CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-107

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
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Reviewer Name	Shen Xiao, M.D., Ph.D.
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Established Name	Aliskiren/Hydrochlorothiazide
(Proposed) Trade Name	Tekturna HCT®
Therapeutic Class	Antihypertensive (Renin inhibitor combined with diuretics)
Applicant	Novartis
Priority Designation	S
Formulation	Oral tablet
Dosing Regimen	Aliskiren/Hydrochlorothiazide: 150/12.5 mg, 150/25mg, 300/12.5mg, and 300/25mg
Indication	Treatment of hypertension
Intended Population	Adult patients with hypertension

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Abbreviations

ACE	angiotensin converting enzyme
ACEI	angiotensin converting enzyme inhibitor
ABPM	ambulatory blood pressure monitoring
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase (SGPT)
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
AST	aspartate aminotransferases (SGOT)
AUC	area under the curve
BID	twice a day
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
CAT	coaxial tomography
CK	creatine kinase
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CRF	case report form
CVA	cerebrovascular accident
DBP	diastolic blood pressure
DSI	Division of Scientific Investigation (FDA)
ECG	electrocardiogram
EEG	electroencephalogram
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GFR	glomerular filtration rate
GI	gastrointestinal
GLP	Good Laboratory Practices
HbA1c	hemoglobin A1c
HGB	hemoglobin
HCTZ	hydrochlorothiazide
HF	heart failure
ICH	International Conference on Harmonization
IRB	institutional review board
ISE	Integrated Summary (Review) of Efficacy
ISS	Integrated Summary (Review) of Safety
ITT	intention-to-treat
LOCF	last observation carried forward
LSM	least squares mean
LVH	left ventricular hypertrophy
MI	myocardial infarction
MRI	magnetic resonance imaging

MSDBP	mean seated diastolic blood pressure
MSSBP	mean seated systolic blood pressure
NDA	New Drug Application
NOS	not otherwise specified
NS	not significant
OD	once a day
PD	pharmacodynamics
PEY	person-exposure-year
PK	pharmacokinetic
PRA	plasma renin activity
PRC	plasma renin concentration
PTCA	percutaneous coronary angioplasty
QD	once a day
QTc	QT interval corrected (for heart rate)
RAAS	renin-angiotensin-aldosterone system
RBC	red blood cells
SAE	serious adverse event
SAS	Statistical Analysis System
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SLE	systemic lupus erythromatosus
SPA	special protocol assessment
TIA	transient ischemic attack
ULN	upper limit of normal
US	United States

1 Executive Summary

1.1 Recommendation on Regulatory Action

From a clinical perspective I recommend that Tekturna HCT®, the combination of aliskiren and Hydrochlorothiazide (HCTZ), be approved for the treatment of hypertension. This combination product demonstrated clinically and statistically significant reductions in both diastolic and systolic blood pressure compared to placebo and each respective monotherapy in one randomized, double-blind, placebo-controlled trial and several other active-controlled trials. The maximum antihypertensive effect was generally attained after 4 weeks of therapy.

The adverse event profile of the combination is similar to each component monotherapy. The incidence of significant AEs identified during aliskiren monotherapy clinical development program including angioedema, and GI events are also similar in the aliskiren/HCTZ combination therapy. Regarding laboratory parameters, both aliskiren and HCTZ monotherapies increased the serum level of uric acids; the combination of aliskiren/HCTZ increased serum level of uric acid even further. There was no difference of incidence rates of gout and kidney stones in short-term studies. In the long-term open label study, however, the incidence rate of gout was 0.5% (4 cases) in the combination therapy and 0.1% (1 case) in the aliskiren monotherapy. Difference for the incidence of kidney stones was not observed in this long-term open label study although the higher serum level of uric acid was observed in the combination therapy. Overall, AE profile is considered to be acceptable for antihypertensive therapy.

1.2 Recommendation on Post-marketing Actions

1.2.1 Risk Management Activity

None

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

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[redacted] should be evaluated.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Aliskiren (Tekturna) is an inhibitor of renin, the enzyme that converts angiotensinogen to angiotensin I in the first and rate-limiting step of the renin-angiotensin-aldosterone system (RAAS). Aliskiren is the first and the only approved renin inhibitor so far.

Tekturna HCT® is a new combination product of Aliskiren with Hydrochlorothiazide (HCTZ) for the treatment of patients with ——— hypertension. It is formulated as film-coated tablets for oral administration. The recommended doses of the combination of aliskiren/HCTZ included 150/12.5 mg; 150/25 mg; 300/12.5 mg; and 300/25 mg. b(4)

The sponsor provided eight clinical studies in the original submission and one study in a later submission (120-day safety update) for the evaluation of efficacy and safety to support this combination product for the treatment of hypertension. These studies included one pivotal study, two short term active-controlled studies, two long-term open label studies and one long-term active-controlled study. Two other studies (conducted in Japan and Ireland, respectively) with small numbers of patients were also provided in the original submission. In the 120-day safety update, one short term active-controlled study was submitted for further safety evaluation. There were 2776 patients in the pivotal trial and a total of 7451 patients were evaluated in the safety database and extent of exposure.

1.3.2 Efficacy

The overall clinical design is to assess whether both monotherapy treatments contribute to the overall effect in blood pressure reduction of the combination treatment. There are a total of eight studies provided to support the efficacy claim. The Study SPP 100A 2204 is the pivotal study which provides a critical appraisal for the efficacy. Other studies provide efficacy support for both short term and long term use.

The primary endpoint was change from baseline in seated trough (i.e., prior to next treatment at the end of the 24-hour inter dosing interval) cuff diastolic blood pressure (DBP). Seated trough cuff systolic blood pressure (SBP), percent responders (DBP < 90 mmHg and/or ≥ 10 mmHg less than baseline), and control rate (SBP<140 and DBP <90 mmHg) were analyzed as the secondary endpoints.

In the pivotal study, the tested drugs and doses included 1) aliskiren 75, 150 or 300 mg monotherapy; 2) HCTZ 6.25, 12.5 or 25 mg monotherapy; 3) aliskiren 75 with HCTZ 6.25, 12.5 or 25 mg combination therapy; 4) aliskiren 150 with HCTZ 6.25, 12.5, or 25 mg combination therapy; 5) aliskiren 300 mg with HCTZ 12.5 or 25 mg combination therapy; and 6) the placebo.

The study results showed that a significant greater change from baseline in mean sitting DBP at Week 8 was observed with the combination therapy compared with aliskiren and HCTZ monotherapies. Most individual combinations of aliskiren/HCTZ generally produced clinically

and statistically significant reductions in the DBP compared to placebo and each respective monotherapy in the studied dose range (P< from 0.01 to 0.0001) except the aliskiren/HCTZ 150/6.25 mg vs each monotherapy, and aliskiren/HCTZ 75/12.5 mg vs HCTZ 12.5 mg.

For the secondary endpoint of SBP in this pivotal study, the pairwise comparison showed that the combination of aliskiren/HCTZ generally produced a greater reduction of SBP at Week 8 from baseline, compared with the placebo and each monotherapy (P< from 0.02 to 0.0001).

The dose-response relationship study showed that reduction in msDBP was positively related to the dose of both aliskiren and HCTZ. For the response rate (defined as DBP < 90 mmHg or fall in DBP ≥ 10 mmHg compared to baseline) and the control rate (defined as DBP < 90 mmHg and SBP < 140 mmHg), all combinations containing aliskiren 150 or 300 mg with HCTZ 12.5 or 25 mg produced statistically greater effects than the corresponding monotherapy (P<0.05), except for the aliskiren/HCTZ 150/12.5 mg.

There are similar reductions of BP between ages of <65 years (no children were included) and ≥65 years, gender, and baseline obesity of BMI< 30 kg/m^2 and BMI≥ 30 kg/m^2 after the combined therapy.

There are two other short-term active-controlled studies, Study 2309 and Study 2303. In study 2309, aliskiren/HCTZ 300/25 mg produced a statistically significant reduction in msDBP and msSBP compared to HCTZ 25 mg alone (P< 0.0001) at the Week 8 endpoint. In Study 2303, aliskiren and lisinopril were tested with the addition of HCTZ in patients with uncomplicated severe hypertension. Both treatment regimens showed clinically significant reductions in msDBP and msSBP at all time points.

The assessment for long-term use of this product was conducted in a 12-month long-term open-label study (Study 2302) and its 4-month extension (Study 2302E1). In addition, a 26-week, active-controlled study (Study 2306) was conducted in patients with mild to moderate hypertension. In all of these three studies, there was no direct efficacy comparison between the monotherapy and the combination treatment. Patients who received the HCTZ add-on were those whose blood pressure was not adequately controlled by aliskiren monotherapy. This may demonstrate additional and sustained blood pressure reduction if the blood pressure could be controlled by the addition of HCTZ. Study results indicated that both combination therapy and monotherapy produced clinically meaningful reduction of msDBP and msSBP from baseline and maintained throughout the whole study duration.

A pooled analysis of efficacy data was not performed due to the differences in study design, patient characteristics and length of treatment. Due to the paucity of non-Caucasian patients in the studies, the subgroup analysis for race/ethnicity (Caucasian, Black, Asian, Native American, Pacific Islander, and Other) was not performed.

b(4)

1.3.3 Safety

Overall, the adverse events including the mortality rate, SAEs, common AEs, discontinuation rates due to AEs, etc., in the combination of aliskiren and HCTZ were generally comparable with each of monotherapy.

Orthostatic changes were comparable between the combination of aliskiren with HCTZ and each of monotherapy in the short-term studies. In the long-term studies, however, the incidence of patients with orthostatic changes at any visit was slightly higher in the combination therapy group than in the aliskiren monotherapy group (12% vs 8%). There was no comparison between the combined therapy group and HCTZ group.

As expected, hypokalemia with $K+ < 3.5$ mmol/L was more common in the HCTZ monotherapy and HCTZ-containing combination groups than in placebo and aliskiren monotherapy groups. The incidence of hyperkalemia was low and similar between the monotherapy and the combination therapy patients. No patients discontinued due to abnormal potassium values.

Since both of aliskiren and HCTZ can increase the serum level of uric acid, larger mean increases from baseline in uric acid occurred with the aliskiren/HCTZ and ACEI/HCTZ groups compared with aliskiren and ACEI monotherapy in the long-term studies. There was no difference of incidence rates of gout and kidney stone in short-term studies. In the long-term open label study, however, the incidence rate of gout was 0.5% (4 cases) in the combination therapy and 0.1% (1 case) in the aliskiren monotherapy. Difference for the incidence of kidney stone was not observed in this long-term open label study.

The incidence rate of other important AEs which were found in aliskiren monotherapy (NDA 21-985) including diarrhea, cough, angioedema, and slight decreases in hemoglobin and related parameters were similar or lower in the combination monotherapy compared to the aliskiren monotherapy.

Based on the provided short- and long-term studies, the AE profile with this combination product is considered to be acceptable for antihypertensive therapy.

1.3.4 Dosing Regimen and Administration

Tekturna HCT®, the combination of aliskiren with HCTZ, should be indicated for the treatment of hypertension. The fixed combinations may be used as replacement therapy for the titrated components. In addition, a patient whose blood pressure is not adequately controlled with aliskiren alone or HCTZ alone may switch to aliskiren/HCTZ daily treatment.

The sponsor proposed 4 fixed dosage strengths: 150/12.5 mg, 150/25 mg, 300/12.5 mg, and 300/25 mg. Based on the pivotal study, all of these four fixed doses produced clinically and statistically significant reductions in both msDBP and msSBP compared to placebo and each respective monotherapy at the same dose levels. In the safety analysis, the adverse event profile of these combination is similar to each component monotherapy. Therefore, it is reasonable to

approve all of these 4 dosages. The dosage may be started with the 150/12.5 mg and titrated to a maximum of one 300/25 mg tablet once daily.

1.3.5 Drug-Drug Interactions

In the 120-day safety update, the sponsor provided a new study (study 2331) for the comparison of triple combination of aliskiren/valsartan/HCTZ with the combination studies of aliskiren/HCTZ and valsartan/HCTZ as well as the monotherapy of HCTZ alone.

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No other drug-drug interaction studies were conducted.

1.3.6 Special Populations

Aliskiren/HCTZ was effective regardless of gender, age, and disease factor of obesity. Regarding the race/ethnicity, however, due to the paucity of non-Caucasian patients in the studies, the subgroup analysis for race/ethnicity (Caucasian, Black, Asian, Native American, Pacific Islander, and Other) was not performed. Children were not studied, and the Division granted a deferral of pediatric studies for the severe hypertension indication.

Studies of either aliskiren monotherapy or the combination of aliskiren with HCTZ were not conducted in pregnant women. The sponsor is proposing a black box warning in the label regarding use in pregnancy as is currently included in the labels for ACEIs and ARBs. There are three pregnant cases in the studies. While there have not been definite fetal abnormalities reported following these pregnancies, the experience with human pregnancies is obviously limited.

2 Introduction and Background

2.1 Product Information

Tekturna HCT® is a new combination product of Aliskiren with Hydrochlorothiazide (HCTZ). Aliskiren is a novel anti-hypertensive agent, which acts by inhibiting the enzyme renin to block the conversion of angiotensinogen to angiotensin I (Ang I), the precursor of angiotensin II (Ang II). Hydrochlorothiazide (HCTZ) is a thiazide diuretic, widely used to treat hypertension, especially with other agents. Thiazides inhibit renal tubular re-absorption and thereby increase sodium chloride and water excretion and lower plasma volume, which, in turn, lowers BP. Tekturna HCT® is expected to provide more optimal blood pressure control than the component monotherapies through the complementary effects of the two drugs. This fixed-dose combination

tablet of aliskiren/HCTZ was developed for use in the targeted population of patients with essential hypertension at all ages.

Tekturna HCT® is a biconvex ovaloid film-coated tablet with different colors and labelings based on the dosage. White tablet imprinted with "LCI" on one side and "NVR" on the other side means 150/12.5 mg; pale yellow tablet imprinted with "CLL" on one side and "NVR" on the other side means 150/25 mg; violet white tablet imprinted with "CVI" on one side and "NVR" on the other side means 300/12.5 mg; light yellow tablet imprinted with "CVV" on one side and "NVR" on the other side means 300/25 mg.

2.2 Currently Available Treatment for Indications

Many drugs are approved for the treatment of hypertension. The most relevant approved drugs are those that also work by inhibiting the renin-angiotensin-aldosterone system (RAAS). RAAS inhibitors approved for hypertension include the newly approved renin inhibitor (Aliskiren), angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and aldosterone receptor antagonists (eplerenone, spironolactone). Aliskiren inhibits the conversion of angiotensinogen to angiotensin I by renin. ACEIs inhibit the conversion of angiotensin I to angiotensin II by ACE. ARBs block the action of angiotensin II at its receptor. Eplerenone and spironolactone block the effects of aldosterone, whose release is stimulated by angiotensin II.

Regarding the combination product, there are several products of fixed combination doses of ACEIs/HCTZ or ARBs/HCTZ available for the treatment of hypertension. There is no combination product of renin inhibitors/HCTZ on the market.

2.3 Availability of Proposed Active Ingredient in the United States

Aliskiren is approved as NDA 21-985 for monotherapy of the hypertension. Tekturna HCT® is not currently marked in this country.

2.4 Important Issues With Pharmacologically Related Products

RAAS inhibitors share certain adverse events (AEs). Because all affect aldosterone, all can cause increases in serum potassium and hyperkalemia. All, either through effects on aldosterone or angiotensin II or both, can cause decreases in renal function. In addition to these AEs shared by all RAAS inhibitors, ACEIs cause cough, presumably through effects of ACE on the bradykinin pathway. ACEIs, and to a lesser extent ARBs, cause angioedema. Whether the latter is mediated through the bradykinin pathway is not clear. Some experts have hypothesized that renin inhibitors should not cause these latter AEs, but whether they do or don't has not been confirmed in clinical trials. Finally, ARBs have recently been implicated in rare cases of rhabdomyolysis.

Tekturna HCT® as a new combination of renin inhibitor and diuretics may have a relatively low incidence for some adverse effects caused by RAAS inhibitors such as hyperkalemia. However, HCTZ as a thiazide diuretics may cause some metabolic disorders related to glucose, uric acid, calcium, and potassium.

2.5 Pre-submission Regulatory Activity

At the end-of-phase II meeting on February 11, 2004 for the aliskiren development program, the Division agreed that the multi-factorial design study 2204 evaluating various combinations of Aliskiren with HCTZ can be considered a single, pivotal efficacy trial for the approval of an NDA for a fixed-dose combination of aliskiren with HCTZ with the addition of PK data.

On June 3, 2004, the Division sent a letter to the sponsor regarding a special protocol assessment (SPA) for Study 2204. The Division noted that the protocol did not include pharmacokinetic (PK) and/or pharmacodynamic (PD) assessments. The interaction between aliskiren and HCTZ should be evaluated in this study by using a sparse sampling approach. A blood sample for aliskiren assay should be collected as close as possible to the occurrence of the adverse event.

At the pre-NDA meeting for Tekturna HCT® submission on September 8, 2006, the Division sent a letter to the sponsor that the Division granted a waiver of pediatric assessments in the original NDA supporting the product.

2.6 Other Relevant Background Information

N/A

3 Significant Findings from Other Review Disciplines

3.1 CMC (and Product Microbiology, if Applicable)

The CMC reviewer, Dr. Xavier Ysern, judges this application approvable from the CMC perspective pending satisfactory responses to some questions regarding assays and batch reprocessing specifications. Other CMC issues appear to have been addressed adequately by the sponsor and are described well in the FDA CMC review. Please see the Chemistry review.

3.2 Animal Pharmacology/Toxicology

No preclinical pharmacodynamic or pharmacokinetic studies were performed with the new combination product. Toxicity studies were conducted with aliskiren and HCTZ as free combinations in the rat with dose range-finding and 13-week studies. The animal pharmacology and toxicology reviewer, Dr. G. Jagadeesh, judges this application approvable from the pharmacology and toxicology perspective. Please see Dr. Jagadeesh's review for the pre-clinical findings.

4 Data Sources, Review Strategy, and Data Integrity

4.1 Sources of Clinical Data

The primary source of clinical data for this review was the initial NDA submission dated March 19, 2007. This submission included electronic study reports for studies SPP100A0014, SPP100A 2204, SPP100A2302, SPP100A2302E1, SPP100A2303, SPP100A2306, SPP100A2309 and SPP100A1202.

In the 120-day safety update, the sponsor sent the electronic study report for study SPP 100A 2331 dated July 19, 2007.

4.2 Tables of Clinical Studies

The sponsor conducted eight clinical studies for the evaluation of efficacy and safety to support this combination product for the treatment of the primary hypertension in the initial submission. Three other studies are ongoing and data are not provided with original submission (table 2). One of these three studies (study 2331) was submitted later in a 120-day safety update. In addition, the sponsor has conducted PK, and bioavailability and bioequivalence studies in healthy volunteers with this combination product. Please see the FDA clinical pharmacologist's review for tabulations and reviews of those studies. Studies for efficacy and safety evaluation of this product included in this initial NDA are displayed in the following Table 1.

Table 1: Studies Supporting Efficacy and Safety in Hypertension

(w: white, b: black, a: asia, o: others)

Studies	Total No & race	Dose (mg)	Duration	Design	Comment
#2204	2776 2372w 127b 69a 208 o	Aliskiren: 75, 150, 300 HCTZ: 6.25, 12.5, 25 Aliskiren/HCTZ: 75/6.25, 75/12.5, 75/25, 150/6.25, 150/12.5, 150/25, 300/12.5, 300/25	8-week	Double blind, multicenter, randomized multifactorial, placebo-controlled, parallel group study in patients with essential hypertension (msDBP ≥ 95 mmHg and < 110 mmHg)	Pivotal study in multiple countries including US.
#2303	183 182w, 1o	Aliskiren: 150, 300 Aliskiren/HCTZ: 300/25 Lisinopril: 20, 40 Lisinopril/HCTZ: 40/25	8-week	Double blind, randomized, active controlled, parallel group study in patients with uncomplicated severe hypertension	Not in US
# 2309	489 487w, 2o	HCTZ: 25 Aliskiren/HCTZ: 150/25, 300/25 Irbesartan/HCTZ: 150/25, 300/25 Amlodipine/HCTZ: 5/10, 5/25	12-week	Double blind, parallel group study in patients with BMI ≥ 3kg/m^2 in adequately responsive to HCTZ 25 mg.	Not in US Change from baseline in msDBP at week 8 as the primary endpoint
#2306	842 638w, 151b, 27a, 26o	Aliskiren: 300 Aliskiren/HCTZ: 300/12.5, 300/25 Ramipril: 10 Ramipril/HCTZ: 10/12.5, 10/25	26-week	Double blind, randomized, multicenter, parallel group, active-controlled study over a period of 26 weeks following by a 4-week double blind, randomized placebo-controlled withdrawal.	Patients were titrated after 6 weeks and randomized withdrawal.
#2302	1955 1687w 115b, 15a, 138o	Aliskiren 75, 150, 300 HCTZ 12.5, 25 Aliskiren/HCTZ 300/12.5, 300/25	12 month	Open-label, multicenter, study to assess the long-term effect of aliskiren with or without HCTZ.	
#2302E1	198 186w, 9b, 1a, 2o	Aliskiren/HCTZ 300/25	4 month	4 month high dose combination open label treatment	
#1202	344 a	Aliskiren 75, 150, 300 Aliskiren/calcium channel blocker Aliskiren/diuretic	44-week	Extension trial for Aliskiren monotherapy (#1201). Open label, parallel group, long-term treatment for essential hypertension	Conducted in Japan only
#0014	23w	Aliskiren 150 Aliskiren/HCTZ 150/25	6-week	Open label, randomized study to evaluate the effect of the combination of aliskiren and HCTZ.	Conducted only in Ireland

Table 2: Ongoing Studies to Support Efficacy and Safety in Hypertension

Studies	Total No & race	Dose (mg)	Duration	Design	Comment
#2331	641	HCTZ 25 Aliskiren/HCTZ 150/25, 300/25 Valsartan/HCTZ 160/25, 320/25 Aliskiren/Valsartan/HCTZ 150/160/25, 300/320/25	8-week	Randomized, double blinded, parallel group, multicenter comparing efficacy and safety study in patients not adequately responding to HCTZ	Ongoing and no result available (only in Europe)

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4.3 Review Strategy

I initially reviewed all of the eight trials as shown in table 1. I performed detailed reviews of the pivotal placebo-controlled trial (protocol CSPP100A 2204) for approval from an efficacy aspect. For an integrated review of safety, I relied primarily upon analyses of all of the trials from table 1 and study 2331 in the 120-day safety update.

4.4 Data Quality and Integrity

Since this NDA is a drug combination application and all of the studies have been conducted in nearly all of the same sites as the approved NDA 21-985 (Aliskiren monotherapy) where some of them have been audited by DSI, I do not think any additional audits are required.

From the provided dataset, I did not identify any problems or major discrepancy which might confound the efficacy and safety results of this NDA.

4.5 Compliance with Good Clinical Practices

Based on the sponsor's claims, all studies were conducted in full compliance with Good Clinical Practice and in accordance with the following directives:

1. Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Patients).

2. Directive 91/507/EEC: The Rules Governing Medicinal Products in the European Community.

3. US 21 Code of Federal Regulations dealing with clinical studies, parts 50 and 56, concerning informed patient consent and Institutional Review Board approval.

4.6 Financial Disclosures

The sponsor provided a detailed lists of all the clinical investigators participating in studies SPH100A2101, SPH100A2102, SPH100A2103, SPH100A2104, SPP100A2204, SPP100A2302, SPP100A2302E1, SPP100A2303, SPP100A2306, SPP100A2309, SPP100A1202 conducted at US and non-US sites. From the list, one investigator from study 2306 reported "Grants, Honoraria, Travel Expenses" exceeding $25,000. The first four studies (2101, 2102, 2103 and 2104) are clinical pharmacology, bioavailability and bioequivalence studies.

This one potential conflicts of interest should not prejudice the results greatly even if there were overt manipulation.

5 Clinical Pharmacology

Since this NDA is a combination of two approved drugs, a bridge pharmacokinetic drug-drug interaction study with aliskiren and HCTZ was conducted. This study was performed in healthy subjects and summarized in section 5.1 (below). For more details see the FDA clinical pharmacology review.

5.1 Pharmacokinetics

The study was an open label, two-period, multiple dose trial to investigate pharmacokinetic drug-drug interaction potential between aliskiren and HCTZ following multiple oral dose administration in healthy subjects.

Twenty-two (22) healthy volunteers participated in the study. In Period 1 (study days 1-4), subjects received a single 25 mg daily dose of HCTZ. Period 1 was followed by a 4-day washout period (study days 5-8). In Period 2 (study days 9-19), subjects received aliskiren 300 mg once a day for a total of 11 days (study days 9-19), with a single 25 mg daily dose of HCTZ co-administered for 4 days (study days 16-19). All drug administration was conducted under fasted conditions.

Pharmacokinetic parameters of aliskiren and HCTZ at steady-state are summarized in table 3 and table 4 (provided by sponsor), respectively. As shown in the following tables, although there was a moderate decrease in steady-state Cmax (see ratio of genometric means) when two drugs were co-administered as compared to either drug alone, the steady-state overall exposure (AUC_τ) was nearly identical and the 90% CIs of the geometric mean ratios were all contained within 80-125% bioequivalent limits. Therefore, there was no significant pharmacokinetic interaction between aliskiren and HCTZ when co-administered as compared to administration of either drug alone.

Table 3: Mean plus/minus SD (CV%) pharmacokinetic parameters of aliskiren at steady-state following single daily oral administration of 300 mg aliskiren alone (study day 15) or in combination with 25 mg HCTZ daily oral administration (study day 19)

Treatment	C_{max} (ng/ml)	t_{max} (h)	C_{min} (ng/ml)	AUC_T (h•ng/mL)
Aliskiren alone	425 ± 216 (51%)	2.2 (0.5, 6.0)	35 ± 13 (36%)	2310 ± 934 (40%)
Aliskiren + HCTZ	309 ± 150 (49%)	1.5 (0.5, 4.4)	41 ± 20 (47%)	2210 ± 1157 (52%)
Ratio of geometric means	0.78	NA	NA	0.93
90% confidence intervals	0.64 - 0.95	NA	NA	0.83 – 1.05

t_{max} = median (min, max)

Table 4: Mean plus/minus SD (CV%) pharmacokinetic parameters of HCTZ at steady-state following single daily oral administration of 25 mg HCTZ alone (study day 4) or in combination with 300 mg aliskiren daily oral administration (study day 19)

Treatment	C_{max} (ng/ml)	t_{max} (h)	C_{min} (ng/ml)	AUC_T (h•ng/mL)
HCTZ alone	260 ± 86 (33%)	1.5 (1.0, 4.0)	15 ± 6 (41%)	1411 ± 316 (22%)
HCTZ + Aliskiren	187 ± 43 (23%)	2.0 (1.0, 3.4)	20 ± 7 (36%)	1273 ± 297 (23%)
Ratio of geometric means	0.74	NA	NA	0.90
90% confidence intervals	0.69 - 0.79	NA	NA	0.87 – 0.93

t_{max} = median (min, max)

5.2 Pharmacodynamics

Study was not conducted.

5.3 Exposure-Response Relationships

Study was not conducted.

6 Integrated Review of Efficacy

6.1 Indication

The indication for the proposed aliskiren/HCTZ fixed-dose combination tablets (Tekturna HCT) is the treatment of hypertension.

6.1.1 Methods

There are total eight studies were provided to support the efficacy claim as tabulated in Section 4.2.

The Study SPP 100A 2204 is the pivotal study which provides a critical appraisal for supporting the efficacy.

Study SPP 100A 2309 is an active-controlled study in obese patients not adequately responding to HCTZ monotherapy. Study SPP 100A 2303 is an active-controlled study in severe hypertensive patients with the open-label addition of HCTZ to aliskiren or lisinopri. Both of studies provide supportive efficacy information.

The long-term open label Study SPP 100A 2302 and its extension Study SPP 100A 2302 E, as well as the long term active-controlled Study SPP100A 2306 support the long term efficacy. In addition, two studies conducted in Japan (Study SPP 100A 1202) and Ireland (Study SPP 100A0014) were also provided for efficacy information.

For the primary evaluation of efficacy, my review focuses on the Study SPP 100A 2004 for the initial evaluation of the antihypertensive effects. I then examine results of the other studies to answer other critical questions such as the long term effect, population variation, subgroup analysis, etc.

6.1.2 General Discussion of Endpoints

The primary endpoint in the pivotal study (SPP 100A 2204) and other two large, multicenter, randomized, double-blind, controlled, parallel group trials (SPP 100A 2309 and SPP 100A 2306) was change from baseline in seated trough (i.e., prior to next treatment at the end of the 24-hour inter dosing interval) cuff diastolic blood pressure (DBP). Seated trough cuff systolic blood pressure (SBP), percent responders (DBP < 90 mmHg and/or ≥ 10 mmHg less than baseline), and control rate (SBP<140 and DBP <90 mmHg) were analyzed as second secondary endpoints. The proportion of responders and the control rate were analyzed by means of a logistic regression model with treatment and region as factors, and baseline DBP as a covariate. In addition, ambulatory blood pressure measurement (ABPM) was done in Study SPP 100A 0014 to justify the once daily dosing.

6.1.3 Study Design

The overall clinical design in this program is to assess whether both monotherapy treatments contribute to the overall effect in blood pressure reduction of the combination treatment. The clinical studies in this program included patients with mild to moderate essential hypertension (mean diastolic pressure ≥ 90 or 95 and < 110 mmHg), except for study CSPP100A 2303, which recruited patients with sever hypertension (diastolic pressure ≥ 105 and < 120 mmHg).

The baseline demographic characteristics of the treatment groups were comparable within each study, and were generally comparable across the different studies except for differences specified in the protocols: baseline blood pressure was higher in study 2303 as it enrolled severe hypertensive patients and baseline body weight and BMI (≥ 30 kg/m^2) are greater in study 2309 as it enrolled obese patients.

The dose selection in the combination was based on aliskiren monotherapy clinical trial data and the available marketed doses of HCTZ that are commonly used for the treatment of hypertension.

Study CSPP100A 2204 serves as the pivotal efficacy trial for this submission. It was a placebo-controlled, 4x4 factorial design study in patients with mild to moderate hypertension. This study included a 1-week washout, 2 to 4-week single-blind placebo run-in, and 8-week double-blind treatment. The primary endpoint, change from baseline in seated trough cuff DBP, was analyzed by a two-way analysis of covariance (ANCOVA) with treatment and region as factors, and baseline as a covariate. A statistical adjustment for multiple comparisons using Dunnett's procedure was used for studies including multiple aliskiren doses. The key secondary efficacy endpoint, change from baseline in seated trough cuff SBP, was similarly analyzed. The tested doses included 1) aliskiren 75, 150 or 300 mg monotherapy; 2) HCTZ 6.25, 12.5 or 25 mg monotherapy; 3) aliskiren 75 with HCTZ 6.25, 12.5 or 25 mg combination therapy; 4) aliskiren 150 with HCTZ 6.25, 12.5, or 25 mg combination therapy; 5) aliskiren 300 mg with HCTZ 12.5 or 25 mg combination therapy; and 6) the placebo. The primary objectives are to evaluate the aliskiren monotherapy in comparison to placebo and to evaluate the combinations of aliskiren and HCTZ in comparison to the component monotherapy. The final selection of the recommended dose for the fixed-dose combination of aliskiren/HCTZ was based on the results of this pivotal study.

In addition to the study 2204, other studies also provided supportive efficacy information in sub-groups of the study population and the long-term efficacy information. For the details of the study designs and the individual study results, please see Appendix 10.1.

6.1.4 Efficacy findings

6.1.4.1 Primary Endpoint (DBP) and Major Secondary Endpoints

The changes from baseline for seated trough cuff DBP in the pivotal study (Study CSPP 100A 2204) were summarized in the following table 5. The data showed that, a significantly greater change from baseline in the mean sitting DBP at Week 8, compared with aliskiren and HCTZ

monotherapies. Most individual combinations of aliskiren/HCTZ generally produced clinically and statistically significant reductions in the DBP compared to placebo and each respective monotherapy in the studied dose range except the aliskiren/HCTZ 150/6.25 mg vs each monotherapy, and aliskiren/HCTZ 75/12.5 mg vs HCTZ 12.5 mg. However, the effect size is small for aliskiren between 75 and 150 mg and they are not differentiated. The dosages of HCTZ alone are also not differentiated. Note the substantial placebo effect. (nearly 7 mm Hg.)

Table 5:Sponsor's change from baseline in mean sitting diastolic blood pressure (mmHg) at endpoint (ITT population)

Monotherapy	N	LSM change from Baseline (SE)	Combination therapy	N	LSM change from Baseline (SE)
Aliskiren 75 mg	183	-8.68 (0.59)	Aliskiren 75 mg/HCTZ 6.25 mg	187	-10.76 (0.59)
Aliskiren 150 mg	183	-8.94 (0.59)	Aliskiren 75 mg/HCTZ 12.5 mg	189	-11.14 (0.59)
Aliskiren 300 mg	180	-10.26 (0.60)	Aliskiren 75 mg/HCTZ 25 mg	186	-11.46 (0.59)
HCTZ 6.25 mg	194	-9.07 (0.58)	Aliskiren 150 mg/HCTZ 6.25 mg	173	-10.36 (0.61)
HCTZ 12.5 mg	188	-10.11 (0.59)	Aliskiren 150 mg/HCTZ 12.5 mg	184	-11.90 (0.59)
HCTZ 25 mg	173	-9.37 (0.61)	Aliskiren 150 mg/HCTZ 25 mg	187	-12.65 (0.59)
Placebo	192	-6.93 (0.58)	Aliskiren 300 mg/HCTZ 12.5 mg	180	-13.87 (0.60)
			Aliskiren 300 mg/HCTZ 25 mg	173	-14.26 (0.61)

Pairwise Comparison		LSM difference Change from Baseline (SE)	95% CI	Nominal p-value
Aliskiren 75 mg	vs. placebo	-1.75 (0.83)	(-3.37, -0.13)	0.0344*
Aliskiren 150 mg	vs. placebo	-2.01 (0.83)	(-3.63, -0.39)	0.0152*
Aliskiren 300 mg	vs. placebo	-3.33 (0.83)	(-4.95, -1.70)	< 0.0001*
Aliskiren 75 mg/HCTZ 6.25 mg	vs. aliskiren 75 mg	-2.08 (0.83)	(-3.71, -0.45)	0.0126*
	vs. HCTZ 6.25 mg	-1.69 (0.82)	(-3.30, -0.08)	0.0394*
	vs. placebo	-3.83 (0.82)	(-5.44, -2.22)	< 0.0001*
Aliskiren 75 mg/HCTZ 12.5 mg	vs. aliskiren 75 mg	-2.46 (0.83)	(-4.09, -0.83)	0.0031*
	vs. HCTZ 12.5 mg	-1.03 (0.83)	(-2.65, 0.59)	0.2124
	vs. placebo	-4.21 (0.82)	(-5.82, -2.60)	< 0.0001*
Aliskiren 75 mg/HCTZ 25 mg	vs. aliskiren 75 mg	-2.77 (0.83)	(-4.41, -1.14)	0.0009*
	vs. HCTZ 25 mg	-2.09 (0.85)	(-3.75, -0.43)	0.0136*
	vs. placebo	-4.52 (0.82)	(-6.14, -2.91)	< 0.0001*
Aliskiren 150 mg/HCTZ 6.25 mg	vs. aliskiren 150 mg	-1.41 (0.85)	(-3.08, 0.25)	0.0962
	vs. HCTZ 6.25 mg	-1.29 (0.84)	(-2.93, 0.36)	0.1249
	vs. placebo	-3.42 (0.84)	(-5.07, -1.76)	< 0.0001*
Aliskiren 150 mg/HCTZ 12.5 mg	vs. aliskiren 150 mg	-2.96 (0.84)	(-4.60, -1.32)	0.0004*
	vs. HCTZ 12.5 mg	-1.79 (0.83)	(-3.42, -0.16)	0.0314*
	vs. placebo	-4.97 (0.83)	(-6.59, -3.35)	< 0.0001*
Aliskiren 150 mg/HCTZ 25 mg	vs. aliskiren 150 mg	-3.70 (0.83)	(-5.33, -2.07)	< 0.0001*
	vs. HCTZ 25 mg	-3.28 (0.85)	(-4.94, -1.62)	0.0001*
	vs. placebo	-5.71 (0.82)	(-7.33, -4.10)	< 0.0001*
Aliskiren 300 mg/HCTZ 12.5 mg	vs. aliskiren 300 mg	-3.61 (0.84)	(-5.26, -1.95)	< 0.0001*
	vs. HCTZ 12.5 mg	-3.76 (0.84)	(-5.39, -2.12)	< 0.0001*
	vs. placebo	-6.93 (0.83)	(-8.56, -5.31)	< 0.0001*
Aliskiren 300 mg/HCTZ 25 mg	vs. aliskiren 300 mg	-4.00 (0.85)	(-5.68, -2.33)	< 0.0001*
	vs. HCTZ 25 mg	-4.90 (0.86)	(-6.59, -3.21)	< 0.0001*
	vs. placebo	-7.33 (0.84)	(-8.98, -5.68)	< 0.0001*

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval

For the secondary endpoint of SBP in this pivotal study, the changes from baseline was summarized in the following table 6. The pairwise comparison showed that the combination of aliskiren/HCTZ generally produced a greater reduction of SBP at Week 8 from baseline, compared with the placebo and each monotherapy. There is also a substantial placebo effect (-7.5 mm Hg) as there was for DBP.

Table 6: Sponsor's change from baseline in mean sitting systolic blood pressure (mmHg) at endpoint (ITT population)

Monotherapy	N	LSM change from Baseline (SE)	Combination therapy	N	LSM change from Baseline (SE)
Aliskiren 75 mg	183	-9.37 (0.94)	Aliskiren 75 mg/HCTZ 6.25 mg	187	-14.29 (0.93)
Aliskiren 150 mg	183	-12.24 (0.94)	Aliskiren 75 mg/HCTZ 12.5 mg	189	-15.64 (0.93)
Aliskiren 300 mg	180	-15.74 (0.95)	Aliskiren 75 mg/HCTZ 25 mg	186	-17.32 (0.93)
HCTZ 6.25 mg	194	-10.95 (0.92)	Aliskiren 150 mg/HCTZ 6.25 mg	173	-15.31 (0.97)
HCTZ 12.5 mg	188	-13.92 (0.93)	Aliskiren 150 mg/HCTZ 12.5 mg	184	-17.61 (0.94)
HCTZ 25 mg	173	-14.30 (0.97)	Aliskiren 150 mg/HCTZ 25 mg	187	-19.47 (0.93)
Placebo	192	-7.48 (0.92)	Aliskiren 300 mg/HCTZ 12.5 mg	180	-19.82 (0.95)
			Aliskiren 300 mg/HCTZ 25 mg	173	-21.22 (0.97)

Pairwise Comparison		LSM difference		
		Change from Baseline (SE)	95% CI	Nominal p-value
Aliskiren 75 mg	vs. placebo	-1.69 (1.31)	(-4.46, 0.69)	0.1512
Aliskiren 150 mg	vs. placebo	-4.76 (1.31)	(-7.34, -2.18)	0.0003*
Aliskiren 300 mg	vs. placebo	-8.25 (1.32)	(-10.84, -5.67)	< 0.0001*
Aliskiren 75 mg/HCTZ 6.25 mg	vs. aliskiren 75 mg	-4.93 (1.32)	(-7.52, -2.33)	0.0002*
	vs. HCTZ 6.25 mg	-3.34 (1.30)	(-5.90, -0.79)	0.0103*
	vs. placebo	-6.81 (1.31)	(-9.38, -4.25)	< 0.0001*
Aliskiren 75 mg/HCTZ 12.5 mg	vs. aliskiren 75 mg	-6.27 (1.32)	(-8.86, -3.69)	< 0.0001*
	vs. HCTZ 12.5 mg	-1.71 (1.31)	(-4.28, 0.85)	0.1905
	vs. placebo	-8.16 (1.30)	(-10.71, -5.60)	< 0.0001*
Aliskiren 75 mg/HCTZ 25 mg	vs. aliskiren 75 mg	-7.95 (1.32)	(-10.55, -5.36)	< 0.0001*
	vs. HCTZ 25 mg	-3.02 (1.34)	(-5.66, -0.39)	0.0246*
	vs. placebo	-9.84 (1.31)	(-12.40, -7.27)	< 0.0001*
Aliskiren 150 mg/HCTZ 6.25 mg	vs. aliskiren 150 mg	-3.07 (1.35)	(-5.71, -0.42)	0.0230*
	vs. HCTZ 6.25 mg	-4.36 (1.33)	(-6.97, -1.75)	0.0011*
	vs. placebo	-7.83 (1.33)	(-10.44, -5.21)	< 0.0001*
Aliskiren 150 mg/HCTZ 12.5 mg	vs. aliskiren 150 mg	-5.37 (1.33)	(-7.97, -2.77)	< 0.0001*
	vs. HCTZ 12.5 mg	-3.69 (1.32)	(-6.27, -1.10)	0.0052*
	vs. placebo	-10.13 (1.31)	(-12.70, -7.56)	< 0.0001*
Aliskiren 150 mg/HCTZ 25 mg	vs. aliskiren 150 mg	-7.23 (1.32)	(-9.82, -4.64)	< 0.0001*
	vs. HCTZ 25 mg	-5.17 (1.34)	(-7.81, -2.54)	0.0001*
	vs. placebo	-11.99 (1.31)	(-14.55, -9.43)	< 0.0001*
Aliskiren 300 mg/HCTZ 12.5 mg	vs. aliskiren 300 mg	-4.08 (1.34)	(-6.71, -1.45)	0.0024*
	vs. HCTZ 12.5 mg	-5.89 (1.33)	(-8.49, -3.29)	< 0.0001*
	vs. placebo	-12.33 (1.32)	(-14.92, -9.75)	< 0.0001*
Aliskiren 300 mg/HCTZ 25 mg	vs. aliskiren 300 mg	-5.48 (1.35)	(-8.14, -2.83)	< 0.0001*
	vs. HCTZ 25 mg	-6.92 (1.37)	(-9.60, -4.24)	< 0.0001*
	vs. placebo	-13.74 (1.33)	(-16.35, -11.1)	< 0.0001*

SE = Standard Error; LSM = Least Squares Mean; CI = Confidence Interval