CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203415Orig1s000

PHARMACOLOGY REVIEW(S)

MEMORANDUM

Xtandi (enzalutamide)

Date: August 22, 2012
To: File for NDA 203415
From: John K. Leighton, PhD, DABT
Acting Director, Division of Hematology Oncology Toxicology
Office of Hematology and Oncology Products

I have examined pharmacology/toxicology supporting review of Dr. Brian Chiu and labeling and secondary memorandum provided by Dr. Palmby. I concur with Dr. Palmby's conclusion that Xtandi may be approved and that no additional nonclinical studies are needed for the proposed indication.

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/s/

JOHN K LEIGHTON
08/22/2012

MEMORANDUM

Date: August 20, 2012
From: Todd R. Palmby, Ph.D.
Acting Pharmacology/Toxicology Supervisor
Division of Hematology Oncology Toxicology (DHOT)
Office of Hematology and Oncology Products (OHOP)
To: File for NDA 203415 XTANDI (enzalutamide)
Re: Approvability for Pharmacology and Toxicology
Indication: Treatment of patients with castration-resistant prostate cancer who have received prior docetaxe (b) (4)

Non-clinical pharmacology and toxicology studies to support Xtandi (enzalutamide) NDA 203415 for the treatment of patients with castration-resistant prostate cancer who have received prior docetaxel (b) (4) were reviewed by Haw-Jyh Chiu, Ph.D. Studies conducted with orally administered enzalutamide included pharmacology, toxicokinetics and ADME, safety pharmacology, general toxicology, and genetic toxicology (*in vivo* and *in vitro*).

Pharmacology studies submitted to the NDA indicate that enzalutamide is an androgen receptor inhibitor, and that the effects of enzalutamide may impinge on three steps in androgen signaling through the androgen receptor. Enzalutamide was shown to inhibit the following processes *in vitro*: 1) androgen binding to androgen receptors; 2) androgen-dependent androgen receptor nuclear translocation; 3) androgen-dependent androgen receptor association with DNA. Enzalutamide did not induce androgen receptor nuclear translocation *in vitro* under the conditions tested. A major metabolite found in rats, dogs and humans, N-desmethyl enzalutamide, is an active metabolite based on inhibition of androgen binding to androgen receptors and inhibition of androgen-dependent androgen receptor nuclear translocation, *in vitro*.

Repeat-dose toxicology studies of up to 26-weeks duration in rats and 13-weeks duration in dogs were conducted with oral enzalutamide administered daily. Overall, toxicities were consistent with the pharmacological activity of the drug, which included effects on male reproductive organs (prostate/seminal vesicle/epididymis atrophy and decreased organ weights, hypospermatogenesis), mammary gland in rats (atrophy), adrenal gland in rats (hypertrophy/hyperplasia) and the pituitary in rats (hypertrophy/hyperplasia).

An adverse event of particular concern that was observed in clinical trials conducted with enzalutamide was seizures. Convulsions were observed in nonclinical studies in mice and dogs at clinically relevant exposures. In addition, patients being treated with other androgen receptor inhibitors have experienced seizures.

Enzalutamide was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) assay and was not genotoxic in either the *in vitro* mouse lymphoma TK gene mutation assay or the *in* vivo mouse micronucleus assay.

No nonclinical reproductive or developmental toxicity studies were conducted with enzalutamide. In general, given this patient population, an embryo-fetal development study would normally be expected as described in the Guidance for Industry: ICH S9 Nonclinical Evaluation of Anticancer Pharmaceuticals. However, this study was deemed unwarranted to support the proposed male-specific indication.

Recommendation: I concur with Dr. Chiu's conclusion that pharmacology and toxicology data support the approval of NDA 203415 for Xtandi. There are no outstanding nonclinical issues that would preclude the approval of Xtandi for the proposed indication.

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/s/

TODD R PALMBY
08/20/2012

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:	203415
Supporting document:	0
Applicant's letter date:	May 21, 2012
CDER stamp date:	May 22, 2012
Product:	Xtandi (enzalutamide; MDV3100)
Indication:	Treatment of patients with castration-resistant prostate cancer who have received prior docetaxel (b) (4)
Applicant:	Medivation, Inc. 201 Spear Street Third Floor San Francisco, CA 94105
Review Division:	Division of Hematology Oncology Toxicology (DHOT) for Division of Oncology Products 1 (DOP1)
Reviewer:	Haw-Jyh Chiu, Ph.D.
Acting Team Leader:	Todd R. Palmby, Ph.D.
Division Director:	John K. Leighton, Ph.D., D.A.B.T. (Acting; DHOT) Robert L. Justice, M.D., M.S. (DOP1)
Project Manager:	Christy L. Cottrell

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Reference ID: 3175869

Any information or data necessary for approval of 203415 that Medivation does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of 203415.

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1 Executive Summary

1.1 Introduction

Medivation submitted this 505(b)(1) New Drug Application (NDA) for enzalutamide (MDV3100) for the proposed indication of the treatment of patients with metastatic castration-resistant prostate cancer who have received docetaxel (b) (4). Enzalutamide is administered orally by a once-daily dose of 160 mg (four 40 mg capsules). Non-clinical pharmacology, pharmacokinetic, and toxicology studies have been submitted to support the approval of enzalutamide for the proposed indication.

1.2 Brief Discussion of Nonclinical Findings

Enzalutamide is a new molecular entity, small molecule androgen receptor inhibitor. Pharmacology studies showed that enzalutamide inhibits androgen binding to androgen receptors, inhibits androgen-dependent androgen receptor nuclear translocation, inhibits androgen-dependent androgen receptor association with DNA, and decreased proliferation and induced cell death of prostate cancer cells, *in vitro*. A major metabolite of ezalutamide (N-desmethyl enzalutamide) found in animals and humans was shown to inhibit androgen binding to androgen receptors and inhibit androgen-dependent androgen receptor nuclear translocation *in vitro*. Enzalutamide decreased tumor volume in a mouse xenograft model of human prostate cancer. Based on primary pharmacology data submitted with this NDA and in consideration of all the pertinent information for the clinical use of enzalutamide, the Established Pharmacological Class (EPC) of “androgen receptor inhibitor” was determined to be both clinically meaningful and scientifically valid for enzalutamide.

Major target organ systems of toxicity identified in toxicity studies with enzalutamide in rats and dogs of up to 26 and 13 weeks in duration, respectively, were the central nervous system and reproductive organs. Convulsions were noted in repeat-dose studies in mice and dogs. A dose-dependent increase in convulsions was observed in mice at ≥ 100 mg/kg/day (0.6 times the human exposure based on AUC) and in dogs at 60 mg/kg/day (3.3 times the human exposure based on AUC). Studies submitted by Medivation suggest enzalutamide-induced convulsions may be attributed to the parent drug and its major active metabolite N-desmethyl enzalutamide , both of which have been show to cross the blood brain barrier and bind to the gamma aminobutyric acid (GABA)-gated chloride channel. Consistent with the pharmacological activity of enzalutamide, major toxicity findings were noted in male reproductive organs. In a 26-week study in rats, decreased organ weights were correlated with atrophy of the prostate and seminal vesicles which were observed at ≥ 30 mg/kg/day (similar to the human exposure based on AUC). In 4- and 13-week studies in dogs, decreased organ weights were correlated with hypospermatogenesis and atrophy of the prostate and epididymides, which were observed at ≥ 4 mg/kg/day (0.3 times the human exposure based on AUC). Other nonclinical findings of minimal severity and without significant adverse correlates were noted in the liver (hepatocellular hypertrophy), pituitary

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(hypertrophy and hyperplasia), and kidney (chronic progressive nephropathy) following repeat-dose administration of enzalutamide to rats.

Enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either the *in vitro* mouse lymphoma *tk* gene mutation assay or the *in vivo* mouse bone marrow micronucleus assay.

Medivation did not conduct any carcinogenicity or reproductive and developmental toxicology studies with enzalutamide. However, these studies were not considered to be essential to support approval of enzalutamide in the proposed patient population.

1.3 Recommendations

1.3.1 Approvability

Based on the non-clinical studies submitted with NDA 203415, enzalutamide is recommended for approval for the proposed indication from the perspective of the non-clinical discipline.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

Pharmacokinetic parameters obtained from trial 9785-CL-0007 were used to calculate the steady state human exposure to 160 mg/day oral dose of enzalutamide. The following table summarizing the human pharmacokinetics of 160 mg/day enzalutamide in trial 9785-CL-0007was provided by the clinical pharmacology reviewer (Dr. Jeanne Fourie Zirkelbach).

Table 12. Summary statistics of the multiple dose plasma enzalutamide, M1 and M2 PK parameters after 160 mg enzalutamide QD for 49 days in patients with metastatic castrate-resistant prostate cancer (9785-CL-0007).

Enzalutamide:							
Parameter	**AUC_{tau} (h*μg/mL)**	**C_{0h} (μg/mL)**	**C_{min} (μg/mL)**	**C_{max} (μg/mL)**	**t_{max} (h)**	**CL/F (L/h)**	**PTR**
N	14	14	14	14	14	14	14
Mean	321.5	13.32	12.00	16.59	NA	0.520	1.266
SD (CV%)	85.39 (26.6)	3.341 (25.1)	3.512 (29.3)	3.812 (23.0)	NA	0.0942 (18.1)	0.1271 (10.0)
Min - Max	240-593	9.86-23.4	6.92-22.4	11.8-28.0	0.52-3.02	0.27-0.67	1.09-1.51
Median	295.6	12.70	11.45	15.55	1.02	0.541	1.240
M1:							

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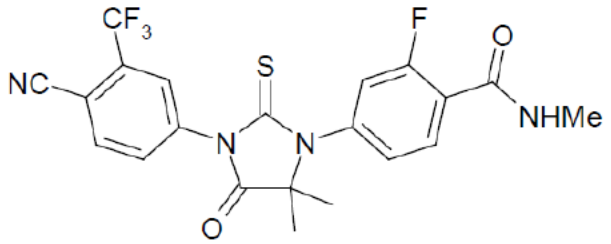
Parameter	AUC_{tau} (h*µg/mL)	C_{0h} (µg/mL)	C_{min} (µg/mL)	C_{max} (µg/mL)	t_{max} (h)	MPR (MWC)
n	13	14	14	14	14	13
Mean	193.3	7.739	6.315	8.867	NA	0.621
SD (CV%)	144.01 (74.5)	6.3111 (81.5)	5.1909 (82.2)	6.5201 (73.5)	NA	0.4931 (79.4)
Min - Max	63.6-466	2.47-20.4	1.97-17.3	2.88-21.5	0.00-24.03	0.20-2.00
Median	145.6	5.135	4.030	6.925	3.517	0.471
M2:						
Parameter	**AUC_{tau} (h*µg/mL)**	**C_{0h} (µg/mL)**	**C_{min} (µg/mL)**	**C_{max} (µg/mL)**	**t_{max} (h)**	**MPR (MWC)**
n	14	14	14	14	14	14
Mean	278.3	11.97	10.57	12.68	NA	0.913
SD (CV%)	85.47 (30.7)	3.716 (31.0)	3.271 (30.9)	3.773 (29.7)	NA	0.2812 (30.8)
Min - Max	182-442	7.80-18.8	6.99-16.5	8.65-19.6	0.00-24.03	0.56-1.66
Median	263.2	11.15	10.23	12.10	4.02	0.886

CV: coefficient of variation; Min – Max: Minimum and maximum recorded values; MPR(MWC): ratio of the metabolite - parent AUC values corrected for the difference in molecular weight; NA: not applicable; qd: once daily.

2 Drug Information

2.1 Drug

CAS Registry Number	915087-33-1
Generic Name	enzalutamide
Code Name	MDV3100
Chemical Name	4-{3-[4-Cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide
Molecular Formula	$C_{21}H_{16}F_4N_4O_2S$
Molecular Weight	464.44
Structure	
Pharmacologic Class	Androgen receptor antagonist

2.2 Relevant IND/s, NDA/s, and DMF/s

INDs 74563 and [redacted] (b) (4)
DMFs [redacted] (b) (4)

2.3 Drug Formulation

40 mg liquid-filled soft gelatin capsules.

Table 1. MDV3100 Drug Product Composition

Component	Function	Amount per capsule
MDV3100	Active Ingredient	40.0 mg
Caprylocaproyl Polyoxylglycerides	[redacted] (b) (4)	
Butylated Hydroxyanisole		
Butylated Hydroxytoluene		
[redacted] (b) (4)		
Gelatin Shell [redacted] (b) (4))	Capsule	1 capsule

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2.4 Comments on Novel Excipients

Caprylocapryol polyoxyglyceride (b) (4) is listed in the FDA Inactive Ingredient Database as an excipient present in previously FDA-approved drug products. Based on the proposed daily dose of enzalutamide, the level of (b) (4) would exceed that present in previously approved drug products. However, the proposed level of (b) (4) (4) is considered to be qualified from the perspective of the nonclinical discipline based on data from the GLP-compliant, 26-week repeat-dose toxicity study in rats which showed that administration of 2300 mg/kg/day (22 g/day HED) (b) (4) to rats did not result in any significant toxicities.

2.5 Comments on Impurities/Degradants of Concern

All impurities present in the clinical lots were also present in the toxicology lots used in repeat-dose toxicity studies submitted in support of this NDA. The proposed acceptance criteria for all impurities in the MDV3100 drug substance were below the qualification threshold described in the ICH Q3A Guidance, except for Impurity (b) (4) and Impurity (b) (4) However, these impurities were present in the batches of MDV3100 tested in GLP-compliant toxicology studies. The amount of Impurity (b) (4) and Impurity (b) (4) that were administered to rats that received 100 mg/kg/day in a 26-week repeat dose toxicology study, which resulted in acceptable toxicities, exceeded the maximum amount of each impurity that would be administered to patients receiving 160 mg/day enzalutamide if each impurity were at their respective proposed acceptance criteria of (b) (4) Impurity (b) (4) and Impurity (b) (4) are thus considered to be qualified up to the proposed acceptance criteria. The table below summarized the information on the qualification of these impurities.

Impurity	Applicant's Proposed Acceptance Criteria	Highest Impurity Level (%) Tested in Toxicology Studies	Maximum MDV3100 Dose (mg/kg/day) Tested in Toxicology Studies in Rats	Human Equivalent Dose of Impurity (µg/kg/day)	Qualified Level (Based on Proposed 160 mg/day)*
(b) (4)	NMT (b) (4)	(b) (4)	100	(b) (4)	
	NMT		100		

* Assumes (b) (4) human.

[a] Human Equivalent Dose and Qualified Level of Impurity (b) (4) were calculated using (b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

- The proposed indication is for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior docetaxel (b) (4).
- The proposed dosing regimen is 160 mg enzalutamide (four 40 mg capsules) administered orally once daily.

2.7 Regulatory Background

Enzalutamide is a new molecular entity which is not approved or marketed in the United States or any other country. In addition to the studies conducted in patients with metastatic, castration-resistant prostate cancer, Medivation is also conducting additional clinical studies in patients with earlier stages of prostate cancer or breast cancer. In this submission, Medivation requested NDA 203415 be granted Priority Review.

Enzalutamide is an androgen receptor antagonist. Currently, there are three other FDA-approved chemotherapeutic agents in the same EPC: flutamide (Eulexin®), nilutamide (Nilandron®), and bicalutamide (Casodex®).

Currently, there are two FDA-approved products for the same proposed indication as enzalutamide in this NDA of treatment of metastatic, castration-resistant prostate cancer after docetaxel-based chemotherapy: cabazitaxel (Jevtana®; microtubule inhibitor) and abiraterone (Zytiga®; CYP17 inhibitor).

3 Studies Submitted

3.1 Studies Reviewed

Pharmacology

Study Number	Study Title	Study Report eCTD Location
PRO3100NC43	AR agonist and antagonist activities of MDV3100 and bicalutamide in a cell-based nuclear translocation assay.	4.2.1.1.
PRO3100NC44	*In vitro* binding of MDV3100 and bicalutamide (MDV3000) to the androgen receptor in a LNCaP cytosolic extract.	4.2.1.1.
PRO3100NC48	Antitumor effects of MDV3100 on LNCaP AR lux human prostate cancer xenografts in castrated SCID mice.	4.2.1.1.
PRO3100NC57	AR agonist and antagonist activities of MDV3100 and bicalutamide (MDV3000) in a cell based nuclear translocation assay (up to 60 μM).	4.2.1.1.
PRO3100NC59	Binding of MDV3100 metabolites M1-M4 to AR in LNCaP cytosolic extract.	4.2.1.1.
PRO3100NC65	*In vitro* binding of MDV3100 metabolites MDPC0001, MDPC0002, MDPC0003 and MDPC0004 to the androgen receptor in a LNCaP cytosolic extract.	4.2.1.1.

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PRO3100NC66	*In vitro* binding of MDV3100 to the androgen receptor in a LNCaP cytosolic extract.	4.2.1.1.
PRO3100NC70	AR agonist and antagonist activities of MDV3100 metabolites M1-M4 in a cell-based translocation assay.	4.2.1.1.
PRO3100NC73	Binding of MDV3100 and metabolites M1-M4 to AR in LNCaP cytosolic extract.	4.2.1.1.
PRO3100NC78	AR agonist and antagonist activities of MDV3100 *in vitro*.	4.2.1.1.
PRO3100NC81	Inhibition by MDV3100 of R1881 AR binding *in vitro*.	4.2.1.1.
PRO3100NC116	*In vitro* binding of MDPC0005 and MDPC0006 to the androgen receptor in a LNCaP cytosolic extract.	4.2.1.1.
PRO3100NC132	*In vitro* binding of MDV3100, bicalutamide, nilutamide and hydroxyflutamide to the androgen receptor in a LNCaP cytosolic extract.	4.2.1.1.
PRO3100NC134	*In vitro* binding of MDV3100, bicalutamide, hydroxyflutamide, and nilutamide to the androgen receptor in a LNCaP cytosolic extract.	4.2.1.1.
PRO3100NC155	Effects of MDV3100 on androgen receptor nuclear translocation, cell viability and induction of apoptotic markers.	4.2.1.1.
9785-PH-0003	Effects of ASP9785, bicalutamide and hydroxyflutamide on the growth of LNCaP and W741C mutated AR-transfected LNCaP, human prostate cancer cells.	4.2.1.1.
9785-PH-0004	Inhibitory effects of ASP9785, bicalutamide and hydroxyflutamide on dihydrotestosterone-induced growth of LNCaP and W741C mutated AR-transfected LNCaP, human prostate cancer cells.	4.2.1.1.
PRO3100NC94*	Cardiovascular safety pharmacology evaluation of MDV3100 administered by oral gavage to naïve telemetry-instrumented conscious male beagle dogs with a toxicokinetic arm.	4.2.1.3.
PRO3100NC95*	Respiratory evaluation of orally administered MDV3100 in male rats.	4.2.1.3.
PRO3100NC96*	Neurobehavioral evaluation of orally administered MDV3100 in rats.	4.2.1.3.
PRO3100NC104*	Effects of MDV3100 on cloned hERG potassium channel expressed in human embryonic kidney cells.	4.2.1.3.
PRO3100NC107*	Effect of MDPC0002 on cloned hERG potassium channels expressed in human embryonic kidney cells.	4.2.1.3.

* Reviewed by Dr. W. David McGuinn, Jr. under IND (b) (4).

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Pharmacokinetics

Study Number	Study Title	Study Report eCTD Location
PRO3100NC11	Pharmacokinetics of single-dose MDV3100 formulated in PEG 400 and ethanol and given intravenously or formulated as either a CMC suspension or (b) (4)) solution and given orally.	4.2.2.2.
PRO3100NC21SR-PK	Pharmacokinetics study of single-dose MDV3100 formulated as either a CMC suspension or (b) (4)) solution and given orally to male CD-1 mice.	4.2.2.2.
PRO3100NC53	Single-dose oral pharmacokinetics study of six formulations of MDV3100 in male beagle dogs: five (b) (4) based liquid formulations (four solutions and one emulsion) administered by gavage (20 mg/kg) and one particulate formulation administered in a hard gelatin capsule (6 mg/kg).	4.2.2.2.
PRO3100NC108	Single-dose pharmacokinetics of MDV3100 following intravenous or oral administration to male Sprague-Dawley rats.	4.2.2.2.
9785-ME-0002	Blood and plasma concentrations and excretion of radioactivity after a single oral administration of ^{14}C-MDV3100 in dogs.	4.2.2.2.
9785-ME-0003	Absorption, distribution, and excretion after a single oral administration of ^{14}C-MDV3100 to rats.	4.2.2.2.
PRO3100NC84	Identification and quantification of MDV3100 and its metabolites in whole brain homogenates after 7-day repeat oral dosing of ^{14}C-MDV3100 in rats.	4.2.2.3.
9785-ME-0006	Metabolite profiles of MDV3100 selected dog plasma, urine, bile, and feces samples after a single oral dose of ^{14}C-MDV3100 in (b) (4) Study No. 8227309.	4.2.2.4.
9785-ME-0007	Metabolite profiles of MDV3100 selected rat plasma, urine, bile, and feces samples after a single oral dose of ^{14}C-MDV3100 in (b) (4) Study No. 8227307.	4.2.2.4.

Toxicology

Study Number	Study Title	Study Report eCTD Location
PRO3100NC18**	4-Week oral capsule toxicity and toxicokinetic study with MDV3100 in dogs with a 4-week recovery period.	4.2.3.2.
PRO3100NC38*	13-Week oral (intragastric intubation) toxicity	4.2.3.2.

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	study of MDV3100 in male dogs including an 8-week recovery period.	
PRO3100NC17**	4-Week oral gavage toxicity and toxicokinetic study with MDV3100 in rats with a 4-week recovery period.	4.2.3.2.
PRO3100NC39*	26-Week oral (intragastric intubation) toxicity study of MDV3100 in rats including an 8-week recovery-period.	4.2.3.2.
PRO3100NC34**	L5178Y $TK^{+/-}$ mouse lymphoma forward mutation assay with a confirmatory assay.	4.2.3.3.1.
PRO3100NC35**	*Salmonella-Escherichia coli*/mammalian-microsome reverse mutation assay with a confirmatory assay.	4.2.3.3.1.
9785-TX-0005**	A micronucleus test in mice orally treated with MDV3100.	4.2.3.3.2.
PRO3100NC31**	2-Week oral gavage bridging toxicity and toxicokinetic study with MDV3100 in rats.	4.2.3.7.6.
MDV3100NC020 (M1)	Bacterial reverse mutation assay	4.2.3.3.1.
MDV3100NC021	Bacterial reverse mutation assay	4.2.3.3.1.

* Reviewed by Dr. W. David McGuinn, Jr. under IND (b) (4).
** Reviewed by Dr. Doo Y. Lee Ham under IND 74563.

3.2 Studies Not Reviewed

Pharmacology

Study Number	Study Title	Study Report eCTD Location
PRO3100NC127	AR agonist and antagonist activities of MDV3100 and –lutamide drugs *in vitro*.	4.2.1.1.
PRO3100NC138	AR agonist and antagonist activities of MDV3100 and –lutamide drugs in a cell-based nuclear translocation assay.	4.2.1.1.
PRO3100NC49	Screen of receptor binding and enzyme inhibition by MDV3100 *in vitro*.	4.2.1.2.
PRO3100NC50	Screen of receptor binding and enzyme inhibition by MDV3100 *in vitro*.	4.2.1.2.
PRO3100NC58	Effect of MDV3100 on AKT kinases *in vitro*.	4.2.1.2.
PRO3100NC63	Screen of receptor binding and enzyme inhibition by MDV3100 metabolites M1-M4 *in vitro*.	4.2.1.2.
PRO3100NC68	Binding of MDV3100 metabolites M5 and M6 to estrogen receptor in MCF-7 cell cytosolic extract.	4.2.1.2.
PRO3100NC72	GABA channel cell-based activity of MDV3100 and metabolites M1-M4.	4.2.1.2.
PRO3100NC129	Estrogen receptor agonist and antagonist	4.2.1.2.

Reference ID: 3175869

	activities of MDV3100 *in vitro*.	
PRO3100NC130	*In vitro* binding of MDV3100 to progesterone receptor.	4.2.1.2.
PRO3100NC131	Progesterone receptor agonist activities of MDV3100 *in vitro*.	4.2.1.2.
PRO3100NC136	Effect of MDV3100 on panel of kinases *in vitro*.	4.2.1.2.
PRO3100NC137	Effect of MDV3100 on panel of deacetylases and kinases *in vitro*.	4.2.1.2.
PRO3100NC141	Effect of MDV3100 metabolites M1 and M2 on panel of kinases *in vitro*.	4.2.1.2.
PRO3100NC142	Effect of MDV3100 metabolites M1 and M2 on panel of kinases *in vitro*.	4.2.1.2.
PRO3100NC145	PR (alpha and beta) agonist and antagonist activities of MDV3100 *in vitro*.	4.2.1.2.
PRO3100NC154	*In vitro* binding of MDV3100 metabolite M2 to progesterone receptor and GABA channel.	4.2.1.2.
PRO3100NC158	*In vitro* binding of MDV3100 metabolite M1 to norepinephrine transporter, CCK1 and A3.	4.2.1.2.
PRO3100NC159	Effect of MDV3100 metabolite M1 on norepinephrine uptake in human MDCK cells *in vitro*.	4.2.1.2.
PRO3100NC160	*In vitro* binding of MDV3100 metabolite M1 to CCK1 receptor and the adenosine A3 receptor.	4.2.1.2.
PRO3100NC91	Effect of MDV3100 on cloned hERG potassium channels expressed in mammalian cells.	4.2.1.3.
PRO3100NC92	Effect of MDPC0002 on cloned hERG potassium channels expressed in mammalian cells.	4.2.1.3.
9785-PT-0005	Convulsion effects of MDV3100 in mice.	4.2.1.3.

Pharmacokinetics

Study Number	**Study Title**	**Study Report eCTD Location**
PRO3100NC02	Method development and validation of an LC/MS/MS assay for the measurement of MDV3100 in rat plasma in support of pharmacokinetic and toxicokinetic investigations.	4.2.2.1.
PRO3100NC03	Long-term stability of MDV3100 in K_3EDTA rat plasma with freezer storage.	4.2.2.1.
PRO3100NC06	Long term stability of MDV3100 in K_3EDTA dog plasma with freezer storage.	4.2.2.1.
PRO3100NC07	Cross-validation of an LC/MS/MS assay using deuterated MDV3100 as an internal standard for the measurement of MDV3100 in dog plasma.	4.2.2.1.
PRO3100NC19	Method development and qualification of an	4.2.2.1.

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	LC/MS/MS assay for the measurement of MDV3100 in mouse plasma in support of pharmacokinetic investigations.	
PRO3100NC97	The LC/MS/MS quantitation of MDV3100 in dog K_2EDTA plasma between 0.0100 and 10.0 μg/mL.	4.2.2.1.
PRO3100NC98	The LC/MS/MS quantitation of MDV3100 in rat plasma between 0.0100 and 10.0 μg/mL.	4.2.2.1.
9785-ME-5001	Validation of an analytical method for the determination of MDV3100, M1, M2 in mouse plasma using LC-MS/MS.	4.2.2.1.
9785-ME-5002	Validation of an analytical method for the determination of MDV3100, M1, and M2 in monkey plasma using LC-MS/MS.	4.2.2.1.
9785-ME-5005	Long-term stability of MDV3100, M1 and M2 in mouse plasma using LC-MS/MS.	4.2.2.1.
9785-ME-5006	Long-term stability of MDV3100, M1 and M2 in monkey plasma using LC-MS/MS.	4.2.2.1.
9785-ME-5014	Validation of an analytical method for the determination of MDV3100, Ma, and M2 in mouse brain using LC-MS/MS.	4.2.2.1.
9785-ME-5015	Long-term stability of MDV3100, M1 and M2 in mouse brain using LC-MS/MS.	4.2.2.1.
9785-ME-5016	Plasma and whole brain concentrations of MDV3100, MDPC0001, and MDPC0002 in a mouse convulsion study.	4.2.2.3.
9785-ME-0014	LC-MS analysis of plasma, urine and bile samples collected from dogs after single oral administration of [^{14}C]MDV3100.	4.2.2.4.
9785-ME-0015	LC-MS analysis of plasma, urine, bile and feces samples collected from rats after single oral administration of [^{14}C]MDV3100.	4.2.2.4.

Toxicology

Study Number	**Study Title**	**Study Report eCTD Location**
9785-TX-0002	A preliminary single oral dose toxicokinetics study of MDV3100 in male and female Crlj:CD1(ICR) mice.	4.2.3.1.
9785-TX-0003	A preliminary single oral dose toxicokinetics study of MDV3100 in cynomolgus monkeys.	4.2.3.1.
PRO3100NC14	Preliminary 14-day oral gavage toxicity and toxicokinetic study with MDV3100 in dogs.	4.2.3.2.
PRO3100NC15	Preliminary 14-day oral gavage toxicity and toxicokinetic study with MDV3100 in rats.	4.2.3.2.
9785-TX-0007	A preliminary 1-week oral dose toxicity study of	4.2.3.2.

Reference ID: 3175869

	MDV3100 in mice.	
PRO3100NC88	5-Amino-2-cyanobenzotrifluoride bacterial mutation assay.	4.2.3.7.6.
PRO3100NC123	Bacterial reverse mutation test of N-(4-cyano-3-trifluoromethylphenyl), O-methyl thiocarbamate.	4.2.3.7.6.
PRO3100NC124	Bacterial mutation test of 4-cyano-3-trifluoromethylphenyl isothiocyanate.	4.2.3.7.6.
PRO3100NC157	Mini-Ames test with TA98 and TA100 for two compounds.	4.2.3.7.6.
PRO3100NC101	Study of subacute oral (intragastric intubation) MDV3100 treatment on male reproductive organs with recovery phase in beagle dogs.	4.2.3.7.7.
9785-TX-0001	A phototoxicity study of MDV3100 in Balb/c 3T3 cells.	4.2.3.7.7.

3.3 Previous Reviews Referenced

- IND 74563 review numbers 1, 2, and 4 by Dr. Doo Y. Lee Ham
- IND (b) (4) original IND review by Dr. W. David McGuinn, Jr.

4 Pharmacology

4.1 Primary Pharmacology

4.1.1. MDV3100 binds to the androgen receptor and inhibits androgen binding to the androgen receptor, *in vitro*.

Medivation conducted a series of screening studies (Study Numbers PRO3100NC44, PRO3100NC66, PRO3100NC132, and PRO3100NC134) to evaluate the binding affinity of MDV3100 (and other androgen receptor inhibitors) to the androgen receptor (AR) and the ability of MDV3100 to inhibit the binding of androgen to the androgen receptor in cytosolic extracts from human LNCaP prostate cancer cell line. This cell line was isolated from a metastatic lesion of a human prostatic adenoma and expresses AR with a threonine to alanine mutation at position 877. Overall, these studies showed MDV3100 has mean (± SEM) K_i and IC_{50} values of 0.023 μM (± 0.005) and 0.062 μM (± 0.016), respectively. The following table summarizes results from these studies:

Table 2. K_i and IC_{50} of MDV3100, bicalutamide, nilutamide, or hydroxyflutamide in cytosolic extract from human LNCaP prostate cancer cell line.

	Study Number			
	PRO3100NC44	**PRO3100NC66**	**PRO3100NC132**	**PRO3100NC134**
MDV3100				
K_i (μM)	0.0130 – 0.0188	0.0131	0.0378	0.0205
IC_{50} (μM)	0.0345 – 0.0516	0.0359	0.108	0.0522

Bicalutamide K_i (μM) IC_{50} (μM)	 0.1880 0.0516	 ND	 0.0564 0.1610	 0.0261 0.0664
Nilutamide K_i (μM) IC_{50} (μM)	 ND	 ND	 0.0078 0.0223	 0.0069 0.0175
Hydroxyflutamide K_i (μM) IC_{50} (μM)	 ND	 ND	 0.0038 0.0109	 0.0037 0.0094

ND = Not Determined

Reviewer's comments:
The results from these studies showed MDV3100 has higher binding affinity (3.9x) and AR inhibitory activity (1.5x) when compared to bicalutamide but lower binding affinity and AR inhibitory activity when compared to nilutamide (-6.7x and -3.1x, respectively) and hydroxyflutamide (-6.1x and -6.1x, respectively), in cytosolic extracts from human LNCaP cells under the conditions tested.

Medivation evaluated the mechanism by which MDV3100 inhibits AR in Study Number PRO3100NC81. Briefly, *in vitro* competition binding studies were performed with the synthetic AR agonist, ^{3}H-R-1881. The results from the study showed that MDV3100 inhibited binding of ^{3}H-R-1881 to the androgen receptor in a concentration-dependent manner. The K_i was largely unaffected by the concentrations of ^{3}H-R-1881 used in the assay, indicating MDV3100 is a competitive inhibitor of AR.

4.1.2. MDV3100 inhibits androgen receptor nuclear translocation and induces apoptosis and decreased cell viability, *in vitro*.

The effect of MDV3100 on nuclear translocation of AR was evaluated using two cell-based assays, a quantitative method using a β-gal enzyme fragment complementation system ([redacted] (b) (4); Study Nos. PRO3100NC43, PRO3100NC57, and PRO3100NC78) and a qualitative method using an AR-fluorescent fusion protein system (Study No. PRO3100NC155). The results obtained from Study Numbers PRO3100NC43, PRO3100NC57, and PRO3100NC78 are summarized below:

Table 3. Effect of MDV3100 and bicalutamide on translocation of AR, *in vitro*.

	Study Numbers		
	PRO3100NC43	**PRO3100NC57**	**PRO3100NC78**
Norgestrol EC_{50} (μM) IC_{50} (μM)	 0.0003 NR	 0.004 NR	 0.002 NR
Geldanamycin EC_{50} (μM) IC_{50} (μM)		 NR 0.024	 NR 0.028
MDV3100 EC_{50} (μM) IC_{50} (μM)	 NR 0.85	 > 60 3.3	 > 60 1.5
Bicalutamide			

EC_{50} (μM) IC_{50} (μM)	> 16 0.8	12 0.25	

NR: No response

Study title: Effects of MDV3100 on androgen receptor nuclear translocation, cell viability and induction of apoptotic markers.

Study no.:	PRO3100NC155
Study report location:	eCTD Section 4.2.1.
Conducting laboratory and location:	Medivation Chile Laboratory Fundacion Ciencias Para la Vida Avda. Zanartu 1482. Nunoa. Santiago. Chile.
Date of study initiation:	August 3, 2009
GLP compliance:	Non-GLP
QA statement:	No
Drug, lot #, and % purity:	MDV3100 (lot numbers and % purity were not reported)

The objective of this non-GLP pharmacology study was to evaluate the effect of MDV3100 and bicalutamide on dihydrotestosterone (DHT)-mediated androgen receptor nuclear translocation, cell viability, and induction of apoptosis, *in vitro*. Briefly, for the nuclear translocation assay, HEK293 cells stably expressing a fluorescent wild type AR-yellow fluorescent protein (YFP) fusion protein (HEK-AR-YFP) were pre-treated with MDV3100 or bicalutamide for 30 minutes and then followed with 1 nM DHT for 2 hours. Cells were then fixed in 4% paraformaldehyde and qualitative analysis of nuclear fluorescence distribution of AR-YFP was evaluated using a fluorescent microscope. For the cell viability and apoptosis assays, androgen-starved LNCaP/AR cells (which overexpress high levels of human wild type AR, growth in an AR-dependent manner, and are bicalutamide-resistant) were treated with MDV3100 and then cell viability and apoptosis in these cells were evaluated using the MTS reduction-based Cell Titer 96 Aqueous Non-Radioactive Cell Proliferation Assay (Promega Corporation, Madison, WI, USA) or Western Blot analysis of caspase-3, respectively.

Summary of results:

- MDV3100 (1 μM), unlike bicalutamide (1 μM), did not induce nuclear translocation of AR-YFP in HEK-YFP-AR cells. (Figure 1.)
- MDV3100 (≥ 1 μM) decreased DHT (1 nM)-induced nuclear translocation of AR-YFP in HEK-YFP-AR cells. (Figure 1.)
- Treatment of LNCaP-AR cells with 1 or 10 μM MDV3100 or bicalutamide for 6 days resulted in reduced cell viability when compared to control. (Figure 2.)
    - At the concentration tested, treatment with MDV3100 appeared to result in lower viability when compared to bicalutamide. (Figure 2.)

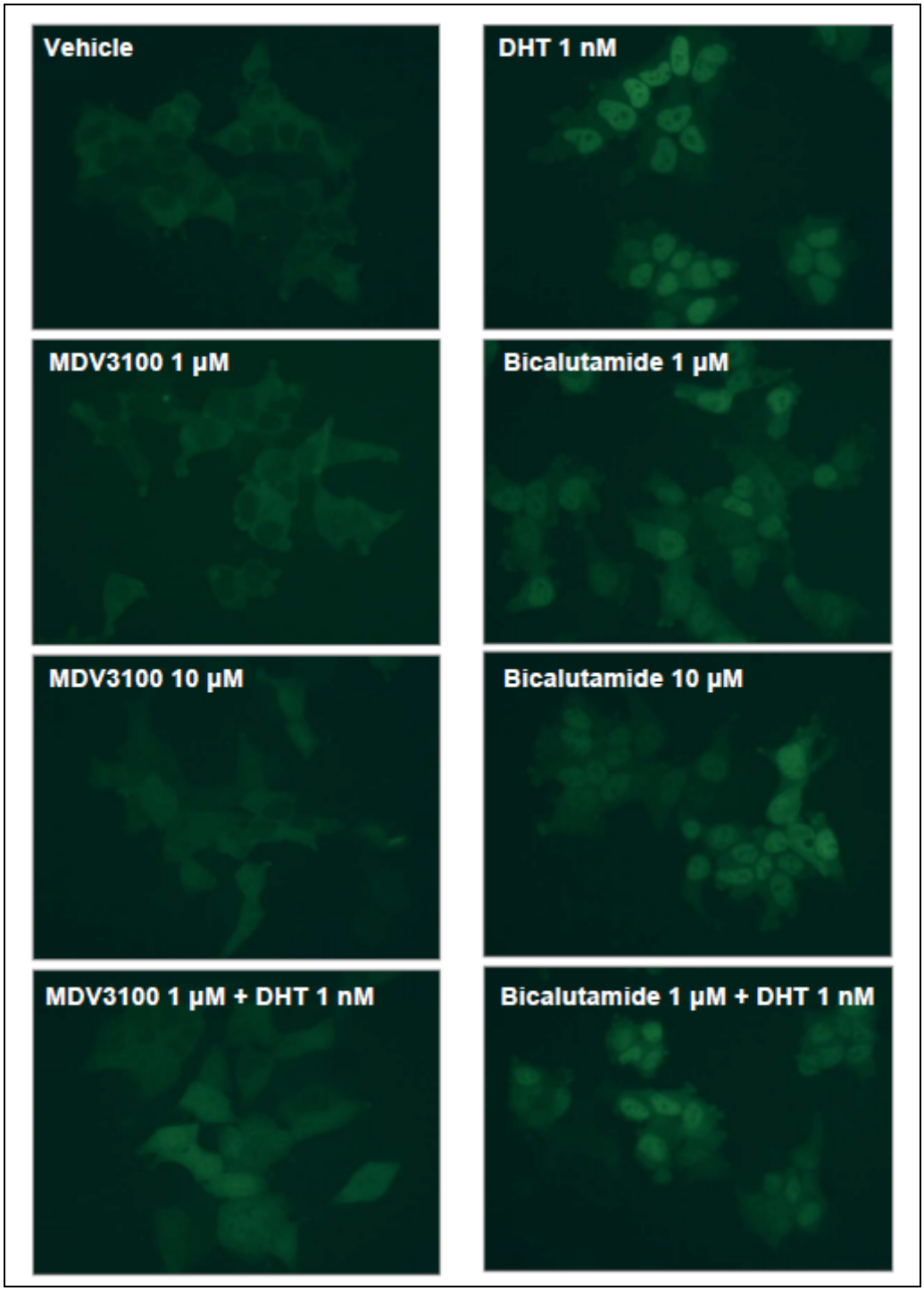
Reference ID: 3175869

- MDV3100-induced decreases in cell viability was correlated with increases in the level of caspase-3 protein, an indicator of increased apoptosis, after treatment of LNCaP with 1 or 10 μM MDV3100 for 2 or 4 days. (Figure 3.)

Reviewer's comments:
Similar studies were conducted by researchers at Memorial Sloan Kettering Cancer Center (Tran et al, 2009)[1] to evaluate the ability of MDV3100 to activate AR. In these studies, using a in vitro fluorescence resonance energy transfer assay, Tran et al. showed that MDV3100, unlike DHT or bicalutamide, did not induce association of AR co-activators to the receptor, a critical step required for AR-induced signal transduction.

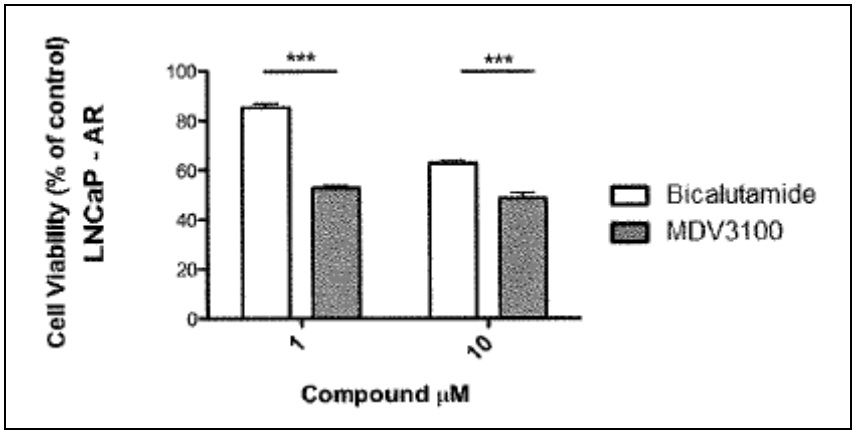
Reference ID: 3175869

Figure 1. MDV3100 inhibits DHT-induced nuclear translocation of AR.



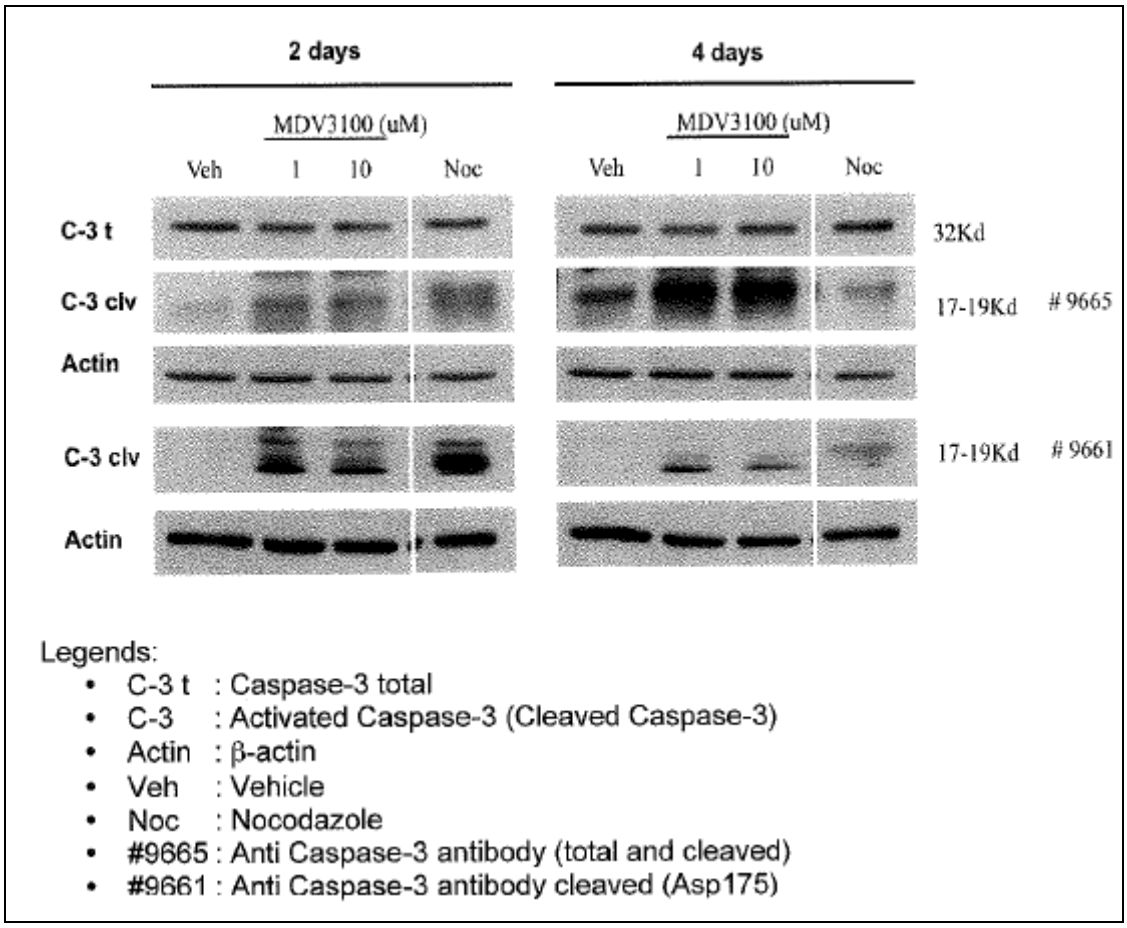
[Excerpted from Applicant's Figure 1 in Study Report Number PRO3100NC155]

Figure 2. MDV3100 decreases cell viability in LNCaP/AR cells.



[Excerpted from Applicant's Figure 2 in Study Report No. PRO3100NC155]

Figure 3. MDV3100 induced cleavage of caspase-3 in LNCaP/AR cells.



[Excerpted from Applicant's Figure 3 in Study Report Number PRO3100NC155]

4.1.3. Effects of MDV3100 on androgen receptor association to DNA.

Medivation provided a literature reference[1] which showed MDV3100 inhibited androgen-dependent androgen receptor association to DNA using a chromatin immunoprecipitation assay. Inhibition of androgen receptor association to DNA resulted in decreased androgen-dependent gene transcription activity.

4.1.4. Effects of MDV3100 on cell viability of LNCaP and W741C-LNCaP cells, *in vitro*.

Study title: Effects of ASP9785, bicalutamide and hydroxyflutamide on the growth of LNCaP and W741C mutated AR-transfected LNCaP, human prostate cancer cells.

Study no.:	9785-PH-0003 (Astellas Study No. PHA100107)
Study report location:	eCTD Section 4.2.1.
Conducting laboratory and location:	Applied Pharmacology Research Laboratories Astellas Pharma Inc. 21, Miyukigaoka, Tsukuba-shi, Ibaraki 305-8585, Japan.
Date of study initiation:	July 22, 2010
GLP compliance:	Non-GLP
QA statement:	No
Drug, lot #, and % purity:	ASP9785 (MDV3100), Lot No. L43672098, (% purity was not reported).

The goal of this non-GLP pharmacology study was to evaluate the effect of MDV3100, bicalutamide, and hydroxyflutamide on the cell viability of LNCaP cells and LNCaP cells expressing AR with the W741C mutation (W741C-LNCaP). Briefly, following an overnight pre-incubation of 5 x 10^3 cells/well in 96-well poly-L-lysine-coated plates, LNCaP and W741C-LNCaP cells were treated with 0.02% dimethylsulfoxide (vehicle control), 0.1 – 30 nmol/L dihydrotestosterone (positive control), or 10 – 3000 nmol/L MDV3100, bicalutamide, or hydroxyflutamide. Cell viability was determined qualitatively 6 days following treatment with DMSO, DHT, MDV3100, bicalutamide, or hydroxyflutamide, using the CellTiter-Glo® Luminescent Cell Viability Assay (Promega Corporation, Madison, WI).

Summary of results:

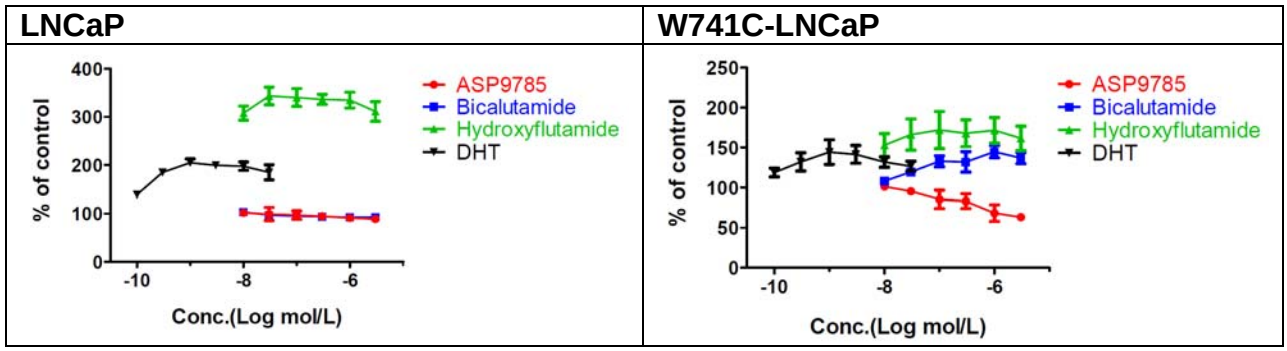
- MDV3100 and bicalutamide had no effect on cell viability of LNCaP cells when compared to vehicle control-treated LNCaP cells.
- Hydroxyflutamide appeared to induce cell proliferation in LNCaP cells when compared to vehicle control-treated LNCaP cells.

Reference ID: 3175869

- MDV3100 induced a decrease in cell viability in W741C-LNCaP cells when compared to vehicle control-treated W741C-LNCaP cells.
- Bicalutamide and hydroxyflutamide induced cell proliferation in W741C-LNCaP cells when compared to vehicle control-treated W741C-LNCaP cells.

Conclusions:
In vitro, MDV3100 did not show agonist effects in LNCaP or W741C-LNCaP cells, under the testing conditions.

Figure 4. Effects of MDV3100 (ASP9785) on cell viability and proliferation of LNCaP and W741-LNCaP cells.



[Excerpted from Applicant's Figure 1 and 2 in Study Report Number 9785-PH-0003]
Values are the means ± SE of three independent experiments.

Study title: Inhibitory effects of ASP9785, bicalutamide and hydroxyflutamide on dihydrotestosterone-induced growth of LNCaP and W741C mutated AR-transfected LNCaP, human prostate cancer cells.

Study no.:	9785-PH-0004 (Astellas Study No. PHA100108)
Study report location:	eCTD Section 4.2.1.
Conducting laboratory and location:	Applied Pharmacology Research Laboratories Astellas Pharma Inc. 21, Miyukigaoka, Tsukuba-shi, Ibaraki 305-8585, Japan.
Date of study initiation:	July 22, 2010
GLP compliance:	Non-GLP
QA statement:	No
Drug, lot #, and % purity:	ASP9785 (MDV3100), Lot No. L43672098 (% purity was not reported).

The goal of this non-GLP pharmacology study was to evaluate the effect of MDV3100, bicalutamide, and hydroxyflutamide on dihydrotestosterone-induced cell proliferation of

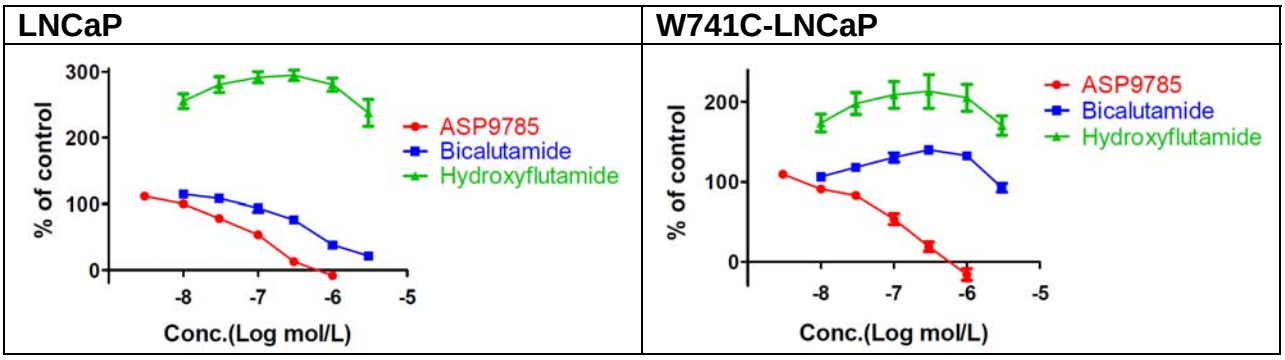
LNCaP and W741C-LNCaP cells. Briefly, following an overnight pre-incubation of 5 x 10^3 cells/well in 96-well poly-L-lysine-coated plates, LNCaP and W741C-LNCaP cells were treated with 0.04% dimethylsulfoxide (vehicle control), 1 nmol/L DHT, and 3 – 1000 nmol/L MDV3100, 10 - 3000 nmol/L bicalutamide, or 10 – 3000 nmol/L hydroxyflutamide. Cell viability was determined qualitatively 6 days following treatment with DMSO, DHT, MDV3100, bicalutamide, or hydroxyflutamide, using the CellTiter-Glo® Luminescent Cell Viability Assay (Promega Corporation, Madison, WI).

Summary of results:

- MDV3100 inhibited DHT-induced LNCaP and W741C-LNCaP cell proliferation with IC_{50} values of 93 and 100 nmol/L, respectively.
- Bicalutamide inhibited DHT-induced cell proliferation of LNCaP cells (IC_{50} = 780 nmol/L), but not W741C-LNCaP cells.
- Hydroxyflutamide did not inhibit DHT-induced cell proliferation in either LNCaP or W741C-LNCaP cells. Data suggest hydroxyflutamide has an agonist effects in these cells.

Conclusions:
In vitro, MDV3100 did not show agonist effects in LNCaP or W741C-LNCaP cells, under the testing conditions.

Figure 5. Effects of MDV3100 (ASP9785) on DHT-induced cell proliferation of LNCaP and W741C-LNCaP cells.



[Excerpted from Applicant's Figure 1 and 2 in Study Report Number 9785-PH-0004]
Values are the means ± SE of three independent experiments.

Study title: AR agonist and antagonist activities of MDV3100 and bicalutamide in a cell-based nuclear translocation assay.

Study no.:	PRO3100NC48
Study report location:	eCTD Section 4.2.1.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Not reported.
GLP compliance:	Non-GLP
QA statement:	None
Drugs, lot #, and % purity:	MDV3100 and bicalutamide. (Lot numbers and % purity were not reported.)

The goal of this non-GLP pharmacology study was to evaluate the anti-tumor activity of MDV3100 in a mouse xenograft model of human castration-resistant prostate cancer. Briefly, surgically castrated 5 – 9 week-old male CB17SCID mice (b) (4) were implanted with $2x10^6$ LNCaP/AR tumor cells subcutaneously in the suprascapular region. Once tumors reached a minimum volume of 100 mm^3, mice were administered vehicle control (Tween 80:polyethelene glycol 400), MDV3100 (1, 10, 50 mg/kg/day), or bicalutamide (50 mg/kg/day) once-daily for 28 days, via oral gavage. During the treatment period, tumor size and body weights were recorded every 2 -3 day intervals.

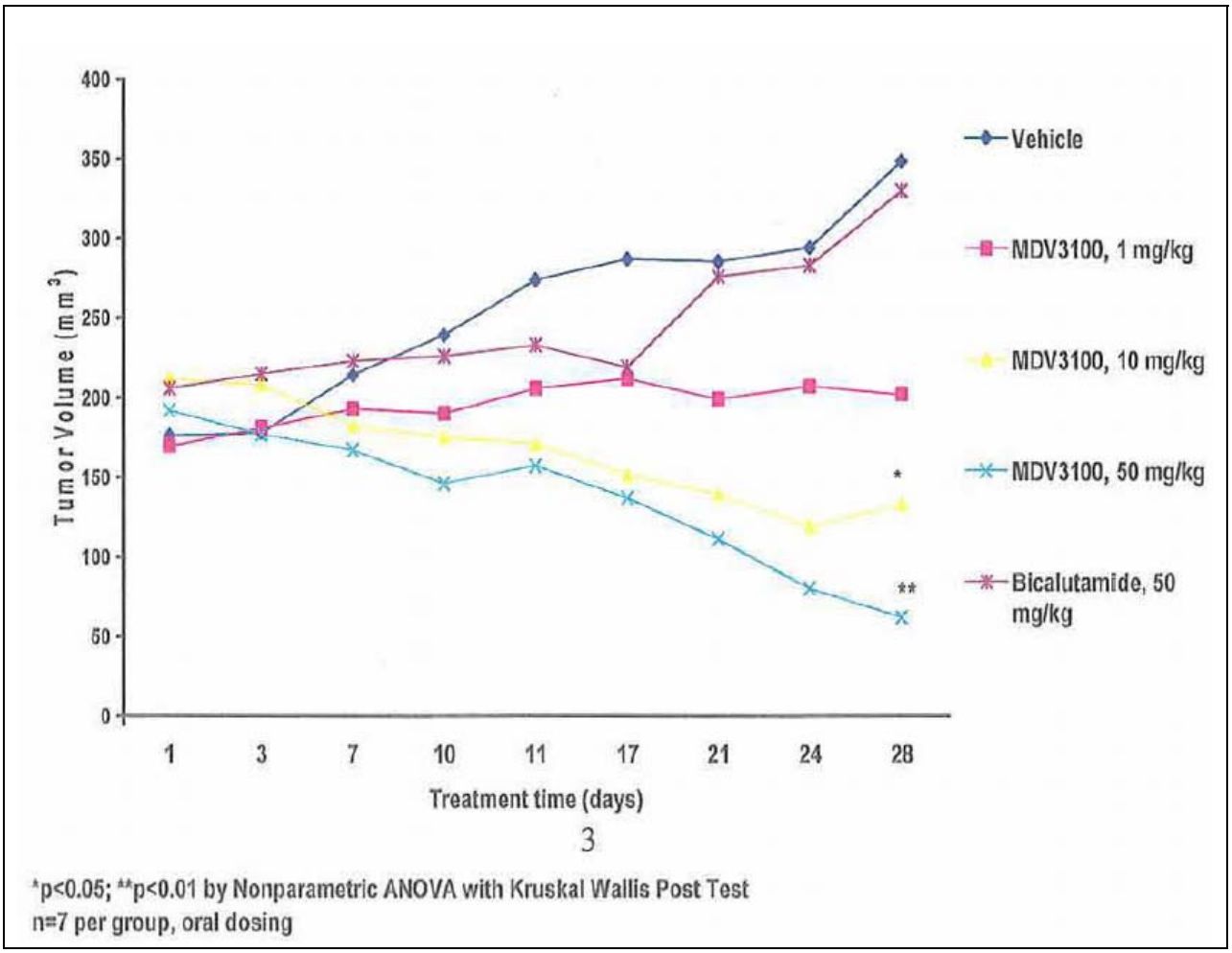
Summary of results:

- Administration of MDV3100 resulted in dose-dependent decreases in tumor growth in tumor-bearing mice when compared to vehicle control- or bicalutamide-treated tumor bearing mice.
- Administration of MDV3100 did not result in decreases in body weight in tumor bearing mice.
- Bicalutamide had no significant effects on tumor growth when compared to vehicle control-treated mice.

Conclusions:

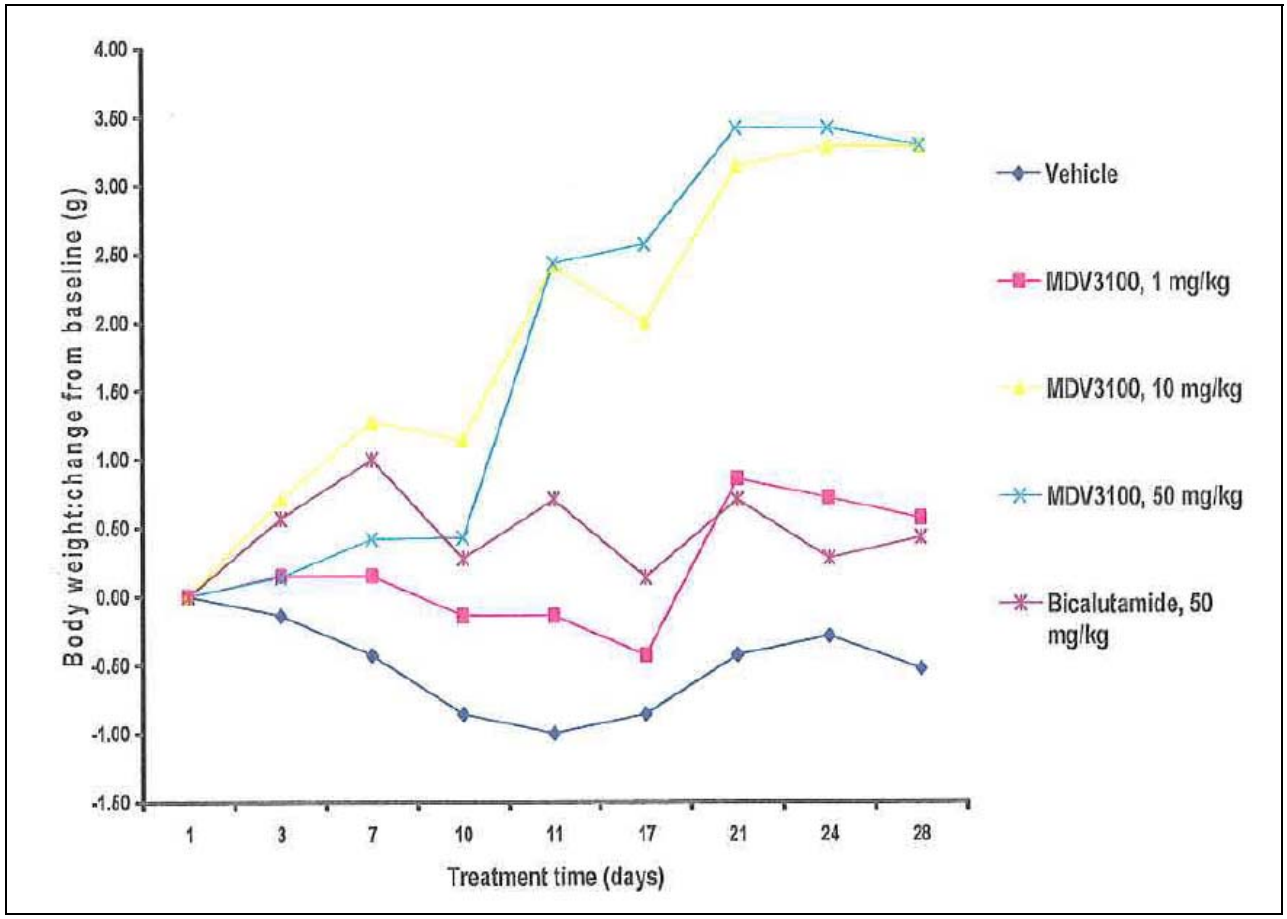
MDV3100 exhibits dose-dependent antitumor activity in a mouse model of human castration-resistant prostate cancer.

Figure 6. Effect of MDV3100 on tumor growth in a mouse xenograft model of human castration-resistant prostate cancer.



[Excerpted from Applicant's Figure 1 in Study Report Number PRO3100NC48]

Figure 7. Effect of MDV3100 on body weight in tumor bearing mice.



[Excerpted from Applicant's Figure 2 in Study Report Number PRO3100NC48]

Table 4. Summary of MDV3100-induced tumor growth inhibition,

Treatment Group	No. Mice (n)	Mean ± SD Tumor Vol. in mm^3 (Day 28)	% Tumor Growth Inhibition at Day 28	Number Non-Measurable Tumors/ Number of Mice
Vehicle Control	7	348 ± 192	-	0/7
MDV3100 1 mg/kg	7	202 ± 98	42	1/7
MDV3100 10 mg/kg	7	133± 93	62	0/7
MDV3100 50 mg/kg	7	62 ± 65	82	3/7
Bicalutamide 50 mg/kg	7	330 ± 198	5	0/7

[Excerpted from Applicant's Table 1 in Study Report No. PRO3100NC48]

4.1.5. Pharmacological activity of MDV3100 metabolites.

Six metabolites of MDV3100 (M1, M2, M3, M4, M5, and M6) have been characterized in non-clinical studies. Of these metabolites, only M1 and M2 (also referred to as MDPC0001 and MDPC0002, respectively) have been detected in human plasma as major metabolites. Medivation conducted a series of *in vitro* pharmacology studies to evaluate the ability of MDV3100 metabolites to bind to AR and cause nuclear translocation of AR.

In Study Numbers PRO3100NC59, PRO3100NC65, and PRO3100NC73, Medivation evaluated the binding affinity of MDV3100 metabolites M1, M2, M3, and M4 to AR (K_i) and the ability of MDV3100 to inhibit the binding of testosterone to AR (IC_{50}) in cytosolic extracts from human LNCaP prostate cancer cell line. The results from these studies show that M2 has similar AR binding affinity and inhibitory activity when compared to MDV3100. The following table summarizes results from these studies:

	Study Number		
	PRO3100NC59	**PRO3100NC65**	**PRO3100NC73**
MDV3100			
K_i (μM)			0.057
IC_{50} (μM)			0.130
M1			
K_i (μM)	N/A	N/A	N/A
IC_{50} (μM)	N/A	> 0.0003	N/A

M2 K_i (μM) IC_{50} (μM)	 0.074 0.17	 0.0589 0.176	 0.051 0.120
M3 K_i (μM) IC_{50} (μM)	 0.83 1.90	 0.314 0.938	 1.500 3.400
M4 K_i (μM) IC_{50} (μM)	 0.69 1.60	 0.361 1.080	 0.970 2.200

N/A Not available because no significant changes were detected.

Reviewer's comments:
Study Number PRO3100NC73 is the only study described above which used MDV3100 as a positive control in the assay and allowed a direct comparison of its binding and inhibitory properties to MDV3100 metabolites, under the same testing conditions.

In Study Number PRO3100NC70, Medivation evaluated the ability of MDV3100 metabolites M1, M2, M3, and M4 to either induce AR nuclear translocation or inhibit norgesterol-induced AR translocation using the PathHunter NHRPro Protein Interaction and Nuclear Translocation assay (DiscoverRx, Fremont CA). The results from this study show that, similarly to MDV3100, metabolites M1, M2, M3, and M4 did not induce AR nuclear translocation. However, metabolites M2, M3, and M4 can inhibit norgesterol-induced AR nuclear translocation. The following tables summarize results from this study:

Table 5. Effect of metabolites of MDV3100 on AR nuclear translocation.

	Induction of AR Nuclear Translocation EC_{50} (μM)
Norgesterol	0.004
M1	N/A
M2	N/A
M3	N/A
M4	N/A

N/A Not available because no significant changes were detected.

Table 6. Effect of metabolites of MDV3100 on inhibition of androgen-induced AR nuclear translocation.

	Inhibition of AR Nuclear Translocation IC_{50} (μM)
Galdanamycin	0.018
M1	> 60
M2	3.2
M3	16.2
M4	11.6

N/A Not available because no significant changes were detected.

Reference ID: 3175869

Reviewer's comments:

- *Although MDV3100 was not tested in the same assay with its metabolites, Study Numbers PRO3100NC43 and PRO3100NC57 (summarized above in Section 4.1.2.) showed that under similar testing conditions, MDV3100 also did not induce AR nuclear translocation (EC_{50} > 60 μM) and inhibited norgesterol-induced AR nuclear translocation with an IC_{50} value of 3.3 μM.*
- *Overall, based on the results of the studies with MDV3100 metabolites submitted in this NDA, M1 appears to be an inactive metabolite of MDV3100 while M2, M3, and M4 appear to be active metabolites of MDV3100. Furthermore, M2 appear to have similar activity when compared to MDV3100, as measured by either AR binding affinity or inhibition of ligand binding to AR and AR nuclear translocation.*

4.2 Secondary Pharmacology

Secondary pharmacology studies were not reviewed in detail for this NDA submission.

Based on the summary provided by the Applicant, MDV3100 and M2 showed inhibitory activity towards the human progesterone receptor (IC_{50} = 16.1 μM and 6.2 μM, respectively) and the rat gamma aminobutyric acid (GABA)-gated chloride channel (IC_{50} = 2.6 μM and 7.1 μM, respectively), *in vitro*. M1 did not bind to the GABA-gated chloride channel.

4.3 Safety Pharmacology

Study Number: **PRO3100NC94 (b) (4) Study Number 8215116)**
Study Title: **Cardiovascular safety pharmacology evaluation of MDV3100 administered by oral gavage to naïve telemetry-instrumented conscious male beagle dogs with a toxicokinetic arm.**

[The review of Study No. PRO3100NC94 is reproduced verbatim below, with some changes in formatting for consistency purposes, as it appeared in the review (dated June 15, 2012) of IND (b) (4) for MDV3100 conducted by W. David McGuinn, Jr., M.S., Ph.D., D.A.B.T.]

Study number	8215116
File name	PRO3100NC94-nonclinical-report.pdf
Laboratory	(b) (4)
Study Date	March 2010
GLP	Yes
Audited	Yes
Drug	MDV3100, Lot number 09070028, purity 98.3%
Methods	
Species	Four male beagle dogs 12.9 to 13.2 months old; body weight range 9.9 to 11.4 kg
Doses	0, 5, 15, 30 mg/kg (0, 100, 300, 600 mg/m^2)

Reference ID: 3175869

Schedule Each different dose given once every 14 days to each dog in a Latin Squares design. The following table from the study report shows this design.

Animal	Dose Level Designation on Specified Dosing Days				
Male	Day 1	Day 15	Day 29	Day 43	Day 57[a]
H03548	Low	Control	High	Mid	Mid
H03549	Mid	High	Control	Low	Mid
H03550	High	Low	Mid	Control	High
H03551	Control	Mid	Low	High	High

a Toxicokinetic dosing only. No telemetry collection.

Vehicle (b) (4)
Clinical signs Twice daily
Toxicokinetics Mid- and high doses, two animals each dose group on day 57. Sampling pre-dose and 2, 4, 8, 12, 24, 48, 72 120, and 168 hours post-dose.

Pressure transducers and temperature telemeters were surgically implanted at least two weeks prior to dosing. Cardiac telemetry was initiated at least 90 minutes before dosing and continued at least 20 hours after dosing. After the end of the continuous data collection, telemetry data were recorded for at least 15 minutes every hour through at least 48 hours, and for 30 minutes every 12 hours through 96 hours post-dose.

Results

Mortality – All dogs survived to the end of the study

Clinical signs – Occasional dose-related vomiting

Body Wt – No toxicologically significant changes

Body Temp – No toxicologically significant changes

ECG – No abnormal ECG waveforms or arrhythmias were attributable to the administration of 5, 15, or 30 mg/kg. The ECG data were qualitatively and quantitatively within normal limits.

Blood Pressure – No toxicologically significant changes

Toxicokinetics – The lower limit of detection of MDV3100 was 0.0100 µg/mL. At the higher doses, the drug did not completely wash out during the 14 day interval between doses. Two dogs had quantifiable amounts of MDV3100 prior to dosing at the day 57 toxicokinetic assessment.

Reference ID: 3175869

Toxicokinetic analysis showed a less than 2-fold variation in plasma MDV3100 concentrations between 2 and 24 hours post-dose in MDV3100-treated animals. For doses of 15 and 30 mg/kg, mean t_{max} values were 10 and 24 hours respectively; C_{max} values were 11.5 and 8.07 µg/mL (25 and 17 mM respectively), suggesting delayed or saturated absorption of the high dose. The AUC_{last} was 448 and 582 µg•h/mL or 964 and 1254 µM*h, respectively. Thus, exposure in the high dose group was about twice that seen in human studies at the phase 2 dose of 160 mg/day. The elimination $t_{1/2}$ was 32.7 and 42.9 hours, respectively, for the two dose levels.

		Toxicokinetic Parameters					
Dose (mg/kg)	Dog	C_{max} (µg/mL)	t_{max} (h)	AUC_{last} (µg·h/mL)	$t_{1/2}$ (h)	C_{max}/Dose ([µg/mL]/[mg/kg])	AUC_{last}/Dose ([µg·h/mL]/[mg/kg])
15	H03548	11.3	8.0	418	38.2	0.8	27.9
	H03549	11.6	12	477	27.1	0.8	31.8
	Mean	11.5	10	448	32.7	0.8	29.9
30	H03550	9.16	24	654	40.1	0.3	21.8
	H03551	6.97	24	510	45.6	0.2	17.0
	Mean	8.07	24	582	42.9	0.3	19.4

Study Number: **PRO3100NC95 (b) (4) Study Number 1284-029)**
Study Title: **Respiratory evaluation of orally administered MDV3100 in male rats.**

[The review of Study No. PRO3100NC95 is reproduced verbatim below, with some changes in formatting for consistency purposes, as it appeared in the review (dated June 15, 2012) of IND (b) (4) for MDV3100 conducted by W. David McGuinn, Jr., M.S., Ph.D., D.A.B.T.]

Study number 1284-029
File name PRO3100NC95-nonclinical-report.pdf
Laboratory (b) (4)
Study Date March 2010
GLP Yes
Audited Yes
Drug MDV3100, Lot number 09070028, purity 98.3%

Methods
Species male CD® [Crl:CD®(SD)] rats (approximately 6 weeks of age at receipt)

Doses The following table shows the doses and the number of animals used in each group

Group Number	Dose mg/kg	Dose mg/m^2	Dose Volume	N
1	0	0	2.2	8
2	30	180	2.2	8
3	100	600	2.2	8
4	0	0	4.4	8
5	200	1200	4.4	8

Route PO gavage
Schedule Single dose
Formulation (b) (4)
Cage side Twice daily
Clinical exam Pre-dose, 2, 6 and 72 hours post dose
Body Weights Daily

Pulmonary Monitoring

Each animal was placed in a plethysmograph chamber at least 2 hours prior to dosing. After at least 1 hour of acclimation, pulmonary monitoring was initiated to establish baseline data. The animals were temporarily removed from the plethysmograph chambers for dosing after at least 1 hour of continuous baseline recording. Immediately following dosing, the animals were returned to the plethysmograph chambers, and pulmonary monitoring was continued for at least 8 hours. On Day 4, animals were returned to the plethysmograph chambers for 30 minutes of additional baseline monitoring. At approximately 72 hours post-dose on Day 4, pulmonary monitoring was continued for a period of at least 1 hour. Data were logged into 1-minute intervals and reported in 15-minute intervals. Only 1 hour of baseline data were reported.

Results

No toxicologically significant changes.

Study Number: **PRO3100NC96 ((b) (4) Study Number 1284-030)**
Study Title: **Neurobehavioral evaluation of orally administered MDV3100 in rats.**

[The review of Study No. PRO3100NC96 is reproduced verbatim below, with some changes in formatting for consistency purposes, as it appeared in the review (dated June 15, 2012) of IND (b) (4) for MDV3100 conducted by W. David McGuinn, Jr., M.S., Ph.D., D.A.B.T.]

Reference ID: 3175869

Study number 1284-030
File name PRO3100NC96-nonclinical-report.pdf
Laboratory [redacted] (b) (4)
Study Date March 2010
GLP Yes
Audited Yes
Drug MDV3100, Lot number 09070028, purity 98.3%
Methods
Species: Male CD® [Crl:CD®(SD)] rats (approximately 6 weeks of age at receipt)
Doses The following table shows the doses and the number of animals used in each group

Group Number	Dose mg/kg	Dose mg/m^2	Dose Volume	N
1	0	0	2.2	10
2	30	180	2.2	10
3	100	600	2.2	10
4	0	0	4.4	10
5	200	1200	4.4	10

Route PO gavage
Schedule Single dose
Formulation [redacted] (b) (4)
Cage side Twice daily
Clinical exam Predose, 2, 6 and 72 hours post dose
Body Weights Daily
Tests Functional Observation Battery (FOB)

Results

Mortality – None
FOB – No toxicologically significant changes

Study Number: PRO3100NC104 ([redacted] (b) (4) Study Number 090908.NOW)
Study Title: Effects of MDV3100 on cloned hERG potassium channels expressed in human embryonic kidney cells.

[The review of Study No. PRO3100NC104 is reproduced verbatim below, with some changes in formatting for consistency purposes, as it appeared in the review (dated June 15, 2012) of IND [redacted] (b) (4) for MDV3100 conducted by W. David McGuinn, Jr., M.S., Ph.D., D.A.B.T.]

Study number 090908.NOW

Reference ID: 3175869

File name	PRO3100NC104-nonclinical-report.pdf
Laboratory	(b) (4)
Study Date	February 2010
GLP	Yes
Audited	Yes
Drug	MDV3100, Lot number 09070028, purity 98.3%
Methods	
Cells	hERG potassium channels stably expressed in a human embryonic kidney (HEK293)
Concentrations	0, 3, 10, 26.1 and 60.6 μM
N	3 to 4 cells per dose group
Positive Control	Terfenadine

MDV3100 inhibited hERG current by (Mean ± SEM) 12.0 ± 1.0% at 3 μM, 33.8 ± 0.3% at 10 μM, 65.2 ± 0.4% at 26.1 μM and 88.7 ± 1.2% at 60.5 μM versus 0.6 ± 0.1% in the controls. Inhibition of hERG current at 3, 10, 26.1 and 60.5 μM was statistically significant ($P < 0.05$) when compared to vehicle control values. The IC_{50} for the inhibitory effect of MDV3100 on hERG potassium current was 15.7 μM (Hill coefficient = 1.3). Under identical conditions, the positive control (60 nM terfenadine) inhibited hERG potassium current by (Mean ± SEM; n = 3) 82.8 ± 2.9%.

[End of review of Study Number PRO3100NC104 excerpted from Dr. W. David McGuinn, Jr.'s review.]

Reviewer's comment:
The IC_{50} (15.7 μM) of MDV3100 on hERG potassium current is approximately 17 times the human exposure to unbound MDV3100 based on C_{max}.

Study Number:	**PRO3100NC107 (** (b) (4) **Study Number 090909.NOW)**
Study Title:	**Effects of MDPC0002 on cloned hERG potassium channels expressed in human embryonic kidney cells.**

[The review of Study No. PRO3100NC107 is reproduced verbatim below, with some changes in formatting for consistency purposes, as it appeared in the review (dated June 15, 2012) of IND (b) (4) *for MDV3100 conducted by W. David McGuinn, Jr., M.S., Ph.D., D.A.B.T.]*

Study number	090909.NOW
File name	PRO3100NC107-nonclinical-report.pdf
Laboratory	(b) (4)
Study Date	November 2009
GLP	Yes
Audited	Yes
Drug	MDPC0002, Lot number KRI-F-178 (2), and purity 97.5%

Reference ID: 3175869

Methods

Cells	hERG potassium channels stably expressed in a human embryonic kidney (HEK293)
Concentrations	0, 3, 10, 30 and 60 μM nominal
N	3 to 4 cells per dose group
Positive Control	Terfenadine

MDPC0002 is a metabolite of MDV3100. It inhibited hERG current by (Mean ± SEM) 13.6 ± 0.8% at 3 μM (n = 3), 33.7 ± 0.3% at 10 μM (n = 3), 61.1 ± 1.0% at 30 μM (n = 3) and 79.2 ± 0.4% at 60 μM (n = 3) versus 0.6 ± 0.1% in control (n = 3). hERG inhibition at 3, 10, 30 and 60 μM was statistically significant ($P < 0.05$) when compared to vehicle control values. The IC_{50} for the inhibitory effect of MDPC0002 on hERG potassium current was 18.6 μM (Hill coefficient = 1.1).

[End of review of Study Number PRO3100NC107 excerpted from Dr. W. David McGuinn, Jr.'s review.]

Reviewer's comment:
The IC_{50} (18.6 μM) of M2 on hERG potassium current is approximately 14 times the human exposure to unbound M2 based on C_{max}.

Study Number: 9785-PT-0005 (11K1511N)
Study Title: Convulsion effects of MDV3100 in mice.

The objective of this non-GLP study was to evaluate MDV3100-induced convulsion in mice. Seven-week old Crlj:CD1 (ICR) mice were administered either vehicle control (0.5% methylcellulose 400 or (b) (4), 400 mg/kg MDV3100 for 1 day, or 60 and 200 mg/kg MDV3100 for 7 days, via oral gavage. In the animals administered a single dose of 400 mg/kg MDV3100, clonic convulsions and tonic convulsions were observed in 7 out of 10 animals between 4 and 24 hours post-dose. In animals administered MDV3100 for 7 days, clonic convulsions and tonic convulsions were observed between 1 and 24 hours post-dose on Days 1, 2, and 3, in 9 out of 10 animals administered 200 mg/kg MDV3100 (3.3 times the human exposure based on AUC). Other observed clinical signs in the study included bradypnea, hypolocomotion, and decreased food consumption.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

5.1.1 Absorption

Study title: Pharmacokinetics study of single-dose MDV3100 formulated as either a CMC suspension or [redacted] (b) (4) solution and given orally to male CD-1 mice.

Study no.:	PRO3100NC21 ([redacted] (b) (4) Study Number 1284-005)
Study report location:	eCTD Section 4.2.2.2.
Conducting laboratory (In-Life) and location:	[redacted] (b) (4)
Conducting laboratory (bioanalytics) and location:	[redacted] (b) (4)
PK Data Analysis:	[redacted]
Date of study initiation (bioanalytics):	November 2006
GLP compliance:	No.
QA statement:	No.
Drug, lot #, and % purity:	MDV3100, Lot # 194-186-024 (CMC/Tween) and Lot # EWK-K-32(1) [redacted] (b) (4)

Key Study Findings

- Based on a 1-compartment PK model, T_{max} ranged from approximately 3.86 to 6.44 hours, $T_{1/2}$ ranged from 7.90 to 11.6 hours, and V_F ranged from 1140 to 2740 mL/kg. There were no significant differences in $T_{1/2}$ values between the two formulation.
- Based on C_{max} and AUC values, exposure to MDV3100 was approximately 3 times higher in animals administered MDV3100 in [redacted] (b) (4) compared to that in CMC/Tween.

Methods

Doses:	Group 1: 1 mg/kg MDV3100 in 1% CMC, 0.1% Tween 80, and water (CMC/Tween) Group 2: 10 mg/kg MDV3100 in CMC/Tween Group 3: 50 mg/kg MDV3100 in CMC/Tween Group 4: 50 mg/kg MDV3100 in (b) (4)
Frequency of dosing:	Single dose.
Route of administration:	Oral gavage.
Dose volume:	5 mL/kg
Formulation/Vehicle:	(b) (4) Lot # RM06-012)
Species/Strain:	Mouse/CD-1
Number/Sex/Group:	33 male mice/group
Age:	Not reported.
Weight:	30 - 35 g
Satellite groups:	None.
Unique study design:	None reported.
Deviation from study protocol:	None reported.

Table 7. Summary of study design in Study Number PRO3100NC21.

Group	Number of Males	Dose Route	Vehicle	Dose Level (mg/kg)	Dose Volume (mL/kg)	Sampling
1	33	Oral, gavage	a	1	5	Plasma[c]
2	33	Oral, gavage	a	10	5	Plasma[c]
3	33	Oral, capsule	a	50	5	Plasma[c]
4	33	Oral, capsule	b	50	5	Plasma[c]

[a] 1% carboxymethylcellulose (CMC) and 0.1% Tween 80 in deionized water
[b] 100% (b) (4)
[c] Plasma was collected pre-dose and at 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours after dosing.

[Excerpted from Applicant's Table 1 in Study Report Number PRO3100NC21]

Observations

Blood Sample Collection	Three mice/group were sacrificed at 1, 2, 3, 5, 6, 8, 10, 12, 24, 36, and 48 hours after dosing and blood was collected via cardiac puncture under CO2 anesthesia and placed in tubes containing K_3EDTA.
Bioanalytical Procedures	Plasma samples were analyzed by high performance liquid chromatography (LC) in conjunction with a triple quadrupole mass spectrometer that used electrospray ionization in tandem with positive ionization (MS/MS). The lower limit of quantitation (LLOQ) was 0.0100 μg/mL. The quantitative range of the assay was 0.0100 to 8 μg/mL.
Pharmacokinetics	PK modeling was performed using WinNonlin (version 4.0.1:

Reference ID: 3175869

Analysis	Pharsight Corp., Mountain View, CA). The following PK parameters were reported and summarized in this review: Cmax: Maximum (peak) plasma concentration DN-Cmax: Dose-normalized Cmax Tmax: Time at Cmax AUC: Area under the concentration-time curve DN-AUC: Dose-normalized AUC T1/2: Terminal half life V_F: Apparent volume of distribution

Results

Based on a 1-compartment PK model, T_{max} ranged from approximately 3.86 to 6.44 hours, $T_{1/2}$ ranged from 7.90 to 11.6 hours, and V_F ranged from 1140 to 2740 mL/kg. There were no significant differences in $T_{1/2}$ values between the two formulations.

- Exposure to MDV3100 formulated in CMC/Tween increased less than dose-proportionally with increasing doses.
- Based on C_{max} and AUC values, exposure to MDV3100 was approximately 3x higher in animals administered MDV3100 in (b) (4) compared to that in CMC/Tween.

Table 8. Summary of PK parameters following administration of a single dose of MDV3100 in male CD-1 mice (Study Number PRO3100NC21).

Treatment	C_{max} (µg/mL)	DN-C_{max} (µg/mL)/(mg/kg)	T_{max} (hr)	AUC (µg·hr/mL)	DN-AUC (µg·hr/mL)/(mg/kg)	$T_{1/2}$ (hr)
Group 1 (1 mg/kg, CMC/Tween)	0.577	0.577	3.88	10.7	10.7	9.74
Group 2 (10 mg/kg, CMC/Tween)	3.83	0.383	4.46	83.9	8.39	11.6
Group 3 (50 mg/kg, CMC/Tween)	10.4	0.207	6.44	208	4.16	7.90
Group 4 (50 mg/kg (b) (4)	34.3	0.686	3.86	689	13.8	10.9

[Excerpted from Applicant's Table 7 in Study Report Number PRO3100NC21]

Study title: Single-dose pharmacokinetics of MDV3100 following intravenous or oral administration to male Sprague-Dawley rats.

Study no.:	PRO3100NC108 (In-life (b) (4) Study Number 1284-034)
Study report location:	eCTD Section 4.2.2.2.
Conducting laboratory (in-life) and location:	(b) (4)
Bioanalytical site:	(b) (4)
PK analysis site:	Medivation, Inc., San Francisco, CA
Date of study initiation:	October 2009
GLP compliance:	No.
QA statement:	No.
Drug, lot #, and % purity:	MDV3100, Lot # 09080067

Key Study Findings

In Sprague-Dawley rats, following a single oral dose of 20 mg/kg MDV3100, the mean C_{max}, T_{max}, and $T_{1/2}$ values were 11.1, 6.0, and 9.79, respectively.

Methods

Doses:	20 mg/kg MDV3100
Frequency of dosing:	Single dose.
Route of administration:	Intravenous injection into lateral tail vein or oral gavage.
Dose volume:	2 mL/kg
Formulation/Vehicle:	- 50% polyethylene glycol 400 (PEG 400)/20% ethanol/30% sterile water for injection, USP - 100% (b) (4)
Species/Strain:	Naïve jugular vein cannulated rat/Sprague-Dawley [Crl:CD®(SD)]
Number/Sex/Group:	6 male mice/group
Age:	12 weeks old.
Weight:	0.334 – 0.381 kg.
Satellite groups:	None.
Unique study design:	None reported.
Deviation from study protocol:	None reported.

Reference ID: 3175869

Table 9. Summary of study design in Study Number PRO3100NC108.

Group	Number of Males	Dose Route	Dosage Form	Dose Level (mg/kg)	Dose Volume (mL/kg)	Plasma Sampling Schedule
1	6	IV	Solution[a]	20	2	See below[c]
2	6	PO	Solution[b]	20	2	See below[d]
[a] MDV3100 (b) (4) lot 09080067) was dissolved in 50% polyethylene glycol 400 (PEG 400) / 20% ethanol (200 proof) / 30% Sterile Water for Injection, USP						
[b] MDV3100 ((b) (4) lot 09080067) was dissolved in 100% (b) (4)						
[c] IV PK time points: 0.25, 0.5, 1, 3, 6, 12, 24, 36, 48, 60, and 72 hours post-dose						
[d] PO PK time points: 1, 3, 6, 12, 24, 36, 48, 60, and 72 hours post-dose						

[Excerpted from Applicant's Table 1 in Study Report No. PRO3100NC108.]

Observations

Blood Sample Collection	Samples were collected from animals administered intravenous MDV3100 at 0.25, 0.5, 1, 3, 6, 12, 24, 36, 48, 60, and 72 hours after dosing. Samples were collected from animals administered oral MDV3100 at 1, 3, 6, 12, 24, 36, 48, 60, and 72 hours after dosing. Blood was collected into tubes containing K_3EDTA.
Bioanalytical Procedures	Plasma samples were analyzed and quantified by high performance liquid chromatography (HPLC) and tandem mass spectrometry. The lower limit of quantitation (LLOQ) was reported to be 0.0100 μg/mL.
Pharmacokinetics Analysis	PK parameters were estimated using WinNonlin (Version 5.2, Pharsight Corp., Mountain View, CA). For the IV dose group, a two-compartment model was used with instantaneous (bolus) input into the central compartment, first-order distribution between the central and peripheral compartments, and first-order elimination from the central compartment. For the oral dose group, PK parameters were calculated by standard non-compartmental methods.

Results

In Sprague-Dawley rats, following a single oral dose of 20 mg/kg MDV3100, the mean C_{max}, T_{max}, and $T_{1/2}$ values were 11.1, 6.0, and 9.79, respectively.

Table 10. Summary of PK parameters following administration of a single dose of MDV3100 in male Sprague-Dawley rats (Study Number PRO3100NC108).

Intravenous

Rat Number	CL (mL/h/kg)	Vc (mL/kg)	Vss (mL/kg)	MRT (h)	$AUC_{0\text{-}inf}$ (µg.h/mL)	α-Phase		β-Phase	
						α $t_{1/2}$ (h)	α %AUC	β $t_{1/2}$ (h)	β %AUC
401	(b) (4)								
402									
403									
404									
405									
406									
Mean	86.7	737	1110	12.9	232	0.404	2%	9.10	98%
SD	6.03	164	58.2	0.967	16.1	0.283	1%	0.605	1%
Geo. Mean[a]	86.5	722	1110	12.8	231	0.334	2%	9.08	98%

[a] Geometric mean

Oral

Rat Number	C_{max} (µg/mL)	t_{max}[a] (h)	$AUC_{0\text{-}t}$ (µg.h/mL)	$AUC_{0\text{-}inf}$ (µg.h/mL)	$t_{1/2}$ (h)	F (%)
407	(b) (4)					
408						
409						
410						
411						
412						
Mean	11.1	6.0	224	225	9.79	97.4
SD	1.11	6.0 - 6.0	40.6	41.7	1.60	18.1
Geometric Mean	11.1	NA	221	222	9.67	96.1
95% CI Lower Mean	9.98	NA	181	182	8.10	78.8
95% CI Upper Mean	12.3	NA	266	269	11.5	116

NA, not applicable

[a] For t_{max}, the median and range of observed values (minimum to maximum) are reported rather than the mean and SD.

[Excerpted from Applicant's Tables 4 and 5 in Study Number PRO3100NC108]

Study title: Absorption, distribution, and excretion after a single oral administration of ^{14}C-MDV3100 to rats.

Study no.:	9785-ME-003 ([redacted] (b) (4) Study Number 8227307)
Study report location:	eCTD Section 4.2.2.2.
Conducting laboratory and location:	[redacted] (b) (4)
Date of study initiation:	Not reported.
GLP compliance:	No.
QA statement:	Yes.
Drug, lot #, and % purity:	MDV3100, Lot No. 09090046 ^{14}C-MDV3100, Lot No. 3620101, Radiopurity = 96.4%

Key Study Findings

- ^{14}C-MDV3100-derived radioactivity was rapidly and widely distributed to most tissues, with the highest concentrations of radioactivity observed in liver, fat, stomach, adrenal gland, Harderian gland, small intestine, and kidney.
- ^{14}C-MDV3100-derived radioactivity was excreted by a combination of urinary and fecal routes.
- Fecal elimination was primarily through the bile and enterohepatic recirculation of ^{14}C-MDV3100-derived radioactivity was observed.

Methods

Doses:	30 mg/kg
Frequency of dosing:	Single dose
Route of administration:	Groups 1 -4: Oral gavage Group 5: Intraduodenal via cannula
Dose volume:	2 ml /kg
Formulation/Vehicle:	[redacted] (b) (4)
Species/Strain:	Rat/Sprague-Dawley [Hla(SD)CVF]
Number/Sex/Group:	4 – 21 male rats/group (See Table 11, below)
Age:	7 – 8 weeks old
Weight:	271 – 306 g (non-cannulated rats) 317 – 342 g (bile duct-cannulated rats)
Satellite groups:	None.
Unique study design:	None.
Deviation from study protocol:	None deemed to have significantly impacted the conduct of this study or interpretation of study results.

Table 11. Summary of study design in Study Number 9785-ME-003.

Phase/ Group	Number of Male Animals	Dose Route	Target Dose Level (mg/kg)	Target Dose Volume (mL/kg)	Samples Collected
1/1	21	Oral	30	2	Blood and Tissues
1/2	14	Oral	30	2	Blood and Carcass for WBA
1/3	4	Oral	30	2	Urine and Feces
1/4	4 BDC	Oral	30	2	Bile, Urine, and Feces
2/5[a]	4 BDC	Intraduodenal	NA[b]	NA[b]	Bile, Urine, and Feces

BDC Bile duct-cannulated.
WBA Whole-body autoradiography.
Note: The dose was approximately 4 MBq/kg (108 µCi/kg).
a There were 14 days between the end of Phase 1 and the beginning of Phase 2, which was designed to measure enterohepatic recirculation, and was performed since bile excretion in Phase 1 was greater than 30% of dose.
b The amount of bile administered was 0.5 mL/animal (0.391 ± 0.006 µCi/animal).

[Excerpted from Applicant's table on page 11 of Study Report Number 9785-ME-003]

Observations

Clinical Signs	Twice-daily for mortality and signs of pain and distress. One-daily for cageside observations for general health and appearance.
Body Weights	At baseline and on day of dosing for the purposed of dosing calculations.
Blood and Tissue Collection[1] (Group 1)	Three animals/time point were sacrificed by exsanguination (cardiac puncture) under isoflurane anesthesia at 1, 4, 8, 24, 48, 72, and 168 hours post-dose. Blood samples were collected into tubes containing K_2EDTA to obtain plasma. Tissues were collected from each animal.
Blood and carcasses for WBA (Group 2)	Two animals/time point were prepared for WBA at 1, 4, 8, 24, 48, 72, and 168 hours post-dose. Animals were sacrificed by exsanguination (cardiac puncture) under isoflurane anesthesia and blood samples were collected into tubes containing K_2EDTA to obtain plasma. Only one animal/time point was analyzed by WBA.
Urine and Feces (Group 3)	Urine was collected at 0-8 and 8-24 hours post-dose and at 24-hour intervals through 168 hours post-dose. Feces were collected at 24-hour intervals through 168 hours post-dose.
Urine, Feces, and Bile (Group 4)	Urine, feces, and bile samples were collected from all four animals in Group 4 for analysis of excretion of radioactivity and mass balance.[2] Urine was collected at 0-8 and 8-24 hours post-dose and at 24-hour intervals through 168 hours post-dose. Feces were collected at 24-hour intervals through 168 hours post-

	dose. Bile was collected at 0-8 and 8-24 hours post-dose and at 24-hour intervals through 168 hours post-dose.
Urine, Feces, and Bile (Phase2, Group 5)	Phase 2 was performed 14 days after the completion of Phase 1 collections. Urine, feces, and bile samples were collected from four animals for analysis of excretion of radioactivity and mass balance. Urine was collected at 0-8 and 8-24 hours post-dose and at 24-hour intervals through 1172 hours post-dose. Feces were collected at 24-hour intervals through 172 hours post-dose. Bile was collected at 0-8 and 8-24 hours post-dose and at 24-hour intervals through 172 hours post-dose.

[1] Tissues collected from Group 1: adrenals, aorta, blood, bone marrow, cerebellum, cerebrum, epididymis, eyes, fat, femur, harderian glands, heart, hypothalamus, kidneys, large intestine, liver, lungs, pancreas, pituitary gland, plasma, prostate gland, skeletal muscle, skin, small intestine, spleen, stomach, submaxillary glands, testis, thymus, and thyroid gland.

[2] Except Animal No. B21981 which was found dead the morning of the 48-hour collection time point. Data from this animal were excluded from interpretation of results and calculations of mean standard deviations.

Results

Mortality

Group 4 Animal No. B21981 was found dead the morning of the 48-hour collection time point. This animals was noted to have:

- Low qualitative food consumption during the 0- to 24-hour post-dose period.
- Small amount of urine present at the 8- to 24- to 48-hour collection intervals.
- Few feces present at the 0- to 24- to 48-hour collection intervals.
- No remarkable observations in standard necropsy.

Clinical Signs

There were no remarkable clinical signs noted in other surviving animals.

Pharmacokinetics and Tissue Distribution of Radioactivity (Group 1)

- ^{14}C-MDV3100-derived radioactivity was eliminated from the blood and plasma with $t_{1/2}$ values of 8.94 and 8.56, respectively.
- ^{14}C-MDV3100-derived radioactivity distributed into all collected tissues by 1 hour post-dose after oral administration and concentrations of radioactivity were quantifiable through 48 hours post-dose. By 72 hours post-dose, concentrations of radioactivity were quantifiable in all collected tissues with the exception of the cerebellum and pituitary gland. Radioactivity was BLQ in most tissues by 168 hours post-dose. C_{max} ranged from 1 to 8 hours post-dose. Tissues with the highest mean

Reference ID: 3175869

concentration at 4 hours post-dose were liver, fat, stomach, adrenal glands, Harderian gland, small intestine, and kidneys. Elimination $t_{1/2}$ values in tissues ranged from 7.27 hours in the hypothalamus to 29.5 hours in the liver.

Table 12. Pharmacokinetic parameters for radioactivity in blood, plasma, and tissues collected from male rats after a single oral administration of 30 mg/kg ^{14}C-MDV3100 in Study Number 9785-ME-0003.

Tissue or matrix	T_{max} (hours)	C_{max} (ng eq/g)	$t_{½}$ (hours)	AUC_{0-t} (ng eq×hours/g)	$AUC_{0-\infty}$ (ng eq×hours/g)	AUC_{0-t} tissue/ AUC_{0-t} plasma
Adrenal gland(s)	8	56900	16.8	1324917	1325316	3.18
Aorta	4	21700	NC[a]	490736	NC[a]	1.18
Blood	8	9030	8.94	219067	220245	0.525
Bone marrow	8	9620	7.89	213650	214267	0.512
Cerebellum	4	10800	9.08	206548	212760	0.495
Cerebrum	4	10500	8.06	201494	201997	0.483
Epididymis	8	26000	7.94	583156	584736	1.40
Eye(s)	8	4740	10.4	118730	119973	0.285
Fat	8	102000	16.2	2064588	2064967	4.95
Femur (both)	4	7860	8.75	167332	168071	0.401
Harderian gland	4	50900	19.9	1151450	1152311	2.76
Heart	4	23500	8.11	493982	495457	1.18
Hypothalamus	4	10900	7.27	207348	207647	0.497
Kidney(s)	4	39300	23.1	1197078	1200952	2.87
Large intestine	8	22200	9.93	581760	586990	1.39
Liver	4	78500	29.5	2654502	2684236	6.36
Lungs	4	19700	16.9	453663	453801	1.09
Muscle (skeletal)	4	13400	7.89	294723	295469	0.706
Pancreas	4	32900	8.08	757490	759762	1.82
Pituitary gland	4	21100	10.7	433950	455804	1.04
Plasma	8	17800	8.56	417238	419017	1.00
Prostate gland	4	21600	18.4	480721	480943	1.15
Skin	8	16000	10.5	347102	350389	0.832
Small intestine	4	46000	18.4	1146204	1147015	2.75
Spleen	4	11900	8.59	257931	258989	0.618
Stomach	1	97700	16.1	845163	846755	2.03
Submaxillary glands	4	26700	18.6	611111	611435	1.46
Testis(es)	4	11000	8.37	244786	245677	0.587
Thymus	4	13600	21.9	289328	289605	0.693
Thyroid	4	24900	9.23	536634	539392	1.29

eq Equivalents ^{14}C-MDV3100.
NC Not calculated.
a $t_{1/2}$ and $AUC_{0-\infty}$ could not be calculated, as no discernable terminal elimination phase was observed.

[Excerpted from Applicant's Table 10 in Study Report Number 9785-ME-0003]

Tissue Distribution of Radioactivity by Whole-Body Autoradiography (Group 2)

- Mean blood:plasma concentration ratios of total radioactivity ranged from 0.481 to 0.659, consistent with those observed in Group 1 animals.
- ^{14}C-MDV3100-derived radioactivity distributed into most tissues by 1 hour post-dose after oral administration. Concentrations of radioactivity were quantifiable in most

tissues through 48 hours post-dose. Radioactivity was BLQ in most tissues by 168 hours post-dose, with the exception of eye lens and liver. C_{max} values were similar to those observed in Group 1. Tissues with the highest mean concentration at 4 hours post-dose, excluding gastrointestinal contents, were liver, urine, adrenal gland cortex, subcutaneous fat, kidney, kidney medulla, and adrenal gland.

Excretion and Mass Balance after Oral Administration of ^{14}C-MDV3100 (Groups 3 and 4)

- The overall mean recovery of radioactivity was 97.20% for bile duct-intact rats through 168 hours post-dose.
    - Most radioactivity (91.90%) was excreted by 72 hours after dose administration by combined urinary (44.20% of administrated dose) and fecal (49.80% of administered dose) routes of elimination.

- The overall mean recovery of radioactivity was 98.00% for bile duct-cannulated rats through 168 hours post-dose.
    - Most radioactivity (89.10%) was excreted by 48 hours after dose administration.
    - Mean biliary, fecal, and urinary excretion of ^{14}C-MDV3100-derived radioactivity accounted for 50.60%, 8.39%, and 36.60% of the administered radioactivity through 168 hours post-dose, respectively.

Table 13. Mean cumulative percent of radioactive dose after a single oral administration of 30 mg/kg ^{14}C-MDV3100 to male rats in Study Number 9785-ME-0003.

Bile duct-intact animals (Group 3)

	Percent of Radioactive Dose							
	Urine		Feces		Other[a]		Total	
Time Point	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0 - 8 h	5.12	2.70	NA	NA	NA	NA	5.12	2.70
0 - 24 h	31.30	4.35	22.20	4.84	1.46	0.99	55.00	3.58
0 - 48 h	41.40	6.65	44.20	6.16	1.87	0.99	87.40	1.68
0 - 72 h	43.60	6.99	48.30	6.39	2.02	1.05	93.80	1.08
0 - 96 h	44.00	7.04	49.20	6.49	2.06	1.05	95.20	0.79
0 - 120 h	44.10	7.04	49.50	6.50	2.10	1.06	95.60	0.71
0 - 144 h	44.10	7.03	49.70	6.54	2.13	1.07	95.90	0.66
0 - 168 h	44.20	7.03	49.80	6.56	2.87	1.91	97.20	0.41

h Hours.
NA Not applicable.
SD Standard deviation.
Notes: In the carcass, 0.39% ± 0.05% of the radioactive dose was detected at 168 hours.
All values are reported to 3 significant figures and 2 decimal places, for a total of up to 5 digits; only the first 3 digits are significant.
a Sum of cage rinse, cage wash, and cage wipe, as applicable.

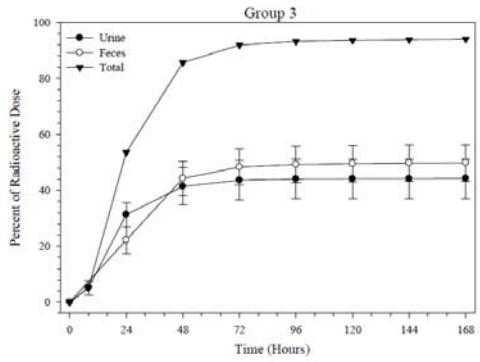
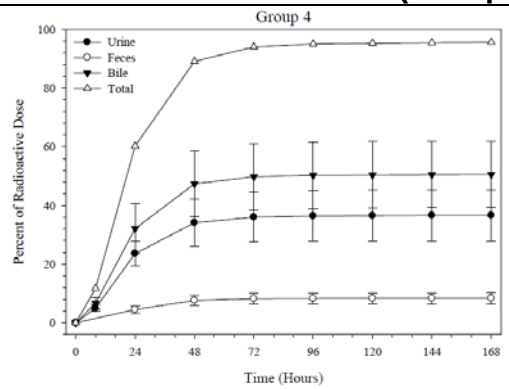
Bile duct-cannulated animals (Group 4)

	Percent of Radioactive Dose											
	Urine		Feces		Bile		Other[a]		Bile + Urine		Total	
Time Point	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0 - 8 h	5.03	1.12	NA	NA	6.70	2.06	NA	NA	11.70	1.09	11.70	1.09
0 - 24 h	23.60	4.21	4.52	1.26	32.10	8.50	1.09	0.87	55.60	4.30	61.20	2.67
0 - 48 h	34.10	8.01	7.60	1.68	47.40	11.30	1.53	1.23	81.40	3.35	90.50	0.85
0 - 72 h	36.00	8.48	8.23	1.81	49.80	11.30	1.70	1.31	85.80	2.84	95.70	0.25
0 - 96 h	36.40	8.61	8.32	1.84	50.30	11.30	1.72	1.31	86.60	2.65	96.70	0.24
0 - 120 h	36.50	8.68	8.35	1.85	50.40	11.30	1.75	1.33	87.00	2.58	97.10	0.29
0 - 144 h	36.60	8.71	8.37	1.85	50.50	11.20	1.78	1.35	87.10	2.54	97.30	0.37
0 - 168 h	36.60	8.72	8.39	1.86	50.60	11.20	2.14	1.54	87.20	2.53	98.00	0.57

h Hours.
NA Not applicable.
SD Standard deviation.
Notes: In the carcass, 0.28% ± 0.01% of the radioactive dose was detected at 168 hours.
The mean and standard deviation were calculated using data from Animal Nos. B21978, B21979, and B21980. Animal No. B21981 was excluded from these calculations.
All values are reported to 3 significant figures and 2 decimal places, for a total of up to 5 digits; only the first 3 digits are significant.
a Sum of cage rinse, cage wash, cage wipe, bile cannula, and jacket rinse, as applicable.

[Excerpted from Applicant's Tables 23 and 24 in Study Report Number 9786-ME-0003]

Table 14. Mean cumulative percent of radioactive dose in urine and feces after a single oral administration of 30 mg/kg ^{14}C-MDV3100 to male rats in Study Number 9785-ME-0003.

Bile duct-intact animals (Group 3)	Bile duct-cannulated animals (Group 4)
 Note: The urine and feces values presented in this figure are the mean ± standard deviation (n = 4).	 Notes: The urine, feces, and bile values presented in this figure are the mean ± standard deviation (n = 3). (Values were calculated using data from Animal Nos. B21978, B21979, and B21980. Animal No. B21981 was excluded from the mean and standard deviation calculations.)

[Excerpted from Applicant's Figures 8 and 9 in Study Report Number 9786-ME-0003]

Excretion and Mass Balance after Intraduodenal Administration of Group 4 bile (Groups 5)

After an intraduodenal dose of bile obtained from Group 4 animals into bile duct-cannulated Group 5 rats, the cumulative amount of radioactivity absorbed and subsequently excreted into bile and urine was 74.10%, indicative of enterohepatic recirculation of ^{14}C-MDV310-derived radioactivity.

Dosing Formulation Analysis

- Radiopurity and Stability
  - HPLC analysis showed the radioputity of ^{14}C-MDV3100 to be 96.4% pre- and post-dose.

- Adsorption
  - The following table summarizes adsorption of the test article to pipette tips, glassware, containers, and dosing apparatus:

^{14}C-MDV3100 Concentration	Apparatus Tested	Recovery (%)
10 µg/mL	Pipette Tips	101
	Glassware	43.2
	Polypropylene	51.4
	Dosing Apparatus	102

Note: For adsorption experiments, 1 mL is considered equivalent to 1 g.

[Excerpted from Applicant's table on page 22 of Study Report Number 9785-ME-0003.]

- Concentration and Homogeneity
  - Samples were shown to be homogenous during the dosing periods.

- Samples that were analyzed for radioactivity concentration and homogeneity met the acceptance criteria of ± 10% and 5% of theoretical, respectively.

Study title: Pharmacokinetics study in dogs of single-dose MDV3100 formulated in PEG 400 and ethanol and given intravenously or formulated as either a CMC suspension or (b) (4) solution and given orally.

Study no.:	PRO3100NC11 ((b) (4) Study Number 1284-001)
Study report location:	eCTD Section 4.2.2.2.
Conducting laboratory (in-life) and location:	(b) (4)
Date of study initiation:	Not reported
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	MDV3100, Lot No. 194-170-003

Key Study Findings

- Following a single oral dose in dogs, MDV3100 exhibited a fast absorption rate and a relatively slow rate of elimination ($T_{1/2}$ ranging from 1.34 – 1.71 days).
- MDV3100 formulated in (b) (4) has greater bioavailability, leading to higher exposure in dogs, when compared to MDV3100 formulated in CMC/Tween suspension.

Methods

Doses:	3 mg/kg
Frequency of dosing:	Single dose
Route of administration:	Intravenous bolus or oral gavage
Dose volume:	0.3 mL/kg
Formulation/Vehicle:	Intravenous: 50% PEG 400, 20% ethanol, and 30% sterile water for injection Oral: 1% carboxymethylcellulose (CMC) with 0.1% Tween 80 or (b) (4)
Species/Strain:	Dog/Beagle
Number/Sex/Group:	3 male dogs/group
Age:	Not reported.
Weight:	9 – 11 kg
Satellite groups:	None.
Unique study design:	None.
Deviation from study protocol:	None reported.

Reference ID: 3175869

Table 15. Study design in Study Number PRO3100NC11.

Group	Number of Males	Dose Route	Vehicle	Dose Level (mg/kg)	Dose Volume (mL/kg)	Sampling
1	3	IV	c	3	0.3	Plasma[a]
2	3	Oral, gavage	d	3	0.3	Plasma[b]
3	3	Oral, capsule	e	3	0.3	Plasma[b]
4	3	Oral, capsule	f	3	0.3	Plasma[b]

[a] IV: Plasma collected pre-dose and at 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours post-dose.
[b] PO: Plasma collected pre-dose and at 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours post-dose
[c] 50% PEG 400 / 20% ethanol (200 proof) / 30% sterile water for injection (USP)
[d] 1% carboxymethylcellulose (CMC) and 0.1% Tween 80 in deionized water
[e] 100% (b) (4) (b) (4)
[f] 90% (b) (4) 10% Tween 80

[Excerpted from Applicant's Table 1 in Study Report Number PRO3100NC11]

Observations

Blood Sample Collection	Intravenous: blood samples were collected pre-dose and at 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 after dosing. Oral: blood samples were collected pre-dose and at 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 after dosing. Samples were collected from jugular vein and placed in tubes containing K_3EDTA to obtain plasma.
Bioanalytical Procedures	Plasma samples were analyzed by high performance liquid chromatography (LC) in conjunction with a triple quadrupole mass spectrometer that used electrospray ionization in tandem with positive ionization (MS/MS). The lower limit of quantitation (LLOQ) was 0.0100 μg/mL. The quantitative range of the assay was 0.0100 to 8 μg/mL.
Pharmacokinetics Analysis	PK modeling was performed using WinNonlin (version 4.0.1: Pharsight Corp., Mountain View, CA).

Results

- Following a single dose intravenous administration of MDV3100
  - C_{max} ranged from 4 to 6 μg/mL
  - Plasma concentrations of MDV3100 remained above LLOQ for 6 to 7 days post-dose.

The table below summarizes results from this study.

Table 16. Plasma PK parameters after a single dose administration of 3 mg/kg MDV3100 in male Beagle dogs.

IV Dose Group	C_{max} (µg/mL)	$T_{1/2}$ (days)	V_{ss} (mL/kg)	CL (mL/hr/kg)
Mean	4.60	1.46	1200	23.9
SD	*1.14*	*0.800*	*762*	*5.01*

PO Dose Groups	C_{max} (µg/mL)	AUC_{last} (µg/mL·hr)	$T_{1/2}$ (days)	F[a]
CMC/Tween Suspension				
Mean	0.403	21.9	1.34	18.3%
SD	*0.344*	*20.8*	*0.710*	*16.6%*
(b) (4)				
Mean	3.03	88.5	1.39	72.5%
SD	*1.27*	*41.9*	*0.288*	*32.9%*
(b) (4) Tween				
Mean	2.99	101	1.71	85.4%
SD	*2.13*	*47.8*	*0.205*	*40.6%*

a, Derived by dividing the mean CL with IV dosing (23.9 mL/kg/hr) by CL/F.

[Excerpted from Applicant's table on page 4 of Study Report Number PRO3100NC11]

Study title: Single-dose oral pharmacokinetics study of six formulation of MDV3100 in male beagle dogs: five (b) (4) based liquid formulation (four solutions and one emulsion) administered by gavage (20 mg/kg) and one particulate formulation administered in a hard gelatin capsule (6 mg/kg).

Study no.:	PRO3100NC53
Study report location:	eCTD Section 4.2.2.2.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	
GLP compliance:	No.
QA statement:	No.
Drug, lot #, and % purity:	MDV3100, Lot No. EWK-K-32(1)

Key Study Findings

- Oral availability of MDV3100 is higher when dosed as a solution than when dosed as a particulate formulation.
- MDV3100 formulated in (b) (4) has a high oral availability, which is not increased by combining (b) (4) with other solvents or surfactant used in this study.

Methods

Doses:	6 or 20 mg/kg
Frequency of dosing:	Single dose
Route of administration:	Oral
Dose volume:	0.5 mg/mL (Groups 1 – 5)
Formulation/Vehicle:	See Table 17 for a list of formulations used in this study.
Species/Strain:	Dog/Beagle
Number/Sex/Group:	3 male dogs/group
Age:	Not reported.
Weight:	10 – 14 kg
Satellite groups:	None.
Unique study design:	None reported.
Deviation from study protocol:	None reported.

Reference ID: 3175869

Table 17. Study design in Study Number PRO3100NC53.

Dose Group [a]	Formulation Designation [f]	Composition of Formulation	MDV3100 Dose (mg/kg)
Solution 1 [c, d]	Formulation A, 100% (b) (4) Lot F-3020-038D	(b) (4)	20
Solution 2 [c, d]	Formulation B, F-3020-009 I [g], Lot F-3020-038A		20
Solution 3 [c, d]	Formulation C, F-3020-009 II [g], Lot F-3020-038B		20
Solution 4 [c, d]	Formulation D, F-3020-009 III [g], Lot F-3030-038C		20
Emulsion [c]	Formulation E, F-3020-030 A [g], Lot F-3020-039 (SED)		20
Particulate Formulation [e]	Formulation F, F-3020 [g] Lot F-3020-040		6

[a] In each dose group, three male beagle dogs received a single oral dose of MDV3100 and plasma PK samples were collected pre-dose and at 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours post-dose.

[b] The dose group nomenclature in the in-life and bioanalytical records correspond to the dose groups here as follows: "Solution 1" = Group 1; "Solution 2" = Group 2; "Solution 3" = Group 3; "Solution 4" = Group 4; "Emulsion" = Group 5; "Particulate Formulation" = Group 6.

[c] Dosed by oral gavage via a gastric tube in a dose volume of 0.5 mL/kg.

[d] (b) (4)

[e] (b) (4) gelatin capsules (one capsule/dog).

[f] Per records provided by the producer of the formulations, (b) (4) (b) (4)

[g] Reflected in the in-life records.

[h] (b) (4)

[Excerpted from Applicant's Table 1 in Study Report Number PRO3100NC53]

Observations

Blood Sample Collection	Blood samples were collected pre-dose and at 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 after dosing. Samples were collected from the jugular vein and placed in tubes containing K_3EDTA to obtain plasma.

Bioanalytical Procedures	Plasma samples were analyzed by LC-MS/MS. The lower limit of quantitation (LLOQ) was 0.0100 μg/mL. The quantitative range of the assay was 0.0100 to 10 μg/mL.
Pharmacokinetics Analysis	PK modeling was performed using WinNonlin (version 5.2: Pharsight Corp., Mountain View, CA).

Results

The table below summarizes results from this study.

Table 18. Plasma PK parameters and oral bioavailability after a single dose administration of MDV3100 in various vehicles in male beagle dogs.

Dose Group	MDV3100 Dose (mg/kg)	Dog	C_{max} (μg/mL)	t_{max} [a] (h)	AUC_{0-24h} (μg.h/mL)	AUC_{0-7d} (μg.h/mL)	$t_{1/2}$ (days)
Solution 1	20	201	7.92	4	120	341	1.38
		202	20.1	2	236	633	1.62
		203	16.8	1	230	730	1.28
		Mean	15.0	2	195	568	1.43
		SD	6.31	(1 to 4)	65.6	203	0.18
Solution 2	20	204	13.6	6	172	620	1.80
		205	5.64	24	75.5	254	1.27
		206	16.4	24	241	1040	1.95
		Mean	11.9	24	163	638	1.68
		SD	5.59	(6 to 24)	82.9	394	0.36
Solution 3	20	207	3.38	0.5	36.0	133	2.22
		208	7.95	2	103	397	1.96
		209	17.1	24	251	1010	2.12
		Mean	9.47	2	130	512	2.10
		SD	6.97	(0.5 to 24)	110	447	0.13
Solution 4	20	210	9.48	4	149	461	1.68
		211	4.74	2	58.4	196	2.22
		212	9.53	2	141	435	1.11
		Mean	7.92	2	116	364	1.67
		SD	2.75	(2 to 4)	50.3	146	0.55
Emulsion	20	213	10.2	2	168	415	1.13
		214	5.17	2	65.6	214	1.37
		215	11.2	1	165	615	2.29
		Mean	8.85	2	133	415	1.60
		SD	3.23	(1 to 2)	58.4	201	0.61
Particulate Formulation	6	216	1.29	2	51.9	16.2	1.45
		217	0.827	24	58.4	11.5	1.80
		218	1.02	6	55.6	14.3	1.78
		Mean	1.05	6	55.3	14.0	1.68
		SD	0.235	(2 to 24)	3.28	2.39	0.20

[a] For t_{max}, the median and range (minimum to maximum) are reported.

Dose Group	Composition of Formulation	%Relative Bioavailability
Solution 1 [a,b]	(b) (4)	100% ± 36%
Solution 2 [b]		112% ± 69%
Solution 3 [b]		90% ± 79%
Solution 4 [b]		64% ± 26%
Emulsion		73% ± 35%
Particulate Formulation		8% ± 1%

[a] The mean dose-normalized $AUC_{0\text{-}7\,d}$ for Solution 1 was used as the reference treatment in the calculations of %Relative Bioavailability.

[b] (b) (4)

[c]

Values are the means ± SD of n=3 dogs.

[Excerpted from Applicant's Tables 8 and 9 in Study Report Number PRO3100NC53]

Study title: Blood and plasma concentrations and excretion of radioactivity after a single oral administration of ^{14}C-MDV3100 to dogs.

Study no.:	9785-ME-0002 ((b) (4) Study Number 8227309)
Study report location:	eCTD Section 4.2.2.2.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Not reported.
GLP compliance:	No.
QA statement:	Yes
Drug, lot #, and % purity:	MDV3100, Lot No. 09090046 ^{14}C-MDV3100, Lot No. 3620101, 95.9% radiopurity

Table 19. Summary of study design in Study Number 9785-ME-0002.

Group	Number of Male Animals	Dose Route	Target Dose Level (mg/kg)	Target Dose Volume (mL/kg)	Samples Collected
1	3	Oral	20	0.44	Blood, urine, and feces
2	3 BDC	Oral	20	0.44	Bile, urine, and feces

BDC Bile duct-cannulated.
Note: The target dose was approximately 2 MBq/kg (54 µCi/kg).

[Excerpted from table on page 9 of Study Report No. 9785-ME-0002]

Key Study Findings

Following a single oral administration in male beagle dogs, ^{14}C-MDV3100 was well-absorbed, with a combined sum of urinary and biliary excretion of 62.00 – 68.30%, and ^{14}C-MDV3100-derived radioactivity was quantitatively excreted by a combination of urinary, fecal, and biliary routes.

Methods

Doses: 20 mg/kg
Frequency of dosing: Single dose
Route of administration: Oral
Dose volume: 0.44 mL/kg
Formulation/Vehicle: (b) (4)
Species/Strain: Dog/Beagle
Number/Sex/Group: 3 male animals/group
Age: 7 months
Weight: 10.1 – 11.5 kg
Satellite groups: None.
Unique study design: Half of the animals underwent bile duct cannulation surgery.
Deviation from study protocol: None reported.

Observations

Clinical Signs	Twice-daily for mortality and signs of pain and distress. One-daily for cage-side observations for general health and appearance.
Blood, Urine, and Feces (Group 1)	Blood was collected via a jugular vein into tubes containing K_2EDTA at 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 120, 168, 216, 264, and 336 hours post-dose. Urine was collected at 0-8 and 8-24 hours post-dose, and at 24-hour intervals through 504 hours post-dose. Feces were collected at 24-hour intervals through 504 hours post-dose.

Urine, Feces, and Bile (Group 2)	Urine was collected at 0-8 and 8-24 hours post-dose and at 24-hour intervals through 168 or approximately 173 hours post-dose. Feces were collected at 24-hour intervals through 168 or approximately 173 hours post-dose. Bile was collected at 0-8 and 8-24 hours post-dose and at 24-hour intervals through 168 or approximately 173 hours post-dose.

Results

Mortality

None

Clinical Signs

Sporadic incidences of vomitus containing food, liquid feces, and non-formed feces were noted.

Concentrations of radioactivity and pharmacokinetics in blood and plasma

- The calculated mean C_{max} of radioactivity in plasma after a single 20 mg/kg oral dose of ^{14}C-MDV3100 was 24100 ng equivalents ^{14}C-MDV3100/g and the calculated mean T_{max} was at 6.00 hours post-dose.
- The calculated mean C_{max} of radioactivity in plasma after a single 20 mg/kg oral dose of ^{14}C-MDV3100 was 11867 ng equivalents ^{14}C-MDV3100/g and the calculated mean T_{max} was at 6.67 hours post-dose.
- Mean blood:plasma concentration ratios ranged from 0.456 to 0.552 over the course of the study, indicating no partitioning into cellular component of blood.
- The mean terminal elimination half-lives (t1/2) of radioactivity in blood and plasma, as determined by the area under the concentration-time curve (AUC0-∞), were 682333 and 1316667 ng equivalents x hours/g.

Excretion and Mass Balance

- The mean recovery of radioactivity in bile duct-intact male dogs was 92.30% thorough 504 hours post-dose.
    - The majority (approximately 87%) of ^{14}C-MDV3100-derived radioactivity was excreted by 192 hours after dose administration.
    - The mean urinary and fecal excretion were 62.00% and 22.30% of the administered radioactivity, respectively.

- The mean recovery of radioactivity in bile duct-cannulated male dogs was 96.5% thorough 168 hours post-dose.
    - The majority (approximately 89%) of ^{14}C-MDV3100-derived radioactivity was excreted by 96 hours after dose administration.

Reference ID: 3175869

- The mean urinary, fecal, and biliary excretion were 20.4%, 23.30%, and 47.90% of the administered radioactivity, respectively.

Dosing Formulation Analysis

- Dosing formulation was homogenous during the dosing periods.
- Samples that were analyzed for radioactivity concentration and homogeneity met the acceptance criteria of ± 10% and 5% of theoretical, respectively.

Study title: Identification and quantification of MDV3100 and its metabolites in whole brain homogenates after 7-day repeat oral dosing of ^{14}C-MDV3100 in rats.

Study no.:	PRO3100NC84 (b) (4) Study Number 8211209)
Study report location:	eCTD Section 4.2.2.3.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Not reported
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	MDV3100, Lot No. (b) (4) 09080067 ^{14}C-MDV3100, Lot No. 3620101

Key Study Findings

- The mean blood:plasma and brain:plasma ratios for total radioactivity were 0.618 and 0.560, respectively.
- Feces was the major route of excretion of radioactivity (57.8% of administered dose).
- Based on metabolite profiling, ^{14}C-MDV3100 was metabolized via oxidation, hydrolysis, and *N*-demethylation.
- MDPC0001 and MDPC0002 were two major metabolites identified in plasma, brain, and CSF.
- MDV3100 and MDPC0002 appear to partition into brain and achieve concentrations that are roughly equivalent to those in plasma, while MDPC0001 appears to have low penetration into brain.
- The following table summarizes the concentration ratios of MDV3100 and its metabolites in brain and CSF relative to plasma:

Metabolite Designation	Brain:Plasma Ratio	CSF:Plasma Ratio
MDV3100	0.841	0.0271
MDPC0001	0.0211	0.00416
MDPC0002	1.13	0.0529
MDPC0003	0.921	0.0943
MDPC0004	1.22	0.100
MDV3105	NC	NC
MDV3106	0.230	0.00904

NC Not calculated; the ratio could not be computed because MDV3105 was not detected in brain.

[Excerpted from Applicant's table on page 15 of Study Report No. PRO3100NC84]

Methods

Doses: 100 mg/kg/day (250 μCi/kg/day)
Frequency of dosing: Once-daily for 7 days.
Route of administration: Oral
Dose volume: 2.2 mL/kg
Formulation/Vehicle: (b) (4)
Species/Strain: Rat/Sprague-Dawley (Hsd:Sprague Dawley SD)
Number/Sex/Group: 3 male animals/group
Age: 8 weeks
Weight: 288 – 294 g
Satellite groups: None.
Unique study design: None.
Deviation from study protocol: None deemed to have significantly impacted the conduct of this study or interpretation of study results.

Table 20. Summary of study design in Study Number PRO3100NC84.

Group	Number of Male Animals	Dose Route	Target Dose Level (mg/kg/day)[a]	Target Dose Level (μCi/kg/day)[a]	Target Dose Volume (mL/kg)	Samples and Collection Schedule[b]
1	3	Oral	100	250	2.2	Urine and feces during the 24 hours post-dose on Day 6 Blood, brain, and CSF at 4 hours post-dose on Day 7

CSF Cerebrospinal fluid.
a Animals were dosed once daily for 7 consecutive days.
b Animals were sacrificed by exsanguination (cardiac puncture) under isoflurane anesthesia.

[Excerpted from Applicant's table on page 8 of Study Report No. PRO3100NC84]

Observations and Results

Mortality

None.

Clinical Signs

No remarkable clinical signs were noted.

Concentrations of Radioactivity in Blood, Plasma, Brain, and Cerebrospinal Fluid.

- At 4 hours post-dose on Day 7, the mean concentrations of radioactivity in blood and plasma were 21000 and 33900 nq equivalents ^{14}C-MDV3100/g, respectively.
- The mean concentrations of radioactivity in brain and CSF were 18900 and 945 ng equivalents ^{14}C-MDV3100/g respectively.
- The mean blood:plasma ratio was 0.618 and the mean brain:plasma ratio was 0.560.

Excretion

During the 24-hour period post-dose on Day 6, the respective mean recoveries in urine and feces were 29.0% and 57.8% of the administered radioactivity on Day 6, respectively.

Metabolite Profiles of ^{14}C-MDV3100

- Plasma
    - Unchanged parent drug accounted for 54.59% of the plasma radioactivity, corresponding to concentration of 18200 ng equivalents/g.
    - MDPC0001 was the major circulating metabolite, accounting for 32.17% of the plasma radioactivity, corresponding to concentration of 10700 ng equivalents/g.
    - No other metabolites were present at ≥ 10% of the plasma radioactivity.
    - The table below summarizes the levels of metabolites detected in plasma in this study.

Reference ID: 3175869

Table 21. Summary of plasma radioactivity of ^{14}C-MDV3100 and its metabolites in Study Number PRO3100NC84.

Final Metabolite Designation	Peak Number	Retention Time (Minutes)	Collection Time (Day/Hours) 7/4
			Percent of Radioactivity Injected (% of Run)
MDPC0003	1	14.92	0.69[a]
MDV3106	2	15.92	4.05
MDPC0004	3	17.75	4.43
MDPC0002	4	18.92	2.61
MDV3105	5	20.75	1.12
MDV3100	6	22.58	54.59
MDPC0001	7	24.42	32.17
		Total	99.7
			Concentration (ng equivalents ^{14}C-MDV3100/g)
MDPC0003	1	14.92	229
MDV3106	2	15.92	1350
MDPC0004	3	17.75	1470
MDPC0002	4	18.92	868
MDV3105	5	20.75	372
MDV3100	6	22.58	18200
MDPC0001	7	24.42	10700
		ng equivalents/g quantitated:	33100
		ng equivalents/g in sample:	33900
		Extraction Recovery (%):	100
		Reconstitution Recovery (%):	98.1

a Value is below the established limit of quantitation (1% of run), but was reported due to the presence of MDPC0003 in brain and cerebrospinal fluid samples.

[Excerpted from Table 4-1 in Study Number PRO3100NC84]

- Brain
  - Unchanged parent drug accounted for 81.15% of the radioactivity in brain extracts, corresponding to concentration of 15300 ng equivalents/g.

- MDPC0004 was the major metabolite in brain extracts, accounting for 9.57% of the radioactivity in brain, corresponding to concentration of 1800 ng equivalents/g.
- The table below summarizes the levels of metabolites detected in brain in this study.

Table 22. Summary of brain radioactivity of ^{14}C-MDV3100 and its metabolites in Study Number PRO3100NC84.

Final Metabolite Designation	Peak Number	Retention Time (Minutes)	Collection Time (Day/Hours) 7/4
			Percent of Radioactivity Injected (% of Run)
MDPC0003	1	14.92	1.12
MDV3106	2	15.92	1.65
MDPC0004	3	17.75	9.57
MDPC0002	4	18.92	5.21
MDV3100	6	22.58	81.15
MDPC0001	7	24.58	1.20
		Total	99.9
			Concentration (ng equivalents ^{14}C-MDV3100/g)
MDPC0003	1	14.92	211
MDV3106	2	15.92	310
MDPC0004	3	17.75	1800
MDPC0002	4	18.92	980
MDV3100	6	22.58	15300
MDPC0001	7	24.58	226
	ng equivalents/g quantitated:		18800
	ng equivalents/g in sample:		18900
	Extraction Recovery (%):		100
	Reconstitution Recovery (%):		99.5

[Excerpted from Table 4-2 in Study Number PRO3100NC84]

- Cerebrospinal Fluid
  - Unchanged parent drug accounted for 59.61% of the radioactivity in the CSF, corresponding to concentration of 494 ng equivalents/g.
  - MDPC0004 was the major metabolite in the CSF, accounting for 17.75% of the radioactivity in the CSF, corresponding to concentration of 147 ng equivalents/g.
  - The table below summarizes the levels of metabolites detected in CSF in this study.

Table 23. Summary of CSF radioactivity of ^{14}C-MDV3100 and its metabolites in Study Number PRO3100NC84.

Final Metabolite Designation	Peak Number	Retention Time (Minutes)	Collection Time (Day/Hours) 7/4
			Percent of Radioactivity Injected (% of Run)
Unknown	CSF 1	11.75	3.91
MDPC0003	1	14.92	2.61
MDV3106	2	15.92	1.47
MDPC0004	3	17.58	17.75
MDPC0002	4	18.92	5.54
MDV3100	6	22.58	59.61
MDPC0001	7	24.92	5.37
		Total	96.3
			Concentration (ng equivalents ^{14}C-MDV3100/g)
Unknown	CSF 1	11.75	32.4
MDPC0003	1	14.92	21.6
MDV3106	2	15.92	12.2
MDPC0004	3	17.58	147
MDPC0002	4	18.92	45.9
MDV3100	6	22.58	494
MDPC0001	7	24.92	44.5
	ng equivalents/g quantitated:		798
	ng equivalents/g in sample:		945
	Centrifugation Recovery (%):		87.7

[Excerpted from Table 4-3 in Study Number PRO3100NC84]

Dosing Formulation Analysis

- The radiopurity of the dosing formulation was 99.0% and 98.8% on Day 1 (prior to first dose) and on Day 7 (after the final dose), respectively.
- The dosing formulation was homogenous during the dosing periods.

Metabolism and Excretion

Study title: Metabolite profiles of MDV3100 in selected rat plasma, urine, bile, and feces samples after a single oral dose of ^{14}C-MDV3100 in [redacted] (b) (4) Study No. 8227307.

Study no.:	9785-ME-0007 ([redacted] (b) (4) Study Number 8230326)
Study report location:	4.2.2.4.
Conducting laboratory and location:	[redacted] (b) (4)
Date of study initiation:	August 21, 2010 (Sample analysis outline finalized)
GLP compliance:	No
QA statement:	Yes (with signature)
Drug, lot #, and % purity:	Not reported

Key Study Findings

- MDV3100 is extensively metabolized following a single oral dose in dogs.
- MDV3100 and its metabolite M1 (MDPC0001) were the two major compounds detected in plasma, bile, and feces.
- Metabolite M1 was the major compound detected in urine.

Objective

The objective of this study was to determine the metabolite profiles of ^{14}C-MDV3100 using high performance liquid chromatography (HPLC) in plasma, urine, bile, and feces samples collected in Study Number 9785-ME-0002 from rats after administration of a single oral dose of 30 mg/kg ^{14}C-MDV3100. Radioactivity in the samples was profiled and quantified by HPLC and metabolites were identified by spiking known reference standard solutions into plasma, urine, bile, and feces samples.

Summary of Results

- Plasma
  - MDV3100 and metabolite M1 (MDPC0001) were the two compounds detected at the highest concentration in plasma samples. MDV3100 accounted for 73.1%, 48.8%. 48.3%, 29.9%, 20.2%, and 6.46% at 1, 4, 8, 24, 48, and 72 hours, respectively, as a percentage of sample

Reference ID: 3175869

radioactivity. M1 accounted for 21.8%, 43.5%. 44.3%, 54.6%, 56.3%, and 65.8% at 1, 4, 8, 24, 48, and 72 hours, respectively, as a percentage of sample radioactivity.

Table 24. Metabolite profile of MDV3100 in plasma samples of male rats following a single oral administration of 30 mg/kg ^{14}C-MDV3100.

Peak Number	Tentative Assignment	HPLC Peak Designation	Retention Time (Minutes)	Collection Time (Hours) 1	4	8	24	48	72
				Percent of Radioactivity Injected (% of Run)					
4	MDV3105	1	47.38	ND	ND	ND	2.15	3.75	8.05
8	MDPC0001	2	52.88-53.13	21.77	43.53	44.33	54.58	56.32	65.76
13	MDV3106	3	74.63	1.55	2.15	1.21	1.38	ND	ND
14	MDPC0004	4	76.63-76.88	2.00	2.42	3.51	8.89	12.47	14.88
15	MDPC0002	5	78.38-78.63	ND	1.24	1.00	1.43	ND	ND
16	MDV3100	6	81.63-81.88	73.12	48.84	48.30	29.86	20.23	6.46
			Total	98.4	98.2	98.4	98.3	92.8	95.2
				Concentration (ng equivalents ^{14}C-MDV3100/g)					
4	MDV3105	1	47.38	ND	ND	ND	164	47.8	11.2
8	MDPC0001	2	52.88-53.13	1380	7240	8430	4160	718	91.1
13	MDV3106	3	74.63	98.5	358	230	105	ND	ND
14	MDPC0004	4	76.63-76.88	127	402	668	678	159	20.6
15	MDPC0002	5	78.38-78.63	ND	206	190	109	ND	ND
16	MDV3100	6	81.63-81.88	4650	8120	9190	2280	258	8.95
			ng equivalents/g quantitated:	6260	16300	18700	7500	1180	132
			ng equivalents/g in sample:	5940	15700	17800	7010	1270	144
			Extraction Recovery (%):	100	99.0	99.9	98.0	96.5	77.6
			Reconstitution Recovery (%):	107	107	107	111	104	124

ND Peak not detected or below the established limit of quantitation (1% of run).

[Excerpted from Applicant's Table 1 in Study Number 9785-ME-0007]

- Urine
  - Urinary excretion of radioactivity accounted for 43.6% and 44.2% of the radioactive dose through 72 and 168 hours post-dose, respectively.
  - Metabolites M1 (MDPC0001) and MDV3105 were the major compounds detected in urine samples. M1 accounted for 90.3%, 88.5%, 77.9%, and 65.4% of the sample radioactivity at 0-8, 8-24, 24-48, and 48-72 hours, respectively. MDV3105 accounted for 6.85%, 9.97%, 21.3%, and 34.4% of the sample radioactivity at 0-8, 8-24, 24-48, and 48-72 hours, respectively.

Table 25. Metabolite profile of MDV3100 in urine samples of male rats following a single oral administration of 30 mg/kg ^{14}C-MDV3100.

Peak Number	Tentative Assignment	HPLC Peak Designation	Retention Time (Minutes)	Collection Interval (Hours) 0-8	8-24	24-48	48-72	
				Percent of Radioactivity Injected (% of Run)				
4	MDV3105	1	47.88-48.13	6.85	9.97	21.31	34.41	
8	MDPC0001	2	53.38-53.63	90.31	88.53	77.92	65.35	
			Total	97.2	98.5	99.2	99.8	
				Percent of Radioactive Dose				Total
4	MDV3105	1	47.88-48.13	0.349	2.48	2.10	0.713	5.65
8	MDPC0001	2	53.38-53.63	4.61	22.0	7.70	1.35	35.7
			Percent of Dose Quantitated:	4.95	24.5	9.80	2.07	41.3
			Percent of Dose in Sample:	5.12	26.2	10.1	2.15	43.6
			Centrifugation Recovery (%):	99.6	94.9	97.8	96.4	NA

NA Not applicable.

[Excerpted from Applicant's Tables 2 in Study Number 9785-ME-0007]

- Bile
  - Biliary excretion of radioactivity accounted for 49.8% and 50.6% of the radioactive dose through 72 and 168 hours post-dose, respectively.
  - Metabolites M1 and MDV3105 were the major compounds detected in rat bile samples. M1 was the major metabolite detected and accounted for 52.3% to 85.4% of the sample radioactivity and for 33.8% of the radioactive dose through 72 hours post-dose. MDV3100 increased in a time-dependent manner to a maximum 22.3% of the sample radioactivity and accounted for 4.71% of the radioactive dose through 72 hours post-dose.

Table 26. Metabolite profile of MDV3100 in bile samples of male rats following a single oral administration of 30 mg/kg ^{14}C-MDV3100.

Bile samples

Peak Number	Tentative Assignment	HPLC Peak Designation	Retention Time (Minutes)	Collection Interval (Hours) 0-8	8-24	24-48	48-72	
				Percent of Radioactivity Injected (% of Run)				
2	-	1	42.38	ND	ND	1.12	1.30	
3	-	2	45.88-46.38	4.34	3.46	3.09	2.87	
4	MDV3105	3	47.13-47.63	4.68	8.01	14.31	22.28	
5	-	4	48.13-48.63	6.48	3.78	2.40	1.76	
6	-	5	48.88	ND	ND	1.24	2.06	
7	-	6	51.38-51.88	6.22	5.15	4.88	4.99	
8	MDPC0001	7	52.63-53.13	63.92	70.96	64.56	52.25	
9	-	8	55.13	ND	ND	ND	2.53	
10	-	9	57.13	1.77	1.11	ND	ND	
11	-	10	62.38	1.43	ND	ND	ND	
12	-	11	65.13	ND	ND	ND	1.51	
14	MDPC0004	12	76.88	ND	ND	ND	1.00	
15	MDPC0002	13	78.63-79.13	ND	ND	1.53	1.40	
16	MDV3100	14	81.63	1.28	ND	ND	ND	
			Total	90.1	92.5	93.1	94.0	
				Percent of Radioactive Dose				Total
2	-	1	42.38	ND	ND	0.156	0.0297	0.185
3	-	2	45.88-46.38	0.235	0.747	0.430	0.0656	1.48
4	MDV3105	3	47.13-47.63	0.253	1.73	1.99	0.509	4.48
5	-	4	48.13-48.63	0.350	0.816	0.334	0.0402	1.54
6	-	5	48.88	ND	ND	0.172	0.0471	0.220
7	-	6	51.38-51.88	0.336	1.11	0.679	0.114	2.24
8	MDPC0001	7	52.63-53.13	3.46	15.3	8.98	1.19	28.9
9	-	8	55.13	ND	ND	ND	0.0578	0.0578
10	-	9	57.13	0.0957	0.240	ND	ND	0.335
11	-	10	62.38	0.0773	ND	ND	ND	0.0773
12	-	11	65.13	ND	ND	ND	0.0345	0.0345
14	MDPC0004	12	76.88	ND	ND	ND	0.0228	0.0228
15	MDPC0002	13	78.63-79.13	ND	ND	0.213	0.0320	0.245
16	MDV3100	14	81.63	0.0692	ND	ND	ND	0.0692
			Percent of Dose Quantitated:	4.87	20.0	13.0	2.15	39.9
			Percent of Dose in Sample:	6.70	25.4	15.3	2.41	49.8
			Centrifugation Recovery (%):	80.7	85.0	90.9	94.8	NA

NA Not applicable.
ND Peak not detected or below the established limit of quantitation (1% of run).
\- No tentative assignment.

Bile pellet extract samples

Peak Number	Tentative Assignment	HPLC Peak Designation	Retention Time (Minutes)	Collection Interval (Hours) 0-8	8-24	
				Percent of Radioactivity Injected (% of Run)		
3	-	1	45.13	2.17	1.92	
4	MDV3105	2	46.38	2.33	4.57	
5	-	3	47.63	1.99	1.70	
7	-	4	50.88	3.62	3.01	
8	MDPC0001	5	51.88	83.08	85.40	
16	MDV3100	6	80.88	ND	1.13	
			Total	93.2	97.7	
				Percent of Radioactive Dose		Total
3	-	1	45.13	0.0310	0.0814	0.112
4	MDV3105	2	46.38	0.0333	0.194	0.227
5	-	3	47.63	0.0284	0.0721	0.101
7	-	4	50.88	0.0517	0.128	0.179
8	MDPC0001	5	51.88	1.19	3.62	4.81
16	MDV3100	6	80.88	ND	0.0479	0.0479
			Percent of Dose Quantitated:	1.33	4.15	5.48
			Percent of Dose in Sample:	6.70	25.4	32.1
			Extraction Recovery (%):	21.3	16.7	NA

NA Not applicable.
ND Peak not detected or below the established limit of quantitation (1% of run).
\- No tentative assignment.

[Excerpted from Applicant's Tables 3 and 4 in Study Number 9785-ME-0007]

- Feces
  - Fecal excretion of radioactivity accounted for 48.3% and 49.8% of the radioactive dose through 72 and 168 hours post-dose, respectively.
  - M1 was the major compound detected in rat feces and accounted for 66.2% to 74.1% of the sample radioactivity, and for 34.9% of the total administered radioactive dose through 72 hours post-dose.

Table 27. Metabolite profile of MDV3100 in feces samples of male rats following a single oral administration of 30 mg/kg ^{14}C-MDV3100.

Peak Number	Tentative Assignment	HPLC Peak Designation	Retention Time (Minutes)	Collection Interval (Hours) 0-24	24-48	48-72	
				Percent of Radioactivity Injected (% of Run)			
1	-	1	37.13	1.09	ND	ND	
4	MDV3105	2	47.63-48.13	10.08	17.35	26.48	
8	MDPC0001	3	53.13-53.38	70.51	74.07	66.15	
13	MDV3106	4	75.63	1.26	ND	ND	
15	MDPC0002	5	78.38-79.38	1.23	1.36	1.06	
16	MDV3100	6	81.63-82.38	4.91	2.08	1.11	
			Total	89.1	94.9	94.8	
				Percent of Radioactive Dose			Total
1	-	1	37.13	0.237	ND	ND	0.237
4	MDV3105	2	47.63-48.13	2.20	3.95	1.08	7.22
8	MDPC0001	3	53.13-53.38	15.4	16.9	2.70	34.9
13	MDV3106	4	75.63	0.274	ND	ND	0.274
15	MDPC0002	5	78.38-79.38	0.268	0.309	0.0432	0.621
16	MDV3100	6	81.63-82.38	1.07	0.473	0.0453	1.59
			Percent of Dose Quantitated:	19.4	21.6	3.87	44.9
			Percent of Dose in Sample:	22.2	22.0	4.10	48.3
			Extraction Recovery (%):	91.7	94.9	93.0	NA
			Reconstitution Recovery (%):	107	109	107	NA

NA Not applicable.
ND Peak not detected or below the established limit of quantitation (1% of run).
\- No tentative assignment.

[Excerpted from Applicant's Table 5 in Study Number 9785-ME-0007]

Study title: Metabolite profiles of MDV3100 in selected dog plasma, urine, bile, and feces samples after a single oral dose of ^{14}C-MDV3100 in [redacted] (b) (4) Study No. 8227309.

Study no.:	9785-ME-0006 [redacted] (b) (4) Study Number 8230327)
Study report location:	4.2.2.4.
Conducting laboratory and location:	[redacted] (b) (4)
Date of study initiation:	August 21, 2010 (Sample analysis outline finalized)
GLP compliance:	No.
QA statement:	Yes (with signature).
Drug, lot #, and % purity:	Not reported.

Key Study Findings

- MDV3100 is extensively metabolized following a single oral dose in dogs.
- MDV3100 and its metabolite M1 (MDPC0001) were the two major compounds detected in plasma, bile, and feces.
- Metabolite M1 was the major compound detected in urine.

Objective

The objective of this study was to determine the metabolite profiles of ^{14}C-MDV3100 using high performance liquid chromatography (HPLC) in plasma, urine, bile, and feces samples collected in Study Number 9785-ME-0002 from dogs after administration of a single oral dose of 20 mg/kg ^{14}C-MDV3100. Radioactivity in the samples was profiled and quantified by HPLC and metabolites were identified by spiking known reference standard solutions into plasma, urine, bile, and feces samples.

Summary of Results

- Plasma
  - MDV3100 and metabolite M1 (MDPC0001) were the two compounds detected at the highest concentration in plasma samples. As a percentage of sample radioactivity, MDV3100 and M1 accounted for 60.0% and 27.5%, respectively, 168 hours following administration of a single oral dose of ^{14}C-MDV3100.

Reference ID: 3175869

Table 28. Metabolite profile of MDV3100 in plasma samples of male dogs following a single oral administration of 20 mg/kg ^{14}C-MDV3100 to male dogs.

Peak Number	Tentative Assignment	HPLC Peak Designation	Retention Time (Minutes)	Collection Time (Hours) 1	4	8	24	72	168
				Percent of Radioactivity Injected (% of Run)					
8	MDPC0001	1	50.88-51.13	3.86	10.53	7.37	18.62	22.62	27.52
13	MDV3106	2	72.63-72.88	ND	1.22	1.03	1.12	1.04	1.26
14	MDPC0004	3	74.88	1.78	2.30	2.90	2.16	2.30	3.50
15	MDPC0002	4	76.63-76.88	ND	1.06	1.94	2.97	4.82	4.45
16	MDV3100	5	80.13	91.73	84.75	86.11	75.62	68.87	60.00
			Total	97.4	99.9	99.4	100	99.7	96.7
				Concentration (ng equivalents ^{14}C- MDV3100/g)					
8	MDPC0001	1	50.88-51.13	525	2020	1820	3110	1620	413
13	MDV3106	2	72.63-72.88	ND	234	254	187	74.4	18.9
14	MDPC0004	3	74.88	242	441	714	361	165	52.6
15	MDPC0002	4	76.63-76.88	ND	203	478	496	345	66.8
16	MDV3100	5	80.13	12500	16200	21200	12600	4930	901
			ng equivalents/g quantitated:	13200	19100	24500	16800	7130	1450
			ng equivalents/g in sample:	12800	18600	23300	15900	6960	1430
			Extraction Recovery (%):	98.3	100	98.8	100	97.9	104
			Reconstitution Recovery (%):	108	103	107	105	105	101

ND Peak not detected or below the established limit of quantitation (1% of run).

[Excerpted from Applicant's Table 1 in Study Number 9785-ME-0006]

- Urine
  - Urinary excretion of radioactivity accounted for 60.1% and 62.0% of the radioactive dose through 216 and 504 hours post-dose, respectively.
  - Metabolite M1 (MDPC0001) was the major compound detected in urine samples, accounting for 58.8% of the total administered radioactive dose in urine.

Table 29. Metabolite profile of MDV3100 in urine samples and pellet extracts of male dogs following a single oral administration of 20 mg/kg ^{14}C-MDV3100.

Urine samples

Peak Number	Tentative Assignment	HPLC Peak Designation	Retention Time (Minutes)	Collection Interval (Hours) 0-8	8-24	24-48	48-72	72-96	96-120	120-144	144-168	168-192	192-216	
				Percent of Radioactivity Injected (% of Run)										
17	-	1	14.63	1.18	ND	ND	ND	ND	ND	ND	ND	ND	ND	
4	MDV3105	2	45.88-46.13	3.10	1.90	1.56	1.51	1.71	1.80	1.77	2.12	5.14	2.64	
8	MDPC0001	3	50.63-51.38	91.40	96.50	97.50	98.08	96.62	97.63	97.53	97.14	93.76	95.87	
			Total	95.7	98.4	99.1	99.6	98.3	99.4	99.3	99.3	98.9	98.5	
				Percent of Radioactive Dose										Total
17	-	1	14.63	0.0179	ND	ND	ND	ND	ND	ND	ND	ND	ND	0.0179
4	MDV3105	2	45.88-46.13	0.0471	0.116	0.155	0.108	0.0992	0.0763	0.0524	0.0470	0.0649	0.0272	0.793
8	MDPC0001	3	50.63-51.38	1.39	5.90	9.69	7.00	5.61	4.14	2.88	2.15	1.18	0.989	40.9
			Percent of Dose Quantitated:	1.45	6.02	9.84	7.11	5.71	4.22	2.94	2.20	1.25	1.02	41.7
			Percent of Dose in Sample:	1.67	8.71	17.4	10.8	7.46	5.64	3.48	2.47	1.36	1.12	60.1
			Centrifugation Recovery (%):	91.0	70.2	57.1	66.1	77.8	75.2	85.0	89.7	92.9	92.1	NA

NA Not applicable.
ND Peak not detected or below the established limit of quantitation (1% of run).
- No tentative assignment.

Urine pellet extracts

Peak Number	Tentative Assignment	HPLC Peak Designation	Retention Time (Minutes)	Collection Interval (Hours) 8-24	24-48	48-72	72-96	96-120	
				Percent of Radioactivity Injected (% of Run)					
4	MDV3105	1	46.13	ND	ND	ND	ND	1.09	
8	MDPC0001	2	51.63-51.88	98.66	98.94	98.78	99.35	98.76	
			Total	98.7	98.9	98.8	99.4	99.9	
				Percent of Radioactive Dose					Total
4	MDV3105	1	46.13	ND	ND	ND	ND	0.0153	0.0153
8	MDPC0001	2	51.63-51.88	3.52	6.85	3.53	2.56	1.39	17.9
			Percent of Dose Quantitated:	3.52	6.85	3.53	2.56	1.40	17.9
			Percent of Dose in Sample:	8.71	17.4	10.8	7.46	5.64	50.0
			Extraction Recovery (%):	41.0	39.8	33.1	34.6	24.9	NA

NA Not applicable.
ND Peak not detected or below the established limit of quantitation (1% of run).

[Excerpted from Applicant's Tables 2 and 3 in Study Number 9785-ME-0006]

- Bile
  - Biliary excretion of radioactivity accounted for 47.4% and 47.9% of the radioactive dose through 144 and 168 hours post-dose, respectively.
  - Metabolite M1 was the major compound detected in dog bile and accounted for 76.0% to 89.7% of the sample radioactivity and 43.2% of the total administered radioactive dose through 144 hours post-dose.

Table 30. Metabolite profile of MDV3100 in bile samples of male dogs following a single oral administration of 20 mg/kg ^{14}C-MDV3100.

Peak Number	Tentative Assignment	HPLC Peak Designation	Retention Time (Minutes)	Collection Interval (Hours) 0-8	8-24	24-48	48-72	72-96	96-120	120-144	Total
				Percent of Radioactivity Injected (% of Run)							
4	MDV3105	1	44.38-45.38	3.23	2.04	2.21	2.34	3.03	4.34	4.77	
22	-	2	47.63-48.38	1.39	1.25	ND	ND	1.06	1.42	1.12	
23	-	3	48.63-49.13	1.69	1.48	1.46	1.47	1.19	ND	1.31	
8	MDPC0001	4	49.38-50.88	76.03	87.51	88.04	88.29	86.77	89.71	84.05	
13	MDV3106	5	72.63	1.07	ND	ND	ND	ND	ND	ND	
16	MDV3100	6	79.88-80.13	6.21	4.00	3.46	3.01	2.50	2.75	2.72	
			Total	89.6	96.3	95.2	95.1	94.6	98.2	94.0	
				Percent of Radioactive Dose							Total
4	MDV3105	1	44.38-45.38	0.143	0.251	0.356	0.221	0.128	0.0956	0.0520	1.25
22	-	2	47.63-48.38	0.0617	0.154	ND	ND	0.0449	0.0313	0.0122	0.304
23	-	3	48.63-49.13	0.0750	0.182	0.235	0.139	0.0504	ND	0.0143	0.696
8	MDPC0001	4	49.38-50.88	3.37	10.8	14.2	8.34	3.68	1.98	0.916	43.2
13	MDV3106	5	72.63	0.0475	ND	ND	ND	ND	ND	ND	0.0475
16	MDV3100	6	79.88-80.13	0.276	0.492	0.558	0.284	0.106	0.0605	0.0296	1.81
			Percent of Dose Quantitated:	3.98	11.8	15.3	8.99	4.01	2.16	1.02	47.3
			Percent of Dose in Sample:	3.73	11.5	16.2	9.00	3.96	2.02	1.00	47.4
			Centrifugation Recovery (%):	119	107	99.5	105	107	109	109	NA

NA Not applicable.
ND Peak not detected or below the established limit of quantitation (1% of run).
\- No tentative assignment.

[Excerpted from Applicant's Table 4 in Study Number 9785-ME-0006]

- Feces
  - Fecal excretion of radioactivity accounted for 19.9% and 22.3% of the radioactive dose through 120 and 504 hours post-dose, respectively.
  - MDV3100 and metabolite M1 were the major compounds detected in dog feces and accounted for 8.59% and 9.54% of the total administered radioactive dose through 120 hours post-dose, respectively.

Table 31. Metabolite profile of MDV3100 in feces samples of male dogs following a single oral administration of 20 mg/kg ^{14}C-MDV3100.

Peak Number	Tentative Assignment	HPLC Peak Designation	Retention Time (Minutes)	Collection Interval (Hours) 0-24	24-48	48-72	72-96	96-120	
				Percent of Radioactivity Injected (% of Run)					
18	-	1	35.38	ND	2.77	ND	ND	ND	
19	-	2	41.38	ND	3.66	ND	ND	ND	
20	-	3	44.38	ND	ND	ND	ND	1.99	
21	-	4	45.63-45.88	ND	4.62	3.41	3.14	3.12	
8	MDPC0001	5	50.63-51.13	5.65	74.80	81.06	80.53	76.52	
24	-	6	60.38-60.88	ND	2.74	1.04	ND	1.08	
14	MDPC0004	7	74.38	1.07	ND	ND	ND	ND	
15	MDPC0002	8	76.13-76.63	ND	ND	1.15	1.81	1.77	
16	MDV3100	9	79.38-79.88	83.63	2.21	6.56	10.25	10.16	
			Total	90.4	90.8	93.2	95.7	94.6	
				Percent of Radioactive Dose					Total
18	-	1	35.38	ND	0.143	ND	ND	ND	0.143
19	-	2	41.38	ND	0.189	ND	ND	ND	0.189
20	-	3	44.38	ND	ND	ND	ND	0.0252	0.0252
21	-	4	45.63-45.88	ND	0.239	0.112	0.0592	0.0395	0.449
8	MDPC0001	5	50.63-51.13	0.536	3.87	2.66	1.52	0.969	9.54
24	-	6	60.38-60.88	ND	0.142	0.0341	ND	0.0137	0.189
14	MDPC0004	7	74.38	0.102	ND	ND	ND	ND	0.102
15	MDPC0002	8	76.13-76.63	ND	ND	0.0377	0.0341	0.0224	0.0942
16	MDV3100	9	79.38-79.88	7.93	0.114	0.215	0.193	0.129	8.59
			Percent of Dose Quantitated:	8.57	4.69	3.05	1.80	1.20	19.3
			Percent of Dose in Sample:	9.07	4.91	2.95	1.80	1.21	19.9
			Extraction Recovery (%):	95.1	94.0	94.9	94.3	96.0	NA
			Reconstitution Recovery (%):	110	112	117	111	109	NA

NA Not applicable.
ND Peak not detected or below the established limit of quantitation (1% of run).
\- No tentative assignment.

Peak Number	Tentative Assignment	HPLC Peak Designation	Retention Time (Minutes)	Collection Time (Hours) 1	4	8	24	72	168
				Percent of Radioactivity Injected (% of Run)					
8	MDPC0001	1	50.88-51.13	3.86	10.53	7.37	18.62	22.62	27.52
13	MDV3106	2	72.63-72.88	ND	1.22	1.03	1.12	1.04	1.26
14	MDPC0004	3	74.88	1.78	2.30	2.90	2.16	2.30	3.50
15	MDPC0002	4	76.63-76.88	ND	1.06	1.94	2.97	4.82	4.45
16	MDV3100	5	80.13	91.73	84.75	86.11	75.62	68.87	60.00
			Total	97.4	99.9	99.4	100	99.7	96.7
				Concentration (ng equivalents ^{14}C- MDV3100/g)					
8	MDPC0001	1	50.88-51.13	525	2020	1820	3110	1620	413
13	MDV3106	2	72.63-72.88	ND	234	254	187	74.4	18.9
14	MDPC0004	3	74.88	242	441	714	361	165	52.6
15	MDPC0002	4	76.63-76.88	ND	203	478	496	345	66.8
16	MDV3100	5	80.13	12500	16200	21200	12600	4930	901
			ng equivalents/g quantitated:	13200	19100	24500	16800	7130	1450
			ng equivalents/g in sample:	12800	18600	23300	15900	6960	1430
			Extraction Recovery (%):	98.3	100	98.8	100	97.9	104
			Reconstitution Recovery (%):	108	103	107	105	105	101

ND Peak not detected or below the established limit of quantitation (1% of run).

[Excerpted from Applicant's Table 5 in Study Number 9785-ME-0006]

5.2 Toxicokinetics

(Reviews of MDV3100 toxicokinetic analyses conducted as part of repeat-dose toxicity studies are included in the reviews of the toxicity studies)

6 General Toxicology

6.1 Single-Dose Toxicity

Single-dose toxicity studies with MDV3100 were not reviewed for this NDA.

6.2 Repeat-Dose Toxicity

Study Number: **PRO3100NC18 (b) (4) Study Number 7792-110)**
Study Title: **2-Week oral gavage bridging toxicity and toxicokinetic study with MDV3100 in rats.**

[The review of Study No. PRO3100NC18 is reproduced verbatim below, with some changes in formatting for consistency purposes, as it appeared in the review (dated June 28, 2007) of IND 74563 for MDV3100 conducted by Doo Y. Lee Ham, Ph.D.]

Study title: 15-Day (2 Week) oral gavage bridging toxicity and toxicokinetic study with MDV3100 in Rats

Key findings:

- Bridging toxicology study (15-day) was conducted to test the comparability of previously proposed clinical lot 09060031that contained Unknown C at 0.7% to the Lot EWK-K-32(1) that did not contain Unknown C. Lot EWK-K-32(1) was used in 28-day toxicity study.
- Mortality was observed in this study in control and treated rats and was attributed to aspiration of small amounts of (b) (4) and not to MDV3100; this same conclusion was made in the 28-day study.
- Slight changes in hematology and clinical chemistry parameters were similar between the 28-day and 15-day studies.
- Significant increases in absolute and relative organ weights of liver, kidneys, and adrenals and decreases in epididymis, seminal vesicles, and prostate were seen in 15-day and 28-day studies.
- The NOAEL was >100 mg/kg for lot EWK-K-32(1) and lot 09060031.

Study no:	PRO3100NC31
Volume/Pages:	Vol. 2, Pages 1-306
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 13, 2007

Reference ID: 3175869

GLP compliance:	Yes
QA report:	Yes
Drug, lot # and % purity:	MDV3100 lot# 09060031(15-day study) MDV3100 lot# EWK-K-32(1) (28-day study), 99% purity
Formulation/vehicle:	(b) (4)
Dosing:	Once daily for 15 days
Species/strains:	Crl:CD(SD) rats
#group or time point (main study):	10/sex/group
Satellite group used for toxicokinetics:	3 or 9/sex/group
Age:	Approximately 7 weeks old
Weight:	166 to 194 g

Doses were administered as depicted in the following table:

Group[a]	No. of Animals[b] Male	Female	Dose Level (mg/kg)	Dose Concentration (mg/mL)
1 (Control)	10	10	0	0
2 (Low)	10	10	10	4.5
3 (Mid)	10	10	30	13
4 (High)	10	10	100	45
Toxicokinetic Animals				
5 (Control)	3	3	0	0
6 (Low)	9	9	10	4.5
7 (Mid)	9	9	30	13
8 (High)	9	9	100	45

[a] Groups 1 and 5 received control article only.
[b] At initiation of treatment, mean body weights ranged from 190–194 g for males and from 166–169 g for females.

[Excerpted from Applicant's submission]

Observations and times:

Clinical signs:	Twice daily
Body weight:	Pre-dose -1, weekly
Food consumption:	Weekly
Ophthalmology:	Pre-dose-3, day 12
Hematology:	Day 15
Clinical chemistry:	Day 15
Gross pathology:	Day 15
Histopathology:	Day 15
Toxicokinetics:	Blood samples were collected on Days 1 and 14: Day 1: pre-dose, 3, 6, 9, 12, and 24 hrs post-dose Day 14: pre-dose, 3, 6, 9, 12, 24, 36, 48, and 72 hrs post-dose.

Reference ID: 3175869

Results:

Mortality:

Mortality in this study was limited to a control male on day 3 and a HD male on day 5 (both animals were replaced). Two HD females (B18825 and B18857) were found dead on day 9. These findings were consistent with previous rat toxicology studies (pilot 2 week and 28-day studies), mortality was observed in this study in control and treated rats and was attributed to aspiration of small amounts of (b) (4) and not to MDV3100; this same conclusion was made in the 28-day study where mortality was documented in one control female and two 10 mg/kg females (one main study, one TK).

Clinical signs:

Clear oral discharges in both males and females (treated and control), and audible respiration were observed in both males (1/10, 0/10, 1/10, 1/10) and females (1/10, 1/10, 0/10, 1/10) for control, LD, MD, and HD group, respectively. Rough hair coat was seen 1/10♂, 3/10♀at HD, and yellow-stained haircoat was noted in ventral abdomen and perineal area in the HD females.

Body weight/food consumption: Not remarkable

Ophthalmology: Not remarkable

Clinical Pathology:

Treatment-related changes in hematology and clinical chemistry values were similar between the 28-day and 15-day studies in male and female rats (Table 3 and 4).

Reference ID: 3175869

Table 32: Mean Values of Clinical Pathology Parameters Affected by MDV3100 Following 15-Days and 28-Days of Treatment in Male Rats

Parameter	Study	Dose Groups (mg/kg)			
		Control	10	30	100
RBC (E6/µL)	15-Day Study	7.37	7.08	7.25	7.08
	28-Day Study	8.05	7.86	7.95	7.51[a]
HGB g/dL	15-Day Study	15.7	15.1[a]	15.4	14.8[a]
	28-Day Study	15.8	15.5	15.2	14.9[a]
HCT %	15-Day Study	43.5	41.4[a]	42.7	40.8[a]
	28-Day Study	44.5	43.3	42.6	41.7
Platelets E3/µL	15-Day Study	1387	1461	1479	1425
	28-Day Study	1174	1156	1377	1383
Reticulocytes (%)	15-Day Study	4.1	3.8	3.8	4.2
	28-Day Study	1.9	2.1	2.1	2.3
Cholesterol mg/dL	15-Day Study	72	85	86	93
	28-Day Study	52	68	82[a]	99[a]
Albumin g/dL	15-Day Study	4.0	4.0	4.2[a]	4.2[a]
	28-Day Study	4.1	4.2	4.4[a]	4.5[a]
Total Protein (g/dL)	15-Day Study	5.4	5.4	5.7	5.7
	28-Day Study	5.7	5.9	6.1[a]	6.2[a]
AGR	15-Day Study	2.8	2.8	2.9	2.8
	28-Day Study	2.6	2.5	2.5	2.6

[a] Statistical significance $p < 0.05$
15-day study: Study PRO3100NC31 (b) (4) Study 7792-110)
28-day study: Study PRO3100NC17 Study 7792-102)

[Excerpted from the Applicant's submission]

Table 33: Mean Values of Clinical Pathology Parameters Affected by MDV3100 Following 15-Days and 28-Days of Treatment in Female Rats

Parameter	Study No	Dose Groups (mg/kg)			
		Control	10	30	100
RBC (E6/µL)	15-Day Study	7.5	7.62	7.26	7.3
	28-Day Study	8.14	8.24	7.9	7.33[a]
HGB g/dL	15-Day Study	15.8	15.9	15.0[a]	15.1[a]
	28-Day Study	15.8	16.0	15.2	14.2[a]
HCT %	15-Day Study	42.1	42.4	40.2[a]	40.5
	28-Day Study	43.5	43.9	41.7	39.4[a]
Platelets E3/µL	15-Day Study	1308	1433	1475[a]	1550[a]
	28-Day Study	1145	1171	1400[a]	1487[a]
Reticulocytes (%)	15-Day Study	2.4	2.4	3.0[a]	2.8
	28-Day Study	1.6	1.7	1.8	2.3[a]
Cholesterol mg/dL	15-Day Study	76	79	95[a]	107[a]
	28-Day Study	73	79	110[a]	130[a]
Albumin g/dL	15-Day Study	5.0	4.7	4.4[a]	4.5[a]
	28-Day Study	5.0	4.8	4.8	5.0
Total Protein (g/dL)	15-Day Study	6.3	6.2	5.9	6.0
	28-Day Study	6.5	6.3	6.5	6.9
AGR	15-Day Study	3.9	3.3	3.0[a]	2.9[a]
	28-Day Study	3.5	3.2	2.9	2.7[a]

[a] Statistical significance $p < 0.05$
15-day study: Study PRO3100NC31 ((b) (4) Study 7792-110)
28-day study: Study PRO3100NC15 (Study 7792-100)

[Excerpted from the Applicant's submission]

Gross pathology:

Table 34: Mean Values of Organ: Body Weight Ratios Affected by MDV3100 Followign 2-4 Weeks of Treatment in Male Rats

Parameter	Study	Dose Groups (mg/kg)			
		Control	10	30	100
Liver	15-Day Study	3.83	4.30	4.17	4.66[a]
	28-Day Study	3.42	3.50	3.93[a]	4.35[a]
Adrenal	15-Day Study	.021	.025[a]	.026[a]	.028[a]
	28-Day Study	.019	.022	.022	.025[a]
Spleen	15-Day Study	.26	.27	.27	.31[a]
	28-Day Study	.21	.19	.21	.25
Epididymis	15-Day Study	.28	.25	.23[a]	.24[a]
	28-Day Study	.30	.26[a]	.24[a]	.24[a]
Seminal vesicles	15-Day Study	.36	.19[a]	.17[a]	.18[a]
	28-Day Study	.32	.19[a]	.17[a]	.14[a]
Prostate	15-Day Study	.29	.22[a]	.17[a]	.19[a]
	28-Day Study	.28	.22[a]	.17[a]	.18[a]
Testes	15-Day Study	1.11	1.11	1.13	1.11
	28-Day Study	.922	.951	.893	1.01

[a] Statistical significance $p < 0.05$
Study PRO3100NC31 ((b) (4) Study 7792-110)
Study PRO3100NC17 (Study 7792-102)

[Excerpted from the Applicant's submission]

Table 35: Mean Values of Organ: Body Weight Ratios Affected by MDV3100 Following 2-4 Weeks of Treatment in Female Rats

Parameter	Study No	Dose Groups (mg/kg)			
		Control	10	30	100
Liver	15-Day Study	4.06	4.23	4.86[a]	5.02[a]
	28-Day Study	3.50	3.75	4.63[a]	5.83[a]
Heart	15-Day Study	.40	.41	.45[a]	.47[a]
	28-Day Study	.41	.40	.40	.45
Adrenal	15-Day Study	.036	.039	.044[a]	.041
	28-Day Study	.034	.036	.043	.042
Kidney	15-Day Study	.87	.93	.98[a]	.95[a]
	28-Day Study	.84	.86	.89	.96[a]
Spleen	15-Day Study	.26	.28	.35[a]	.34[a]
	28-Day Study	.23	.23	.28	.29

[a] Statistical significance $p < 0.05$
Study PRO3100NC31 ((b) (4) Study 7792-110)
Study PRO3100NC17 (Study 7792-102)

[Excerpted from the Applicant's submission]

No treatment-related macroscopic findings were observed. As in the 28-day study, the absolute weights of liver, kidney, and adrenal were higher in females

receiving MDV3100. In males, absolute weights of liver, adrenal, spleen were increased in both current study and the 28-day study, whereas absolute weights of epididymis, seminal vesicles, and prostate were reduced in male rats in both studies.

Histopathology: Not performed.

Toxicokinetics:

Toxicokinetic data for the 15-day and 28-day study in rats are presented in the following table.

	C_{max} (µg/mL)		AUC_{24hr} (µg*hr/mL)	
	28-Day Study	15-Day Study	28-Day Study	15-Day Study
10 mg/kg				
Males	4.69	3.40	56.6	44.0
Females	9.42	7.98	135	142
30 mg/kg				
Males	13.0	14.7	152	144
Females	24.5	28.8	303	361
100 mg/kg				
Males	24.2	16.6	290	226
Females	38.6	32.9	427	349

Data represent values on last day of each study
28-day study: Study PRO3100NC17 (b) (4) Study 7792-102)
15-day study: Study PRO3100NC31 Study 7792-110)

[Excerpted from the Applicant's submission]

Study Number: **PRO3100NC17 ((b) (4) Study Number 7792-102)**
Study Title: **4-Week oral gavage toxicity and toxicokinetic study with MDV3100 in rats with a 4-week recovery period.**

[The review of Study No. PRO3100NC17 is reproduced verbatim below, with some changes in formatting for consistency purposes, as it appeared in the review (dated April 12, 2007) of IND 74563 for MDV3100 conducted by Doo Y. Lee Ham, Ph.D.]

Study title: 4-Week oral gavage toxicity and toxicokinetic study with MDV3100 in rats with a 4-Week recovery period

Key findings:

- Mortality occurred in one female at LD on D18 (main study), and two females on D19 and 22 (TK study)
- Clinical signs were clear oral discharge and audible respiration at HD groups
- No significant treatment-related changes were noted in body weight, hematology, clinical chemistry parameters

- Statistically significant decreases in organ weights were observed in epididymis, seminal vesicles and prostate
- The NOAEL was >100 mg/kg (>600 mg/m^2)

Study no:	Study no. 0078-2004-R
Volume/Pages:	Volume 3 and 4, Pages 1-279
Conducting laboratory and location:	PRO3100NC17(Applicant reference number)/ 7792-102 (b) (4) study number) (b) (4)
Date of study initiation:	25-Sep-2006
GLP compliance:	Yes
QA report:	Yes
Drug, lot #, radiolabel, and % purity:	MDV3100 lot#/Batch# EWK-K-32(1)/0609031, 99.0% purity
Formulation/vehicle:	(b) (4) ™ lot# 102776, 100% purity
Dosing:	Once daily for 28 days or 4 weeks
Species/strains:	Crl:CD(SD) rats
#/group or time point (main study):	10 or 15/sex/group
Satellite groups used for toxicokinetics:	3 or 9/sex/group
Age:	Approximately 7 weeks old
Weight:	161-237 g

Doses were administered as the following table:

Group[a]	No. of Animals[b, c] Male	Female	Dose Level (mg/kg/day)	Dose Concentration (mg/mL)
Toxicity Animals				
1 (Control)	15	15	0	0
2 (Low)	15	15	10	4.5
3 (Mid)	10	10	30	13.6
4 (High)	15	15	100	45
Toxicokinetic Animals				
5 (Control)	3	3	0	0
6 (Low)	9	9	10	4.5
7 (Mid)	9	9	30	13.6
8 (High)	9	9	100	45

a Groups 1 and 5 received control article only.
b Toxicity animals designated for final sacrifice (10/sex in Groups 1, 2, 3 and 4) were terminated after at least 4 weeks of dose administration.
c Toxicity animals designated for recovery sacrifice [five animals/sex in Groups 1, 2 (males only), and 4; Group 2 females had four recovery animals due to one death)] underwent 4 weeks of recovery following dose administration.

[Excerpted from Applicant's submission]

Observations and times:

Clinical signs:	Twice daily on Day 1 and weekly thereafter
Body weight:	Weekly
Food consumption:	Weekly

Ophthalmoscopy:	Pre-dose -4, days 24 and 27
Hematology:	Day 30 and recovery day 29
Clinical chemistry:	Day 30 and recovery day 29
Urinalysis:	Day 30
Gross Pathology:	Day 29
Histopathology:	Day 29
Toxicokinetics:	Blood samples were collected on days 1, 14, and 28 as follow: In the Group 5 (vehicle control), TK samples were taken 24 hrs after dosing on Days 1, 14, and 28. In the Groups 6, 7, and 8 (MDV3100-treated), TK samples were obtained on Days 1 at 6 and 24 hrs after dosing, at 6 hrs after dosing on Day 14, and at the following times prior to the Day 28 dose: pre-dose, and 6, 12, 24, 36, 48, and 72 hrs.

Results:

Mortality:

Unscheduled 3 female deaths occurred: one female (B11474) at 10 mg/kg/day found dead on day 18 due to gavage injury, had clear oral discharge, and slight to moderate acute inflammation in the trachea and esophagus (secondary to the gavage process).

One female (B11512) at 10 mg/kg/day (TK group) found dead on Day 19, and one control female (B11502) at TK group sacrificed on Day 22. These females in the TK groups had no macroscopic findings, but exhibited labored and audible respiration days prior to termination, possibly indications of aspiration.

Clinical signs:

Only remarkable findings were clear oral discharge seen in two females at HD and one female at 10 mg/kg/day, and audible respiration in one control male and one female at HD. The audible respiration may be related to aspiration of (b) (4) rather than to the test drug.

Body weight/food consumption: Not remarkable

Ophthalmic examination: Not remarkable

Hematology:

Treatment-related mild decreases in red cell parameters were observed in the HD males and females on day 29. The reticulocyte counts were slightly higher in these rats, indicating that marrow erythrocytes were not suppressed.

Report Title	Hematology Findings 4-Week Oral Gavage Toxicity Study with MDV3100 in Rats with 4-Week Recovery Period			
Dose, mg/kg/day	0	10	30	100

Reference ID: 3175869

Sex of Animals	M	F	M	F	M	F	M	F
Number of Animals	10	10	10	10	10	10	10	10
Hematology Day 29								
RBC (E6/uL)	8.05	8.14	7.86	8.24	7.95	7.90	**7.51**	**7.33**
Hemoglobin (g/dL)	15.8	15.8	15.5	16.0	14.2	15.2	**14.9**	**14.2**
Hematocrit (%)	44.5	43.5	43.9	43.9	42.6	41.7	41.7	**39.4**
Reticulocytes (%)	1.9	1.6	1.7	1.7	2.1	1.8	**2.3**	**2.3**

Clinical chemistry:

Slightly higher mean cholesterol values in MD and HD rats and slightly higher total protein values in the MD males and HD rats were observed. Slightly higher albumin values were noted in the MD and HD males and A/G ratios were slightly lower in the HD females.

	Serum Chemistry Findings Following 4-Week Oral Gavage Toxicity Study with MDV3100 in Rats with 4-Week Recovery Period							
Dose, mg/kg/day	0		10		30		100	
Sex of Animals	M	F	M	F	M	F	M	F
Number of Animals	10	10	10	10	10	10	10	10
Serum Chemistry Day 29								
Cholesterol (mg/dL)	52	73	68	79	**82**	**110**	**99**	**130**
Total Protein (g/dL)	5.7	6.5	5.9	6.3	**6.1**	6.5	**6.2**	**6.9**
Albumin (g/dL)	4.1	5.0	4.2	4.8	**4.4**	4.8	**4.5**	5.0
A/G Ratio	2.6	3.5	2.5	3.2	2.5	2.9	2.6	**2.7**

The clinical pathology data were generally unremarkable and comparable between the control and the treated rats at recovery Day 29.

Urinalysis: Not remarkable

Gross Pathology:

There were no treatment-related macroscopic findings. In males and females at the 4-week terminal necropsy, significant treatment-related increases in absolute and relative liver weights, kidneys and adrenal weights were noted at doses ≥30 mg/kg.

Significant treatment-related decreases in absolute weights of epididymides, seminal vesicles, and prostate were observed in all treated males.

Reference ID: 3175869

	Absolute Organ Weights Following 4-Week Oral Gavage Toxicity Study with MDV3100 in Rats with 4-Week Recovery Period							
Dose, mg/kg/day	0		10		30		100	
Sex of Animals	M	F	M	F	M	F	M	F
Number of Animals	10	10	10	10	10	10	10	10
Organ Weights:								
Adrenal	0.019	0.034	0.022	0.036	0.022	**0.043**	0.025	**0.042**
Kidney	0.78	0.84	0.76	0.86	0.80	0.89	0.82	**0.96**
Liver	3.42	3.50	3.50	3.75	**3.93***	**4.63**	**4.35**	**5.83**
Epididymides	0.30	-	**0.26**	-	**0.24**	-	**0.24**	-
Seminal vesicle	0.32	-	**0.19**	-	**0.17**	-	**0.14**	-
Prostate	0.28	-	**0.22**	-	**0.17**	-	**0.18**	-

Note- Group means for the absolute weights are shown. * $p < 0.05$ compared to controls

Histopathology:

Dose, mg/kg/day	0		10		30		100	
No. Animals Examined	10	10	10	10	10	10	10	10
Sex of Animals	M	F	M	F	M	F	M	F
Terminal Sacrifice (Day 30)								
Lung								
-Focal inflammation	2/10						1/10	
-Vascular mineralization	1/10							
-Chronic, active multifocal inflammation	1/10						2/10	1/10
-Increased alveolar macrophages		2/10		1/10			2/10	1/10
-Hemorrhage		1/10					1/10	
-Chronic active, focal inflammation				1/10				
-Eosinophils, perivascular		3/10		1/10				
-Congestion								
Liver								
-Diffuse hepatocellular hypertrophy						4/10	2/10	8/10
-Increased cytoplasmic eosinophils					1/10			
Spleen								
-Increased hematopoiesis								1/10
-Slight lymphoid depletion							1/10	
Reproductive								
Seminal vesicle								
-focal, chronic inflammation							1/10	
Prostate								
-Chronic, multifocal inflammation							2/10	

Reference ID: 3175869

-Chronic active, multifocal inflammation	1/10						2/10	
Recovery Animals	5M	5F	5M	5F	5M	5F	5M	5F
Lung								
-Chronic active, multifocal inflammation	1/5						1/5	
-Chronic, multifocal inflammation	1/5						1/5	
-Increased alveolar macrophages	1/5 1/5							
-Hemorrhage		1/5						1/5
-Chronic active, focal inflammation		1/5						
-Eosinophilic perivascular inflammation								
Reproductive								
Epididymis								
-Focal, mononuclear cell infiltrate							2/5	
Prostate	3/5						1/5	
-Chronic, multifocal inflammation							1/5	
-Chronic active, multifocal inflammation								

[End of review of Study No. PRO3100NC17 excerpted from Dr. Doo Y. Lee Ham's review.]

<u>Reviewer's comments:</u>
The following table summarizes the toxicokinetic parameters of MDV3100 obtained in Study No. PRO3100NC17:

Table 36. Summary of toxicokinetic parameters of MDV3100 in rats. (Study No. PRO3100NC17)

Plasma Toxicokinetic Parameters for MDV3100
Reported values were derived by pooling data from multiple rats as described in the text.

	Last Dose (Day 28) C_{max} (µg/mL)	Last Dose (Day 28) AUC_{24hr} (µg/mL·hr)	$T_{1/2}$ (hr)	Accumulation Index†
Low Dose, 10 mg/kg				
Males	4.69	56.6	23.0	1.94
Females	9.42	135	NR	NR
Mid Dose, 30 mg/kg				
Males	13.0	152	17.4	1.63
Females	24.5	303	23.9	2.00
High Dose, 100 mg/kg				
Males	24.2	290	16.4	1.57
Females	38.6	427	17.5	1.63

†Derived from $T_{1/2}$ and the dosing interval as follows: accumulation index = $1/(1-e^{-k\tau})$, where k (the elimination rate constant) was $0.693/T_{1/2}$, and τ was the dosing interval (24 hours).
NR, non-reportable because the correlation coefficient for the terminal slope (r^2) was less than 0.7.

[Excerpted from Applicant's table in Study Report Number PRO3100NC17]

Study Number: **PRO3100NC39**
Study Title: **Rat 26 week toxicity study with 8 week recovery.**

[The review of Study No. PRO3100NC39 is reproduced verbatim below, with some changes in formatting for consistency purposes, as it appeared in the review (dated June 15, 2012) of IND (b) (4) *for MDV3100 conducted by W. David McGuinn, Jr., M.S., Ph.D., D.A.B.T.]*

26-Week Oral (Intragastric Intubation) Toxicity Study of MDV3100 in Rats Including an 8-Week Recovery Period

Study number	1284-015
File name	pro3011NC39-nonclinical-report.pdf
Laboratory	(b) (4)
Study Date	June 2008
GLP	Yes
Audited	Yes
Drug	MDV3100 API, Lot Numbers: 9070028 (RM07-046), 09060031 (RM06-090), 0610034, EWK-K-32-1 (RM06-071). Purity > 99%

Methods
Species: Male and female CD® [Crl:CD®(SD)] rats
Males 337 to 371 g and females 221 to 250 g,

Doses – 0, 10, 30, 100 or 200 mg/kg/day (0, 60, 180, 600 or 1200 mg/m^2/day). The following table from the study report shows the dose groups and toxicokinetic groups in this study.

Group Assignments

Group Number	Dose Level (mg/kg/day)	Number of Animals	
		Male	Female
1	0	18	18
2	10	14[b]	14[b]
3	30	14[b]	14[b]
4	100	14[b]	14[b]
5	200	18	18
6[a]	0	4	4
7[a]	10	9[b]	9[b]
8[a]	30	9[b]	9[b]
9[a]	100	9[b]	9[b]
10[a]	200	11	11

[a]TK animals.
[b]Two animals/sex originally assigned to the TK groups as spares (not used for blood sampling) were moved to the main study groups starting in Week 22 in order to facilitate a more robust assessment of recovery in these groups.

Schedule In the main study group, rats were given doses of 0, 10, 30, or 100 mg/kg/day once daily for 183 days. Additional animals were treated once per day for 35 days via oral gavage with 0 (vehicle) or 200 mg/kg/day of MDV3100. TK animals received the vehicle or test article in the same manner and dose levels as the main study groups.

Vehicle	(b) (4)®
Route	PO gavage
Dose volume	2.2 mL/kg/dose
Cage side exam	Twice daily
Clinical exam	Daily for the first week of dose administration and twice weekly thereafter
Body weights	Twice weekly
Food cons.	Weekly
Hematology	Day 22, 36 (vehicle and 200 mg/mL), 92, 183 and 239
Clinical chem.	Same as Hematology

Ophthalmology	Pre-test and on Days 35, 36, and 89
Histopathology	Adequate battery
Necropsy	TK Interim Terminal (dosed 5 weeks) Interim Recovery (dosed 5 weeks recovered 21 weeks) Main group dosed 26 weeks Recovery 34 weeks (dosed 26 weeks, recovered 8 weeks)
Toxicokinetics	Days 1, 28, 90 and 182 0, 2, 4, 8, 12, and 24 hours postdose, 36 and 48 hours post dose on day 180. Non-compartmental analysis with WinNonLin.

Results

Mortality The following tables from the study report shows the deaths in the main study group and the TK group. There is no pattern to indicate that any of the deaths were dose-related.

Reference ID: 3175869

MAIN STUDY ANIMALS			
Dose Level (mg/kg/day)	Animal Number and Sex	Day of Death	Cause of Death
0	1512 M	158 D	Dosing Error
0	1621 F	183 D	Died after blood collection
0	1634 F	103 E	Dosing Error
10	1527 M	31 D	Undetermined
30	1531 M	183 D	Undetermined, found dead within 6 hours of final blood collection
30	1661 F	155 E	Mammary Tumor (adenocarcinoma neoplasm)
100	1664 F	98 E	Dosing Error
100	1729 F	148 E	Undetermined
200	1683 F	8 E	Dosing Error
M-male; F-female; D-found dead; E-euthanized *in extremis*			

TOXICOKINETIC ANIMALS			
Dose Level (mg/kg/day)	Animal Number and Sex	Day of Death	Cause of Death
10	1578 M	88 E	Likely dosing error
30	1594 M	118 D	Unknown
30	1597 M	32 D	Unknown
30	1710 F	90 D	Died after blood collection
100	1606 M	180 E	Likely dosing error
M-male; F-female; D-found dead; E-euthanized *in extremis*			

Clinical Signs No toxicologically significant findings

Body Weight There were no statistically discernable differences, possibly because of bell shaped dose response curves to separate pharmacological and toxicologically effects at low and high doses. A bell-shaped dose response will confound an ANOVA. The following table from the study report shows the body weight change for males and females at different times in the study.

Male Total Mean Body Weight in Grams and Percent Change Compared To Control				
Dose Group (mg/kg/day)	Day -1 to 36	Day 36-180 Recovery	Day -1 to 183	Day 183 to 236 Recovery
0	103.0 (NA)	223.0 (NA)	298.7 (NA)	59.0 (NA)
10	NA	NA	322.7 (↑8%)	80.7 (↑37%)
30	NA	NA	251.0 (↓16%)	84.5 (↑43%)
100	NA	NA	241.3 (↓19%)	116 (↑97%)[b]
200	105.7 (↑3%)	253.5 (↑14%)	NA	NA
Female Mean Body Weight in Grams and Percent Change Compared To Control				
Dose Group (mg/kg/day)	Day -1 to 36	Day 36-183 Recovery	Day -1 to 183	Day 183 to 236 Recovery
0	46.75 (NA)	68.5 (NA)	84.7 (NA)	40.3 (NA)
10	NA	NA	99.5 (↑17%)	38.5 (↓4%)
30	NA	NA	106.7 (↑26%)	57.0 (↑41%)
100	NA	NA	127.0 (↑50%)	53.5 (↑33%)
200	43.7 (↓7%)	96.3 (↑41%)	NA	NA

NA – Not applicable
↓ decreased
↑ increased
b = significant at 0.01 level of significance

Food consumption – No toxicologically significant changes

Ophthalmology – No toxicologically significant changes

Clinical Chemistry – The following table shows that treatment with MDV3100 caused mild hepatic derangement. Again some of the parameters suggest a bell shaped dose response curve. The decrease in Cl- is unusual as Cl- is tightly controlled. It suggests the possibility of mild adrenal toxicity.

Male	control	10 mg/kg	30 mg/kg	100 mg/kg
Alkaline Phosphatase	75.5	-0.7%	20.5%	**80.0%**
AST	79.5	-22.0%	-19.6%	-27.2%
ALT	36.3	**-31.1%**	**-32.8%**	-26.2%
Creatinine	0.38	10.5%	10.5%	**21.1%**
Total protein	6.87	1.6%	**6.3%**	**6.8%**
Albumin	3.19	-0.3%	**5.6%**	**6.6%**
Globulin	3.68	3.3%	**6.8%**	**7.1%**
A/G	0.87	-3.5%	-1.1%	-0.5%
Cholesterol	73.00	**38.4%**	**57.9%**	**88.4%**
Female	**control**	**10 mg/kg**	**30 mg/kg**	**100 mg/kg**
Chloride	101.8	-1.3%	**-2.9%**	**-3.2%**
Calcium	11.13	4.8%	**6.7%**	**5.8%**
AST	80	98.3%	94.4%	-10.0%
ALT	37.7	123.3%	72.9%	-15.6%
Total protein	7.55	**6.5%**	**14.6%**	**12.7%**
Albumin	3.8	6.3%	**8.4%**	5.8%
Globulin	3.75	6.9%	**20.8%**	**19.7%**
A/G	1.01	-0.6%	**-10.2%**	**-11.6%**
Cholesterol	92.60	**37.8%**	**88.2%**	**117.3%**
Triglyceride	59.30	70.5%	78.6%	**102.4%**

Hematology – Mild (<10%) anemia in dosed females with no clear dose dependence and no change in reticulocytes or MCV

Coagulation – Dose dependent increase in APPT, ~30% in 100 mg/kg males on day 183, not statistically significant; Dose dependent decrease in APPT, ~ 30% in 100 mg/kg females on day 183, statistically significant; Dose dependant decrease in prothrombin time, ~12% in 100 mg/kg females on day 183, statistically significant

Urinalysis – There were no toxicologically significant changes in urine parameters; nevertheless, in both sexes and mostly at the 30 and 100 mg/kg/day dose groups beginning on Day 22 and persisting through Day 183 there were sporadic incidences of an unclassified rectangular-shaped crystal observed in urine specimens. The investigators could not explain the etiology and significance of these crystals, but the majority them were seen in groups that had the highest frequency of other clinical pathology alterations, leading this reviewer to believe that they are test drug and possibly a metabolic product. Nevertheless, the rare occurrence of these structures in controls confounds this interpretation and suggests some relationship to the vehicle. These structures were not seen at recovery.

Reference ID: 3175869

Gross pathology
Interim Terminal – no toxicologically significant pathology
Interim Recovery – no toxicologically significant pathology

Main group

- Minimal to severe decreases in prostate gland size in males dosed with 30 mg/kg/day or more
- Minimal to severe decreases in seminal vesicle size in males dosed with 10 mg/kg/day or more
- Mildly enlarged uteri in females dosed with 100 mg/kg/day or more
- Minimally enlarged pituitary gland sizes in females dosed with 10 mg/kg/day
- A single splenic mass (hemangiosarcoma neoplasm) in one male dosed with 100 mg/kg/day – etiology unknown

Recovery – Mildly enlarge pituitary glands in females

Organ Weights
Interim Terminal – Not statistically evaluable
Interim Recovery – Not statistically evaluable

Main Group – The following table from the study report shows the percentage changes in organ weights in the main group animals after 26 weeks of dosing.

Reference ID: 3175869

Test article-Related Organ Weight Changes
Terminal
Male and Female (Percent change relative to controls)

Dose level: mg/kg/day	10		30		100	
Sex	M	F	M	F	M	F
Body Weight	7	5	3	1	1	10
Liver (g)	↑15	↑30 [b]	↑30 [b]	↑62 [b]	↑44 [b]	↑102 [b]
Liver /BWt %	↑8	↑24 [a]	↑27 [b]	↑61 [b]	↑44 [b]	↑84 [b]
Liver /BrWt ratio	↑12	↑33 [b]	↑31 [b]	↑66 [b]	↑41 [b]	↑103 [b]
Prostate gland (g)	↓33 [b]	NA	↓51 [b]	NA	↓55 [b]	NA
Prostate gland /BWt %	↓37 [b]	NA	↓54 [b]	NA	↓56 [b]	NA
Prostate gland /BrWt ratio	↓34 [b]	NA	↓49 [b]	NA	↓55 [b]	NA
Seminal Vesicles (g)	↓46 [b]	NA	↓59 [b]	NA	↓76 [b]	NA
Seminal Vesicles /BWt %	↓50 [b]	NA	↓60 [b]	NA	↓76 [b]	NA
Seminal Vesicles /BrWt ratio	↓48 [b]	NA	↓59 [b]	NA	↓77 [b]	NA
Pituitary gland (g)	↑23 [a]	↑32	↑28 [b]	↑36	↑18	↑27
Pituitary gland /BWt %	↑14	↑30	↑24 [b]	↑39	↑17	↑17
Pituitary gland /BrWt ratio	↑20	↑35	↑31 [b]	↑40	↑16	↑29
Adrenal gland (g)	↑27	↑12	↑23	↑23	↑8	↑42 [b]
Adrenal gland /BWt %	↑20	↑10	↑20	↑24	↑9	↑30 [a]
Adrenal gland /BrWt ratio	↑25	↑13	↑25	↑26	↑5	↑42 [b]
Epididymides gland (g)	↓16 [b]	NA	↓21 [b]	NA	↓27 [b]	NA
Epididymides /BWt %	↓21 [b]	NA	↓23 [b]	NA	↓27 [b]	NA
Epididymides /BrWt ratio	↓18 [b]	NA	↓20 [b]	NA	↓29 [b]	NA

↑ - Increased; ↓ - Decreased
BWt – Body Weight; BrWt – Brain Weight
NA – Not Applicable
[a] = Significantly different from control; ($p<0.05$)
[b] = Significantly different from control; ($p<0.01$)

[Excerpted from Applicant's submission]

Histopathology –
Interim Terminal – The following table from the study report shows the incidence of microscopic pathology in rats treated for five weeks. There was also centrilobular hypertrophy of the hepatocytes in 8/12 males and 9/12 females (not shown in this table). This hepatocyte hypertrophy consisted of cytoplasmic enlargement and eosinophilic alteration of the hepatocytes in the centrilobular regions of the liver.

Reference ID: 3175869

Interim Terminal Necropsy Test Article-Related Microscopic Observations Summary Table
Interim Terminal
Male and Female

Dose level: mg/kg/day		**0**		**10[a]**		**200**	
Sex		**M**	**F**	**M**	**F**	**M**	**F**
Number Examined		**2**	**2**	**1**	**0**	**12**	**12**
minimal		0	0	0	0	8	9
Prostate							
Depletion, secretory		0	NA	0	NA	6	NA
	-minimal	0	NA	0	NA	2	NA
	-mild	0	NA	0	NA	3	NA
	-moderate	0	NA	0	NA	1	NA
Seminal vesicles							
Depletion, secretory		0	NA	0	NA	10	NA
	-minimal	0	NA	0	NA	7	NA
	-mild	0	NA	0	NA	3	NA
Mammary gland							
Atrophy		0	0	1	0	9	0
	-mild	0	0	1	0	6	0
	-moderate	0	0	0	0	2	0
	-severe	0	0	0	0	1	0
Uterus with cervix							
Dilatation, gland/lumen, minimal		NA	0	NA	0	NA	6
Pituitary gland							
Hyperplasia, diffuse, pars distalis, minimal		0	0	0	0	0	2
Hypertrophy/hyperplasia, minimal		0	0	0	0	7	0
Thyroid gland							
Hypertrophy/hyperplasia, follicular cell		0	0	0	0	8	2
	-minimal	0	0	0	0	6	2
	-mild	0	0	0	0	2	0
Adrenal gland							
Hypertrophy/hyperplasia, diffuse cortical, minimal		0	0	1	0	6	11

NA – Not Applicable/Not Available
[a] Unscheduled Death

[Excerpted from Applicant's submission]

Terminal Necropsy
The following tables from the study report show the incidence and severity of microscopic pathologies in the main group of animals at terminal necropsy.

Terminal Necropsy Test Article-Related Microscopic Observations Summary Table
Male and Female
Terminal

Dose Level (mg/kg/day)		**0**		**10**		**30**		**100**	
Sex		**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Number Examined		**11**	**11**	**10**	**10**	**10**	**11**	**10**	**12**
Liver									
Hypertrophy, hepatocyte, centrilobular, minimal		0	0	0	2	2	3	1	0
Mammary gland									
Atrophy		0	0	10	0	10	0	8	0
	-mild	0	0	2	0	1	0	0	0
	-moderate	0	0	5	0	6	0	5	0
	-severe	0	0	3	0	3	0	3	0
Dilatation, gland/lumen		0	1	0	3	0	3	0	4
	-minimal	0	0	0	3	0	2	0	0
	-mild	0	1	0	0	0	1	0	4
Hyperplasia, lobular		0	1	0	0	0	2	0	3
	-minimal	0	1	0	0	0	1	0	2
	-mild	0	0	0	0	0	1	0	1
Prostate gland									
Atrophy		0	NA	0	NA	2	NA	4	NA
	-minimal	0	NA	0	NA	2	NA	3	NA
	-mild	0	NA	0	NA	0	NA	1	NA
Depletion, secretory		0	NA	4	NA	10	NA	9	NA
	-mild	0	NA	4	NA	4	NA	2	NA
	-moderate	0	NA	0	NA	5	NA	6	NA
	-severe	0	NA	0	NA	1	NA	1	NA
Seminal vesicle									
Atrophy		0	NA	1	NA	5	NA	6	NA
	-minimal	0	NA	0	NA	1	NA	1	NA
	-mild	0	NA	1	NA	4	NA	5	NA

Terminal Necropsy Test Article-Related Microscopic Observations Summary Table
Male and Female
Terminal

Dose Level (mg/kg/day)	**0**		**10**		**30**		**100**	
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Number Examined	**11**	**11**	**10**	**10**	**10**	**11**	**10**	**12**
Depletion, secretory	0	NA	8	NA	9	NA	10	NA
-minimal	0	NA	1	NA	0	NA	0	NA
-mild	0	NA	3	NA	3	NA	0	NA
-moderate	0	NA	4	NA	6	NA	10	NA
Uterus with cervix								
Dilatation, gland/lumen	NA	0	NA	2	NA	3	NA	4
-minimal	NA	0	NA	0	NA	1	NA	0
-mild	NA	0	NA	2	NA	2	NA	4
Adrenal gland								
Hypertrophy/hyperplasia, diffuse cortical	0	0	0	1	0	2	0	7
-minimal	0	0	0	1	0	2	0	6
-mild	0	0	0	0	0	0	0	1
Pituitary gland								
Hyperplasia, diffuse, pars distalis, minimal	0	0	0	1	0	5	0	7
Hypertrophy/hyperplasia	0	0	7	0	10	0	8	0
-minimal	0	0	7	0	9	0	2	0
-mild	0	0	0	0	1	0	6	0
Thyroid gland								
Hypertrophy/hyperplasia, follicular cell, minimal	0	0	0	1	0	5	0	9
Kidneys[a]								
Nephropathy, chronic progressive	2	0	3	2	4	4	7	6
-minimal	2	0	3	2	3	4	6	5
-mild	0	0	0	0	1	0	1	1

NA – Not Applicable/Not Available
[a]change considered to be possibly test article related.

[Excerpted from Applicant's submission]

Liver hepatocyte hypertrophy manifested as cytoplasmic enlargement and eosinophilic alteration of the hepatocytes in the centrilobular regions of the liver.

Mammary gland atrophy was limited to male rats and appeared as decrease in size and numbers of the glandular cells comprising the mammary gland. Mammary gland lobular hyperplasia was limited to females and consisted of an increase in the number of glandular cells comprising the mammary gland. Mammary gland dilatation was limited to females and consisted of an expansion or widening of mammary tissue lumens and ducts.

Atrophy within the prostate and seminal vesicles consisted of a decreased size and number of glandular cells. There was secretory depletion within the prostate and seminal vesicles. Uterine dilatation manifested as enlargement of the lumen. These toxicities are directly related to the mechanism of action of MDV3100.

Adrenal gland hypertrophy and hyperplasia primarily affected the zona fasciculata cortical cells that manifested as diffuse cytoplasmic enlargement and eosinophilic alteration with an overall increased number of cortical cells and increase in adrenal gland volume. Pituitary gland hypertrophy and hyperplasia in males affected the pars distalis and appeared as an increased number of cells. The cells were enlarged with cytoplasmic vacuoles which often displaced the nucleus peripherally.

Pituitary gland hyperplasia in females affected the pars distalis diffusely and consisted of an increased basophilia and number of cells, leading to an overall increase in the pituitary gland size. Thyroid gland hypertrophy and hyperplasia was limited to females and consisted of a slight enlargement and number of follicular cells, usually with follicular infoldings and a reduction colloid. The investigators considered that thyroid follicular cell hypertrophy and hyperplasia were associated with the liver hepatocyte hypertrophy present, because increases in functional hepatocellular mass can cause thyroid proliferation through alterations in thyroxine metabolism and release of thyroid stimulating hormone from the pituitary.

Chronic progressive nephropathy appeared as one or more of the following microscopic findings; tubular degeneration, tubular basophilia, tubular casts, glomerular and basement membrane thickening, interstitial fibrosis, and interstitial subacute to chronic inflammation. While chronic progressive nephropathy is common in rats, the dose-related increase in incidence and severity suggests that this is a drug-related toxicity.

At the recovery necropsy, some pathology remained in the mammary gland from male (100 mg/kg/day), and female (≥10 mg/kg/day) rats, but this effect showed signs of resolution. There was also residual diffuse hyperplasia of the pars distalis pituitary gland in females (100 mg/kg/day) and chronic progressive nephropathy in females (≥30 mg/kg/day). It is not clear if these latter two toxicities were resolving.

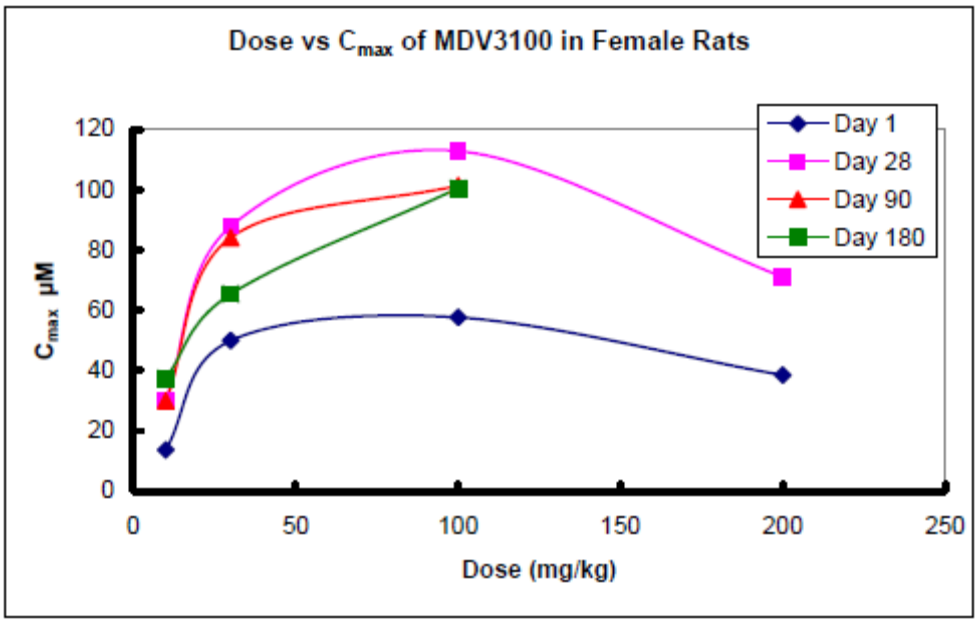
Toxicokinetics

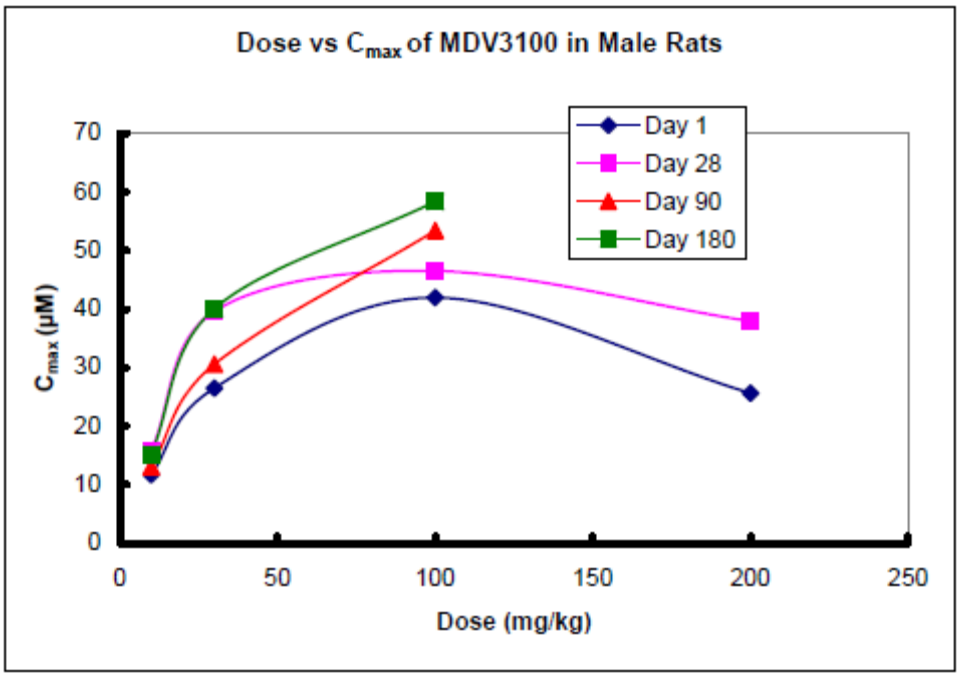
The following table shows the C_{max} values for male and female rats at different times during the study. Values in females are consistently higher when compared to males. This is possibly due to significant first pass metabolism that is greater in males.

Reference ID: 3175869

C_{max} µM				
Dose Female	Day 1	Day 28	Day 90	Day 180
10	13.7	30.1	29.9	37.5
30	50.0	87.9	84.2	65.5
100	57.7	112.8	101.4	100.6
200	38.5	71.1		
Dose Male	Day 1	Day 28	Day 90	Day 180
10	11.7	15.8	13.0	15.2
30	26.5	39.6	30.6	40.1
100	42.0	46.5	53.4	58.4
200	25.6	37.9		

The following graphs show that C_{max} does not increase linearly with dose, but rather reaches a maximal value at the 100 mg/kg dose. The C_{max} values increase with time on study. This unusual pattern suggests changes in absorption.

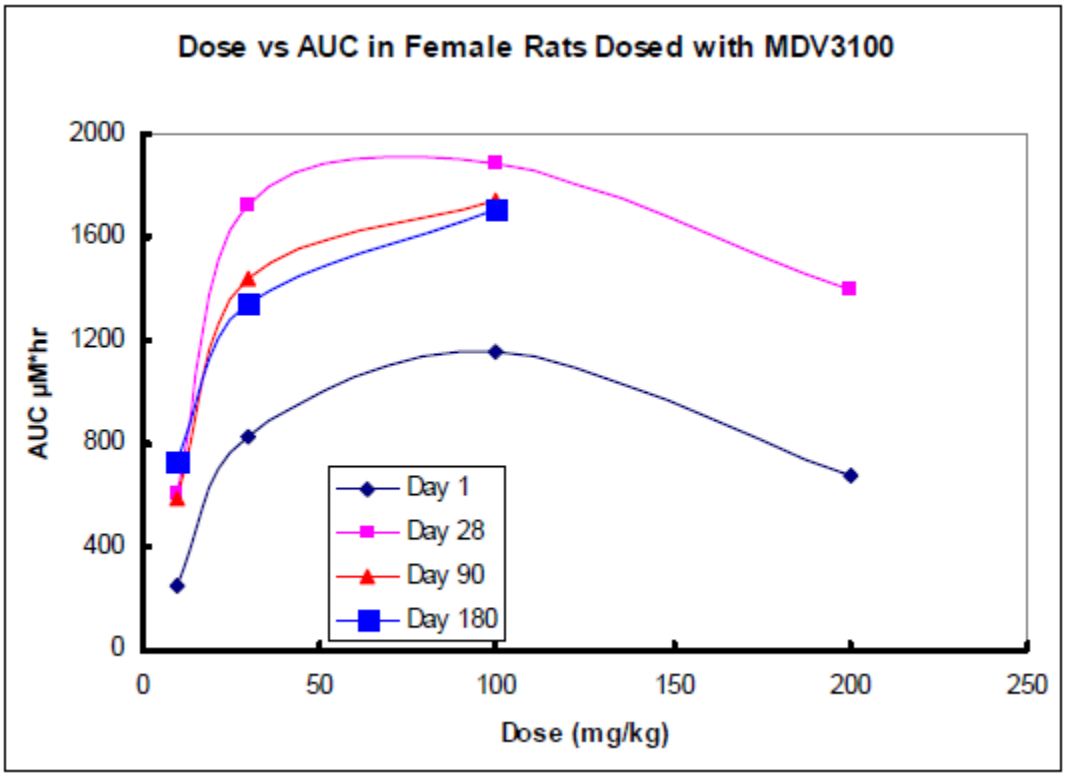


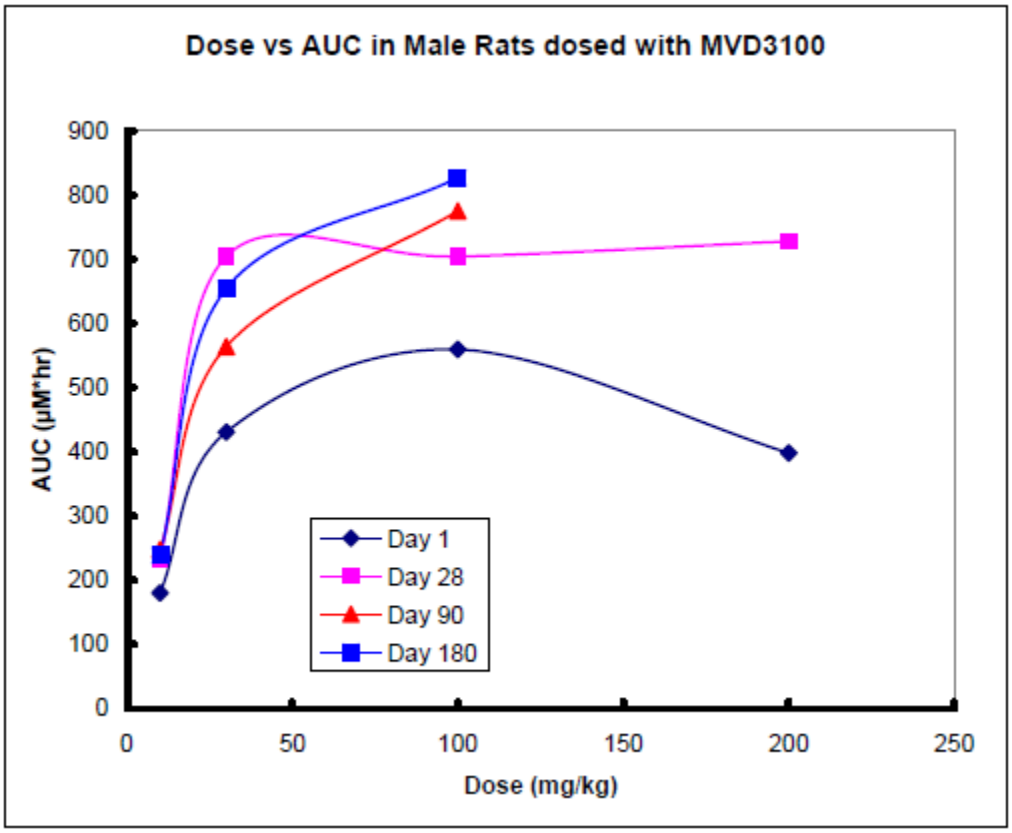


The following table shows that, like C_{max}, AUC does not increase linearly with dose. Exposure is significantly greater in females.

AUC µM*hr				
Dose Female	Day 1	Day 28	Day 90	Day 180
10	249.8	602.9	587.9	732.1
30	822.6	1727.0	1436.3	1345.8
100	1154.2	1882.0	1744.2	1707.6
200	678.3	1395.3		
Dose Male	Day 1	Day 28	Day 90	Day 180
10	180.4	232.6	247.6	239.0
30	430.7	704.1	564.2	654.6
100	559.9	704.1	775.2	826.9
200	398.4	727.8		

The following two graphs show AUC as a function of dose.





[End of review of Study No. PRO3100NC39 excerpted from Dr. W. David McGuinn, Jr.'s review.]

Reviewer's comments:
The Applicant stated that the dose selection was based on toxicity data from previously conducted 1-month, repeat-dose toxicity studies in rats, reported NOAEL for (b) (4) ® *(3 g/kg), and and the maximum feasible dose of MDV3100 which can be administered to rats due to the limit of solubility of MDV3100 in* (b) (4) ® *(45 mg/mL) . The concentrations of enzalutamide for the 100mg/kg and 200 mg/kg dosing formulations were 45 and 90 mg/mL, respectively. Analysis of dosing formulations showed that all dosing formulations appeared to be solutions, except the high-dose formulation, 90 mg/mL (200 mg/kg/day dose group) which appeared to be a suspension.*

Study Number: **PRO3100NC18 ((b) (4) Study Number 7792-103)**
Study Title: **4-Week oral capsule toxicity and toxicokinetic study with MDV3100 in dogs with a 4-week recovery period.**

[The review of Study No. PRO3100NC18 is reproduced verbatim below, with some changes in formatting for consistency purposes, as it appeared in the review (dated April 12, 2007) of IND 74563 for MDV3100 conducted by Doo Y. Lee Ham, Ph.D.]

Study title: 4-Week oral capsule toxicity and toxicokinetic study with MDV3100 in dogs with a 4-Week recovery period

Key findings:

- Seven dogs (3M and 3F at HD and 1M control) were euthanized on D4-29
- Excessive salivation was seen in HD group, and vomitus and fecal changes were noted in HD group and 1 or 2 dogs at LD and MD and control (this may be related to the vehicle)
- Dose-related decreases in serum testosterone values at MD and HD, increased serum cholesterol values at HD and hyperglycemic effect were noted in all treated groups
- Major target organs: lung and GI tract (M and F at HD) and male reproductive organs (seminiferous tubular degeneration, testicular toxicity, and prostatic atrophy).
- All clinical findings were reversible and the reproductive tract findings in the LD males were less severe following a 28-day recovery period.
- The NOAEL is 30 mg/kg (600 mg/m^2).

Study no:	Study no. 0078-2004-R
Volume/Pages:	Volume 5 and 6, Pages 1-581
Conducting laboratory and location:	PRO3100NC18(Applicant reference number)/ 7792-103 ((b) (4) study number) (b) (4)
Date of study initiation:	20-Sep-2006
GLP compliance:	Yes
QA report:	Yes
Drug, lot #, radiolabel, and % purity:	MDV3100 lot#/Batch# 09060031, 99.0% purity
Formulation/vehicle:	(b) (4) ™ lot# 102776, 100% purity
Dosing:	Once daily for 28 days or 4 weeks
Species/strains:	Beagle dogs
#/group or time point (main study):	4 or 6/sex/group
Satellite groups used for toxicokinetics:	3 or 9/sex/group
Age:	Approximately 12 months old
Weight:	7.9-12.2 kg

Doses were administered as the following table:

Reference ID: 3175869

Group[a]	No. of Animals Male	No. of Animals Female	Dose Level[b] (mg/kg/day)	Dose Concentration (mg/mL)
1 (Control)[c, d, e]	6	6	0	0[e]
2 (Low)[c,d]	6	6	10	45
3 (Mid)[c,d]	4	4	30	45
4 (High)[c,d]	6	6	100/60	45

a Group 1 received gelatin capsules filled with (b) (4)
b The dose levels and concentrations were based upon the outcome of (b) (4) Study No. 7792-101.
c Surviving toxicity animals designated for final sacrifice (4 animals/sex in Groups 1, 2, and 3) were terminated on Day 30 after 28 days of dose administration. Group 4 animals were all terminated after 25 days of dose administration on Day 30. The number of dosing days was reduced from 28 in Group 4 due to toxicity noted at 100 mg/kg/day during the first 4 days of dosing. A brief treatment-free period (3 days) was implemented prior to the reintroduction of MDV3100 in this group on Day 8 at 60 mg/kg/day.
d Toxicity animals designated for recovery sacrifice [(1male in Group 1 and 2 animals/sex in Groups 1 (females) and 2 (both sexes)] underwent 4 weeks of recovery following 28 days of dose administration. There were no Recovery animals assigned for Group 4 due to mortality.
e Control capsules were filled with the same volume of (b) (4) used to fill the 100/60 mg/kg/day group's capsules based on individual animal weights.

(Excerpted from Applicant's submission)

Observations and times:

Clinical signs:	Twice daily on Day 1 and weekly thereafter
Body weights:	Weekly
Food consumption:	Weekly
Ophthalmoscopy	Pre-dose -4, days 24 and 27
ECG:	Days 1 and 28 ~2-6 hrs post-dose
Hematology:	Day 30 and recovery day 29
Clinical chemistry:	Day 30 and recovery day 29
Gross Pathology:	Day 30
Histopathology:	Day 30
Toxicokinetics:	Blood samples were collected on days 1, 14, and 28 as follow: Day 1: pre-dose, 2, 4, 8, 12, and 24 hrs post-dose Day 14: pre-dose, 2, 4, 8, 12, and 24 hrs post-dose Day 28: pre-dose, 2, 4, 8, 12, 24, 36, and 48 hrs post-dose In the recovery animals, an additional sample was scheduled after the Day 28 dose at 72 hrs post-dose

Results:

Mortality:

Prior to scheduled necropsy, three HD males (H45664, H45668 and H45669) on days 4, 29 and 5, respectively) and three HD females (H45687, H45690, and H45691) on days 11, 29 and 15, respectively) at the HD (100/60 mg/kg/day), and one control male (H45648 on day 5) were euthanized.

Clinical signs:

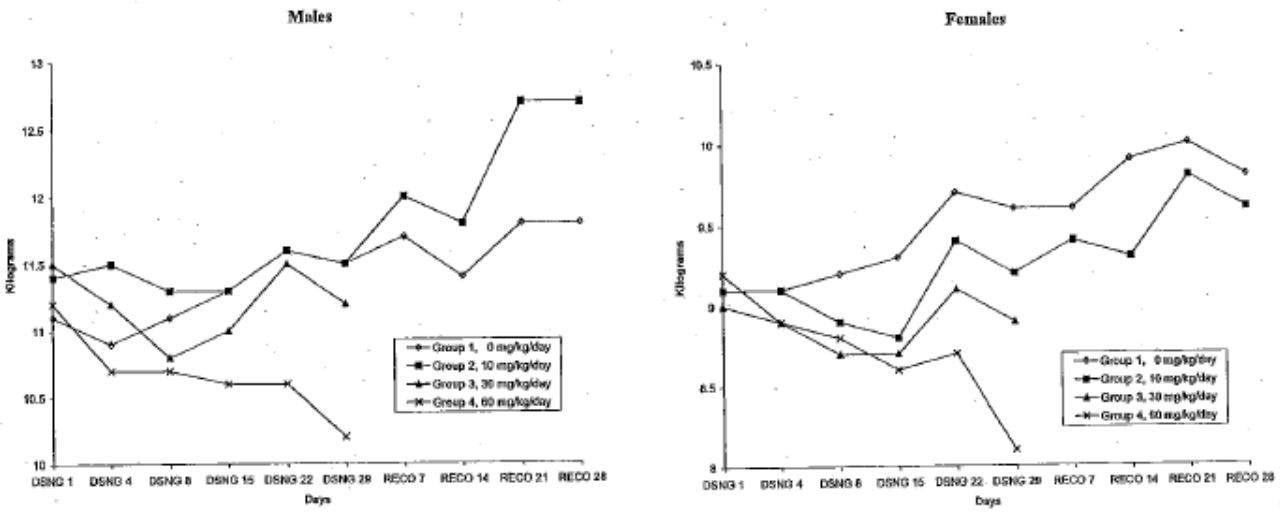
Clinical signs of toxicity observed in all dogs at HD included ataxia, decreased reactivity to stimuli, face pressing, hypoactivity, excessive salivation, vomitus, dilated pupils and/or red conjunctivae and/or facial changes. Excessive salivation was seen in most of the HD group, about 50% at the MD and 25% at control dogs. Vomitus was noted in all the treated dogs, including controls and was attributed to the vehicle, (b) (4) ™. Fecal changes were seen sporadically in the HD dogs and 1 or 2 dogs at LD and MD and in controls (this may be related to the vehicle, for this finding was not noted in recovery).

Body temperatures were normal. No treatment-related clinical signs were seen during the recovery period.

Body weight/food consumption:

Significant decreases (11-15.6%) in body weight change were observed in males at 30 mg/kg for the days 1 to 8, 22 to 29 intervals and at 100/60 mg/kg for days 1 to 29. Males at 100/60 mg/kg lost 0.8 kg over 29 days. Significant decreases were observed in females at doses of 10 and 30 mg/kg for the study day 1 to 8 and at 100/60 mg/kg for the study day 1 to 15, 22 to 29.

Figure 8. Mean Body Weight Data in Dogs

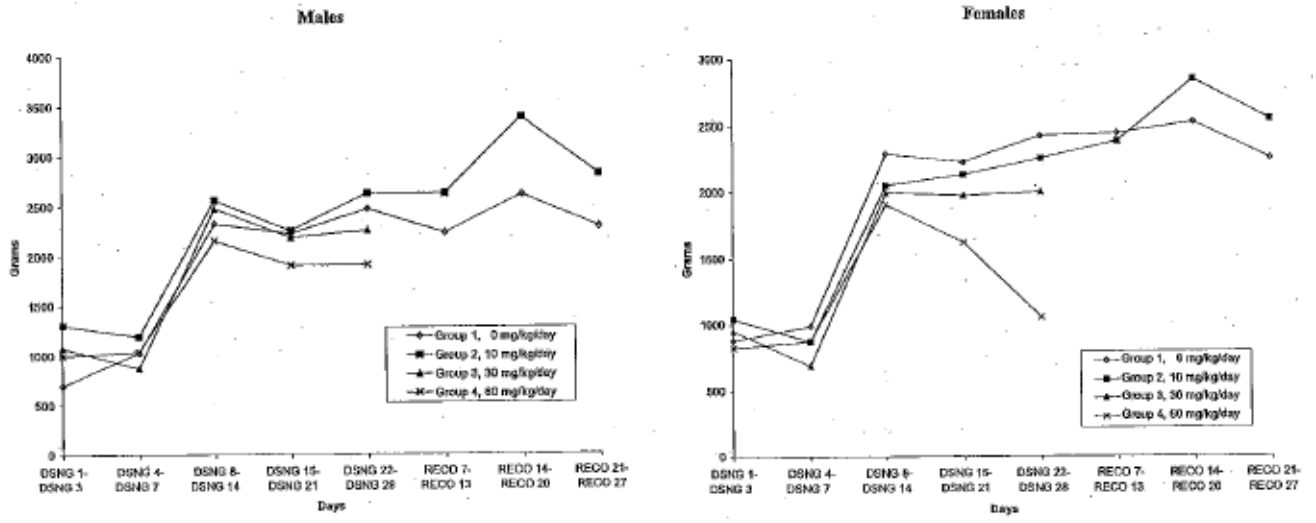


[Excerpted from Applicant's submission]

Similarly significant decreases in mean food consumption were observed in 30 mg/kg females at the day 1 to 4, 8 to 15, and in both sexes at 100/60 mg/kg between the 14 to 28 day interval when compared to controls. There were no effects on food consumption during the recovery period.

Reference ID: 3175869

Figure 9. Mean Food Consumption Data in Dogs



[Excerpted from Applicant's submission]

Ophthalmic examinations:

No treatment-related ophthalmic changes were observed.

ECG measurements:

No treatment-related ECG changes (i.e., RR or QTc intervals) were observed.

Hematology: Not remarkable
Coagulation: Not remarkable
Urinalysis: Not remarkable

Clinical chemistry:

On day 29, dose-related reductions in serum testosterone values were observed at doses ≥30 mg/kg. Serum cholesterol values increased at HD and glucose values were increased in all treated groups relative to control during the treatment period. Cholesterol and glucose differences were not considered to be of toxicological significance.

	Serum Chemistry Findings Following 4-Week Oral Gavage Toxicity Study with 4-Week Recovery Period							
Dose, mg/kg/day	0		10		30		60/100	
Sex of Animals	M	F	M	F	M	F	M	F
Number of Animals	6	6	6	6	4	4	6	6
Serum Chemistry Day 29								
Cholesterol (mg/dL)	119	73	**137**	79	**149**	110	**162**	**130**
Glucose (g/dL)	75	74	**88**	83	**93**	86	**103**	**101**
Testosterone (ng/dL)	281	NA	304	NA	**42**	NA	**21**	NA

Note: Bold= statistically significant at p<0.05; NA= Not Applicable

Gross Pathology:

Gross necropsy findings in moribund animals included discolored mucosa in the stomach, colon, ileum, and in jejunum in one control male dog and one HD female, which correlated with mucosal congestion microscopically. Some of males had mottled and/or uncollapsed lungs. Slight pulmonary inflammation was also noted in the control animal that was terminated moribund.

Pathological findings from the 7 dogs that died/euthanized early revealed the followings:

Dog (H45664♂, HD)- no cause of death but macroscopic mottled lung

Dog (H45668♂, HD)- no cause of death but had small foci of hemorrhage and myofiber necrosis in the heart and in papillary muscle of the septum; macroscopic findings in stomach and thyroid with no microscopic correlative findings

Dog (H45669♂, HD)- had an uncollapsed mottled lung, pulmonary inflammation, similar to that of the control male but of greater severity. Moderate to severe pulmonary inflammation could be the cause of the moribund sacrifice.

Dog (H-45687♀, HD)-moderate pulmonary inflammation similar to that of the HD male.

Dog (H-45690♀, HD)-no cause of death but had convulsions prior to termination and necropsy findings included GI discoloration, and increased mucosal congestion.

Dog (H-45691♀, HD)-no cause of death but skin abrasion was noted

Dog (H-45648♂,Control)-no cause of death but had hypoactivity, vomitus, and GI tract discoloration correlated increased mucosal congestion, and had mild, acute pulmonary inflammation.

Dose, mg/kg/day	0		10		30		60/100	
No. of Animals[a] Examined	4	4	4	4	4	4	3	3
Sex of Animals	M	F	M	F	M	F	M	F
Gross Pathology (Day 30)								
Lung, Mottled	0/1[b], 0/4	1/4	1/4	1/4	1/4	1/4	2/3[b], 1/3	1/3[b], 0/3
Lung, Uncollapsed							1/3	0/3[b], 0/3
Lungs, Discolored	0/1[b], 0/4	0/4	1/4	0/4	0/4	0/4	0/3[b], 0/3	0/3[b], 0/3

Reference ID: 3175869

Stomach, duodenum, colon, ileum, jejunum, and/or cecum discolored (mucosa)	0/1[b], 0/4	0/4	0/4	0/4	0/4	0/4	0/3[b], 0/3	1/3[b], 0/3

[a] One control male and 3 HD males and females were terminated early. High dose was reduced during week 1 from 100 to 60 mg/kg
[b] First number in column represents dogs terminated early due to moribund.

Organ weights:

The relative prostate weights for all males given MDV3100 were markedly reduced in a statistically significant fashion compared to the control.

Table 37. Relative Reproductive Organ Weights at 28-day Necropsy in Dogs

Organ	Control	10 mg/kg	30 mg/kg	100/60 mg/kg
Prostate	0.103	0.032[a]	0.025[a]	0.028[a]
Epididymis	0.037	0.034	0.030	0.028
Testis	15.39	17.75	12.10	10.39

[a] Statistically significant

`Histopathology:

MDV3100-induced microscopic findings were observed mainly in the male reproductive organs for all treated animals at all dose levels compared to the control group. All clinical findings were reversible but the reproductive tract findings in the LD males were less severe following a 28-day recovery period.

Dose, mg/kg/day	0		10		30		60/100	
No. of Animals[a] Examined	4	4	4	4	4	4	3	3
Sex of Animals	M	F	M	F	M	F	M	F
Terminal Sacrifice (Day 30)								
Lung								
-Acute inflammation	1/1[b],1/4						1/3[b],1/3	2/3[c]
-Chronic inflammation	2/4	1/4	4/4	0/4	3/4	2/4	2/3	2/3
-Lung hemorrhage	1/1[c]						1/1[c]	1/1[c]
-Pulmonary edema							1/1[c]	
Reproductive organs								
-Epididymis Hypospermia	0/4		1/4		1/4		1/3	
-Epididymis exfoliated cells	0/4		1/4		3/4		3/3	
	0/4		4/4		4/4		3/3	
-Epididymis vacuolation	0/4		4/4		4/4		3/3	
-Prostate atrophy	0/4		2/4		2/4		0/3	
-Testis hypospermatogenesis	0/4		2/4		4/4		3/3	
-Testis degeneration of seminiferous tubules								
Recovery Animals	1M	2F	2M	2F	-	-	-	-
Lung								
-Lung chronic	1/1	1/1	1/2	1/2	-	-	-	-

inflammation								
Reproductive organs	0/1		2/2		-		-	
-Prostate atrophy	0/1		1/2		-		-	
-Testis	0/1		2/2		-		-	
hypospermatogenesis	0/1		2/2		-		-	
-Testis degeneration of seminiferous tubules								

[a] One control male and 3 HD males and females were terminated early. High dose was reduced during week 1 from 100 to 60 mg/kg
[b] First number in column represents dogs terminated early due to moribund.
[c] Reported in unscheduled death.
- No MD and HD recovery groups

[End of review of Study No. PRO3100NC18 excerpted from Dr. Doo Y. Lee Ham's review.]

<u>Reviewer's comments:</u>
The following table summarizes the toxicokinetic parameters of MDV3100 obtained in Study No. PRO3100NC18:

Table 38. Summary of toxicokinetic parameters of MDV3100 in dogs. (Study No. PRO3100NC18)

TABULATED SUMMARY
Plasma Toxicokinetic Parameters for MDV3100

	Last Dose (Day 28)[a] C_{max} (µg/mL)	Last Dose (Day 28) AUC_{24hr} (µg/mL·hr)	$T_{1/2}$ (hr)
Group 2, 10 mg/kg			
Males (N = 6)	22.2 ± 7.62	424 ± 116	42.9 ± 0.178[c]
Females (N = 6)	20.2 ± 4.62	355 ± 89.2	72.5 ± NC[d]
Group 3, 30 mg/kg			
Males (N = 4)	41.9 ± 6.72	794 ± 91.8	NR ± NC[e]
Females (N = 4)	41.8 ± 11.1	735 ± 179	21.7 ± NC[d]
Group 4, 100/60 mg/kg[b]			
Males (N = 6)	56.0 ± 17.5[g]	1070 ± 349[g]	NR ± NC[e]
Females (N = 6)	59.6 ± 10.5[g]	1180 ± 155[g]	50.5 ± 37.4[f]

	Accumulation AUC_{24hr} Ratio		DN-AUC_{24hr} ([µg/mL·hr]/[mg/kg])
	Day 14/Day 1	Day 28/Day 1	Day 28
Group 2, 10 mg/kg			
Males (N=6)	3.23 ± 0.648	3.12 ± 0.987	42.4 ± 11.6
Females (N=6)	3.16 ± 0.761	3.01 ± 0.943	35.5 ± 8.92
Group 3, 30 mg/kg			
Males (N=4)	1.99 ± 0.280	2.50 ± 0.936	26.5 ± 3.06
Females (N=4)	2.02 ± 0.414	2.21 ± 0.692	24.5 ± 6.00
Group 4, 100/60 mg/kg[b]			
Males (N=6)	4.49 ± 2.51[g]	3.88 ± 0.873[g]	17.8 ± 5.83[g]
Females (N=6)	3.28 ± 0.917[h]	4.23 ± 1.78[g]	19.6 ± 2.60[g]

NR, non-reportable
NC, not calculated
a. Last dose was given on Day 28.
b. Group 4 (high-dose) dogs received 100 mg/kg on Days 1 to 4, during which time poor tolerability was noted. Treatment was withheld on Days 5 to 7. On Days 8 to 28, the dogs were treated at 60 mg/kg.
c. The terminal slope was not adequately described in any of the animals to reliably estimate this parameter (all values were non-reportable, NR).
d. The reported values correspond to observations in 1 dog.
e. The reported values correspond to observations in 2 dogs.
f. The reported values correspond to observations in 3 dogs.
g. The reported values correspond to observations in 4 dogs.
h. The reported values correspond to observations in 5 dogs.

[Excerpted from Applicant's table in Study Number PRO3100NC18.]

Study Number: **PRO3100NC38**
Study Title: **Dog 13 week toxicity study with 8 week recovery.**

[The review of Study No. PRO3100NC38 is reproduced verbatim below, with some changes in formatting for consistency purposes, as it appeared in the review (dated June 15, 2012) of IND (b) (4) for MDV3100 conducted by W. David McGuinn, Jr., M.S., Ph.D., D.A.B.T.]

13-Week Oral (Intragastric Intubation) Toxicity Study of MDV3100 in Male Dogs Including an 8-Week Recovery Period

Study number 1284-014
File name pro3011NC38-nonclinical-report.pdf
Laboratory (b) (4)
Study Date January 2008
GLP Yes
Audited Yes
Drug MDV3100, lot number 9070028, purity 98.3% Methods
Species: Male beagle dogs, 8 to 11 months old
Males 6.52 to 13.56 kg
Doses and N – The following table from the study report shows the allocation of dogs to the different study doses.

Group Assignments				
Group Number	Dose Level (mg/kg/day)	Number of Animals		
		Male		
		Total	Interim Recovery[a]	Recovery[b]
1	0	8	1	1
2	4	5		1
3	20	5		1
4	45	8	3	

[a] Following 10 weeks of dosing, selected animals were retained for an 8 week recovery period.
[b] Following 13 weeks of dosing, selected animals were retained for an 8 week recovery period.

Doses 0, 4, 20 or 45 mg/kg/day (0, 80, 400 or 900 mg/m^2/day).
Schedule Daily for 13 weeks in the 4 and 20 mg/kg dose groups and 5 controls
Daily for 10 weeks in the 45 mg/kg dose group and 3 controls
Formulation (b) (4)®
Route PO gavage
Dose volume 10 mL/kg per dose
Cage side exam Twice daily
Clinical exam A detailed clinical examination of each animal was performed on Day 3, daily from Days 6 to 12 (1 ± 0.25 hours postdose), and twice

Reference ID: 3175869

weekly starting on Day 13 through the end of the study (detailed clinical observations on Day 14 were conducted at 1 ± 0.25 hours postdose).

Body weights Pre-study then twice weekly

Food cons. Weekly

Hematology The following table shows the schedule for blood sampling

Sample Collection for Plasma Analysis

Dose level (mg/kg/day)	Study Intervals (Days)	Collection Intervals (Hours Postdose)	Volume (mL)	Collection Method
0[a], 4, 20, 45	1, 42	Predose, 2, 4, 8, 12, 24	1	Jugular Vein
0[a, b], 45[a]	70	Predose, 2, 4, 8, 12, 24	1	Jugular Vein
0[a, c], 45[c]	70	Predose, 2, 4, 8, 12, 24, 48, 72, 120, 168	1	Jugular Vein
0[a, d], 4, 20	85	Predose, 2, 4, 8, 12, 24	1	Jugular Vein

[a] Only the samples at 4 and 8 hours postdose were analyzed.
[b] Animals designated for the interim terminal necropsy.
[c] Animal(s) designated for the interim recovery necropsy.
[d] Animals designated for the terminal and recovery necropsies.

Clinical chem. Same as Hematology

Ophthalmology Pre-test and prior to necropsy

ECG Pre-test, pre-dose and approximately 4 hours post-dose during Weeks 1 and 13 (excluding the animals scheduled for the interim recovery necropsy), and again during Week 21. In addition three animals at 0 mg/kg/day and eight animals at 45 mg/kg/day received and ECG examination pre-dose and approximately 4 hours post-dose during Week 10 and all animals designated for the interim recovery necropsy during Week 18.

Urinalysis SD-1 prior to dosing then prior to necropsy

Histopathology Adequate battery

Necropsy Day 92 for 4 control, low dose (LD) and mid-dose (MD) dogs
Day 71 for 5 high dose (HD) and 2 control dogs
Day 126 for 3 HD and 1 control dogs (8 week recovery)
Day 147 for 1 control, 1 LD and 1 MD dog (8 week recovery)

Toxicokinetics The following table shows the toxicokinetic sampling

Reference ID: 3175869

Group	Treatment	Males	Toxicokinetics Blood Collection Times
1	0	8[a,b,c]	Predose and 2, 4, 8, 12, and 24 hr after dosing on Days 1, 42, 70, and 85; for the "recovery animals" the schedule on Day 70 was 2, 4, 8, 12, 24, 48, 72, 120, and 168 hr after dosing [c]
2	4	5[a]	Predose and 2, 4, 8, 12, and 24 hr after dosing on Days 1, 42, and 85.
3	20	5[a]	Predose and 2, 4, 8, 12, and 24 hr after dosing on Days 1, 42, and 85.
4	45	8[a,b]	Predose and 2, 4, 8, 12, and 24 hr after dosing on Days 1, 42, and 70; for animals designated for termination after the recovery period, the schedule on Day 70 was 2, 4, 8, 12, 24, 48, 72, 120, and 168 hr after dosing.

[a] Five animals were designated for termination on Day 92.
[b] Three animals were designated for termination after the recovery period. These dogs are referred to as "recovery animals."
[c] The toxicokinetics sampling schedule for the Group 1 dogs roughly matched that of the Group 4 animals for consistency among groups; however, only the 4- and 8-hr samples from the Group 1 dogs were analyzed for MDV3100 concentrations.

Results

Mortality – All animals survived to scheduled necropsy

Clinical Signs – No toxicologically significant changes

Body Weights – No toxicologically significant changes

Food Consumption – No toxicologically significant changes

Ophthalmology – No toxicologically significant changes

ECG – No toxicologically significant changes

Hematology – No toxicologically significant changes

Clinical chemistry – Minor increase in A/G ratio in MD and HD dogs animals

Urinalysis – No toxicologically significant changes

Coagulation – No toxicologically significant changes

Gross findings – A moderately small prostate was observed in one male at 4 mg/kg/day terminal necropsy. The microscopic correlate was a severe atrophy of the prostatic gland.

Organ Weights – There was a decrease in the absolute and relative epididymal (~37-39%) and prostatic weights (~66-72%) compared to control at the interim necropsy in HD dogs. The following table from the study report shows the decreases in prostate and epididymal weights in LD and MD dogs.

Treatment-Related Organ Weight Changes
Terminal Necropsy
Compared Control (% Difference)

Dose level	4 mg/kg/day	20 mg/kg/day
Sex	Male	Male
Epididymides absolute	↓26.4	↓18.8
Epididymides/Bwt	↓16.2	↓17.8
Epididymides /Brwt	↓32.6	↓23.9
Prostate gland absolute	↓75.1	↓50.1
Prostate gland /Bwt	↓69.9	↓47.5
Prostate gland /Brwt	↓76.4	↓51.8

↓ Value decreased compared to control

[Excerpted from Applicant's submission]

Histopathology – The following tables from the study report shows the drug related changes seen microscopically

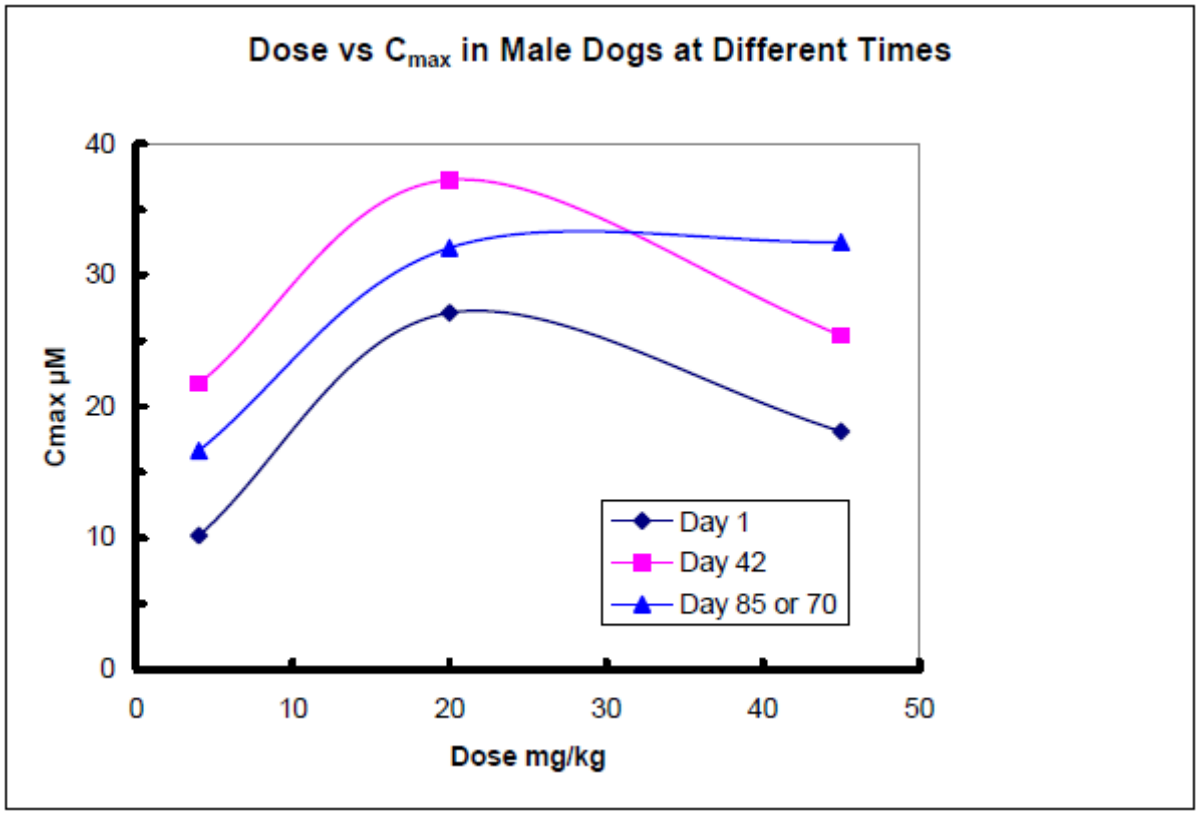
Treatment-Related Microscopic Changes Interim Necropsy Male		
Dose level: mg/kg/day	**0**	**45**
Number Examined	**2**	**5**
Prostate		
Atrophy, severe	0	5
Epididymides		
Atrophy	0	5
-minimal	0	1
-mild	0	3
-moderate	0	1
Oligospermia/germ cell debris, bilateral	0	5
-minimal	0	2
-mild	0	2
-moderate	0	1
Testes		
Hypospermatogenesis, bilateral, mild	0	1

Treatment-Related Microscopic Changes Terminal Necropsy Male			
Dose level: mg/kg/day	**0**	**4**	**20**
Number Examined	**4**	**4**	**4**
Prostate			
Atrophy, severe	0	4	4
Epididymides			
Atrophy	0	1	4
-minimal	0	0	3
-mild	0	1	1
Oligospermia/germ cell debris, bilateral, mild	0	0	2
Testes			
Hypospermatogenesis, bilateral, minimal	0	1	2
Hypospermatogenesis, unilateral, minimal	0	1	0

[Excerpted from Applicant's submission]

Toxicokinetics

The following graph shows that the increase in C_{max} with increasing dose is again nonlinear, suggesting a limiting gastric absorption.

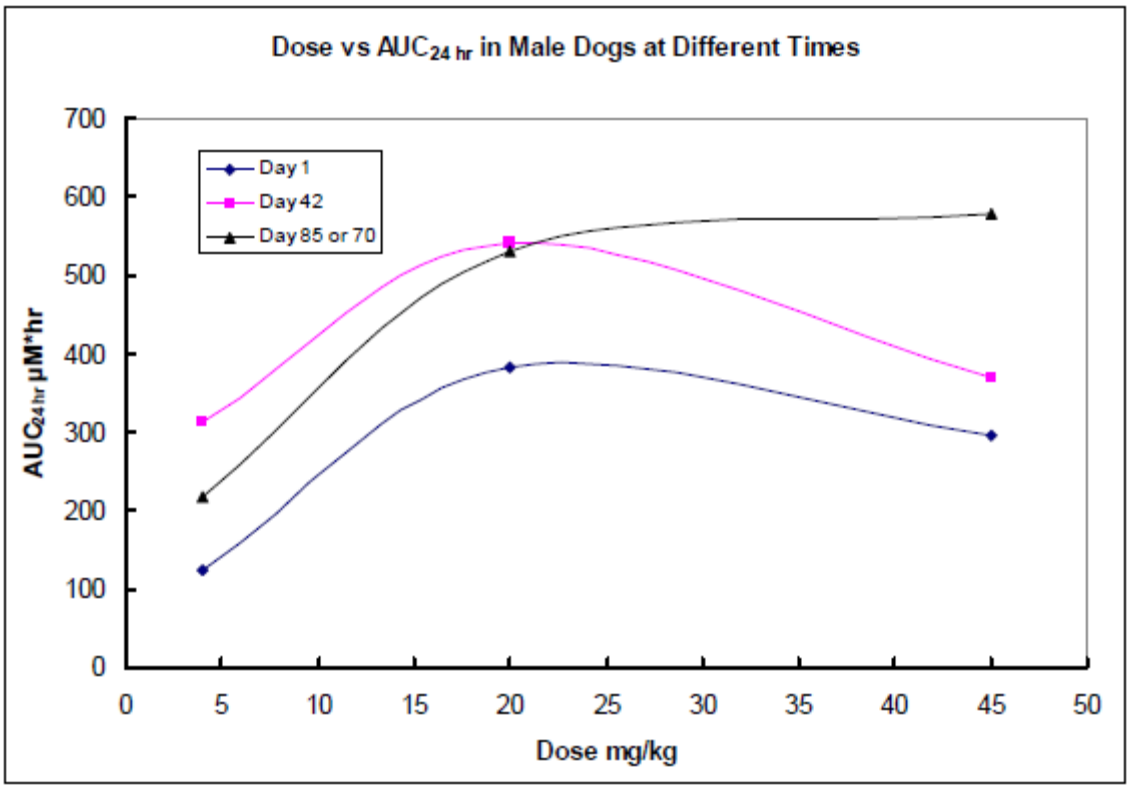


The following table shows that C_{max} values range from about 18 to 33 µM in the MD and HD groups and that the values are highly variable. This is almost exactly the range seen in clinical studies at steady state. There is some degree of accumulation, but it is less than two-fold.

C_{max} in Male Dogs at Different Days on Study

Dose mg/kg	Day 1	SD	Day 42	SD	Day 85 or 7	SD
4	10.2	2.1	21.7	3.4	16.6	4.8
20	27.1	10.9	37.3	7.3	32.1	8.9
45	18.1	5.8	25.4	8.5	32.5	10.1

The following graph shows the drug exposure, AUC, as a function of dose and day on study. Again the increase in exposure is non-linear and there is some accumulation with time on study.



The following table shows that AUC at 24 hours ranges from about 300 to about 580 µM*hr in the MD and HD dogs. This is slightly lower than the value of 650 µM*hr seen in humans over 24 hours with the 160 mg/day dose. At the end of the study, the AUC at 168 hours was 1335 µM*hr. Elimination appeared first order. The investigators did not calculate volume or clearance. T_{max} ranged from 2 to 4 hours. The mean terminal elimination half-life was 26 ± 2 hours in male dogs.

[End of review of Study No. PRO3100NC38 excerpted from Dr. W. David McGuinn's review.]

Reviewer's comments:
The following table summarizes the exposure values (AUC_{24hr}) of MDV3100 obtained in Study No. PRO3100NC38:

Table 39. Summary of AUC_{24hr} of MDV3100 in dogs. (Study No. PRO3100NC38)

Table Q. Summary of Descriptive Statistics for AUC_{24hr}

Dose Level (mg/kg/day)	AUC_{24hr} (µg*hr/mL)						AUC_{24hr}/Dose [(µg*hr/mL)/(mg/kg)]					
	Day 1		Day 42		Day 85 or Day 70[a]		Day 1		Day 42		Day 85 or Day 70[a]	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
4	57.9	11.7	145	32.4	101	28.3	14.5	2.93	36.2	8.11	25.3	7.08
20	178	82.2	251	53.8	246	95.1	8.89	4.11	12.6	2.69	12.3	4.75
45	137	50.9	172	47.9	269	87.6	3.04	1.13	3.82	1.06	5.97	1.95

[a] Day 85 for 4 and 20 mg/kg/day, and Day 70 for 45 mg/kg/day

[Excerpted from Applicant's Table Q in Study Report Number PRO3100NC38.]

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study Number: **PRO3100NC35 (b) (4) Study Number 7792-108)**
Study Title: **Salmonella-Escherichia coli/Mammalian-microsome reverse mutation assay with a confirmatory assay.**

[The review of Study No. PRO3100NC35 is reproduced verbatim below, with some changes in formatting for consistency purposes, as it appeared in the review (dated June 28, 2007) of IND 74563 for MDV3100 conducted by Doo Y. Lee Ham, Ph.D.]

Key findings:

- Tester strains (TA98, TA100, TA1535, TA1537, and WP2uvrA) incubated with MDFV3100 at concentrations of 156, 313, 625, 1250, 2500, and 5000 ug/plate with and without S9 did not induce reverse mutation at the histidine locus of S. typhimurium and tryptophan locus of E. Coli.

Methods

Strains/species/cell lines: S. typhimurium - TA98, TA100, TA1535, TA1537,
E. Coli – WP2uvrA

Reference ID: 3175869

Doses used in definitive study:
TA98, TA100, TA1535, TA1537, and WP2uvrA – 156, 313, 625, 1250, 2500, and 5000 ug/plate with and without S9

Basis of dose selection: Dose range finding experiment using plate incorporation and pre-incubation methods

Negative controls: DMSO

Positive controls: See Table below

Test Strain	S9 Mix	Positive Controls	Concentration (ug/plate)
TA98	+	Benzo[a]pyrene	2.5
TA98	-	2-nitrofluorene	1.0
TA100, TA1535, TA1537	+	2-aminoantracene	2.5
TA100, TA1535	-	Sodium azide	2.0
TA1537	-	ICR-191	2.0
WP2uvrA	+	2-aminoantracene	25.0
WP2uvrA	-	4-nitroquinoline-N-oxide	1.0

Incubation and sampling time: 3 hours in the presence of S9 and 24 hours in the absence of S9

Results:
In Vitro mutagenicity testing in the bacterial microsomal activation assay

Reference ID: 3175869

	Dose/Plate	Mean Revertants Per Plate with Standard Deviation										Back-ground Lawn[a]
		TA98		TA100		TA1535		TA1537		WP2*uvr*A		
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	
Microsomes: Rat Liver												
Vehicle Control		20	1	137	11	8	2	7	2	23	2	N
Test Article	156 µg	24	6	126	11	5	3	7	3	27	2	N
	313 µg	20	5	137	9	12	6	8	4	23	3	N
	625 µg	29	5	137	17	8	3	6	2	23	3	N
	1250 µg	32	7	157	16	8	2	13	5	25	4	N/NP[d]
	2500 µg	21	7	150	14	5	1	8	6	19	7	NP
	5000 µg	18	6	130	22	7	4	3	2	10	5	NP
Positive Control[b]		442	15	1130	77	95	2	124	19	373	32	N
Microsomes: None												
Vehicle Control		14	6	89	13	6	4	7	1	21	2	N
Test Article	156 µg	14	5	83	17	3	2	8	2	21	6	N
	313 µg	14	3	87	14	2	1	6	2	18	1	N
	625 µg	14	3	104	6	4	1	6	3	24	4	N
	1250 µg	11	3	106	4	5	2	8	2	21	3	N/NP[e]
	2500 µg	15	3	96	4	2	1	4	3	15	1	NP
	5000 µg	7	1	88	2	4	2	8	3	18	1	NP
Positive Control[c]		314	86	984	90	5	3	258	32	295	35	N

[a] Background Lawn Evaluation Codes:
N = normal R = reduced O = obscured A = absent P = precipitate

[b] TA98	benzo[a]pyrene	2.5 µg/plate	[c] TA98	2-nitrofluorene	1.0 µg/plate
TA100	2-aminoanthracene	2.5 µg/plate	TA100	sodium azide	2.0 µg/plate
TA1535	2-aminoanthracene	2.5 µg/plate	TA1535	sodium azide	2.0 µg/plate
TA1537	2-aminoanthracene	2.5 µg/plate	TA1537	ICR-191	2.0 µg/plate
WP2*uvr*A	2-aminoanthracene	25.0 µg/plate	WP2*uvr*A	4-nitroquinoline-N-oxide	1.0 µg/plate

[d] The first entry is the lawn evaluation for tester strains TA98, TA100, TA1537, and WP2*uvr*A.
The second entry is the lawn evaluation for tester strain TA1535.
[e] The first entry is the lawn evaluation for tester strain WP2*uvr*A.
The second entry is the lawn evaluation for tester strains TA98, TA100, TA1535, and TA1537.

[Excerpted from the Applicant's submission]

Study validity: The study was accepted as valid. Second experiment gave similar results. Test article did not show dose-dependent increase in revertant frequency or at least 2-fold increase as compared to control values.

Study outcome: MDV3100 was negative in the *in vitro* bacterial/microsomal activation reverse mutation assay.

Study title: Bacterial Mutation Assay.

Study no.:	MDV3100NC020 (M1) (b) (4) Study Number AD50VW.5021CH.BTL)
Study report location:	eCTD Section 4.2.3.3.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 17, 2012
GLP compliance:	Yes.
QA statement:	Yes. (E-signature)
Drug, lot #, and % purity:	MDPC0001, Batch (Lot) No. UP-05-88, Purity = 97.5%

Key Study Findings

In the *in vitro* bacterial reverse mutation assay with the plate incorporation method, MDPC0001, did not produce genotoxic responses with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2 *uvr*A, in the absence or presence of S9 activation.

Reference ID: 3175869

Methods

Strains:	*Salmonella typhimurium* strains TA98, TA1535, TA1537, TA100, and *Escherichia coli* strain WP2 *uvr*A
Concentrations in definitive study:	Plate incorporation method: 50 – 5000 μg/plate in the presence or absence of Aroclor 1254-induced rat liver S9 mix
Basis of concentration selection:	In a preliminary toxicity assay, MDPC0001 was assessed for cytotoxicity and mutagenicity at doses of 6.7, 10, 33, 67, 100, 333, 667, 1000, 333, and 5000 µg/plate with TA98, TA1535, TA1537, and TA100 in the presence or absence of the metabolic activation system. Cytotoxicity was assessed by examining bacterial lawn density and numbers of spontaneous revertants per plate. Toxicity was observed at 5000 µg/plate with all Salmonella tester strains in the absence of metabolic activation. No precipitation was observed.
Negative control:	Dimethyl sulfoxide (DMSO)
Positive control:	2-Nitrofluorene (2NF), sodium azide (SA), 9-aminoacridine (9AAD), methyl methanesulfonate (MMS)
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Tester strains, S9 or sham mix, and vehicle or MDPC0001 were added to molten selective top agar. After vortexing, the mixture was overlaid onto the surface of minimal bottom agar. After the overlay had solidified, the plates were inverted and incubated for 48 to 72 hours at 37°C. All dose levels of test article, vehicle control, and positive controls were plated in triplicate. The metabolic activation system consisted of an S-9 fraction prepared from livers obtained from Aroclor 1254 pretreated male Sprague-Dawley rats. The S-9 percentage was 10%, which is within the acceptable range. Plates were scored either entirely by an automated colony counter or entirely by hand, unless the plate exhibited toxicity. Cytotoxicity was assessed by examining bacterial lawn density by using a dissecting microscope.

Reference ID: 3175869

Study Validity

Selection of bacterial tester strains was adequate based upon Guideline for Industry: Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals (ICH S2A, April 1996). Positive controls produced expected responses. Dose selection for the plate incorporation method was adequate based upon use of a high dose of 5000 µg/plate which showed some toxicity without precipitation. The S9 concentration was 10% which it is within acceptable limits.

Criteria for a valid test was provided in the study report and all of the following criteria must have been met for the assay to be considered valid:

- All *Salmonella* tester strain cultures must demonstrate the presence of the deep rough mutation (*rfa*) and the deletion in the *uvr*B gene.
- Cultures of tester strains TA98 and TA100 must demonstrate the presence of the pKM101 plasmid R-factor.
- All WP2 *uvr*A cultures must demonstrate the deletion in the *uvr*A gene.
- All cultures must demonstrate the characteristic mean number of spontaneous revertants in the vehicle controls as follows (inclusive): TA98, 10 - 50; TA100, 80 - 240; TA1535, 5 - 45; TA1537, 3 - 21; WP2 *uvr*A, 10 - 60.
- To ensure that appropriate numbers of bacteria are plated, tester strain culture titers must be greater than or equal to 0.3×10^9 cells/mL.
- The mean of each positive control must exhibit at least a 3.0-fold increase in the number of revertants over the mean value of the respective vehicle control.
- A minimum of three non-toxic dose levels is required to evaluate assay data.
- A dose level is considered toxic if one or both of the following criteria are met: (1) A > 50 % reduction in the mean number of revertants per plate as compared to the mean vehicle control value. This reduction must be accompanied by an abrupt dose-dependent drop in the revertant count. (2) At least a moderate reduction in the background lawn (background code 3, 4 or 5).

Results

Solubility Test

The test article formed a clear solution in DMSO at approximately 500 mg/mL, the maximum concentration tested in the solubility test.

Sterility Results

No contaminant colonies were observed on the sterility plates for the vehicle control, the test article dilutions, and the sham mixes.

Preliminary Toxicity Assay

A preliminary toxicity assay was performed for dose selection. The dose levels tested were 6.7, 10, 33, 67, 100, 333, 667, 1000, 3333, and 5000 µg/plate. No precipitation was observed. Toxicity was observed at 3333 µg/plate (slightly reduced background) and 5000 µg/plate (moderately reduced background) with all *Salmonella* tester strains in

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the absence of S9 activation. Based of the findings of the toxicity assay, the maximum dose tested in the mutagenicity assay was 5000 μg/plate.

Definitive Assay

Treatment with 50 – 5000 μg MDPC0001 did not cause any positive mutagenic response in any of the tester strains in either the presence or absence of S9 activation.

- No precipitate was observed.
- No toxicity was observed at dose levels < 5000 μg/plate in any tester strains under any testing conditions.
- Toxicity was observed at 5000 μg/plate with all Salmonella tester strains in the absence of S9 activation.

Table 40. Summary of results from Ames Assay with MDPC0001 in the absence of S9 activation (Study No. MDV3100NC020).

Test Article, Concentration/Plate	Bacterial Strain and Mean Revertants/Plate ± Standard Deviation (Individual Counts)				
	TA98	TA100	TA1535	TA1537	WP2*uvrA*
DMSO, 50 μL	24 (6)	123 (11)	7 (3)	7 (3)	30 (6)
2NF, 1 μg	162 (32)				
SA, 1 μg		685 (55)	570 (10)		
9AAD, 75 μg				159 (27)	
MMS, 1000 μg					408 (18)
MDPC0001, 50 μg	22 (5)	127 (12)	10 (5)	7 (3)	31 (2)
MDPC0001, 150 μg	29 (6)	124 (5)	9 (1)	6 (2)	36 (3)
MDPC0001, 500 μg	18 (7)	118 (4)	9 (4)	7 (2)	38 (9)
MDPC0001, 1500 μg	28 (10)	108 (11)	8 (3)	8 (3)	35 (9)
MDPC0001, 5000 μg	29 (3)*	116 (9)*	6 (2)*	3 (2)*	28 (9)

* Moderately reduced background. (Defined as a marked thinning of the microcolony lawn resulting in an increase in the size of the microcolonies compared to vehicle control plate such that the microcolony lawn is visible to the unaided eye as isolated colonies.)

Table 41. Summary of results from Ames Assay with MDPC0001 in the presence of S9 activation (Study No. MDV3100NC020).

Test Article, Concentration/Plate	Bacterial Strain and Mean Revertants/Plate (Standard Deviation)				
	TA98	TA100	TA1535	TA1537	WP2*uvrA*
DMSO, 50 μL	36 (6)	111 (22)	9 (1)	4 (1)	23 (6)
2AA, 1 μg	669 (88)		85 (11)	83 (17)	
2AA, 2 μg		1115 (84)			
2AA, 15 μg					143 (32)
MDPC0001, 50 μg	28 (9)	139 (21)	9 (1)	7 (1)	19 (1)
MDPC0001, 150 μg	29 (9)	132 (23)	10 (4)	4 (2)	29 (3)
MDPC0001, 500 μg	30 (7)	127 (10)	8 (2)	5 (5)	33 (4)
MDPC0001, 1500 μg	29 (11)	140 (13)	13 (2)	4 (1)	21 (6)
MDPC0001, 5000 μg	30 (7)	142 (3)	8 (2)	4 (3)	21 (2)

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Dosing Formulation Analysis

- The actual concentration of the target 1.0 and 100 mg/mL MDPC0001 dosing formulations were 112.8% and 107.3% of the target concentrations, respectively, with < 5.0% relative standard deviation (RSD) and therefore met the acceptance criteria of 85.0 – 115.0% of target concentration and ≤ 5.00% RSD.
- No test article was detected in the vehicle control formulation.

Reference ID: 3175869

Study title: Bacterial Reverse Mutation Assay.

Study no.:	MDV3100NC021 ([redacted] (b) (4) Study Number AD50VX.5021CH.BTL)
Study report location:	eCTD Section 4.2.3.3.1
Conducting laboratory and location:	[redacted] (b) (4)
Date of study initiation:	April 17, 2012
GLP compliance:	Yes.
QA statement:	Yes. (E-signature)
Drug, lot #, and % purity:	MDPC0002, Batch (Lot) No. 11AK0027C, Purity = 99.0%

Key Study Findings

In the *in vitro* bacterial reverse mutation assay with the plate incorporation method, MDPC0002, did not produce genotoxic responses with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2 *uvr*A, in the absence or presence of S9 activation.

Methods

Strains:	*Salmonella typhimurium* strains TA98, TA1535, TA1537, TA100, and *Escherichia coli* strain WP2 *uvr*A
Concentrations in definitive study:	Plate incorporation method: 50 – 5000 μg/plate in the presence or absence of Aroclor 1254-induced rat liver S9 mix
Basis of concentration selection:	In a preliminary toxicity assay, MDPC0001 was assessed for cytotoxicity and mutagenicity at doses of 6.7, 10, 33, 67, 100, 333, 667, 1000, 333, and 5000 µg/plate with TA98, TA1535, TA1537, and TA100 in the presence or absence of the metabolic activation system. Cytotoxicity was assessed by examining bacterial lawn density and numbers of spontaneous revertants per plate. Toxicity was observed at 5000 µg/plate with all Salmonella tester strains in the absence of metabolic activation. No precipitation was observed.
Negative control:	Dimethyl sulfoxide (DMSO)
Positive control:	2-Nitrofluorene (2NF), sodium azide (SA), 9-aminoacridine (9AAD), methyl methanesulfonate (MMS)
Formulation/Vehicle:	DMSO
Incubation & sampling time:	Tester strains, S9 or sham mix, and vehicle or MDPC0002 were added to molten selective top agar. After vortexing, the mixture was overlaid onto the surface of minimal bottom agar. After the overlay had solidified, the plates were inverted and incubated for 48 to 72 hours at 37°C. All dose levels of test article, vehicle control, and positive controls were plated in triplicate. The metabolic activation system consisted of an S-9 fraction prepared from livers obtained from Aroclor 1254 pretreated male Sprague-Dawley rats. The S-9 percentage was 10%, which is within the acceptable range. Plates were scored either entirely by an automated colony counter or entirely by hand, unless the plate exhibited toxicity. Cytotoxicity was assessed by examining bacterial lawn density by using a dissecting microscope.

Reference ID: 3175869

Study Validity

Selection of bacterial tester strains was adequate based upon Guideline for Industry: Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals (ICH S2A, April 1996). Positive controls produced expected responses. Dose selection for the plate incorporation method was adequate based upon use of a high dose of 5000 µg/plate which showed some toxicity without precipitation. The S9 concentration was 10% which it is within acceptable limits.

Criteria for a valid test was provided in the study report and all of the following criteria must have been met for the assay to be considered valid:

- All *Salmonella* tester strain cultures must demonstrate the presence of the deep rough mutation (*rfa*) and the deletion in the *uvr*B gene.
- Cultures of tester strains TA98 and TA100 must demonstrate the presence of the pKM101 plasmid R-factor.
- All WP2 *uvr*A cultures must demonstrate the deletion in the *uvr*A gene.
- All cultures must demonstrate the characteristic mean number of spontaneous revertants in the vehicle controls as follows (inclusive): TA98, 10 - 50; TA100, 80 - 240; TA1535, 5 - 45; TA1537, 3 - 21; WP2 *uvr*A, 10 - 60.
- To ensure that appropriate numbers of bacteria are plated, tester strain culture titers must be greater than or equal to 0.3×10^9 cells/mL.
- The mean of each positive control must exhibit at least a 3.0-fold increase in the number of revertants over the mean value of the respective vehicle control.
- A minimum of three non-toxic dose levels is required to evaluate assay data.
- A dose level is considered toxic if one or both of the following criteria are met: (1) A > 50 % reduction in the mean number of revertants per plate as compared to the mean vehicle control value. This reduction must be accompanied by an abrupt dose-dependent drop in the revertant count. (2) At least a moderate reduction in the background lawn (background code 3, 4 or 5).

Results

Solubility Test

The test article formed a clear solution in DMSO at approximately 500 mg/mL, the maximum concentration tested in the solubility test.

Sterility Results

No contaminant colonies were observed on the sterility plates for the vehicle control, the test article dilutions, and the sham mixes.

Preliminary Toxicity Assay

A preliminary toxicity assay was performed for dose selection. The dose levels tested were 6.7, 10, 33, 67, 100, 333, 667, 1000, 3333, and 5000 (100 mg/mL) µg/plate. Precipitation was observed at ≥ 3333 µg/plate. No toxicity was observed. Based of the findings of the toxicity assay, the maximum dose tested in the mutagenicity assay was 5000 µg/plate.

Reference ID: 3175869

Definitive Assay

Treatment with 50 – 5000 μg MDPC0002 did not cause any positive mutagenic response in any of the tester strains in either the presence or absence of S9 activation.

- Precipitate was observed at 500 or 1500 μg/plate.
- No toxicity was observed.

Table 42. Summary of results from Ames Assay with MDPC0002 in the absence of S9 activation (Study No. MDV3100NC021).

Test Article, Concentration/Plate	Bacterial Strain and Mean Revertants/Plate ± Standard Deviation (Individual Counts)				
	TA98	TA100	TA1535	TA1537	WP2*uvrA*
DMSO, 50 μL	20 (2)	83 (15)	11 (3)	5 (3)	42 (5)
2NF, 1 μg	131 (14)				
SA, 1 μg		492 (91)	406 (26)		
9AAD, 75 μg				320 (93)	
MMS, 1000 μg					291 (37)
MDPC0002, 50 μg	16 (4)	106 (7)	8 (3)	2 (2)	31 (3)
MDPC0002, 150 μg	17 (5)	96 (4)	12 (3)	4 (3)	21 (4)
MDPC0002, 500 μg	15 (7)	93 (4)	10 (3)	5 (1)	22 (2)
MDPC0002, 1500 μg	20 (4) NP	89 (9) NP	11 (3) NP	5 (1) NP	21 (9) NP
MDPC0002, 5000 μg	19 (3) #, IP	94 (17) #, NP	9 (2) #, NP	8 (2) #, NP	27 (7) #, NP

Background obscured by particulate.
IP Interfering particulate.
NP Non-interfering particulate.

Table 43. Summary of results from Ames Assay with MDPC0002 in the presence of S9 activation (Study No. MDV3100NC021).

Test Article, Concentration/Plate	Bacterial Strain and Mean Revertants/Plate (Standard Deviation)				
	TA98	TA100	TA1535	TA1537	WP2*uvrA*
DMSO, 50 μL	17 (3)	81 (7)	8 (1)	5 (1)	24 (6)
2AA, 1 μg	474 (47)		132 (9)	54 (7)	
2AA, 2 μg		774 (167)			
2AA, 15 μg					76 (17)
MDPC0002, 50 μg	19 (4)	82 (10)	7 (2)	5 (3)	17 (6)
MDPC0002, 150 μg	17 (6)	90 (14)	7 (5)	6 (2)	19 (5)
MDPC0002, 500 μg	15 (3) P	89 (11)	7 (3) IP	5 (2)	19 (3) NP
MDPC0002, 1500 μg	16 (1) P	87 (4) IP	7 (4) IP	4 (2) IP	19 (3) P
MDPC0002, 5000 μg	12 (2) #, IP	70 (5) #, IP	3 (2) #, P	5 (1) #, IP	11 (2) #, IP

Background obscured by particulate.
IP Interfering particulate.
NP Non-interfering particulate.

Dosing Formulation Analysis

- The actual concentration of the target 1.0 and 100 mg/mL MDPC0002 dosing formulations were 111.0% and 104.9% of the target concentrations, respectively, with < 5.0% relative standard deviation (RSD) and therefore met the acceptance criteria of 85.0 – 115.0% of target concentration and ≤ 5.00% RSD.

Reference ID: 3175869

- No test article was detected in the vehicle control formulation.

7.2 *In Vitro* Assays in Mammalian Cells

Study Number: **PRO3100NC34 (b) (4) Study Number 7792-109)**
Study Title: **L5178Y TK+/- mouse lymphoma forward mutation assay with a confirmatory assay.**

[The review of Study No. PRO3100NC34 is reproduced verbatim below, with some changes in formatting for consistency purposes, as it appeared in the review (dated June 28, 2007) of IND 74563 for MDV3100 conducted by Doo Y. Lee Ham, Ph.D.]

Methods

Strains/species/cell line: L5178Y TK+/- 3.7.2C mouse lymphoma cell line

Doses used in definitive study: 5.0, 25.0, 37.5, 50.0, 75.0, 100, 150, and 200 ug/mL without S9 for 24 hour and with S9 for 4 hour treatment, respectively.

Basis of dose selection: Dose-range finding study using 10 concentrations ranged from 0.393 to 200 ug/mL with and without S9

Negative controls: DMSO

Positive controls: Methyl methanesulfonate (MMS) with S9
3-Methylcholanthrene (3-MCA) without S9

Incubation and sampling times: 4 hours in the presence of S9 and 24 hours in the absence of S9 activation.

Results:

Mutation Assay with Activation

Test Condition	Daily Cell Density/mL (x 10^5)		Cumulative RSG[a]		Total Mutant Colonies	Total Viable Colonies	Cloning Efficiency[b]		Relative Growth (%)[c]	Mutant Frequency (x 10^{-6})[d]
	Day 1	Day 2		AVG VC				AVG VC		
Activation Controls[e]										
Vehicle Control	11.9	12.6	16.7		126	475	79.2		90.3	53.0
Vehicle Control	10.8	12.5	15.0		130	635	105.8		108.5	40.8
Vehicle Control	12.2	11.9	16.1	15.9	130	542	90.3	91.8	99.7	47.8
MCA 5 µg/mL	5.0	7.6	4.2		531	242	40.4		11.7	438.2[f]
MCA 10 µg/mL	4.0	6.6	2.9		588	267	44.6		8.9	440.0[f]
Test Article (µg/mL)			Relative to Vehicle Control (%)				Relative to Vehicle Control (%)			
5.00	11.5	12.2	97.9		112	901	163.6		160.1	24.8
25.0	10.6	13.0	96.1		126	642	116.5		112.0	39.3
37.5	10.0	11.1	77.4		139	613	111.4		86.2	45.3
50.0	6.2	10.0	43.2		139	561	101.9		44.1	49.6
75.0	3.9[h]	7.3	15.3		102	502	91.1		13.9	40.8
100	4.0	5.4	15.1		122	486	88.3		13.3	50.4
150[g]	3.6[h]	6.1	12.8		119	469	85.3		10.9	50.6
200[g]	2.7[h]	5.4	11.3		i	373	67.8		7.7	j

[a]RSG = (Day 1 Count/3) x (Day 2 Count)/3 (or Day 1 Count if not subcultured)
[b]Cloning Efficiency = Total Viable Colony Count/Number of Cells Seeded x 100
[c]Relative Growth = (Relative Suspension Growth x Relative Cloning Efficiency) / 100
[d]Mutant Frequency = (Total Mutant Colonies/Total Viable Colonies) x (2 x 10^{-4})
Decimal is moved to express the frequency in units of 10^{-6}
[e]Vehicle Control = 1% DMSO
Positive Control: MCA = Methylcholanthrene
[f]Mutagenic. Exceeds Minimum Criterion of 137.2 x 10^{-6}
[g]Precipitate observed at termination of treatment.
[h]Not subcultured.
[i]Not scored due to excessive cytotoxicity.
[j]Insufficient data for calculations.

[Excerpted from the Applicant's submission]

Mutation Assay without Activation

Test Condition	Daily Cell Density/mL (x 10^5)		Cumulative RSG[a]		Total Mutant Colonies	Total Viable Colonies	Cloning Efficiency[b]		Relative Growth (%)[c]	Mutant Frequency (x 10^{-6})[d]
	Day 1	Day 2								
Nonactivation Controls[e]				AVG VC				AVG VC		
Vehicle Control	13.4	12.8	19.1		131	486	81.0		92.6	53.8
Vehicle Control	13.1	11.2	16.3		126	568	94.7		92.6	44.4
Vehicle Control	14.7	10.6	17.3	17.6	130	655	109.1	94.9	113.4	39.6
MMS 10 µg/mL	10.0	11.7	13.0		319	316	52.7		41.1	201.5[f]
MMS 15 µg/mL	8.8	9.5	9.3		317	164	27.3		15.2	387.0[f]
Test Article (µg/mL)			Relative to Vehicle Control (%)				Relative to Vehicle Control (%)			
5.00	11.2	13.3	94.3		99	478	83.9		79.1	41.3
25.0	12.4	10.6	83.2		125	588	103.3		85.9	42.4
37.5	9.6	14.2	86.3		121	620	108.9		93.9	39.1
50.0	8.5	11.8	63.5		162	631	110.8		70.3	51.2
75.0	6.7	6.0	25.4		111	524	92.0		23.4	42.2
100	7.7	5.8	28.3		93	488	85.7		24.2	38.0
150[g]	7.7	6.3	30.7		102	455	79.9		24.5	44.9
200[g]	4.4	4.9	13.6		119	412	72.4		9.9	57.6

[a]RSG = (Day 1 Count/3) x (Day 2 Count)/3 (or Day 1 Count if not subcultured)
[b]Cloning Efficiency = Total Viable Colony Count/Number of Cells Seeded x 100
[c]Relative Growth = (Relative Suspension Growth x Relative Cloning Efficiency) / 100
[d]Mutant Frequency = (Total Mutant Colonies/Total Viable Colonies) x (2 x 10^{-4})
Decimal is moved to express the frequency in units of 10^{-6}
[e]Vehicle Control = 1% DMSO
Positive Control: MMS = Methyl methanesulfonate
[f]Mutagenic. Exceeds Minimum Criterion of 135.9 x 10^{-6}
[g]Precipitate observed at termination of treatment.

[Excerpted from the Applicant's submission]

Study Validity: (confirmatory) The study was accepted as valid. Second experiment gave similar results.

Study outcome: MDV3100 was negative in the L5178Y TK+/- mouse lymphoma assay.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: A micronucleus test in mice orally treated with MDV3100.

Study no:	9785-TX-0005 ([redacted] (b) (4) Study Number M-1468)
Study report location:	eCTD Section 4.2.3.7.6.
Conducting laboratory and location:	[redacted] (b) (4)
Date of study initiation:	June 1, 2011
GLP compliance:	Yes. (Ordinance No. 21 and No. 114 of the [redacted] (b) (4))
QA statement:	Yes.
Drug, lot #, and % purity:	MDV3100, Lot Number GLP-09090046-093, 99% purity.

Key Study Findings

MDV3100 tested negative in the *in vivo* micronucleus assay. The results from this study indicate MDV3100 does not have clastogenic potential in bone marrow cells of Crlj:CD1(ICR) mice under the conditions of the study.

Methods

Doses in definitive study:	MDV3100: 0, 7.5, 15, 30 mg/kg/day Mitomycin C: 1 mg/kg/day
Frequency of dosing:	One-daily for two days.
Route of administration:	Oral gavage
Dose volume:	10 mL/kg
Formulation/Vehicle:	[redacted] (b) (4)
Species/Strain:	Mouse/Crlj:CD1(ICR)
Number/Sex/Group:	5
Satellite groups:	Vehicle control: 3/sex/group 30 mg/kg/day MDV3100: 17/sex/group
Basis of dose selection:	The high dose selected (30 mg/kg/day) was the maximum tolerated dose in a dose-finding 1-week oral toxicity study in mice (Study Number C-B579)
Negative control:	[redacted] (b) (4) vehicle control
Positive control:	Mitomycin C ([redacted] (b) (4), Lot Number 547AIJ)

Table 44. Main study animal group assignment and dosing levels in Study Number 9785-TX-0005.

Group	Dose Level (mg/kg/day)	Test Article Concentration (mg/mL)	Dose Volume (mL/kg)	Frequency of Dose	Sex	No. of Animals	Animal No.	Time for Bone Marrow Collection
Vehicle Control	0	0	10	2	Male Female	5 5	1001 to 1005 1101 to 1105	about 24 hours a)
Low Dose	7.5	0.75	10	2	Male Female	5 5	2001 to 2005 2101 to 2105	about 24 hours a)
Middle Dose	15	1.5	10	2	Male Female	5 5	3001 to 3005 3101 to 3105	about 24 hours a)
High Dose	30	3	10	2	Male Female	5 5	4001 to 4005 4101 to 4105	about 24 hours a)
Positive Control	1.0*	0.1*	10	1	Male Female	5 5	5001 to 5005 5101 to 5105	about 24 hours

* Dose level and concentration of MMC a): Hours after the second administration

[Excerpted from Applicant's Test Table 1 in Study Report Number 9785-TX-0005]

Table 45. Satellite animal group assignment and dose levels in Study Number 9785-TX-0005.

Group	Dose Level (mg/kg/day)	Test Article Concentration (mg/mL)	Dose Volume (mL/kg)	Frequency of Dose	Sex	No. of Animals	Animal No.
Vehicle Control	0	0	10	2	Male Female	3 3	1201 to 1203 1301 to 1303
High Dose	30	3	10	2	Male Female	17 17	4201 to 4217 4301 to 4317

[Excerpted from Applicant's Test Table 2 in Study Report Number 9785-TX-0005]

Observations

Clinical Observations	Before, immediately after, and approximately 2 hours after dosing on each dosing day and on the day following the last dose.
Body Weight	Once-daily on dosing days and on the day following the last dose.
Bone Marrow Smears	Collected from the femurs of each main study animal 24 hours after the last dose. The numbers of polychromatic erythrocytes (PCE) and normochromatic erythrocytes per 200 erythrocytes were counted. In addition, the number of micronucleated polychromatic erythrocytes (MNPCE) per 200 PCE were counted. For each animal, the number and proportion (%) of MNPCE per 2000 PCE and the number and proportion (%) of PCE per 200 erythrocytes were determined. For each group, mean with standard deviation, and the maximum and minimum of the numbers and proportions (%) of MNPCE and PCE were calculated.

Reference ID: 3175869

Toxicokinetics	Plasma samples were collected from satellite group animals (3/sex/time point) via the inferior vena cava. Vehicle control: 4 hours after the second dosing. MDV3100: Before second dose, and 1, 4, 8, and 24 hours after the second dosing.

Study Validity

The study was deemed valid for the following reasons: 1) toxicokinetic analysis demonstrated systemic exposure; 2) dosing appeared to be adequate based on the result of the dose-ranging study; 3) preparation of the test substance was acceptable; 4) the species and number of animals used were acceptable; 5) tissue sampling and analysis was acceptable; 6) positive control exhibited appropriate response; and 7) the proportion of immature erythrocytes among total erythrocytes was not less than 20% of the control value.

Results

Clinical Signs

- There were no remarkable findings in clinical signs.

Body Weight

- There were no remarkable changes in body weight.

Bone Marrow Smears

- There were no statistically significant differences in the incidence of MNPCE and PCE in 200 erythrocytes in MDV3100-treated animals when compared to vehicle control-treated animals.

Reference ID: 3175869

Table 46. Results of in vivo micronucleus assay in mice following oral dosing with MDV3100 (Study Number 9785-TX-0005).

Male

Group	Dose (mg/kg/day)		No. of MNPCE in 2000 PCE	MNPCE(%) [a]	No. of PCE in 200 erythrocytes	PCE(%) [b]
Vehicle control	0	N	5	5	5	5
		Mean ± S.D.	2 ± 1	0.09 ± 0.07	114 ± 7	56.8 ± 3.3
		Min. / Max.	0 / 4	0.00 / 0.20	106 / 122	53.0 / 61.0
Low	7.5	N	5	5	5	5
		Mean ± S.D.	2 ± 2	0.12 ± 0.08[d]	117 ± 9	58.3 ± 4.4[e]
		Min. / Max.	0 / 4	0.00 / 0.20	107 / 128	53.5 / 64.0
Middle	15	N	5	5	5	5
		Mean ± S.D.	3 ± 2	0.17 ± 0.08[d]	113 ± 11	56.3 ± 5.3[e]
		Min. / Max.	2 / 6	0.10 / 0.30	102 / 126	51.0 / 63.0
High	30	N	5	5	5	5
		Mean ± S.D.	3 ± 2	0.14 ± 0.09[d]	111 ± 6	55.3 ± 2.9[e]
		Min. / Max.	0 / 5	0.00 / 0.25	102 / 117	51.0 / 58.5
Positive control [c] (Mitomycin C)	1.0	N	5	5	5	5
		Mean ± S.D.	57 ± 18	2.84 ± 0.90	96 ± 8	47.8 ± 4.1
		Min. / Max.	40 / 85	2.00 / 4.25	85 / 103	42.5 / 51.5

a) : Proportion(%) of micronucleated polychromatic erythrocytes (MNPCE) per 2000 polychromatic erythrocytes (PCE)
b) : Proportion(%) of polychromatic erythrocytes (PCE, including MNPCE) per 200 erythrocytes
c) : Administration was done only once for the positive control group.
d) : No significant difference between the vehicle control group and any treated group (Kastenbaum & Bowman's statistical table and Cochran-Armitage test)
e) : No significant difference between the vehicle control group and any treated group (Dunnett's test)

Female

Group	Dose (mg/kg/day)		No. of MNPCE in 2000 PCE	MNPCE(%) [a]	No. of PCE in 200 erythrocytes	PCE(%) [b]
Vehicle control	0	N	5	5	5	5
		Mean ± S.D.	3 ± 1	0.14 ± 0.07	114 ± 4	56.9 ± 1.8
		Min. / Max.	2 / 5	0.10 / 0.25	109 / 117	54.5 / 58.5
Low	7.5	N	5	5	5	5
		Mean ± S.D.	2 ± 2	0.11 ± 0.08[d]	110 ± 7	54.8 ± 3.4[e]
		Min. / Max.	1 / 5	0.05 / 0.25	103 / 120	51.5 / 60.0
Middle	15	N	5	5	5	5
		Mean ± S.D.	2 ± 1	0.11 ± 0.07[d]	115 ± 8	57.6 ± 3.8[e]
		Min. / Max.	1 / 4	0.05 / 0.20	103 / 123	51.5 / 61.5
High	30	N	5	5	5	5
		Mean ± S.D.	2 ± 1	0.10 ± 0.06[d]	114 ± 10	57.2 ± 4.8[e]
		Min. / Max.	0 / 3	0.00 / 0.15	104 / 125	52.0 / 62.5
Positive control [c] (Mitomycin C)	1.0	N	5	5	5	5
		Mean ± S.D.	41 ± 8	2.03 ± 0.41	104 ± 10	51.9 ± 5.1
		Min. / Max.	27 / 47	1.35 / 2.35	92 / 117	46.0 / 58.5

a) : Proportion(%) of micronucleated polychromatic erythrocytes (MNPCE) per 2000 polychromatic erythrocytes (PCE)
b) : Proportion(%) of polychromatic erythrocytes (PCE, including MNPCE) per 200 erythrocytes
c) : Administration was done only once for the positive control group.
d) : No significant difference between the vehicle control group and any treated group (Kastenbaum & Bowman's statistical table and Cochran-Armitage test)
e) : No significant difference between the vehicle control group and any treated group (Dunnett's test)

[Excerpted from Applicant's Table 3-1 and Table 3-2 in Study Report Number 9785-TX-0005]

Toxicokinetics

- In the vehicle control group, plasma concentrations of MDV3100, M1, and M2 were below the lower limit of quantitation (< 0.02 μg/mL).
- The following table summarizes the results obtained from the toxicokinetic analysis of plasma samples from MDV3100-treated animals:

Table 47. Summary of plasma toxicokinetic parameters of MDV3100, M1, and M2 in Study Number 9785-TX-0005.

Dose level (mg/kg/day)	Sex	Analyte	C_{max} (µg/mL)	t_{max} (h)	AUC_{24} (µg·h/mL)
30	Male	MDV3100	21.32	8.0	393
		M1	1.79	8.0	34.4
		M2	1.89	8.0	39.6
	Female	MDV3100	20.28	8.0	376
		M1	1.13	8.0	23.7
		M2	1.63	24.0	36.4

In the vehicle control group, plasma concentrations of MDV3100, M1, and M2 at 4 hours after the second dose were below the LLOQ (0.02 µg/mL).

[Excerpted from Applicant's Text Table 3 in Study Report Number 9785-TX-0005]

Reviewer's comments:

- *Based on AUC_{0-24} values, M1 and M2 had plasma exposures that were approximately 10% of the plasma exposure of the parent drug.*
- *There were no apparent sex differences in the TK parameters of MDV3100.*
- *C_{max} and AUC_{0-24} values of M1 appeared to be approximately 1.5-fold higher in males when compared to females.*
- *There were no apparent sex differences in the TK parameters of M2.*

7.4 Other Genetic Toxicity Studies

None.

8 Carcinogenicity

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of enzalutamide. Based on the current ICH S9 Guidance, "Nonclinical evaluation for anticancer pharmaceuticals", carcinogenicity studies with MDV3100 are not warranted to support approval of MDV3100 in the proposed patient population.

9 Reproductive and Developmental Toxicology

Reproductive and developmental toxicology studies with enzalutamide have not been conducted. Based on the proposed indication of treatment of men with advanced prostate cancer, these studies are not considered to be necessary to support approval of MDV3100 in the proposed patient population.

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10 Special Toxicology Studies

None.

11 Integrated Summary and Safety Evaluation

Enzalutamide is a new molecular entity, small molecule androgen receptor inhibitor. Medivation submitted NDA 203415 for enzalutamide for the proposed indication of treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel (b) (4) Medivation submitted non-clinical pharmacology, pharmacokinetic, and toxicology studies to support approval of enzalutamide for the proposed indication.

Pharmacology studies showed that enzalutamide binds to the androgen receptors (ARs) and inhibits androgen binding to these receptors, with mean K_i and IC_{50} values of 0.023 μM and 0.062 μM, respectively, *in vitro*. Downstream effects of inhibition of androgen binding to ARs include inhibition of AR nuclear translocation, inhibition of AR association with DNA, induction of apoptosis, and decreased cell viability. *In vivo*, enzalutamide decreased tumor volume in a mouse xenograft model of human castration-resistant prostate cancer.

Medivation conducted a battery of *in vitro* and *in vivo* safety pharmacology studies to evaluate the effect of enzalutamide on the cardiovascular, respiratory, and nervous systems. These studies showed that enzalutamide had no toxicologically significant and clinically relevant effects in these organ systems.

Six metabolites were identified in non-clinical pharmacokinetic/ADME studies with enzalutamide. Of these, MDPC0001 (M1; a carboxylic acid derivative) and MDPC0002 (M2; N-desmethyl enzalutamide) were the major metabolites in both rats and dogs. In rats, enzalutamide, M1, and M2 represent approximately 55%, 32%, and 3% of the plasma radioactivity, respectively. Enzalutamide, M2, and to a smaller degree M1, were shown to readily cross the blood-brain barrier in rats, with brain to plasma ratios of 0.841, 0.0211, and 1.13, respectively. Consistent with the findings in animals, clinical studies with enzalutamide also showed that M1 and M2 are the two major human metabolites of enzalutamide. Metabolite M2, or N-desmethyl enzalutamide, represented approximately 50% of AUC in humans following enzalutamide administration, while enzalutamide represented approximately 30% of the AUC. *In vitro* pharmacology studies demonstrated that M1 is an inactive metabolite. However, M2 was shown to inhibit androgen binding to androgen receptors and inhibit androgen receptor nuclear translocation *in vitro* indicating it is an active metabolite.

Major target organ systems of toxicity of enzalutamide identified in toxicity studies with enzalutamide in rats and dogs of up to 26 and 13 weeks in duration were the central nervous system and reproductive organs. Consistent with the pharmacological activity

Reference ID: 3175869

of enzalutamide, major toxicity findings were noted in male reproductive organs. In a 26-week study in rats, decreased organ weights were correlated with atrophy of the prostate and seminal vesicles which was observed at ≥ 30 mg/kg/day (similar to the human exposure based on AUC). In 4- and 13-week studies in dogs, decreased organs weights were correlated with hypospermatogenesis and atrophy of the prostate and epididymides which were observed at ≥ 4 mg/kg/day (0.3 times the human exposure based on AUC). In addition, toxicity findings were also noted in the liver (hepatocellular hypertrophy), pituitary (hypertrophy and hyperplasia), and kidney (chronic progressive nephropathy) following repeat-dose administration of enzalutamide to rats. However, these changes were either considered to be due to the secondary effect of the pharmacological action of enzalutamide (pituitary) or minimal in nature and without clinical pathology correlates (liver and kidney). To note, although chronic progressive nephropathy is often a background findings in rats, enzalutamide caused a dose-dependent increase in the incidence and severity of this histopathological finding in rats, which suggest this finding may be a drug-related toxicity. Overall, toxicity findings noted in non-clinical studies appeared to be consistent with those observed during clinical studies with enzalutamide and there appeared to be no clinically significant toxicities noted in non-clinical studies which were not observed in clinical studies with enzalutamide.

Convulsion is the other clinically-relevant, significant toxicity finding noted in repeat-dose studies in mice and dogs. A dose-dependent increase in convulsions was observed in mice ≥ 100 mg/kg/day (0.6 times the human exposure based on AUC) and in dogs at 60 mg/kg/day (3.3 times the human exposure based on AUC). In clinical studies of enzalutamide, seizure occurred in 0.9% of patients receiving enzalutamide. Results from pharmacology studies submitted in support of this NDA showed that the convulsive effects of enzalutamide may also be attributed to an off-target, secondary pharmacology of the drug. Specifically, *in vitro*, MDV3100 and M2 showed inhibitory activity towards the gamma aminobutyric acid (GABA)-gated chloride channel with IC_{50} of 2.6 μM and 7.1 μM, respectively. Publicly available literature references have shown that blockade of this inhibitory neurotransmitter pathway can result in increased excitation which can result in seizure.[2] Furthermore, similar drugs in the same pharmacological class have also been shown to cause convulsions.[3] At the time of this NDA submission, there is no clinical trial experience with enzalutamide in patients who have had a seizure, in patients with predisposing factors for seizure, or in patients using concomitant medications that may lower the seizure threshold. Risk of seizure is included in the Warning and Precautions section of the Prescribing Information for enzalutamide.

Medivation conducted a complete battery of genotoxicity testing with enzalutamide. These studies showed that enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either the *in vitro* mouse lymphoma *tk* gene mutation assay or the *in vivo* mouse micronucleus assay. M1 and M2 also did not induce mutations in the Ames assay.

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Long-term animal studies have not been conducted to evaluate the carcinogenic potential of enzalutamide. Based on the current ICH S9 Guidance, "Nonclinical evaluation for anticancer pharmaceuticals", carcinogenicity studies with enzalutamide are not warranted to support approval of enzalutamide in the proposed patient population.

Reproductive and developmental toxicology studies with enzalutamide have not been conducted. Based on the proposed indication of treatment of men with advanced prostate cancer, these studies are not considered to be necessary to support approval of enzalutamide in the proposed patient population.

In conclusion, the non-clinical studies submitted in this NDA support the use of enzalutamide in patients with metastatic castration-resistant prostate cancer who have previously received docetaxel (b) (4). From the perspective of the non-clinical discipline, there are no recommendations for additional non-clinical studies and enzalutamide is recommended for approval for the proposed indication.

12 Appendix/Attachments

References

1. Tran C. *Science* (2009); 324: 787 – 790.
2. Treiman DM. *Epilepsia* (2001); 42: 8 - 12.
3. Foster WR, et al. *The Prostate* (2011); 71: 480 - 488.

Reference ID: 3175869

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/s/

HAW-JYH CHIU
08/20/2012

TODD R PALMBY
08/20/2012

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 203415 **Applicant:** Medivation, Inc. **Stamp Date:** May 22, 2012

Drug Name: Enzalutamide (MDV3100) **NDA Type:** 505 (b)(1); Type 1 – New Molecular Entity

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?		X	Some non-clinical studies FDA requested at the pre-NDA meeting were still in preparation at the time of this NDA filing review. However, this is not a filing issue at this time, based on the commitment by Medivation to submit these studies by the end of June, 2012.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable. The formulation to be marketed is the same as the formulation used in the toxicology studies submitted to support this NDA submission.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?		X	See Comment for #4.

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		Medivation stated all impurities in MDV3100 have been qualified by non-clinical studies. Impurity issues will be evaluated in detail during the pharmacology/toxicology review of this NDA application.
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes.

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Haw-Jyh Chiu, Ph.D. June 11, 2012
Reviewing Toxicologist Date

Anne M. Pilaro, Ph.D. June 11, 2012
Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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/s/

HAW-JYH CHIU
06/12/2012

ANNE M PILARO
06/12/2012

I concur with the reviewer's conclusion that from the nonclinical perspective, this application is fileable. There are no comments or deficiencies to be included in the filing or 74-day letters from the nonclinical discipline.