CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206927Orig1s000

NON-CLINICAL REVIEW(S)

MEMORANDUM

MEMO DATE: 09/18/2019

TO: the file for NDA 206927

FROM: Matthew D Thompson, PhD, MPH
Pharmacology/Toxicology Reviewer
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THROUGH: Haleh Saber, PhD, MS
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Background

The Applicant, Dr. Reddy's Laboratories, submitted a 505(b)(2) NDA for a bortezomib product. The listed drug, Velcade, is a lyophilized powder with 3.5 mg of bortezomib and 35 mg of mannitol. Dr. Reddy's bortezomib contains 3.5 mg of bortezomib, 8.4 mg of tromethamine, 10 mg of anhydrous citric acid, (b) (4)

Dr. Reddy's Laboratories relied upon the FDA's previous findings of safety and effectiveness for Velcade, as described in the drug's approved labeling. In the nonclinical review by Dr. Christopher Sheth (6/3/2014), four nonclinical studies were reviewed, and no approvability issues were identified. The Agency issued a complete response letter on May 4, 2016 (b) (4) No nonclinical issues were communicated. During the current review cycle, the Applicant is only seeking approval for NDA 206927/Original 1 (intravenous route).

Pharmacology/Toxicology Comments

The labeling for Dr. Reddy's bortezomib is consistent with the Velcade label.

Recommendation

From the Pharmacology/Toxicology perspective, Dr. Reddy's bortezomib Class 2 resubmission for NDA 206927/Original 1 (intravenous route) has no approvability issues.

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/s/

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 206927
Supporting document/s:	1 (eCTD sequence no. 0)
Applicant's letter date:	March 03, 2014
CDER stamp date:	March 04, 2014
Product:	Bortezomib for Injection
Indication:	Multiple Myeloma and Mantle Cell Lymphoma
Applicant:	Dr Reddy's Laboratories 107 College Road East Princeton, NJ 08540
Review Division:	Division of Hematology Oncology Toxicology (DHOT) for Division of Hematology Products (DHP)
Reviewer:	Christopher M. Sheth, Ph.D.
Secondary Reviewer:	Brenda J. Gehrke, Ph.D. (DHOT)
Division Director:	John Leighton, Ph.D., DABT (DHOT) Ann Farrell, M.D. (DHP)
Project Manager:	Alycia Anderson, CCRP

Disclaimer

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1 Executive Summary

1.1 Introduction

Velcade (bortezomib) is a proteasome inhibitor that was approved in 2003 (NDA 021602) for the treatment of relapsed/refractory multiple myeloma. Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis, which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death.

The Applicant, Dr. Reddy's Laboratories, has submitted this 505(b)(2) NDA for a bortezomib product that is intended to be used at the same dose levels and for the same indications as the listed drug (LD), Velcade. Dr. Reddy's Laboratories to-be-marketed formulation that is the subject of this NDA is different from the Velcade formulation. It will be supplied as a white to off-white powder in individually cartoned 10 mL vials containing 3.5 mg of bortezomib, 8.4 mg of tromethamine, 10 mg of anhydrous citric acid, (b) (4) The LD is a lyophilized powder of 3.5 mg of bortezomib and 35 mg of mannitol. The vials of bortezomib are reconstituted with 0.9% sodium chloride prior to injection (see approved Velcade label for dosing solution concentrations and exact dose volumes which vary based on route of administration).

Dr. Reddy's Laboratories included in this NDA a request for waiver of in vivo bioavailability or bioequivalence requirements for bortezomib 3.5 mg/vial (eCTD module 1.12.15). Inclusion of the biowaiver request was based on pre-IND meeting correspondence (June 21, 2013), in which the Agency indicated that such a waiver may be granted if Dr. Reddy's Laboratories provided adequate scientific information/data to support the bridging of their proposed product to the LD product, in addition to any information/data justifying why any differences between their product and the LD product would not affect the safety and/or effectiveness of their proposed product. Dr. Reddy's Laboratories submitted a comparative bioavailability study of bortezomib in rats, 2 GLP-compliant subacute (31 day) comparative toxicity and toxicokinetic studies in rats administered bortezomib by the intravenous (IV) (b) (4) and a comparative in vitro hemolysis study in rat whole blood to support their biowaiver request.

1.2 Brief Discussion of Nonclinical Findings

Dr. Reddy's Laboratories relies upon the FDA's previous findings of safety and effectiveness for Velcade, as described in the drug's approved labeling. The Applicant has not performed any animal pharmacology studies in support of the NDA approval for bortezomib. Dr. Reddy's laboratories compared their bortezomib product to Velcade in

4 nonclinical studies: a bioavailability study of bortezomib in rats, two comparative toxicity and toxicokinetic studies in rats administered bortezomib [redacted] (b) (4), as well as a comparative in vitro hemolysis study using rat whole blood. These studies demonstrated that Dr. Reddy's bortezomib was comparable to Velcade. Both products displayed similar toxicokinetics in the rat, and produced overt toxicity (with unscheduled deaths) with similar clinical signs and effects on body weight and food consumption at the 250 µg/kg dose level. Hematological findings were similar for both products, e.g., decreased red cell parameters, decreased platelets, and increased hyperchromic cells. Organ weight changes suggested similar organs (liver, spleen, and thymus) were being targeted for toxicity, and microscopic findings in the adrenals, gastrointestinal tract, glandular tissue, and bone marrow were similar between the products as well.

1.3 Recommendations

1.3.1 Approvability

From the Pharmacology/Toxicology perspective, Dr. Reddy's bortezomib may be approved for the proposed indications.

1.3.2 Additional Non Clinical Recommendations

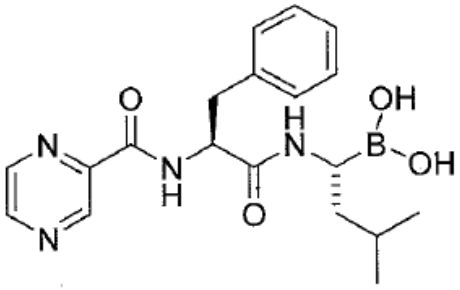
None

1.3.3 Labeling

The nonclinical sections of the label will be comparable to the label of the LD, Velcade.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional)	179324-69-7
Generic Name	Bortezomib
Code Name	N/A
Chemical Name	[(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]-bornoic acid
Molecular Formula/Molecular Weight	$C_{19}H_{25}BN_4O_4$ / 382.24 g/mol
Structure or Biochemical Description	
Pharmacologic Class	Proteasome inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 021602 (Velcade), IND 118389 (pre-IND)

2.3 Drug Formulation

Table 1 Comparative composition of the dosage forms for Velcade and Dr. Reddy's bortezomib

Components	Function	VELCADE® (Bortezomib) for Injection Millennium Pharmaceuticals, Inc. (Quantity/vial)	Bortezomib for Injection Dr. Reddy's Laboratories (Quantity/vial)
Bortezomib	Active Pharmaceutical Ingredient	3.5 mg	3.5 mg
Mannitol	(b) (4)	35 mg	-
Tromethamine		-	8.4 mg
Anhydrous Citric Acid		-	10.0 mg
			(b) (4)

(Excerpted from Applicant's submission)

Table 2 Reconstitution volumes and final concentration for IV (b) (4) administration

Route of administration	Bortezomib (mg/vial)	Diluent (0.9% Sodium Chloride)	Final Bortezomib concentration (mg/mL)
Intravenous	3.5 mg	3.5 mL	1 mg/mL
			(b) (4)

(Excerpted from drug label)

2.4 Comments on Novel Excipients

Dr. Reddy's Laboratories developed their bortezomib product using different excipients than those used in the LD (see table in Section 2.3). Dr. Reddy's bortezomib will be supplied in vials containing 3.5 mg of bortezomib, 8.4 mg of tromethamine, 10 mg of anhydrous citric acid, (b) (4) rather than the lyophilized powder of 3.5 mg of bortezomib and 35 mg of mannitol that constitutes the formulation of the LD.

2.5 Comments on Impurities/Degradants of Concern

The impurity profile of Dr. Reddy's bortezomib and the LD is similar. No additional impurities were identified due to the change in excipients. All the impurities are within the ICH Q3B limits.

2.6 Proposed Clinical Population and Dosing Regimen

Dr. Reddy's Laboratories proposed dosing recommendations consistent with current Velcade labeling for the treatment of patients with multiple myeloma or patients with mantle cell lymphoma who have received at least 1 prior therapy. The recommended dose is 1.3 mg/m^2 administered as a 3 to 5 second bolus injection. Dosing recommendations also include statements to use a lower starting dose for patients with moderate or severe hepatic impairment, and that doses must be individualized to prevent overdose. See approved Velcade label for detailed information on the dosage and administration of bortezomib.

2.7 Regulatory Background

The Applicant submitted NDA 206927 on March 03, 2014. The listed drug is Velcade (NDA 021602). The Agency sent responses to questions (re: regulatory, clinical and toxicology aspects of the submission) submitted in a pre-IND meeting package to the Applicant as a correspondence dated June 21, 2013.

3 Studies Submitted

3.1 Studies Reviewed

Study Number	Title	Location
P139/SE/007	Single Dose Comparative Bioavailability Study of Bortezomib by Both Intravenous and Subcutaneous Administrations in Rats Under Normal Fed Conditions Using Two Different Formulations	4.2.2.7
		(b) (4)
G8897	Bortezomib and Velcade: Subacute Toxicity and Toxicokinetic Study with Two Weeks Recovery Period in Wistar Rats by Intravenous Injection	4.2.3.2
G8898	Bortezomib: In Vitro Hemolysis Assay in Rat Whole Blood Test Item: Bortezomib for Injection 3.5 mg/vial S-1	4.2.3.7.7

3.2 Studies Not Reviewed

Study Number	Title	Location
		(b) (4)

3.3 Previous Reviews Referenced

N/A

4 Pharmacology

No pharmacology studies were submitted.

5 Pharmacokinetics

5.1 PK

Dr. Reddy's Laboratories submitted a side-by-side comparative bioavailability study (Study No. P139/SE/007) of their product (test formulation) and the listed drug Velcade (reference formulation); summary data is presented below. Wistar rats were administered either bortezomib formulation at a dose of 0.25 mg/kg via the lateral tail vein (IV groups) (b) (4) and blood was collected from the retro-orbital sinus at 2 (IV only), 5, 15, 30 min, and 1, 2, 6, and 24 hours post dose for analysis. As shown in the PK parameter summaries and concentration x time plots below, in general, the two formulations exhibit similar pharmacokinetics (b) (4) at this dose in the rat. Minimally greater C_0, C_{max} and $AUC_{0-\infty}$ values and a slightly longer $t_{1/2}$ value were observed for the IV Velcade group compared to the IV Dr. Reddy's bortezomib group.

Table 3 Study design and dose levels

Group No.	Treatment	Route	Dose (mg/kg)	Strength (mg/ml)	Dose volume (ml/kg)	Animal Numbers Male
G1	Reference Formulation	IV	0.25	1	0.25	1-8
G2	Test Formulation	IV	0.25	1	0.25	9-16
(b) (4)						

(Excerpted from Applicant's submission)

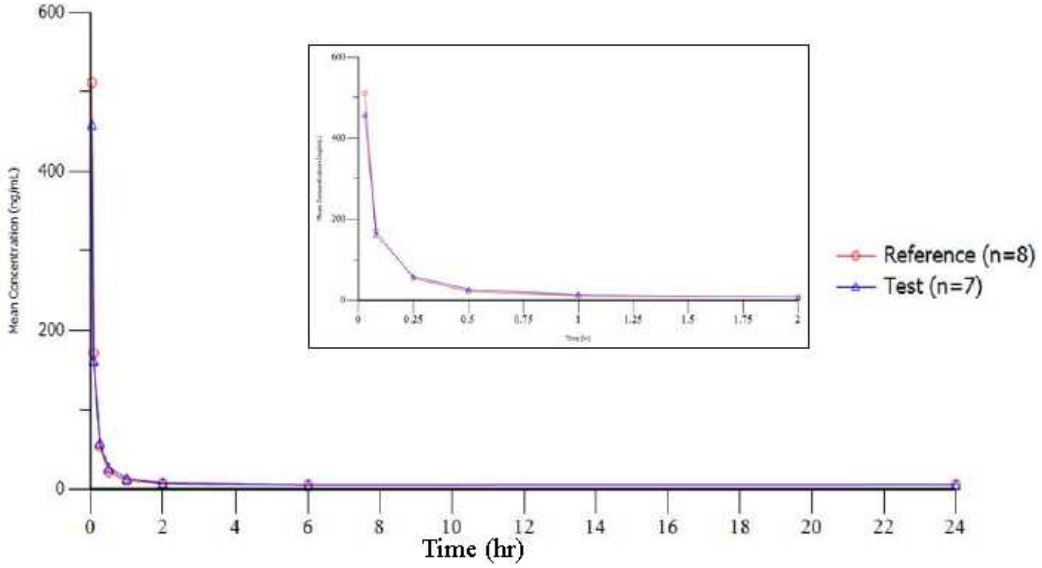
Table 4 PK parameters of Dr. Reddy's bortezomib and Velcade following single dose (0.25 mg/kg) IV bolus administration to Wistar rats

PK Parameters	Units	Test formulation (N=7)[$]		Reference formulation (N=8)		p-Value[#]
		Geo Mean	% CV	Geo Mean	% CV	
C_0	ng/mL	791.316	49.1	914.045	54.2	> 0.05
C_{max}	ng/mL	432.401	37.1	482.960	37.0	> 0.05
AUC_{0-t}	ng.hr/mL	221.371	13.8	225.376	13.4	> 0.05
$AUC_{0-\infty}$	ng.hr/mL	349.107	59.7	492.796	40.9	> 0.05
T_{max}	hr	0.03	0.0	0.03	0.0	-
MRT_{last}	hr	8.196	9.1	7.945	10.0	-
$^{**}t_{1/2}$	hr	8.406	163.3	14.982	77.7	-

[$]Animal_ID A#13 was excluded from pharmacokinetic analysis due to abnormal dosing pattern as observed.
* Median; ** Harmonic Mean; [#]Insignificant at p> 0.05.

(Excerpted from Applicant's submission)

Figure 1 Mean concentration versus time profile of Dr. Reddy's bortezomib and Velcade (0.25 mg/kg) following IV administration



(Excerpted from Applicant's submission)

(b) (4)

(b) (4)

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Study title: Bortezomib and Velcade: Subacute Toxicity and Toxicokinetic Study with Two Weeks Recovery Period in Wistar Rats by Intravenous Injection

Study no.:	G8897
Study report location:	4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 19, 2013
GLP compliance:	Statement included and signed
QA statement:	Statement included and signed
Drug, lot #, and % purity:	Dr. Reddy's Laboratories: bortezomib, batch EH12023, 100.6% Velcade (LD): bortezomib, lot CILS100, 99.4%

Key Study Findings

- There were 6 unscheduled deaths on the study (2 treated with Dr. Reddy's bortezomib and 4 treated with Velcade).
- Overall, the bortezomib-related changes in body weight, hematology, clinical chemistry, organ weights, and histopathology were comparable between the Dr. Reddy's bortezomib and Velcade groups at matching dose levels.
- The toxicokinetic properties of Dr. Reddy's bortezomib given IV were shown to be comparable to those of IV Velcade.

Methods

Doses:	0, 62.5, 125, or 250 µg/kg (Dr. Reddy's bortezomib and Velcade)
Frequency of dosing:	Days 1, 4, 8, 11, 21, 24, 28 and 31 (5 week treatment period)
Route of administration:	IV bolus
Dose volume:	1 mL/kg
Formulation/Vehicle:	0.9% normal saline
Species/Strain:	Wistar rat
Number/Sex/Group:	10/sex/group (main study) 5/sex/group (recovery; vehicle, high dose Dr. Reddy's bortezomib and high dose Velcade groups)
Age:	6 to 8 weeks at start of treatment
Weight:	150.4 to 221.8 g (males), 125.5 to 163.9 g (females)
Satellite groups:	Toxicokinetic: 3/sex/control group and 9/sex/treatment group
Unique study design:	Local tolerance at the site of injection was scored. Functional observation battery, open field observation, and functional tests were incorporated into the study design
Deviation from study protocol:	None

Study Design (Excerpted from Applicant's submission)

Toxicity Groups (Main Study)

Group No.	Treatment	Treatment Group	Colour of cage card	Dose (µg/kg)	Dose volume (mL/kg)	Conc. (µg/mL)	No. of Rats	Sex	Rat Numbers	
									From	To
G1	0.9% Normal Saline	Vehicle Control	White	0	1	0	10 10	M F	Ro7911 Ro7921	Ro7920 Ro7930
G2a	Bortezomib for injection 3.5 mg S-1 (Test Item)	Low dose	Yellow	62.5	1	62.5	10 10	M F	Ro7931 Ro7941	Ro7940 Ro7950
G3a		Mid dose	Green	125	1	125	10 10	M F	Ro7951 Ro7961	Ro7960 Ro7970
G4a		High dose	Pink	250	1	250	10 10	M F	Ro7971 Ro7981	Ro7980 Ro7990
G2b	Velcade® 3.5 mg (Reference Item)	Low dose	Yellow	62.5	1	62.5	10 10	M F	Ro7991 Ro8001	Ro8000 Ro8010
G3b		Mid dose	Green	125	1	125	10 10	M F	Ro8011 Ro8021	Ro8020 Ro8030
G4b		High dose	Pink	250	1	250	10 10	M F	Ro8031 Ro8041	Ro8040 Ro8050

Recovery Groups

Group No.	Treatment	Treatment Group	Colour of cage card	Dose (µg/kg)	Dose volume (mL/kg)	Conc. (µg/mL)	No. of Rats	Sex	Rat Numbers From	Rat Numbers To
G1R	0.9% Normal Saline	Vehicle Control	White	0	1	0	5 5	M F	Ro8051 Ro8056	Ro8055 Ro8060
G4aR	Bortezomib for injection 3.5 mg S-1 (Test Item)	High dose	Pink	250	1	250	5 5	M F	Ro8061 Ro8066	Ro8065 Ro8070
G4bR	Velcade® 3.5 mg (Reference Item)	High dose	Pink	250	1	250	5 5	M F	Ro8071 Ro8076	Ro8075 Ro8080

Toxicokinetic Groups

Group No.	Treatment	Treatment Group	Colour of cage card	Dose (µg/kg)	Dose volume (mL/kg)	Conc. (µg/mL)	No. of Rats	Sex	Rat Numbers From	Rat Numbers To
G1TK	0.9% Normal Saline	Vehicle Control	White	0	1	0	3 3	M F	Ro8081 Ro8084	Ro8083 Ro8086
G2aTK	Bortezomib for injection 3.5 mg S-1 (Test Item)	Low dose	Yellow	62.5	1	62.5	9 9	M F	Ro8087 Ro8096	Ro8095 Ro8104
G3aTK		Mid dose	Green	125	1	125	9 9	M F	Ro8105 Ro8114	Ro8113 Ro8122
G4aTK		High dose	Pink	250	1	250	9 9	M F	Ro8123 Ro8132	Ro8131 Ro8140
G2bTK	Velcade® 3.5 mg (Reference Item)	Low dose	Yellow	62.5	1	62.5	9 9	M F	Ro8141 Ro8150	Ro8149 Ro8158
G3bTK		Mid dose	Green	125	1	125	9 9	M F	Ro8159 Ro8168	Ro8167 Ro8176
G4bTK		High dose	Pink	250	1	250	9 9	M F	Ro8177 Ro8186	Ro8185 Ro8194

M: Male F: Female Conc.: concentration

Observations and Results

Mortality

Rats were observed twice daily during the treatment period (only once on Day 12). Six rats treated at the 250 µg/kg level died on study (2 treated with Dr. Reddy's bortezomib and 4 treated with Velcade). The deaths were likely associated with overt toxicity.

Table 14 Early mortalities during IV comparative toxicology study

Dr. Reddy's bortezomib			Velcade		
Ro7984F main	Found dead	Day 22	Ro8043F main	Moribund sac.	Day 22
Ro8062M rec.	Found dead	Day 29	Ro8046F main	Moribund sac.	Day 22
-	-	-	Ro8188F tk	Found dead	Day 29
-	-	-	Ro8182M tk	Found dead	Day 31

M: male; F: female; sac: sacrificed; main: main study group ; rec: recovery group; tk: toxicokinetic group

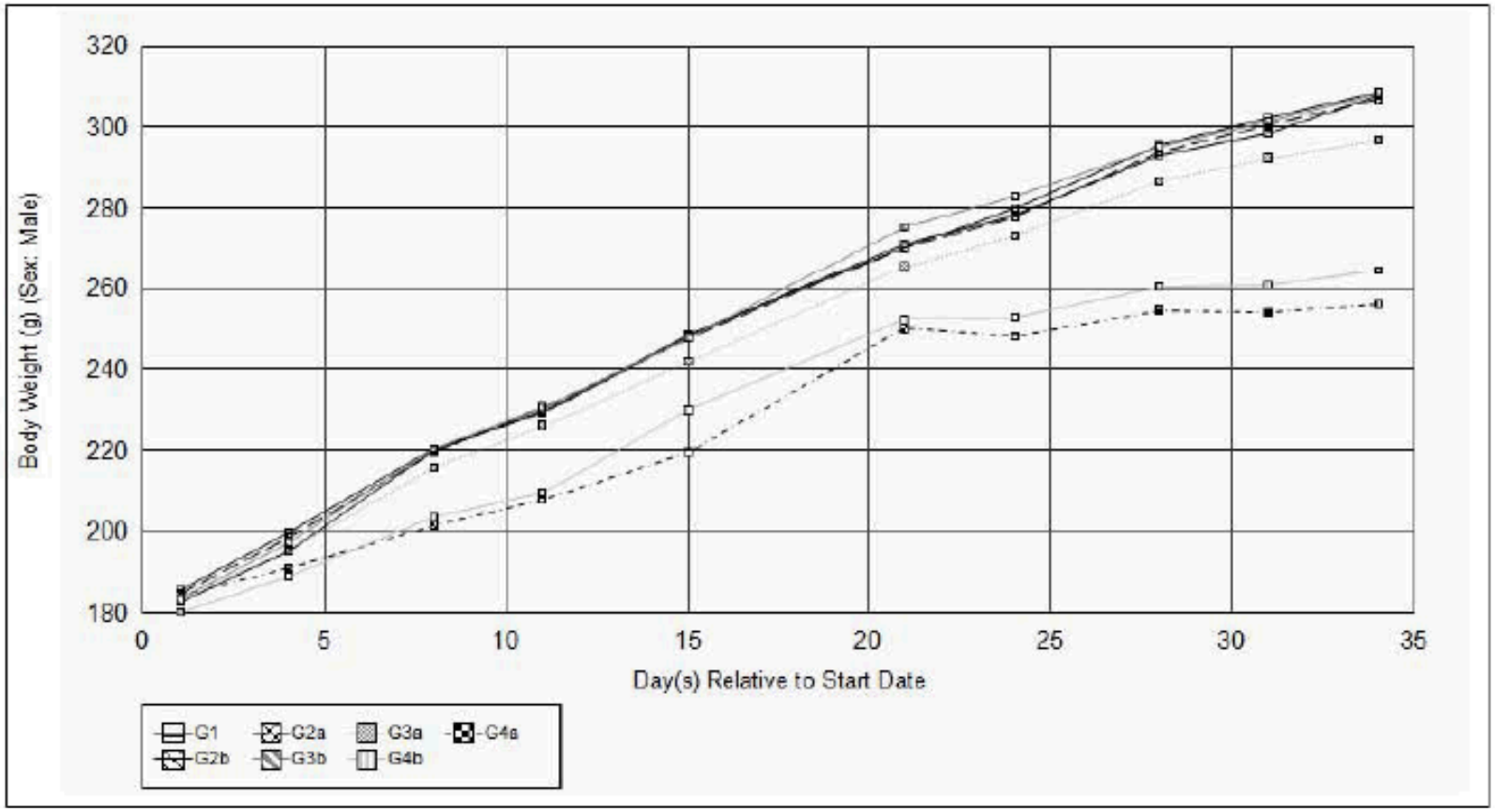
Clinical Signs

Rats were observed once daily (three times on Day 21). Detailed clinical exams were conducted weekly. Signs of toxicity were limited to males and females treated at the 250 µg/kg dose level. Poorly formed watery feces, gait abnormalities (walking on tips of toes), hypoactivity, and piloerection were common findings in both sexes for both products. Females (2/10) treated with Velcade also exhibited slight dehydration and/or recumbent posture. Overall, the observations were comparable between the Dr. Reddy's bortezomib and Velcade groups.

Body Weights

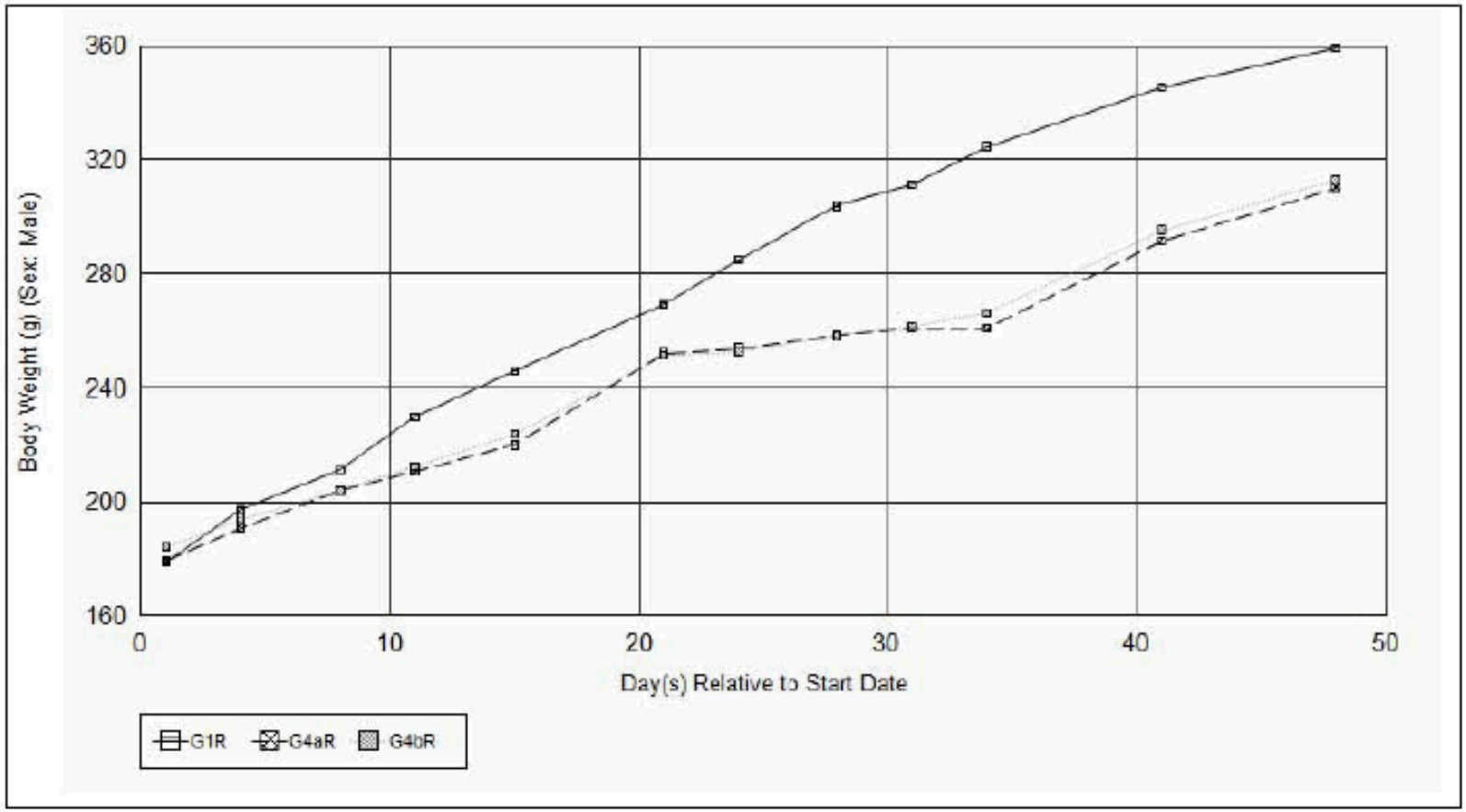
Measured on Days 1, 4, 8, 11, 15, 21, 24, 28, 31 and 34 (toxicity groups); and on Days 41 and 48 for recovery groups. Noteworthy effects were observed in males receiving 250 µg/kg at the terminal and recovery sacrifice; body weights were decreased 17 and 14% (Dr. Reddy's) and 14 and 13% (Velcade), respectively, compared to controls.

Figure 7 Body weights of main study males (IV)



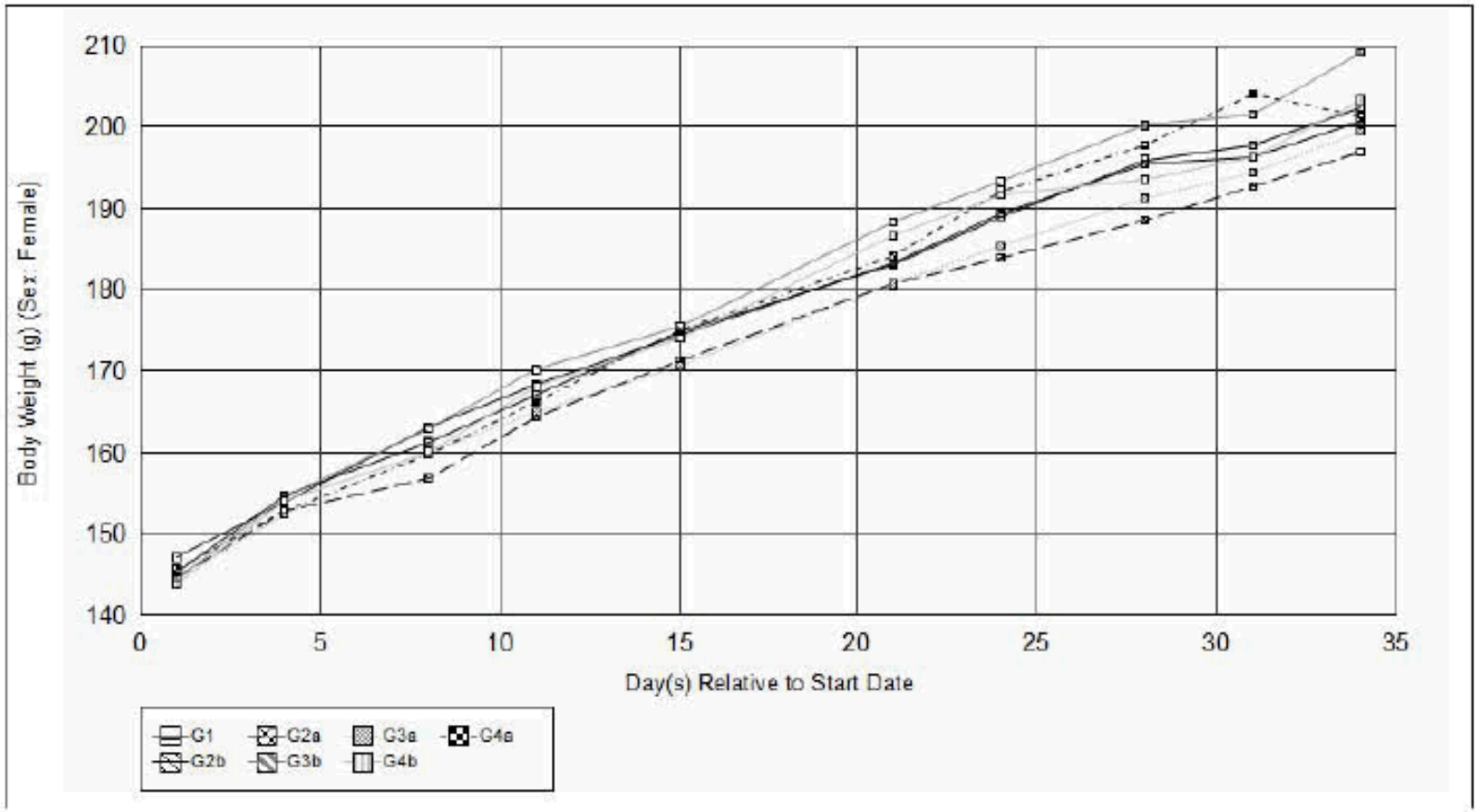
(Excerpted from Applicant's submission)

Figure 8 Body weights of recovery males (IV)



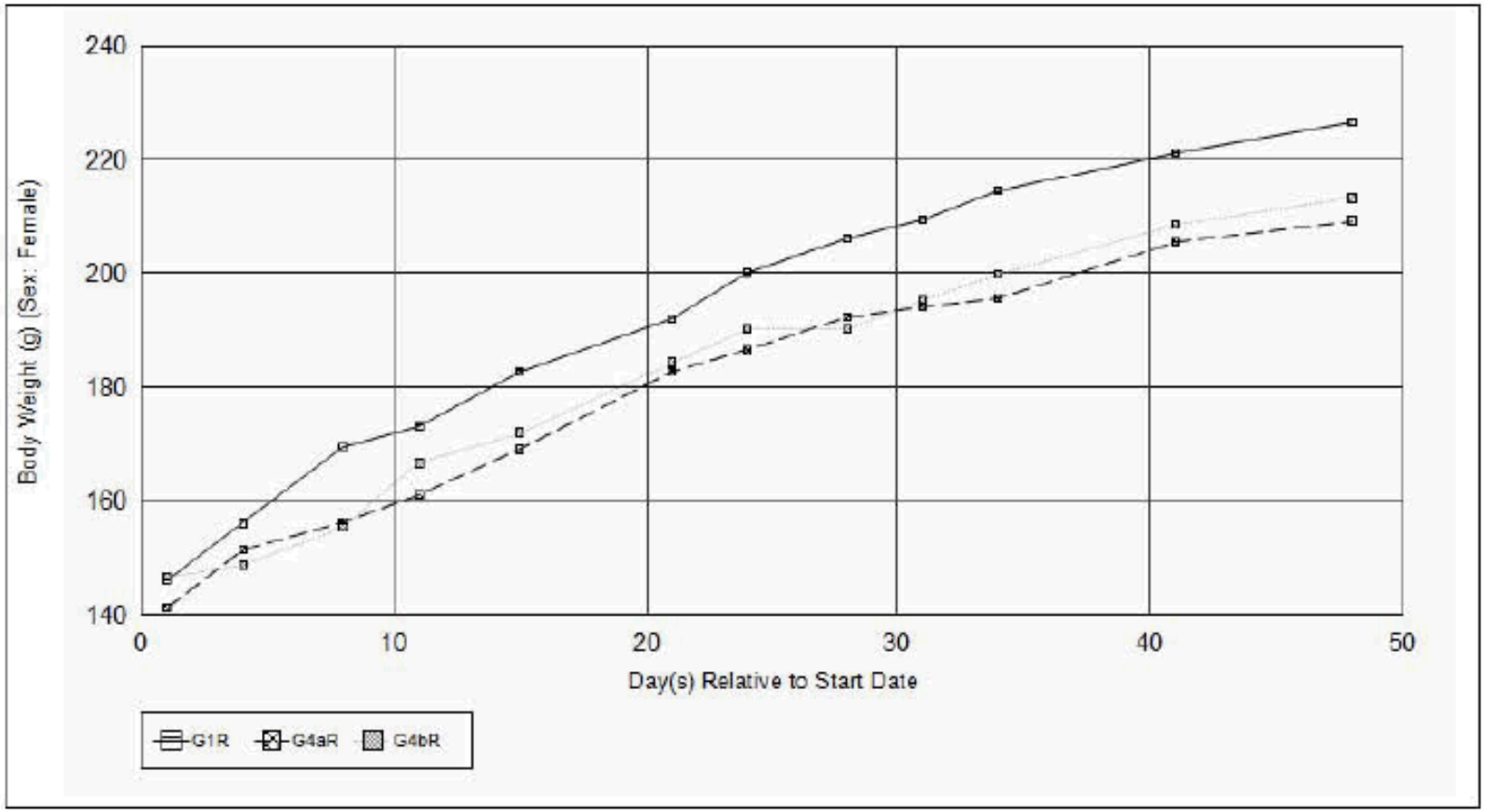
(Excerpted from Applicant's submission)

Figure 9 Body weights of main study females (IV)



(Excerpted from Applicant's submission)

Figure 10 Body weights of recovery females (IV)



(Excerpted from Applicant's submission)

Feed Consumption

Measured on Days 8, 15, 21, 28 and 34 (main study and recovery groups); and on Days 41 and 48 for recovery groups. During the treatment period, both Dr. Reddy's bortezomib and Velcade produced statistically significant reductions (↓12 to 24% in males and ↓10 to 28% in females) in food consumption at the 250 µg/kg dose level compared to vehicle controls.

Ophthalmoscopy

Exams were conducted once before the start of treatment and at the end of the treatment (Day 34) and recovery (Day 48) periods. Ophthalmological examinations did not reveal any abnormalities.

Functional Observational Battery

The battery was evaluated on Days 29 (main study group males) and 30 (main study group females) during the treatment period and Day 47 during the recovery period. The parameters selected to assess the behavioral and neurological status of the rats included: home cage observations, handling observations, open field observations, functional tests, motor activity, sensory reactivity measurements, landing hind limbs footsplay, grip performance and physiological observations (body temperature). There were no toxicologically significant findings to distinguish between Dr. Reddy's bortezomib and Velcade.

Hematology

Blood was collected (for hematology, coagulation, and clinical chemistry) from the retro-orbital plexus from animals at the scheduled sacrifices on Days 35 (main study males) and 36 (main study females) and recovery groups on Day 49 (both sexes). No toxicologically significant effects on coagulation were observed. Hematological responses observed in animals treated with Dr. Reddy's bortezomib were generally comparable to those observed in animals treated with Velcade.

Table 15 Hematology changes following exposure to IV bortezomib in males

	(Percent change compared to control)							
	Dr. Reddy's bortezomib				Velcade			
Interval	Main			Rec.	Main			Rec.
Dose (µg/kg)	62.5	125	250	250	62.5	125	250	250
No. of animals	10	10	10	4	10	10	10	5
RBC (10^{12}/L)	–	↓(5)	↓(9)	–	↓(6)	↓(6)	↓(13)	–
Hgb (g/L)	↓(7)	↓(9)	↓(11)	–	↓(6)	↓(9)	↓(13)	–
Hct (L/L)	–	↓(5)	↓(9)	–	↓(4)	↓(6)	↓(9)	–
MCV	–	–	–	–	–	–	↑(5)	–
MCHC	–	–	–	–	–	↓(4)	↓(4)	–
RDW (%)	↑(19)	↑(29)	↑(46)	–	↑(19)	↑(27)	↑(62)	–
HDW (g/L)	↑(93)	↑(111)	↑(125)	–	↑(87)	↑(111)	↑(139)	–
Plat (10^9/L)	–	↓(15)	↓(21)	–	–	↓(8)	↓(34)	–
MPV (fL)	–	↑(6)	↑(22)	–	–	↑(8)	↑(31)	–
Retic (%)	↑(40)	↑(81)	↑(87)	–	↑(23)	↑(75)	↑(155)	–
Retic (10^9/L)	↑(43)	↑(88)	↑(107)	–	↑(15)	↑(64)	↑(121)	–
Hyper (%)	↑(1143)	↑(1297)	↑(1537)	–	–	–	–	–

	(Percent change compared to control)							
	Dr. Reddy's bortezomib				Velcade			
Interval	Main			Rec.	Main			Rec.
Dose (µg/kg)	62.5	125	250	250	62.5	125	250	250
No. of animals	10	10	10	4	10	10	10	5
Hypo (%)	↑(118)	↑(346)	↑(964)	–	–	–	–	–

Main: main study; rec.: recovery group; ↑: increased; ↓: decreased; –: no change; RBC: red blood cell; Hgb: hemoglobin; Hct: hematocrit; RDW: red cell distribution width; HDW: hemoglobin distribution width; plat: platelets; MPV: mean platelet volume; Retic: reticulocyte; Hyper: hyperchromic cells; hypo: hypochromic cells

Table 16 Hematology changes following exposure to IV bortezomib in females

	(Percent change compared to control)							
	Dr. Reddy's bortezomib				Velcade			
Interval	Main			Rec.	Main			Rec.
Dose (µg/kg)	62.5	125	250	250	62.5	125	250	250
No. of animals	10	10	10	4	10	10	10	5
RBC (10^{12}/L)		↓(5)	↓(12)		↓(5)	↓(8)	↓(14)	
Hgb (g/L)	–	↓(5)	↓(10)	–	–	↓(7)	↓(11)	–
Hct (L/L)	–	–	↓(6)	–	–	–	↓(6)	–
MCV	–	–	↑(6)	–	↑(4)	↑(5)	↑(9)	–
MCHC	–	–	–	–	–	↓(3)	↓(6)	–
RDW (%)	↑(18)	↑(27)	↑(57)	↑(30)	↑(19)	↑(29)	↑(71)	↑(22)
HDW (g/L)	↑(78)	↑(92)	↑(123)	↑(82)	↑(72)	↑(87)	↑(123)	↑(52)
Plat (10^9/L)	–	↓(9)	↓(15)	–	–	↓(18)	↓(23)	–
MPV (fL)	↑(14)	↑(16)	↑(39)	↑(9)	↑(28)	↑(32)	↑(57)	–
Retic (%)	–	↑(47)	↑(113)	↑(100)	–	↑(42)	↑(206)	↑(69)
Retic (10^9/L)	–	↑(40)	↑(89)	↑(92)	–	↑(30)	↑(166)	↑(56)
Hyper (%)	↑(925)	↑(1056)	↑(1258)	↑(365)	↑(744)	↑(823)	↑(1047)	↑(273)
Hypo (%)	–	↑(121)	↑(797)	↑(400)	–	↑(143)	↑(1364)	↑(171)
Macro (%)	–	–	↑(493)	–	–	–	↑(1483)	–

Main: main study; rec.: recovery group; ↑: increased; ↓: decreased; –: no change; RBC: red blood cell; Hgb: hemoglobin; Hct: hematocrit; RDW: red cell distribution width; HDW: hemoglobin distribution width; plat: platelets; MPV: mean platelet volume; Retic: reticulocyte; Hyper: hyperchromic cells; hypo: hypochromic cells; macro: macrocytes

Clinical Chemistry

Notable clinical chemistry effects in males were limited to the high dose group (250 µg/kg), where both products resulted in elevated total bilirubin (↑83 to 87%) and inorganic phosphorous (↑14 to 17%) compared to controls. Females exhibited increased inorganic phosphorous (↑17 to 28%) at ≥125 µg/kg of either product; however, elevated total bilirubin (↑88% compared to controls) was limited to the Velcade group. Females assigned to the Velcade recovery group (250 µg/kg) had greatly increased ALT levels (↑2365%), AST levels (↑700%) and LDH levels (↑803%) compared to controls at the recovery sacrifice.

Urinalysis

Samples were collected from main study animals at the end of the treatment period and from recovery animals at the end of the recovery period. There were no toxicologically significant effects on urinalysis parameters for animals treated IV with either bortezomib product during the main study or recovery periods.

Gross Pathology

Organs and tissues were examined macroscopically at the scheduled sacrifices on Days 35 (main study males) and 36 (main study females). There were no major differences in gross observations between dose-matched Dr. Reddy's bortezomib and Velcade groups.

Organ Weights

Designated organs were collected and weighed from all rats at the scheduled sacrifices except from those found moribund and/or dead. Noteworthy changes (presented below) occurred in the weights of the liver, spleen, thymus, prostate and seminal vesicles, compared to controls. Overall, the effects were similar between both products.

Table 17 Organ weight changes following exposure to IV bortezomib in males

		Dr. Reddy's bortezomib				Velcade			
Interval		Main			Rec.	Main			Rec.
Dose (µg/kg)		62.5	125	250	250	62.5	125	250	250
No. of animals		10	10	10	5	10	10	10	5
Body Weight		–	–	↓(17)	↓(15)	–	–	↓(15)	↓(12)
Liver	Abs wt	–	–	–	–	–	–	–	–
	Rel wt	↑(5)	↑(5)	↑(15)	–	–	↑(6)	↑(7)	–
Spleen	Abs wt	–	–	–	–	–	–	–	–
	Rel wt	–	–	↑(25)	↑(29)	–	–	↑(22)	↑(15)
Thymus	Abs wt	–	–	↓(74)	–	–	–	↓(74)	–
	Rel wt	–	–	↓(68)	–	–	–	↓(69)	–
Prostate	Abs wt	–	–	↓(17)	–	–	–	↓(18)	–
Seminal vesicles	Abs wt	–	–	↓(24)	–	–	–	–	–

Main: main study; rec.: recovery group; ↑: increased; ↓: decreased; –: no change; abs wt: absolute organ weight; rel wt: relative to body weight

Table 18 Organ weight changes following exposure to IV bortezomib in females

		Dr. Reddy's bortezomib				Velcade			
Interval		Main			Rec.	Main			Rec.
Dose (µg/kg)		62.5	125	250	250	62.5	125	250	250
No. of animals		10	10	10	5	10	10	10	5
Liver	Abs wt	–	↑(13)	↑(35)	–	–	↑(20)	↑(34)	↑(15)
	Rel wt	–	↑(16)	↑(34)	–	–	↑(17)	↑(34)	↑(20)
Spleen	Abs wt	–	↑(17)	↑(24)	–	–	↑(20)	↑(28)	–
	Rel wt	–	↑(20)	↑(24)	–	–	↑(18)	↑(29)	–
Thymus	Abs wt	–	–	↓(62)	–	–	–	↓(72)	–
	Rel wt	–	–	↓(62)	–	–	–	↓(72)	–

Main: main study; rec.: recovery group; ↑: increased; ↓: decreased; –: no change; abs wt: absolute organ weight; rel wt: relative to body weight

Histopathology

Microscopic examinations were conducted on the protocol-designated tissues of vehicle control and high dose animals. All gross lesions were also examined microscopically. In organs and tissues where there were suspected test/reference item-related

histopathological changes in high dose (250 µg/kg) animals, microscopic examinations were extended to include the low and mid (62.5 and 125 µg/kg) dose main study groups as well as to the high dose recovery groups. Noteworthy histopathological observations for animals that survived until the main study scheduled sacrifice are presented below.

Adequate Battery: Yes

Peer Review: Yes

Histological Findings

Table 19 Histopathology incidence in male rats treated with IV bortezomib

		No. of animals affected						
		VH	Dr. Reddy's			Velcade		
Dose (µg/kg)		0	62.5	125	250	62.5	125	250
No. of animals		10	10	10	10	10	10	10
Finding								
Adrenal g.	Vacuolation; zona fasciculata/reticularis; bilateral; minimal	–	–	–	5	–	2	8
	Vacuolation; zona fasciculata/reticularis; bilateral; mild	–	–	–	3	–	–	–
	Vacuolation; zona fasciculata; bilateral; minimal	–	–	–	–	–	1	–
	Lymphatic infiltration; bilateral; minimal	–	–	–	2	–	–	–
	Lymphatic infiltration; bilateral; mild	–	–	–	1	–	–	1
Cecum	Cystic gland with cell debris; minimal	–	–	–	1	–	–	–
Coagulating g.	Atrophy; minimal	–	–	–	2	–	–	–
Epididymis	Aspermia	–	–	–	–	–	1	–
Harderian gland	Inflammation; perivascular; minimal	–	–	–	1	–	–	–
Heart	Hemorrhage; minimal	–	–	–	1	–	–	–
	Inflammatory focus(i); minimal	–	–	–	1	–	–	–
Kidney	Inflammation; perivascular; minimal	–	–	–	1	–	–	–
Lacrimal g.	Hemorrhage; mild	–	–	–	2	–	–	–
	Inflammation; perivascular; minimal	–	–	–	1	–	–	–
	Single cell necrosis; minimal	–	–	–	–	–	–	1
	Chronic inflammation; focal; minimal	–	–	–	–	–	–	1
Liver	Hepatocellular hypertrophy; minimal	–	–	–	3	–	–	2
	Hepatocellular hypertrophy; mild	–	–	–	1	–	–	1
Lungs	Chronic inflammation focal; minimal	–	–	–	–	–	–	1
Pancreas	Lobular atrophy; minimal	–	–	–	–	–	–	1
Prostate	Atrophy; minimal	–	–	–	2	–	–	–
Salivary g.	Inflammation; perivascular; mild	–	–	–	1	–	–	–
Seminal vesicle	Atrophy; minimal	–	–	–	2	–	–	–
	Single cell necrosis; minimal	–	–	–	1	–	–	–
Spleen	Increased extramedullary hematopoiesis; minimal	1	4	9	7	6	10	7
	Increased extramedullary hematopoiesis; mild	–	1	1	3	–	–	3
	Histiocytosis; mild	–	–	–	1	–	–	–
	Connective tissue proliferation; perivascular; mild	–	–	–	1	–	–	–

		No. of animals affected						
		VH	Dr. Reddy's			Velcade		
Dose (µg/kg)		0	62.5	125	250	62.5	125	250
No. of animals		10	10	10	10	10	10	10
Finding								
Stomach	Inflammatory focus(i); glandular mucosa; minimal	–	–	–	2	–	–	–
Testes	Atrophy; unilateral; mild	–	–	–	–	–	1	–
Thymus	Lymphoid depletion; moderate	–	–	–	3	–	–	2
	Lymphoid depletion; severe	–	–	–	7	–	–	7

VH: vehicle control; g: gland; –: not observed

Table 20 Histopathology incidence in female rats treated with IV bortezomib

		No. of animals affected						
		VH	Dr. Reddy's			Velcade		
Dose (µg/kg)		0	62.5	125	250	62.5	125	250
No. of animals		10	10	10	10	10	10	10
Finding								
Adrenal g.	Vacuolation; zona fasiculata; bilateral; minimal	–	–	–	–	–	–	1
Femur	Hypocellularity; minimal	–	–	–	1	–	–	2
Duodenum	Single cell necrosis; crypt epithelium; minimal	–	–	–	–	–	–	1
Eye w/ optic nerve	Retinal atrophy; unilateral; minimal	–	–	–	1	–	–	–
	Retinal atrophy; bilateral; minimal	3	–	–	3	–	–	2
	Retinal atrophy; bilateral; mild	3	–	–	1	–	–	1
Ileum w/ peyers patch	Single cell necrosis; crypt epithelium; minimal	–	–	–	–	–	–	1
Jejunum	Single cell necrosis; crypt epithelium; minimal	–	–	–	–	–	–	1
Kidney	Basophilic tubules; minimal	–	–	–	1	–	–	–
Liver	Hepatocellular hypertrophy; minimal	–	–	–	5	–	–	3
	Hepatocellular hypertrophy; mild	–	–	–	1	–	–	2
	Hepatocellular necrosis; focal; minimal	–	–	–	–	–	–	2
	Hepatocyte vacuolation; minimal	–	–	–	–	–	–	–
	Hepatocyte vacuolation; mild	–	–	1	6	–	1	6
	Inflammatory focus(i); minimal	–	–	–	1	–	–	2
	Pigmentation; mild	–	–	–	–	1	–	–
Lung	Hemorrhage	–	–	–	1	–	–	–
Spleen	Increased extramedullary hematopoiesis; minimal	–	4	4	5	3	2	3
	Increased extramedullary hematopoiesis; mild	–	–	4	4	2	3	5
	Increased extramedullary hematopoiesis; moderate	–	–	–	1	–	–	2
	Lymphoid depletion; mild	–	–	–	1	–	–	1
	Lymphoid depletion; moderate	–	–	–	–	–	–	1
Sternum w/ marrow	Hypocellularity; minimal	–	–	–	1	–	–	2
Stomach	Thinning; non-glandular; mild	–	–	–	–	–	–	2
Thymus	Lymphoid depletion; minimal	–	–	–	1	–	–	–
	Lymphoid depletion; moderate	–	–	–	5	–	–	–
	Lymphoid depletion; severe	–	–	–	4	–	–	8

VH: vehicle control; g: gland; l.n.: lymph node; –: not observed

Toxicokinetics

The comparative toxicokinetics of Dr. Reddy's product and Velcade were assessed in animals dosed with 62.5, 125 or 250 µg/kg bortezomib by intravenous injection on Days 1, 4, 8, 11, 21, 24, 28 and 31. Blood samples were collected on Days 1 and 31 from the retro-orbital plexus at 0, 5 and 30 minutes, and at 2, 6, 12, 24, 48 and 72 hours post administration. The toxicokinetic properties of Dr. Reddy's bortezomib given IV were shown to be comparable to those of IV Velcade i.e., similar plasma exposures in animals treated with either product, consistent effects in both sexes, similar mean resistance times, and Day 31 exposures approximately 2-fold higher than Day 1 exposures.

Table 21 TK parameters for Dr. Reddy's bortezomib (IV) compared to Velcade (IV)

Treatment	Gender	Day	Dose (µg/kg)	C_0 (ng/mL)	AUC_{last}[a] (ng.h/mL)	$AUC_{0\text{-}24h}$ (ng.h/mL)
Bortezomib (Test item)	Male	1	62.5	16.90	193.22	49.05
			125	63.65	292.41	96.02
			250	154.49	493.88	186.51
		31	62.5	110.19	576.80	215.07
			125	132.85	703.80	279.28
			250	262.48	1158.06	436.87
	Female	1	62.5	22.26	174.40	54.05
			125	41.08	261.65	76.84
			250	219.32	517.05	195.02
		31	62.5	36.57	468.50	175.78
			125	124.47	732.58	250.47
			250	329.52	1063.54	452.45
Velcade (Reference item)	Male	1	62.5	17.89	168.44	42.63
			125	88.28	404.88	125.44
			250	240.03	584.53	206.59
		31	62.5	39.98	548.48	194.00
			125	158.96	855.29	313.96
			250	340.90	1243.63	505.76
	Female	1	62.5	26.30	156.29	45.06
			125	69.82	363.47	118.96
			250	218.31	647.16	243.69
		31	62.5	58.62	435.70	165.14
			125	134.46	727.31	291.57
			250	312.48	1042.63	461.46

[a] T_{last}=72 h

(Excerpted from Applicant's submission)

Dosing Solution Analysis

Dose formulations prepared with Dr. Reddy's bortezomib (3.5 mg/vial) and Velcade (3.5 mg) were found to have similar concentrations of the active ingredient, i.e., within the acceptance limit of 85-115% of the theoretical concentrations (RSD was less than 10% on both Days 1 and 31). Stability of the dose formulations were confirmed for up to 24 hours under room temperature and refrigerated conditions.

7 Genetic Toxicology

Not submitted

8 Carcinogenicity

Not submitted

9 Reproductive and Developmental Toxicology

Not submitted

10 Special Toxicology Studies

As Dr. Reddy's bortezomib is a reformulation of an approved drug substance (b) (4) Dr. Reddy's submitted a nonclinical report for a comparative blood compatibility (in vitro hemolysis) study of their product with the LD Velcade. The hemolytic potential of Dr. Reddy's bortezomib was tested side-by-side with Velcade at concentrations of 50, 250 and 500 ng/mL in Wistar rat whole blood incubated for 4 hours at 37°C. There was a concentration-related increase in hemolysis for Dr. Reddy's bortezomib (see table below), however, the % hemolysis values would generally be considered non hemolytic (>10% being hemolytic) according to a published experimental analysis cited by the Applicant (Amin and Dannenfelser, 2006); it should be noted that rat blood was not actually part of the cited study.

Table 22 Percent hemolysis of Dr. Reddy's bortezomib or Velcade in rat whole blood

Concentration (ng/mL) in rat whole'blood #	% Hemolysis
Test item- Bortezomib for Injection 3.5 mg/vial S-1	
50	2.00
250	3.28
500	5.65
Reference item- Velcade ® 3.5 mg	
50	0.00*
250	0.00*
500	0.00*

: Concentrations of 50, 250 and 500 ng/mL of blood corresponds to 100, 500 and 1000 ng/mL of test or reference item solution tested.

* : Calculated values were negative (-6.19, -6.74 and -8.38%, respectively), these values were considered as zero for reporting.

(Excerpted from Applicant's submission)

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/s/

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06/03/2014

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06/03/2014