I through 30 days after the last dose of bortezomib in Induction II.

Adverse Events Leading to Discontinuation
None reported.

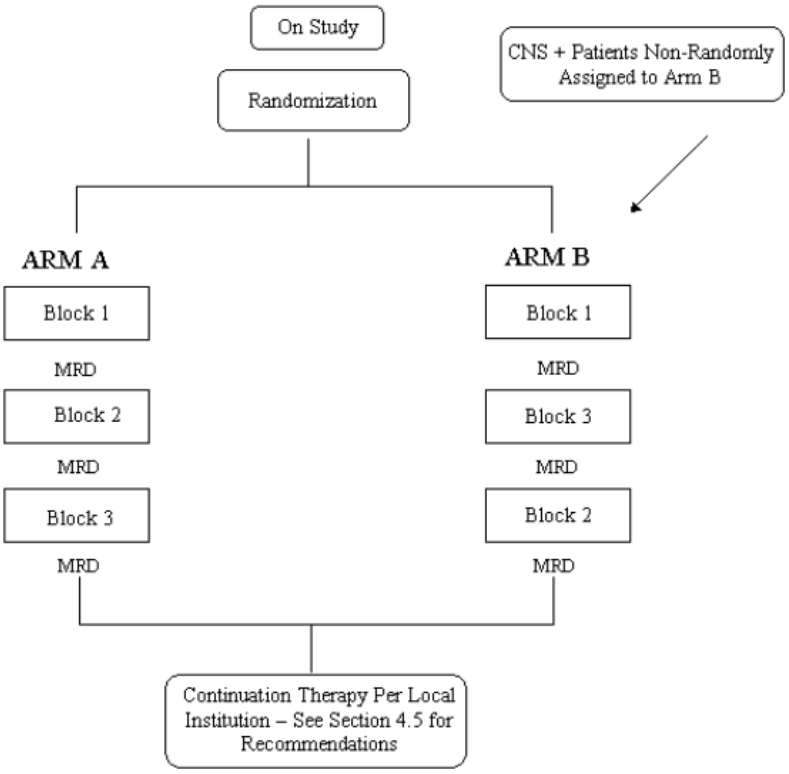
Conclusion:
(copied from submission Section 5.3.5.2 AAML1031 Study Report page 30 of 32)
The 54 pediatric patients diagnosed with de novo AML included in this report were part of the larger COG Study AAML1031 investigating the use of VELCADE with a standard chemotherapy regimen. Of these 54 patients, no deaths were reported from their first dose of bortezomib through 30 days after their last dose of bortezomib in Induction II. Whether the addition of bortezomib to the backbone chemotherapy added or increased toxicity compared with the backbone regimen alone is beyond the scope of this report.

5.3.5 AALL01P2 Phase 2 (Control for AALL07P1)

Number/Clinical Trial Title: AALL01P2 / Intensive Induction Therapy for Children with Acute Lymphoblastic Leukemia who Experience a Bone Marrow Relapse

Schedule:

Study Schema



Block 1
Vincristine
Prednisone
PEG-asparaginase
Doxorubicin
IT Cytarabine
IT Methotrexate (or ITT)
Imatinib Mesylate (STI571) (Ph+ALL)

Block 2
Etoposide
Cyclophosphamide
Methotrexate
IT Methotrexate (or ITT)
Imatinib Mesylate (STI571) (Ph+ALL)

Block 3
Cytarabine
L-asparaginase
Imatinib Mesylate (STI571) (Ph+ALL)

Details regarding doses of this chemotherapy schedule are presented in Appendix 9.3.
Note: Subjects enrolled on the AALL07P1 study with Ph+ ALL were required to have failed at least 1 TKI and did not receive a TKI as a component of the AALL07P1 study.

Population:

- Ages 1 to 21 years
- First isolated or combined marrow relapse.
  - B-precursor ALL
  - T-cell ALL

Enrollment:

The study enrolled 145 patients. After the first 21 patients, Block 1 therapy was modified due to unacceptable toxicity, which included three early deaths from infections. The control group for comparison was derived from the 124 patients who received the modified regimen. There were 69 patients with early relapse defined as < 36 months and 55 with late relapse. The early relapse population is the subset of interest for comparison to AALL07P1. (Raetz 2008)

Date of Study

January 2003 to December 2005 (Raetz 2008)

Results:

Demographics:
(copied from Raetz 2008)

Table 27: AALL01P2 Demographics

Table 2. Clinical and Demographic Characteristics

	Risk Group					
	Early Relapse		Late Relapse		Total	
Characteristic	No.	%	No.	%	No.	%
Median age, years	9.5		10.4		10.0	
Range	1.6-21.4		4.3-21.1		1.6-21.4	
Sex						
Male	43	62	37	67	80	65
Female	26	38	18	33	44	35
Immunophenotype						
B lineage	63	91	54	98	117	94
T lineage	6	9	1	2	7	6
Ph+						
No	67	97	53	96	120	97
Yes	2	3	2	4	4	3

Efficacy:
CR2 – CR Rate at the End of Block 1
(derived from submission Section 5.3.5.2 COG Study AALL01P2 COG Memo page 1)
The CR rate at the end of Block 1 of therapy was provided by the Children's Oncology Group (COG) statistician. This analysis included the subset of patients that met the eligibility criteria for patients included in stratum 1 and stratum 2. Patients with Ph+ All were excluded from the AALL0P2 comparator cohort.

The CR rate for patients who relapsed very early (< 18 months) was 53% (8/15); for patients who relapsed early (18 to 36 months)was 81% (33/41); total group (< 36 months) was 73% (41/56).

EFS at 4 Months
(derived from Raetz 2008)
For patients with B lineage Philadelphia chromosome negative ALL the estimated EFS at 4 months for patients who relapsed very early (< 18 months) was 38%; for patients who relapsed early (18 to 36 months) was 76%; for the entire group of patients who relapsed early was 65%.

Safety:
A comparison of the safety profile of AALL01P2 to AALL07P1 is presented in section 7 of this review.

5.4 Exclusivity Review

#	Written Request Sections	Provided in sNDA
1	*Type of Studies:* These studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities	Studies were open to all participants regardless of gender or ethnicity. Enrollment by ethnicity/race is provided.
	Phase 1 Studies: Studies, including pharmacokinetics, that define age appropriate dosing in pediatric patients.	Study ADVL0317: A Phase 1 Study of PS-341 (VELCADE, Bortezomib) in Pediatric Patients With Refractory/Recurrent Leukemias. This study included pharmacokinetics analysis. Study ADVL0015 CSR: A Phase 1 Study of PS-341 (NSC#681239, IND #58443) in Pediatric Patients With Refractory Solid Tumors.
	Phase 2 Study: A non-randomized, drug activity, safety and pharmacokinetic trial in children with acute lymphocytic leukemia (ALL) in first relapse, assessing the activity of the addition of bortezomib to multi-agent re-induction chemotherapy, limited to those patients with first relapse of pre-B ALL between the ages of 1 and 21 years and considered to be in "early" relapse, defined as relapse within 18 months of diagnosis (stratum 1) or relapse 18-36 months from diagnosis (stratum 2).	Phase 2 Study: Open-label phase 2 pilot 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 LL. 60 evaluable patients were enrolled in Strata 1 and 2: Stratum 1: pre-B-cell ALL patients less than or equal to 21 years old with relapse less than 18 months from diagnosis Stratum 2: pre-B-cell ALL patients less than or equal to 21 years old with relapse 18 to 36 months from diagnosis
	The study will have a stratified two-stage design. Patients enrolled in Stage 1 should be evaluated at the end of the stage for second complete response (CR2). The decision to enroll additional patients in the study, in Stage 2, should depend on whether the number of patients with CR2 at the end of Stage 1 meets the pre-specified decision boundaries.	A stratified phase 2 design was used to determine the sample size due to the difference in CR2 rates for early and late relapse in pre-B-cell ALL patients less than 21 years at enrollment

REVIEWER COMMENT:
Agree that the type of studies and study design conducted were in accordance with the written request.

#	Written Request Sections	Provided in sNDA
2	*Indication(s) to be studied:* Phase 1 Studies: Relapsed or refractory solid tumors and/or leukemias. Phase 2 Study: Pre-B-cell ALL in first relapse.	**Phase 1 Studies** **ADVL0015** - Refractory Solid Tumors **ADVL0317** - Refractory/Recurrent Leukemia **Phase 2 Study - AALL07P1** Relapsed B-precursor acute lymphoblastic leukemia (ALL), All patients in first relapse

REVIEWER COMMENT:
Agree that the subjects treated in these studies met the indications for the studies as specified in the written request.

#	Written Request Sections	Provided in sNDA
3	*Objectives:* Phase 1 Studies: To determine the maximum tolerated dose and/or pharmacokinetics.	**Phase 1 Studies** **ADVL0015** • To estimate the **maximum tolerated dose (MTD)** of VELCADE or the dose of VELCADE which resulted in 80% proteasome inhibition. • To determine the dose-limiting toxicities (DLT) and other toxicities of intravenous PS- 341 given on this schedule **ADVL0317** • To estimate the **maximum tolerated dose (MTD) and recommended phase 2 dose** of PS-341 administered as an intravenous bolus twice weekly for two weeks every three weeks to children with refractory/relapsed leukemia • To define and describe the toxicities of PS-341 administered on this schedule • **To characterize the pharmacokinetics** of PS-341 in children with refractory/ relapsed leukemia **Phase 2 Study** **AALL07P1** • To estimate the toxicity, CR2 rate at the end of Block 1 therapy, and 4-month EFS for pediatric and young adult patients with relapsed ALL treated with bortezomib in combination with intensive re- induction chemotherapy • To evaluate bortezomib pharmacokinetics (PK) in patients receiving the combination regimen
	Phase 2 Study: To estimate the rate of second complete response (CR2) achieved in each of the two strata at the end of Block 1 therapy, and the four month event-free survival; to describe the toxicity of the regimen; to evaluate pharmacokinetics by sparse PK sampling.	

REVIEWER COMMENT:
Agree that the studies evaluated the objectives as outlined in the written request.
ADVL0015
There were 15 patients enrolled with solid tumors. The MTD was 1.2 mg/m^2 BIW for 2 weeks. There were 2 DLTs (Grade 3 platelet count) reported at the 1.6 mg/m^2 dose level.
ADVL0317
There were 12 patients enrolled with leukemia. The MTD was 1.3 mg/m^2 BIW for 2 weeks. The drug related ≥ Grade 3 adverse events that were reported in ≥ 10% of the patient included: abnormal liver enzymes, anemia, thrombocytopenia, leukopenia, increased creatinine, febrile neutropenia, infections, hypokalemia, and nausea/vomiting, decreased appetite, GI hemorrhage, hypotension, confusion, and peripheral neuropathy. These adverse events commonly occur in the study patient population receiving chemotherapy. Two patients experienced DLTs. These included febrile neutropenia grade 4, and hypotension grade 4, increased creatinine grade 3; and confusion grade 3.

The clinical pharmacology reviewer has determined the PK analysis was performed adequately and agrees with the sponsor's conclusions.

AALL07P1

The CR at the end block 1 of therapy and the estimated 4 month event free survival compared to a matched historical control treated with the same backbone chemotherapy were included in the submission. There was no evidence of activity. The point estimate of the CR at day 36 in overall population was lower in the AALL07P1 population. There was no evidence of improved 4 month EFS with the addition of borezomib to the backbone chemotherapy.

Comparison AALL07P1 and AALL01P2 Analysis Populations		
Relapsed < 36 months		
	ALL07P1 n=60 Bortezomib	**AALL01P2 n=56**
CR End Block 1	68% (41/60)	73% (41/56)
Estimated 4 month EFS	55%	65%
Relapsed < 18 months (Stratum 1) n=27		
	ALL07P1 Bortezomib	**AALL01P2 n=15**
CR End Block 1	63% (17/27)	53% (8/15)
Estimated 4 month EFS	41%	38%
Relapsed 18 to 36 months (Stratum 2) n=33		
	ALL07P1 Bortezomib	**AALL01P2 n=41**
CR End Block 1	73% (24/33)	81% (33/41)
Estimated 4 month EFS	66%	76%

#	Written Request Sections	Provided in sNDA
4	*Age group in which the study will be performed*: Phase 1 Studies: Patients 1 to 18 years of age.	**Phase 1 Studies** **ADVL0015** At enrollment, the median age of patients in the safety population was 10.0 years (range 4-17; N=15) **ADVL0317** • At enrollment, the mean age of patients in the safety population (n=11) was 12.8 (range: 1-18) years
	Phase 2 Study: 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. Although the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(g) states "including neonates in appropriate cases" as one of the pediatric age groups for pediatric studies, the proposed trial includes children no younger than 2 years of age. Neonates would not be an appropriate group for inclusion for two reasons: 1) the proposed trial's eligibility criteria require that pediatric patients must have relapsed disease following first complete remission; and, 2) the treatment of infants with leukemia differs from the treatment of older children in which the proposed backbone therapy is appropriate.	**Phase 2 Study** **AALL07P1** • The majority of the patients (63%) were between the ages of 2 and 11 years, inclusive, with a median age of 8.0 years at enrollment • For the first 60 evaluable patients in Strata 1 and 2, age at enrollment: o <2 years- N=4 o 2-11 years- N=38 o 12-16 years- N=9 o >16 years- N=9

REVIEWER COMMENT:
Agree that the studies included the required number of subjects at the specified ages.

#	Written Request Sections	Provided in sNDA
5	*Number of patients to be studied:* Phase 1 Studies: The number of patients entered must be sufficient to achieve Phase 1 objectives.	**Phase 1 Studies** **ADVL0015** A total of 15 patients were enrolled into the study (9 patients in the 1.2 mg/m^2 treatment group and 6 patients in the 1.6 mg/m^2 treatment group). **ADVL0317** A total of 12 patients were enrolled in this study (6 patients in the 1.3 mg/m^2 treatment group and 6 patients in the 1.7 mg/m^2 treatment group), although 1 patient was not administered VELCADE due to an infection. None of the patients completed protocol therapy.
	Phase 2 Study: 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 according to the protocol stopping rules, 30 additional patients will be enrolled in Stage 2.	**Phase 2 Study** **AALL07P1** Per Amendment 5 of the Study AALL07P1 protocol, enrollment remained open beyond the originally planned 60 evaluable patients in Strata 1 and 2. A snapshot of the study database was taken approximately 9.5 months after the 60th evaluable patient was enrolled to enable analysis of 4-month EFS. As of the data cutoff of 31 Dec 2013, VELCADE had been administered to 140 patients across the 5 strata as follows: Stratum 1: pre-B-cell ALL patients less than or equal to 21 years old with first relapse less than 18 months from diagnosis (47 patients) Stratum 2: pre-B-cell ALL patients less than or equal to 21 years old with first relapse within 18 to 36 months from diagnosis (57 patients) Stratum 3: pre-B-cell ALL patients greater than 21 years old (4 patients) Stratum 4: T-cell ALL in first relapse (22 patients) Stratum 5: T-cell LL (10 patients)

REVIEWER COMMENT:
Agree that the studies included the minimum required number of subjects.

#	Written Request Sections	Provided in sNDA
6	*Study endpoints:* Phase 1 Studies: 1. Determine the maximum tolerated dose (MTD), dose-limiting and other toxicities in pediatric patients with cancer. 2. Assess patients for responses to therapy and duration of responses.	**Phase 1 Studies** **ADVL0015** Primary Endpoints: • To estimate the MTD of VELCADE or the dose of VELCADE which resulted in 80% proteasome inhibition, whichever was obtained first when administered as an intravenous (IV) bolus twice weekly for 2 consecutive weeks, beginning every 3 weeks, to children with refractory solid tumors. • To determine the dose-limiting toxicities (DLTs) and other toxicities of IV VELCADE given on this schedule. • To evaluate the inhibition of the 20S proteasome in whole blood following IV administration. Secondary Endpoints • To preliminarily define the antitumor activity of VELCADE within the confines of a Phase I study • To obtain additional preliminary information about the biologic activity of VELCADE, through correlative studies assessing NF-κB regulation and apoptosis **ADVL0317** Primary Endpoints • To estimate the MTD and recommended phase 2 dose of VELCADE administered as an intravenous (IV) bolus twice weekly for 2 weeks every 3 weeks to children with refractory/relapsed leukemia • To define and describe the toxicities of VELCADE administered on this schedule. • To characterize the pharmacokinetics of bortezomib in children with refractory/relapsed leukemia. Secondary Endpoints • Preliminary evaluation of efficacy (tumor response) presented in a by-patient listing for this report.
	Phase 2 Study: 1. To determine the toxicities of bortezomib when administered in combination with intensive re-induction chemotherapy in patients with relapsed ALL 2. To estimate for patients in strata 1 and 2 with pre-B ALL, the rate of re-induction of CR and the 4 month EFS (as an indication of potential transplant eligibility) for this regimen	**Phase 2 Study** **AALL07P1** Primary objectives: • To estimate the toxicity, second complete remission (CR2) rate at the end of Block 1 therapy, 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. • To evaluate bortezomib pharmacokinetics in patients receiving the combination regimen.
	All Studies: Pharmacokinetic data should be appropriately analyzed using methods such as nonlinear mixed effects modeling. A minimum of 20 patients in each age group of 2-11 and 12-16 years must be sampled for pharmacokinetics. To enable this analysis, data from this Phase 2 study may be combined with PK data collected in other pediatric studies of VELCADE. The data from the relevant studies must then be used to explore the exposure response relationship for safety and effectiveness endpoints.	**Population PK Report** **Population Pharmacokinetic Analysis of Bortezomib After VELCADE Administration in Pediatric Cancer Patients Protocols AALL07P1 and AAML1031** **Exposure Response Report** **Clinical Pharmacology Pediatric Exposure-Response Report**

ADVL0015
There were 15 patients enrolled with solid tumors. The MTD was 1.2 mg/m^2 BIW for 2 weeks. There were no responses.
ADVL0317
There were 12 patients enrolled with leukemia. The MTD was 1.3 mg/m^2 BIW for 2 weeks.

AALL07P1
The toxicity profiles of the backbone chemotherapy with and without bortezomib were similar. No novel toxicities were identified when bortezomib was added. The combination of the backbone chemotherapy and bortezomib was tolerated in the study population.

All Studies
The clinical pharmacology reviewer has determined the PK analysis was performed adequately and agrees with the sponsor's conclusions.

#	Written Request Sections	Provided in sNDA
7	*Drug information* • *dosage form* Bortezomib for injection will be provided in the marketed formulation. • *route of administration* Intravenous • *Regimen* Phase 1 Studies: Bortezomib 1-1.7 mg/m^2 on days 1, 4, 8, and 11 every 3 weeks. Phase 2 Study: Bortezomib 1.3 mg/m^2 will be given on days 1, 4, 8, and 11 during the first 35 days of treatment, then again on days 1, 4, and 8 of the second 35 day treatment block, for a total of 7 injections.	**Phase 1 Studies** **ADVL0015** Dosage form: VELCADE was supplied as a lyophilized powder in sterile vials containing 3.5 mg and 35 mg mannitol, USP VELCADE was administered as an IV bolus (over 3 to 5 seconds) twice weekly on Days 1, 4, 8, and 11 that was followed by a 10-day rest period. The initial dose for the 21-day cycle was 1.2 mg/m^2, which was 80% of the MTD determined in a phase 1 study of VELCADE in adults.(7) Subsequent planned dose escalations were 1.6 mg/m^2 per dose, 2.1 mg/m^2 per dose, 2.7 mg/m^2 per dose, and 3.5 mg/m^2 per dose. **ADVL0317** Dosage form: VELCADE was supplied as a lyophilized powder in sterile vials containing 3.5 mg and 35 mg mannitol, USP VELCADE was administered as an IV bolus (over 3 to 5 seconds) twice weekly on Days 1, 4, 8, and 11 followed by a 10 day rest period (21-day treatment cycle). Drug doses were adjusted based
		on the body surface area determined at the beginning of each cycle. Planned dose escalation levels included 1.3 mg/m^2, 1.7 mg/m^2, and 2.1 mg/m^2. **Phase 2 Study** **AALL07P1** Dosage form: VELCADE was supplied as a lyophilized powder in sterile vials containing 3.5 mg and 35 mg mannitol, USP VELCADE was administered intravenously (over 3 – 5 seconds) at 1.3 mg/m^2 per dose on Days 1, 4, 8, and 11 of Block 1 and Days 1, 4, and 8 of Block 2. Duration of Treatment: Each of the 3 blocks of reinduction treatment was 35 days in duration. VELCADE administration was limited to Blocks 1 and 2. **Phase 3 Study** **AAML1031** Dosage form: VELCADE was supplied as a lyophilized powder in sterile vials containing 3.5 mg and 35 mg mannitol, USP Treatment Regimen and Sampling in patients who received VELCADE was as follows:
		Induction I & II: VELCADE 1.3 mg/m^2 IV on Days 1, 4, and 8 in combination with other chemotherapeutic agents.

REVIEWER COMMENT:
Agree that the studies were conducted using the specified doses and schedules of Velcade.

#	Written Request Sections	Provided in sNDA
8	*Drug specific safety concerns*: In adults receiving bortezomib on a similar schedule cycled every three weeks, neurologic toxicity (peripheral sensory neuropathy) is usually cumulative and dose-limiting. Ileus has also been observed. Provide safety information on these and other toxicities encountered.	**Phase 1 Studies** **ADVL0015** Safety information on toxicities was reported. Adverse events of interest were reported. A separate listing of TEAEs of interest is provided. Protocol-specified TEAEs of interest were peripheral neuropathy (based on the MedDRA high-level term of peripheral neuropathy not elsewhere classified [NEC]) and ileus. There was a report of Grade 1 peripheral neuropathy in 1 patient; however, there were no reports of dose-limiting peripheral neuropathy. There were no reports of ileus during this study
		ADVL0317 Safety information on toxicities was reported. A separate listing of TEAEs of special interest (defined as peripheral neuropathy [based on the MedDRA high-level term of peripheral neuropathy], or ileus) is provided. Treatment-emergent AEs of interest (peripheral neuropathy and ileus) are summarized in Table 14.4.2.3. A total of 2 patients (1 in each treatment group) experienced events of interest. Both patients experienced 1 event each of ileus, gastrointestinal (functional obstruction of bowel). Events were moderate in severity and considered unrelated to study treatment.
		Peripheral neuropathies and ileus were considered events of interest per the pediatric WR. Twenty-five of 140 patients (18%) in the safety population experienced PNs that included peripheral sensory neuropathy in 20 patients (14%) and peripheral motor neuropathy in 11 patients (8%). For 16 of these patients, the neuropathy was considered possibly or probably related to VELCADE. Four patients (3%) experienced ileus with 3 in whom the event was considered possibly related to VELCADE. **Phase 3 Study** **AAML1031** Treatment-emergent AEs were defined as any AE that occurred after the start of Induction I and within 30 days after the last dose of VELCADE in Induction II. Adverse event reporting was required for AdEERS-reported events, Grade 3 or higher

		Peripheral neuropathies and ileus were considered events of interest per the pediatric WR. Twenty-five of 140 patients (18%) in the safety population experienced PNs that included peripheral sensory neuropathy in 20 patients (14%) and peripheral motor neuropathy in 11 patients (8%). For 16 of these patients, the neuropathy was considered possibly or probably related to VELCADE. Four patients (3%) experienced ileus with 3 in whom the event was considered possibly related to VELCADE. **Phase 3 Study** **AAML1031** Treatment-emergent AEs were defined as any AE that occurred after the start of Induction I and within 30 days after the last dose of VELCADE in Induction II. Adverse event reporting was required for AdEERS-reported events, Grade 3 or higher nonhematological AEs, all grades of left ventricular systolic dysfunction, heart failure, ECG QT-corrected interval prolonged, peripheral neuropathy, ileus, and dose-limiting toxicities as defined in the protocol. Relationship to study drug was not recorded. Five patients experienced Grade 1 peripheral sensory neuropathy, and none had ileus.

REVIEWER COMMENT:
Agree that the studies comprehensively evaluated patients for neuropathy and ileus. There did not appear to be a significantly increased incidence of either.

#	Written Request Sections	Provided in sNDA
9	*Statistical information, including power of study and statistical assessments:* 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%.	Due to the observed difference in CR2 rates relative to the time from initial diagnosis to relapse, a stratified phase 2 design was used to determine the needed sample size in Study AALL07P1.
	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.	CR2 response rates were assessed at the end of Stage 1 after 30 patients, and the study continued to enroll patients in Strata 1 and 2. Per Amendment 5 of the Study AALL07P1 protocol, enrollment remained open beyond the originally planned 60 evaluable patients in Strata 1 and 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.	In Study AALL07P1 the CR2 rates were 67% (46.0, 83.5) in patients who relapsed within 18 months of diagnosis (Stratum 1) and 79% (61.1, 91.0) in patients who relapsed 18-36 months after diagnosis (Stratum 2).

REVIEWER COMMENT:
Agree that the statistical analysis as specified was evaluated. At FDA request the applicant submitted a revised analysis revising the subjects included in the first 60 patients. Three patients were excluded as “not evaluable” that FDA considered evaluable these were 2 patients who died during induction therapy, and one patient who was removed from therapy for progressive disease. These patients should be categorized as induction failures and included. This revision did not alter the overall conclusion that there was no evidence of activity.

6 Review of Efficacy

Efficacy Summary

A comparison of the endpoints to assess activity of the addition of bortezomib to the backbone chemotherapy is included in this section. The statistical analysis plan pre-specified the comparison was between comparable populations enrolled on the AALL01P2 (backbone chemotherapy) and AALL07P1 (backbone chemotherapy with bortezomib) studies. Specifically, the population evaluated was patients with B lineage ALL less than 21 years who relapsed < 36 months from original diagnosis. The control comparison group from AALL01P2 study was all patients enrolled who met these criteria (n=56). The experimental population was the first 60 evaluable patients from AALL07P1 who met these criteria. The endpoints to be evaluated were the CR rate on day 36 after Block 1 of therapy and the estimated 4 month EFS.

There was no evidence of activity demonstrated.

6.1 Indication

The indication evaluated was the addition of bortezomib to a multi-agent chemotherapy reinduction regimen to improve outcome in patients less than 21 years with early relapse of ALL.

6.1.1 Methods

For details see sections 5.3.3 and 5.3.5.

6.1.2 Demographics

For details see sections 5.3.3 and 5.3.5.

6.1.3 Subject Disposition

For details see sections 5.3.3 and 5.3.5.

6.1.4 Analysis of Primary Endpoint(s)

Activity Analysis

Table 28: Comparison Activity AALL07P1 Efficacy Population to AALL01P2 Control Population

Comparison AALL07P1 and AALL01P2 Analysis Populations		
Relapsed < 36 months		
	ALL07P1 n=60 Bortezomib	**AALL01P2 n=56**
CR End Block 1	68% (41/60)	73% (41/56)
Estimated 4 month EFS	55%	65%
Relapsed < 18 months (Stratum 1) n=27		
	ALL07P1 Bortezomib	**AALL01P2 n=15**
CR End Block 1	63% (17/27)	53% (8/15)
Estimated 4 month EFS	41%	38%
Relapsed 18 to 36 months (Stratum 2) n=33		
	ALL07P1 Bortezomib	**AALL01P2 n=41**
CR End Block 1	73% (24/33)	81% (33/41)
Estimated 4 month EFS	66%	76%

REVIEWER COMMENT

There was no evidence of activity. The point estimate of the CR at day 36 in overall population was lower in the AALL07P1 population. There was no evidence of improved 4 month EFS with the addition of borezomib to the backbone chemotherapy.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

There was no evidence of activity; therefore, no dosing recommendations are appropriate.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Comparison AALL07P1 safety Population to AALL01P2 Safety Population Demographics
(copied from submission Section 2.7.4 Summary of Clinical Safety of Velcade page 64 of 79)

Table 29: Comparison AALL07P1 and AALL01P2 Demographics - Safety Population

Characteristic, n (%)	VELCADE+Backbone (Study AALL07P1) (N=140)	Backbone Study (Study AALL01P2) (N=124)
Median age (range), years	10 (1-26)	10 (2-21)[a]
Sex		
Male	80 (57)	80 (65)
Female	60 (43)	44 (35)
Immunophenotype		
B lineage	108 (77)	117 (94)
T lineage	32 (23)	7 (6)
Philadelphia chromosome negative	138 (99)	120 (97)
Central nervous system disease		
Negative	128 (91)	110 (89)
Positive	12 (9)	14 (11)

7.1.2 Categorization of Adverse Events

In study AALL01P2 the toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0) (Raetz 2008). In study AALL07P1 the toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0). In general, COG systematically collects toxicities > grade 3.

7.2 Adequacy of Safety Assessments

Data collection of toxicities in these studies was adequate to determine if there were major differences in significant toxicities associated with the addition of bortezomib to the backbone therapy.

7.3 Major Safety Results

7.3.1 Deaths

(copied from submission Section 2.7.4 Summary of Clinical Safety of Velcade page 67 of 79)

Table 30: Comparison AALL07P1 and AALL01P2 Deaths - Safety Populations

Category, n (%)	VELCADE+Backbone (Study AALL07P1) (N=140)	Backbone Study (Study AALL01P2) (N=124)
Deaths within 30 days of last dose	8 (6)	10 (8)[a]
Deaths related to study treatment within 30 days of last dose	4[b] (3)	5[c] (4)
Block 1	2	3[d]
Block 2	2	--
Block 3	--	2
Cause of deaths related to study treatment	Sepsis (*Clostridium septicum*); Septic shock (*Escherichia coli*); Respiratory failure; and Disease progression	Sepsis (*Staphylococcus aureus*, *Clostridium* species, *Pseudomonas aeruginosa*, or alpha hemolytic streptococci)

7.3.2 Nonfatal Serious Adverse Events (Grade 3 and 4 Adverse Events)

(copied from submission Section 2.7.4 Summary of Clinical Safety of Velcade page 66 of 79)

Table 31: Comparison AALL07P1 and AALL01P2 ≥ Grade 3 Adverse Event ≥ 10% - Safety Populations

	Study AALL07P1 (VELCADE+Backbone Study)			Study AALL01P2 (Backbone Study)[a]		
	Block 1 (N=140)	Block 2 (N=102)	Block 3[b] (N=57)	Block 1 (N=124)	Block 2 (N=91)	Block 3 (N=102)
Toxicity, n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Neutrophil count decreased	77 (55)	64 (63)	39 (68)	121 (98)	88 (97)	101 (99)
Platelet count decreased	86 (61)	67 (66)	42 (74)	99 (80)	59 (65)	98 (96)
Hemoglobin/anemia	58 (41)	54 (53)	37 (65)	78 (63)	59 (65)	79 (78)
Febrile neutropenia	34 (24)	26 (25)	18 (32)	50 (40)	26 (29)	45 (44)
Infection with ≥Grade 3 neutropenia	34 (24)	22 (22)	20 (35)	24 (19)	10 (11)	36 (35)
WBC decreased	69 (49)	57 (56)	35 (61)	30 (24)	13 (14)	20 (20)
ALT increased	18 (13)	17 (17)	5 (9)	18 (15)	9 (8)[c]	4 (5)[c]
Hyperglycaemia	19 (14)	6 (6)	1 (2)	15 (12)	2 (2)[c]	2 (2)[c]
Hypotension	18 (13)	8 (8)	2 (4)	3 (2)[c]	3 (3)[c]	1 (1)[c]
Hypokalemia	25 (18)	21 (21)	7 (12)	8 (6)[c]	13 (12)[c]	17 (17)
Fibrinogen decreased	7 (5)	(<10)	(<10)	40 (32)	1 (<1)[c]	0[c]
Lymphocyte count decreased	33 (24)	25 (25)	12 (21)	8 (6)[c]	8 (7)[c]	8 (9)[c]
Hyponatraemia	17 (12)	4 (4)	0	6 (5)[c]	0[c]	2 (2)[c]
Lipase increased	15 (11)	2 (2)	0	10 (8)[c]	3 (3)[c]	2 (2)[c]

7.3.5 Submission Specific Primary Safety Concerns

Peripheral Neuropathy
(copied from submission Section 2.7.4 Summary of Clinical Safety of Velcade page 68 of 79)

Table 32: Comparison AALL07P1 and AALL01P2 ≥ Grade 3 Neuropathy - Safety Population

	Block 1		Block 2		Block 3	
MedDRA Preferred Term, n (%)	VELCADE+ Backbone (N=140)	Backbone (N=127)	VELCADE+ Backbone (N=102)	Backbone (N=110)	VELCADE+ Backbone[a] (N=57)	Backbone (N=86)
Peripheral motor neuropathy	2 (<1)	3 (2)	0	2 (2)	0	1 (<1)
Peripheral sensory neuropathy	4 (3)	0	1 (<1)	2 (2)	0	2 (2)

There was a minimally greater incidence of neuropathy during Block 1 of therapy with bortezomib but not Block 2.

Ileus
There were no reported incidences of ≥ grade 3 ileus in AALL01P2. In AALL07P1 3 of 140 patients (2.1%) experienced ≥ Grade 3 ileus, all reported in Block 1.

Pulmonary Toxicities
In AALL01P2 the incidence of ≥ grade 3 hypoxia reported during Block 1 was 8% compared to 2% in AALL07P1. In Block 2 the incidence was 4% versus 6%.

9 Appendices

9.1 Literature Review/References

Blaney SM, Berstein M, Neville K, et al. Phase I Study of the Proteasome Inhibitor Bortezomib in Pediatric Patients With Refractory Solid Tumors: A Children's Oncology Group Study (ADLV0015). J Clin Oncol. 2004;22(23):4804-4809.

Horton TM, Pati D, Plon SE, Thompson PA, Bomgaars LR, Adamson PC, et al. A Phase 1 Study of the Proteasome Inhibitor Bortezomib in Pediatric Patients With Refractory Leukemia: A Children's Oncology Group Study. Clin Cancer Res 2007;13(5):1516- 22.

Horton TM, Lu X, O'Brien MM, et al and Children's Oncology Group. Bortezomib with reinduction therapy to improve response rates in pediatric ALL in first relapse: A Children's Oncology Group (COG) study (AALL07P1). [ASCO Annual Meeting Abstract 10003]. J Clin Oncol 2013; 31(suppl; abstr 10003).

Horton TM, Lu X, O'Brien MM, et al. AALL07P1: Bortezomib with reinduction chemotherapy for first relapse pediatric ALL. A Children's Oncology Group Study. In: 46th Congress of the International Society of Pediatric Oncology (SIOP) 2014; Toronto, Canada: 22-25 October 2014. Abstr O-121.

Raetz EA, Borowitz MJ, Devidas M, et al: Reinduction platform for children with first marrow relapse of acute lymphoblastic Leukemia: A Children's Oncology Group Study. J Clin Oncol 26(28):3971-8, 2008.

9.2 Labeling Recommendations

8.4 Millennium Version	8.4 FDA Revisions
(b) (4)	The effectiveness of VELCADE in pediatric patients with relapsed pre-B acute lymphoblastic leukemia (ALL) has not been established. The activity and safety of VELCADE in combination with intensive reinduction chemotherapy was evaluated in pediatric and young adult patients with lymphoid malignancies (pre-B cell ALL 77%, 16% with T-cell ALL, and 7% T-cell lymphoblastic lymphoma (LL)), all of whom relapsed within 36 months of initial diagnosis in a single-arm multicenter, non-randomized cooperative group trial. An effective reinduction multiagent chemotherapy regimen was administered in 3 blocks. Block 1 included vincristine, prednisone, doxorubicin and pegaspargase; block 2 included cyclophosphamide, etoposide and methotrexate; block 3 included high dose cytosine arabinoside and asparaginase. VELCADE was administered at a dose of 1.3 mg/m2 as a bolus intravenous injection on days 1, 4, 8, and 11 of block 1 and days 1, 4, and 8 of block 2. There were 140 patients with ALL or LL enrolled and evaluated for safety. The median age was 10 years (range 1 to 26), 57% were male, 70% were white, 14% were black, 4% were Asian, 2% were American Indian/ Alaska Native, 1% were Pacific Islander. The activity was evaluated in a pre-specified subset of the first 60 evaluable patients enrolled on the study with pre-B ALL ≤ 21 years and relapsed < 36 months from diagnosis. The complete remission (CR) rate at day 36 was compared to that in a historical control set of patients who had received the identical backbone therapy without VELCADE. There was no evidence that the addition of VELCADE had any impact on the CR rate.

(b) (4)	
	No new safety concerns were observed when VELCADE was added to a chemotherapy backbone regimen as compared with a historical control group in which the backbone regimen was given without VELCADE..
	The BSA-normalized clearance of bortezomib in pediatric patients was similar to that observed in adults.

9.3 Backbone Chemotherapy

(copied from submission Section 5.3.5.2 ALL07P1 CSR Synopsis page 3 of 9)

Drug	Route	Dose	Block/ Day(s)
Cytarabine	IT	30 mg (Age 1-1.99 yr) 50 mg (Age 2-2.99 yr) 70 mg (Age ≥ 3 yr)	Block 1/At time of diagnostic lumbar puncture[a] OR Day 1
Vincristine	IV push over 1 minute, or by infusion via minibag	1.5 mg/m^2 per dose (maximum dose 2 mg)	Block 1/Days 1, 8, 15, and 22
Doxorubicin	IV over 15 minutes	60 mg/m^2 per dose	Block 1/Day 1
Prednisone	PO	20 mg/m^2 per dose, BID	Block 1/Days 1–28
Pegaspargase	IM or IV over 1-2 hours[b]	2500 IU/m^2 per dose	Block 1/Days 2, 8, 15, and 22
Methotrexate For CNS-negative (CNS 1 or CNS 2) patients only	IT	8 mg (Age 1-1.99 yr) 10 mg (Age 2-2.99 yr) 12 mg (Age 3-8.99 yr) 15 mg (Age ≥ 9 yr)	Block 1/Days 15 and 29 Block 2/ Days 1 and 22. Day 22 administration was dependent on ANC >750/µL and platelet count > 75000/µL off G-CSF for 48 hrs
Triple ITT: Methotrexate, hydrocortisone, and cytarabine For CNS-positive (CNS 3) patients only[c]	IT	MTX/HC/AraC 8 mg/8 mg/16 mg (Age 1-1.99 yr) 10 mg/10 mg/20 mg (Age 2-2.99 yr) 12 mg/12 mg/24 mg (Age 3-8.99 yr) 15 mg/15 mg/30 mg (Age ≥ 9 yr)	Block 1/Days 8, 15, 22, and 29 Block 2/Days 1 and 22. Day 22 administration was dependent on ANC >750/µL and platelet count > 75000/µL off G-CSF
Etoposide	IV over 1–2 hours	100 mg/m^2 per dose	Block 2/Days 1–5
Cyclophosphamide	IV over 15–30 minutes	440 mg/m^2 per dose	Block 2/Days 1–5
Filgrastim (G-CSF)	SC preferred, may be given IV	5 µg/kg per dose	Block 2/Daily, starting on Day 6. Held on Day 8. Block 3/Daily, starting on Day 10
High-dose methotrexate	IV over 24 hours	5000 mg/m^2 per dose (depended on blood counts)	Block 2/Day 22
Leucovorin	IV/PO	Standard dose of 15 mg/m^2 every 6 hours for 3 doses. Continued use and dose depended on methotrexate levels.	Block 2/Days 23 and 24
Cytarabine	IV over 3 hours	3000 mg/m^2/dose every 12 hours for 4 doses, relative to Hour 0.	Block 3/Days 1-2 and 8-9
Escherichia coli L-asparaginase[d]	IM	6000 IU/m^2/dose	Block 3/Days 2 and 9

9.4 Written Request

WRITTEN REQUEST - AMENDMENT #2

NDA 021602

Millennium Pharmaceuticals, Inc.
Attention: Eileen Bedell, M.P.H.
Director Regulatory Affairs
35 Landsdowne Street
Cambridge, Massachusetts 02139

Dear Ms. Bedell:

Please refer to your correspondence dated May 20, 2011, and December 20, 2011, requesting changes to FDA's January 26, 2011 Written Request (WR) for VELCADE (bortezomib) for Injection.

This study investigates the potential use of bortezomib in the treatment of pediatric patients with acute lymphocytic leukemia (ALL).

To obtain needed pediatric information on bortezomib, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

***Type of study(ies)*:**

These studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities.

Phase 1 Studies: Studies, including pharmacokinetics, that define age appropriate dosing in pediatric patients.

Phase 2 Study: A non-randomized, drug activity, safety and pharmacokinetic trial in children with acute lymphocytic leukemia (ALL) in first relapse, assessing the activity of the addition of bortezomib to multi-agent re-induction chemotherapy, limited to those patients with first relapse of pre-B ALL between the ages of 1 and 21 years and considered to be in "early" relapse, defined as relapse within 18 months of diagnosis (stratum 1) or relapse 18-36 months from diagnosis (stratum 2). The study will have a stratified two-stage design. Patients enrolled in Stage 1 should be evaluated at the end of the stage for second complete response (CR2). The decision to enroll additional patients in the study, in Stage 2, should depend on whether the number of patients with CR2 at the end of Stage 1 meets the pre-specified decision boundaries.

Indication(s) to be studied:

Phase 1 Studies: Relapsed or refractory solid tumors and/or leukemias.
Phase 2 Study: Pre-B-cell ALL in first relapse.

Objectives:

Phase 1 Studies: To determine the maximum tolerated dose and/or pharmacokinetics.
Phase 2 Study: To estimate the rate of second complete response (CR2) achieved in each of the two strata at the end of Block 1 therapy, and the four month event-free survival; to describe the toxicity of the regimen; to evaluate pharmacokinetics by sparse PK sampling.

***Age group in which the study will be performed*:**

Phase 1 Studies: Patients 1 to 18 years of age.
Phase 2 Study: 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.

Although the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(g) states "including neonates in appropriate cases" as one of the pediatric age groups for pediatric studies, the proposed trial includes children no younger than 2 years of age. Neonates would not be an appropriate group for inclusion for two reasons: 1) the proposed trial's eligibility criteria require that pediatric patients must have relapsed disease following first complete remission; and, 2) the treatment of infants with leukemia differs from the treatment of older children in which the proposed backbone therapy is appropriate.

Number of patients to be studied:

Phase 1 Studies: The number of patients entered must be sufficient to achieve Phase 1 objectives. Phase 2 Study: 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 according to the protocol stopping rules, 30 additional patients will be enrolled in Stage 2.

Study endpoints:

Phase 1 Studies:

1. Determine the maximum tolerated dose (MTD), dose-limiting and other toxicities in pediatric patients with cancer.
2. Assess patients for responses to therapy and duration of responses.

Phase 2 Study:

1. To determine the toxicities of bortezomib when administered in combination with intensive re-induction chemotherapy in patients with relapsed ALL

2. To estimate for patients in strata 1 and 2 with pre-B ALL, the rate of re-induction of CR and the 4 month EFS (as an indication of potential transplant eligibility) for this regimen

All Studies: Pharmacokinetic data should be appropriately analyzed using methods such as nonlinear mixed effects modeling. A minimum of 20 patients in each age group of 2-11 and 12-16 years must be sampled for pharmacokinetics. To enable this analysis, data from this Phase 2 study may be combined with PK data collected in other pediatric studies of VELCADE. The data from the relevant studies must then be used to explore the exposure-response relationship for safety and effectiveness endpoints.

Drug information

- *dosage form*
  Bortezomib for injection will be provided in the marketed formulation.
- *route of administration*
  Intravenous
- *regimen*
  Phase 1 Studies: Bortezomib 1-1.7 mg/m^2 on days 1, 4, 8, and 11 every 3 weeks.
  Phase 2 Study: Bortezomib 1.3 mg/m^2 will be given on days 1, 4, 8, and 11 during the first 35 days of treatment, then again on days 1, 4, and 8 of the second 35 day treatment block, for a total of 7 injections.

***Drug specific safety concerns*:**

In adults receiving bortezomib on a similar schedule cycled every three weeks, neurologic toxicity (peripheral sensory neuropathy) is usually cumulative and dose-limiting. Ileus has also been observed. Provide safety information on these and other toxicities encountered.

Statistical information, including power of study and statistical assessments:

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.

- *Labeling that may result from the study*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that bortezomib is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports and datasets (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. These postmarketing adverse event reports should be submitted as narrative and tabular reports.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before February 3, 2016. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

Response to Written Request: Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of

the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Amy Baird, Regulatory Project Manager, at (301) 796-4969.

Sincerely,

{See appended electronic signature page}

Richard Pazdur
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA A DINNDORF
08/14/2015

ALBERT B DEISSEROTH
08/15/2015