CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-217

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ADDENDUM TO ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	22-217 (N-000)
Submission Date:	07/10/09 (Amendment 13)
Brand Name:	Valturna
Generic Name:	Aliskiren/Valsartan
Formulation:	Bilayer film-coated oral tablet
Strength:	150/160 mg and 300/320 mg
Sponsor:	Novartis
Type of submission:	07/10/09 Response to 06/16/09 Agency's Letter
Reviewer:	Tien-Mien Chen, Ph.D.

SUBMISSION

This submission includes Norvartis response to the FDA's Letter dated June 16, 2009, requesting tightening the dissolution specifications for Valturna (valsartan/aliskiren) tablets as follows:

From: **Q=(b)(4)% in 30 min for Valsartan and Q=(b)(4)% in 45 min for Aliskiren**

To: **Q=(b)(4)% in 20 min Valsartan and Q=(b)(4)% in 30 min for Aliskiren**

In their response, Norvartis agreed to tighten the specification for Aliskiren from Q=(b)(4)% in 45 min to Q=(b)(4)% in 30 min. However, they requested that the specification for Valsartan of Q=(b)(4)% in 30 min, be remained the same. They explained that a specification of Q=(b)(4)% in 30 min for Valsartan has been accepted in other NDAs containing valsartan (see sponsor's explanation in the attached Appendix).

Reviewer's Comments:

1. The dissolution methodology for the Valturna IR tablets (NDA 22-217) uses USP Apparatus I (basket) with 100 rpm; (b)(4) Therefore, the sponsor's argument for maintaining in both products the 30 minutes dissolution specification for valsartan is not justified and is not acceptable.

2. Additionally, the stability-dissolution data (b)(4) months were revisited to evaluate if the percent of valsartan dissolved was changing with time. No decrease was found. Therefore, their request is not supported by the stability data.

RECOMMENDATION

From the Biopharmaceutics perspective, the Agency's recommendation of tightening the dissolution specification for valsartan remains unchanged. Therefore, the following dissolution specifications for Valturna (valsartan/aliskiren) tablets using the proposed dissolution test [*i.e., USP Apparatus 1 (basket), 100 rpm, and 1000 ml of phosphate buffer pH 6.8 at 37^{o}C*] should be conveyed to the sponsor and implemented:

Valsartan: Q = (b) (4)% for in 20 min,

Aliskiren: Q = (b) (4)% in 30 min

_____ _____08/07/09_____

Tien-Mien Chen, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____08/07/09_____

Patrick Marroum, Ph.D. Date
ONDQA Biopharmaceutics Expert

CC: NDA
Patrick Marroum, Angelica Dorantes, Tien-Mien Chen

NDA 22-217 for Valturna (Aliskiren/Valsartan)
FDC 150/160 and 300/320 mg IR Tablets

Appendix

Sponsor's 07/10/09 Responses to
Agency's 07/06/09 Letter

Introduction

This document provides the complete Novartis response to the FDA information request letter dated 16-Jun-2009, received by Novartis on 18-Jun-2009, regarding Original NDA 22-213 for SPV100 (aliskiren/valsartan) film-coated tablets.

1 Question 1

We are reviewing your request for a bio-waiver and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Both Valsartan and Aliskiren dissolved rapidly in the proposed pH 6.8 medium, therefore, the dissolution specifications need to be tightened. The following revisions proposed by the Agency should be implemented:

- Valsartan: Q=(b) (4)% in 20 min
- Aliskiren: Q=(b) (4)% in 30 min.

Response:

As requested by FDA, Novartis agrees to change the dissolution specification for release of aliskiren in SPV100 from Q=(b) (4)% in 45 minutes to Q=(b) (4)% in 30 min.

Novartis has evaluated FDA's proposed dissolution specification for Valsartan of Q=(b) (4)% in 20 minutes (rather than Q=(b) (4)% in 30 minutes). Based upon this evaluation, Novartis respectfully requests that the Agency reconsider the valsartan specification originally proposed by Novartis. It is our opinion that the originally proposed dissolution specification of Q=(b) (4)% in 30 minutes is the most scientifically sound specification for the following reasons:

- SPV100 is a bilayer tablet, where the valsartan (b) (4) (b) (4) that is used to manufacture the current commercial Diovan® tablet approved by FDA. Since the (b) (4) are identical, the Valsartan dissolution characteristics for both SPV100 and Diovan® are the same. Consequently, Novartis believes that there is a strong scientific rationale to keep the initially proposed valsartan specification for SPV100 tablets (Q=(b) (4)% in 30 minutes).
- Maintaining the 30 minute valsartan dissolution specification will allow us to compare SPV100 tablets with the historical body of data on Diovan®, as well as three other approved Diovan® related fixed dose combination products. The specifications for all of these FDA approved commercial products are identical to the initially proposed specification (Q=(b) (4)% at 30 minutes) for SPV100 tablets. Changing the specification for only one of these valsartan products hampers future understanding and comparability between the products.
- The proposed valsartan specification for SPV100 is consistent with "Dissolution Testing of Immediate release solid dosage forms" Guidance for dosage specification requirements "Q=(b) (4)% in 60 minutes or less"

- Novartis would like to have the same 30 minute sampling point for both valsartan and aliskiren for reasons of harmonization during analytical testing.

Novartis commits to provide the updated testing monographs to the NDA in the first NDA Annual Report.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22217	ORIG 1		ALISKIREN & VALSARTAN

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

/s/

TIEN MIEN CHEN
08/11/2009

PATRICK J MARROUM
08/11/2009

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	22-217 (N-000)
Submission Date:	11/25/08
Brand Name:	Valturna
Generic Name:	Aliskiren/Valsartan
Formulation:	Bilayer film-coated oral tablet
Strength:	150/160 mg and 300/320 mg
Sponsor:	Novartis
Type of submission:	Biowaiver request for lower strength, 150/160 mg
Reviewer:	Tien-Mien Chen, Ph.D.

BACKGROUND

Aliskiren is a direct rennin inhibitor, approved for use in the treatment of hypertension in adults under NDA 21-985 (oral tablets, 150 and 300 mg) on 03/05/07. Valsartan is an angiotensin receptor blocker, approved for use in the treatment of hypertension in adults under NDA 21-283 on 07/18/01 (oral tablets, 80, 160, and 320 mg). Novartis is the innovator for both Aliskiren and Valsartan.

On 11/25/08, the sponsor submitted an NDA 22-127 for a single oral tablet combination of the two active ingredients (Aliskiren/Valsartan) as a bilayer, film-coated, fixed combination tablet (Layer 1: Aliskiren and Layer 2: Valsartan). A new propriety name of Valturna and two strengths are proposed, 150/160 mg and 300/320 mg oral tablets. Valturna is also for the treatment of hypertension.

Under NDA 22-217, the higher strength (300/320 mg) of the to-be-marketed formulation (TBM) was tested in a pivotal bioequivalence (BE) study (No. CSPV100A2111). The study results showed that it's bioequivalent to the clinically tested, a free combination of currently marketed 1 x 300 mg Aliskiren oral tablet + 2 x 160 mg Valsartan oral capsules. A food effect study (No. CSPV100A2114) was also conducted using the higher strength. The study results showed that food had significant effects on bioavailability of Aliskiren (point estimate: mean C_{max} ↓ 88% and mean $AUC_{0-\infty}$ ↓ 76%), but less significant for Valsartan (point estimate: mean C_{max} ↓ 11% and mean $AUC_{0-\infty}$ ↑ 6%).

A biowaiver for the lower strength (150/160 mg) of Valturna oral tablet was submitted. Provided also were 1) comparative dissolution data/profiles of two proposed strengths (n=12/batch) of Valturna TBM formulation in three dissolution media using USP Apparatus 1 (basket), 1000 mL at 37°C and 2) proposed dissolution specifications. The lower strength is reportedly to be exactly half that of the higher strength of the combo tablet. The biowaiver is therefore reviewed here.

FORMULATION COMPARISONS

The TBM formulation of 150/160 mg and 300/320 mg Valturna oral tablets are shown below. Indeed, the lower strength is exactly half that of the higher strength.

Table 1. Formulation/Composition of Valturna Combo Oral Tablets, 150/160 and 300/320 mg

Ingredient	Amount per 150/160 mg tablet (mg)	Amount per 300/320 mg tablet (mg)	Function	Reference to standards
(b) (4)				
Aliskiren hemifumarate (SPP100)	165.750*	331.50**	Active pharmaceutical ingredient	Novartis monograph
Hydroxypropylcellulose			(b) (4)	Ph. Eur. / NF
Cellulose, microcrystalline / microcrystalline cellulose				Ph. Eur. / NF
Crospovidone				Ph. Eur. / USP
(b) (4) / colloidal silicon dioxide				Ph. Eur. / NF
Indigotin (b) (4)				95/45/EC / 21CFR
Magnesium Stearate				Ph. Eur. / NF
(b) (4)				
Valsartan	160.000	320.00	Active pharmaceutical ingredient	Novartis monograph
Cellulose, microcrystalline / microcrystalline cellulose			(b) (4)	Ph. Eur. / NF
Crospovidone				Ph. Eur. / USP
(b) (4) / colloidal silicon dioxide				Ph. Eur. / NF
Magnesium Stearate (b) (4)				Ph. Eur. / NF
Magnesium Stearate (b) (4)				Ph. Eur. / NF
(b) (4)				
Coating				
(b) (4)				Novartis monograph
				Novartis monograph
				Novartis monograph
				Novartis monograph
				Ph. Eur. / USP
Total film-coated tablet weight	**574.000**	**1148.00**		
(b) (4)				

DISSOLUTION COMPARISONS

The two batches used were 1). 300/320 mg strength, No. AEUS/2007-0271 (the biolot for the BE study; size of (b) (4) tablets) and 2). 150/160 mg strength, No. AEUS/2007-0341 (a stability batch, size of (b) (4) tablets). They were reported to be of pilot scale but they are all (b) (4) of a full production size batch.

The comparative dissolution data/profiles of two proposed strengths are shown below.

A. For Valsartan (Layer 2):

Figure 1-1. Dissolution Profile of Valsartan: Aliskiren/Valsartan Combo Tablets 300/320 mg vs. 150/160 mg at pH (b) (4)

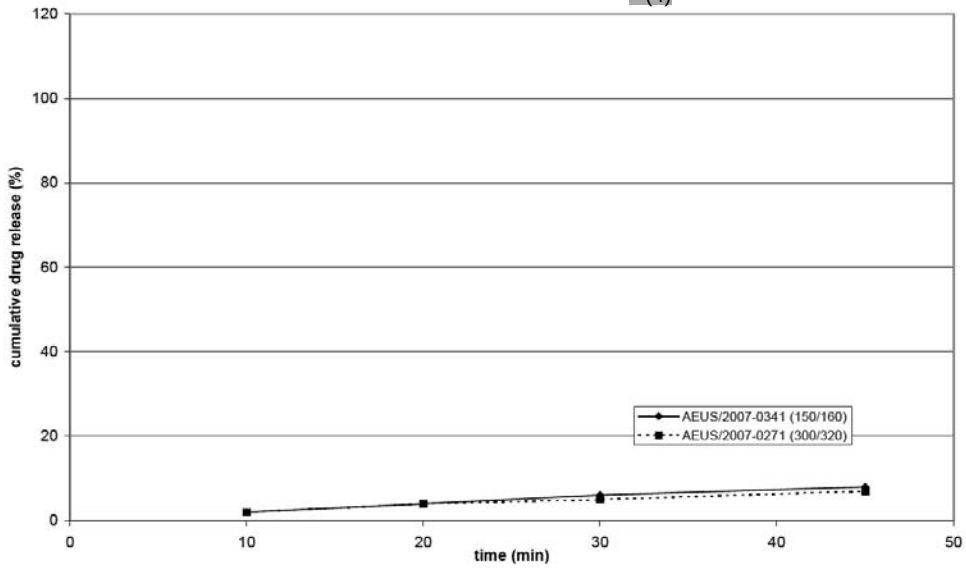


Figure 1-2. Dissolution Profile of Valsartan: Aliskiren/Valsartan Combo Tablets 300/320 mg vs. 150/160 mg at pH (b) (4).

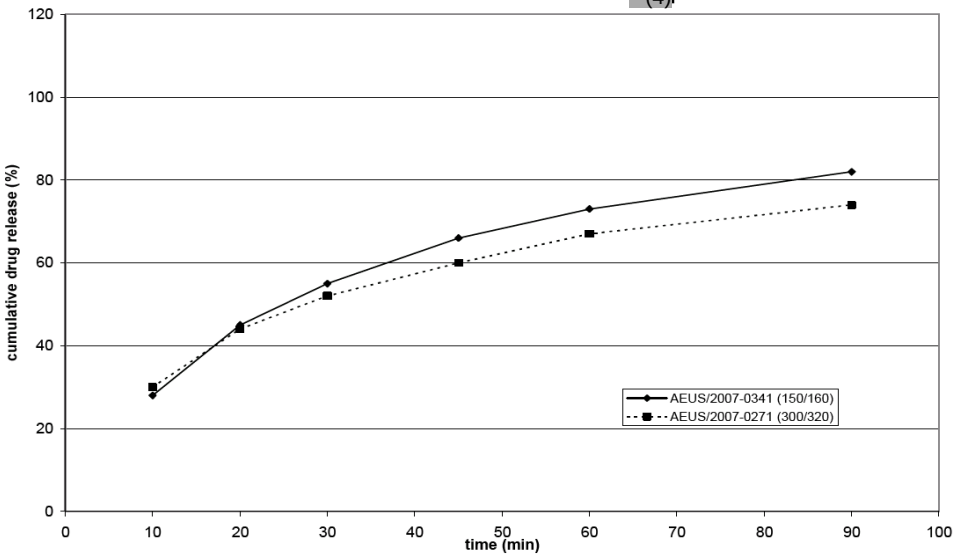
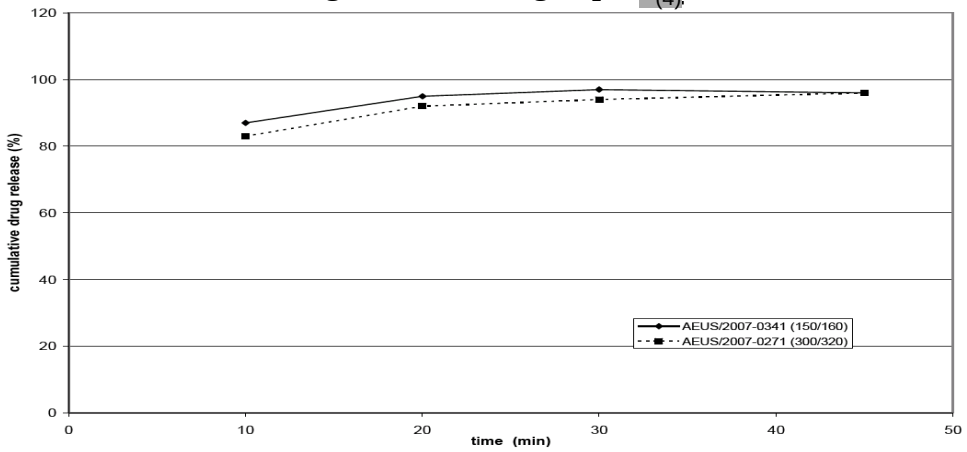


Figure 1-3. Dissolution Profile of Valsartan: Aliskiren/Valsartan Combo Tablets 300/320 mg vs. 150/160 mg at pH (b) (4).



B. For Aliskiren (Layer 1)

Figure 2-1. Dissolution Profile of Aliskiren: Aliskiren/Valsartan Combo Tablets 300/320 mg vs. 150/160 mg at pH (b) (4).

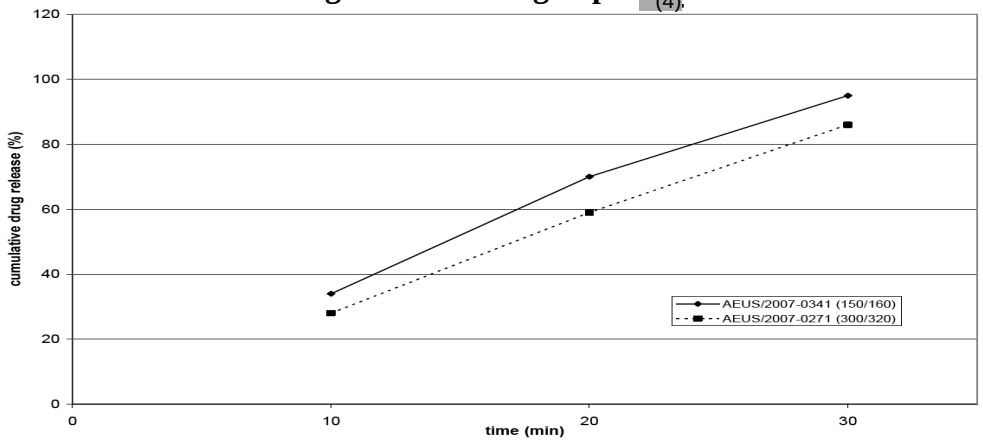


Figure 2-2. Dissolution Profile of Aliskiren: Aliskiren/Valsartan Combo Tablets 300/320 mg vs. 150/160 mg at pH (b) (4)

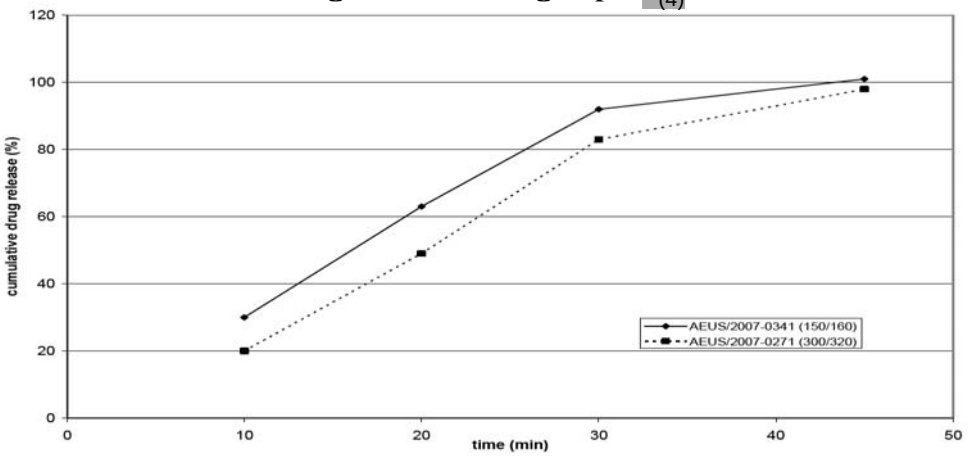
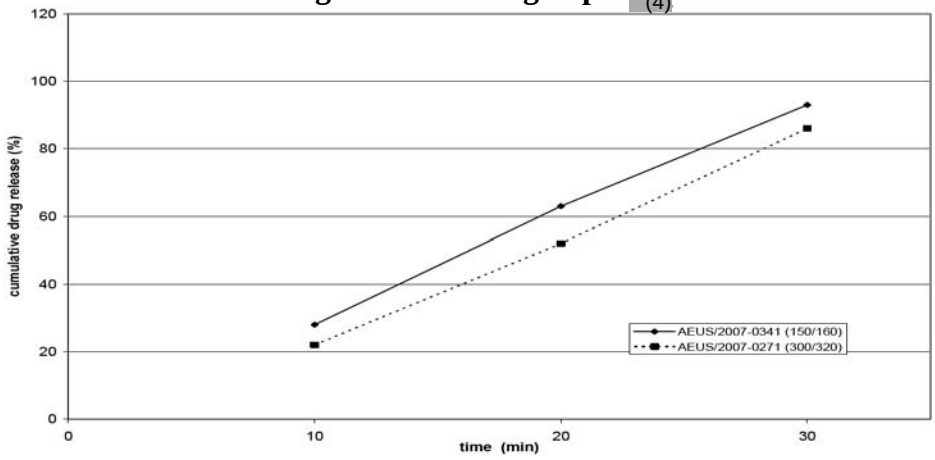


Figure 2-3. Dissolution Profile of Aliskiren: Aliskiren/Valsartan Combo Tablets 300/320 mg vs. 150/160 mg at pH (b) (4)



The f2 values calculated are shown below.

Table 2. Calculations of f2 Values

	Release (mean, %)			
	10 min	**20 min**	**30 min**	**f2**
Aliskiren				
AEUS/2007-0271	22	52	86	--
AEUS/2007-0341	28	63	93	54
Valsartan				
AEUS/2007-0271	83	92	94	--
AEUS/2007-0341	87	95	97	Too fast to calculate

The sponsor's proposed dissolution methodology and specifications are shown below**.**

Table 3. Sponsor's Proposed Dissolution Method and Specifications

Dosage form:	Film coated tablet
Strengths:	150/160 and 300/320 mg
Apparatus type:	Apparatus 1 (basket)
Media:	Phosphate buffer pH 6.8
Volume (mL):	1000
Temperature:	37°C
Speed of rotation (rpm):	100
Sample times (min):	30 and 45
Brief description:	Standard apparatus, standard speed of rotation, standard medium
Dissolution specification (batch release)	Q=(b) (4) for Valsartan in 30 min and Q=(b) (4) in 45 min for Aliskiren

Reviewer's Comments:

1. For Valsartan
   In pH 6.8 medium, it dissolved very fast in 20 min, i.e., a mean of 95% with a CV% of 1.1% (150/160 mg tablet) and a mean of 92% with a CV of 4.1% (300/320 mg tablet).

2. For Aliskiren
   In pH 6.8 medium, it dissolved fairly fast in 30 min, i.e., a mean of 93% with a CV of 5.8% (150/160 mg tablet) and a mean of 86% with a CV of 5.1% (300/320 mg tablet).

Therefore, the proposed dissolution specifications for both Valsartan and Aliskiren need to be revised as follows:

Dissolution specifications (batch release):

Q (b)(4)% for Valsartan in 20 min and Q (b)(4)% in 30 min for Aliskiren

Please see Appendix 1 for drug product dissolution testing for details.

RECOMMENDATION

The biowaiver for a lower strength of Valturna oral combo tablets of Aliskiren and Valsartan (150/160 mg and 300/320 mg) that was submitted under Novartis' NDA 22-217 on 11/25/08 has been reviewed.

Form the Biopharmaceutics perspective, the biowaiver request for the lower strength of Valturna, 150/160 mg oral tablet could be granted, however, the dissolution specifications need to be tightened. The following dissolution specifications proposed by the Agency need to be conveyed to the sponsor for implementation.

COMMENT (Needs to be conveyed to the sponsor)

Both Valsartan and Aliskiren dissolved rapidly in the proposed pH 6.8 medium, therefore, the dissolution specifications need to be tightened. The following revisions proposed by the Agency should be implemented:

From: **Q (b)(4)% for Valsartan in 30 min and Q (b)(4)% in 45 min for Aliskiren**

To: **Q (b)(4)% for Valsartan in 20 min and Q (b)(4)% in 30 min for Aliskiren**

_____	_____06/03/09_____
Tien-Mien Chen, Ph.D. Reviewer ONDQA Biopharmaceutics	Date

_____	_____
Patrick Marroum, Ph.D. ONDQA Biopharmaceutics	Date

CC: NDA
Patrick Marroum, Tien-Mien Chen

8 pp withheld in full immed. after this page as (b)(4) CCI/TS.

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

/s/

Tien-Mien Chen
6/15/2009 04:58:47 PM
BIOPHARMACEUTICS

Patrick Marroum
6/15/2009 05:06:42 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology Review

NDA number:	22-217
Submission type:	Original, N-000
Submission date:	11/26/2008
Applicant name:	Novartis Pharmaceuticals Corporation
Proposed brand name:	Valturna
Generic name:	Aliskiren/Valsartan (A/V)
Dosage form:	Bi-layer oral tablet
Dosage strengths (A/V in mg):	300/320, 150/160
Proposed indication:	Treatment of essential hypertension
OCP division:	DCP1
OND division:	Cardiovascular and renal products
Primary reviewer:	Divya Menon-Andersen, PhD
Secondary reviewer / Team leader:	Angelica Dorantes, PhD

Table of Contents

1 EXECUTIVE SUMMARY

Novartis Pharmaceuticals Corporation is seeking approval via the 505(b) 2 pathway of Valturna, a fixed dose combination (FDC) tablet of aliskiren /valsartan (**A/V**) for use in the treatment of hypertension. Valturna will be marketed in two strengths for once daily administration.

The application contains seven clinical studies in support of the sponsor's claims of efficacy and safety. These include one bioequivalence study (study number SPV100A), one food effect study (study number SPV100A2114), one drug interaction study conducted in healthy subjects (study number SPV100A), one pharmacodynamic study conducted in healthy subjects (study number SPV100A2101), one pivotal, and one supportive placebo controlled efficacy trial (Study numbers CSPP100A2327 and CSPP100A2203), and one long term safety study (study number CSPV100A2301).

1.1 Recommendation

The Office of Clinical Pharmacology (OCP/DCP1) reviewed original NDA 22-217.

Clinical Pharmacology: The results of the bioequivalence study submitted in the application established an adequate link between the results of the pivotal efficacy trial conducted with the free combination, and the final market image tablet (to-be-marketed formulation). Further, it was shown that there was no clinically significant pharmacokinetic or pharmacodynamic drug interaction between the components of the FDC. Administration of the FDC with a high fat meal decreased systemic exposure to aliskiren by > 70%. This is in agreement with the prior knowledge regarding aliskiren disposition, and no dose adjustments are warranted.

Labeling: Clinical pharmacology information included in the proposed labeling is acceptable pending revisions as detailed in Appendix 4.1.

The NDA is considered acceptable from a clinical pharmacology perspective.

1.2 Phase 4 Requirements / Commitments

Not applicable (there are no Phase 4 requirements or commitments).

Divya Menon-Andersen, PhD Date: May 27, 2009
Reviewer, Division of Clinical Pharmacology 1

Angelica Dorantes, PhD
Secondary reviewer / Team leader (Acting), Cardiovascular & Renal Products
Division of Clinical Pharmacology 1

Clinical Pharmacology Briefing:

An optional intra - division level briefing was held on May 18, 2009; and attended by Norman Stockbridge, Bei Yu, Mike Pacanowski, Immo Zdrojewski, Shen Xiao, Mehul Mehta, Ramana Uppoor, Angelica Dorantes and Divya Menon-Andersen.

Cc: DorantesA, UppoorR, MehulM

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Valturna is a FDC tablet of aliskiren (**A)** and valsartan **(V)** for use in the treatment of hypertension. Both the components of Valturna are approved for use in hypertension, and their pharmacokinetic (PK) and pharmacodynamic properties (PD) are well characterized.

The Clinical Pharmacology and Biopharmaceutics program for Valturna was designed primarily to bridge the clinical efficacy and safety data obtained with the free combination to the to-be-marketed formulation. Valturna will be formulated in two strengths – 300/320 mg and 150/160 mg. All studies in the submission were reviewed.

1.3.1 Pharmacokinetics

Following administration of a single dose of Valturna in healthy subjects, peak plasma levels of **A** and **V** were attained approximately at 1h (range: 0.5 to 4 h), and 4h (range: 1 to 12 h), respectively. The mean elimination half-life for **A/V** was estimated to be about 34h (17 to 87 h)*, and 12 h (6 to 26 h), respectively.

*accumulation half-life ~ 24 h

1.3.2 Bioequivalence

A definitive bioequivalence study was conducted to determine the bioavailability of the 300/320 mg strength, relative to the free combination (study number CSPV100A2111). A biowaiver, based on proportionality and compositional similarity, was requested for the lower strength of 150/160 mg (to be reviewed by ONDQA). The rate and extent of absorption of **A**, and **V**, following administration of a single dose of Valturna (300/320 mg) were equivalent to that observed following administration of a single dose of the free combination. **Table 1** presents the results of the bioequivalence studies for Valturna.

Table 1: Relative bioavailabilities of A/V following administration of a single dose of Valturna (Ref: Study CSPV100A2111, Tables)

PK Parameter	Adjusted geometric means		Ratio of geometric means	
	Test (N)	Reference (N)	Estimate	90% Confidence Interval
Aliskiren				
Cmax (ng/mL)	159.44 (80)	164.39 (83)	0.97	0.85 – 1.10
$AUC_{0\text{-tlast}}$ (ng.hr/mL)	792.13 (79)	797.17 (83)	0.99	0.91 – 1.08
$AUC_{0\text{-inf}}$ (ng.hr/mL)	859.32 (77)	860.73 (83)	1.00	0.92 - 1.09
Valsartan				
Cmax (ng/mL)	3833.28 (80)	3532.28 (83)	1.09	0.98 – 1.20
$AUC_{0\text{-tlast}}$ (ng.hr/mL)	31729.8 (79)	29204.2 (83)	1.09	1.01 – 1.17
$AUC_{0\text{-inf}}$ (ng.hr/mL)	32657.2 (74)	29529.5 (80)	1.11	1.02 – 1.19

1.3.3 Food Effect

The effect of food on the disposition of A/V following administration of a single dose of Valturna was evaluated in study SPV100A2114, in healthy subjects. The results of the food effect study are presented in **Figure 1** and **Table 2**.

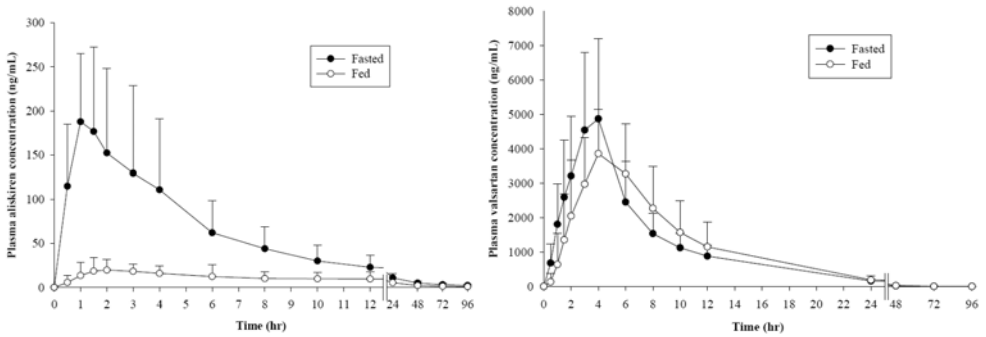


Figure 1: Plots of the mean (± SD) plasma concentration versus time for (a) aliskiren and (b) valsartan. Open circles represent the fasted state and the closed circles represent the fed state.

As seen in **Table 2**, when administered with food, the systemic exposure to aliskiren was decreased by > 70%, and an 11% decrease was observed in mean C_{max} for valsartan.

Table 2: Statistical analysis of log-transformed AUC and C_{max} of Valturna 300/320 mg fed (Test) and Valturna 300/320 mg fasted (Reference).

	Adjusted geometric means		Ratio of means	
Parameter	**Fed (N=30)**	**Fasted (N=33)**	**Estimate**	**90% Confidence Interval**
Aliskiren				
Cmax (ng/mL)	25.82	211.6	0.12	0.11 - 0.14
AUC0-tlast (ng.hr/mL)	347.0	1434	0.24	0.21 - 0.27
AUC0-∞ (ng.hr/mL)	383.4[a]	1574	0.24	0.21 - 0.28
Valsartan				
Cmax (ng/mL)	4212	4724	0.89	0.73 – 1.09
AUC0-tlast (ng.hr/mL)	35160	33140	1.06	0.92 – 1.22
AUC0-∞ (ng.hr/mL)	35330	33350	1.06	0.92 – 1.22

These observations are consistent with prior knowledge regarding **A**, and **V**. A dose adjustment is not required, and therefore these results are not clinically significant.

1.3.4 Drug Interaction

The potential for a PK and PD drug interaction between **A/V** on chronic administration of Valturna was assessed in healthy subjects (study VEA489A2104). At steady state, when administered together, the mean AUC_{last} and C_{max} for **A** decreased by about 25% and that of **V** decreased by about 15%. The 90% confidence intervals for AUC and C_{max} ratios for both **A** and **V** were not within the no effect boundaries (80 to 125%) and were therefore statistically significant. The observed plasma rennin concentrations, following administration of the combination were higher than those observed with either **A** or **V** alone. The observed decrease in plasma rennin activity following administration of the combination was similar to that observed with **A** alone. Hence, given the observed inter-subject variability in **A** and **V** PK (~ 50% CV) and the observed PD effects of the combination, the decreased AUC and C_{max} observed in this study is judged not to be of any clinical significance.

2 QUESTION BASED REVIEW

This is an abridged version of the question based review.

2.1 General Attributes of the individual components and the FDC

Valturna is a film coated fixed dose combination tablet of **aliskiren** and **valsartan**. Both components of Valturna have been previously approved for marketing in the US, for use in the treatment of hypertension.

Individual components:

Aliskiren (A), is a direct rennin inhibitor, approved for use in the treatment of hypertension in adults. A starting dose of 150 mg is recommended, which may be increased to 300 mg to attain adequate blood pressure control. Peak plasma concentrations of aliskiren are reached within one to three hours after dosing. Aliskiren is a poorly absorbed with a bioavailability of about 2.5%. When taken with a high fat meal, mean AUC and C_{max} of aliskiren are decreased by 71% and 85%, respectively. The mean elimination half-life is about 40 h (accumulation half-life is about 24 h).

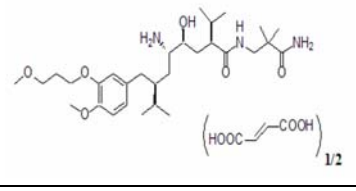
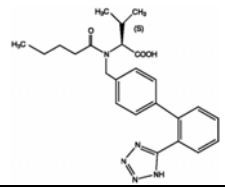
Valsartan (V), an angiotensin receptor blocker, is approved for use in the treatment of hypertension in adults over the dose range of 80 to 320 mg, given once daily. Peak plasma concentrations are attained within two to four hours after dosing. Absolute bioavailability for valsartan (Diovan) is about 25% (range 10%-35%). Food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (Cmax) by about 50%. The mean elimination half-life is about 12 h.

FDC:

Following administration of a single dose of Valturna in healthy subjects, peak plasma levels of A and V were attained approximately at 1h (range: 0.5 to 4 h), and 4h (range: 1 to 12 h), respectively. The mean elimination half-life for A/V was estimated to be about 34h (17 to 87 h), and 12 h (6 to 26 h), respectively.

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Valturna is a fixed dose combination tablet of aliskiren and valsartan.

	Aliskiren	**Valsartan**
Description	White to slightly yellowish crystalline powder	White microcrystalline powder bitter to taste
Chemical name	(2S,4S,5S,7S)-N-(2-Carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamide hemifumarate	N-(1-oxopentyl)-N-[[2′-(1H-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-L-valine
Molecular formula	C30H53N3O6 • 0.5 C4H4O4	C24H29N5O3
Molecular weight	609.8	435.5
Structural formula		
Solubility	Soluble in phosphate buffer, n-Octanol, and highly soluble in water	Soluble in ethanol and methanol and slightly soluble in water

Formulation: The table below lists the formulations for the proposed dosage strengths of Valturna.

Ingredient	**150/160 mg**	**300/320 mg**	**Function**
(b) (4)			
Aliskiren hemifumarate[1)]	165.750	331.500	Active substance
(corresponds to Aliskiren hemifumarate base)	(150.000)	(300.000)	
Valsartan	160.000	320.000	Active substance
Cellulose microcrystalline / Microcrystalline cellulose			(b) (4)
Crospovidone			
Hydroxypropylcellulose			
Magnesium stearate			
(b) (4)/ Colloidal silicon dioxide			
Indigotin Blue Lake (b) (4)			
(b) (4)			
			(b) (4)
			(b) (4)
Total film-coated tablet weight	**574.000**	**1148.000**	

2.1.2 What are the proposed dosages and routes of administration?

Valturna will be formulated in two strengths of **A/V**. These are 300/320 mg, and 150/160 mg.

The approved dosing range for **A**, and **V** in hypertension are 150 to 300 mg, and 80 to 320 mg, respectively.

2.1.3 What are the proposed mechanisms of action and therapeutic indications?

Valturna is indicated in the treatment of hypertension. The mechanisms of action of the individual components of Valturna are state below.

Aliskiren is a direct rennin inhibitor, which decreases plasma rennin activity and thereby decreases the formation of the potent vasoconstrictor angiotensin I. It is approved for use in the treatment of hypertension.

Valsartan is an angiotensin receptor blocker. It blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. It is approved for use in the treatment of (1) hypertension in adults and children above six years (2) heart failure and (3) post myocardial infarction.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and the clinical studies used to support dosing or claims?

Seven clinical studies (four clinical pharmacology + three clinical) were conducted with Valturna to support proposed dosing and claims. All the clinical pharmacology studies were reviewed and the individual study reports are presented in section 4.2. A summary of all seven studies submitted in this application is provided in **Table 3**.

Table 3: Key design features of the clinical pharmacology and clinical studies conducted with Valturna.

Study number	Design	Study population	Treatments	End-point
SPV100A2111 Relative BA/BE 300/320 mg	Single center, open-label, two period, crossover study	Healthy subjects	Single dose of FDC, and the free combination	PK
SPV100A2114 Food effect	Single center, open-label, two period, crossover study	Healthy subjects	Single dose of 300/320 mg FMI tablet fed and fasted	PK
SPP100A2216 Drug Interaction	single center, open label, single sequence, two period study	Healthy subjects	Multiple doses of **A** (300 mg), **V**(320 mg), and **V**+**A** (300 + 320 mg)	PK, PD
SPP100A2101 Pharmaco-dynamics	single-center, double-blind, double-dummy, placebo-controlled, two-panel, sequential-group, randomized, four-period, crossover study	Healthy subjects	High sodium panel: Single dose of **A** (300 mg), **V** (320 mg), **A**+**V** (150 + 160 mg) Low sodium panel: Single dose of **A** (300 mg), **V** (160 mg), **A**+**V** (150 + 80 mg)	PD
SPP100A2327 Efficacy	Multi-center, double-blind, placebo and active controlled, parallel study	Hypertensive patients	**A**: 150 and 300 mg, **V**: 160 and 320 mg, alone and in combination	Blood pressure
SPP100A2203 Efficacy	Multi-center, double-blind, placebo and active controlled, factorial study	Hypertensive patients	**A**: 75, 150, and 300 mg **V**: 80, 160, and 320 mg Hydrochlorothiazide: 12.5 mg	Blood pressure
SPP100A2301 Efficacy	Multi-center, open label, long term safety and tolerability study	Hypertensive patients	**A** (300 mg) + **V** (320 mg)	Safety

2.2.2 Are the active moieties in plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. **A**, and **V** are the only active moieties in Valturna. Please refer to section 2.6 for details of the bioanalytical method.

2.2.3 Exposure-Response

2.2.3.1 Is the dose and dosing regimen selected by the sponsor consistent with the known E-R relationship?

Yes. Valturna is a FDC of aliskiren, and valsartan. The approved dosing range for aliskiren, and valsartan, in hypertension are 150 to 300 mg, and 80 to 320 mg,

respectively. Valturna will be formulated in two strengths of **A/V** that span the approved dosing range of the individual components for oral administration. These are 300/320 mg, and 150/160 mg.

2.2.4 What are the PK characteristics of the drug?

2.2.4.1 What are the single and multiple dose PK parameters?

Please refer to section 2.1.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The effect of intrinsic factors on exposure or response was not evaluated for Valturna.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.4.1.1 Drug Interaction

A drug interaction study was conducted to assess the potential for a PK or PD drug interaction between **A** and **V** when administered together as a dual combination. Plasma AUC and C_{max} of the individual components following administration of the dual combination were compared to that following administration of the **A** and **V** alone. **Tables 4(a)** and **4(b)** present the results of the statistical analysis of the drug interaction study.

Table 4(a): Statistical analysis of log-transformed AUC and C_{max} of aliskiren, alone (reference) and in combination with valsartan (test).

PK measure	Geometric mean		Ratio (%) (Test/Ref)	90 % CI	
	Test	Ref		Lower	Upper
C_{max}	233	323	72	52	99
AUC_{last}	1441	1938	74	63	85

Table 4(b): Statistical analysis of log-transformed AUC and C_{max} of valsartan, alone (reference) and in combination with valsartan (test).

PK measure	Geometric mean		Ratio (%) (Test/Ref)	90 % CI	
	Test	Ref		Lower	Upper
C_{max}	5.8	6.4	88	74	104
AUC_{last}	42	47	86	75	98

As seen in Tables , at steady state, the mean AUClast and Cmax for **A** decreased by about 25% and that of **V** decreased by about 15%. The 90% confidence intervals for AUC and C_{max} ratios (test/ref) for both **A** and **V** were not within the no effect boundaries (80 to 125%) and were therefore statistically significant.

In order to assess the potential for a PD interaction, biomarkers of RAS, namely, plasma renin concentration, plasma renin activity, angiotensin I and II were measured over 24 hours at steady state. The observed plasma rennin concentrations, following administration of the combination was higher than that observed with either **A** or **V** alone. The observed decrease in plasma rennin activity following administration of the combination was similar to that observed with **A** alone.

Hence, given the observed inter-subject variability in **A** and **V** PK (~ 50% CV) and the observed PD effects of the combination, the decreased AUC and C_{max} observed in this study is judged not to be of any clinical significance.

2.4.1.2 Food effect

Influence of food on systemic exposure to **A** and **V** following administration of a single oral dose of Valturna (300/320 mg) was evaluated in study SPV100A2114. Please refer to section 1.3.3 of this document.

2.5 General Biopharmaceutics

2.5.1 Was an adequate link established between the clinical service formulation and the to-be-marketed formulations?

Yes. Valturna will be formulated in two strengths of **A/V** that span the approved dosing range of the individual components for oral administration. These are 300/320 mg, and 150/160 mg. A definitive bioequivalence studies (300/320 mg strength) was conducted to bridge the results of the pivotal efficacy trial to the to-be marketed formulation. A biowaiver, based on proportionality and compositional similarity, was requested for the 150/160 mg strengths (to be reviewed by ONDQA). Please refer to section 1.3.2 of this document.

2.5.2 What is the effect of food on the bioavailability of the drug from the dosage form?

Food does not have an effect on the bioavailability of valsartan, but food decreases the exposure (AUC and C_{max}) of aliskiren by >70%. Please refer to section 1.3.3 of this document.

Although, food decreases the systemic bioavailability of aliskiren, this effect does not have a clinically significant impact on the efficacy of Valturna.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma?

Plasma concentrations of aliskiren, and valsartan were simultaneously determined using a validated HPLC/MS/MS method.

2.6.2 For all moieties measured, is free, bound, or total measured?

Total concentrations of aliskiren, and valsartan were measured.

2.6.3 What bioanalytical methods are used to assess concentrations?

Table 7 provides the details of the bioanalytical method used to support the PK studies. The method satisfied all criteria for 'method validation' and 'application to routine

analysis' set by the '*Guidance for Industry: Bioanalytical Method Development*', and was therefore acceptable.

Simultaneous determination of plasma aliskiren and valsartan concentrations were performed in BE and food effect studies using the method summarized in **Table 7**. Plasma concentrations of aliskiren and valsartan were determined separately in the drug interaction and pharmacodynamics study. A validation report was not provided for this method, however, with-in study validation reports are provided, and reviewed in the individual study report.

Reviewer's comment:

The bioanalytical methods used to determine plasma concentrations of aliskiren and valsartan were reviewed and judged acceptable previously under NDA21-985 (Tekturna) and 21-990 (Exforge), respectively.

Table 7: Assay validation results for aliskiren, and valsartan.

	Aliskiren	**Valsartan**
Standard curve range	0.5 to 500 ng/mL (weighted $1/x^2$, r = 0.99)	5 to 5000 ng/mL (weighted $1/x^2$, r = 0.99)
QC sample concentrations	0.5, 1.5, 80, and 400 ng/mL	5, 15, 800, 4000 ng/mL
Precision (%CV)	Intra-day: 2.5 to 4.9% At LLOQ: 4.9% Inter-day: 3.3 to 5.8% At LLOQ: 7.6%	Intra-day: -4.0 to 0.5% At LLOQ: 4.0% Inter-day: 2.2 to 5.7% At LLOQ: 7.3%
Accuracy (Bias)	Intra-day: -1.4 to -6.3% At LLOQ: -9.8% Inter-day: -8.1 to -2.0% At LLOQ: -3.2%	Inter-day: -4.0 to 0.5% At LLOQ: 13.2% Inter-day: -5.8 to 0.3% At LLOQ: 7.2%
Internal standard	(b) (4) Lot number: 0978/01-1940	Lot number: E-7111079-15
Reference standard	Aliskiren Lot number: 0544031 Purity: 98.2%	Valsartan Lot number: 6BAA9 Purity: 98.7%
Specificity	No interference	No interference
Recovery	Aliskiren: 87.7% D6 – aliskiren: 73.5 %	Valsartan: 67.5% D9 – valsartan: 63.5%
Matrix	Human plasma	Human plasma
Stability (in human plasma)	Benchtop: 24 hours Freeze-thaw: 3 FT cycles	Benchtop: 24 hours Freeze-thaw: 3 FT cycles

3 DETAILED LABELING RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP/DCP-1) has reviewed the package insert labeling for Valturna and finds it acceptable pending the following revisions shown in **Appendix 4.1**. ~~Strikethrough text~~ is recommended to be deleted and underlined text is recommended to be added.

.

.

25 pp withheld in full immed. after this page as (b)(4) draft labeling

4.2 Individual Study Reviews

4.2.1 Study CSPV100A2111 (Bioequivalence – 300/320 mg)

An open-label, randomized, two-treatment, crossover, single-dose study to determine the bioequivalence of fixed combination of aliskiren/valsartan 300/320 mg tablet and the free combination of aliskiren 300 mg and valsartan 320 mg in healthy subjects

Protocol number:	CSPV100A2111
Investigator:	Robert J. Schwab, MD
Study site:	Qualia Clinical Service Omaha, NE
Study dates:	October 20, 2007 to January 02, 2008

Objective

The objectives of this study were to evaluate the bioavailability of a fixed dose combination of aliskiren and valsartan relative to the free combination of aliskiren 300 mg and valsartan 2 x 160 mg, and to assess safety and tolerability of the prototype formulations and the free combination.

Study Design

This was a single center, open-label, randomized, single dose, two period, two sequence, crossover design study. The study design is presented in **Figure 1**.

Figure 1: Schematic of the study design.

Sequence		Period 1 (Day 1)			Period 2 (Day 15)
1	Baseline (Day -1)	Treatment A (Test)	Washout (Day 2-13)	Baseline (Day 14)	Treatment B (Reference)
2		Treatment B (Reference)			Treatment A (Test)

Study medication

- Aliskiren/valsartan (SPV100) 300/320 mg tablets, Batch: AEUS/2007-0271
- Aliskiren 300 mg tablets, Batch: S0050/#6000937.013
- Valsartan (Diovan®) 160 mg capsules, Batch: X125EB/#3748183

Pharmacokinetic sampling

Blood samples were collected at pre-dose and at 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, 24h, 48h, 72h, and 96h post dose.

Pharmacokinetic data analysis

Using noncompartmental methods, the following pharmacokinetic measures were determined for both treatments.

C_{max}, AUC_{last}, AUC_{inf}, T_{max}, λ_z and $t_{1/2}$

Statistical data analysis

Log transformed pharmacokinetic measures of systemic exposure (C_{max}, AUC) were analyzed using ANOVA linear mixed effects model with sequence, period and treatment as fixed effects, and subject within sequence as a random effect. Point estimates and associated 90 % confidence intervals (CI) were determined for the differences of the adjusted treatment means. These were then back transformed to the original scale to give the point estimate and 90% confidence interval for the ratios of the treatment means.

Safety assessments

Physical examination, vital signs, and clinical laboratory tests were performed and evaluated to assess subject safety. All reported adverse events and serious adverse events were collected and evaluated.

Bioanalytical method

Plasma concentrations of A/V were measured simultaneously using a validated HPLC/MS/MS method. The performance measures of the assay are presented in **Table1**.

Table 1: Performance measures of A/V assay in study SPV100A2114.

	Aliskiren	Valsartan
Linearity	0.508 to 484 ng/mL (weighted $1/x^2$, $r > 0.995$)	5.06 to 4820 ng/mL (weighted $1/x^2$, $r > 0.998$)
QCs: Concentration Precision (% CV) Accuracy (% Bias)	 1.2, 80, 400 ng/mL 6.3 to 7.6% 1.7 to 4.1%	 12, 800, 4000 ng/mL 5.4 to 53% * -1.1 to 10.0%

* QCs that failed to qualify were included in the calculation.

Reviewer's comment:

The bioanalytical method employed in this study met the criteria set by the 'Guidance for Industry: Bioanalytical Method Development' and is acceptable.

Study Results

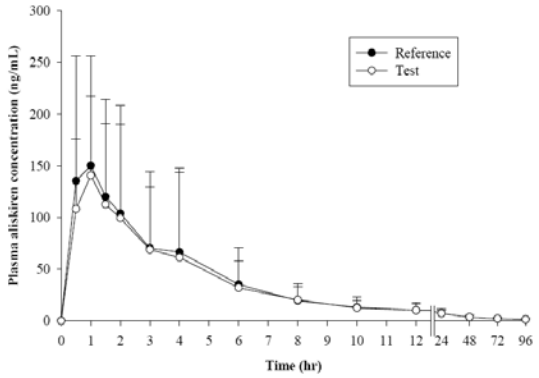
Subject demographics

Eighty four subjects were enrolled in the study, and 78 subjects completed the study. Of the six subjects who discontinued treatment, one (subject # 5116) was withdrawn from the study due to adverse events, and the remaining subjects withdrew consent. The subject demographics were uniform across treatment groups. The mean age and weight were 29.6 years and 82.4 Kg, respectively.

Pharmacokinetic results

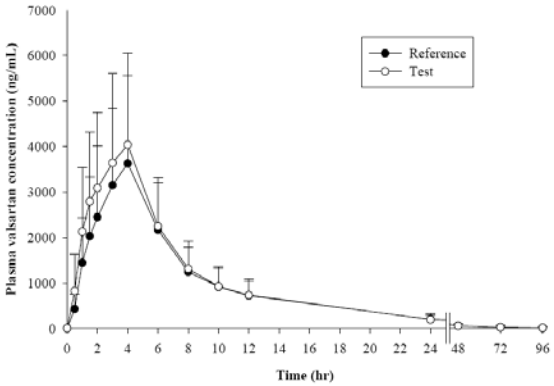
Figure 1 presents a graphical comparison of plasma concentration versus time profiles for each of the components in the FDC (test) and free combination (reference), along with the relevant pharmacokinetic measures.

(a) Aliskiren



Treatment		$AUC_{0\text{-}inf}$ (ng.hr/mL)	$AUC_{0\text{-}tlast}$ (ng.hr/mL)	Cmax (ng/mL)	Tmax (hr)	$T_{1/2}$ (hr)
Test	N	77	79	80	80	77
	Mean	955.38	879.64	183.79	1.27	33.81
	SD	515.82	478.10	108.01	0.86	9.53
	Min	382.24	353.91	48.70	0.48	17.12
	Median	840.70	772.42	154.50	1.00	32.32
	Max	3839.88	3600.60	595.00	4.00	86.43
	%CV	54	54	59	68	28
Reference	N	83	83	83	83	83
	Mean	1005.32	933.19	202.49	1.16	33.63
	SD	673.71	626.74	144.94	0.83	8.20
	Min	323.16	296.67	46.40	0.47	13.95
	Median	803.29	763.81	163.00	1.00	32.58
	Max	4650.05	4248.63	858.00	4.00	55.40
	%CV	67	67	72	72	24

(b) Valsartan



Treatment		$AUC_{0\text{-}inf}$ (ng.hr/mL)	$AUC_{0\text{-}tlast}$ (ng.hr/mL)	Cmax (ng/mL)	Tmax (hr)	$T_{1/2}$ (hr)
Test	N	74	79	80	80	74
	Mean	35468.81	34421.91	4391.13	3.44	12.41
	SD	13652.96	13676.31	2072.49	1.43	4.94
	Min	6414.57	5911.43	345.00	1.00	5.66
	Median	33919.05	32916.35	4275.00	3.01	11.40
	Max	74819.16	74418.20	9140.00	12.00	25.68
	%CV	39	40	47	42	40
Reference	N	80	83	83	83	80
	Mean	31845.23	31509.84	3995.08	3.48	11.80
	SD	12262.22	12315.41	1955.46	1.11	5.21
	Min	8766.14	8598.03	797.00	1.50	5.60
	Median	29509.24	29287.13	3670.00	4.00	9.95
	Max	85004.81	84872.17	11800.00	6.02	34.64
	%CV	39	39	49	32	44

Figure 1: Plots of the mean (± SD) plasma concentration versus time for (a) aliskiren and (b) valsartan. Open circles represent the FDC and the closed circles represent the free combination. The relevant pharmacokinetic measures for the individual components are presented in the panel to the right

As seen in **Figure 1**, the plasma concentration – time profiles for aliskiren and valsartan following administration of a single dose of the free combination and the FDC are comparable.

Statistical data analysis results

A summary of the results of the statistical analysis of pharmacokinetic exposure measures is presented in **Table 2**. As seen in **Table 2**, the rate and extent of absorption of A, and V, following administration of a single dose of Valturna (300/320 mg) were equivalent to that observed following administration of a single dose of the free combination.

Table 1: Relative bioavailabilities of **A/V** following administration of a single dose of Valturna.

PK Parameter	Adjusted geometric means		Ratio of geometric means	
	Test (N)	Reference (N)	Estimate	90% Confidence Interval
Aliskiren				
Cmax (ng/mL)	159.44 (80)	164.39 (83)	0.97	0.85 – 1.10
$AUC_{0\text{-}tlast}$ (ng.hr/mL)	792.13 (79)	797.17 (83)	0.99	0.91 – 1.08
$AUC_{0\text{-}Inf}$ (ng.hr/mL)	859.32 (77)	860.73 (83)	1.00	0.92 - 1.09
Valsartan				
Cmax (ng/mL)	3833.28 (80)	3532.28 (83)	1.09	0.98 – 1.20
$AUC_{0\text{-}tlast}$ (ng.hr/mL)	31729.8 (79)	29204.2 (83)	1.09	1.01 – 1.17
$AUC_{0\text{-}Inf}$ (ng.hr/mL)	32657.2 (74)	29529.5 (80)	1.11	1.02 – 1.19

Safety results

The incidence of adverse events (AEs) appeared to be uniform between treatment groups. Thirty two of the 84 subjects reported at least one adverse event. All AEs were mild to moderate in severity and were resolved at the end of the study. Headache and dizziness were the most commonly reported side effects.

Conclusions

- The rate (C_{max}) and extent (AUC) of absorption of A/V following administration of a single dose of the FDC are not significantly different from that following administration of a single dose of the free combination.
- Valturna is bioequivalent to the free combination of A/V.

4.2.2 Study SPV100A2114 (Food Effect – 300/320 mg)

An open-label, randomized, two-treatment, crossover, single-dose study to determine the effect of food on the bioavailability of fixed combination aliskiren/valsartan 300/320 mg tablets in healthy subjects.

Protocol number: CSPV100A2114

Investigator: (b) (4)

Study site: (b) (4)

Study dates: August 19, 2008 to September 18, 2008

Objectives

The objective of this study was to evaluate the effect of food on the bioavailability of aliskiren/valsartan 300/320 mg final market image (FMI) tablet.

Study design

This was a single center, open label, randomized, two treatment crossover design study. The treatment periods were separated by a washout period of a minimum of 14 days. Each of the subjects was randomized to receive the following:

1. Fixed combination aliskiren/valsartan FMI tablet (300/320 mg) under fasted conditions (Reference)
2. Fixed combination aliskiren/valsartan FMI tablet (300/320 mg) within 30 minutes of a high fat meal (Test). The high fat meal was approximately equivalent to 150, 250, and 500 calories from protein, carbohydrate, and fat, respectively.

Reviewer's comment:

The composition and calorie content of the high fat meal follows the BA/BE guidance and is acceptable.

Study medication

FMI 300/320 mg fixed combination aliskiren/valsartan tablet, Batch # AEUS/2007-0271.

Sample size estimation

A minimum of 30 subjects are required to detect a difference of 60% or greater (since, aliskiren has a significant food effect) in the AUC and C_{max} of aliskiren with 90% power at α=0.1.

Pharmacokinetic sampling

Blood samples were collected at pre-dose and at 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, 24h, 48h, 72h, and 96h post dose.

Pharmacokinetic data analysis

Using noncompartmental methods, the following pharmacokinetic measures were determined for both treatments.

C_{max}, AUC_{last}, AUC_{inf}, T_{max}, λ_z and $t_{1/2}$

Statistical data analysis

Log transformed pharmacokinetic measures of systemic exposure (C_{max}, AUC) were analyzed using ANOVA linear mixed effects model with sequence, period and treatment as fixed effects, and subject within sequence as a random effect. Point estimates and associated 90 % confidence intervals (CI) were determined for the differences of the adjusted treatment means. These were then back transformed to the original scale to give the point estimate and 90% confidence interval for the ratios of the treatment means.

Safety assessments

Physical examination, vital signs, and clinical laboratory tests were performed and evaluated to assess subject safety. All reported adverse events and serious adverse events were collected and evaluated.

Bioanalytical method

Plasma concentrations of A/V were measured simultaneously using a validated HPLC/MS/MS method. The performance measures of the assay are presented in **Table1**.

Table 1: Performance measures of A/V assay in study SPV100A2114.

	Aliskiren	Valsartan
Linearity	0.508 to 484 ng/mL (weighted $1/x^2$, $r > 0.998$)	5.06 to 4820 ng/mL (weighted $1/x^2$, $r > 0.998$)
QCs: Concentration Precision (% CV) Accuracy (% Bias)	 1.46, 28.2, 402 ng/mL 5.5 to 7.5 -4.2 to -2.7	 14.5, 279, 3990 ng/mL 5.3 to 6.9 -7.8 to -5.4
Dilution QC: Concentration Precision (% CV) Accuracy (% Bias)	 - 	 3990 ng/mL 3.8 -5.8

Reviewer's comment:

The bioanalytical method employed in this study met the criteria set by the 'Guidance for Industry: Bioanalytical Method Development' and is acceptable.

Study Results

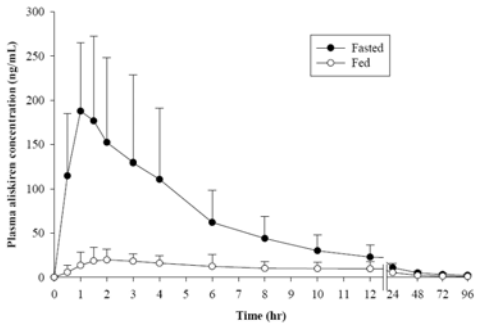
Subject demographics

Thirty four subjects were enrolled in the study, and 29 subjects completed both periods of the study. Of the five subjects who discontinued treatment after study period 1, one (subject # 5132) was withdrawn because of a traffic accident sustained by the subject during the washout period, two subjects (subject # 5101 and 5111) were discontinued from the study because of abnormal lab values after period 1, one subject (subject # 5116) was withdrawn due to an adverse event, and one subject (subject # 5112) was discontinued form study because of use of concomitant medication not approved in the protocol. The subject demographics were uniform across treatment groups. The mean age and weight among the two groups were 31 years (range: 19 to 51 years) and 62 Kg (51 to 85 Kg), respectively. All subjects were Asians.

Pharmacokinetic results

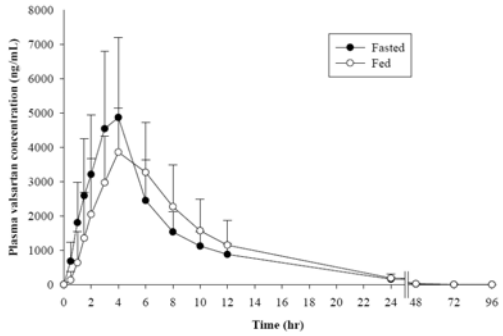
Figure 1 presents a graphical comparison of plasma concentration versus time profiles for each of the components in the fed and fasted condition, along with the relevant pharmacokinetic measures.

(a) Aliskiren



Treatment		AUC0-∞ (ng.hr/mL)	AUC0-tlast (ng.hr/mL)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)
Fed	N	26	30	30	30	26
	Mean	459.99	403.57	28.79	2.72	30.00
	SD	310.25	262.29	14.81	2.21	10.12
	Min	123.05	109.73	11.00	0.50	13.50
	Median	378.84	342.00	24.75	2.00	29.53
	Max	1351.69	1204.34	73.50	12.00	47.50
	% CV	67	65	51	81	34
Fasted	N	33	33	33	33	33
	Mean	1659.35	1512.93	228.72	1.93	41.96
	SD	745.14	685.02	108.60	1.13	9.30
	Min	742.64	667.00	95.60	0.50	24.43
	Median	1485.89	1375.98	195.00	1.50	41.95
	Max	4202.57	3862.77	474.00	4.02	63.10
	% CV	45	45	48	59	22

(b) Valsartan



Treatment		AUC0-∞ (ng.hr/mL)	AUC0-tlast (ng.hr/mL)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)
Fed	N	30	30	30	30	30
	Mean	37705.24	37551.58	4402.67	4.02	6.98
	SD	14314.06	14338.50	1500.59	1.10	1.72
	Min	17155.76	16848.95	2350.00	1.50	4.25
	Median	36172.07	35967.08	4160.00	4.00	6.29
	Max	79158.00	79015.18	9130.00	6.00	10.15
	% CV	38	38	34	27	25
Fasted	N	33	33	33	33	33
	Mean	36588.46	36426.35	5434.58	3.50	7.27
	SD	13448.34	13462.21	2334.71	0.83	2.62
	Min	5960.32	5827.52	400.00	1.50	4.20
	Median	34658.30	34607.46	4790.00	4.00	6.39
	Max	64637.53	64442.65	10300.00	6.00	15.10
	% CV	37	37	43	24	36

Figure 1: Plots of the mean (± SD) plasma concentration versus time for (a) aliskiren and (b) valsartan. Open circles represent the fasted state and the closed circles represent the fed state. The relevant pharmacokinetic measures for the individual components are presented in the panel to the right.

As seen in **Figure 1**, systemic expose (AUC, C_{max}) to aliskiren decreased by > 70% when administered with a high fat meal. Also, there was a small decrease (by about 10%) in the systemic exposure to valsartan when administered with a high fat meal.

Statistical data analysis results

A summary of the results of the statistical analysis of pharmacokinetic exposure measures is presented in **Table 2**. As seen in **Table 2**, following administration of the FMI tablet with food, the bioavailability of aliskiren is significantly reduced. Peak plasma concentrations of valsartan following administration of a single dose under fed conditions were significantly lower than that in the fasted condition.

Table 2: Summary of results of the statistical analysis of PK measures (Ref: Tables).

	Adjusted geometric means		Ratio of means	
Parameter	**Fed (N=30)**	**Fasted (N=33)**	**Estimate**	**90% Confidence Interval**
Aliskiren				
Cmax (ng/mL)	25.82	211.6	0.12	0.11 - 0.14
AUC0-tlast (ng.hr/mL)	347.0	1434	0.24	0.21 - 0.27
AUC0-∞ (ng.hr/mL)	383.4[a]	1574	0.24	0.21 - 0.28
Valsartan				
Cmax (ng/mL)	4212	4724	0.89	0.73 – 1.09
AUC0-tlast (ng.hr/mL)	35160	33140	1.06	0.92 – 1.22
AUC0-∞ (ng.hr/mL)	35330	33350	1.06	0.92 – 1.22

Reviewer's comment:

Administration of Tekturna (aliskiren tablets) along with a high fat meal resulted in > 70% decrease in the systemic exposure to aliskiren. Because of its shallow dose-response relationship, the current PI does not recommend any restrictions on meals. The PI states in the Dosage and Administration section that 'Patients should establish a routine pattern for taking Tekturna with regard to meals. High fat meals decrease absorption substantially'. Results of study SPV100A2114 are therefore consistent with prior knowledge regarding aliskiren and do not impact dosing of aliskiren/valsartan.

Safety results

Eleven of the 33 subjects enrolled in the study experienced adverse events. These included headache, nausea, dizziness, and elevated lab values (CPK, liver enzymes).

Conclusions

Food significantly affects the bioavailability of aliskiren following administration of a single dose of the fixed combination of aliskiren/valsartan 300/320 mg.

4.2.3 Study SPP100A2216 (Drug Interaction)

An open label, multiple dose study to evaluate the pharmacokinetic and pharmacodynamic drug-drug interaction between valsartan and aliskiren when given alone or in combination in healthy volunteers

Protocol number: CSPP100A2216

Investigator: (b) (4)

Study site: (b) (4)

Study dates: 02/03/2005 to 02/26/2005

Objective

The objectives of this study were to evaluate the pharmacokinetic and pharmacodynamic interaction between aliskiren and valsartan when administered together in healthy volunteers, and to assess safety and tolerability of this combination in healthy volunteers.

Study Design

This was a single center, open label, single sequence, two period design study.

Period I (Days 1 – 4)
320 mg valsartan, once daily
Blood sampling on Day 4
Washout period (Days 5 – 7)
Period II (days 8-18)
Days 8 – 14: 300 mg aliskiren, once daily
Days 15 – 18: 300 mg aliskiren + 320 mg valsartan, once daily
Blood sampling on Days 14 and 18

All study medication was administered in the fasted condition. Fluid intake was regulated and monitored in all subjects in the study.

Study medication

1. Aliskiren (SPP100) 300 mg: Novartis Pharmaceuticals, Lot number: X095 0304, Expiration date: 02/2006
2. Valsartan (Diovan) 320 mg: Novartis Pharmaceuticals, Lot number F0112W1, Expiration date: 09/2006

Pharmacokinetic measurements

Blood samples were collected at pre-dose and at 1h, 2h, 3h, 4h, 6h, 8h, 12h, 16h, and 24h post dose on days 4 and 18, and at pre-dose and at 1h, 2h, 4h, 6h, 8h, 12h, 16h, and 24h on day 14 (aliskiren alone). A single pre-dose blood sample was collected on days 2, 3, 12, 13, 16, and 17.

Pharmacodynamic measurements

Biomarkers of RAS, namely, active rennin, aldosterone, angiotensin I, angiotensin II, and plasma renin activity were measured on days 4, 14, and 18. The primary metric of interest were active rennin C_{max} and $AUC_{0\text{-}24h}$ at steady state.

Sample size estimation

A minimum of 18 subjects were required to estimate a 90% CI for PK parameter ratios, the upper limit of which was within 80% of the mean and the lower limit was within 44% of the mean.

Pharmacokinetic and pharmacodynamic data analysis

Using non-compartmental methods, the following measures were determined for aliskiren and valsartan plasma concentrations, PRC, PRA, plasma pro-renin, plasma aldosterone, plasma Ang I and Ang II, blood pressure, sodium urine excretion, and free urinary aldosterone in all treatment cohorts for both panels.

$AUC_{0\text{-}\tau}$, $C_{ss\ max}$, $C_{ss\ min}$, $C_{ss\ average}$, and $t_{ss\ max}$.

Statistical data analysis

Log transformed PK measures of systemic exposure, AUC and C_{max} were analyzed using an linear mixed effects model with treatment as a fixed effect and subject as a random effect. Point estimates and associated 90 % confidence intervals (CI) were determined for the differences of the adjusted treatment means. These were then back transformed to the original scale to give the point estimate and 90% confidence interval for the ratios of the treatment means.

Safety Assessments

Physical examination, vital signs, clinical laboratory tests, ECG assessments, and reports of adverse events and serious adverse events were performed and evaluated to assess subject safety.

Bioanalytical Method

Plasma concentrations of A/V were measured separately using a validated HPLC/MS/MS method. The performance measures of the assays are presented in **Table1**.

Table 1: Performance measures of the assays in study SPV100A2216.

	Aliskiren	Valsartan
Linearity	0.5 to 500 ng/mL (weighted $1/x^2$, $r > 0.998$)	20 to 10000 ng/mL (weighted $1/x^2$, $r > 0.992$)
QCs: Concentration Precision (% CV) Accuracy (% Bias)	 1, 80, 400 ng/mL 3.3 to 4.2% 2.0 to 8.8%	 50, 4000, 8000 ng/mL 3.8 to 32.6% * -0.3 to 14.8%

* QCs that failed to qualify were included in the calculation.

Reviewer's comment:

The bioanalytical method employed in this study met the criteria set by the 'Guidance for Industry: Bioanalytical Method Development' and is acceptable.

Study Results

Subject demographics

Nineteen subjects enrolled in the study and 18 subjects completed both periods of the study. Subject 5116 withdrew consent on study day 14 due to adverse events. The mean (± SD) age and weight were 30.2 y (± 9.3 y) and 74.9 kg (± 9.2 Kg), respectively.

Pharmacokinetic results

Figure 1 presents plots of observed plasma aliskiren and valsartan concentration in study SPP100A2216. As seen in **Figure 1** (right panel), steady state valsartan levels were attained by day 4 in period I, and by day 18 in period II of the study. Similarly, steady state aliskiren levels were attained by day 14 in period II (**Figure 1**(left panel)).

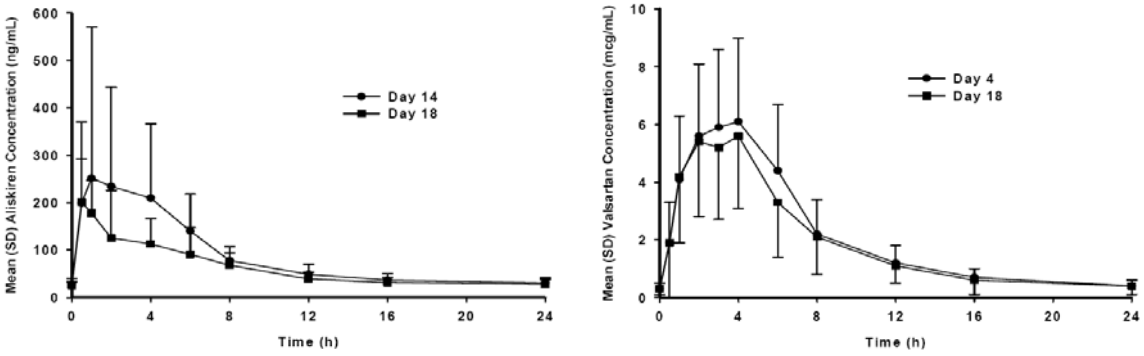


Figure 1: *Left panel:* Plot of plasma aliskiren concentrations on days 14 and 18. *Right panel:* Plot of plasma valsartan concentrations on day 4 and 18. The circles represent plasma concentrations following administration of the single agent and the squares represent plasma concentrations following administration of the combination.

Summary PK measure for aliskiren and valsartan are presented in **Table 2**. As seen in **Figure 1** and **Table 2**, systemic exposure (C_{max} and AUC) to aliskiren was decreased, when administered along with valsartan.

Table 2: Mean (SD) steady state PK measures for aliskiren and valsartan.

	Alsikiren		**Valsartan**	
	Day 14 (alone) n = 19	**Day 18 (comb) n = 18**	**Day 4 (alone) n = 19**	**Day 18 (comb) n = 18**
C_{max} (ng/mL)	420 (328)	249 (96)	7000 (2800)	6400 (2700)
t_{max} (h)*	2.0 (0.5-6)	1.0 (0.5-6.0)	3.0 (1.0-6.0)	3.0 (2.0-4.0)
$AUC_{0-\tau}$ (ng h/mL)	2107 (867)	1502 (425)	51000 (21000)	46000 (23000)
C_{min} (ng/mL)	27 (11)	24 (9)	300 (200)	300 (200)

*median (range)

Pharmacodynamic results

Plasma rennin concentration (PRC)

Steady state PRC at pre-dose on days 4, 14 and 18 were significantly above the normal range (2.4 to 29 mU/L). Following administration of valsartan alone on day 4, the PRC

increased to a mean level of 1159 mU/L at about 6 h post dosing. A similar rise in PRC was observed on day 14 when aliskiren was dosed alone. On day 18 following administration of the combination, mean PRC rose to about 3128 mU/L at about 6 h. PRC values for the study periods I and II are presented in **Table 3**.

Table 3: PRC following administration aliskiren and valsartan, alone and in combination.

	Valsartan Alone	Aliskiren Alone	Combination
Pre-dose (mU/L)	332 (560)	327 (247)	1447 (1297)
Max. post-dose (mU/L)	1159 (1068)	1130 (1121)	3128 (1551)
AUC_{0-24} (mU*h/L)	17242 (23913)	14246 (12292)	54594 (36669)

Plasma rennin activity (PRA)

The plasma rennin activity over 24 h on days 4, 14 and 18 is presented in **Figure 2**. As seen in **Figure 2** administration of the combination resulted in inhibition of plasma rennin activity similar to that seen with aliskiren alone.

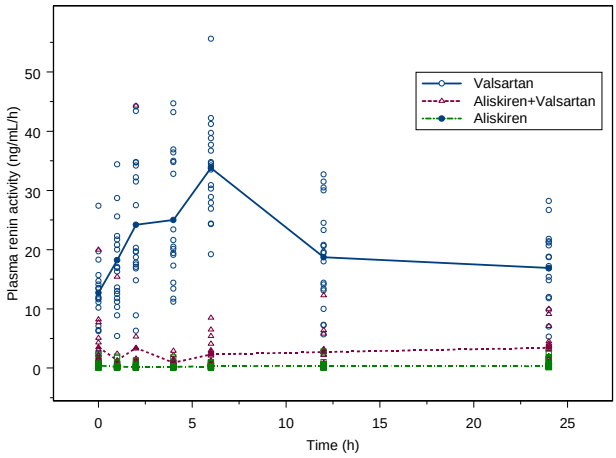


Figure 2: PRA following administration of aliskiren and valsartan, alone and in combination. The open symbols represent the individual values and the solid line represents the mean.

Aldosterone

Mean aldosterone levels over 24 h, following administration of aliskiren or valsartan, alone and in combination, are presented in **Figure 3**.

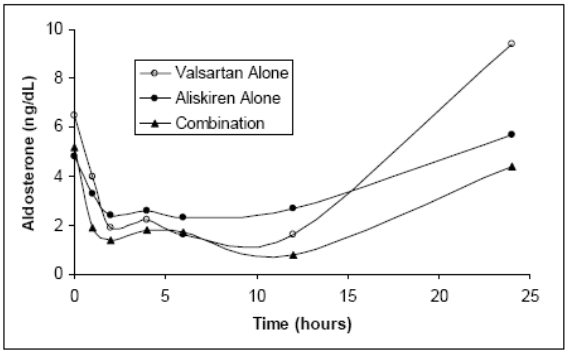


Figure 3: Mean aldosterone levels over 24 h at steady state.

At steady state, a sustained reduction in mean plasma aldosterone is observed for ~ 12h, followed by a slow rise towards baseline levels for the combination (**Figure 3**).

Statistical results

A summary of the results of the statistical analysis of pharmacokinetic exposure measures is presented in **Table 4(a)** and **4(b)**.

Table 4(a): Statistical analysis of log-transformed AUC and Cmax of aliskiren, alone (reference) and in combination with valsartan (test).

PK measure	**Geometric mean**		**Ratio (%) (Test/Ref)**	**90 % CI**	
	Test	**Ref**		**Lower**	**Upper**
C_{max}	233	323	72	52	99
AUC_{last}	1441	1938	74	63	85

Table 4(b): Statistical analysis of log-transformed AUC and Cmax of valsartan, alone (reference) and in combination with valsartan (test).

PK measure	**Geometric mean**		**Ratio (%) (Test/Ref)**	**90 % CI**	
	Test	**Ref**		**Lower**	**Upper**
C_{max}	5.8	6.4	88	74	104
AUC_{last}	42	47	86	75	98

As seen in **Tables 4(a)** and **4(b)**, the 90% confidence limits for the ratio of AUC and Cmax for both aliskiren and valsartan are not within the default equivalence limits (80 to 125), indication the presence of a statistically significant drug interaction between aliskiren and valsartan when administered together.

Safety assessments

Seventeen subjects reported a total of 66 AEs, of which 48 (72.2%) were considered to be related to drug. Of the 48 AEs, 16 occurred during treatment with valsartan alone, 19 with aliskiren alone, and 13 with the combination treatment. Diarrhea was the most frequently reported AE (7 occurrences, 10.6%). During period 2 of the study, while the subjects were receiving aliskiren, there were five instances of increased QT interval over 460 msec. These were not considered to be clinically significant.

Conclusions

- At steady state, mean systemic exposure to aliskiren and valsartan were decreased following administration of the combination. This decrease was statistically significant.
- At steady state, mean PRC levels over 24 h, following administration of the combination were greater than that observed with either aliskiren or valsartan alone.
- At steady state, mean PRA levels over 24 h, following administration of the combination were comparable to that observed with aliskiren alone, and greater than that observed with valsartan alone.
- Given the observed inter-individual variability of (~ 50% CV) in aliskiren and valsartan pharmacokinetics, and the results of the pharmacodynamic interaction studies, the observed decrease in systemic exposure of both aliskiren and valsartan is judged to be clinically not significant.

4.2.4 Study SPP100A2101 (Pharmacodynamics)

A study of the pharmacodynamic (PD) effects of single oral doses of aliskiren, valsartan, their combination, and placebo in high and low sodium status in healthy male volunteers

Protocol number: CSPP100A2101

Investigator: (b) (4)

(b) (4)

Study site: (b) (4)

Study dates: April 07, 2003 to October 22, 2003

Objectives

The primary objective of this study was to assess the pharmacodynamic effects of single oral doses of aliskiren and valsartan, given alone and in combination, in healthy normotensive volunteers. The hypothesis tested in the present study was that the combination of low-to-moderate doses of aliskiren and valsartan would inhibit the RAS and decrease BP more effectively than either blocker given alone at a higher dose.

A secondary objective of the study was to assess the pharmacokinetics of single oral doses of aliskiren and valsartan, given alone and in combination, in healthy normotensive volunteers.

Study Design

This was a single-center, double blind, double dummy, placebo controlled, two panel, sequential group, randomized, four period, crossover study in healthy subjects during sodium depletion (**low sodium panel**) or sodium repletion (**high sodium panel**).

Table 1: Schematic of the study design.

Treatment administration in the **High sodium panel**:

	Aliskiren 300 mg	Aliskiren 150 mg	Valsartan 320 mg	Valsartan 160 mg	Valsartan matching Placebo	Aliskiren matching Placebo
Administration A	X				X*	
Administration B			X*			X
Administration C					X*	X
Administration D		X		X	X	
* : two capsules intake						

Treatment administration in the **Low sodium panel**:

	Aliskiren 300 mg	Aliskiren 150 mg	Valsartan 160 mg	Valsartan 80 mg	Valsartan matching Placebo	Aliskiren matching Placebo
Administration A	X				X	
Administration B			X			X
Administration C					X	X
Administration D		X		X		

Following a 30 day screening period, subjects were randomized to one of the four treatment groups of the high sodium panel (**Table 1**). Baseline PD information was assessed on day -1 of each of the treatment period (days 1 – 3). Treatment periods one to

three (administration A to C) were separated by a ten day washout period. Subjects were enrolled into the low sodium panel similarly.

Sodium repletion was achieved by the oral administration of 0.5 g slow sodium tablets (6g/day) with a regular sodium diet for 6 days before and for 48 hours after study-drug dosing (high sodium panel) during each of the four treatment periods. Sodium depletion was achieved by administration of a single 40-mg oral dose of furosemide 12 hours before study-drug dosing and a sodium-free diet during the 12 hours before and 48 hours after study drug administration (low sodium panel) during each of the four treatment periods.

Study medication

1. Aliskiren 150 mg - Novartis Pharmaceuticals, Lot number: X269 1002
2. Aliskiren 300 mg - Novartis Pharmaceuticals, Lot number: X270 1002
3. Valsartan 80 mg - Novartis Pharmaceuticals, Lot number: X320 1101
4. Valsartan 160 mg - Novartis Pharmaceuticals, Lot number: X323 1101
5. Aliskiren matching placebo - Novartis Pharmaceuticals, Lot number: X271 1002
6. Valsartan matching placebo - Novartis Pharmaceuticals, Lot number: X018 0201

Furosemide capsules and sodium tablets were obtained from the pharmacy of the Georges Pompidou Hospital.

Pharmacokinetic sampling

Blood samples were collected at pre-dose and at 1h, 2h, 4h, 6h, 12h, 24h, 30h and 48h post dose, during each treatment period.

Pharmacodynamic measurements

PRC was the primary PD measure of interest in this study. PRA, plasma aldosterone, Ang I and II, blood pressure, urinary sodium excretion, and urinary aldosterone concentration were secondary measures of interest.

For assessment of the PD measures, blood samples were collected at pre-dose and 1h, 2h, 4h, 6h, 12h, 24h, 30h and 48h post dose, on day 1 of each treatment period.

Urine was collected at -12 h to –6 h, -6 h to 0h (immediately pre-dose), 0 h to 4 h, 4 h to 8 h, 8 h to 12 h, 12 h to 18 h, 18 h to 24 h, 24 h to 36 h, and 36 h to 48 h, on day 1 of each of the treatment periods.

Sample size estimation

A minimum of 12 subjects were required to estimate with 90% power to detect a difference of 500 pg/h/mL in systemic PRC exposure (AUC) at α =0.05.

Pharmacokinetic and pharmacodynamic data analysis

Using non-compartmental methods, the following measures were determined for aliskiren, in all treatment cohorts.

$AUC_{0\text{-}\tau}$, $C_{ss\ max}$, $C_{ss\ min}$, $C_{ss\ average}$, and $t_{ss\ max}$.

Statistical data analysis

To analyze the PD effect of treatment, an analysis of variance appropriate for a four-by-four cross-over design was used for each sodium status panel separately. The factors in the analysis included sequence, subject within sequence, period and treatment. Ninety five percent (95%) confidence intervals were constructed about the treatment mean differences.

Safety assessments

Physical examination, vital signs, clinical laboratory tests, ECG assessments, and reports of adverse events and serious adverse events were performed and evaluated to assess subject safety.

Bioanalytical method

Pharmacokinetics

Plasma concentrations of A/V were measured separately using a validated HPLC/MS/MS method. The performance measures of the assays are presented in **Table2**.

Table 2: Performance measures of the assays in study SPV100A2101.

	Aliskiren	Valsartan
Linearity	0.5 to 100 ng/mL (weighted $1/x^2$, $r > 0.995$)	20 to 10000 ng/mL (weighted $1/x^2$, $r > 0.994$)
QCs: Concentration Precision (% CV) Accuracy (% Bias)	 1, 8, 80 ng/mL 2.5 to 11.5% -2.1 to 1.0%	 30, 1000, 8000 ng/mL 2.9 to 4.7% -9.5 to -3.0%

Reviewer's comment:
The bioanalytical method employed in this study met the criteria set by the 'Guidance for Industry: Bioanalytical Method Development' and is acceptable.

Pharmacodynamics

Radioimmunoassays were employed to measure PRC, PRA, and Ang I and II.

Reviewer's comment:
Details of the assays employed were not provided.

Results

Subject demographics

Twenty four healthy male Caucasian subjects were enrolled in the study, and all 24 completed the study. The demographic characteristics of the subjects in the four treatment groups of the two panels were similar. The mean age and weight in the high sodium panel were 25 y (range 21-30y) and 75.6 Kg (range: 65.9 – 89.4 Kg), respectively. The mean age and weight in the low sodium panel were 25.5 y (21-32y), and 71.0 Kg (range: 62.4 – 95.1 Kg), respectively.

Pharmacokinetic results

The estimated PK measures and parameters for aliskiren alone and in combination with valsartan in the high and low sodium panels are presented in **Table 2**.

Table 2: Summary of the PK measures for aliskiren in the high and low sodium panel following administration of single oral doses of aliskiren, and in combination with valsartan.

	C_{max} (ng/mL) (N=12)	t_{max} (h) (N=12)	$t_{1/2}$ (h) (N=12)	AUC_{0-t} (ng•h/mL) (N=12)	AUC_{0-inf} (ng•h/mL) (N=12)	Cl/F (L/h) (N=12)	Vz/F (L) (N=12)
High Sodium Panel							
A300	203±153	1.3±0.5	22.3±5.2	980±575	1122±655	362.2±188.3	11580.8±6556.2
A150+V160	66±38	1.1±0.3	26.2±8.8	316±138	395±203	463.7±206.4	16177.9±6010.3
Low Sodium Panel							
A300	306±136	2.0±1.0	25.1±4.2	1497±429	1714±497	187.9±51.1	6802.2±2347.3
A150+V80	85±53	2.3±1.5	29.9±8.5	398±239	489±295	434.6±327.0	17757.1±11947.6

The estimated PK parameters for valsartan alone and in combination with aliskiren in subjects in the high and low sodium panels are presented in **Table 3**. The PK of valsartan do not appear to be affected by aliskiren.

Table 3: Summary of the PK measures for valsartan in the high and low sodium panel following administration of single oral doses of valsartan, and in combination with aliskiren.

	C_{max} (ng/mL) (N=12)	t_{max} (h) (N=12)	$t_{1/2}$ (h) (N=12)	AUC_{0-t} (ng•h/mL) (N=12)	AUC_{0-inf} (ng•h/mL) (N=12)	Cl/F (L/h) (N=12)	Vz/F (L) (N=12)
High Sodium Panel							
V320	3.1±2.1	2.7±1.3	8.9±4.1	20.1±10.8	20.6±10.8	19.3±9.2	234.6±128.9
V160+A150	1.5±0.8	2.8±1.0	7.3±2.4	10.6±4.1	11.0±4.2	16.3±5.2	171.5±88.5
Low Sodium Panel							
V160	2.4±1.2	3.1±1.4	8.3±3.8	17.4±7.7	17.8±7.8	11.0±6.1	119.2±53.3
V80+A150	0.7±0.3	2.7±1.0	5.6±1.7	5.7±2.7	6.0±2.7	16.5±8.5	119.9±47.1

As seen in **Table 2**, peak plasma aliskiren levels were attained at about 1 h when administered alone and in combination with valsartan in the high sodium panel subjects. Mean systemic exposure to aliskiren was reduced by about 30% when administered in combination with valsartan. This observation is consistent with those from the steady state drug interaction study. Similar observations (**Table 3**), but of a larger magnitude,

were made in subjects in the low sodium panel, and may be a result of the low sodium status as well.

Pharmacodynamic results

The effect of aliskiren or valsartan, alone and in combination, on PRC is presented in **Figure 1**. As seen in **Figure 1**, when compared to placebo, all three treatments increase PRC over 48 h. Both aliskiren and its combination with valsartan increase PRC to larger extant when compared to valsartan alone. An additive effect on PRC was not observed following administration of the combination.

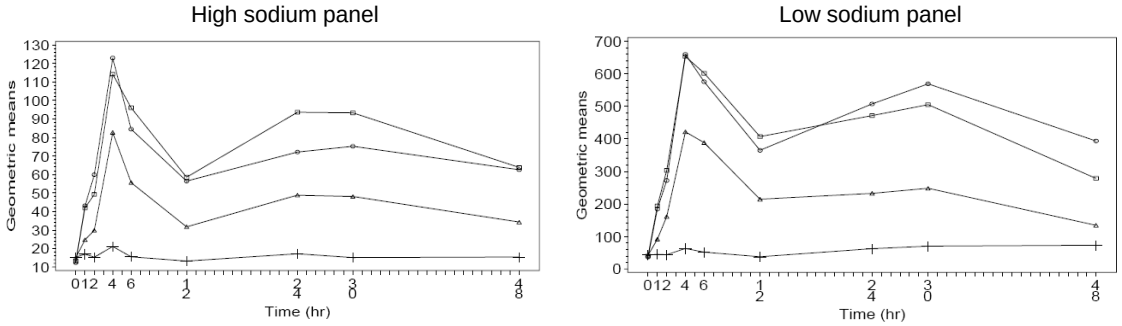


Figure 1: Mean PRC versus time plots in the high sodium and low sodium panels, following administration of placebo (+), aliskiren (◦), valsartan (Δ), and a combination of aliskiren and valsartan (□). Subjects in the high sodium panel received 300 mg aliskiren, 320 mg valsartan, or a combination of 150 mg aliskiren and 160 mg of valsartan. Subjects in the low sodium panel received 300 mg aliskiren, 160 mg valsartan, or a combination of 150 mg aliskiren and 80 mg valsartan.

The effect of aliskiren or valsartan, alone and in combination, on PRA is presented in **Figure 2**. As expected valsartan when administered alone increase PRA, while aliskiren decreases PRA. A similar decrease in PRA, as seen with aliskiren alone, was observed following administration of the combination of aliskiren and valsartan.

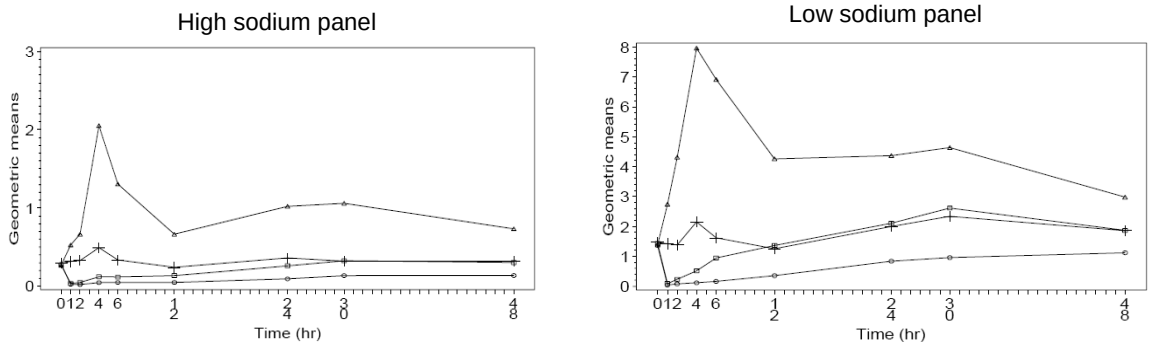


Figure 2: Mean PRA versus time plots in the high sodium and low sodium panels, following administration of placebo (+), aliskiren (◦), valsartan (Δ), and a combination of aliskiren and valsartan (□). Subjects in the high sodium panel received 300 mg aliskiren,

320 mg valsartan, or a combination of 150 mg aliskiren and 160 mg of valsartan. Subjects in the low sodium panel received 300 mg aliskiren, 160 mg valsartan, or a combination of 150 mg aliskiren and 80 mg valsartan.

Blood pressure

The observed mean drop in systolic and diastolic blood pressure following administration of aliskiren or valsartan, alone and in combination, in subjects in the high sodium and low sodium panel is presented in **Figure 3(a)** and **3(b)**, respectively**.**

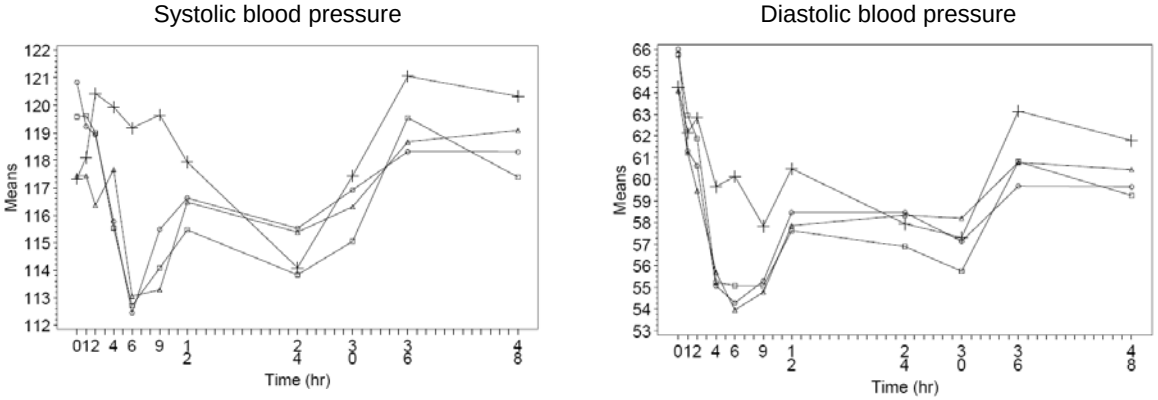


Figure 3(a): Mean blood pressure versus time plots in the high sodium panel, following administration of placebo (+), aliskiren (◦), valsartan (Δ), and a combination of aliskiren and valsartan (□). Subjects in the high sodium panel received 300 mg aliskiren, 320 mg valsartan, or a combination of 150 mg aliskiren and 160 mg of valsartan.

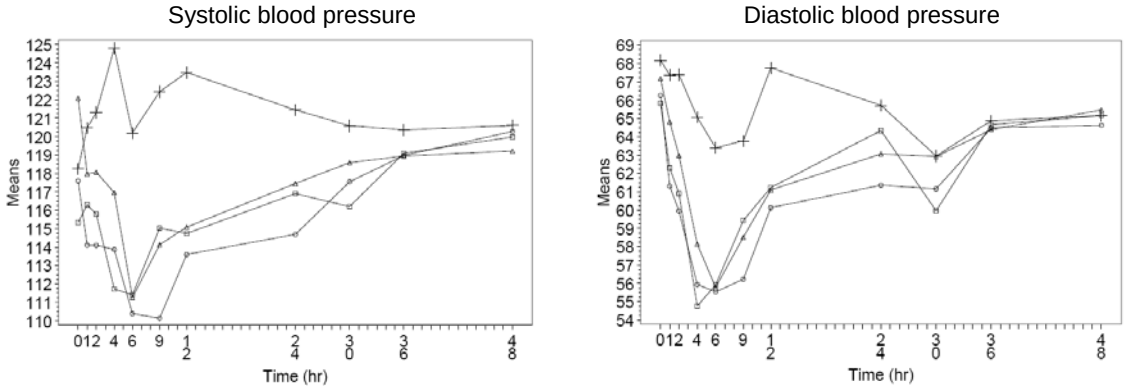


Figure 3(b): Mean blood pressure versus time plots in the low sodium panel, following administration of placebo (+), aliskiren (◦), valsartan (Δ), and a combination of aliskiren and valsartan (□). Subjects in the low sodium panel received 300 mg aliskiren, 160 mg valsartan, or a combination of 150 mg aliskiren and 80 mg valsartan.

As seen in **Figures 3(a)** and **3(b)**, compared to placebo, all three treatments resulted in a decrease in blood pressure to a similar extent. An additive effect of dosing with the combination of aliskiren and valsartan was not observed in subjects in the low sodium panel.

Conclusion

1. Administration of a low dose combination of aliskiren and valsartan did not result in an additional increase, over that observed when administered alone, in PRC, PRA or blood pressure.
2. As observed in previous studies, systemic exposure to aliskiren was decreased when administered along with valsartan in both the high and low sodium panel, while that of valsartan remained unchanged.

5 OCPB FILING FORM

Office of Clinical Pharmacology and Biopharmaceutics

NEW DRUG APPLICATION FILING AND REVIEW FORM

General Information About the Submission

	Information		Information
NDA Number	22-217	**Brand Name**	Valturna® (proposed)
OCPB Division (I, II, III)	OCP I	**Generic Name**	Aliskiren / Valsartan
Medical Division		**Drug Class**	DRI / ARB
OCPB Reviewer	Divya Menon-Andersen, Ph.D	**Indication(s)**	Antihypertensive
OCPB Team Leader	Angelica Dorantes, Ph.D	**Dosage Form**	Bilayer tablet
		Dosing Regimen	QD
Date of Submission		**Route of Administration**	Oral
Estimated Due Date of OCPB Review		**Sponsor**	Novartis
PDUFA Due Date		**Priority Classification**	Standard
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	1	1	Refer to section 5.3.1.4 of eCTD for the bioanalytical data report for study SPV100A2111
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1	-	SPP100A2205 (previously reviewed under NDA 21-985)
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1	1	SPP100A2216; Pharmacodynamics were also evaluated
In-vivo effects of primary drug:	X			
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 1:	X	1	**1**	SPP100A2101
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				

Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	2	1	SPV100A2111 (reviewed) (b) (4)
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	**1**	SPV100A2114
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		**6**	**4**	

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?		
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date	**Divya Menon-Andersen, 12/23/08 (Filing)**	**DMA 5/27/2009 (Final)**
Secondary reviewer Signature and Date	**Angelica Dorantes, 12/23/08 (Filing)**	**AD 5/27/2009 (Final)**

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

/s/

Divya Menon-Andersen
5/28/2009 08:53:36 AM
BIOPHARMACEUTICS

Angelica Dorantes
5/28/2009 11:27:57 AM
BIOPHARMACEUTICS