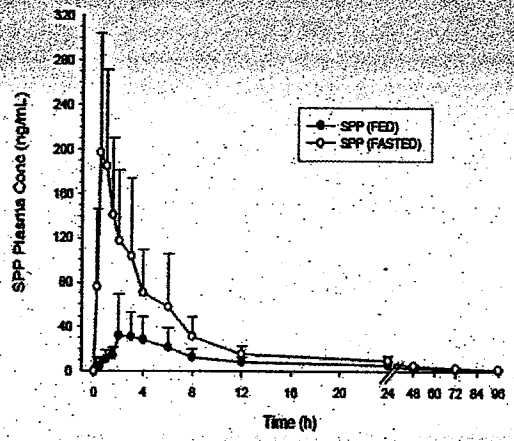
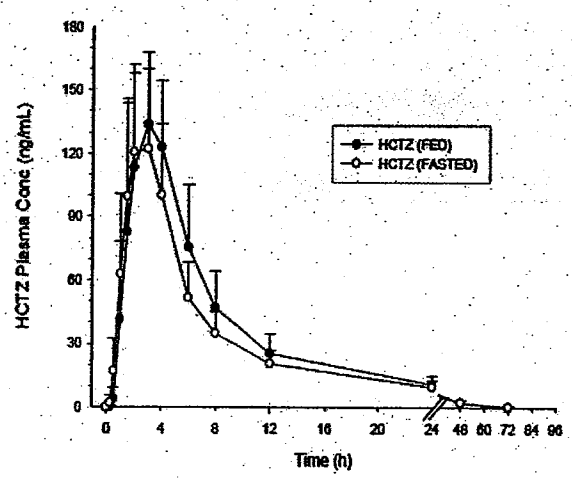
Mean with SD plasma concentrations of aliskiren following single oral doses of 300/25 mg (aliskiren/HCTZ) fixed combination FMI tablet under fed or fasted conditions to healthy subjects



Mean with SD plasma concentrations of HCTZ following single oral doses of 300/25 mg (aliskiren/HCTZ) fixed combination FMI tablet under fed or fasted conditions to healthy subjects



Bioequivalence results for aliskiren and HCTZ pharmacokinetic parameters following single oral doses of SPH100 (aliskiren 300 mg/HCTZ 25 mg) SPH100 (aliskiren 300 mg/HCTZ 25 mg) under fed and fasted conditions to healthy subjects (N=30)

Pharmacokinetic Parameter	Adjusted geometric means		Ratio of geometric means	
	Test[a]	Reference[a]	Estimate	90% Confidence Interval
		Aliskiren		
C_{max} (ng/mL)	39.16	213.81	0.18	0.14 – 0.24
$AUC_{0\text{-}last}$ (h·ng/mL)	457.52	1204.74	0.38	0.33 – 0.44
$AUC_{0\text{-}inf}$ (hr·ng/mL)	522.25	1312.96	0.40	0.34 – 0.46
		HCTZ		
C_{max} (ng/mL)	153.98	136.59	1.13	1.06 – 1.20
$AUC_{0\text{-}last}$ (h·ng/mL)	1103.80	978.07	1.13	1.06 – 1.20
$AUC_{0\text{-}inf}$ (h·ng/mL)	1143.27	1011.82	1.13	1.07 – 1.20

[a]: Test: Fed (Treatment 1); Reference: Fasted (Treatment 2)

Source: Section 14 Table 14.2-1.1

SAFETY:

There were no serious adverse events. AE related to GI disturbances are listed below.

Overall, 7 (23.3%) of the 30 subjects reported at least one or more adverse events during treatment; which were classified as mild.

	Fed	Fasted	Total
Body system	N=29	N=28	N=30
Preferred Term	n (%)	n (%)	n (%)
Any Body System	4 (13.8)	4 (14.3)	7 (23.3)
GASTROINTESTINAL DISORDERS -TOTAL	2 (6.9)	1 (3.6)	3 (10.0)
Diarrhea	1 (3.4)	1 (3.6)	2 (6.7)
Vomiting	1 (3.4)	0 (0.0)	1 (3.3)

CONCLUSIONS:

- Concomitant ingestion of a high-fat meal reduced aliskiren exposure (C_{max} and AUC decreased by 82% and 60%, respectively) and absorption rate (median t_{max} increased by 2 hours).
- Concomitant ingestion of a high-fat meal slightly increased HCTZ exposure (both C_{max} and AUC increased by 13%).

REVIEWER'S COMMENT:

1. The reviewer concurs and findings should be included in the labeling.

STUDY SPH100A 2101 – AN OPEN-LABEL, RANDOMIZED, SINGLE-DOSE, CROSSOVER STUDY TO DETERMINE THE BIOEQUIVALENCE OF A FIXED COMBINATION OF ALOSKIREN/HCTZ (SPH100) 150/25 MG TABLET AND THE FREE COMBINATION OF ALISKIREN (SPP100) 150 MG OVERENCAPSULATED TABLET AND HCTZ 25 MG HARD GELATION CAPSULE.

STUDY INVESTIGATOR AND SITE:

b(4)

REPORT # 2101
EDR VOLUME 6
STUDY DATES: July 17 – August 24, 2006

Objectives:

Primary objective:

- To determine the bioequivalence of a fixed combination of 150/25 mg aliskiren/HCTZ (SPH100) tablet and the free combination of aliskiren (SPP100) 150 mg overencapsulated tablet and HCTZ 25 mg hard gelatin capsule.

Secondary objective:

- To assess the safety and tolerability of a single oral dose of aliskiren/HCTZ (SPH100) 150/25 mg fixed combination tablet.

Formulation:

b(4)

Test	Fixed combination SPH100 150/25 mg (SPP100/aliskiren + HCTZ) tablet by Novartis (Batch No: X012 0206; Batch Size: [redacted] Manuf Date: March 29, 2006) by Novartis
Reference	Free combination of aliskiren 150 mg by Novartis (Batch No: U005 0404; Manuf Date: February 26, 2004) and HCTZ (Esidrex®) 25 mg by Novartis (Batch No: X147 0603; Manuf date: June 26, 2003)

Methodology: This study employed an open-label, randomized, single-dose, two-period, two treatment, crossover design. A total of 70 healthy male and female subjects were enrolled (of these, 68 subjects completed the study).

Each completed subject participated in a 21-day screening period, two baseline and treatment periods and an end-of study evaluation. An inter-dose interval of at least 14 days was observed by all subjects.

Number of subjects (planned and analyzed): Seventy (70) subjects were enrolled and 68 completed the study. All 70 enrolled subjects were included in safety analysis. Pharmacokinetic parameters of aliskiren and HCTZ for the 68 subjects who completed the study and the 2 subjects who only completed the first period, are included in the statistical analysis.

Duration of treatment: Two single dose treatments separated by a minimum 14-day washout period. Each treatment was administered orally under fasted conditions (following an overnight fast of at least ten hours) with 240 mL water.

ANALYTICAL METHODS:

Aliskiren and HCTZ plasma concentrations were measured by a validated HPLC-MS/MS method.

Lower Limit of quantification (LLOQ): 0.500 ng/mL for SPP100 (expressed in base) and 1.00 ng/mL for HCTZ using 200 µL of plasma.

The Coefficient of Determination was $R^2 \geq 0.9790$ for aliskiren and ≥ 0.9877 for HCTZ.

Accuracy:
Aliskiren – 94.0 to 107.3% with %bias of -6.0 to 7.3%
HCTZ – 110.3 to 102.5% with %bias of 0.5 to 5%.

Precision:
Aliskiren – %CV of 4.6 to 5.8 and %bias of -11.4 to 5.0
HCTZ - %CV of 3.8 to 6.0 and %bias of -2.1 to 5.0

Pharmacokinetics: C_{max}, t_{max}, $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}Inf}$, $t_{1/2}$, and CL/F

Statistical methods: Log-transformed AUCs and C_{max} 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 was computed between the two treatments (Test *vs.* Reference) and a 90% two-sided confidence interval (CI) was 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:

Pharmacokinetic results: Pharmacokinetic parameters of aliskiren and HCTZ following single oral doses of SPH100 (aliskiren 150 mg/HCTZ 25 mg) in fixed combination or aliskiren 150 mg and HCTZ 25 mg as free combination in healthy subjects are presented in the table 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, 6.0)	96.6 ± 64.6 (66.9)	492.2 ± 286.9 (58.3)	564.9 ± 338.9 (60.0)	44.5 ± 49.0 (109.9)	356435.4 ± 184921.7 (51.9)
Free combination (N=70)	1.0 (0.5, 6.3)	95.9 ± 60.5 (63.1)	475.4 ± 232.4 (48.9)	530.6 ± 253.5 (47.8)	40.8 ± 13.0 (31.9)	342905.3 ± 150483.9 (43.9)
HCTZ						
Fixed combination (N=68)	2.0 (1.5, 4.0)	174.6 ± 51.3 (29.4)	1125.5 ± 232.1 (20.6)	1159.5 ± 234.6 (20.2)	10.6 ± 1.7 (16.5)	22389.6 ± 4287.3 (19.1)
Free combination (N=69)	2.0 (1.0, 4.0)	178.6 ± 55.7 (31.2)	1144.9 ± 271.1 (23.7)	1192.4 ± 235.9 (19.8)	10.3 ± 1.7 (16.2)	21785.8 ± 4352.6 (20.0)

Statistical analysis results for aliskiren and HCTZ pharmacokinetic parameters following single oral doses of SPH100 (aliskiren 150 mg/HCTZ 25 mg) in fixed combination (Test) or aliskiren 150 mg and HCTZ 25 mg as free combination (Reference) to healthy subjects (N=70) are presented 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)	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)

SAFETY RESULTS: There were no deaths or serious adverse events reported. No subjects were withdrawn due to an adverse event. A total of 16 subjects (23%); n=70) reported 27 separate adverse events during the study. Most (17 of 27) were mild in severity requiring no treatment. Half of the reported events were treatment drug related as determined by the investigator.

The most frequent adverse event was headache (5 events in 5 subjects) followed by emesis (4 events in 3 subjects). No safety trends relating to routine laboratory parameters (hematology, biochemistry, urinalysis), vital signs assessments, ECG evaluations, or physical examinations were identified.

Single oral doses of both the fixed and the free combination of Tekturna/HCT were safe and well tolerated.

CONCLUSIONS:

- The rate and extent of absorption of aliskiren and HCTZ were similar following single oral administration of SPH100 (aliskiren 150 mg/HCTZ 25 mg) fixed combination FMI tablet and aliskiren 150 mg overencapsulated tablet and 25 mg HCTZ hard gelatin capsule as free combination.
- The 90% confidence intervals of C_{max} and AUC geometric mean ratios for both aliskiren and HCTZ were contained within the bioequivalence limits.
- The fixed combination tablet (aliskiren 150 mg/HCTZ 25 mg) is clinically interchangeable with the free combination of aliskiren 150 mg overencapsulated tablet and 25 mg HCTZ hard gelatin capsule.
- The single oral dose of SPH100 (aliskiren 150 mg/HCTZ 25 mg) fixed combination FMI tablet or aliskiren 150 mg overencapsulated tablet and HCTZ 25 mg hard gelatin capsule as free combination were safe and well tolerated in healthy subjects.

REVIEWER'S COMMENT:

1. The reviewer concurs.

STUDY SPH100A 2102 – AN OPEN-LABEL, RANDOMIZED, SINGLE-DOSE, CROSSOVER STUDY TO DETERMINE THE BIOEQUIVALENCE OF A FIXED COMBINATION OF ALISKIREN/HCTZ (SPH100) 300/12.5 MG TABLET AND THE FREE COMBINATION OF ALISKIREN (SPP100)-300 MG TABLET AND HCTZ 12.5 MG HARD GELATION CAPSULE.

STUDY INVESTIGATOR AND SITE:

b(4)

REPORT # 2102
EDR VOLUME 6
STUDY DATES: June 29 – August 9, 2006

OBJECTIVES:

Primary objective:

- To determine the bioequivalence of a fixed combination of 300/12.5 mg aliskiren/HCTZ (SPH100) market formulation tablet and the free combination of the market formulations of aliskiren 300 mg tablet and HCTZ 12.5 mg hard gelatin capsule.

Secondary objective:

- To assess the safety and tolerability of a single oral dose of aliskiren/HCTZ (SPH100) 300/12.5 mg fixed combination market formulation tablet.

FORMULATION:

b(4)

Test	Aliskiren + HCTZ 300/12.5 mg FMI fixed combination tablet (Batch No: X186 0506; Batch size: [redacted] Manuf Date: May 19, 2006) by Novartis
Reference	Aliskiren 300 mg tablet and HCTZ 12.5 mg capsule free combination (**Aliskiren** - Batch No: X301LA, Manuf Date: March 3, 2005 --- **HCTZ** - Batch No. X080 0304; Manuf Date: March 29, 2004) by Novartis

Note: Biobatches are defined by the sponsor as the drug batches used in a definitive bioavailability or bioequivalence trial.

STUDY DESIGN:

Methodology: This study employed an open-label, randomized, single-dose, two-period, two treatment, crossover design. A total of 70 healthy male and female subjects were enrolled (of these, 64 subjects completed the study).

Each completed subject participated in a 21-day screening period, two baseline and treatment periods and an end-of study evaluation. An inter-dose interval of at least 14 days was observed by all subjects.

Number of subjects (planned and analyzed): Seventy (70) subjects were enrolled and 64 completed the study. All 70 enrolled subjects were included in safety analysis. Pharmacokinetic parameters of aliskiren and HCTZ for the 64 subjects who completed the study and the 6 subjects who only completed the first period, are included in the statistical analysis.

Diagnosis and main criteria for inclusion: Seventy (70) non-smoking male and female subjects, ages 18 to 45, who were in good health as determined by past medical history, physical examination, electrocardiograms, and laboratory tests, and who were capable of giving informed consent, were allowed to enroll into the study.

Each eligible subject received the following two treatments under fasting conditions:

Treatment 1: Single oral dose of SPH100 300/12.5 mg (aliskiren/HCTZ) fixed combination tablet [Test]

Treatment 2: Single oral dose of the free combination of SPP100 300 mg (aliskiren) tablet and 12.5 mg HCTZ (ESI879/Esidrex®) hard gelatin capsule [Reference]

Subjects were randomized in a 1:1 ratio to the two treatment sequences: Sequence A (Treatment 1 followed by Treatment 2) or Sequence B (Treatment 2 followed by Treatment 1).

In each treatment period, subjects arrived at the study site on Day –1 (at least 12 hours prior to dosing) for baseline evaluations, and remained domiciled for at least 48 hours after dosing for pharmacokinetic assessments. Results of the baseline safety evaluations were available prior to dosing.

On Day 1 (dosing day) of Period 1, subjects were administered a single oral dose of either the fixed combination (SPH100 [Test]) or the free combination (aliskiren and HCTZ [Reference]), according to the assigned randomization schedule, and following an overnight fast of at least 10 hours. Pharmacokinetic sampling was performed at specified time points from pre-dose (0h) up until 96 hours post-dose.

Subjects remained domiciled at a minimum from the evening prior to dosing through at least 24 hours post-dose for PK sample collection, at which time they were discharged from the study center. They returned to the study center on the next three (3) mornings, under fasted conditions, to complete the remaining PK sample collection period (i.e., 48, 72, and 96-hour post-dose samples).

After a 14-day inter-dose interval, all subjects checked back into the study center at least 12 hours prior to dosing (i.e., Day -1) for Period 2 to undergo the designated baseline evaluations. Subjects received a second and final dose administration on the following day, which comprised the opposite treatment as that received in Period 1. Subjects underwent a 96-hour pharmacokinetic assessment period, after which study completion evaluations were performed. Subjects were then discharged from the study.

The dose levels selected for this study represent the aliskiren dose level (300 mg) used in a pivotal double-blind Phase III safety and efficacy study of aliskiren [Study CSPP100A2204]), and a standard lower therapeutic dose level of HCTZ (12.5 mg), and signify one in a range of therapeutic dose levels planned for development.

ANALYTICAL METHODS:

Analysis for aliskiren and HCTZ was performed by LC-MS/MS methods, with respective LLOQs of 0.5 ng/mL and 1.0 ng/mL.

Lower Limit of quantification (LLOQ)	0.500 ng/mL for SPP100 (expressed in base) and 1.00 ng/mL for HCTZ using 200 µL of plasma.

Aliskiren:

Linearity	Linear within the range of 0.50 to 500 ng/mL with $r^2 \geq 0.9780$

Precision and Accuracy %CV range of 3.6 to 7.2% and -10.4 to 8.0%, respectively.

HCTZ:

Linearity Linear within the range of 1.00 to 200 ng/mL with $r^2 \geq 0.9772$

Precision and Accuracy %CV range of 3.6 to 9.5% and -2.2 to 4.5%, respectively.

PK SAMPLE COLLECTION/CALCULATIONS, PD ASSESSMENTS/CALCULATIONS AND STATISTICAL ANALYSIS:

Pharmacokinetics: C_{max}, t_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, $t_{1/2}$, and CL/F

PK parameters were determined using non-compartmental method(s) using WinNonlin Enterprise (Version 4.0).

Sample collection timepoints are as follows:

- **Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, and 96 hours post-dose**

Statistical methods: Log-transformed AUCs and C_{max} 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 was computed between the two treatments (Test *vs.* Reference) and a 90% two-sided confidence interval (CI) was 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:

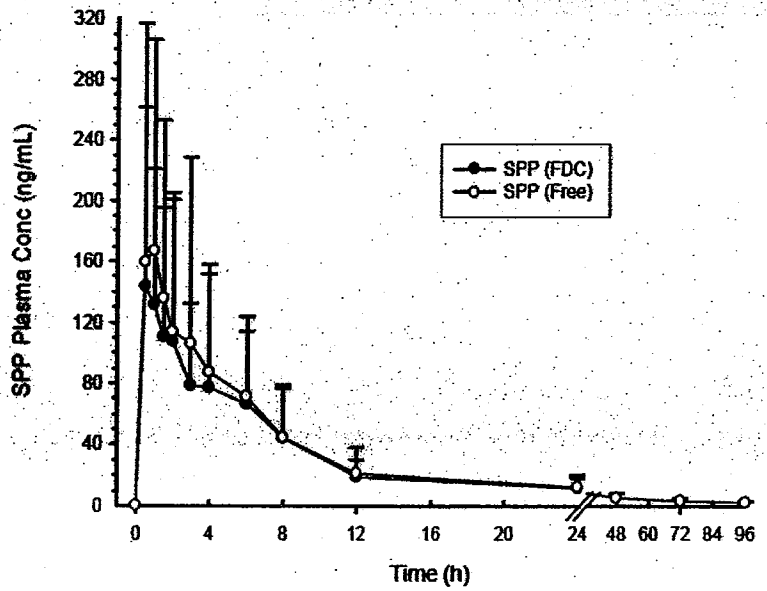
Subjects #5122, #5128, and #5160 were all dropped from the study for having positive cotinine tests at Period 2 check-in (protocol violations). Subject #5125 was dropped for reporting alcohol use within the 48 hours prior to dosing (protocol violation). Subject #5142 was dropped from the study due to having signs of a urinary tract infection, reported as an adverse event. The subject was referred to her private physician for treatment. Subject #5170 was dropped from the study due to abnormal laboratory results [elevated WBC count of 12.1 10^3/µL, and upon repeat 13.6 10^3/µL (ULN being 10.5 10^3/µL), and a decreased hematocrit of 32.1% (LLN being 32.9%)]. Each of these subjects underwent final study evaluations prior to being discharged from the study.

Pharmacokinetic results: Pharmacokinetic parameters of aliskiren and HCTZ following single oral doses of SPH100 (aliskiren 300 mg/HCTZ 12.5 mg) in fixed combination or aliskiren 300 mg and HCTZ 12.5 mg as free combination in healthy subjects are presented in the table 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%)	$AUC_{t,max}$ (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						
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%)	$AUC_{t,max}$ (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%)
(N=66)	(1.5, 4.3)	(29.3)	(24.8)	(22.2)	(19.8)	5105.1 (22.3)

Mean with SD plasma concentration-time profiles of aliskiren following single oral doses of 300/12.5 mg (aliskiren/HCTZ) fixed combination FMI tablet or aliskiren 300 mg FMI tablet and HCTZ 12.5 mg capsule as free combination to healthy subjects



Statistical analysis results for aliskiren and HCTZ pharmacokinetic parameters following single oral doses of SPH100 (aliskiren 300 mg/HCTZ 12.5 mg) in fixed combination (Test) or aliskiren 300 mg and HCTZ 12.5 mg as free combination (Reference) to healthy subjects (N=70) are presented below:

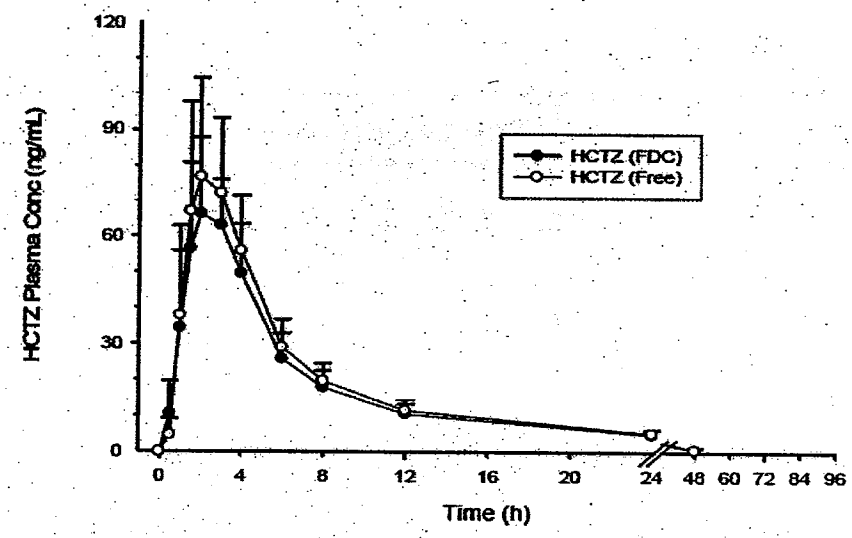
Table 2 **Statistical results of PK parameters following administration of aliskiren and HCTZ as the fixed and free combination**

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
$AUC_{0-tlast}$ (h·ng/mL)	1117.3	1205.3	0.93	0.86 – 1.00
AUC_{0-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
$AUC_{0-tlast}$ (h·ng/mL)	474.56	520.44	0.91	0.88 – 0.94
AUC_{0-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

Mean with SD plasma concentration-time profiles of HCTZ following single oral doses of 300/12.5 mg (aliskiren/HCTZ) fixed combination FMI tablet or aliskiren 300 mg FMI tablet and HCTZ 12.5 mg capsule as free combination to healthy subjects



Safety results: There were no deaths, and no serious adverse events reported in this study. One subject (#5142) was dropped from the study by the investigator prior to Period 2 dosing due to the adverse event of "urinary tract infection." Overall, a total of 27 subjects (39%; n=70) reported 51 adverse events (the most common being "headache") during the study. Most (39 out of 51) were of mild severity, transient in nature, did not require any treatment, and would not be unexpected based upon data from previous studies and the safety profiles of the study drug(s).

Single oral doses of both the fixed and the free combination of SPP100/aliskiren and HCTZ were safe and well-tolerated in the current study.

CONCLUSIONS:

- The 90% confidence intervals of Cmax and AUC geometric mean ratios for HCTZ were contained within the bioequivalence limits.
- The 90% confidence interval of AUC geometric mean ratio for aliskiren was contained within the bioequivalence limits.
- The lower bound of the 90% confidence interval for aliskiren Cmax was 0.75%, below the boundary of 0.80 to 1.25%.

REVIEWER'S COMMENT:
The difference in C_{max} between the fixed and free combination products is about 18%, not of clinical significance for a medication with a wide therapeutic window.

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STUDY SPH100A 2103 – AN OPEN LABEL, RANDOMIZED, SINGLE-DOSE, CROSSOVER STUDY TO DETERMINE THE BIOEQUIVALENCE OF THE FIXED COMBINATION OF 300/25 MG ALSIKIREN/HCTZ MARKET FORMULATION TABLET AND THE FREE COMBINATION OF THE MARKET FORMULATIONS OF 300 MG ALISKIREN TABLET AND 25 MG HCTZ HARD GELATIN CAPSULE

STUDY INVESTIGATOR AND SITE: [redacted] b(4)

Report# 2103
Volumes in EDR Section 6
STUDY DATES: August 8, 2006 – September 27, 2006

Objectives: To determine the bioequivalence of a fixed combination of 300/25 mg aliskiren/HCTZ market formulation tablet and the free combination of the market formulations of 300 mg aliskiren tablet and 25 mg HCTZ hard gelatin capsule and to assess the safety and tolerability of the FMI tablet

FORMULATION:

Test	SPP 100 300 + 25 mg (Aliskiren/HCTZ) market formulation tablets (Batch # X018 0206 #6001850.002; Batch size [redacted] Manuf. Date: March 22, 2003) by Novartis b(4)
Reference	Free combination of SPP100 300 mg tablet (Aliskiren – batch # 301LA #6000937.006; Manuf. Date: March 3, 2005) and HCTZ 25 mg hard gelatin capsule (EZ1879 Batch # X147 0603/3753688.002; Exp. Date: 08/2007) by Novartis

STUDY DESIGN:

This study employed an open-label, randomized, single-dose, two-period, two-treatment, crossover design. A total of 70 healthy male and female subjects were enrolled and 66 subjects completed the study.

Each completed subject participated in a 21-day screening period, two baseline and treatment periods, and an end-of study evaluation. A fixed inter-dose interval (of at least 14 days) was observed by all subjects. Each eligible subject received the following two treatments under fasting conditions:

Treatment A: Single dose of the fixed combination of 300/25 mg (aliskiren/HCTZ) FMI tablet (Test).

Treatment B: Single dose of free combination of 300 mg aliskiren FMI tablet and 25 mg HCTZ hard gelatin capsule (Reference).

Subjects were randomized in a 1:1 ratio to the two treatment sequences: Sequence A or Sequence B.

In each treatment period, subjects arrived at the study site on Day –1 (at least 12 hours prior to dosing) for baseline evaluations, and remained domiciled for at least 96 hours after dosing for pharmacokinetic assessments. Results of the baseline safety evaluations were available prior to dosing.

On Day 1 (dosing day) of Period 1, subjects were administered a single oral dose of either the fixed combination (SPH100 [Test]) or the free combination (aliskiren and HCTZ [Reference]) according to the assigned randomization schedule following an overnight fast of at least 10 hours. Pharmacokinetic sampling was performed at specified time points from pre-dose (0 hour) to 96 hours post-dose.

After a fourteen-day inter-dose interval, all subjects checked back into the study center at least 12 hours prior to dosing (i.e., Day -1) for Period 2 to undergo the designated evaluations. Subjects received a second and final dose administration on the following day, which comprised the alternate treatment to that received in Period 1. Subjects underwent a 96 hour pharmacokinetic assessment period, after which study completion evaluations were performed. Subjects were then discharged from the study.

ANALYTICAL METHODS:

Both Aliskiren and HCTZ concentrations in plasma were analyzed by a validated HPLC-MS/MS method.

Lower Limit of quantification (LLOQ)	**0.500 ng/mL for SPP100 (expressed in base) and 1.00 ng/mL for HCTZ using 200 µL of plasma.**

Aliskiren was linear over the concentration range of 1.5 to 400 ng.mL with $r^2 \geq$ 0.09893

Inter-assay Precision and Accuracy 3.2 to 5.1% (-10.4 to 6.5%)

HCTZ was linear over the concentration range of 3.0 to 160 ng/mL with $r^2 \geq 0.09834$

Inter-assay Precision and Accuracy 3.8 to 7.3% (-2.0 to 4.0)

PK SAMPLE COLLECTION/CALCULATIONS, PD ASSESSMENTS/CALCULATIONS AND STATISTICAL ANALYSIS:

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.

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)..

PHARMACOKINETIC RESULTS:

Aliskiren

Pharmacokinetic parameters for Aliskiren administered as a fixed combination and as free combination are listed below:

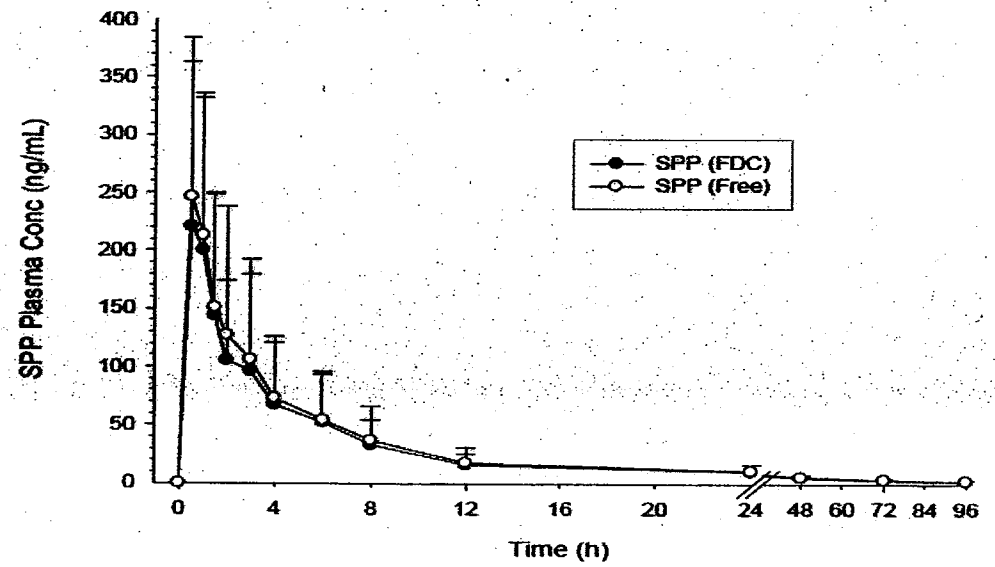
Table 1

Pharmacokinetic parameters of aliskiren following single oral doses of 300/25 mg (aliskiren/HCTZ) fixed combination FMI tablet or aliskiren 300 mg FMI tablet and HCTZ 25 mg capsule as free combination to healthy subjects

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%)
Fixed combination (N=69)	0.5 (0.5, 6.0)	270.9 ± 148.4 (54.8)	1281.8 ± 628.6 (49.0)	1411.9 ± 698.5 (49.5)	38.6 ± 14.5 (37.6)	260219.4 ± 134184.5 (51.6)
Free combination (N=67)	0.5 (0.5, 4.0)	276.9 ± 144.1 (52.0)	1394.4 ± 702.5 (50.4)	1527.6 ± 750.4 (49.1)	38.0 ± 8.3 (21.8)	235487.6 ± 101337.8 (43.0)

Figure 1

Mean with SD plasma concentration-time profiles of aliskiren following single oral doses of 300/25 mg (aliskiren/HCTZ) fixed combination FMI tablet or aliskiren 300 mg FMI tablet and HCTZ 25 mg capsule as free combination to healthy subjects to healthy subjects



Hydrochlorothiazide

Pharmacokinetic parameters for HCTZ administered as a fixed combination and as free combination are listed below:

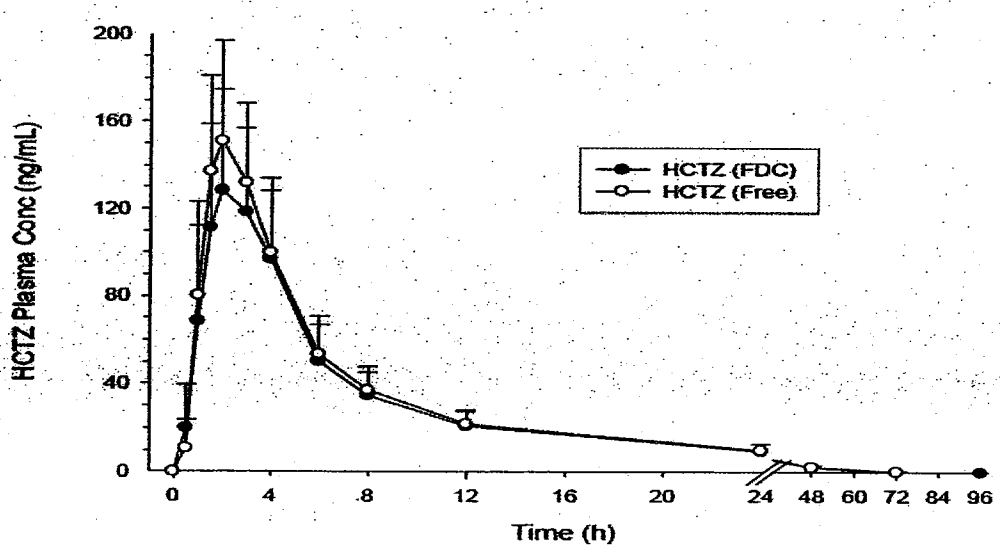
Table 2

Pharmacokinetic parameters of HCTZ following single oral doses of 300/25 mg (aliskiren/HCTZ) fixed combination FMI tablet or aliskiren 300 mg FMI tablet and HCTZ 25 mg capsule as free combination to healthy subjects

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%)	t½ (h) mean ± SD (CV%)	CL/F (mL/h) mean ± SD (CV%)
Fixed combination (N=69)	2.0 (1.0, 4.0)	146.9 ± 42.4 (28.9)	994.8 ± 262.5 (26.4)	1027.6 ± 263.7 (25.7)	11.4 ± 2.7 (23.5)	25883.1 ± 6503.8 (25.1)
Free combination (N=67)	2.0 (1.0, 4.0)	163.8 ± 44.0 (26.8)	1075.7 ± 267.5 (24.9)	1112.0 ± 266.0 (23.9)	11.4 ± 2.1 (18.6)	23785.0 ± 5722.8 (24.1)

Figure 2

Mean with SD plasma concentration-time profiles of HCTZ following single oral doses of 300/25 mg (aliskiren/HCTZ) fixed combination FMI tablet or aliskiren 300 mg FMI tablet and HCTZ 25 mg capsule as free combination to healthy subjects to healthy subjects



Statistical Results

The ratios of the geometric means for both aliskiren and HCTZ parameters were close to unity and the 90% confidence intervals of C_{max}, $AUC_{0\text{-tlast}}$ and $AUC_{0\text{-inf}}$ were contained within the (0.80, 1.25) bioequivalence limits.

Table 3

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
$AUC_{0\text{-}last}$ (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
$AUC_{0\text{-}last}$ (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)

SAFETY:

Four subjects withdrew from the study prematurely after completing Treatment Period 1. They were not replaced because the study was powered to have 64 subjects complete the study and 66 ended up completing both treatment arms.

Overall, 11 (15.7%) of the 70 subjects reported at least one or more adverse events during treatment. All reported AEs were mild with the exception of severe acute cholecystitis reported by one subject.

Subject 5157 (44 year old female) had an episode of acute cholecystitis on [redacted] (12 days after a single dose of study medication). The symptoms required hospitalization and subsequently laparoscopic cholecystectomy was performed. the event was not suspected to be related to the study medication. The subject had no confirmed concomitant medications and/or pain medications administered and completely recovered by [redacted]. she was discharged from the hospital without further follow-up. b(6)

CONCLUSIONS:

- **The rate and extent of absorption of aliskiren and HCTZ were similar following single oral administration of SPH100 (aliskiren 300 mg/HCTZ 25 mg) fixed combination FMI tablet and aliskiren 300 mg FMI tablet and 25 mg HCTZ hard gelatin capsule as free combination.**
- **The 90% confidence intervals of C_{max} and AUC geometric mean ratios for both aliskiren and HCTZ were contained within the bioequivalence limits.**
- **The fixed combination FMI tablet (aliskiren 300 mg/HCTZ 25 mg) is clinically interchangeable with the free combination of aliskiren 300 mg FMI tablet and 25 mg HCTZ hard gelatin capsule.**
- **The single oral dose of SPH100 (aliskiren 300 mg/HCTZ 25 mg) fixed combination FMI tablet or aliskiren 300 mg FMI tablet and HCTZ 25 mg hard gelatin capsule as free combination were safe and well tolerated in healthy subjects.**

REVIEWER'S COMMENT:

1. The reviewer concurs.

Appendix III
Compositional Tables of new formulation
Biowaiver F_2 Similarity Comparisons

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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)

b(4)

F_2 Similarity Comparisons:

For the different pH conditions indicated, the following dissolution media were used: 0.1M HCl, phosphate buffer at pH 4.5 and phosphate buffer pH 6.8.

Batches used for biowaiver request

Dosage strength	Batch	Description
150/12.5 mg	X008 0206	Pilot scale
300/25 mg	X079 0206	Pilot scale

Batch Number X079 0206 was not used in any of the Clinical Trials submitted for this NDA thus far. As a result, an e-mail was sent to the sponsor [redacted] on November 7, 2007 requesting clarification as to why a non-clinical batch was used for establishing F2 similarity comparisons. b(4)

On November 14, 2007 a response was sent via e-mail by the sponsor. Below is the new F_2 Similarity Comparison data submitted with explanations on batch # X079 0206:

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Introduction

The Tekturna HCT (aliskiren-hydrochlorothiazide) tablets NDA (22-107) is currently under review for the treatment of hypertension. In correspondence dated November 7, 2007 the Cardio-Renal Division requested additional CMC information to assist with the review of NDA 22-107. Novartis offers this document in response to the request.

Question 1

Novartis provided *f2* similarity raw data in a previous response to an information request (submission dated May 2, 2007). In Table 1-1, Batch # X018 0206 and Batch # X079 0206 are listed as batches used for dissolution testing for BE or biowaiver request. How does Batch # X079 0206 relate to Batch# X018 0206? Why is Batch # X079 0206 being used for *f2* similarity calculations instead of Batch # X018 0206 (which was used in the BE study 2103)?

Response:

Novartis confirms that the two SPH100 300/25 mg film-coated tablets batches, X018 0206 and X079 0206, have the same formulation and were manufactured using the same process.

The *f2* similarity calculations using X079 0206 as a reference batch were completed prior to the start of the BE study. For reasons of logistics, X018 0206 was the batch that was subsequently used in the study.

A comparison between batch X018 0206 (used in the BE study 2103) and the 150/12.5 mg batch X008 0206 has also been performed. The data used to calculate the similarity factor are presented in Table 2 to Table 4 (full data was provided in the submission of May 2, 2007), the dissolution profiles are presented in Figure 1 to Figure 6.

The *f2* similarity factor was calculated according to the Guidance for Industry entitled "Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system" (2000). The following recommendations associated with the use of the similarity factor *f2* were followed:

- the dissolution measurements of the test and reference batches must be made under exactly the same conditions
- a minimum of 12 dosage units should be evaluated
- only one measurement should be considered after 85% dissolution of both the products.

The dissolution profiles are considered to be similar if the f_2-factor is greater than or equal to 50. As can be seen from the results presented, the two batches are considered to be similar.

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.

Table 1 Batches used

Dosage strength	Batch	Description
150/12.5 mg	X008 0206	Pilot scale
300/25 mg	X018 0206	Pilot scale

Table 2 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

Table 3 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

Table 4 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

Note: Table 4 f2 calculation at pH 6.8 for HCTZ is incorrect. Correct f2 calculation is 63.3

However, the incorrect number has not impact on the sponsor being granted a biowaiver since the f2 number is >50; but not more than 100.

Figure 1 Dissolution profiles of SPH100 300/25mg versus 150/12.5mg: SPP100 in 0.1M HCl (n=12)

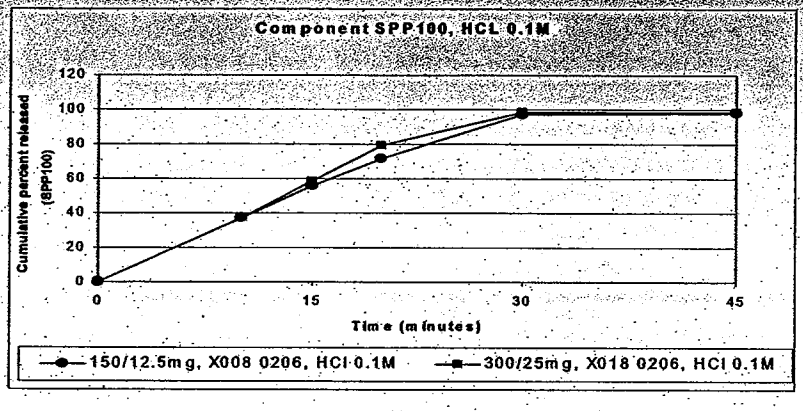


Figure 2 Dissolution profiles of SPH100 300/25mg versus 150/12.5mg: SPP100 in phosphate buffer pH 4.5 (n=12)

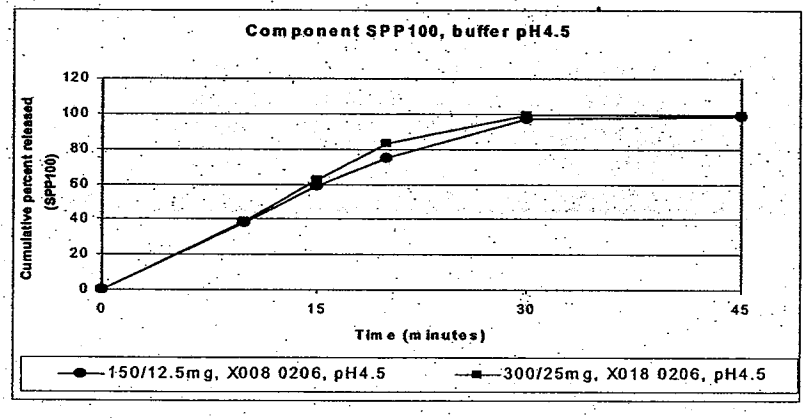


Figure 3 Dissolution profiles of SPH100 300/25mg versus 150/12.5mg: SPP100 in phosphate buffer pH 6.8 (n=12)

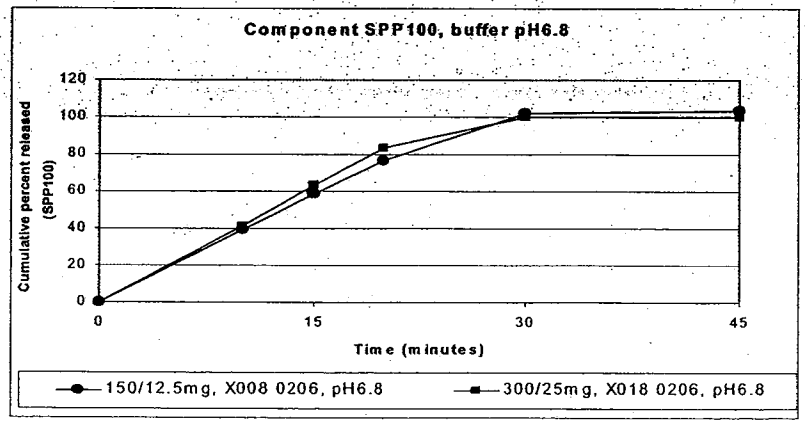


Figure 4 Dissolution profiles of SPH100 300/25mg versus 150/12.5mg: HCTZ in 0.1M HCl (n=12)

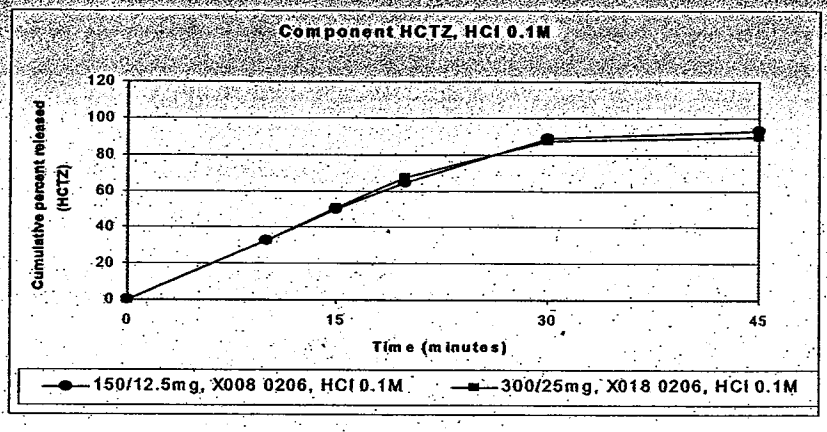


Figure 5 Dissolution profiles of SPH100 300/25mg versus 150/12.5mg: HCTZ in phosphate buffer pH 4.5 (n=12)

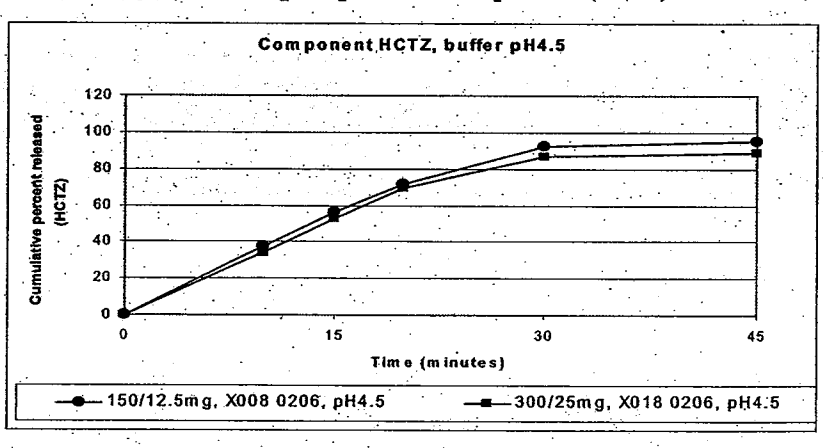
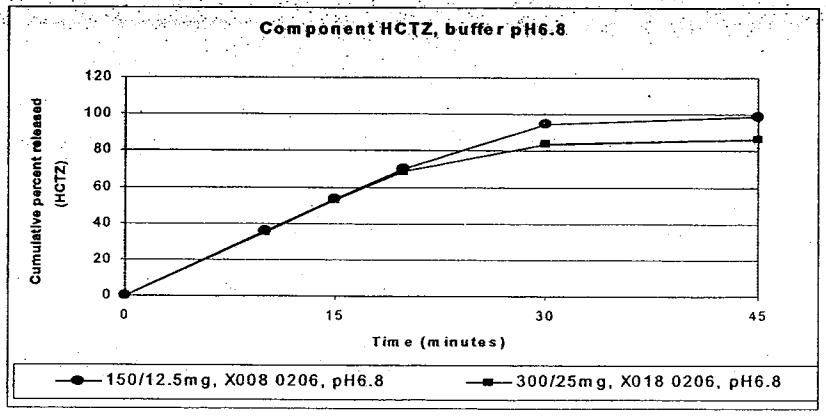


Figure 6 Dissolution profiles of SPH100 300/25mg versus 150/12.5mg: HCTZ in phosphate buffer pH 6.8 (n=12)



Question 2

No Batch size or Manuf/Exp date for Batch # X079 0206 is contained in the information that was submitted for *f2* similarity comparison calculation. What biostudy was Batch # X079 0206 used for?

Response:

The manufacturing details for batch X079 0206 are presented below. The batch has not been used in a biostudy.

Table 5 Manufacturing details for SPH100 film-coated tablets batch X079 0206

Batch number	Dosage Strength	Manufacturing date	Batch size	Manufacturing site
X079 0206	300/25 mg	24-Mar-2006	[redacted] FCT	Novartis, Basel, Switzerland

b(4)

REVIEWER'S COMMENT:

1. The batch # X079 0206 would not have been adequate to assess a biowaiver since the batch (Table 5) is not:
   - At a minimum, one-tenth that of full production, or 100,000 tablets or capsules, whichever is larger (see the FEDERAL REGISTER of Thursday, September 22, 1994, 59 FR 48754-59 and see "Guidance for Industry: Immediate Release Solid Oral Dosage Forms - Scale-up and Postapproval Changes: Chemistry, Manufacturing, and Controls, in *in-vitro* dissolution testing, and *in-vivo* bioequivalence documentation) and
   - Batch X079 0206 was not used in the Bioequivalence study 2103.

2. Based on the 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. The sponsor may be granted a biowaiver for the intermediate strength of 150/12.5 mg Aliskiren/HCT.

Appendix IV
COVER SHEET AND OCPB FILING/REVIEW FORM

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Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22-107**	**Brand Name**	**Tekturna HCT**
OCPB Division (I, II, III)	**DPE 1**	**Generic Name**	**Aliskiren/hydrochlorothiazide**
Medical Division	**HFD-110**	**Drug Class**	**Rennin inhibitor/Thiazide diuretic**
OCPB Reviewer	**Lydia Velazquez**	**Indication(s)**	**Treatment of hypertension alone or in combination with other antihypertensive agents**
OCPB Team Leader	**Patrick Marroum**	**Dosage Form**	**Tablets – 150/12.5, 150/25, 300/12.5, and 300/25 mg**
		Dosing Regimen	**Once Daily**
Date of Submission	**19 March 2007**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**20 November, 2007**	**Sponsor**	**Novartis Pharmaceutical, Corp.**
PDUFA Due Date	**20 January, 2008**	**Priority Classification**	**S**
Division Due Date	**20 November 2007**		

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	5		
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	1		SUBMITTED SEPARATELY AS A STUDY (DMPK R0600 276).
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	4		3BE (A2101, 2102, and 2103), 1 Food Effect (A2104)
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	1		Efficacy trial (CRD07/0014) in mild to moderate HTN patients – used earlier Speedel formulation (capsule). Can not find analytical data.
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				

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	3		SD
replicate design; single / multi dose:				SD
Food-drug interaction studies:	X	1		Food Effect – Healthy Volunteers - SD
Dissolution:	N/A			
(IVIVC):				
Bio-wavier request based on BCS	X	Data Missing		Biowaiver based on F2 – raw data missing
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Permeability				
Efflux				
QT Study				
Total Number of Studies		7		1 Analytical report, 3BE, 1 Food Effect, and 1 Efficacy study. Can't find F2 comparison raw data for 150/12.5 mg or analytical data for CDR07/0014.

Filability and QBR comments

	"X" IF YES	COMMENTS
Application filable ?	X	Have not been able to locate F2 comparison raw data or analytical data for CRD07/0014 efficacy study. Will request that it be submitted ASAP.
Comments sent to firm?		
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 22-107, HFD-110 (FrommE), HFD-860 (MehtaM, MarroumP, VelazquezL), CDR Central Document Room

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

/s/

Lydia Velazquez
12/12/2007 04:26:45 PM
BIOPHARMACEUTICS

Original NDA CPB review

Patrick Marroum
12/13/2007 02:16:13 PM
BIOPHARMACEUTICS