CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-107

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
DIVISION OF PHARMACEUTICAL EVALUATION I

NDA 22-107/N000	SUBMISSION DATE	March 19, 2007
N000BC		March 27, 2007
N000BZ		May 2, 2007
N000BM		May 4, 2007
N000BB		May 11, 2007
N000BZ		September 20, 2007
N000BB		October 2, 2007
N000BC		November 19, 2007
E-mail		November 21, 2007
E-mail		November 26, 2007
N000BZ		November 29, 2007

TYPE:	ORIGINAL NEW DRUG APPLICATION
BRAND NAME:	Tekturna HCT® Tablets
GENERIC NAME:	Aliskiren/Hydrochlorothiazide Film Coated Tablets – Immediate Release
DOSAGE STRENGTH:	150/12.5, 150/25, 300/12.5 and 300/25 mg
INDICATION:	Treatment of hypertension alone or in combination with other antihypertensive agents
SPONSOR:	Novartis Pharmaceuticals, Inc.
PRIMARY REVIEWER:	Lydia Velazquez, Pharm.D.
TEAM LEADER:	Patrick Marroum, Ph.D.

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EXECUTIVE SUMMARY

Novartis is seeking approval of a new fixed combination formulation, Tekturna/HCT (Aliskiren/HCT immediate-release (IR)) tablets. This formulation will contain a rennin inhibitor and a thiazide diuretic. The sponsor is seeking an indication for the treatment of hypertension alone and in combination with other antihypertensive agents. Tekturna/HCT has been developed in four tablet strengths for oral administration: 150/12.5, 150/25, 300/12.5 and 300/25 mg Aliskiren/HCT tablets. The sponsor has submitted 16 clinical and pharmacokinetic studies to the NDA; which includes eleven clinical studies with no pharmacokinetic content and four biopharmaceutic studies considered to be pivotal to the approval of aliskiren/HCTZ in this indication include 2101, 2102, 2103, and 2104. [redacted] b(4)

[redacted]

In addition, F2 similarity comparison data was submitted for the purposes of obtaining a biowaiver for an intermediate strength (150/12.5 mg) of Tekturna/HCT.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 22-107 original NDA submitted on March 19, 2007 and subsequent submissions to the NDA (see above) for Tekturna/HCT® tablets and has the following clinical pharmacology and biopharmaceutics comments:

REVIEWER COMMENTS TO THE SPONSOR:

1. **Biowaiver Request for the 150/12.5 mg intermediate strength:**

A biowaiver for the intermediate strength 150/12.5 mg Aliskiren/HCT is granted based on compositional similarities between the 300/25 mg and the 150/12.5 mg Aliskiren/HCT strengths and the intermediate strength of 150/12.5 mg Aliskiren/HCT passes the F_2 similarity comparison analysis in three different media.

2. **Labeling:**

Please refer to the labeling in Appendix I for recommendations made.

Lydia Velazquez, Pharm.D.
Division of Pharmaceutical Evaluation I
Primary Reviewer

FT Initialed by Patrick Marroum, Ph.D. _____

OCP Briefing was not held.

CC list: HFD-110: NDA 22-107 (DavidJ, StockbridgeN); HFD-860: (VelazquezL, MarroumP, MehtaM, UppoorR); CDER Central Document Room

Summary of Important CPB Findings

Formulations used in Pivotal Clinical Trials: The free combination of Aliskiren and HCTZ were used in the clinical trials submitted. In an effort to blind medications used for some of the clinical studies, the sponsor inadvertently created a new formulation according to SUPAC Guidance since backfill material was used as filler when aliskiren 150 mg was over-encapsulated.

Food Effect: Food had a significant impact on the rate and extent of absorption of the new formulation; which is reflected in the suggested changes of the product labeling. For aliskiren, C_{max} decreased by 80% and AUC decreased by about 6% with food consumption. Changes in the pharmacokinetics of HCT when administered with food were of no clinical significance.

Mean Aliskiren and HCTZ pharmacokinetic parameters under fed and fasted conditions in healthy volunteers

Treatment	t_{max} (h) median (min, max)	C_{max} (ng/mL) mean ± SD (CV%)	AUC_{0-last} (h·ng/mL) mean ± SD (CV%)	AUC_{0-inf} (h·ng/mL) mean ± SD (CV%)	$t_{½}$ (h) mean ± SD (CV%)	CL/F (mL/h) mean ± SD (CV%)
Aliskiren						
Fed (N=29)	3.0 (0.3, 6.0)	49.1 ± 38.8 (78.9)	492.8 ± 179.1 (36.4)	558.9 ± 195.0 (34.9)	37.8 ± 10.8 (28.5)	614949.9 ± 242715.6 (39.5)
Fasted (N=28)	1.0 (0.5, 4.0)	235.2 ± 90.2 (38.4)	1273.8 ± 444.3 (34.9)	1387.4 ± 483.7 (34.9)	36.0 ± 8.4 (23.2)	241416.9 ± 83615.1 (34.6)
HCTZ						
Fed (N=29)	3.0 (1.5, 6.0)	154.7 ± 28.0 (18.1)	1129.4 ± 258.9 (22.9)	1168.6 ± 259.8 (22.2)	10.3 ± 2.1 (20.0)	22416.6 ± 4955.1 (22.1)
Fasted (N=28)	2.5 (1.0, 4.0)	139.8 ± 36.0 (25.8)	996.9 ± 241.7 (24.2)	1030.4 ± 242.8 (23.6)	12.0 ± 3.4 (28.4)	25713.8 ± 6672.2 (25.9)

Source: Appendix 16.2.5

Patients should establish a routine pattern for taking Tekturna HCT® with regard to meals since high fat meals decrease absorption substantially.

Bioequivalence Studies: The sponsor conducted three bioequivalence studies (Studies 2101, 2102 and 2103).

Study 2101 - open-label, randomized, single-dose, cross-over study in 70 male and female volunteers. The study was conducted in order to establish bioequivalence between the fixed combination of Aliskiren/HCTZ 150/25 mg tablet final market image formulation and the free combination of Aliskiren 150 mg over-encapsulated tablet and HCTZ 25 mg since the sponsor blinded some of their studies. In so doing, they created another formulation since the backfill material constituted a SUPAC IR level-3 change in the formulation's components and composition. As a result, demonstration of bioequivalence between the clinical trial formulation and the to-be-marketed formulation (Final Market Image-FMI) was required for the 150 mg strength. Bioequivalence was demonstrated.

Pharmacokinetic Parameter	Adjusted geometric means		Ratio of geometric means	
	Test [a]	Reference [a]	Estimate	90% Confidence Interval
		Aliskiren		
C_{max} (ng/mL)	70.06	79.53	0.99	0.87 – 1.14
$AUC_{0\text{-}tlast}$ (h·ng/mL)	429.00	428.51	1.00	0.92 – 1.09
$AUC_{0\text{-}inf}$ (h·ng/mL)	487.72	480.45	1.02	0.92 – 1.12
		HCTZ		
C_{max} (ng/mL)	168.33	174.52	0.96	0.93 – 1.00
$AUC_{0\text{-}tlast}$ (h·ng/mL)	1100.7	1138.1	0.97	0.94 – 0.99
$AUC_{0\text{-}inf}$ (h·ng/mL)	1135.0	1169.2	0.97	0.95 – 1.00

[a]: Test: SPH100 (aliskiren 150 mg/HCTZ 25 mg) fixed combination tablet (Treatment 1); Reference: aliskiren 150 mg tablet and HCTZ 25 mg hard gelatin capsule as free combination (Treatment 2)

Study 2102 - single-dose, randomized, open-label, crossover, fasted study in 70 healthy male and female volunteers. The study was conducted in order to establish bioequivalence between the fixed combination Aliskiren/HCTZ 300/12.5 mg final market image tablet and the free combination of aliskiren 300 mg tablet and HCTZ 12.5 mg hard gelatin capsule used in clinical trials.

Results below seem to indicate a lack of bioequivalence between the final market image and free combination for Aliskiren in regards to C_{max}. All other aspects for Aliskiren were bioequivalent as demonstrated below:

Table 2 Statistical results of PK parameters following administration of aliskiren and HCTZ as the fixed and free combination

Pharmacokinetic Parameter	Adjusted geometric means		Ratio of geometric means	
	Test [a]	Reference [a]	Estimate	90% Confidence Interval
		Aliskiren		
C_{max} (ng/mL)	166.00	188.27	0.88	0.75 – 1.04
$AUC_{0\text{-}tlast}$ (h·ng/mL)	1117.3	1205.3	0.93	0.86 – 1.00
$AUC_{0\text{-}inf}$ (h·ng/mL)	1226.6	1309.2	0.94	0.87 – 1.01
		HCTZ		
C_{max} (ng/mL)	71.94	81.58	0.88	0.85 – 0.92
$AUC_{0\text{-}tlast}$ (h·ng/mL)	474.56	520.44	0.91	0.88 – 0.94
$AUC_{0\text{-}inf}$ (h·ng/mL)	512.89	558.91	0.92	0.89 – 0.94

[a]: Test: SPH100 (aliskiren 300 mg/HCTZ 12.5 mg) fixed combination tablet (Treatment 1); Reference: aliskiren 300 mg tablet and HCTZ 12.5 mg hard gelatin capsule as free combination (Treatment 2)

Source: Section 14 Table 14.2-1.1

The difference in C_{max} between the fixed and free combination products is about 18% (166.0 versus 188.27 ng/mL, respectively), not of clinical significance for a medication that is considered to be a wide therapeutic window drug.

HCTZ free hard gelatin capsule was bioequivalent to the fixed combination formulation.

Study 2103 - open-label, randomized, single-dose, crossover study also in 70 male and female subjects to demonstrate bioequivalence between the final market image formulation of 300/25 mg Aliskiren/HCTZ and the free combination used in clinical trials of Aliskiren 300 mg tablet and HCTZ 25 mg hard gelatin capsule. Bioequivalence was demonstrated with both Aliskiren and HCTZ as seen below:

Bioequivalence results for aliskiren and HCTZ pharmacokinetic parameters following single oral doses of SPH100 (aliskiren 300 mg/HCTZ 25 mg) in fixed combination tablet (Test) or aliskiren 300 mg tablet and HCTZ 25 mg capsule as free combination (Reference) to healthy subjects (N=70)

Pharmacokinetic Parameter	Adjusted geometric means		Ratio of geometric means	
	Test [a]	Reference [a]	Estimate	90% Confidence Interval
		Aliskiren		
C_{max} (ng/mL)	233.71	247.34	0.94	0.82 –1.08
$AUC_{0\text{-}tlast}$ (h·ng/mL)	1156.32	1266.99	0.91	0.83 – 1.00
$AUC_{0\text{-}inf}$ (h·ng/mL)	1271.81	1392.98	0.91	0.83 – 1.00
		HCTZ		
C_{max} (ng/mL)	140.45	157.86	0.89	0.85 – 0.93
$AUC_{0\text{-}tlast}$ (h·ng/mL)	961.90	1037.95	0.93	0.89 – 0.96
$AUC_{0\text{-}inf}$ (h·ng/mL)	995.33	1075.78	0.93	0.89 – 0.96

[a]- Test: SPH100 (aliskiren 300 mg/HCTZ 25 mg) fixed combination tablet (Treatment A); Reference: aliskiren 300 mg tablet and HCTZ 25 mg hard gelatin capsule as free combination (Treatment B)

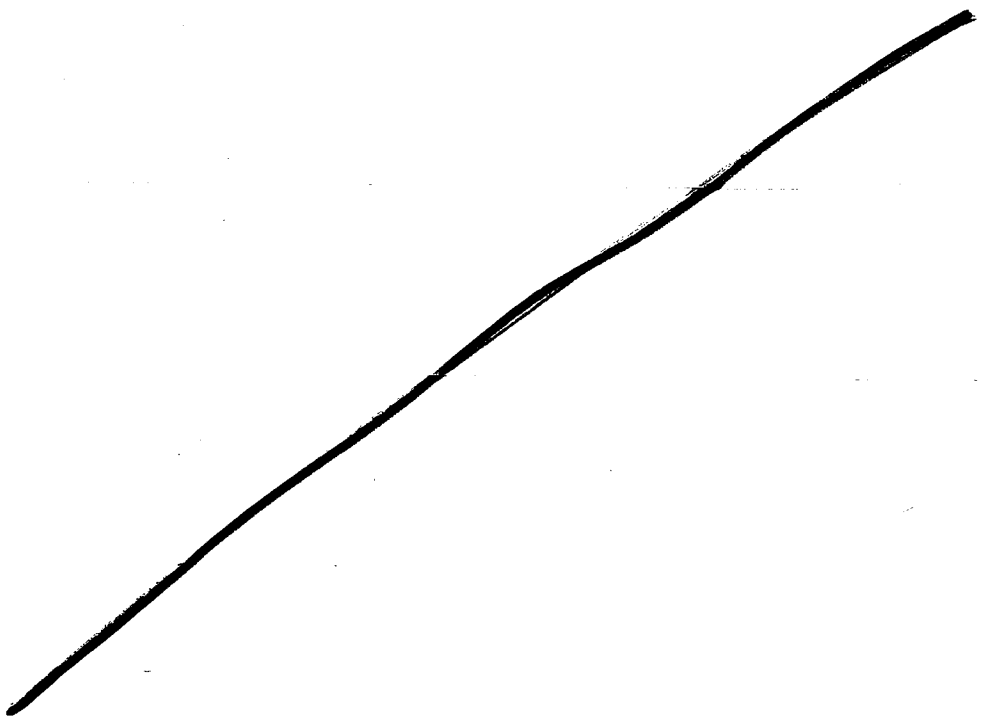
Biowaiver of Intermediate Strengths: A biowaiver for the intermediate strength 150/12.5 mg Aliskiren/HCT is being granted based on:

1. Compositional similarities between the 300/25 mg (reference) and the 150/12.5 mg (test) Aliskiren/HCT strengths.

Composition of Aliskiren/HCTZ Fixed Combination Formulation (mg/dosage unit)

Ingredient	150/12.5 mg	150/25 mg	300/12.5 mg	300/25 mg	Function
Tablet core					
Aliskiren hemifumarate[1]					Active substance
Hydrochlorothiazide					Active substance
Cellulose microcrystalline / Microcrystalline cellulose					
Crospovidone					
Lactose					
Wheat starch					
Povidone					
Magnesium stearate					
Silica, colloidal					
Colloidal silicon dioxide					
Talc					
Core tablet weight					
Total film-coated tablet weight	441.00	528.00	806.00	876.00	

b(4)



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2. Information submitted for batch number X018 0206 (300/25 mg) and X008 0206 (150/12.5 mg), the intermediate strength of 150/12.5 mg Aliskiren/HCT passes the F_2 similarity comparison analysis in three different media to include the proposed dissolution specifications (0.1M HCl, 100 rpm, 900 mL USP apparatus 1, 37°C).

Dissolution testing was performed according to USP level 1 and 2 requirements, using basket method (apparatus 1) at 100 rpm. For the different pH conditions indicated, the following dissolution media were used (900 ml): 0.1M HCl, phosphate buffer at pH 4.5 and phosphate buffer pH 6.8. Determination of the amount of drug substance dissolved (%) was performed by HPLC with UV detection.

F2 calculation in 0.1M HCl

	Release (mean %)				
	10min	15min	20min	30min	f2
SPP100					
X018 0206	37.2	58.7	79.3	98.8	---
X008 0206	36.9	55.7	71.4	96.9	68
HCTZ					
X018 0206	32.7	50.5	67.6	87.1	---
X008 0206	32.9	50.2	64.5	88.5	85

F2 calculation at pH 4.5

	Release (mean %)				
	10min	15min	20min	30min	f2
SPP100					
X018 0206	39.0	62.2	83.0	99.2	---
X008 0206	38.0	59.2	74.9	96.9	67
HCTZ					
X018 0206	34.0	52.8	69.7	86.7	---
X008 0206	37.4	56.4	71.2	92.1	71

F2 calculation at pH 6.8

	Release (mean %)				
	10min	15min	20min	30min	f2
SPP100					
X018 0206	41.3	63.2	83.5	99.7	---
X008 0206	39.5	58.8	76.7	102.2	68
HCTZ					
X018 0206	35.3	52.6	68.4	84.0	---
X008 0206	35.8	53.3	70.0	94.5	57

Assay Validation: Aliskiren and HCTZ plasma concentrations were analyzed by a validated LC-MS/MS method with the following parameters:

LLOQ	**SPP100: 0.500 ng/mL using 200 µL of human plasma (expressed as SPP100 free base)** **Hydrochlorothiazide: 1.00 ng/mL using 200 µL of human plasma**
Specificity	**The method is specific in human plasma for SPP100 (maximum interference 16.9% of signal at LLOQ), for [D_6] SPP100 (maximum interference 0.1% of signal at working concentration), for HCTZ (maximum interference 4.4% of signal at LLOQ) and for $D_2{}^{15}N_2$-HCTZ (maximum interference 0.1% of signal at working concentration).**
Matrix effect	**SPP100: mean recovery 115%** **[D_6] SPP100: mean recovery 107%** **HCTZ: mean recovery 446%** **$D_2{}^{15}N_2$-HCTZ: mean recovery 437%**
Absolute recovery	**SPP100: mean 66.6%** **[D_6] SPP100: mean 69.0%** **HCTZ: mean 63.5%** **[D_2] $^{15}N_2$-HCTZ: mean 67.4%**

Intra-day accuracy and precision	**For SPP100:** **At LLOQ: bias of -3.2%, precision of 5.2%** **Above LLOQ: bias within the range of -7.8% to -1.3%, precision within the range of 3.1% to 4.8%** **For HCTZ:** **At LLOQ: bias of 5.0%, precision of 4.9%** **Above LLOQ: bias within the range of -4.4% to 1.8%, precision within the range of 2.3% to 4.2%**
Inter-day accuracy and precision	**For SPP100:** **At LLOQ: bias -6.4%, precision 10.0%** **Above LLOQ: bias within the range of -0.7% to 4.5%, precision within the range of 6.1% to 7.1%.** **For HCTZ:** **At LLOQ: bias 3.0%, precision 13.2%** **Above LLOQ: bias within the range of -0.3% to -3.8%, precision within the range of 3.5% to 4.5%.**

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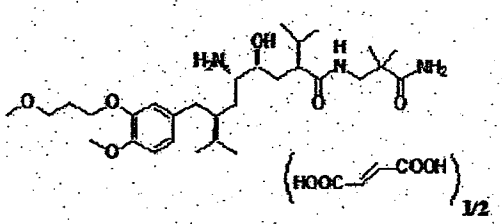
QUESTION BASED REVIEW

I. GENERAL ATTRIBUTES OF THE DRUG

A. WHAT ARE THE HIGHLIGHTS OF THE CHEMISTRY AND PHYSICAL-CHEMICAL PROPERTIES OF THE DRUG SUBSTANCE?

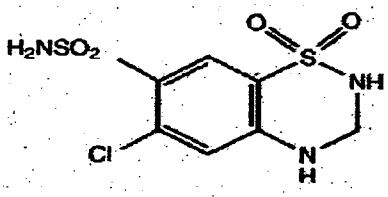
Aliskiren is chemically described as (2S,4S,5S,7S)-N-(2-Carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamide hemifumarate and its structural formula is



Molecular Formula: $C_{30}H_{53}N_3O_6 \cdot 0.5\ C_4H_4O_4$

Aliskiren is a white to slightly yellowish crystalline powder with a molecular weight of 609. 8 (free base- 551.8). It is soluble in phosphate buffer, n-Octanol, and highly soluble in water.

HCTZ is chemically described as 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiazide-7-sulfonamide 1,1-dioxide. Its structural formula is



Molecular Formula: $C_7H_8ClN_3O_4S_2$

HCTZ USP is a white, or practically white, practically odourless, crystalline powder with a molecular weight of 297.73. It is slightly soluble in water; freely soluble in sodium hydroxide solution, in *n*-butylamine, and in dimethylformamide; sparingly soluble in methanol; and soluble in ether, in chloroform, and in dilute mineral acids.

B. WHAT ARE THE HIGHLIGHTS OF THE FORMULATION OF THE DRUG PRODUCT?

The sponsor has developed an immediate-release product that is a fixed combination film-coated tablet of Aliskiren and HCT. Aliskiren/HCT is being developed in four tablet strengths (150/12.5, 150/25, 300/12.5 and 300/25 mg; respectively) for oral administration. The composition of the product is depicted below:

C. WHAT IS THE PROPOSED MECHANISM OF ACTION AND THERAPEUTIC INDICATIONS?

Aliskiren

Rennin is secreted by the kidney in response to decreases in blood volume and renal perfusion. This response initiates a cycle that includes the rennin angiotensin system (RAS) and a homeostatic feedback loop. Rennin cleaves angiotensinogen to form the inactive decapeptide angiotensin I (Ang I), which is converted to the active octapeptide angiotensin II (Ang II) by angiotensin converting enzyme (ACE) and non-ACE pathways. Ang II is a powerful vasoconstrictor and leads to the release of catecholamines from the adrenal medulla and prejunctional nerve endings. It also promotes aldosterone secretion and sodium reabsorption. Together, these effects increase blood pressure. Chronic increases in Ang II result in the expression of markers and mediators of inflammation and fibrosis that are associated with end organ damage. Ang II also inhibits rennin release, thus providing a negative feedback to the system. Elevated plasma rennin activity (PRA) has been independently associated with increased cardiovascular risk in hypertensive and normotensive patients.

Aliskiren is a rennin inhibitor that targets the cycle at its point of activation, inhibiting the conversion of angiotensinogen to Ang I. This action suppresses the entire system, resulting in a reduction in PRA, Ang I, and Ang II. All agents that inhibit this system, including rennin inhibitors, suppress the negative feedback loop, leading to a compensatory rise in plasma rennin concentration. When this rise occurs during treatment with ACE inhibitors and ARBs, it is accompanied by increased levels of PRA. During treatment with aliskiren, the feedback loop effects are neutralized. As a result, PRA, Ang I and Ang II are all reduced, whether aliskiren is used as monotherapy or in combination with other antihypertensive agents.

HCTZ

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of agents that block the production or function of angiotensin II tends to reverse the potassium loss associated with these diuretics.

The mechanism of action of the antihypertensive effect of thiazides is unknown.

Aliskiren/HCT is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

D. WHAT ARE THE PROPOSED DOSAGES AND ROUTE OF ADMINISTRATION?

The usual recommended starting dose of Aliskiren/HCT is 150/12.5 mg orally once daily. Titration of the dose should be approached by clinical effect.

II. General Clinical Pharmacology

A. What clinical pharmacology and clinical studies submitted to support dosing or claims?

A total of 16 clinical/clinical pharmacology studies were submitted to the NDA of which four were reviewed for Clinical Pharmacology/Pharmacokinetic content. The four studies reviewed (2101, 2102, 2103, and 2104) from the clinical pharmacology and biopharmaceutics perspective were three bioequivalence and one food effect study. [redacted] b(4)

[redacted] Eleven studies were not reviewed because there was no pharmacokinetic data. An additional study was submitted with F2 similarity comparison data in order to obtain a biowaiver of the 150/12.5 mg strength; which was reviewed.

B. What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

The major endpoint is decrease in blood pressure since the indication is for treatment of hypertension with Aliskiren/HCT. The endpoints of interest being measured is Systolic and Diastolic sitting blood pressure.

C. Extrinsic Factors

a. Were any drug interactions explored?

Yes. An earlier drug interaction study between Aliskiren and HCTZ was performed and reviewed (NDA 21-985) that resulted in no pharmacokinetic interaction between the two moieties.

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

As demonstrated in study 2104, food had a significant impact on the rate and extent of absorption of Aliskiren/HCT. It was a randomized, open-label, single-dose, two-period, crossover study in healthy subjects to evaluate the effect of food on the bioavailability of Aliskiren/HCTZ (300/25 mg) fixed combination versus the final market image tablet. Aliskiren C_{max} fasted versus fed was 82% lower (235.2 and 49.1 ng/mL, respectively) with a CV% of 38.4 and 78.9%. T_{max} was delayed by two hours (1.0 versus 3.0 hours, fasted to fed) and Aliskiren $AUC_{0\text{-}last}$ dropped by 61% (1273.8 versus 492.8 ng·h/mL with a CV% 34.9% for both). The $AUC_{0\text{-}\infty}$ also dropped by 60% (from 1387.4 to 558.9 ng·h/mL) when food was given. The CV% was 34.9% for both again. Aliskiren's half-life slightly increased from 36.0 to 37.8 hours when food was given and the clearance increased from 241416.9 mL/h under fasted to 614949.9 mL/h under fed conditions (155%) indicating that the small amount absorbed upon drug administration with food underwent increased oral clearance. However, the half-life was delayed. All pharmacokinetic variables had a high CV%. Food effects should be noted in the labeling for Aliskiren/HCTZ.

HCTZ C_{max} was slightly different from fasted versus fed state being 11% higher (139.8 and 154.7 ng/mL, respectively) with a CV% of 25.8 and 18.1%. T_{max} was similar as well (2.5 versus 3.0 hours, fasted to fed) and HCTZ $AUC_{0\text{-}last}$ slightly increased by 13% (996.9 versus 1129.4 ng·h/mL with a CV% 24.2 and 22.9%, respectively). The $AUC_{0\text{-}\infty}$ also increased slightly by 13% (from 1030.4 to 1168.6 ng·h/mL) when food was given.

The CV% was 23.6 and 22.2%, respectively. HCTZ's half-life decreased from 12.0 to 10.3 hours when food was given and the clearance slightly decreased from 25713.8 mL/h under fasted to 22416.6 mL/h under fed conditions (13%) indicating that a food effect for HCTZ was of no clinical significance.

Mean Aliskiren/HCT concentrations under fed and fasted conditions in healthy volunteers

Treatment	t_{max} (h) median (min, max)	C_{max} (ng/mL) mean ± SD (CV%)	$AUC_{0\text{-}tlast}$ (h·ng/mL) mean ± SD (CV%)	$AUC_{0\text{-}Inf}$ (h·ng/mL) mean ± SD (CV%)	$t_{½}$ (h) mean ± SD (CV%)	CL/F (mL/h) mean ± SD (CV%)
Aliskiren						
Fed (N=29)	3.0 (0.3, 6.0)	49.1 ± 38.8 (78.9)	492.8 ± 179.1 (36.4)	558.9 ± 195.0 (34.9)	37.8 ± 10.8 (28.5)	614949.9 ± 242715.6 (39.5)
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HCTZ						
Fed (N=29)	3.0 (1.5, 6.0)	154.7 ± 28.0 (18.1)	1129.4 ± 258.9 (22.9)	1168.6 ± 259.8 (22.2)	10.3 ± 2.1 (20.0)	22416.6 ± 4955.1 (22.1)
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Source: Appendix 16.2.5

III. General Biopharmaceutics

A. Where different formulations used throughout the development program of Aliskiren?

Free combinations of Aliskiren and HCTZ were used in the clinical trials submitted. In an effort to blind medications used for some of the clinical studies, the sponsor inadvertently created a new formulation according to SUPAC Guidance since backfill material was used as filler when aliskiren 150 mg was over-encapsulated.

B. Was an adequate link established between the clinical and to-be-marketed formulations?

The sponsor conducted three bioequivalence studies (Studies 2101, 2102 and 2103).

Study 2101 was an open-label, randomized, single-dose, cross-over study in 70 male and female volunteers. The study was conducted in order to establish bioequivalence between the fixed combination of Aliskiren/HCTZ 150/25 mg tablet final market image formulation and the free combination of Aliskiren 150 mg over-encapsulated tablet and HCTZ 25 mg since the sponsor blinded some of their studies. In so doing, they created another formulation since the backfill material constituted a SUPAC IR level-3 change in the formulation's components and composition. As a result, demonstration of bioequivalence between the clinical trial formulation and the to-be-marketed formulation (Final Market Image-FMI) was required for the 150 mg strength. Bioequivalence was demonstrated.

Pharmacokinetic Parameter	Adjusted geometric means		Ratio of geometric means	
	Test [a]	Reference [a]	Estimate	90% Confidence Interval
		Aliskiren		
C_{max} (ng/mL)	70.06	79.53	0.99	0.87 –1.14
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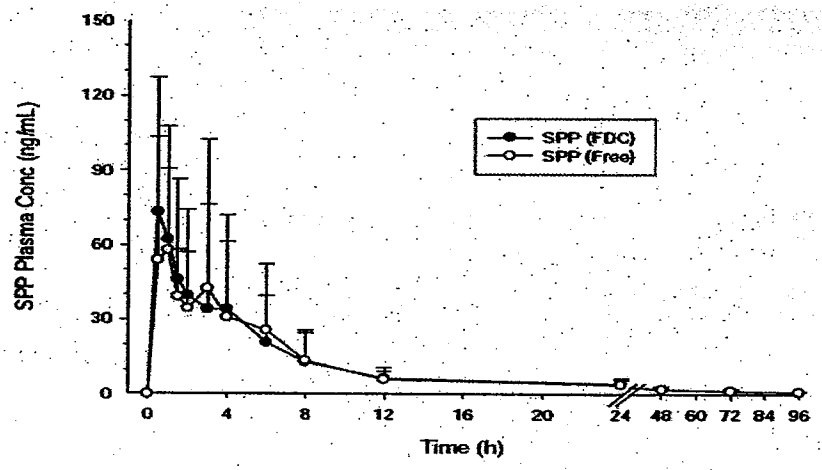
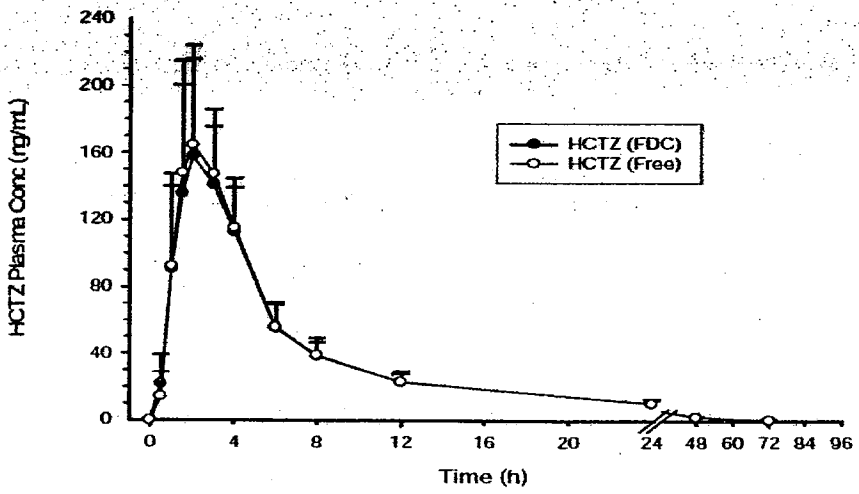
		HCTZ		
C_{max} (ng/mL)	168.33	174.52	0.96	0.93 – 1.00
AUC_{0-last} (h·ng/mL)	1100.7	1138.1	0.97	0.94 – 0.99
AUC_{0-inf} (h·ng/mL)	1135.0	1169.2	0.97	0.95 – 1.00

[a]: Test: SPH100 (aliskiren 150 mg/HCTZ 25 mg) fixed combination tablet (Treatment 1);
Reference: aliskiren 150 mg tablet and HCTZ 25 mg hard gelatin capsule as free combination (Treatment 2)

Mean (SD) plasma concentration-time profiles of aliskiren (SPP) following single oral doses of 150/25 mg (aliskiren/HCTZ) fixed combination FMI tablet or aliskiren 150 mg overencapsulated tablet and HCTZ 25 mg capsule as free combination to healthy subjects



Mean (SD) plasma concentration-time profiles of HCTZ following single oral doses of 150/25 mg (aliskiren/HCTZ) fixed combination FMI tablet or aliskiren 150 mg overencapsulated tablet and HCTZ 25 mg capsule as free combination to healthy subjects



Study 2102 was a single-dose, randomized, open-label, crossover, fasted study in 70 healthy male and female volunteers. The study was conducted in order to establish bioequivalence between the fixed combination Aliskiren/HCTZ 300/12.5 mg final market image tablet and the free combination of aliskiren 300 mg tablet and HCTZ 12.5 mg hard gelatin capsule used in clinical trials.

Results below seem to indicate a lack of bioequivalence between the final market image and free combination for Aliskiren in regards to Cmax. All other aspects for Aliskiren were bioequivalent as demonstrated below:

Table 1 **Pharmacokinetic parameters of aliskiren and HCTZ after administration as the fixed and free combination**

Treatment	t_{max} (h) median (min, max)	C_{max} (ng/mL) mean ± SD (CV%)	$AUC_{0\text{-}tlast}$ (h·ng/mL) mean ± SD (CV%)	$AUC_{0\text{-}inf}$ (h·ng/mL) mean ± SD (CV%)	$t_{½}$ (h) mean ± SD (CV%)	CL/F (mL/h) mean ± SD (CV%)
Aliskiren						
Fixed combination (N=68)	1.0 (0.5, 6.3)	203.8 ± 138.9 (68.2)	1279.5 ± 674.4 (52.7)	1401.7 ± 730.4 (52.1)	37.7 ± 16.7 (44.3)	281057.3 ± 157512.4 (56.0)
Free combination (N=66)	1.0 (0.5, 12)	248.5 ± 199.6 (80.3)	1400.4 ± 800.0 (57.1)	1512.8 ± 846.7 (56.0)	35.9 ± 9.5 (26.3)	266685.0 ± 150930.6 (56.6)
HCTZ						
Fixed combination (N=68)	2.0 (1.5, 4.2)	73.5 ± 18.5 (25.1)	485.0 ± 116.9 (24.1)	521.3 ± 112.5 (21.6)	10.0 ± 2.1 (21.2)	25068.2 ± 5361.6 (21.41)
Free combination	2.0	85.4 ± 25.0	537.7 ± 133.3	574.2 ± 127.6	9.8 ± 2.0	22857.7 ±
Aliskiren						
Treatment	t_{max} (h) median (min, max)	C_{max} (ng/mL) mean ± SD (CV%)	$AUC_{0\text{-}tlast}$ (h·ng/mL) mean ± SD (CV%)	$AUC_{0\text{-}inf}$ (h·ng/mL) mean ± SD (CV%)	$t_{½}$ (h) mean ± SD (CV%)	CL/F (mL/h) mean ± SD (CV%)
(N=66)	(1.5, 4.3)	(29.3)	(24.8)	(22.2)	(19.8)	5105.1 (22.3)

Table 2 **Statistical results of PK parameters following administration of aliskiren and HCTZ as the fixed and free combination**

Pharmacokinetic Parameter	Adjusted geometric means		Ratio of geometric means	
	Test [a]	Reference [a]	Estimate	90% Confidence Interval
Aliskiren				
C_{max} (ng/mL)	166.00	188.27	0.88	0.75 – 1.04
$AUC_{0\text{-}tlast}$ (h·ng/mL)	1117.3	1205.3	0.93	0.86 – 1.00
$AUC_{0\text{-}inf}$ (h·ng/mL)	1226.6	1309.2	0.94	0.87 – 1.01
HCTZ				
C_{max} (ng/mL)	71.94	81.58	0.88	0.85 – 0.92
$AUC_{0\text{-}tlast}$ (h·ng/mL)	474.56	520.44	0.91	0.88 – 0.94
$AUC_{0\text{-}inf}$ (h·ng/mL)	512.89	558.91	0.92	0.89 – 0.94

[a]: Test: SPH100 (aliskiren 300 mg/HCTZ 12.5 mg) fixed combination tablet (Treatment 1); Reference: aliskiren 300 mg tablet and HCTZ 12.5 mg hard gelatin capsule as free combination (Treatment 2)

Source: Section 14 Table 14.2-1.1

The difference in C_{max} between the fixed and free combination products is about 18%, not of clinical significance for a medication that is considered to be a wide therapeutic window drug.

HCTZ free hard gelatin capsule was bioequivalent to the fixed combination formulation.

Study 2103 was an open-label, randomized, single-dose, crossover study also in 70 male and female subjects to demonstrate bioequivalence between the final market image formulation of 300/25 mg Aliskiren/HCTZ and the free combination used in clinical trials of Aliskiren 300 mg tablet and HCTZ 25 mg hard gelatin capsule. Bioequivalence was demonstrated with both Aliskiren and HCTZ as seen below:

Bioequivalence results for aliskiren and HCTZ pharmacokinetic parameters following single oral doses of SPH100 (aliskiren 300 mg/HCTZ 25 mg) in fixed combination tablet (Test) or aliskiren 300 mg tablet and HCTZ 25 mg capsule as free combination (Reference) to healthy subjects (N=70)

Pharmacokinetic Parameter	Adjusted geometric means		Ratio of geometric means	
	Test [a]	Reference [a]	Estimate	90% Confidence Interval
		Aliskiren		
C_{max} (ng/mL)	233.71	247.34	0.94	0.82 – 1.08
$AUC_{0\text{-}tlast}$ (h•ng/mL)	1156.32	1266.99	0.91	0.83 – 1.00
$AUC_{0\text{-}inf}$ (h•ng/mL)	1271.81	1392.98	0.91	0.83 – 1.00
		HCTZ		
C_{max} (ng/mL)	140.45	157.86	0.89	0.85 – 0.93
$AUC_{0\text{-}tlast}$ (h•ng/mL)	961.90	1037.95	0.93	0.89 – 0.96
$AUC_{0\text{-}inf}$ (h•ng/mL)	995.33	1075.78	0.93	0.89 – 0.96

[a]: Test: SPH100 (aliskiren 300 mg/HCTZ 25 mg) fixed combination tablet (Treatment A); Reference: aliskiren 300 mg tablet and HCTZ 25 mg hard gelatin capsule as free combination (Treatment B)

C. WAS A BIOWAIVER REQUESTED FOR INTERMEDIATE STRENGTHS OF ALISKIREN/HCTZ?

A biowaiver for the intermediate strength 150/12.5 mg Aliskiren/HCT is being granted based on:

- Compositional similarities between the 300/25 mg (reference) and the 150/12.5 mg (test) Aliskiren/HCT strengths and

- Information submitted for batch number X018 0206 (300/25 mg) and X008 0206 (150/12.5 mg), the intermediate strength of 150/12.5 mg Aliskiren/HCT passes the F_2 similarity comparison analysis in three different media (900 mL of 0.1M HCl, phosphate buffer at pH 4.5 and phosphate buffer pH 6.8) to include the proposed dissolution specifications (0.1M HCl, 100 rpm, 900 mL USP apparatus 1, 37°C) tested. Dissolution testing was performed according to USP level 1 and 2 requirements, using basket method (apparatus 1) at 100 rpm.

D. WERE THE ASSAYS USED FOR ALISKIREN AND HCTZ QUANTITATION VALIDATED?

Both Aliskiren and HCTZ were simultaneously assayed in human plasma by a validated LC-MS/MS method:

LLOQ	SPP100: 0.500 ng/mL using 200 µL of human plasma (expressed as SPP100 free base) Hydrochlorothiazide: 1.00 ng/mL using 200 µL of human plasma

Conclusion	**The method is suitable for the determination of SPP100 and HCTZ in human plasma with anticipated limits of quantification of 0.500 ng/mL and 1.00 ng/mL, respectively using 0.2 mL of human plasma. The inter-day accuracy of the method during the validation was within the range -6.4 - 4.5% for SPP100 and within the range -3.8 - 3.0% for HCTZ and the precision was within the range 6.1 - 10.0% for SPP100 and within the range 3.5 - 13.2% for HCTZ.**

IV. LABELING

A. IS THE PROPOSED LABELING FOR ALISKIREN/HCT ACCEPTABLE?

The proposed labeling is acceptable provided the Reviewer Labeling Comments described in the Recommendations section are addressed by the sponsor. A copy of the proposed package insert is included in Appendix I.

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DETAILED LABELING RECOMMENDATIONS

Please refer to the proposed Label in Appendix I for recommended changes (Marked in Red and Blue).

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Appendix I:
Proposed Package Insert

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On Original

21 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Clin Pharm/Bio- 1

Appendix II:
Individual Review of Studies

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STUDY SPH100A 2104 – A RANDOMIZED, OPEN-LABEL, SINGLE-DOSE, TWO-PERIOD, CROSSOVER STUDY IN HEALTHY SUBJECTS TO EVALUATE THE EFFECT OF FOOD ON THE BIOAVAILABILITY OF ALISKIREN/HCTZ (300/25 MG) FIXED COMBINATION (SPH100) FINAL MARKET IMAGE (FMI) TABLET.

STUDY INVESTIGATOR AND SITE:

b(4)

REPORT # 2104
VOLUME in EDR, Section 6
STUDY DATES: September 19 – October 26, 2006

Objectives: To evaluate the effect of food on the rate and extent of absorption of the SPH100 300-mg/25-mg FMI tablet and to assess the safety and tolerability under fed and fasted conditions

To assess the safety and tolerability of the 300/25 mg aliskiren/HCTZ FMI tablet.

FORMULATION:
Aliskiren/HCTZ fixed combination tablet (SPH100 300+25mg FMI Tablets Batch X018 0206/6001850.002) were prepared by Novartis and supplied to the investigator as open labeled bulk medication.
Manufacturing Date: March 22, 2006

At the investigator's site, the pharmacist dispensed and labeled the study medication in individual subject specific package. Appropriate documentation of the subject specific packaging process are maintained.

Overall study design

This study employed an open-label, randomized, single-dose, two-period, two-treatment, crossover design. A total of 30 healthy male and female subjects were enrolled and 27 subjects completed the study.

Study subjects were within the ages of 18 to 45 years.

Treatment 1: Single dose of 300/25 mg aliskiren/HCTZ FMI tablet under fed conditions (Test).

Treatment 2: Single dose of 300/25 mg aliskiren/HCTZ FMI tablet under fasting conditions (Reference).

Exclusion Criteria included:
All subjects that smoked or used tobacco products previously in the last 3 months and
Use of any prescription drugs within four (4) weeks prior dosing, or over-the-counter (OTC) medication within two (2) weeks prior to dosing. Acetaminophen is acceptable, but must be documented in the Concomitant medications / Significant non-drug therapies page of the CRF.

All subjects fasted overnight for at least 10 and no longer than 12 hours prior to each dose of study medication. For Treatment 1, subjects were administered their SPH100 dose immediately (within 5 minutes) after completion of the high fat breakfast (standard FDA breakfast). During Treatment 2, no breakfast was allowed and subjects continued to fast for at least four (4) hours post-dose. Study medication was administered by the study center personnel with 180 mL of water between 0800 and 0828. Water was allowed ad libitum after 2 hours. All subjects were dosed within ~30 minute interval. They were instructed not to chew the medication, but to swallow the tablet whole. The investigator checked each subject's mouth to ensure that the medication was swallowed.

For pharmacokinetic assessment days, subjects rested quietly in the upright position for the next four (4) hours after dosing, unless performing a study assessment.

All prescription medications taken within one month, and over-the-counter drugs (including vitamins) taken within 14 days prior to the start of study were recorded on the Concomitant Medications/ Non-Drug Therapies page of the eCRF.

ANALYTICAL METHODS (REPORT #DMPK RCSPH100A2104):

Analysis for aliskiren and HCTZ was performed by HPLC-MS/MS methods with an LLOQ of 0.5 ng/mL and 1.0 ng/mL, respectively.

Accuracy:

Aliskiren – In the range of 1.00 to 200 ng/mL the %Bias was -3.0 to 2.0 with a %CV of 4.4 to 8.3

HCTZ - In the range of 0.500 to 500 ng/mL the %Bias was -11.4 to 9.0 with a %CV of 2.9 to 5.0

Precision:

Aliskiren – In the range of 1.00 to 200 ng/mL the %Bias was -3.0 to 2.0 with a %CV of 4.4 to 8.3

HCTZ - In the range of 0.500 to 500 ng/mL the %Bias was -11.4 to 9.0 with a %CV of 2.9 to 5.0

Coefficient of Variation:

Aliskiren – $r^2 \geq 0.9917$

HCTZ - $r^2 \geq 0.9912$

PK SAMPLE COLLECTION, CALCULATIONS, AND STATISTICAL ANALYSIS:

Pharmacokinetic assessments

Pharmacokinetic parameters calculated included C_{max}, t_{max}, $AUC_{0\text{-}tlast}$ $AUC_{0\text{-}inf}$, $t_{1/2}$, and CL/F. All blood samples were taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein at the following time points: predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72 and 96 hours. post dosing.

All subjects who had adequate plasma concentration vs. time profiles were included in the pharmacokinetic data analysis. Concentrations were given in mass per volume units. Missing values or those below the limit of quantification were indicated in the data listings and treated as zero in data presentations and calculations. Pharmacokinetic parameters, expressed either as mean, SD, and CV, with any geometric means indicated, or as median and range of values, were to be determined using non-compartmental method with WinNonlin Pro (Version 5.0.1, Pharsight, Mountain View, CA) and tested with the ANOVA. The aliskiren and HCTZ pharmacokinetic parameters determined in plasma are listed below:

Pharmacokinetic parameters

$AUC_{0\text{-}tlast}$	The area under the concentration-time curve from time zero to t, where t is the last time point with measurable concentration [amount x time x volume^{-1}]
$AUC_{0\text{-}inf}$	The area under the plasma concentration-time curve from time zero to infinity [amount x time x volume^{-1}]
CL/F	The total body clearance of drug from the plasma [volume x time^{-1}]
C_{max}	Maximum (peak) plasma drug concentration after drug administration [amount x volume^{-1}]
$t_{½}$	The elimination half-time associated with the terminal slope (λz) of a semi logarithmic concentration-time curve [time].
t_{max}	Time to reach peak or maximum concentration following drug administration [time]

Statistical Analysis

Log-transformed AUCs and Cmax of aliskiren and HCTZ were analyzed separately using a linear mixed effect model, with fixed effects from sequence, treatment, and period, and random effects from subject nested in sequence.

The contrast were computed between the two treatments (Test *vs.* Reference) and a 90% two-sided confidence interval (CI) were formed. The least square mean treatment difference and confidence intervals were transformed back to the original scale to give the ratio of the geometric means for the two treatments together with the corresponding 90% confidence intervals. Bioequivalence between treatments were assessed separately for each PK parameter based on the 90% CI for the ratio being contained within the range (0.80-1.25).

RESULTS:

All 27 subjects who completed the study and the 3 who dropped out after Period 1 were included in aliskiren and HCTZ pharmacokinetic analysis.

Aliskiren

Special issues

For one subject SPP100 was measured at a concentration of [redacted], which was above the LLOQ (0.500 ng/mL) at predose of the second period in spite of 10 days washout period. This concentration was confirmed by reanalysis. b(4)

There is a 62% reduction in $AUC_{0\text{-}last}$ and 60% reduction in $AUC_{0\text{-}inf}$ on the fed condition. The ratio (fed/fast) of the geometric means of $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ are 0.38 and 0.40, respectively. Their corresponding 90% CIs are (0.33, 0.44) and (0.34, 0.46).

There is a 82% reduction in C_{max} value on the fed condition. The ratio of the geometric means is 0.18. The corresponding 90% CI is (0.14, 0.24).

In summary, there was noticeable food effect present on aliskiren for SPH100 FMI tablet.

HCTZ

There are 13% increase in $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ on the fed condition. The ratio (fed/fast) of the geometric means of both $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ is 1.13. Their corresponding 90% CIs are (1.06, 1.20) and (1.07, 1.20).

There is a 13% increase in C_{max} value on the fat condition. The ratio of the geometric means is 1.13. The corresponding 90% CI is (1.06, 1.20).

In summary, there was no significant food effect present on HCTZ for SPH100 FMI tablet.

Treatment	t_{max} (h) median (min, max)	C_{max} (ng/mL) mean ± SD (CV%)	$AUC_{0\text{-}last}$ (h·ng/mL) mean ± SD (CV%)	$AUC_{0\text{-}inf}$ (h·ng/mL) mean ± SD (CV%)	$t_{½}$ (h) mean ± SD (CV%)	CL/F (mL/h) mean ± SD (CV%)
Aliskiren						
Fed (N=29)	3.0 (0.3, 6.0)	49.1 ± 38.8 (78.9)	492.8 ± 179.1 (36.4)	558.9 ± 195.0 (34.9)	37.8 ± 10.8 (28.5)	614949.9 ± 242715.6 (39.5)
Fasted (N=28)	1.0 (0.5, 4.0)	235.2 ± 90.2 (38.4)	1273.8 ± 444.3 (34.9)	1387.4 ± 483.7 (34.9)	36.0 ± 8.4 (23.2)	241416.9 ± 83615.1 (34.6)
HCTZ						
Fed (N=29)	3.0 (1.5, 6.0)	154.7 ± 28.0 (18.1)	1129.4 ± 258.9 (22.9)	1168.6 ± 259.8 (22.2)	10.3 ± 2.1 (20.0)	22416.6 ± 4955.1 (22.1)
Fasted (N=28)	2.5 (1.0, 4.0)	139.8 ± 36.0 (25.8)	996.9 ± 241.7 (24.2)	1030.4 ± 242.8 (23.6)	12.0 ± 3.4 (28.4)	25713.8 ± 6672.2 (25.9)

Source: Appendix 16.2.5